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REVIEW

Targeting non-apoptotic regulated cell death (RCD) to treat neurodegenerative diseases

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Abstract Regulated cell death (RCD) is well-known as a controlled form of cell death regulated by one or more cascading signaling pathways. Over the past few decades, increasing evidence has implicated various non-apoptotic forms of RCD in neurons—including ferroptosis, parthanatos, necroptosis, pyroptosis, autophagic cell death, paraptosis, and cuproptosis—in the pathogenesis of neurodegenerative diseases (NDs) and their associated clinical manifestations. We provide an in-depth analysis of the associations between these RCDs and NDs, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), and highlight the potential of modulating non-apoptotic RCD subtypes as neuroprotective targets. Besides, we highlight the crosstalk mechanisms among different non-apoptotic RCDs in NDs and the key targets regulating the crosstalk, which hold significant promise for developing dual-functional inhibitors that precisely modulate the pathological microenvironment and overcome drug resistance. As our understanding of death signaling networks deepens, such strategies may lead to breakthrough therapies for multiple NDs. Moreover, we further discuss the emerging small molecule compounds targeting non-apoptotic RCDs and their current research progress in clinical trials for the treatment of NDs, which may provide novel directions for related drugs. This comprehensive analysis paves the way for future research and therapeutic strategies aimed at harnessing non-apoptotic RCD pathways to mitigate neurodegeneration and improve patient outcomes.

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1. Introduction

The study of regulated cell death (RCD) has redefined our understanding of cellular demise, transitioning from the classical paradigm of apoptosis to encompass a diverse array of non-apoptotic mechanisms. These pathways—including ferroptosis, parthanatos, necroptosis, pyroptosis, autophagic cell death, paraptosis, and cuproptosis—constitute distinct forms of RCD, each governed by unique molecular triggers and signaling cascades[1−3]. Their identification in recent decades has revealed profound implications for various pathological processes, particularly neurodegenerative diseases (NDs) Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), are characterized by chronic neuronal loss, often linked to dysregulated cell death[4]. Despite extensive research, effective treatments remain elusive. This highlights the urgent need to unravel the complex interplay between RCD pathways and neurodegeneration.

Traditional research on cell death in neurodegeneration has primarily focused on apoptosis. While this pathway remains a hallmark of neuronal loss, it fails to capture the full diversity of cell death mechanisms in NDs. Clinical and animal studies reveal a key discrepancy: classical apoptotic markers (*e.g.*, caspase activation, DNA fragmentation) often appear less prominently in brain tissues than oxidative stress or inflammatory response markers. Furthermore, certain neurons exhibit a prolonged degenerative process, which markedly contrasts with the typically swift progression of apoptotic cell death[5]. Morphologically, apoptotic cells exhibit characteristic features including cytoplasmic shrinkage, intact plasma membranes, and minimal inflammatory activation. In contrast, non-apoptotic RCD demonstrates cellular swelling, plasma membrane rupture, and robust pro-inflammatory signaling. Critically, mounting evidence links neuroinflammation to major NDs such as AD, PD, and ALS. This association substantiates the necessity of investigating non-apoptotic RCD mechanisms within NDs pathogenesis[6−8]. Non-apoptotic RCD pathways have emerged as critical mediators, offering alternative explanations for the molecular and cellular events underlying neurodegeneration. For example, because of the aberrant buildup of iron and oxidative stress in impacted brain areas, ferroptosis, an iron-dependent form of RCD marked by lipid peroxidation, has been linked to numerous NDs[9,10]. Similarly, necroptosis, a caspase-independent type of cell death[11], is shown to exacerbate neuroinflammation and neuronal damage. Non-apoptotic RCDs are more closely associated with the pathophysiological progression of NDs than apoptosis. This not only accounts for the persistence of chronic neurological damage but also reveals potential therapeutic targets through specific signaling proteins. These discoveries of non-apoptotic RCDs offer new therapeutic possibilities for addressing complex pathological mechanisms and delivering disease-specific interventions.

Among these pathways, the concept of targeting RCD in NDs has gained significant traction. Modulating ferroptosis, for example, has demonstrated potential in alleviating iron-induced oxidative damage and preserving neuronal function. Similar metal-induced death mechanisms are observed in cuproptosis. Specifically, in AD and PD, ferroptosis exacerbates neuronal oxidative stress and death by inducing lipid peroxidation and glutathione (GSH) depletion through iron accumulation. For instance, it promotes amyloid β peptide (Aβ) proteotoxicity in AD and intensifies α-syn aggregation in PD; conversely, cuproptosis involves copper-dependent protein misfolding and mitochondrial dysfunction, exacerbating Tau protein phosphorylation in AD and DA neuronal damage in PD. Both mechanisms drive neurodegenerative processes *via* metal ion imbalance[12,13]. Likewise, inhibition of necroptosis has shown promise in preclinical models of ALS[14] and MS[15]. Furthermore, emerging evidence suggests that pyroptosis, a pro-inflammatory RCD mediated by inflammasomes, contributes to the neuroinflammatory milieu observed in many NDs[16]. Targeting pyroptosis-related components may therefore offer dual benefits of reducing inflammation and mitigating neuronal loss[17]. The activation state of PARP plays a modulatory role in parthanatos, which is closely associated with energy metabolism and apoptosis-inducing factor (AIF) translocation. Evidence suggests that parthanatos is implicated in multiple NDs[18]. These insights underscore the therapeutic relevance of non-apoptotic RCDs and necessitate a comprehensive evaluation of their roles across various neurodegenerative contexts. Recent advances in omics technologies, including transcriptomics, proteomics, and metabolomics, have provided a systems-level perspective on RCD regulation. These approaches have unveiled key molecular players and signaling networks involved in ferroptosis, necroptosis, and other RCD pathways. For instance, the glutathione peroxidase 4 (GPX4)-dependent axis in ferroptosis, the PI3K/AKT in autophagic cell death, the poly(ADP-ribose) polymerase 1 (PARP1) in parthanatos, and the RIPK1/RIPK3/MLKL complex in necroptosis represent pivotal nodes amenable to therapeutic intervention[19]. Small molecule compounds targeting these pathways include α-lipoic acid, an inhibitor of ferroptosis, which reduces oxidative stress in various NDs in clinical trials; MC2050, a PARP1 inhibitor that antagonizes parthanatos-induced death; SZM679, which inhibits the formation of the RIPK1/RIPK3/MLKL complex thereby inhibiting necrotic progression of apoptosis; carveol, which attenuates pyroptosis in a PD mouse model; and trientine, a copper chelator that resolves cuproptosis in the context of ALS in mice[20−24]. These drugs have exhibited neuroprotective effects in preclinical studies or clinical trials. Meanwhile, in NDs, there may be overlapping regulatory proteins or pathways between multiple non-apoptotic RCDs, which we call crosstalk. For example, ferroptosis and cuproptosis may be simultaneously affected by proteins that regulate lipid oxidation, and targeting these proteins will inhibit both RCDs[25]. However, translating these findings to diagnostic applications is still a formidable challenge, necessitating further investigation into the specificity, efficacy, and safety of such interventions.

This review synthesizes current understanding of non-apoptotic RCD pathways in neurodegenerative disorders, elucidating their molecular mechanisms and evaluating potential therapeutic applications. By integrating current evidence, we examine

the interplay between ferroptosis, necroptosis, pyroptosis, and other RCD subroutines in driving neuronal loss and disease progression. Furthermore, we analyze crosstalk mechanisms among different RCDs in NDs and identify key regulatory targets, potentially offering novel therapeutic perspectives. We also highlight emerging drug candidates targeting multiple RCD pathways, including their preclinical and clinical progress, to provide holistic therapeutic strategies. Ultimately, this review aims to bridge fundamental research with clinical translation, fostering innovative therapies against neurodegeneration. Understanding the complex roles of non-apoptotic RCDs in NDs advances disease biology knowledge and enables targeted treatments. Leveraging insights from this evolving field, we envision RCD modulation transforming the therapeutic landscape of neurodegenerative disorders, improving patient outcomes and quality of life.

2. An overview of neuronal non-apoptotic RCDs

Non-apoptotic RCD is a cell death mode distinct from the classical apoptotic pathway. Apoptosis is typically initiated by endogenous or exogenous apoptotic signaling pathways, involving cell shrinkage, nuclear condensation, and apoptotic body formation. This process remains relatively quiet, as it aims to eliminate redundant or damaged cells without triggering inflammation, thereby maintaining homeostasis. In contrast, non-apoptotic RCD often induces inflammation, which can lead to nerve cell death and contribute to NDs such as AD and PD. Targeting regulated RCD pathways may alleviate inflammation, offering potential for ND treatment. The following section introduces key RCD types closely linked to NDs.

2.1. Ferroptosis

In 2012, ferroptosis was first described by Dixon[26]. Emerging as a multi-layered regulatory process, ferroptosis integrates iron-mediated lipid peroxidation with systemic metabolic coordination across redox signaling, iron trafficking, mitochondrial bioenergetics, and nutrient metabolism pathways, constituting a unique cell death paradigm[27].

The regulatory mechanisms of ferroptosis mainly encompass the GPX4-dependent regulatory pathway, the GPX4-independent regulatory pathway, the lipid metabolism pathway, and the iron metabolism pathway. GPX4 serves as an essential barrier against lipid peroxidation toxicity in cells, directly maintaining cell membrane stability and survival. Without GPX4, cells lose their ability to clear lipid peroxides and inevitably undergo ferroptosis. This irreplaceability establishes GPX4's central role in defending against oxidative damage and regulating cell fate, making it a key molecular target for disease intervention. The GPX4-dependent pathway primarily involves the cystine-glutamate antiporter system (System xc^-)−GSH−GPX4 axis. This GPX4-centered axis is responsible for reducing cystine to cysteine, an essential amino acid that serves as a critical cellular antioxidant and a key component of GSH[27]. The enzymatic regeneration of oxidized glutathione is mediated by glutathione reductase through NADPH-dependent electron transfer. Concurrently, system xc^- stability is maintained through OTU deubiquitinase, ubiquitin aldehyde binding 1, and nuclear factor erythroid 2-related factor 2 (NRF2) transcriptional regulation, whereas its degradation is potentiated by BRCA1-associated protein 1-mediated suppression[1]. Beyond its canonical functions, the mevalonate pathway contributes to selenocysteine biosynthesis—a critical substrate for GPX4 activation through selenoprotein co-translational incorporation[28]. Recent studies have also found that mevalonate pathway metabolites, such as panthenol and 7-dehydrocholesterol[27,29], can inhibit ferroptosis.

The GPX4-independent pathways mainly include two routes: ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) and GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4). The FSP1-CoQ10 axis operates through FSP1-mediated enzymatic reduction of CoQ10, generating reduced ubiquinol that exerts radical-trapping antioxidant activity to suppress phospholipid peroxidation and block ferroptotic cascade initiation[30,31]. FSP1 also converts vitamin K into vitamin KH2, which is a radical-scavenging antioxidant[32]. In this axis independent of GPX4, the farnesoid X receptor can upregulate FSP1 and peroxisome proliferator-activated receptor-α (PPARα). PPARα upregulates the levels of anti-ferroptotic monounsaturated fatty acids-PL and FSP1, while dihydroorotate dehydrogenase (DHODH), as a cofactor, can also upregulate the sensitivity of FSP1 to ferroptosis. In the GCH1−BH4 axis, GCH1 is the rate-limiting enzyme for BH4 synthesis. The antioxidant effect of BH4 prevents lipid peroxidation and avoids ferroptosis[33].

Lipid peroxidation can drive ferroptosis, with acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) being the first identified pro-ferroptotic gene products. They are involved in activating polyunsaturated fatty acids (PUFAs) such as arachidonic acid and incorporating them into membrane-localized lipids, driving subsequent cell death[34]. In this process, protein kinase C beta II (PKCβII) promotes the phosphorylation of ACSL4, increasing lipid peroxidation and ferroptosis, while FBXO10 exhibits the opposite effect. The energy stress-adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) signaling axis exerts anti-ferroptotic effects *via* ACC-dependent mechanisms, where AMPK-mediated Ser79 phosphorylation of ACC disrupts *de novo* lipogenesis, ultimately preventing peroxidation of polyunsaturated fatty acids in cellular membranes.

Iron metabolic disorder is a crucial factor in ferroptosis. Iron is imported *via* the endocytosis pathway mediated by transferrin receptor 1 (TFR1). Studies have found that abnormal accumulation of TFR1 on the cell surface is a characteristic of ferroptosis[35]. Under normal circumstances, iron entering the cell is reduced to ferrous ions to participate in various biochemical reactions. Iron dyshomeostasis induces pathological accumulation of redox-active Fe^{2+}, establishing a labile iron pool that propagates Fenton chemistry—catalyzing hydroxyl radical ($\cdot$OH) generation through Fe^{2+}-mediated H_2O_2 reduction, thereby amplifying oxidative stress *via* reactive oxygen species (ROS) cascade propagation. ROS buildup causes membrane lipid peroxidation, which impairs cell activity and ultimately causes cell death[27]. Notably, STAT3 regulates iron metabolism. As a core hub in cellular signal transduction, STAT3 coordinates proliferation, immunity, and metabolism by responding to microenvironmental signals. It is a key component of the Janus kinase (JAK)−STAT signaling pathway. Upon stimulation by cytokines and growth factors, STAT3 rapidly activates and regulates transcription of target genes. Studies demonstrate that under pathological conditions, inflammatory factors such as IL-6 accelerate phosphorylation of JAK−STAT3, activating the signaling pathway and driving hepcidin expression[36,37]. Hepcidin accelerates iron transport, prevents the formation of iron pools, and ultimately suppresses

ferroptosis. In NDs, the brain experiences iron metabolism disorders and lipid peroxidation accumulation. The failure of key antioxidant defense systems renders neurons particularly susceptible to ferroptosis. This oxidative damage directly leads to neuronal loss and accelerates disease progression. Based on this, there is substantial evidence indicating that inhibiting ferroptosis will effectively improve various NDs.

2.2. *Parthanatos*

The term "parthanatos" was coined by David in 2009[38]. Parthanatos is a novel RCD form triggered by PARP1. PARP1 is a relatively large protein with a weight of about 113 kDa. It is like a modular structure composed of several distinct functional domains, which are connected by flexible linker regions. This modular structure allows PARP1 to perform different functions and interact with various molecules. In eukaryotic cells, as a DNA repair enzyme, PARP1 is primarily located in the nucleus. Although it may not directly catalyze the DNA repair process, PARP1 plays a role in the activation of various DNA repair enzymes, such as DNA topoisomerases, DNA helicases, and DNA ligases[39]. Under typical physiological circumstances, PARP1 contributes to DNA damage repair. However, significant DNA damage causes PARP1 to become overactivated in pathological situations[40]. Toxic stimuli such as ROS, ischemia, alkylating agents, IR, and UVR can directly or indirectly activate PARP1 by activating nitric oxide synthase (NOS). The overactivated PARP1 catalyzes the decomposition of intracellular nicotinamide adenine dinucleotide (NAD) into nicotinamide and poly ADP-ribose (PAR), leading to a significant accumulation of PAR within the cell. This accumulation of PAR induces the release of AIF, which then translocates to the nucleus along with macrophage migration inhibitory factor (MIF). In the nucleus, they induce chromatin condensation and subsequent extensive DNA fragmentation, ultimately resulting in neuronal loss[41]. Studies have shown that activation of the c-Jun N-terminal kinase (JNK) signaling pathway can induce the production of ROS and mitochondrial superoxide anions within cells, which are typical drivers of PARP1. In glutamate-treated HT22 neurons, the JNK signaling pathway is activated[42], accelerating parthanatos and subsequent neuronal death. In conclusion, as a key factor in cell death, PARP1 plays two important roles: that of a master in DNA repair and that of the initiator of parthanatos. Currently, PARP1 inhibitors targeting PARP1 have been widely studied and applied in NDs. A large number of studies reported that PARP1 inhibitors can protect neurons from parthanatos and are important therapeutic drugs for central nervous system diseases.

Now, a number of studies show that mitochondria are the key organelles for regulating parthanatos. Parthanatos is notably characterized by interactions between the nucleus and mitochondria and mitochondrial malfunction during the cell death process. These features are of vital significance in CNS injury. Mitochondria are crucial for maintaining the physiological integrity of cells, primarily through energy production. Nevertheless, when cells are exposed to certain stimuli, mitochondrial membranes become permeable. As a result, apoptosis-inducing factor (AIF) is released, triggering parthanatos. Therefore, the close association of parthanatos with the CNS suggests that it may be one of the key mechanisms leading to irreversible neuronal loss in disease. Targeting the parthanatos pathway holds promise as a novel therapeutic strategy to delay or halt the progression of NDs.

2.3. *Necroptosis*

The concept of necroptosis was first proposed by Degterev in 2005[43]. The activation of tumor necrosis factor receptor (TNFR) leads to the formation of complex I, which is a common step in initiating both apoptosis and necroptosis. However, the distinction between the two is that necroptosis is a caspase-independent RCD, and this pathway is inhibited by the small molecule nec-1[43]. In addition, the essence of necrotic apoptosis is "regulated necrosis", and the inflammation triggered by RIPK3-mediated MLKL phosphorylation and plasma membrane rupture is the gold standard that distinguishes it from other forms of cell death.

Necroptosis is initiated through the activation of specialized cellular receptors, including death receptors, Toll-like receptors, and cytoplasmic nucleic acid sensors such as stimulator of interferon genes (STING). These receptors establish an autocrine signaling mechanism wherein their activation stimulates the synthesis of IFN-I and TNFα, which subsequently reinforce the necroptotic pathway through receptor-mediated signaling cascades[44]. The ubiquitination of RIPK1 in complex I forms a scaffold for the binding of the linear ubiquitin chain assembly complex (LUBAC) and the transforming growth factor-β-activated kinase 1 (TAK1)−TAK1-binding protein complex. LUBAC, under the action of Caspase 8, induces apoptosis. When Caspase 8 activity is inhibited and RIPK1 is deubiquitinated by deubiquitinating enzymes such as cylindromatosis, ovarian tumor like integrase, and tumor necrosis factor alpha-induced protein 3, necroptosis is triggered. At this point, RIPK1 is released from complex I into the cytoplasm, where it undergoes autophosphorylation and binds to RIPK3, leading to the autophosphorylation of RIPK3 as well. RIPK1 and RIPK3 form a necrosome, and ultimately, the RIPK1/RIPK3 complex phosphorylates MLKL. Phosphorylated MLKL oligomerizes to form the necrosome. The MLKL oligomer creates pores in the plasma membrane by translocating to areas that are rich in phosphatidylinositol phosphate. Lastly, the MLKL pores let ion inflow, which results in membrane rupture and cell enlargement. This is followed by the unchecked release of intracellular contents, which causes necroptosis[44]. Interestingly, current research indicates that, under pathological conditions, autocrine IL-6 silences *TNFA* expression by activating the signal transducer and activator of transcription 3-DNA methyltransferases (STAT3-DNMT) epigenetic axis, thereby inhibiting TNFα-mediated RIPK1-dependent necroptosis, maintaining cell survival, and promoting accumulation[45]. In NDs, signals such as TNFα can excessively activate RIPK1/MLKL-mediated necroptosis, leading to neuronal death. Conversely, IL-6 suppresses this pathway through STAT3-mediated epigenetic mechanisms, generating compensatory survival signals. This disruption of the delicate balance between survival and death is pivotal in disease progression, making it a critical therapeutic target.

2.4. *Pyroptosis*

In 2001, pyroptosis was first defined by Cookson and Brennan[46]. An essential immunological response, pyroptosis has been observed in several illnesses, such as cancer, neurological conditions, and inflammatory diseases. It is distinguished by cytoplasmic inflammation, mitochondrial malfunction, and nuclear DNA fragmentation. The canonical pyroptotic signaling pathway is predominantly orchestrated by Caspase 1 activation, whereas the non-canonical pathway engages alternative executioners,

including the inflammatory caspase subfamily. Crucially, both pathways demonstrate functional convergence through proteolytic cleavage of gasdermin D (GSDMD)[47]. Pyroptosis is a programmed lytic death triggered by inflammasome activation and mediated by GSDMD. Its core characteristics are: gasdermin-N forms pores in the cell membrane, causing osmotic imbalance, cell swelling, and membrane rupture. This type of death does not involve DNA fragmentation, and the nucleus exhibits condensation.

In the classic cascade, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) induce the formation of inflammasomes, which are composed of NOD-like receptor family pyrin-domain-containing 3 (NLRP3), the bridging factor ASC, and pro-Caspase 1[48]. Following inflammasome assembly, pro-Caspase 1 undergoes oligomerization and autoproteolytic activation. The activated Caspase 1 proteolytically processes GSDMD, liberating its N-terminal fragment that oligomerizes to generate membrane pores. These pores facilitate the release of pro-inflammatory cytokines IL-1β and IL-18, culminating in cytoplasmic content efflux, plasma membrane disintegration, and pyroptosis[49]. Currently, multiple cytokines have been identified that promote the activation of caspase, thereby inducing pyroptosis. Studies have shown that p-STAT3 promotes *Anxa2* expression at the transcriptional level, thereby activating Caspase 1[50]. Additionally, there is evidence that activated STAT3 promotes GSDME transcription. Subsequently, upregulated GSDME enhances Caspase3 activity and promotes the conversion of apoptosis to pyroptosis[51]. In the non-canonical pyroptosis pathway, Caspases 4, 5, and 11 directly recognize and are activated by bacterial lipopolysaccharide (LPS), further activating GSDMD into GSDMD-N to trigger pyroptosis[52]. Evidence suggests that p-STAT3 can physically interact with PD-L1, promoting its nuclear translocation and enhancing the transcription of GSDMC. Under TNFα stimulation, Caspase 8 specifically cleaves GSDMC, releasing the N-terminal domain to form pores in the plasma membrane, inducing cells to undergo non-classical pyroptosis[53]. Pyroptosis is closely linked to NDs by mediating neuroinflammation. In pathological conditions such as AD, signals like Aβ activate inflammasomes, triggering GSDMD-mediated pyroptosis. This leads to neuronal death and the release of large amounts of inflammatory factors, exacerbating neuroinflammation and pathological protein aggregation. This self-perpetuating cycle underscores pyroptosis as a pivotal therapeutic target in NDs.

2.5. Autophagic cell death

The concept "autophagy" was first described by Deter[54]. As a well-established form of RCDs, autophagy enables cells to degrade and recycle cytosolic constituents such as proteins and organelles, thereby preserving cellular equilibrium[55,56]. Under physiological conditions, this process sustains homeostasis and modulates diverse bodily functions. Conversely, excessive autophagic activity disrupts this balance, resulting in autophagic cell death and subsequently contributing to disease pathogenesis.

Autophagic cell death is primarily regulated by autophagy-related genes, with AMPK and mammalian target of rapamycin (mTOR) signaling serving as autophagy initiators. Factors such as hunger and oxidative stress can activate these signals. Autophagosomes are generated through multiple pathways working in concert. AMPK delays mTORC1 complex formation, thereby reducing mTORC1's inhibitory effect on unc-51-like autophagy-activating kinase 1 (ULK1) complex formation and promoting autophagosome generation. Activated JNK disrupts the Beclin1/BCL2 (B cell lymphoma 2) and Beclin1/BIM complexes by phosphorylating BCL2 and BIM to release Beclin1. Free Beclin1 assembles with vacuolar protein sorting 34 (VPS34) to form an enzymatic complex that catalyzes phosphatidylinositol 3-phosphate production, facilitating autophagosome membrane expansion. The autophagy-related gene (ATG) 5−ATG12 conjugate subsequently binds ATG16L to constitute a trimeric complex that assembles onto developing autophagosomes. Following proteolytic cleavage of LC3 by ATG4 into LC3-I, sequential enzymatic processing by ATG7, ATG3, and phosphatidylethanolamine covalently conjugates these components to generate membrane-anchored LC3-II. After that, LC3-II joins the autophagosome. Finally, syntaxin 17 binds to synaptosomal-associated protein 29 and vesicle-associated membrane protein 8 to form the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor complex, which transfers to the autophagosome membrane, enabling lysosome fusion with the autophagosome to form the autolysosome[57]. The substances inside are degraded by the hydrolases in the lysosome. During this process, the cytoplasm of the cell gradually diminishes, while the cell nucleus generally remains intact until the cell eventually dies.

Autophagic cell death is also regulated by multiple cytokines. Evidence suggests that cyclopyrone inhibits the growth of gastric cancer cells and autophagic cell death by inhibiting the phosphorylation of STAT3 at the Tyr705 and Ser727 residues[58]. In addition, studies have shown that ubiquitin-specific protease 19 (USP19) can inhibit mTORC1 by mediating NEK9 deubiquitination and induce autophagic cell death[59]. In conditions such as AD, dysregulation of autophagy represents a core pathology. Abnormal accumulation of Aβ and Tau proteins can excessively activate the autophagic flux, potentially driving neurons from protective autophagy toward autophagic cell death. This leads to irreversible neuronal loss, thereby accelerating disease progression.

2.6. Paraptosis

The term "paraptosis" was proposed by Sperandio in 2000[60]. Paraptosis represents a non-apoptotic RCD modality defined by extensive cytoplasmic vacuolation in mitochondrial and endoplasmic reticulum (ER) compartments, accompanied by progressive organelle dilation in the absence of classical apoptotic markers. It is independent of caspases and lacks the typical morphological changes of apoptosis, such as cell contraction and DNA fragmentation. This non-apoptotic cell death program may be mediated by mitogen-activated protein kinase (MAPK) and inhibited by ALG-2-interacting protein 1/ALG-2-interacting protein X (AIP-1/Alix)[61].

During paraptosis, the MAPK pathway is mainly regulated by pro-inflammatory cytokines, of which TNFα is the core inducer. TNFα directly triggers the overactivation of the MAPK pathway through the activation of the death receptor TNFR1, which leads to ER stress and cytoplasmic vacuolization, driving paraptosis[62]. In addition, inflammatory factors such as IL-1β and IL-6 can enhance MAPK signaling through paracrine or autocrine modes, further promoting paraptosis-associated mitochondrial or ER damage. Paraptosis exhibits distinct morphological changes. Prominently, it features cytoplasmic vacuolation along with the swelling of vital cellular organelles, namely mitochondria and the ER. Subsequently, the integrity of the plasma membrane is compromised. This progressive breakdown ultimately results in

cell death. The regulatory mechanisms of paraptosis involve diverse signaling molecules, with their involvement contingent on the specific triggers that initiate this form of cell death. It is noteworthy that this form of cell death, accompanied by extensive cavitation, may lead to neuronal dysfunction and death, thereby accelerating the progression of NDs.

2.7. Cuproptosis

Copper constitutes an essential micronutrient ubiquitously required across biological systems. Biochemical studies confirm its indispensable role as a catalytic cofactor for metalloenzymes governing redox homeostasis, mitochondrial respiration, and neurotransmitter biosynthesis[63]. Copper homeostasis requires stringent systemic regulation through dedicated control mechanisms to preserve optimal biochemical functionality. Contemporary studies have identified cuproptosis—a novel RCD modality mediated by copper-dependent proteotoxic mechanisms. This copper-induced lethality initiates through direct coordination of copper ions with lipoylated mitochondrial tricarboxylic acid cycle (TCA) enzymes, inducing oligomerization-driven proteostatic collapse[64]. This binding results in the aggregation of proteins, leading to proteotoxic stress and ultimately causing cell death[65]. Evidence indicates that excessive Cu^{2+} may directly induce mitochondrial protein lipidation stress and aggregation in neurons, leading to unique mitochondrial toxicity that drives neuronal loss and triggers the onset of NDs (Table 1 and Fig. 1).

3. The role of non-apoptotic RCDs in NDs

3.1. Non-apoptotic RCDs in AD

Clinically, AD is characterized by personality problems, cognitive impairment, and progressive memory loss. In contrast, AD is characterized neuropathologically by a build-up of Tau protein, Aβ, and significant neuroinflammation. In AD, Tau—a microtubule-binding protein—is hyperphosphorylated, and Aβ is sheared from amyloid precursor protein (APP)[66]. Hyperphosphorylated p-Tau is a component of neurofibrillary tangles (NFTs), contributing to synapse loss, neuroinflammation, and neuronal damage. Given the multiple pathologic changes in the AD brain, various RCD mechanisms have been observed in AD.

Among the obvious types of RCDs, disorders of iron metabolism and ferroptosis due to lipid peroxidation are among the most closely linked to AD. A non-apoptotic kind of cell death that relies on intracellular iron, ferroptosis differs from other types of cell death in terms of morphology, biochemistry, and genetics[12]. Earlier studies have concluded that abnormal accumulation of iron in cortical regions of the brain may bind to NFT and Aβ, thereby accelerating cognitive decline in AD patients[67]. Recently, a close association of Aβ with ferroptosis was observed for the first time in human brain tissue. IHC staining and positive pixel density scoring of postmortem brain tissue from AD patients (Brodmann Area 17) showed significantly different levels of ferroptosis-related markers in Aβ plaques compared with plaque-free areas, such as elevated expression of nuclear receptor coactivator 4 (NCOA4) and reduced expression of NRF2 and GPX4[68,69]. As our understanding of ferroptosis and its role in disease has advanced, research has demonstrated that ferroptosis plays a critical role in the pathophysiology of AD by inhibiting the GSH−GPX4 axis, dysregulating iron metabolism, and promoting lipid peroxidation[70]. In addition, ACSL4 promotes PUFA integration into cell membrane phospholipids, enhances lipid peroxide sensitivity, and synergizes with iron overload and GPX4 activity inhibition. This implies that ACSL4 is also one of the important targets of ferroptosis[71]. The pathological accumulation of cerebral iron in AD pathogenesis arises from multifactorial dysregulation of iron homeostasis. A key contributor involves proteopathic sequestration

Table 1 Comparison of different non-apoptotic regulated cell deaths (RCDs) types.

Type of regulated cell deaths (RCDs)	Initiators	Signaling pathway	Mediators	Inhibitors	Outcome
Ferroptosis	Iron, glutamate	(System xc^-)−GSH −GPX4, FSP1−CoQ10, GCH1−BH4, JAK −STAT	Fe^{2+}, ROS, ACSL4, LPCAT3, PKCβII	GSH, GPX4, FSP1, CoQ10, DHODH, GCH1, BH4, STAT3	Plasma membrane rupture *via* ROS
Parthanatos	DNA damage	PARP1, JNK	PARP1, PAR, AIF, MIF, NOS	−	Plasma membrane rupture *via* chromatin lysis
Necroptosis	TNF, IAP	RIPK3−MLKL	RIPK, TNFα1/3, MLKL, STING	Caspase8, STAT3, DNMT	Plasma membrane rupture *via* MLKL
Pyroptosis	Inflammation	NLRP3, GSDMD	Caspase1, GSDMD, PAMPs, DAMPs, STAT3	−	Plasma membrane rupture *via* inflammation
Autophagic cell death	Stress	AMPK, mTOR	ATGs, ULK1, USP19	BCL2, mTORC1, STAT3	Plasma membrane rupture *via* the release of lysosomal hydrolase
Paraptosis	MAPK	MAPK	MAPK, TNFα, IL-1β, IL-6	AIP-1/Alix	Plasma membrane rupture *via* MAPK
Cuproptosis	Cu^{2+}	TCA	Dihydrolipoic acid transacetylase (DLAT), Ferredoxin 1 (FDX1)	GSH	Plasma membrane rupture *via* Fe−S cluster protein synthesis

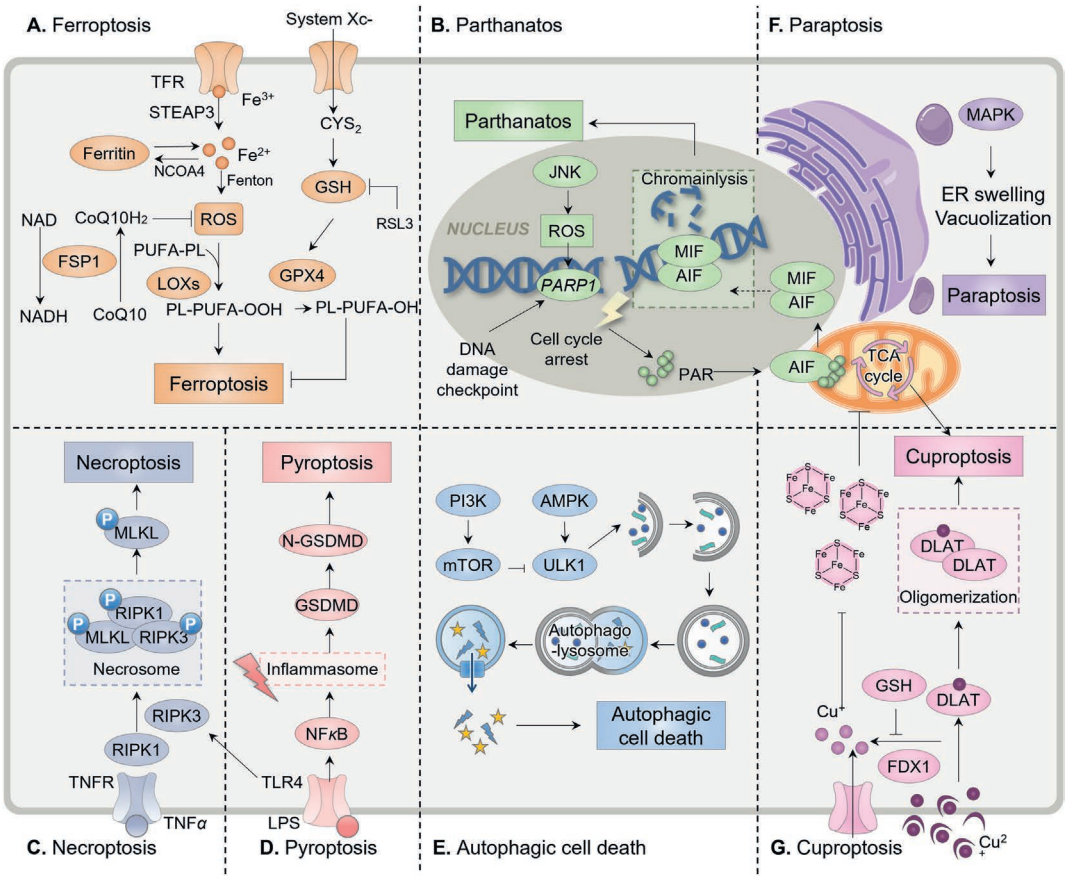

Figure 1 Common types of regulated cell deaths (RCDs). (A) Iron overload increases reactive oxygen species, and the inactivation of the GSH−GPX4 axis both lead to an increase in lipid peroxides, resulting in ferroptosis. Generation of RSL3 and $CoQ_{10}H_2$ reduces ROS levels and inhibits ferroptosis. (B) DNA damage events activate DNA damage checkpoints, pause the cell cycle, and initiate PARP1 repair, which mediates translocation to the nucleus in conjunction with MIF, thereby inducing DNA damage. (C) A form of cell death triggered by TNFα and mediated by RIPK3 and MLKL. (D) A form of regulated cell death triggered by the inflammasome and mediated by GSDMD. (E) The activation of AMPK and the inhibition of mTOR will promote the formation of autophagosomes, thereby inducing autophagic cell death. (F) Paraptosis is typically induced by the activation of the MAPK pathway and is accompanied by ER swelling. (G) Cu^{2+} binds to lipoylated proteins in the TCA, causing these proteins to aggregate abnormally. They also interfere with the iron-sulfur cluster proteins in the respiratory chain complexes. Ultimately, this triggers a proteotoxic stress response, leading to cuproptosis.

of soluble Tau into NFTs, which impairs iron efflux capacity through destabilization of ferroportin1 (FPN)—mechanistically linked to Tau's physiological role in APP trafficking-mediated FPN membrane stabilization[72]. Normally, soluble Tau facilitates APP shuttling to neuronal membranes, a process critical for maintaining FPN-mediated iron export, whereas Tau aggregation disrupts APP trafficking, triggering iron retention *via* FPN internalization and lysosomal degradation. APP knockout mice exhibit reduced FPN, increased iron accumulation, and oxidative stress in cortical neurons[73]. Recent research has demonstrated that Aβ contributes to ferroptosis by upregulating TFR levels and downregulating GPX4 and SLC7A11. Furthermore, *via* the CD36/PINK1/Parkin pathway, Aβ causes mitosis-dependent ferroptosis in pericytes[74,75]. It has been demonstrated that Tau-dependent iron increase occurs in mice as a result of Aβ poisoning. Therefore, protein buildup and altered iron transport linked to Tau and Aβ may result in iron alterations in AD[12]. Increased amounts of certain aldehyde byproducts, such as 4-hydroxy-2-nonenal (4-HNE), MDA, and acrolein, have been seen in AD brains as a result of lipid peroxidation[76]. Furthermore, it has been noted that lipid peroxidation products and Aβ plaques co-localize in AD patients' brains[77]. Aβ peptides induce lipid peroxidation and increase APP processing, leading to a vicious cycle between Aβ and lipid peroxidation in AD pathology[78]. The most prevalent non-protein sulfhydryl group, GSH, protects neurons from oxidative stress and preserves redox balance. By attaching to ferrous ions and preventing iron-dependent oxidation, GSH preserves redox equilibrium and serves as a substrate for lipid detoxification mediated by GPX4. When ferroptosis occurs, lipid peroxides build up due to decreased GSH and GPX4 activity, which pushes the cell closer to death[69]. In animal models of AD, decreased levels of GPX4 and GSH have been noted[79]. Overexpression of GPX4 inhibits lipid peroxidation and protects cortical neurons from Aβ-induced cytotoxicity. In 5 × FAD mice, experiments revealed that GPX4 overexpression significantly reduced neuronal loss and lipid ROS production, which in turn led to a decrease in amyloid plaque formation in frontal cortical tissues and an improvement in learning and memory. However, ferroptosis marker 4-HNE was found to be reduced[80]. Overall, the occurrence of ferroptosis is strongly implicated in the pathogenesis of AD. In addition, the

influence of gut flora on AD through the brain−gut axis is one of the pathogenic hypotheses, and a recent study found that ferroptosis is involved in this process. Specifically, AD mice (5 × FAD model) were observed to have a significant correlation between the development of AD pathology and changes in gut microflora. Expansion of Clostridium spp. and absence of Anabaena spp. were key features associated with Aβ load in AD mice. Improvements in the pathologic manifestations of AD were also seen, including a reduction in Aβ plaque loading, salvage of synaptic function, amelioration of cognitive deficits, and reduction of glial cell proliferation and attenuation of myelin degeneration[71].

Parthanatos is a caspase-independent RCD mediated by PARP1. In the normal state, PARP1 primarily functions in repairing damaged DNA, whereas its overactivation results in the accumulation of ADP-ribose polymers and the translocation of large amounts of AIF and MIF into the nucleus, ultimately triggering parthanatos. The discovery of co-distributed PARP1/Aβ and PARP1/Tau, as well as unusually high PAR levels in AD human brain samples, suggested the occurrence of parthanatos in AD patients' brains[81]. Interestingly, excess ROS enhances PARP1 activity, and oxidative stress due to the accumulation of Aβ has been observed to generate ROS and ultimately enhances PARP1 activity[82]. And, some researchers have hypothesized that the overactivation of PARP1 in AD patients may be caused by increased DNA damage and reduced repair activity due to AD[83,84]. In addition, AIF and MIF migration to the nucleus was also observed in the AD mouse model[84,85]. In conclusion, these experimental phenomena demonstrate the mutual reinforcement between parthanatos and AD pathology.

The contribution of necroptosis in AD-associated neuronal death is more pronounced[86]. In contrast to the activation pathway of pyroptosis, necroptosis is a caspase-independent mechanism of cell death mediated by the mixed-lineage kinase domain-like protein. The researchers discovered that GVD, an AD co-pathology that also contains TDP43 and other AD-related proteins, had all of the proteins needed for necroptosis execution[87]. It is believed that MLKL causes fewer synapses surrounding Aβ plaques, presumably *via* activating the necroptosis pathway in response to Aβ oligomers. GVD vesicle development has also been observed in APP transgenic mouse brain. The GVD vesicle contains the necroptosis-related proteins pRIPK1, pRIPK3, and pMLKL. The autophosphorylation of the Ser161 residue at the N-terminal of the first RIPK1 occurs during the process of neuronal necroptosis. Functional heterodimeric amyloid structures, often referred to as RIPK1/RIPK3 necroptosis complexes, are formed when RIPK1 recruits RIPK3 *via* their respective RIP homotypic interaction motif structural domains upon activation[88]. The generation of ROS in mitochondria contributes to the autophosphorylation of active RIPK1, which in turn causes RIPK3 to be recruited and the RIPK1/RIPK3 necroptosis complex to be produced. MLKL is found in cytoplasmic lysate as a monomer in its native state. When MLKL monomers are phosphorylated, they transform into MLKL oligomers[89]. The RIPK1/RIPK3/MLKL necroptosis complex moves to the outer mitochondrial membrane, where phosphorylated RIPK3 triggers phosphoglycerate mutase 5 (PGAM5), which triggers necroptosis by activating dynamin-related protein 1 (Drp1), causing mitochondrial fission that speeds up the neuronal necroptosis process[90]. Interestingly, the necroptosis pathway can be initiated by the long non-coding RNA MEG3, and the corresponding neurons are accompanied by phosphorylation of the Tau protein, which has been shown to induce activation of the necroptosis pathway associated with GVD[91]. According to a different study, AD hippocampus neurons exhibited increased TNFR1/RIPK1 signaling, and female AD brain samples tended to have higher levels of TNF and TNFR1 than male samples. In addition to AD brain, TNFR1 activates necroptosis in human glutamatergic neurons generated from iPSCs. Furthermore, the AD hippocampus exhibits changes in the endosomal sorting complexes needed for transport group III (ESCRT III) pathway proteins. Furthermore, it has recently been suggested that ESCRT III acts as a counterbalance to necroptosis and may have an innate ability to stop or postpone cell death after necroptosis has begun[92]. Neuroinflammation has also been implicated as one of the links between necroptosis and AD. Necroptosis-induced neuronal death results in the release of inflammatory cytokines, including as IL-6 and IL-1, and DAMP, both of which are potent inducers of neuroinflammation. Increased neuroinflammation, which is mostly caused by microglia, is a side effect of AD development. In the brain, neuroinflammation raises blood glucose levels, starting a vicious cycle of hyperglycemia that ultimately results in necroptosis[93].

In recent years, pyroptosis mediated by GSDMD, a member of the Gasdermin family of proteins, has been extensively studied, and several studies have demonstrated that GSDMD is an executioner of pyroptosis that can be activated by an inflammatory vesicle-mediated pathway[49,94]. The researchers used immunohistochemistry analysis of autopsy brain tissue from AD patients to confirm the link between AD and pyroptosis. Most patients' brain tissue contains cleaved GSDMD, albeit it varies depending on the cell type and the area of the brain[95]. The findings demonstrated a strong correlation between the expression of NLRP3 inflammatory vesicle proteins and pyroptosis-related proteins in microglia. Interestingly, activation of the NLPR3 inflammatory vesicle was linked to p-τ and Aβ pathology[96]. Astrocytes exhibited NLRP3 and cleaved GSDMD but not ASC, Caspase 1, or IL-18. Interestingly, a subset of astrocytes from AD patients exhibited strong Caspase 8 immunoreactivity, which may suggest a link between cleaved GSDMD and the presence of Caspase[95]. In addition, ASC have been shown to bind and cross-inoculate Aβ and amplify the pro-inflammatory response, leading to microglia pyroptosis *in vitro*[97]. In summary, pyroptosis of multiple activation pathways occurs in different regions of the AD brain, and there is a vicious cycle between pyroptosis and AD exacerbation.

One way to think of autophagy is as a dynamic recycling system that is mostly in charge of breaking down intracellular proteins and organelles[98]. And cell death driven by autophagy mechanism is called autophagic cell death. Researchers have found that autophagy induction is increased but autophagy lysosome formation is decreased in brain-associated cells of AD patients, and the reason for the formation of this autophagic dysfunction is not yet clear. Other researchers have suggested that defects in the autophagy pathway associated with cellular senescence lead to the accumulation of Aβ in neurons[99]. It appears improbable that excessive activation and execution of autophagic degradation would result in cell death in AD given autophagic malfunction and reduced autophagy lysosome formation. The proteins p-Tau and pTDP43, which ought to have been eliminated, instead build up inside cells. These protein aggregates cause autophagic cell death when they attach to the autophagy-associated protein P62/SQSTM1, which typically directs ubiquitinated proteins to LC3-II and phagocytic vesicles. This function is absent when autophagy is impaired, and AD is characterized by an increase in free LC3-II in the neuronal cytoplasm[99]. One upstream process in NDs like AD is the deregulation of autophagic breakdown of protein aggregates.

Paraptosis is still not recognizable by *in vitro* biochemical assays, and researchers generally need to determine whether paraptosis is occurring by cellular morphological features. Specific structural alterations, including cytoplasmic vacuolization and expansion of essential organelles such as mitochondria and the ER, characterize paraptosis. The integrity of the plasma membrane is then compromised, which eventually results in cell death. The regulation of paraptosis involves specific signaling molecules, contingent on the particular stimuli initiating it.ER enlargement is predominantly triggered by cellular damage induced by MAPK, JNK, and ROS, or misfolded protein accumulation. In contrast, mitochondrial swelling often stems from calcium ion overload[100].

Cuproptosis is associated with excessive protein lipoylation in the TCA cycle, a process that is regulated by FDX1, such as its promotion of lipoylation by dihydrolipoic acid transacetylase (DLAT) with the help of lipoic acid synthase. FDX1 also regulates the proteins that reduce cuproptosis ions to the more toxic Cu^{+}, which promotes binding of Cu^{+} to lipoylated fraction of the protein and leads to cell death and proteotoxicity[101,102]. Thus, the accumulation of Cu^{2+} in the brain also contributes to the accelerated condition of AD patients, and it has been shown that imbalances in copper homeostasis are closely associated with the accumulation of Aβ, Tau hyperphosphorylation, and the development of neuroinflammation. For example, in a co-localization experiment studied, copper concentrations in Aβ plaques of AD patients were nearly five times higher than those of the healthy population[103]. There are two Cu^{2+} binding regions on APP, one of which is located in the Aβ region, so Cu^{2+} can also interact with APP, and when this occurs, Cu^{2+} can likewise be reduced. Specifically, His6, His13 and His14 on Aβ are key residues for coordination with Cu^{2+}, which bind to Aβ to form insoluble Aβ aggregates, which are more toxic and also enhance the binding stability between Aβ peptides[104]. It has been found that Cu^{2+} reduce the efficiency of Aβ clearance by upregulating β-site APP cleaving enzyme 1 (BACE1)[105]. In addition to this, the researchers found in copper-treated N2a cells that copper promotes APP mRNA and protein levels in a dose-dependent manner as a way to lead to an increase in Aβ secretion, a result that exacerbates AD pathology[106]. Studies have shown that Cu^{2+} are generally transported into cells *via* elesclomol or copper transporter protein 1, where they are reduced to Cu^{+} and then promote ATPase7 degradation, leading to copper retention in mitochondria and ROS accumulation[101]. The above results suggest that the role of cuproptosis in exacerbating AD pathology due to fluctuations in copper levels is worth investigating, and that targeting cuproptosis may help to mitigate AD disease progression (Fig. 2).

3.2. *Non-apoptotic RCDs in PD*

In addition to non-motor symptoms like anosmia, constipation, anxiety, depression, and more, PD is a common ND that is marked by motor dysfunction, such as bradykinesia and stiffness. Dopaminergic axonal neurodegeneration, which begins in the striatum and progresses to the death of dopaminergic neurons in the substantia nigra (SN) pars compacta, both of which occur during the prodromal phase, is linked to the motor impairments commonly associated with PD. Currently, the mechanisms underlying PD primarily focus on mitochondrial dysfunction, intracellular deposition of α-syn, ER stress, and lysosomal and proteasomal system dysfunction[107]. Other important aspects, including lipid peroxidation damage, increased oxidative stress, and iron accumulation, are further significant features of PD pathophysiology. However, the potential links between these pathological features and the pathogenesis of PD remain unclear. As of now, the development of anti-PD drugs has largely focused on supplementing dopaminergic neurotransmission and antagonizing cholinergic neurotransmission. Substantial evidence suggests that the deposition of α-syn may be the primary pathogenic mechanism of PD, potentially causing dopaminergic neuron death either directly or indirectly[108].

The abnormal aggregation of α-syn leads to PD-related neurodegeneration, further resulting in the loss of dopaminergic neurons. Oxidative stress, excessive activation of glial cells, and PD-related gene mutations can all contribute to varying degrees of α-syn accumulation[109]. FSP1 can reduce ubiquinone to ubiquinol, an important antioxidant that inhibits lipid peroxidation[30]. DHODH, as a cofactor, upregulates FSP1 to increase sensitivity to ferroptosis, thereby inhibiting ferroptosis[110]. In a study, 17β-estradiol prevented neuronal degeneration and inhibited ferroptosis by upregulating DHODH levels, improving memory decline induced by ovariectomy[111]. Ferroptosis induced by excessive activation of glial cells is a significant factor in PD, and α-syn aggregation in glial cells is a key pathogenic factor of PD[13]. Normally, the number of glial cells in the brain, including microglia and astrocytes, is maintained within a certain range. Glial cells provide nutritional support to dopaminergic neurons[112]. Pathological stimuli can induce dysregulated glial cell activation and proliferation, triggering the release of inflammatory mediators. These substances suppress FSP1 expression while enhancing divalent metal transporter 1 (DMT1) activity, thereby driving iron deposition in neuronal cells[70,113]. Evidence suggests that intercellular adhesion molecule 1 (ICAM-1/CD54) can activate glial cells directly or indirectly, thereby inducing ferroptosis[114]. In postmortem examinations of PD patients, redox-active iron was found to coexist with α-syn in Lewy bodies in the midbrain[115]. Different forms of aggregated α-syn can be transferred between non-neuronal and neuronal cells and can spread from peripheral tissues to the central nervous system[116]. Therefore, reducing α-syn aggregation and increasing its clearance rate may be an effective therapeutic strategy for PD. A systematic investigation of ferroptosis regulation in CNS-resident microglia employing genome-wide CRISPR-Cas9 forward genetic screening revealed secretory 24 B (SEC24B)—a component of the coat protein 2 vesicular trafficking machinery—as a critical molecular determinant. SEC24B emerged as a potent modulator of microglial ferroptosis susceptibility, with its transcriptional elevation shown to accelerate ferroptotic progression kinetics through compromised ER-to-Golgi trafficking efficiency that amplifies lipid peroxidation cascades[117]. Similarly, calcium-independent phospholipase A2 beta has also been defined as a new ferroptosis regulator, and its mutation may be related to the pathogenesis of PD[118]. Interestingly, current studies have also found a certain connection between melatonin M1 receptor-related genes and ferroptosis[119]. In summary, there may be a vicious cycle of α-syn aggregation and ferroptosis. Without breaking this cycle, PD symptoms are difficult to truly alleviate. The existence of this cycle may further explain why current dopamine-mimetic drugs, such as levodopa, have not completely stabilized or reversed the symptoms of PD patients within a 3−5 year treatment period and may induce a more severe series of motor dysfunction[120].

Parthanatos is a distinct type of RCD that is started by intrinsic or extrinsic stressors that activate the DNA damage-sensing enzyme PARP1, leading to cellular demise. We have found that in NDs, particularly PD, this pathway serves as the primary route

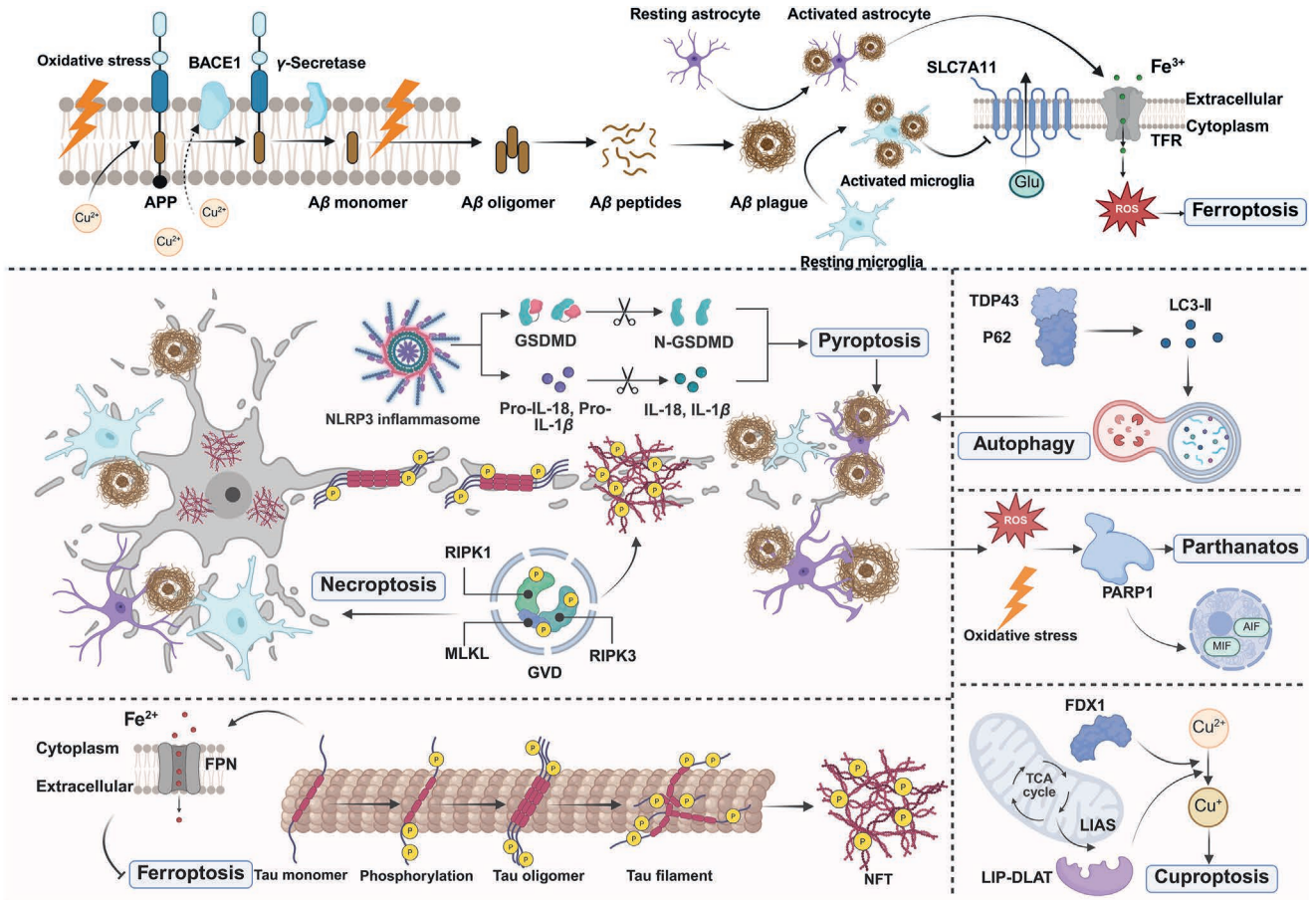

Figure 2 Mechanisms of different regulated cell deaths (RCDs) in Alzheimer's disease (AD) and causes of AD formation. The pathology of AD is characterized by hyperphosphorylation of Tau protein and accumulation of Aβ, which is sheared from APP. Ferroptosis was triggered mainly by increased ROS and intracellular free iron and increased levels of lipid peroxide. NLRP3 inflammasome cleavage releases multiple inflammatory factors to trigger pyroptosis. TDP43 and P62 accumulate intracellularly and bind to autophagy-associated proteins, targeting LC3-II and ultimately triggering autophagic cell death. ROS accumulation and increased oxidative stress elevate PARP1 levels, triggering Parthanatos while inducing AIF and MIF to move into the nucleus. GVD vesicles contain phosphorylated RIPK1/RIPK3/MLKL complexes that mediate necroptosis while triggering demyelination. Excess intracellular Cu^{2+} are converted to more toxic Cu^{+} by the LIP-DLAT protein of the TCA cycle, triggering cuproptosis.

of cellular death. Excessive accumulation of α-syn and glutamate excitotoxicity are crucial pathogenic mechanisms in PD. The massive release of pathological α-syn and glutamate can act as stressors to activate the parthanatos pathway, which in turn further induces oxidative stress and DNA damage. Oxidative stress disrupts cellular homeostasis and neuronal depolarization, causing central neuronal death or the release of excessive glutamate, thereby enhancing Glu excitotoxicity[121]. This cycle accelerates the formation of pathogenic factors in PD, such as pathological α-syn. Experiments have shown that PARP1 activation and PAR accumulation can accelerate α-syn fibrillation and alter the biochemical properties of α-synuclein preformed fibrils (PFFs), converting them into more toxic strains. Conversely, PARP inhibitors or genetic deletion of PARP1 can prevent the toxicity of pathological α-syn[38,122]. Studies reveal that microglial hyperactivation and astroglial reactivity coincide with dopaminergic neuron degeneration in the SN striatum and associated brain regions[108]. The parthanatos-mediated neuroinflammatory cascade orchestrates glial recruitment to pathological loci characterized by oxidative damage and proteopathic stress. Within specific microenvironments, hyperactivation of PARP1 induces IL-1β and TNFα production *via* NFκB-mediated transcriptional mechanisms, thereby stimulating pattern recognition receptors on resident microglia and astrocytes. This PAR polymer signaling-triggered feedforward loop perpetuates reactive gliosis while exacerbating mitochondrial ROS generation, thereby establishing a self-amplifying inflammatory loop that accelerates neurodegenerative proteostasis collapse[123]. Recent research indicates a potential link between vitamin D and PD. In animal models of PD, vitamin D and its derivatives have demonstrated protective benefits. And the evidence demonstrated that Calcitriol has been shown to significantly ameliorate parthanatos in both MPP^{+}-induced and MPTP cell models. This protective effect may be partially mediated through the VDR/PARP1 signaling pathway[124].

Research has indicated the potential involvement of necroptosis in the death process of dopaminergic neurons in patients diagnosed with PD[125]. In the midbrains of mice treated with MPTP, low levels of DA and dopaminergic neurons were found alongside high levels of RIPK1, RIPK3, and MLKL proteins. Knockout of the *RIPK3/MLKL* gene prevented the loss of dopaminergic neurons[126]. This confirms that necroptosis and the pathogenic factors of PD may be connected through this pathway.

The selective vulnerability of midbrain dopaminergic neurons in PD pathogenesis has been mechanistically linked to mitochondrial bioenergetic collapse initiated through death receptor (DR) mediated activation of programmed necroptosis pathways[127]. Mitochondrial phosphatase PGAM5 is a convergence point for multiple necroptosis pathways. PGAM5 recruits the mitochondrial fission factor Drp1, and Drp1 activation leads to mitochondrial fragmentation, which is an early and mandatory step in the execution of necroptosis[128,129]. In an experiment, researchers treated PC12 cells, which were scheduled to be exposed to 6-hydroxydopamine (6-OHDA), with the necroptosis inhibitor nec-1. Experimental data demonstrated that nec-1 enhanced PC12 cell cytoprotective efficacy through preserving mitochondrial transmembrane potential homeostasis, concomitantly suppressing autophagic flux (evidenced by LC3-II downregulation and lysosomal cathepsin B attenuation) while upregulating anti-apoptotic BCL2 expression[130]. Mutations in the *LRRK2* gene are associated with both genetic and sporadic forms of PD. Recent studies have identified a link between the disease-related gain-of-function allele leucine-rich repeat kinase 2 (Lrrk2G2019S) and mitochondrial imbalance. When inflammasomes in Lrrk2G2019S macrophages are activated, elevated mitochondrial ROS direct the binding of the pore-forming protein GSDMD to the mitochondrial membrane[131]. The present study offers further support to the hypothesis that mitochondrial dysfunction-induced necroptosis may be a key factor in the onset of PD. Recent studies have shown that the degeneration of dopaminergic neurons in PD may also be related to axonal dysfunction caused by necroptosis. Axonal degeneration is associated with impaired memory ability in humans, and axonal integrity is important for hippocampal function[132]. Necroptosis can be activated by brain aging, which is associated with the deterioration of axonal and synaptic function, increasing neuroinflammation, and affecting cognitive processes such as learning and memory[133]. Experiments have shown that when 6-OHDA acts on midbrain and cortical neurons in culture, pMLKL levels are significantly elevated, accompanied by extensive axonal degeneration, manifested as beading and retraction of neuronal projections. Treatment of cells with necroptosis inhibitors, nec-1 or GW80, significantly reduced 6-OHDA-dependent neurodegeneration. This indicates that necroptosis is closely related to 6-OHDA-mediated axonal degeneration[134].

Mediated by GSDMD, a pore-forming protein, pyroptosis constitutes a form of RCD. This process is initiated through inflammatory stimuli activating Caspase 1 or Caspase 4/5/11, which then cleaves GSDMD to facilitate secretion of biologically active IL-1β and IL-18[4,124]. Disulfiram, an inhibitor that blocks GSDMD pore formation, can effectively decrease pyroptosis and alleviate PD symptoms[135]. The NLRP3 inflammasome exerts various biological effects through the pyroptosis pathway, and its absence allows mice to exhibit a certain resistance to PD induction in PD models[136,137]. The results of both *in vivo* and *in vitro* studies demonstrated that the downregulation of triggering receptor expressed on myeloid cells 2 facilitated the activation of the NLRP3 inflammasome and its downstream inflammatory responses. In addition, the same studies showed that this process enhanced pyroptosis and exacerbated the loss of dopaminergic neurons[138]. This point further supports the potential relationship between PD and pyroptosis.

Autophagic cell death is also an important pathogenic factor of PD. Autophagy aims to eliminate misfolded and defective organelles to maintain intracellular homeostasis. Autophagy can be classified into canonical autophagy and non-canonical autophagy. Canonical autophagy typically occurs in normal cells and is usually accompanied by lysosomal degradation. In contrast, non-canonical autophagy involves various processes that do not entail lysosomal delivery of cytosolic components[134]. Lysosomes, as the hubs of cellular growth, division, and differentiation, serve as the terminal degradation stations and guardians of cellular homeostasis through autophagic pathways[139]. When lysosomal growth and catabolic programs malfunction, cells often exhibit uncontrolled autophagy, leading to increased protein accumulation and induction of cytotoxicity, which contributes to various NDs, including PD[139]. Autophagy is a major clearance pathway for misfolded α-syn. However, autophagic cell death will lead to abnormal lysosomal function, which in turn causes abnormal accumulation of α-syn. Mutations in lysosome-related genes can cause lysosomal storage diseases, which are common neurodegenerative disorders in children[140]. Several genes involved in PD pathology, including *LRRK2*, *GBA*, *PINK1* and *PRKN*, *PARK9*, *RAB39B*, *APOE4*, *VPS35*, *WDR45*, *FBXO7* and *DJ1*, have been reported to regulate autophagy[141,142]. In the SN of brains affected by PD, Lewy bodies exhibit heightened expression of the autophagy-associated LC3 protein[143]. Within dopaminergic neuronal populations, cathepsin D (CTSD) functions as an indispensable aspartic protease governing lysosomal proteostasis through regulation of proenzyme activation cascades. Experimental modeling of parkinsonian neurodegeneration reveals that CTSD loss-of-function mutations disrupt autophagic flux *via* impaired cathepsin maturation, thereby facilitating the pathogenic prion-like propagation of phosphorylated α-syn assemblies through exosome-mediated intercellular transfer mechanisms. This lysosomal proteolytic failure creates a self-reinforcing cycle wherein accumulated α-syn oligomers further compromise lysosome-mitochondria crosstalk, exacerbating oxidative protein misfolding cascades characteristic of Lewy pathology initiation[144]. Recent studies have shown that rHsCTSD can enhance lysosomal CTSD activity, increase the clearance rate of α-syn in human and mouse neurons and tissues, and restore endolysosomal and autophagic functions. The use of enzyme replacement therapy targeting CTSD may provide a novel therapeutic strategy for PD caused by excessive α-syn accumulation[145]. It is noteworthy that transcription factor EB (TFEB) may serve as a bridge connecting ferroptosis and autophagy[146]. TFEB has been identified as a key regulator of both autophagy and lysosome biogenesis, with lysosomes playing a crucial role in cellular iron storage. Current research indicates that TFEB overexpression provides protection against ferroptosis and iron overload[147]. Studies demonstrate cytoplasmic retention of TFEB in both PD mouse models and patients, notably impairing lysosomal activity and autophagic flux[148,149].

Cuproptosis represents a novel cellular demise pathway that distinguishes itself from other established forms of cell death in terms of its morphology, biochemical attributes, and underlying mechanisms. Copper binding to lipoylated TCA cycle enzymes induces proteotoxic stress, ultimately triggering cuproptosis[150]. It has been demonstrated that PD is associated with biochemical characteristics, including mitochondrial impairment and reduced concentrations of copper and glutathione in specific brain regions. These biochemical changes are intricately linked to the underlying mechanism of cuproptosis. However, the precise connection between the development of PD and cuproptosis remains elusive. The copper content in the SN of the brain is significantly decreased in patients with PD[151]. Scientific evidence indicates that excessive accumulation of copper within the central nervous

system constitutes a pathological feature of PD progression. Recent pharmacological investigations reveal that metal-chelating agents demonstrate therapeutic potential through distinct mechanisms. Specifically, ATH434 (a triazinylamine derivative) ameliorates both motor dysfunction and olfactory deficits in PD patients by modulating copper ion bioavailability. This chelation process appears to disrupt the metal-mediated aggregation of α-syn proteins. Furthermore, blood−brain barrier-permeable compounds like PBT2 and TDMQ20 exhibit neuroprotective properties, with their efficacy being contingent upon copper concentration regulation. These parallel findings collectively reinforce the pathophysiological correlation between cerebral copper dysregulation and neurodegenerative disease trajectories[152−154]. Abnormalities in copper metabolism-related proteins are key factors affecting copper levels. This situation is particularly prominent in PD patients. Ceruloplasmin, a copper-binding α2-glycoprotein, functions as the principal copper transporter in plasma, critically regulating copper metabolism. Research indicates that ceruloplasmin concentrations are markedly diminished in the cerebrospinal fluid (CSF) of PD patients[155]. Furthermore, alterations in the expression of cuproptosis and copper metabolism-associated genes, including *DLAT*, *DBT*, *SLC31A1*, *FDX1*, *ATP7A*, and *ATP7B*, have been observed in patients with PD, potentially influencing the progression of the disease[156].

Cu^{2+} speeds up α-syn oxidation by generating ROS, forming harmful oligomers that damage neurons. Some findings indicate that Cu^{2+} modifies the brief interactions within α-syn, leading to a higher exposure of its hydrophobic, aggregation-prone NAC domain to solvents[157]. Under oxidative stress and when treated with Cu^{2+}, the expression of heat-shock protein 27 (HSP27) increases. It is important to note that increased HSP27 levels have been observed in the brains of patients with AD and PD. One research reveals that HSP27 binds Cu^{2+} with high affinity, resulting in beneficial effects, and that it possesses the ability to displace Cu^{2+} from α-syn and inhibit the formation of amyloid fibrils[158]. Recently, studies using circular dichroism and nuclear magnetic resonance have confirmed that Cu^{2+} affects the secondary structure of α-syn at the atomic level[159], further indicating a close link between copper-induced cell death and PD (Fig. 3).

3.3. Non-apoptotic RCDs in HD

Ferroptosis is involved in the pathogenesis of HD, which is also associated with lipid peroxidation. HD is mainly caused by mutant huntingtin (mHtt), which aggregates into toxic macromolecules that lead to neuronal damage and death, and toxic fragments located in both the nucleus and cytoplasm induce mitochondrial dysfunction, leading to increased ROS production[160]. Similarly, immune cells secrete pro-inflammatory cytokines in response to glial cell-expressed mHtt, which exacerbates mitochondrial dysfunction and alters the redox status of neurons. A byproduct of lipid peroxidation, 4-HNE disrupts signaling and nucleophilic molecules that control a number of physiological functions and dysregulates system xc^{-}[161]. In animal models of HD, mice exhibited both strong immunoreactivity to mHtt and high immunoreactivity to 4-HNE adducts in striatal neurons. Oxidative stress enhanced Tet-mHtt-Q103-EGFP HD cells' cellular immunoreactivity to 4-HNE *in vitro*[162]. The accumulation of unstable iron in HD mitochondria, according to the researchers, can result in mitochondrial malfunction, including alterations in oxygen consumption, ATP, GSH, lipid peroxidation products, and mitochondrial membrane potential[163]. In addition to this, phospholipids with diacyl-PUFA tails (PL-PUFA2s) have been suggested to be a biomarker of ferroptosis, and depletion of PL-PUFA2s interacts with the mitochondrial electron transport chain to generate ROS to initiate lipid peroxidation. A significant reduction of PL-PUFA2s was detected in HD tissues compared to normal brain tissues[164]. Notably, researchers have recently categorized HD-associated ferroptosis into ACSL4-dependent ferroptosis induced by GPX4 inhibitors and ACSL4-nondependent ferroptosis induced by high levels of ROS. They also found that ALOX5 is a major factor required for HTTQ94-induced ACSL4 non-dependent ferroptosis and may be a potential new target for HD[165]. Overall, these data support a strong association of ferroptosis with HD.

As with other NDs, neuronal loss within the cortex and striatum is a common pathology in HD patients. It has been demonstrated in the literature that DNA damage and fragmentation have been detected in both *in vitro* models and *in vivo* samples from HD patients, accompanied by hyperactivation of PARP1, which, as previously described, depletes large amounts of ATP and NAD^{+}, while causing parthanatos. Moreover, neurons in HD brains have strong PARP immunoreactivity, which implies that PARP1 may lead to neuronal dysfunction or even death[166].

Recently, it has been shown that HD is associated with inflammatory vesicles and caspase-dependent pyroptosis[167]. The striatum of 13-week-old R6/2 mice with HD showed markedly increased expression of NLRP3 and Caspase 1, which were primarily seen in spiny projection neurons that were immunofluorescence-labeled with calcium-binding protein, which are severely degraded in HD[168,169]. However, low amounts of NLRP3 are expressed by striatal interneurons (*e.g.*, cholinergic neurons) that are resistant to neurodegeneration in HD. This implies that whereas degenerating neurons exhibit pyroptosis, healthy neurons do not[167]. In any case, pyroptosis contributes to striatal neuron loss in HD (Fig. 4).

3.4. Non-apoptotic RCDs in ALS

Motor neurons in the brain and spinal cord typically die selectively in ALS, a rapidly progressing and extremely deadly illness. Within three to five years of the onset of ALS, motor neuron loss causes muscle atrophy, weakness, and paralysis, which typically results in death[170].

Ferroptosis, iron dysregulation, and abnormal GSH metabolism have already been found to occur in ALS, and to explore even further the other roles ferroptosis plays in mediating motor neuron death in ALS, the researchers analyzed other signatures of ferroptosis activation in ALS. GPX4 is a major regulator of iron death, and its depletion predicts the activation of iron death. In spinal cord samples from non-neurologic control, familial (fALS) and sporadic ALS (sALS) patients, GPX4 was severely downregulated in both fALS and sALS spinal cords[171]. Comparative analyses of ALS mouse models and human subjects demonstrate pronounced redox imbalance across neural and peripheral systems, with ROS accumulation observed in spinal cord tissue, peripheral blood, and striated muscle compartments, which may in turn cause ferroptosis[172]. One of the main regulators of oxidative metabolism and mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma co-activator-1α (PGC1α). A study in an ALS mice model demonstrated the protective role of PGC1α. In *SOD1*(*G93A*) mice, PGC1α specifically enhanced

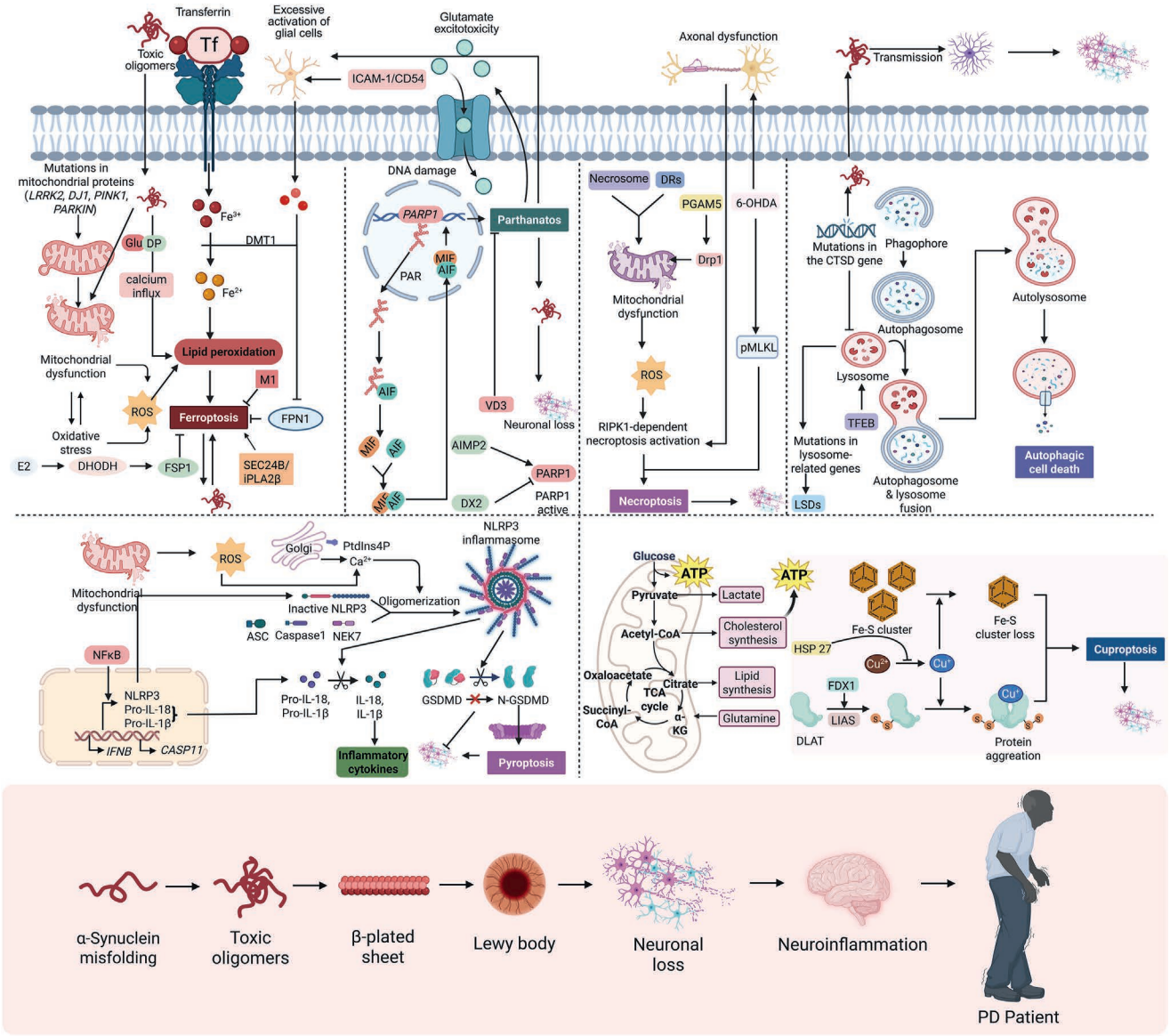

Figure 3 Mechanisms of different regulated cell deaths (RCDs) in Parkinson's disease (PD) and causes of PD formation. All types of RCDs are important factors inducing PD. Transferrin in excess of the normal level will transport an abnormal amount of iron ions, causing the iron pool to become saturated. This will lead to lipid peroxidation. Moreover, mitochondrial damage and calcium influx caused by glutamate excitotoxicity can also result in lipid peroxidation, further triggering ferroptosis. Eventually, this will cause abnormal accumulation of α-syn protein and promote the development of PD. DNA damage events activate PARP1, causing AIF to translocate from the mitochondria and bind to MIF, then move to the nucleus, triggering parthanatos. This will lead to the abnormal accumulation of α-syn protein. Meanwhile, this event can also cause Glu excitotoxicity and the abnormal accumulation of α-syn protein, exacerbating the symptoms of PD. Moreover, the accumulation of ROS triggered by mitochondrial damage can also induce necroptosis and autophagic cell death resulting from the formation of autophagosomes, leading to the loss of neurons and greatly increasing the probability of PD. ROS generated by mitochondrial damage leads to the formation of the NLRP3 inflammasome, which converts GSDMD into N-GSDMD and induces pyroptosis. This causes the loss of neurons and exacerbates PD. Copper ions bind to lipoylated proteins in the TCA cycle, causing these proteins to aggregate abnormally. They also interfere with the iron-sulfur cluster proteins in the respiratory chain complexes. Ultimately, this triggers a proteotoxic stress response, leading to cuproptosis and loss of neurons, then significantly increases the prevalence of PD.

motor function and survival, accompanied by a decrease in motor neuron damage and a repair of the mitochondrial electron transport chain[173]. NOX2 (NADPH oxidase 2), a membrane-bound enzymatic component of the NADPH oxidase family, catalyzes pathological oxidative stress through its hyperactivation-driven overproduction of superoxide anions. This enzymatic dysregulation directly impairs cellular redox homeostasis by overwhelming endogenous antioxidant defenses, thereby propagating lipid peroxidation cascades and macromolecular damage[174,175]. Typically, this type of oxidative stress induces the Fenton reaction, leading to ROS generation, which subsequently triggers lipid peroxidation and ferroptosis[176]. Collectively, these findings significantly strengthen the mechanistic link between ferroptosis and ALS pathogenesis.

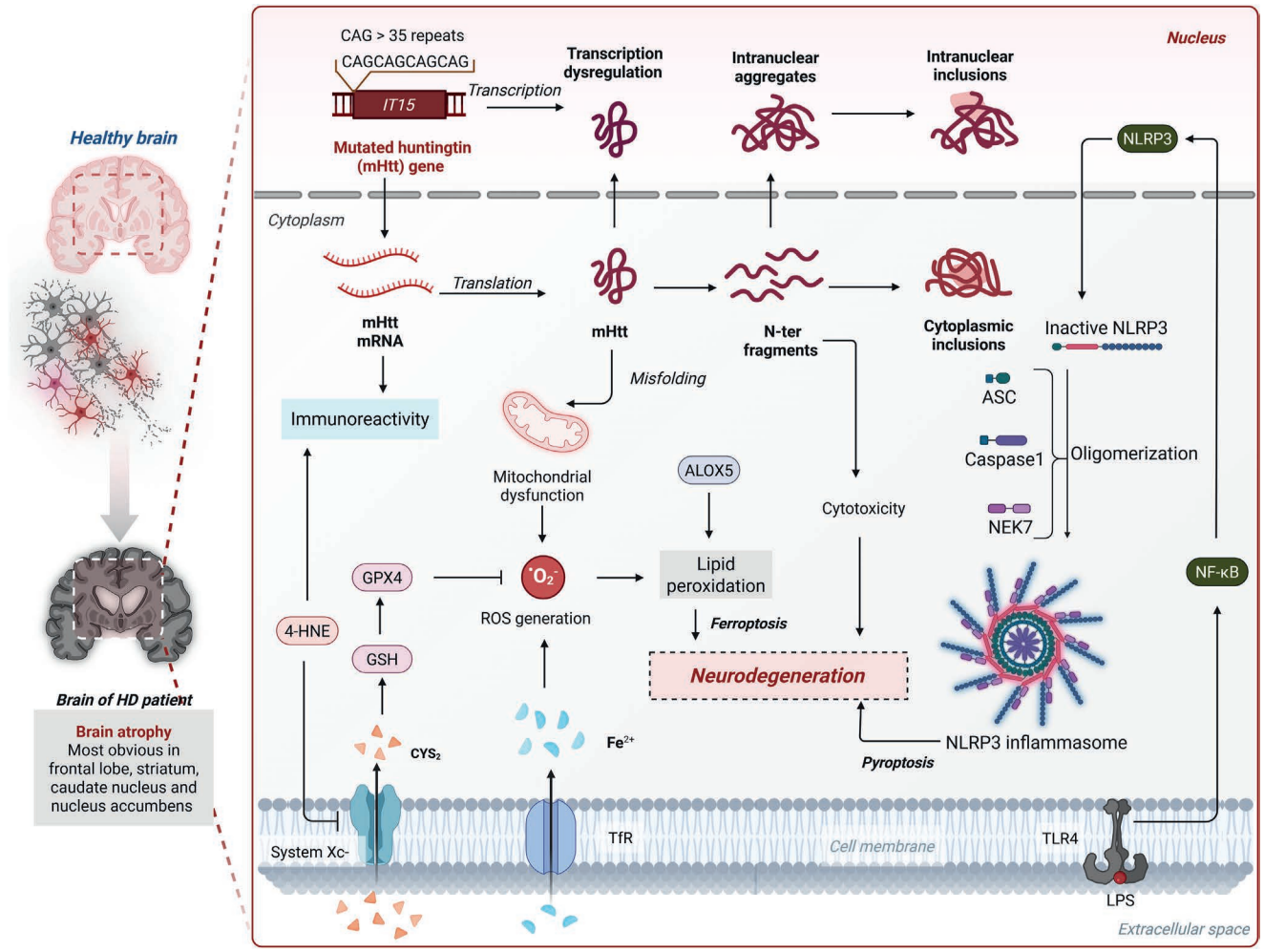

Figure 4 Mechanisms of different regulated cell deaths (RCDs) in Huntington's disease (HD) and the pathology of the brain in patients with HD. HD is mainly caused by HTT mutations, which aggregate into toxic macromolecules that lead to neuronal damage and death. Mitochondrial dysfunction and increased free iron levels cause elevated ROS levels, which in turn cause increased lipid peroxide, inducing ferroptosis. NLRP3 inflammasome is stimulated to release inflammatory mediators to induce pyroptosis.

Recent genetic studies have shown that the fused in sarcoma/translated in liposarcoma (*FUS/TLS*) mutation is one of the etiologic factors of ALS, with 4% of fALS patients having the mutation of note, and that this mutation reduces the ability of DNA repair, which is one of the causes of PARP1 overactivation[177]. The specific binding of excess PAR to *FUS* confirms that PARP1-mediated parthanatos contributes to ALS onset and progression. Furthermore, the observed translocation of AIF from mitochondria to the nucleus in the spinal cords of SOD1 mutant ALS models provides compelling *in vivo* evidence for the execution phase of this cell death pathway within relevant neuronal tissues. Therefore, targeting key nodes within the parthanatos cascade, especially PARP1 overactivity and PAR signaling, emerges as a promising avenue for developing potential therapeutic interventions aimed at halting or slowing ALS progression[85].

A decade earlier, researchers designed a fully humanized co-culture model consisting of human adult sALS astrocytes and human embryonic stem cell-derived motor neurons, an experiment that demonstrated that ALS astrocytes trigger necroptosis in motor neurons in a RIPK1/RIPK3/MLKL-dependent manner[178]. However, pyramidal neurons of the subiculum, hippocampus, and dentate gyrus showed activated necrosomes in GVD vesicles; however, immunohistochemical techniques were unable to validate this finding in ALS-infected areas of the human brain and spinal cord. According to other research, ALS is thought to be caused by a disruption of optineurin (OPTN) activity, and axonal degeneration and demyelination are caused by mutations in the *OPTN* gene. By managing its turnover, OPTN was found to actively downregulate RIPK1-dependent signaling. OPTN oligodendrocytes are more susceptible to TNF-induced necroptosis than wild-type oligodendrocytes[179,180].

Activation of the pyroptosis pathway and the existence of inflammatory vesicles have been reported to be detected in ALS, despite the fact that ALS is primarily a motor neuron disease[181]. Transcription-responsive DNA-binding protein 43 (TDP43) is a multifunctional nucleic acid-binding protein. Mutations linked to ALS in the glycine-rich C-terminal structural domain of TDP43 describe neuronal loss and gain of function and indicate a causal link between TDP43 and illness. The researchers speculated that TDP43 stimulation of CD14-mediated activation of microglial NF-κB and AP-1 pathways, as well as NLRP3 inflammatory vesicles, was responsible for the notable elevation of NOX2, TNFα, and IL-1β they observed in ALS microglia[182]. In a

different investigation, microglia from ALS human motor cortex and spinal cord were shown to produce IL-18 and cleaved GSDMD, indicating that pyroptosis is typically activated by inflammatory vesicles. However, the authors do not believe that this phenomenon is directly related to TDP43[183]. In conclusion, pyroptosis driven by microglia NLRP3 inflammatory vesicles plays a significant role in the pathogenesis and neurodegeneration of ALS.

The role of autophagy in ALS pathology has now been reported in several papers. Interestingly, autophagy in ALS often occurs in spinal motoneurons rather than in the motor cortex. For example, a significant increase in the autophagy protein marker LC3-II was observed in spinal motoneurons in a mouse model, and autophagic vesicles accumulated in dystrophic axons in ALS mice. Meanwhile, P62/SQSTM1 gradually accumulated in the spinal cord. The lifetime of ALS animals was significantly reduced, and motor neuron degeneration was hastened after the researchers added the autophagy enhancer rapamycin[184]. By crossing ATG7 mutant mice with ALS mice, another team of researchers demonstrated that autophagy suppression decreased glial inflammation and prevented the activation of the stress-related transcription factor c-Jun in spinal interneurons, but it did not stop motor neuron cell death[185]. According to the aforementioned findings, autophagy promotes the advancement of the disease in its later stages while preventing neuronal degeneration in its early stages.

Currently, there are fewer studies related to the pathogenesis of ALS and cuproptosis. The connection between ALS and cuproptosis-related genes (*CuRGs*) has been documented by researchers. ALS patients had considerably greater expression levels of *CuRGs*, including *FDX1*, *PDHB*, *DLD*, *LIPT1*, and *DLAT*, compared to the general population. Additionally, functional enrichment analysis revealed elevated levels of glycolysis-related pathways, including the TCA cycle, acetyl coenzyme A synthesis, and pyruvate metabolism, in the peripheral blood of ALS patients. The beginning and development of cuproptosis are closely linked to these events[186]. Specifically, the identified alterations in core metabolic processes—essential for both energy production and copper-dependent enzyme function—provide a mechanistic link to the initiation and progression of cuproptosis itself. Therefore, investigating the precise interplay between aberrant CuRG expression, disrupted metabolic flux, and the execution of cuproptosis offers a crucial new avenue for understanding ALS etiology and identifying novel therapeutic targets aimed at modulating this copper-regulated cell death pathway (Fig. 5).

3.5. *Non-apoptotic RCDs in MS*

MS is an autoimmune disorder, inducing inflammatory injury to the central nervous system. It is marked by oligodendrocyte loss and demyelination, occurring in the MS-affected regions of the brain and spinal cord, the transmission of nerve signals is slowed or blocked, leading to a variety of neurological symptoms and ultimately to a decline in quality of life and physical disability[187]. Its aetiology may be influenced by both genetic and environmental factors[188]. There is a close correlation between inflammation and axonal and neuronal damage in MS. Axonal damage is particularly evident in the earliest stages of the disease, and neuronal loss may begin early on but becomes more pronounced in tissue samples from patients with progressive MS[189].

Studies have found alterations in ACSL4, a key protein involved in ferroptosis, in the genomic databases of people with MS. Experiments have confirmed that ferroptosis is an early event in experimental autoimmune encephalomyelitis (EAE), with associated ROS accumulation and mitochondrial constriction promoting T-cell activation and inducing cellular degeneration in MS[190,191]. Recent research has suggested that the relationship between MS and ferroptosis is mediated by activation of the neuronal STING by glutamate-induced excitotoxicity and subsequent non-canonical STING signaling. This process leads to autophagic degradation of GPX4, thereby inducing the occurrence of ferroptosis[192]. Another study demonstrated that neuroinflammation induced by MS significantly promotes the generation of the inhibitory epigenetic marker H3K9me2, catalyzed by the histone methyltransferase G9a. G9a activity reduces the expression of anti-ferroptotic genes and intracellular glutathione, and triggers ferroptosis[193]. Additionally, sustained glycolysis may be linked to ferroptosis in MS diseases, which is associated with disrupted proteasome homeostasis. In the EAE model, IFN-γ-mediated increases in proteasome 20S subunit beta 8 (PSMB8) abundance reduce proteasome activity, leading to direct accumulation of phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), enhanced neuronal glycolysis, and ultimately triggering oxidative stress and ferroptosis. In neurons, this manifests specifically as proteasome 20S subunit beta 5 (PSMB5) being replaced by PSMB8, with a similar phenomenon observed in IFN-α-induced models. Following intervention with ferroptosis inhibitors, PSMB5 expression increases again, a process accompanied by a reduction in the lipid peroxidation marker 4-HNE. Interestingly, other markers of ferroptosis, such as ACSL4, GPX4, and FSP1, remained unaffected. These findings suggest that the shift toward sustained glycolytic metabolism increases neuronal susceptibility to ferroptosis[194].

MS, as an autoimmune-mediated inflammatory disease, is also affected by the pro-inflammatory effects of PARP1. Hyperactivation of PARP1 was found in oligodendrocytes from MS patients, and similar findings were also present in peripheral blood monocytes[195]. Similarly, B cells, $CD4^+$ T cells, and $CD8^+$ T cells showed increased PARP1 expression, although $CD14^+$ monocytes did not increase significantly[196]. Critically, this widespread PARP1 dysregulation provides a compelling mechanistic foundation for the initiation and amplification of neuroinflammation and tissue damage. Therefore, the *in vivo* evidence collectively suggests that PARP1-mediated pathways, ultimately leading to parthanatos, play a significant detrimental role in the pathological environment of MS. Targeting this pathway offers considerable potential for the development of novel therapeutic strategies designed to modulate neuroinflammation and halt disease progression.

RIPK1 mediates inflammatory signaling and cell death. This phenomenon increased in brain samples from MS patients[197]. Studies have shown that neuronal death in the MS cortex occurs through necroptosis stimulated by TNF/TNFR1 rather than apoptosis. In this study, researchers compared patients with secondary progressive multiple sclerosis (SPMS) with non-neurological controls. They found that the SPMS group had increased expression of several components of the TNF/TNFR1 pathway. In particular, key proteins showed increased levels[15]. Immunopathological analysis revealed that meningeal inflammatory exacerbation in MS patients was mechanistically linked to TNF receptor signaling axis polarization within cortical parenchyma. This shift involved downregulation of TNFR1/TNFR2−NFκB-mediated cyto-protective signaling, concomitant with pathological amplification of TNFR1−RIPK3 co-activated

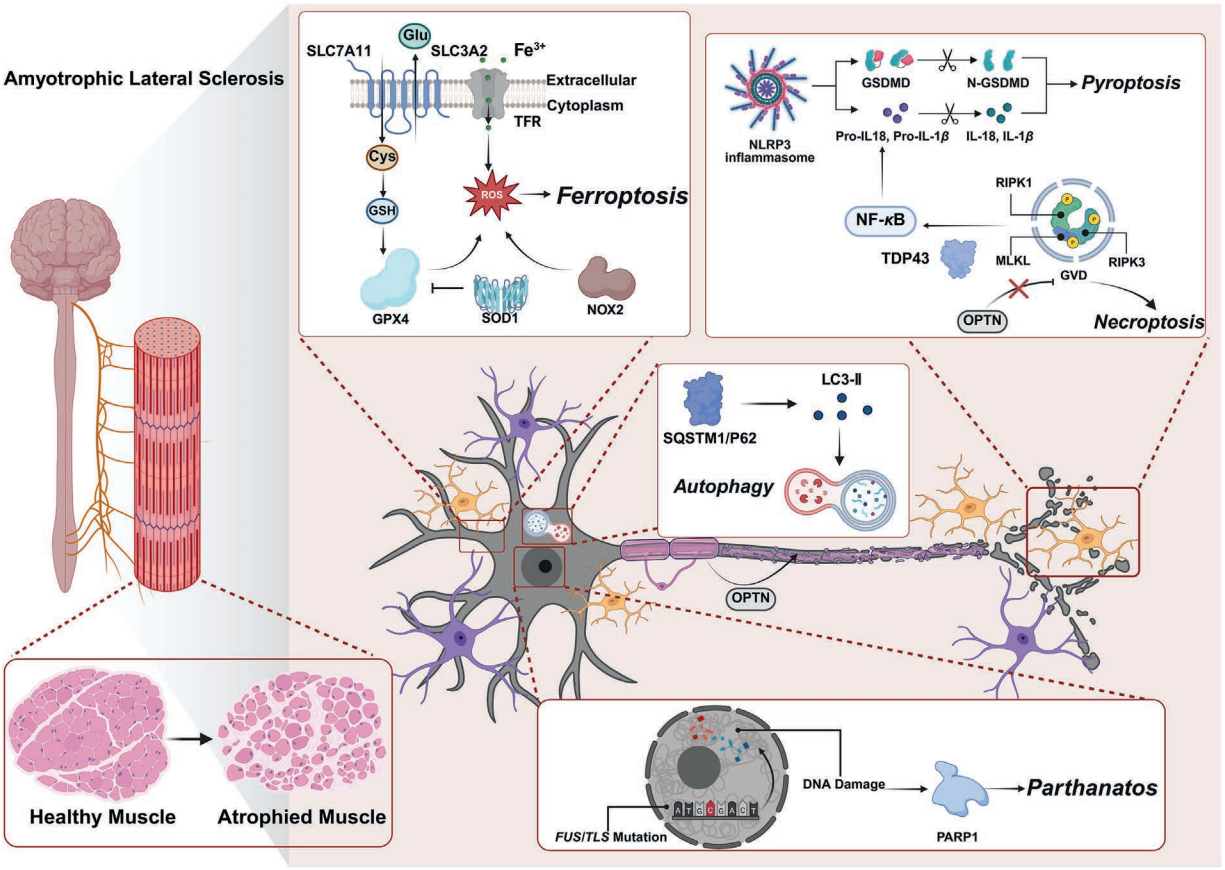

Figure 5 Mechanisms of different regulated cell deaths (RCDs) in amyotrophic lateral sclerosis (ALS) and the pathologic status of muscle tissue in patients with ALS. Muscle tissue in ALS patients is more atrophied than in the healthy population. Both NOX2 and excess GSH lead to elevated ROS levels, ultimately leading to ferroptosis, aggravating ALS. NLRP3 inflammatory vesicles release large amounts of inflammatory mediators, triggering pyroptosis. Cleavage of GVD vesicles also elevates inflammation levels while generating phosphorylated RIPK1/RIPK3/MLKL complexes, inducing necroptosis. P62/SQSTM1 targets the autophagy-related protein LC3-II to trigger autophagic cell death. *FUS*/*TLS* mutations cause DNA damage, and PARP1 levels rise in order to repair the damage, triggering parthanatos.

programmed death pathways. Cellular mapping demonstrated differential TNF receptor tropism: TNFR1 showed preferential localization on neuronal populations and oligodendroglial lineages, whereas TNFR2 exhibited astroglial and microglial predominance within disease-specific neuroglial subsets of demyelinated cortices[198]. Interestingly, dimethyl fumarate, a first-line treatment for relapsing-remitting multiple sclerosis (RRMS), has been shown to inhibit the RIPK1/RIPK3/MLKL axis by blocking mitochondrial reverse electron transport (RET) induced by mitochondrial necroptosis stimulation, thereby inhibiting cellular necroptosis[199]. This further suggests a potential link between the occurrence of MS and the necroptosis pathway.

Pyroptosis is a pro-inflammatory RCD driven by inflammasomes. Recent studies have investigated GSDMD-induced pyroptosis in oligodendrocytes and microglia, finding that Caspase 1 inhibitors can prevent pyroptosis in experimental models of MS, reducing demyelination and neurodegeneration[200]. Inhibition of Caspase 3/7 and Caspase 1 expression also prevents plasma membrane rupture during pyroptosis[201]. Increasing evidence suggests that GSDMD is a target of fumarates, with both exogenous and endogenous fumaric acid esters capable of reacting with GSDMD at critical cysteine residues to form *S*-(2-succinyl)-cysteine. This succinylation prevents GSDMD from interacting with caspases. Thus, the final phase of pyroptosis is terminated[202]. Evidence indicates that Epstein−Barr virus (EBV) may be a culprit in causing MS, as patients infected with EBV have a significantly increased prevalence of MS[203]. Notably, the G protein-coupled receptor BILF1 encoded by EBV can activate the NLRP3 inflammasome[204]. BILF1 is therefore a promising new therapeutic target for MS. It is noteworthy that recent studies have found that deficiency of interleukin-1 receptor-associated kinase-M enhances the activation of microglia, increases the production of NLRP3 inflammasome, and enhances GSDMD-mediated pyroptosis of microglia in EAE[205] (Fig. 6 and Table 2).

4. Mechanisms of non-apoptotic RCD crosstalk in NDs

In NDs, multiple RCDs are interconnected through crosstalk. This crosstalk often requires passage through key hubs, which may become promising targets for the treatment of NDs. Identifying and analyzing these hubs among RCDs in NDs is crucial for targeting and treating related diseases. However, only a small number of studies have addressed this aspect so far. Therefore, we summarize the possible RCD crosstalk in NDs to provide value for clinical studies.

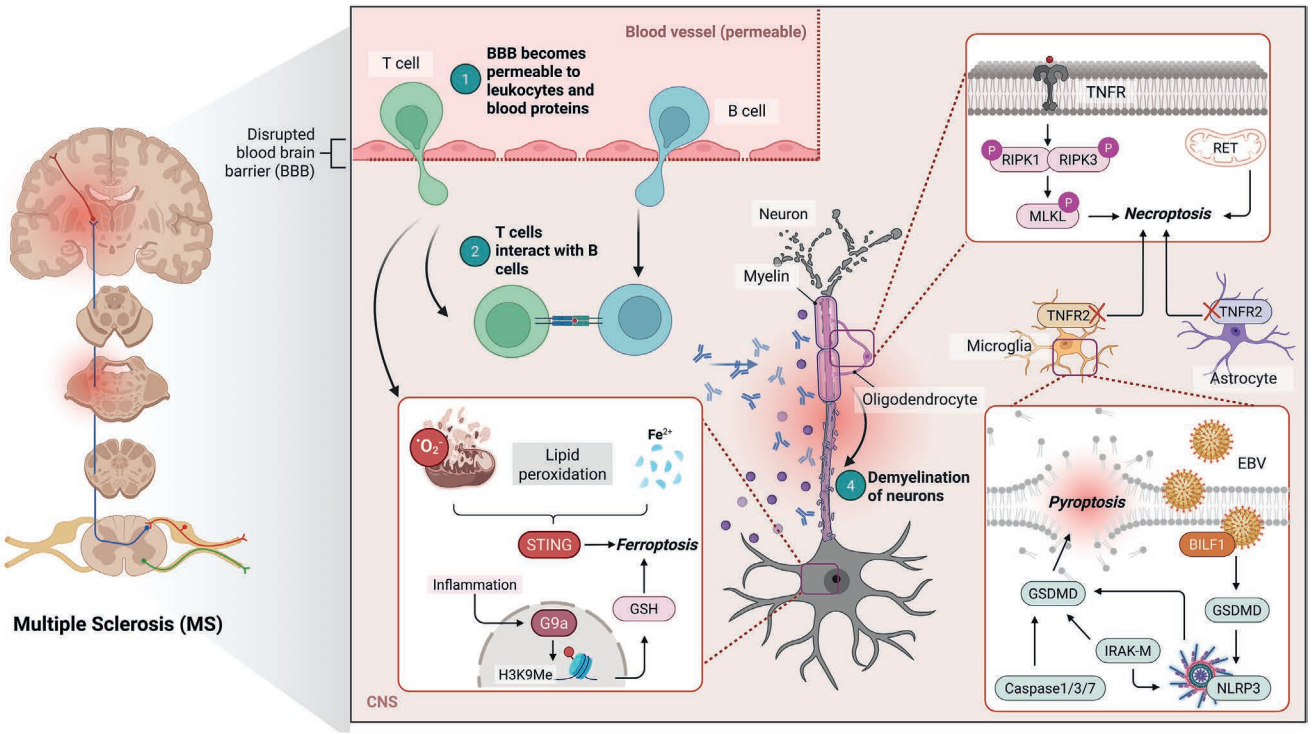

Figure 6 Mechanisms of different regulated cell deaths (RCDs) in multiple sclerosis (MS) and the process of MS formation. Activated T cells, accumulated ROS, abnormally accumulated iron ions, and increased activity of G9a by inflammation will all promote ferroptosis and induce MS. TNF binds to TNFR1, leading to the phosphorylation of RIPK1 and RIPK3. Subsequently, the phosphorylation of MLKL results in necroptosis. Similarly, RET as well as the activation of microglia and astrocytes can also induce this form of cell death, which leads to the development or exacerbation of MS. The activation of Caspase 1/3/7 enables GSDMD to mediate pyroptosis. The BILF1 encoded by EBV activates the NLRP3 inflammasome, which also leads to this form of cell death. Ultimately, it results in MS.

4.1. Crosstalk between non-apoptotic RCDs in AD

The pathological process of AD is highly complex and involves aberrant activation of multiple cell death pathways. Recent studies have reported that non-apoptotic RCDs do not act in isolation in AD, but instead exhibit extensive crosstalk. Key regulatory proteins, including ATG7, SLC7A11, and RIPK3, mediate the interactions among these pathways. Collectively, these pathways affect neuronal death, neuroinflammation, and mitochondrial dysfunction, offering novel insights into the pathogenesis of AD and highlighting potential avenues for therapeutic intervention.

Recently, a special class of crosstalk between autophagic cell death and ferroptosis has been reported. The hub between the two is ATG7, which, unlike other types of crosstalk, inhibits ferroptosis-associated pathways and promotes the onset of autophagic cell death when ATG7 is activated. ATG7 is an autophagic cell death-associated protein in AD. The mechanism in which ATG7 acts is to participate in the formation of LC3-II. Specifically, ATG7 activates pro-LC3, which is cleaved by protease to generate LC3-I. Subsequently, LC3-I is delivered to ATG3 *via* ATG7, which facilitates the binding of LC3-I to phosphatidylethanolamine to form LC3-II. Extensive spreading of Aβ plaques with more severe axonal damage has been reported in microglial cells of ATG7-deficient AD mice. FTH overexpression in murine microglia (confirmed by qPCR) directly correlated with intensified oxidative damage, particularly lipid peroxidation. These phenomena imply the presence of iron homeostasis dysregulation and ferroptosis in microglia. Interestingly, the microglia number stabilized over time as the mice aged over weeks, and no study has yet revealed the mechanism by which this phenomenon occurs[206]. Overall, the crosstalk between ATG7-mediated ferroptosis and autophagic cell death provides a new direction for future AD therapy.

GSH is an important player in antioxidation in neurons. In ferroptosis, it acts as a cofactor for GPX and is directly involved in the scavenging of lipid peroxides. And in cuproptosis, it is an endogenous copper chelator that chelates with Cu^{+}. With this in mind, it has recently been shown that the protein SLC7A11, which regulates the production of GSH, is a key protein in the crosstalk that occurs between ferroptosis and cuproptosis. The SLC7A11 transporter transports cystine into the cell, and when there are sufficient intracellular cysteine−glutamate transporter receptors, excess cystine will be converted to cysteine, and ultimately, cysteine generates glutathione[207]. In addition, mitochondria are a key site for the onset of ferroptosis and cuproptosis in AD. Ferroptosis directly disrupts the mitochondrial membrane structure through lipid peroxidation, whereas cuproptosis leads to impairment of the mitochondrial respiratory chain and elevated ROS levels through inhibition of Fe−S cluster proteins and enzyme function in the mitochondrial TCA cycle[208]. In conclusion, the crosstalk mechanisms of ferroptosis and cuproptosis in AD involve multiple intersections of metal homeostasis, mitochondrial function, and oxidative stress.

The NLRP3 inflammatory vesicle is a complex of multiple proteins that typically contains NLRP3, ASC, and Caspase 1. In the development of AD, activation of the NLRP3 inflammatory

Table 2 Modulation of the regulated cell deaths (RCDs) in neurodegenerative diseases (NDs) and its own effects.

Neurodegenerative diseases (NDs)	Regulated cell death (RCDs)	Target proteins or signaling pathways	Cell types/animal models/human tissues	Mechanisms	Effects on NDs	Effects on RCDs	Ref.
Alzheimer's disease (AD)	Ferroptosis	NCOA4	Brain tissue of the human right occipital cortex	NCOA4 enhances Fenton reaction-mediated oxidative stress	Regulation of elevated ferritin levels and accelerated ferroptosis	Upregulation ferroptosis	68
		NRF/ SLC7A11/ GPX4	D-Gal combined with $AlCl_3$ induced an AD rat model	Excess GPX4 expression scavenges lipid peroxide and maintains membrane lipid bilayer homeostasis	Reduced levels of ROS in cells and reduced damage to cell membranes and mitochondria	Downregulation ferroptosis	69
		ACSL4	5 × FAD mice model	ACSL4 promotes PUFA integration into cell membrane phospholipids, enhances lipid peroxide sensitivity, and synergizes with iron overload and GPX4 activity inhibition.	Loss of synaptic function, myelin degeneration	Upregulation ferroptosis	71
		FPN, TFR	$App^{-/-}$ mice model	Responsible for the transport of ferrous ions in and out of the cell membrane, an imbalance will lead to intracellular iron overload	Increased intracellular iron ions and hyperphosphorylation of Tau lead to ferroptosis	Upregulation ferroptosis	72
	Parthanatos	PARP1	SK-N-SH cells	Overactivation of PARP1 leads to NAD^+ depletion, AIF-dependent DNA fragmentation	Mitochondrial membrane depolarization and increased AIF release	Upregulation parthanatos	82
		AIF, MIF	TgCRND8 mice model	AIF and MIF synergistically drive parthanatos through PARP1-dependent DNA damage response, mitochondrial−nuclear signaling, and oxidative stress-inflammatory loops	DNA fragmentation, cell death in the cerebral cortex	Upregulation parthanatos	85
	Necroptosis	RIPK1, RIPK3, MLKL	Brain tissue of AD patients	RIPK1/RIPK3 activate and form necrotic vesicles and phosphorylate MLKL *via* TNFα, disrupting cell membrane integrity	Autophosphorylation leads to neuronal loss near Aβ	Upregulation necroptosis	87
		MEG3	Human neuron xenografts AD mice model	MEG3 drives necroptosis in AD through a triple mechanism of RIPK1/ RIPK3/MLKL pathway activation-inflammatory positive feedback, and autophagy inhibition	Promote Tau phosphorylation and Aβ formation	Upregulation necroptosis	91

	ESCRT III	Human hippocampus tissue	Elevated expression of components of ESCRT-III prevents necroptosis and is upregulated as a compensatory mechanism in AD patients	Constitutive GVD delays neuronal death	Downregulation necroptosis	92
	Caspase 4	Human hippocampus tissue	Caspase 4 is highly expressed in microglia and exacerbates neuroinflammation	Promote Aβ deposition and phosphorylation of Tau and induce neuronal death	Upregulation pyroptosis	95
	Caspase 1, Caspase 8, IL-18	*THY-Tau22* transgenic mice model, *Asc*$^{-/-}$ mice model and *Nlrp3*$^{-/-}$ mice model	Caspase 1, Caspase 8, and IL-18 through inflammatory vesicle activation and GSDMD protein-mediated membrane perforation	Cause inflammation, death of astrocytes	Upregulation pyroptosis	96
	NLRP3, GSDMD, ASC	*Asc*$^{-/-}$ mice model	NLRP3 inflammatory vesicles trigger a sustained inflammatory response *via* Aβ, and GSDMD mediates membrane perforation and drives microglia pyroptosis	Cause inflammation, death of microglia and astrocytes	Upregulation pyroptosis	97
Autophagic cell death	TDP43	*Terc*$^{-/-}$ mice model, 5xFAD transgenic mice model	TDP43 mitochondrial localization triggers oxidative stress, activates AMPK/mTOR imbalance, and promotes autophagy overactivation.	Protein ubiquitination, organelle degradation	Upregulation autophagic cell death	99
Paraptosis	MAPK, JNK	*App695/Swe* and *Tau*$^{-/-}$ transgenic mice model	MAPK and JNK drive ER-mitochondrial axis dysfunction through chronic stress signaling	Calcium ion overload, mitochondrial swelling, ER stress	Upregulation paraptosis	57
Cuproptosis	FDX1	SH-SY5Y cells	FDX1 mediates an imbalance in mitochondrial copper homeostasis, leading to abnormal aggregation of copper-dependent lipoylated proteins	Increased cuprous ions, neuronal loss	Upregulation cuproptosis	102
	BACE1	N2a-*APP695* cells, *App/ps1* mice model	BACE1 drives neuronal cuproptosis through the Aβ-dependent copper accumulation-mitochondrial oxidative stress-lipoylated protein aggregation axis	Binds to Aβ to form toxic aggregates	Upregulation cuproptosis	106

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Table 2 (*continued*)

Neurodegenerative diseases (NDs)	Regulated cell death (RCDs)	Target proteins or signaling pathways	Cell types/animal models/human tissues	Mechanisms	Effects on NDs	Effects on RCDs	Ref.
Parkinson's disease (PD)	Ferroptosis	α-syn	*SNCA* iPSC-derived neurons	Recombinant oligomers and oligomers produced in SNCA ×3 cells induce PUFA oxidation	Elevated levels of lipid peroxide in cells and damage to cell membranes and mitochondria	Upregulation ferroptosis	109
		DHODH	Hippocampal tissue of SD rats	DHODH blocks the lipid peroxidation chain reaction by regenerating oxidized CoQ10	Reduce oxidative stress and mitochondrial damage, improve spatial memory	Downregulation ferroptosis	111
		NRF/ SLC7A11/ GPX4	Human iPSC-derived microglia	Excess GPX4 expression scavenges lipid peroxide and maintains membrane lipid bilayer homeostasis	Reduced levels of ROS in cells and reduced damage to cell membranes and mitochondria	Downregulation ferroptosis	117
	Parthanatos	Iduna	Iduna transgenic mice model	Iduna reduces NMDA receptor-mediated glutamate excitotoxicity and prevents AIF translocation from mitochondria to the nucleus	Reduction of DNA breaks triggered by PAR accumulation	Downregulation parthanatos	121
		PARP1	α-syn PFF mice model	Overactivation of PARP1 leads to NAD^+ depletion, AIF-dependent DNA fragmentation	Mitochondrial membrane depolarization and increased AIF release	Upregulation parthanatos	38
		AIF, MIF	α-syn PFF mice model	AIF and MIF synergistically drive parthanatos through PARP1-dependent DNA damage response, mitochondrial−nuclear signaling, and oxidative stress-inflammatory loops	Dopaminergic neuron loss and behavioral deficits	Upregulation parthanatos	122
	Necroptosis	RIPK1, RIPK3, MLKL	MPTP-induced PD mice model	RIPK1/RIPK3 activate and form necrotic vesicles and phosphorylate MLKL *via* TNF-α, disrupting cell membrane integrity	Increased production of necrotic vesicles and disruption of mitochondrial membranes	Upregulation necroptosis	126
		BCL2	6-OHDA-treated PC12 cells	BCL2 binds to RIPK3 or inhibits PGAM5 and reduces necrotic vesicle production	Inhibits mitochondrial damage and oxidative stress	Downregulation necroptosis	130
	Pyroptosis	NLRP3, GSDMD	MPTP-induced PD mice model	NLRP3 and GSDMD activation releases pro-	Increased inflammatory factors, ROS production	Upregulation pyroptosis	138

				inflammatory cytokines that sensitize microglia to brain α-syn deposition	and neuronal toxicity		
	Autophagic cell death	CTSD	SH-SY5Y cells	Removal of α-syn, maintenance of lysosomal integrity and membrane permeability	Dysfunctions of the lysosomal and autophagosomal system	Upregulation autophagic cell death	145
	Cuproptosis	Ceruloplasmin	Brain tissue of PD patients	Translocation of intracellular copper ions	Reduces mitochondrial thioctylation products and decreases cellular damage	Downregulation cuproptosis	155
Huntington's disease (HD)	Ferroptosis	PUFA	Brain tissue of HD patients	PL-PUFA2s interact with the mitochondrial electron transport chain to generate ROS	Generation of ROS and thus elevated levels of lipid peroxidation	Upregulation ferroptosis	164
		ALOX5	HT22 cells, *Alox5*$^{-/-}$ mice model, HD transgenic mice model	ALOX5 overexpression increases HTTQ94-mediated oxidative stress	Increase the number of neuronal deaths in the mouse striatum	Upregulation ferroptosis	165
	Parthanatos	PARP1	*Parp1*$^{-/-}$ mice model	Overactivation of PARP1 leads to NAD^+ depletion, AIF-dependent DNA fragmentation	Mitochondrial membrane depolarization and increased AIF release	Upregulation parthanatos	38
	Pyroptosis	NLRP3	R6/2 mice model	High NLRP3 expression increases secretion of IL-1β and IL-18	Increase inflammatory factors, ROS production, and neuronal toxicity	Upregulation pyroptosis	169
Amyotrophic lateral sclerosis (ALS)	Ferroptosis	GPX4	*Sod1*(*G93A*) mice model	Excess GPX4 expression scavenges lipid peroxide and maintains membrane lipid bilayer homeostasis	Reduced levels of ROS in cells and reduced damage to cell membranes and mitochondria	Downregulation ferroptosis	171
		PGC1α	*TgSod1*(*G93A*)/*TgPgc1A* mice model	PGC1A increases mitochondrial biosynthesis and enhances antioxidant defenses	Regulate iron metabolism and participate in ROS scavenging	Downregulation ferroptosis	173
		NOX2	Ra2 cells, *Sod1*(*G93A*) mice model	NOX2 overconsumes GSH and inhibits GPX4 activity	Generate excess ROS and promote oxidative stress	Upregulation ferroptosis	175
	Parthanatos	PARP1	*Fus-H509D* mice model	Overactivation of PARP1 leads to NAD^+ depletion, AIF-dependent DNA fragmentation	Mitochondrial membrane depolarization and increased AIF release	Upregulation parthanatos	177
	Necroptosis	RIPK1, RIPK3, MLKL	Astrocyte of ALS patients	RIPK1/RIPK3 activate and form necrotic vesicles and phosphorylate MLKL *via* TNFα, disrupting cell membrane integrity	GVD vesicle necrosis, astrocyte death	Upregulation necroptosis	178
		OPTN	*Sod1*(*G93A*) mice model	OPTN inhibits RIPK1 −RIPK3−MLKL complex formation and	Reduce axonal degeneration and demyelination	Downregulation necroptosis	180

(*continued on next page*)

Table 2 (*continued*)

Neurodegenerative diseases (NDs)	Regulated cell death (RCDs)	Target proteins or signaling pathways	Cell types/animal models/human tissues	Mechanisms	Effects on NDs	Effects on RCDs	Ref.
				mediates autophagic clearance of necroptosis components			
	Pyroptosis	TDP43	Microglia of C57BL/6 mice	A mutant form of TDP43 activates microglia and upregulates NOX2, TNFα, and IL-1β	Inflammatory vesicle lysis, inflammatory factor release	Upregulation pyroptosis	182
	Autophagic cell death	P62/SQSTM1	*Sod1*(*G93A*) mice model	Progressive accumulation of P62/SQSTM1 in the spinal cord impairs autophagic flux in mice	Obstruction of motor neuron development and eventual degeneration	Upregulation autophagic cell death	184
	Cuproptosis	FDX1	Peripheral blood of ALS patients	FDX1 mediates an imbalance in mitochondrial copper homeostasis, leading to abnormal aggregation of copper-dependent lipoylated proteins	Mitochondrial respiratory chain dysfunction and accelerated motor neuron degeneration	Upregulation cuproptosis	186
Multiple sclerosis (MS)	Ferroptosis	FSP1	EAE mice model	FSP1 mediates NADPH-catalyzed CoQ10 regeneration	Scavenging of ROS and lipid peroxyl radicals	Downregulation ferroptosis	191
		GPX4	EAE mice model	Excess GPX4 expression scavenges lipid peroxide and maintains membrane lipid bilayer homeostasis	Reduced levels of ROS in cells and reduced damage to cell membranes and mitochondria	Downregulation ferroptosis	190
	Parthanatos	PARP1, AIF, MIF	Cuprizone mice model	Overactivation of PARP1 leads to NAD^+ depletion, AIF-dependent DNA fragmentation	Attenuated oligodendrocyte depletion and decreased demyelination	Upregulation parthanatos	195
	Necroptosis	RIPK1, RIPK3, MLKL	EAE mice model	RIPK1/RIPK3 activate and form necrotic vesicles and phosphorylate MLKL *via* TNFα, disrupting cell membrane integrity	Increased production of necrotic vesicles and disruption of mitochondrial membranes	Upregulation necroptosis	197
		PGAM5, Drp1	BV-2 cells	PGAM5 and Drp1 exacerbate oligodendrocyte death and neuroinflammation	Oligodendrocyte death and neuroinflammation	Upregulation necroptosis	129
	Pyroptosis	NLRP3, GSDMD	EAE mice model	High NLRP3 expression increases secretion of IL-1β and IL-18	GSDMD-mediated inflammasome activation and pyroptosis in both myeloid cells	Upregulation pyroptosis	200

vesicle is often thought to lead to neuronal pyroptosis. RIPK3 acts as an essential regulator of necroptosis; its activation phosphorylates MLKL, ultimately compromising plasma membrane integrity[209]. It has been suggested that there is some kind of interaction between NLRP3 and RIPK3 and that this interaction directly leads to crosstalk between necroptosis and pyroptosis in AD. The exact mechanism is still debated. One explanation is that phosphorylated RIPK3 activates Caspase 8, which induces NLRP3 activation[210]. Yet another explanation is that RIPK3-mediated MLKL oligomerization drives mitochondrial ROS (mROS) generation, activating NLRP3 inflammasomes *via* the AKT phosphorylation cascade[211]. In addition, PGAM5 is also a downstream protein of RIPK3 that induces mitochondrial membrane damage and necroptosis caused by translocation of Drp1 to mitochondria. Mechanistic findings suggest that this mitochondrial damage generates mROS and ultimately activates NLRP3 to release inflammatory factors. Interestingly, NLRP3 activation in this context is reversed by Drp1 inhibitors[212]. In AD, NLRP3−RIPK3 crosstalk bridges necroptosis and pyroptosis *via* Caspase 8 activation, mROS−AKT signaling, and Drp1-mediated mitochondrial damage. Targeting these interactions may offer therapeutic potential, though precise mechanisms require further elucidation to clarify AD progression.

4.2. Crosstalk between non-apoptotic RCDs in PD

More and more studies have found that the two organelles, mitochondria and lysosomes, can be connected and communicate through common sites, and regulate their own functions as well as those of each other[213]. In addition, mitochondrial dysfunction can induce pyroptosis, necroptosis, and ferroptosis in cells, while lysosomal dysfunction can induce autophagic cell death. Some studies have shown that neurons of PD patients with GBA1 mutations have regulatory defects in the uncoupling protein TBC1D15 and exhibit prolonged mitochondria-lysosome contacts. This indicates that GBA1 is not only a key protein for the connection between mitochondria and lysosomes, but also may be a key protein connecting autophagy with other forms of RCD[214,215]. Mutations in parkin are an important cause of early-onset PD. Relevant studies have demonstrated that parkin-mutated neurons exhibit reduced mitochondria-lysosome contacts through the degradation of active Rab7, However, knocking down the Rab7 GTPase-activating protein TBC1D15 can restore the mitochondria-lysosome connection. This also suggests to us that parkin may be a key protein in RCD[38].

cGAS−STING pathway induction critically contributes to PD pathogenesis. An increasing amount of evidence indicates that the cGAS−STING effector signaling can trigger a neuroinflammatory response, thereby increasing the risk of developing PD[216,217]. Studies have shown that the activation of the cGAS−STING signaling pathway can promote the accumulation of the downstream NLRP3 inflammasome, which is manifested as the secretion of mature Caspase 1 and IL-1β, as well as the formation of pyroptotic bodies, thereby inducing pyroptosis[218]. In addition, this signaling pathway is also closely related to necroptosis, as a signaling amplifier, cGAS−STING is involved in TNF-driven necroptosis both *in vitro* and *in vivo*[219]. Some studies have shown that the release of mitochondrial DNA and nuclear DNA into the cytoplasm will activate the cGAS−STING1 pathway[220]. Notably, an increasing number of studies have begun to focus on the relationship between cGAS−STING and ferroptosis, and elucidating this relationship is crucial for targeted disease treatment. Although such research rarely involves PD, existing evidence suggests that STING agonists can significantly reduce the nuclear localization of NCOA4, impair the co-regulatory function of NCOA4 as a transcription factor, and increase the level of intracellular free iron, thereby inducing ferroptosis[221]. Some studies have indicated that TFEB can contribute to the STING1-mediated response by regulating the transcription of genes related to lysosomes, autophagy, and immunity. Interestingly, TFEB, as a key regulator of the autophagy−lysosome pathway, can counteract lysosomal depletion and autophagic vesicle accumulation, thereby preventing the occurrence of autophagic cell death[222]. In addition, the overexpression of TFEB can increase the synthesis of TfR1 and enhance the distribution of TfR1 in lysosomes. This is conducive to the uptake and temporary storage of iron by lysosomes, thereby preventing the occurrence of ferroptosis in PD[147].

4.3. Crosstalk between non-apoptotic RCDs in ALS

Disorders of lipid metabolism and metal homeostasis are key pathogenic mechanisms in neurodegenerative diseases. Recent studies have shown that ARF1 protein regulates lipid droplet homeostasis by inhibiting the lipid synthesis pathway, and its deficiency triggers the abnormal accumulation of lipids and activates the cGAS−STING inflammatory pathway. Meanwhile, the abnormal aggregation of TDP43 protein induced copper ion accumulation by interfering with autophagy homeostasis, suggesting that the cuproptosis pathway is involved in neuronal injury. Lipid dysregulation and metal toxicity independently modulate ALS cell death networks, revealing crosstalk between necroptosis and ferroptosis pathways.

ARF1 regulates lipid droplet formation and fatty acid storage, and its aberrant activity may lead to lipid overload or metabolic imbalance. In a *Drosophila* model, ARF1 knockdown triggers an abnormal accumulation of lipid droplets and an organelle stress cascade, culminating in ALS disease characterized by demyelination. Lipid droplets are cytoplasmic organelles specialized in storing fatty acids. In a recent report, the expression levels of a family of fatty acid transporter proteins involved in lipid uptake did not change significantly in RNA-seq of ARF1-deficient N2a cells, suggesting that ARF1 may not be involved in lipid uptake. However, when the researchers administered a cellular FASN inhibitor to suppress lipid *de novo* synthesis, the lipid accumulation caused by ARF1 knockdown was reversed. Combined with previous findings, the authors hypothesize that ARF1 exerts its role in inhibiting lipid *de novo* synthesis through inhibition of the AKT−mTORC1−SREBP1−FASN axis. Validation experiments reinforced this hypothesis with a significant increase in pAKT, pS6K (used to characterize mTORC1 activity), and cleaved mature SREBP1 in ARF1 knockout cells compared to control cells. AKT and mTOR signaling proteins regulate cellular energy metabolism, and their dysregulation leads to aberrant AMPK signaling that inhibits autophagic cell death. Interestingly, the authors found that N2a cells from ARF1 knockdown activated the cGAS−STING signaling pathway and NLRP3 inflammatory vesicles, which may suggest the possibility that there is an inhibition of pyroptosis in ALS by ARF1. The ability of ARF1 activation to inhibit autophagic cell death while promoting pyroptosis may lead to the development of a vicious cycle of autophagy−pyroptosis imbalance in ALS patients[223]. This crosstalk reveals that future studies need to further resolve the regulatory network between the two in terms of spatiotemporal

dynamics and develop multipathway therapies that jointly target autophagy and pyroptosis.

TDP43 is one of the key pathogenic proteins in ALS, and its aberrant aggregation and dysfunction significantly contribute to neuronal degeneration by interfering with autophagy (especially autophagic cell death). The possible mechanism is that TDP43 aggregation inhibits mTORC1 activity, but sustained autophagic overactivation leads to cellular energy depletion and ultimately triggers an irreversible cell death program through the AMPK−p53 pathway. It has been shown that in the spinal cord of mice, overexpression of TDP43 is accompanied by elevated copper levels. Specifically, in ALS mice, overexpression of TDP43 resulted in impaired locomotor performance. Taken together, this analysis suggests that cuproptosis may be present in TDP43 overexpressing mice, and these phenomena reflect the crosstalk between cuproptosis and autophagic cell death in ALS mice with TDP43 as the crossover point[224].

4.4. Crosstalk between non-apoptotic RCDs in MS

The pathology of MS involves aberrant activation of multiple RCD pathways. cGAS−STING signaling pathway activation exacerbates MS progression by promoting neuronal ferroptosis and autophagic cell death, whereas up-regulated expression of NINJ1 protein in the blood−brain barrier mediates inflammatory cell infiltration and triggers multiple forms of RCD.

The activation of cGAS−STING is also an important pathogenic factor for MS. Neuron-specific deletion of STING1 can improve the EAE disease progression and alleviate neuronal damage. This is achieved by reducing autophagic degradation of GPX4, suppressing lipid peroxidation, and inhibiting ferroptosis. Furthermore, the activation of the non-canonical STING signaling pathway can even lead to autophagic cell death of neurons[225].

The transmembrane protein Ninjurin-1 (NINJ1) is an interacting component of the eukaryotic cell membrane and acts as a built-in breaking site upon the activation of cell death. NINJ1 mediates various types of RCD[226]. NINJ1 is also a crucial participant in the release of inflammatory molecules. Existing evidence shows that NINJ1 has a low expression level in the central nervous systems of healthy humans and mice. Nevertheless, during the course of EAE and in active MS lesions, the expression of NINJ1 on blood−brain barrier (BBB) endothelial cells and infiltrating antigen-presenting cells is significantly increased. Additionally, blocking NINJ1 can reduce the clinical disease activity and histopathological indicators of EAE, and also decrease the infiltration of macrophages, dendritic cells, and antigen-presenting cells into the central nervous system[227]. This suggests that, as a key protein in MS, NINJ1 may be involved in and regulate different types of RCD in MS (Fig. 7).

5. Non-apoptotic RCDs inhibitors in NDs

5.1. Non-apoptotic RCDs inhibitors in AD

Ferroptosis inhibitors show potential to alleviate pathology and improve cognitive function in AD models by inhibiting lipid peroxidation, modulating iron homeostasis, and enhancing antioxidant defenses. Activation of the NRF2/GPX4 axis is the main therapeutic target for ferroptosis-driven AD. In addition to this, inhibition of ACSL4, NOX4 or activation of PPARα are also mechanisms of action of ferroptosis inhibitors for the treatment of AD, which are also effective in reducing lipid peroxide and intracellular free radicals and iron. In summary, their ultimate purpose is to reduce Aβ deposition and Tau protein hyperphosphorylation and ultimately attenuate cognitive impairment. Salidroside is a type of *p*-hydroxyphenyl-β-glucoside present in various parts of plants, with a variety of biological activities and a wide range of pharmacological properties. In particular, salidroside repaired neuronal damage, decreased Aβ deposition, and mitigated cognitive impairment treatment in a dose-dependent manner. Mechanistic investigations showed that *via* activating the NRF2/GPX4 axis, salidroside increased the expression of SLC7A11 and GPX4 while decreasing iron deposition, TFR1, and ACSL4. Additionally, in the brain of SAMP8 mice, salidroside enhanced mitochondrial metabolism, iron metabolism, lipid metabolism, and redox while suppressing oxidative stress, inflammatory cytokines, and $CD8^+$ T-cell infiltration[228]. Another study also demonstrated the correlation between the neuroprotective effects of salidroside and NRF2-associated ferroptosis. Salidroside reduced neuronal ferroptosis in Aβ_{1-42}-induced AD mice and glutamate-injured HT22 cells by triggering the NRF2/HO1 signaling pathway, as demonstrated by elevated expression of GPX4 and SLC7A11, reduced levels of lipid peroxidation and ROS, and altered mitochondrial and Aβ ultrastructure[229]. Enhancement targeting the NRF2/HO1 pathway is not an isolated case in plant-derived drugs. Eriodictyol is a naturally occurring flavonoid compound found mainly in citrus fruits and some herbs, has also been reported to have NRF2/HO1 pathway-dependent neuroprotective effects. Eriodictyol can exert anti-ferroptosis effects through VDR-induced activated NRF2/HO1 signaling pathway *in vitro* and *in vivo*. This mechanism inhibited Aβ aggregation and Tau phosphorylation, and significantly reduced cognitive deficits in the mouse model[230]. Recently, it was found that avicularin (Avi), a flavonoid from the pericarp of *Zanthoxylum bungeanum Maxim*, was demonstrated to be neuroprotective against AD. Avi could promote NRF2 entry into the nucleus and enhance antioxidant defenses by directly inhibiting NOX4. Meanwhile, Avi alleviated H_2O_2-induced ferroptosis, significantly improved mitochondrial morphology, and showed effectiveness in reducing intracellular lipid peroxidation markers and Fe^{2+} levels[231]. ACSL4 catalyzes the binding of long-chain PUFA to CoA, which in turn synthesizes readily oxidizable membrane phospholipids and increases oxidative stress during ferroptosis. Senegenin is one of the major and most active components of *Radix Polygala*. A recent study has shown that its antioxidant and neuroprotective effects are associated with ferroptosis. Senegenin raised the expression of GPX4 and reduced the expression of PEBP1 and ACSL4 at the molecular level. The study found that in a model of Aβ_{25-35}-induced neurological damage in PC12 cells, this therapy reversed mitochondrial depolarization and decreased the degree of oxidative stress[232]. Tetrahydroxy stilbene glycoside (TSG) is the main active substance that comes from *Polygonum multiflorum*. By activating the KEAP1/NRFf2/ARE and GSH/GPX4/ROS signaling pathways, TSG therapy controlled ferroptosis-related proteins in a mouse model, preventing Aβ-induced dose-dependent neuronal loss. Decreases were observed in NLRP3-associated neuroinflammation, lipid peroxidation levels, ferroptosis markers, and the expression of NCOA4, ACSL4, and DMT1. By up-regulating the expression of SOD and CD98, FTH1 and xCT, TSG also decreased the amounts of oxidative products and lessened inflammatory damage and cellular oxidative stress brought on by Aβ[233]. α-Lipoic acid is a naturally occurring iron chelator and antioxidant cofactor in enzymes, and

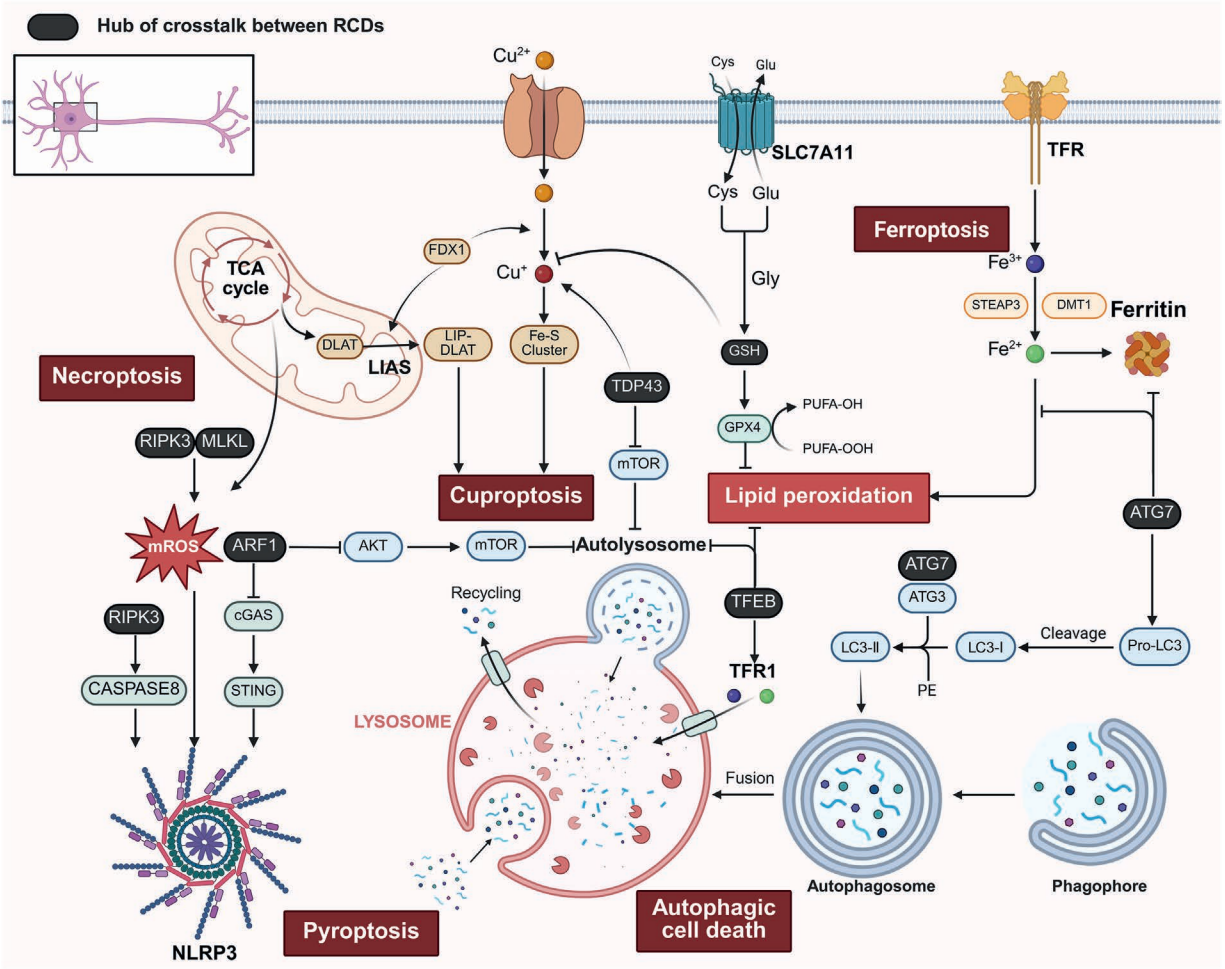


Figure 7 Molecular mechanisms and therapeutic targets of regulated cell death (RCD) crosstalk in neurons. RIPK3 induces necroptosis upon autophosphorylation, while activation of NLRP3 inflammatory vesicles promotes pyroptosis. ARF1 promotes autolysosome formation but inhibits NLRP3 activation, reflecting the crosstalk between pyroptosis and autophagic cell death. TDP43 overexpression promotes autolysosome formation while disrupting Cu^{+} homeostasis to promote cuproptosis. GSH inhibits oxidative stress and ferroptosis while binding Cu^{+} to inhibit cuproptosis. TFEB inhibits both ferroptosis and autophagic cell death. It reduces intracellular ferrous ions and lipid peroxide distribution and inhibits autolysosome formation. ATG7 inhibits ferric ion release from ferritin and inhibits ferroptosis, but promotes autophagosome formation and autophagic cell death.

has been applied in numerous clinical trials. α-Lipoic acid has been shown to stabilize cognitive function in AD patients, and animal investigations have verified its anti-amyloidogenic qualities. P301S Tau transgenic mice were used to study the connection between RCDs and α-lipoic acid. α-Lipoic acid was discovered to significantly prevent a number of ferroptosis-related events, such as lipid peroxidation, inflammation, and Tau-induced iron overload[20]. Inhibitors screened based on molecular docking showed excellent inhibitory activity against various markers of ferroptosis in AD. A high-throughput pharmacological screening of 4207 natural derivatives across structurally diverse chemical libraries identified 1,6-*O*,*O*-diacetylbritannilactone (OABL)—a novel sesquiterpenoid isolated from *Inula britannica* (Asteraceae family), as a CNS-penetrant anti-neuroinflammatory agent. Mechanistic profiling in activated BV-2 microglia revealed OABL's multimodal action: dose-dependent suppression of LPS-induced pro-inflammatory mediators (NO, PGE2, TNFα) *via* dual inhibition of iNOS/COX-2 enzymatic systems, coupled with NF-κB nuclear translocation[234]. Beyond classical pathways, emerging targets show potential in regulating neuronal ferroptosis. The PPARα activator GW7647 demonstrated dual benefits in APP/PS1 mice by reducing Aβ deposition and improving cognitive function, while simultaneously suppressing ferroptosis and neuronal loss through decreased lipid peroxidation and inflammatory responses. *in vitro* experiments using APPsw cells revealed PPARα′s direct binding to intron 3 of GPX4 enhances its transcription while diminishing iron transport activity. Mechanistically, GW7647-induced PPARα activation facilitates GPX4 upregulation through interactions with its non-coding regions, thereby restoring cerebral iron balance and mitigating neuroinflammation and lipid oxidation in the AD mouse model[235].

PARP1 is a DNA repair enzyme located primarily in the nucleus of eukaryotic cells. Inhibition of PARP1 activation is currently one of the effective ways to inhibit parthanatos. AD drosophila models that expressed Aβ42 were given standard saccharomyces cerevisiae media supplemented with either MC2050 (100 μmol/L) or Olaparib (25 μmol/L). Ten to twelve days after feathering, the climbing activity of the models was

measured. As mentioned previously, excessive activation of PARP1 also causes NAD depletion. The researchers showed restoration of climbing ability and reversal of NAD depletion in the Aβ_{42}-induced AD *Drosophila* model using both the PARP1 inhibitors Olaparib and MC2050. Interestingly, Olaparib and MC2050 also inhibited Aβ_{42} accumulation in the brains of adult AD patients. This indicates that PARP1 activation levels have been reduced by the inhibitors, a phenomenon that may suggest that death due to parthanatos has been suppressed[21].

Necroptosis is physiologically closely related to the degree of brain aging. Deletion of MLKL, an effector of necroptosis, delays the onset of axonal degeneration and neuroinflammation associated with aging. Pharmacologically, inhibitors of necroptosis that inhibit RIPK1/RIPK3/MLKL also have superior palliative effects on AD pathology. The RIPK3 inhibitor GSK-872 reverses aging-associated neurodegenerative symptoms through inhibition of the necroptotic pathway. GSK-872 specifically decreased pro-inflammatory cytokine levels. Furthermore, RIPK3's regulation of late and short-term necroptosis reversed the loss of synaptic strength, improved memory and learning deficits in aged mice, and significantly decreased hippocampal index of vulnerability[133]. RIPK1 is recruited to the receptor and activates downstream RIPK3, so direct targeting of upstream RIPK1 is also a potent means of inhibition. A highly selective RIPK1 inhibitor called SZM679 was created with exceptional anti-necroptotic action and was studied for its potential to totally reverse the systemic inflammatory response syndrome brought on by tumor necrosis factor. SZM679 appeared to improve memory and learning deficits in the mouse model of AD-like conditions caused by streptozocin according to behavioral testing. Neuronal loss was improved by SZM679 according to Nissl staining. Additionally, the SZM679-treated group showed a significant decrease in neuroinflammation, Tau hyperphosphorylation, and RIPK1 phosphorylation levels in the cortex and hippocampal regions[22]. Inflammatory factors such as TNFα trigger chronic inflammation through the sustained activation of RIPK1 by TNFR1. Edaravone (Eda) is a diterpenoid that inhibits the release of inflammatory factors. Drugs using Eda as the main ingredient are already approved for the treatment of ALS patients in the phase, and it also has the potential to target necroptosis in AD and has already entered the Phase II clinical trial stage. In animal models of the preclinical stage, Eda improved cognitive function in AD mice. Histopathologic data showed that Eda significantly improves Aβ pathology, including Aβ load, astrocyte hyperplasia/microglia hyperplasia, and Tau phosphorylation. Furthermore, Eda inhibition decreased Aβ-induced neuronal injury, such as neuronal synapse destruction, mitochondrial damage, reactive oxygen species generation, and NAD depletion, and inhibited TNFα-triggered neuronal necroptosis[236].

Inhibition of pathways associated with autophagy and thus attenuation of autophagic cell death may exist as a better therapeutic option for NDs, including AD. Selaginella tamariscina ethanolic extract (STE) was observed to provide neuronal protection, possibly by inhibiting autophagic cell death or oxidative stress. It was shown that reduced expression of autophagy degradation protein P62 was observed in glutamate-exposed HT-22 hippocampal cells, along with a significant decrease of p-mTOR, p-PI3K, and p-AKT, which was reversed by the action of STE, and the STE pretreatment up-regulated the phosphorylation level of the PI3K−AKT−mTOR pathway, so that it was learned that STE could inhibit autophagic cell death and glutamate-induced cytotoxicity, which may provide new options for AD and PD treatment[237].

Metal chelation therapy is currently the main method of inhibiting cuproptosis, and clioquinol is a chelator that crosses the blood−brain barrier and has a much greater affinity for Cu^{2+} than other ions. A clinical study showed that Tau protein in the CSF of AD patients was elevated on Day 7 after clioquinol was administered. However, it began to decrease on Day 21. The researchers suggest that the initial increase in Tau protein may be due to its release from senile plaques into the CSF, while the later decline is due to the role of clioquinol in the brains of AD patients. Notably, Tau protein levels in the CSF were significantly correlated with copper levels in the serum, suggesting that chelation of Cu^{2+} reduces cuproptosis in cells and thus slows AD[238].

5.2. *Non-apoptotic RCDs inhibitors in PD*

Ferroptosis, an iron-dependent form of RCD, has been mechanistically implicated in the neurodegenerative processes underlying PD, driving therapeutic exploration of ferroptosis-modulating agents. (−)-Clausenamide (Clau), a bioactive amide alkaloid isolated from *Clausena lansium* (Lour.) Skeels (Rutaceae family), demonstrates multimodal neuroprotective efficacy through stereoselective targeting of ferroptotic drivers. Recent crystallographic studies reveal Clau's allosteric modulation of the PKCα−ALOX5 signaling axis *via* competitive binding to Ser663 phosphorylation motifs on PKCα, effectively blocking ALOX5 nuclear translocation required for biosynthesis of 5-hydroxyeicosatetraenoic acid—a lipid peroxidation mediator that exacerbates mitochondrial iron overload in dopaminergic neurons. These therapeutic outcomes correlated with Clau-mediated restoration of redox homeostasis and suppression of gliosis, substantiating its disease-modifying potential through simultaneous targeting of ferroptotic lipid peroxidation cascades, neuroinflammatory amplification loops, and synaptic integrity maintenance[239]. Complementing the ALOX5-targeted neuroprotection by Clau, recent studies further delineate thonningianin A (ThA) and hinokitiol as mediators counteracting ferroptosis through NRF2−KEAP1 axis activation and iron homeostasis modulation, synergistically alleviating dopaminergic neuronal demise in PD models. ThA reduced ferroptosis-induced α-syn aggregation, iron buildup, lipid peroxidation, GSH depletion, and overall swimming distance in zebrafish with PD[240]. The natural small molecule hinokitiol rescues damaged neurons by acting as a strong ferroptosis inhibitor. The mechanism of hinokitiol involves chelation of iron and activation of the cytoprotective transcription factor NRF2 to up-regulate antioxidant genes, including *SLC7A11*, *GPX4*, and *HO1*. Hinokitiol was shown to improve zebrafish motor activity and neurodevelopmental deficiencies *in vivo*[241]. Although NRF2 is a well-researched target, adverse effects are caused by the electrophilic chemistry of traditional NRF2-based medications, which irreversibly alkylate cysteine residues on cellular proteins. Bach1 is a known transcriptional inhibitor of the NRF2 pathway. Therefore, targeting Bach1 may circumvent these alkylation side effects. The substituted benzimidazole compound HPPE was identified as a Bach1 inhibitor by using a proprietary translational technology platform developed by vTv Therapeutics, which was validated as a non-electrophilic reagent. The Bach1 inhibitor reduced oxidative damage, neuroinflammation, and dopaminergic neurotoxicity brought on by MPTP when taken orally. In line with the findings in Bach1 KO mice, activation of the Bach1-targeted pathway was linked to Bach1 inhibitor-induced neuroprotection[242]. Triacsin C is a potent inhibitor of ACSL4 and ACSL1, and it prevents ischemic brain

injury by inhibiting ACSL4. Here, researchers assessed that Triacsin C ameliorated the MPTP-induced significant reduction of tyrosine hydroxylase and DA. Triacsin C also ameliorated motor deficits in PD mice *in vivo*[243].

PARP1 overactivation is also a cause of rotenone-induced PD, a phenomenon that implies that disease progression in PD may be related to parthanatos. Veliparib is a general PARP1 inhibitor. Rotenone primarily activated PARP1/TEEB/NLRP3 signaling to induce PD. Following veliparib treatment, SN4741 cells had increased ASC and NLRP3 levels along with higher ELISA-detected amounts of IL-1β and IL-18. But PARP1 inhibitor therapy successfully blocked rotenone-induced NLRP3 activation as well as IL-18 and IL-1β activation in SN4741. Veliparib also reduced NLRP3 and IL-1β levels in mice's SNpc as determined by WB and ELISA[244].

α-Syn protofibrils induce necroptosis in neurons by activating the RIPK1/RIPK3/MLKL pathway, which is blocked by MLKL inhibitors. Necrosulfonamide (NSA) is a specific MLKL inhibitor that inhibits its phosphorylation, ubiquitination, and oligomerization. Modulation of necroptosis by NSA inhibits microglia activation, reactive astrocyte proliferation, and MPTP-induced expression of proinflammatory molecules, leading to impaired motor performance and recovery of dopaminergic degeneration. In addition, NSA inhibits oligomerization and phosphorylation of α-syn in PD mice by inhibiting GSK3β and MMP-3-related pathways[245]. It was recently discovered that the anticancer medication pazopanib improved rotenone-induced PD rats by blocking several RCD pathways, including as the p-RIPK1/p-RIPK3/p-MLKL pathway with anti-necroptotic properties and ferroptosis-related potential pathway VEGFR2/PKCβII/PLCγ/ACSL4[246].

Activation of inflammatory mediators and inflammatory vesicles is the main cause of pyroptosis-induced cell death and ultimately PD, and current PD inhibitors involving pyroptosis also target inflammatory mediators for research. Carveol is a natural terpenoid with strong antioxidant properties. At a dose of 50 mg/kg, a significant decrease in lipid peroxidation and ROS and an increase in protein expression of HO-1 and NRF2 were observed by Western blotting in PD mice in the Carveol group. In addition, pyroptosis markers such as IL-1β and NFκB were also found to be down-regulated, which further demonstrated the inhibitory effect of Carveol on pyroptosis[23]. Recently, it has been reported that exogenous β-hydroxybutyrate (BHB) supplementation also inhibits pyroptosis by suppressing the activation of NLRP3 inflammatory vesicles. The researchers found by Western blotting analysis that in the MPTP-induced PD model, as with other pyroptosis markers, elevated p-STAT3 expression in the mouse striatum was reversed by BHB pretreatment. Similar results were obtained in *in vitro* experiments in microglia, which may indicate that STAT3 is located at an upstream position in the NLRP3 signaling pathway[247]. Notably, the G protein-coupled estrogen receptor (GPER) has also been implicated in the activation of NLRP3 inflammatory vesicles. Baohuoside I, a herbal extract, has been shown to inhibit the maturation of pro-caspase-1, ASC, NLRP3, and IL-1β, thereby exerting an anti-pyroptotic effect in BV2 cells and microglia. In contrast, the anti-inflammatory effect of Baohuoside I was eliminated in the GPER knockout PD mouse model, which may indicate that GPER is a key target for inhibiting pyroptosis in the PD model[248].

In PD, inhibitors dedicated to autophagic cell death are currently not often reported; however, inhibition of the markers of autophagic cell death has been demonstrated by other inhibitors that have been identified in other RCDs. Nec-1 is an inhibitor of necroptosis, and additional evidence suggests that Nec-1 acts by inhibiting autophagic cell death in a 6-OHDA-induced PD cell model. A 6-OHDA-induced decrease in mitochondrial membrane potential was observed in PC12 cells under fluorescence microscopy, which was attenuated upon Nec-1 treatment. Evidence from Western blotting indicated that Nec-1 pretreatment inhibited the activation of LC3-II and increased the expression level of BCL2 in cells[130]. In a recent study, the authors selected among 19 newly synthesized arylpiperazine compounds *N*-(3-(2-(4-phenylpiperazin-1-yl)-ethyl)-phenyl)-picolinamide (6b), which reduces cellular invasion by 6-OHDA neurotoxin. In this study, the authors found that the mechanism of action of 6b is upstream of the autophagy AKT pathway-dependent, and that it inhibits autophagic cell death generated by 6-OHDA stimulation by activating the AKT pathway[249].

5.3. *Non-apoptotic RCDs inhibitors in HD*

Promising treatment options for ferroptosis in HD include NRF2 activation or Bach1 inhibition alone. Therefore, drugs that have dual action as Bach1 inhibitors and NRF2 activators may offer stronger anti-inflammatory and antioxidant benefits as well as improved neuroprotection in general. Cannabidiol (CBD) is a phytocannabinoid that inhibits Bach1 but has no discernible NRF2 activating effects. A recent study based on this scaffold developed a novel CBD derivative, *O*-methyl-*para*-cannabidiol quinone, which is highly potent in both Bach1 inhibition and NRF2 activation. This new CBD derivative provided neuroprotection in a cellular model associated with HD, significantly reducing 3-NP-induced cytotoxicity[250]. Emerging evidence highlights complementary pharmacological strategies targeting ferroptosis in HD through NRF2 pathway modulation. While novel CBD derivatives demonstrate dual-target efficacy in simplified cellular models, recent investigations extend this paradigm to multifactorial tissue systems. Notably, MIND4 exemplifies a refined dual-target approach in neurologically complex *ex vivo* models, where its potent antioxidant activity and transcriptional regulation mirror the neuroprotective mechanisms observed in single-cell studies. MIND4 is a dual-targeted inhibitor of NRF2 and SIRT2, and researchers used rat cortical striatal brain slice explants to test the neuroprotective potential of MIND4 in the complex neurological tissue system of HTT exon 1. The data showed that a 10 μmol/L concentration of MIND4 had neuroprotective effects comparable to those of a 100 μmol/L pan-cysteinyl asparaginase inhibitor. Moreover, in primary striatal neurons and astrocytes of WT rats, 5 μmol/L MIND4 treatment also induced strong expression of classical NRF2 targets. The inhibition of oxidative stress upon NRF2 activation suggests its role in inhibiting ferroptosis in HD[251].

5.4. *Non-apoptotic RCDs inhibitors in ALS*

Ferroptosis during ALS disease progression is primarily inhibited by iron chelators. Iron chelators exhibit therapeutic potential in mitigating ferroptosis in ALS by addressing iron dyshomeostasis, a key driver of lipid peroxidation. By sequestering redox-active iron, agents like deferiprone suppress Fenton reactions, attenuate oxidative stress, and preserve GPX4 activity, which is in Phase III clinical trials. In SOD1 (G37R) transgenic ALS mice, aberrant accumulation of ferroptosis and associated protein dysregulation occurred in neurons and glial cells. When using a high-affinity, lipophilic iron chelator salicylaldehyde isonicotinoyl hydrazone

(SIH) treatment, SOD1 (G37R) mice extended their lifespan by 5 weeks while increasing spinal motor neuron survival and improving motor function[252]. SOD1 (G37R) transgenic ALS mice with reduced iron accumulation and motor neuron loss in the spinal cord also showed enhanced motor function and survival time when treated with VAR10303, another monoamine oxidase inhibitor/iron chelating free radical scavenging medication[253]. Similarly, 2-(2-hydroxyphenyl)-benzoxazole (HBX) is a small molecule compound with metal chelating ability. There was a notable delay in the start of ALS disease and varying degrees of maximal lifetime lengthening in the treated group following the researchers' administration of HBX to ALS animals in the G93A mouse model. The G93A mice had markedly higher levels of F2-isoprostanes, an indication of oxidative damage, before dosing, and this increase was reduced following HBX treatment. In addition to this, HBX treatment reduced the aggregation of mutant SOD1 protein in the spinal cord. Overall, iron chelation is a meaningful therapy by reducing free iron levels in the body and thus further alleviating ALS[254].

ALS research has identified the RIPK1/RIPK3/MLKL pathway as a key therapeutic target for inhibiting necroptosis. At present, existing experiments with drugs targeting this pathway for the treatment of ALS have shown that treatment with RIPK1 inhibitors leads to increased survival and reduced axonal lesions in a mouse model. SAR443820 is a selective, orally bioavailable, brain-permeable, reversible RIPK1 inhibitor. The in-human evaluation of RIPK1 inhibitor SAR443820 (NCT05795907) established its pharmacologic profile as a CNS-penetrant, orally administered kinase-targeted therapeutic exhibiting dual selectivity for RIPK1/RIPK3 with reversible binding kinetics. Comprehensive PK/PD profiling during dose-ranging regimens revealed superior blood−brain barrier penetration and favorable therapeutic index compared to first-generation necroptosis inhibitors, coupled with sustained target engagement. These early-stage clinical data validate therapeutic potential, warranting advancement to Phase II evaluation in neurodegenerative pathobiology characterized by RIPK-mediated inflammatory cascades, including ALS and MS indications[255].

Specifically, autophagic cell death is strongly associated with the onset and progression of ALS. Evidence suggests that overexpression of LC3-II, a marker of autophagic cell death, is detected in the spinal cord of ALS patients. Use of the autophagy inducer rapamycin in a mouse model of ALS dramatically shortens mouse lifespan and accelerates motor neuron death[184,256]. A small molecule compound derived from natural angelica, *n*-butylidenephthalide (*n*-BP), was initially found to modulate autophagy by mediating ER stress and is primarily used in the treatment of prostate cancer[257]. In an *in vitro* ALS cell line, *n*-BP inhibited the expression of the apoptotic protein caspase-3 and the autophagy marker LC3-II in a dose-dependent manner. Transmission electron microscopy revealed no significant changes in mitochondrial cristae morphology, indicating suppression of autophagy activation. The researchers further observed the mechanism of action of *n*-BP. The expression of ATG1 and ATG5 was reduced in the ALS mouse model after the action of *n*-BP, while the expression of mTOR was elevated in the spinal cord, which may indicate that mTOR is the target of the action of *n*-BP in the regulation of autophagic cell death. mTOR can inactivate autophagic complexes by phosphorylating specific sites, such as the serine site of ULK1. Consequently, autophagic cell death in ALS may be inhibited by *n*-BP-regulated mTOR phosphorylation[258]. Currently, *n*-BP has entered Phase I clinical trials for the treatment of ALS.

In general, copper chelators are currently the main inhibitors of cuproptosis in the pathogenesis of ALS. Trientine is a copper chelator and has been widely used as a replacement for D-penicillamine due to the presence of fewer adverse effects. In G93A mice carrying the mutant human *SOD1* gene, the use of trientine significantly delayed the onset of FALS mice while prolonging survival, and prevented the deterioration of locomotor function when used in combination with ascorbic acid, which may be attributed to the fact that the combination was effective in decreasing the copper-induced Fenton reaction and attenuating the ROS-mediated lipid peroxidation[24].

5.5. *Non-apoptotic RCDs inhibitors in MS*

In both active and chronic patients with MS, the researchers observed the occurrence of some of the more pronounced ferroptosis lesions, such as increased intracellular unstable iron and lipid peroxides and their metabolites. Unlike ferroptosis inhibitors for other NDs, the mechanism of action of ferroptosis inhibitors for MS also includes upregulation of the AXL receptor. AXL inhibits ferroptosis in multiple ways by activating the antioxidant pathway through GAS6/AXL signaling, regulating iron metabolism to reduce free iron, and inhibiting pro-inflammatory responses. Since the *Axl* gene is extensively expressed in the nervous system, animal models where *Axl* was knocked out showed more severe axonal damage and spinal cord injury. A recent report initially investigated the possible mechanism of MS treatment with dabrafenib, a marketed drug used to treat melanoma, from the perspective of ferroptosis. In an EAE model, dabrafenib markedly reduced spinal cord inflammation and improved limb weakness, paralysis, and aberrant gait. In the EAE spinal cord tissue, it simultaneously prevented microglial cells from ferroptosis. Second, in a BV2 inflammatory cell model induced by LPS, dabrafenib was able to decrease ROS levels, halt the S phase, and restore mitochondrial activity. Ultimately, an *Axl* knockout EAE model could confirm that dabrafenib prevents ferroptosis in microglia through upregulation of the AXL receptor, thereby reducing the inflammatory demyelination[259]. In MS, the amount of cell death gradually increases with disease progression. This is because when the disease is in the acute phase, neurons begin to degenerate as soon as axons intersect. Therefore, it is particularly important to inhibit ferroptosis and thus disease progression in the early stage of MS. Recent data suggest that UAMC-3203 treatment prevents early progressive disease course in MS. UAMC-3203, a third-generation ferritinase inhibitor analog, enhanced experimental relapsing-remitting EAE by inhibiting ferroptosis. UAMC-3203 extended the duration between relapses and reduced overall clinical illness scores. After receiving UAMC-3203 treatment, the damaged spinal cord's demyelination may have significantly decreased, which could account for this clinical improvement. APP deposition, however, did not decrease[190].

The primary means of inhibiting parthanatos in MS patients relies on inhibiting PARP1 hyperactivation. PJ34, a PARP1 inhibitor, negatively regulates cell maturation and cytokine production in mouse bone marrow-derived dendritic cells while reversing NFκB activation. In C57BL mice with chronic EAE, PJ34 reduced DC migration and demyelination in the central nervous system. Interestingly, PJ34 was also effective in inhibiting epitope spreading in response to encephalitis[260]. This study highlights the potential of PJ34 to suppress PARP1-driven

parthanatos, neuroinflammation, and demyelination in MS. By targeting PARP1 hyperactivation, it may offer dual neuroprotection and immune modulation, particularly in curbing epitope spreading. Further exploration of parthanatos inhibitors could advance MS therapeutic strategies.

Necroptosis due to hyperphosphorylation of RIPK1 and its subsequent pathways is one of the pathogenic mechanisms of MS. At the same time, inhibition of RIPK1 reduces inflammation and cellular damage, with beneficial effects on both MS and other NDs. SIR2446M is an effective, selective novel small-molecule RIPK1 inhibitor currently in Phase 1 clinical trials. Its inhibitory effects on multiple NDs (including MS) were evaluated in a clinical trial (ACTRN12621001621808). The experimental results demonstrated the safety and pharmacokinetic profile of SIR2446M compared to other RIPK1 inhibitors. In addition to this, lower doses of SIR2446M were sufficient to achieve a high level of target inhibition and achieved 90% inhibition of MLKL and RIPK1 phosphorylation after just one day of administration[261]. The clinical evaluation of SIR2446M underscores its promise as a targeted necroptosis inhibitor, demonstrating rapid, low-dose suppression of RIPK1/RIPK3/MLKL pathway activation. Its favorable safety profile and potent efficacy position it as a novel therapeutic candidate for MS and neurodegeneration, meriting expanded clinical validation.

Inhibition of inflammatory vesicles and delivery of inflammatory mediators is likewise one of the measures to target cell pyroptosis in the treatment of MS. Ketotifen is a mast cell stabilizer and is one of the powerful drugs for the treatment of allergic diseases. In gene expression analysis using real-time RT-PCR, researchers found that mRNA expression of *Casp1*, *Nlrp3*, and *Il1B* was significantly reduced in a mouse model of MS following ketotifen action. This may indicate that mast cells are one of the sources of these inflammatory mediators, and targeting mast cells may also be an effective strategy for treating MS[262]. Inhibiting the activation phase of NLRP3 is also one of the strategies employed by the oral MS treatment agent fingolimod to suppress pyroptosis, which is in Phase III trials. Notably, the researchers assessed the degree of activation of NLRP3 inflammatory vesicles by observing the number of ASC oligomers, as NLRP3 activation promotes ASC oligomer formation and pyroptosis. The results showed that Fingolimod reduced the activation of NLRP3 in bone marrow cells in MS patients[263]. These studies suggest that targeting mast cell-derived NLRP3 inflammasome activation and pyroptosis could mitigate neuroinflammation in MS. This dual strategy highlights the therapeutic potential of suppressing inflammatory vesicle pathways and pyroptosis mechanisms to alleviate MS progression, warranting further clinical exploration (Table 3).

6. Clinical trials of non-apoptotic RCDs inhibitors in NDs

Previously in this article, we discussed preclinical studies of small-molecule compounds targeting non-apoptotic RCDs for treating NDs. Encouragingly, a subset of these compounds has entered clinical trials. Systematic clinical trials and accumulation of clinical data are essential for drug recognition and assessing safety and efficacy. Unfortunately, clinical trial reports rarely detail the specific mechanism of action. Therefore, in this section, we rely on preclinical mechanistic studies to summarize, as possible, the dependent pathways by which these small-molecule compounds exert clinical effects.

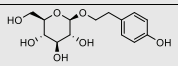
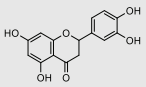
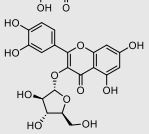
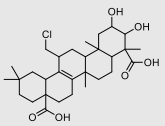
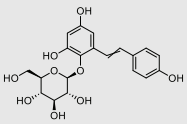
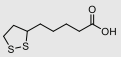
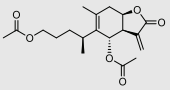
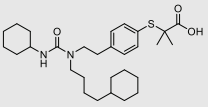
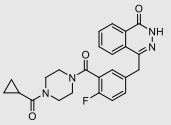
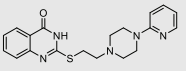
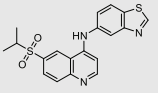
6.1. Clinical trials of non-apoptotic RCDs inhibitors in AD

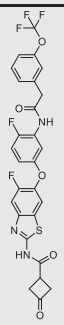
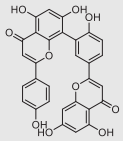
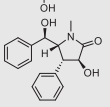
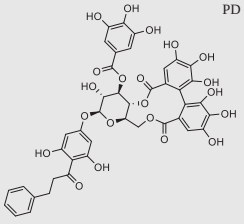
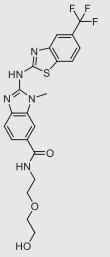
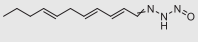
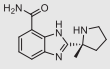
In AD, oxidative stress is closely associated with several RCDs, particularly ferroptosis. Antioxidant supplementation has demonstrated neuroprotective effects in AD patients in preclinical trials. α-Lipoic acid, a typical antioxidant, delays oxidative stress, inflammatory progression, and ferroptosis in Tau transgenic mice, thereby improving AD behavior[20]. Contrary to preclinical results, patients in the α-lipoic acid group showed no significant change in Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS−ADL) scores or Minimum Mental State Examination (MMSE) scores, indicating no significant cognitive or behavioral improvement; some patients even developed more serious dysfunction. Similarly, the antioxidant coenzyme Q group demonstrated no elevation in ADCS−ADL and MMSE scores compared to the placebo group, reflecting limited potential for α-lipoic acid and coenzyme Q in AD patients (NCT00117403). In another trial, α-lipoic acid was combined with omega-3 fatty acids as the test group. Over an 18-month treatment period, ADCS−ADL data showed no desired efficacy, with serious adverse effects such as cardiac disorders and gastrointestinal disorders observed in 29.41% ($n = 34$) of patients (NCT01058941). Unfortunately, no clinical trials have tested α-lipoic acid alone for AD, and its ability to target ferroptosis may be diminished in combination therapies. In conclusion, current clinical trial results for α-lipoic acid fall far short of expectations.

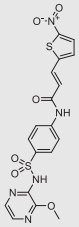
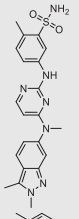
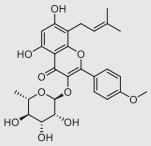
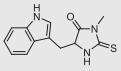
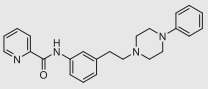
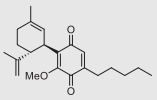
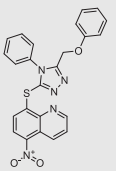
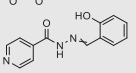
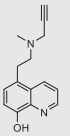
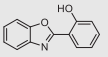
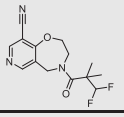
6.2. Clinical trials of non-apoptotic RCDs inhibitors in PD

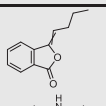
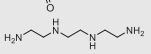
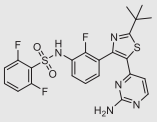
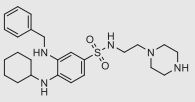
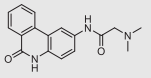
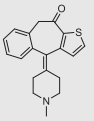
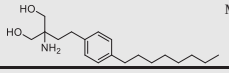
The iron chelator deferiprone is important for improving iron overload in the substantia nigra and CSF. There are preclinical studies demonstrating that deferiprone appears to correlate with the activity of ceruloplasmin in the treatment of PD. Ceruloplasmin plays a key role in iron accumulation, and the lower its activity, the more pronounced the role that Deferiprone plays. In a clinical trial, researchers utilized the Unified Parkinson's Disease Rating Scale (UPDRS) to assess the degree of dyskinesia in patients with PD and simultaneously tested for markers of ferroptosis in CSF and substantia nigra. MRI images of the group of PD patients who received daily oral liquid deferiprone showed substantially lower iron levels in CSF and substantia nigra after 6 and 12 months compared to placebo controls. GPX, the marker of antagonistic ferroptosis in CSF, increased from 27 to 35 U/L with a concomitant decrease in plasma. At the same time, patients in the deferiprone group had a mean reduction in UPDRS score of 1.1, which indicated improved exercise capacity. However, during the trial period, more severe hematologic disorders were seen in PD patients in the deferiprone group, including one case of granulocyte deficiency (2.5%) and two cases of neutropenia (5%). Therefore, the safety of deferiprone for clinical use needs to be more closely evaluated (NCT00943748). The antioxidant coenzyme Q has also been subjected to a clinical trial in a population of PD patients. Compared to iron chelators, coenzyme Q demonstrated excellent safety and tolerability in the trial, with patients experiencing only minor adverse effects that occurred at a rate not significantly different from that of the placebo group. It worked best at a high dose of 1200 mg/day, as evidenced by a dramatic reduction in UPDRS scores (NCT00004731). The adverse effects of long-term high-dose administration still need to be studied in greater depth. In another clinical trial sponsored by the National University Hospital of Singapore, coenzyme Q was

Table 3 Small molecule compounds targeting regulated cell deaths (RCDs) in neurodegenerative diseases (NDs).

Compound	SMILES	Structure	Type of neurodegenerative diseases (NDs)	Animal or cell type	Effect on regulated cell deaths (RCDs)	Target protein or signaling pathways	Ref.
Salidroside	OC(C=C1)=CC=C1CCO[C@H]2[C@H](O)[C@@H](O)[C@H](O)[C@@H](CO)O2		Alzheimer's disease (AD)	SAMP8 mice	Inhibit ferroptosis	NRF2, GPX4	229
Eriodictyol	O=C1CC(C2=CC=C(O)C(O)=C2)OC3=C1C(O)=CC(O)=C3		AD	*App*/*ps1* mice, HT-22 cells	Inhibit ferroptosis	NRF2, HO-1	231
Avi	OC1=CC(C2=C(O[C@@H]3O[C@@H](CO)[C@H](O)[C@H]3O)C(C(C(O)=CC(O)=C4)=C4O2)=O)=CC=C1O		AD	*App*/*ps1* mice, SH-SY5Y cells	Inhibit ferroptosis	NOX4, NRF2	232
Senegenin	O=C(O)C12CCC(C)(C)CC1C3=C(C(CCC4C5(C)CC(O)C(O)C4(C(O)=O)C)(C)C5CC3CCl)CC2		AD	PC12 cells	Inhibit ferroptosis	ACSL4, PEBP1, GPX4	233
TSG	OC1=CC(O)=C(O[C@H]2[C@@H]([C@H]([C@@H]([C@@H](CO)O2)O)O)O)C(C=CC3=CC=C(O)C=C3)=C1		AD	*App*/*ps1* mice	Inhibit ferroptosis	NLPR3, ACSL4, DMT1, NCOA4	234
α-Lipoic acid	O=C(O)CCCCC1SSCC1		AD	*TgTau*(*P301S*) mice	Inhibit ferroptosis	Tau	20
OABL	CC1=C([C@H](CCCOC(C)=O)C)[C@@H](OC(C)=O)[C@H]2[C@H](OC(C2=C)=O)C1		AD	5×FAD mice	Inhibit ferroptosis	GSH, MDA, SOD	235
GW7647	O=C(N(CCCCC1CCCCC1)CCC2=CC=C(SC(C)(C)C(O)=O)C=C2)NC3CCCCC3		AD	*App*/*ps1* mice, *APPsw*/SH-SY5Y cells	Inhibit ferroptosis	PPARα, GPX4	236
Olaparib	O=C1C2=CC=CC=C2C(CC3=CC(C(N4CCN(CC4)C(C5CC5)=O)=O)=C(C=C3)F)=NN1		AD	*Drosophila* models	Inhibit parthanatos	PARP1	21
MC2050	O=C1NC(SCN2CCN(C3=NC=CC=C3)CC2)=NC4=CC=CC=C41		AD	*Drosophila* models	Inhibit parthanatos	PARP1	21
GSK-872	CC(S(C1=CC2=C(N=CC=C2NC3=CC4=C(C=C3)SC=N4)C=C1)(=O)=O)C		AD	Wild-type (WT) C57BL/6J male mice	Inhibit necroptosis	RIPK3	134

SZM679	FC(F)(F)OC1=CC=CC(CC(NC2=C(F)C=CC(OC3=C(F)C=C(N=C(NC(C4CC(C4)=O)=O)S5)C5=C3)=C2)=O)=C1		AD	HT-29 cells/C57 mice	Inhibit necroptosis	RIPK1	22
Eda	O=C1N(C2=CC=CC=C2)N=C(C)C1		AD	5×FAD mice/SH-SY5Y cell lines	Inhibit necroptosis	P62, RIPK1/RIPK3/MLKL	237
STE	O=C1C=C(C2=CC=C(O)C=C2)OC3=C(C4=CC(C5=CC(C6=C(O)C=C(O)C=C6O5)=O)=CC=C4O)C(O)=CC(O)=C13		AD, Parkinson's disease (PD)	HT-22 cells	Inhibit autophagic cell death	PI3K, AKT, mTOR	238
Clioquinol	ClC1=CC(I)=C(O)C2=NC=CC=C12		AD	–	Inhibit cuproptosis	Cu	239
Clau	CN1C([C@@H](O)[C@H](C2=CC=CC=C2)[C@]1([H])[C@H](O)C3=CC=CC=C3)=O		PD	MPTP/C57BL/6 mice	Inhibit ferroptosis	PKCα, ALOX5	240
ThA	OC1=CC(O[C@H](O2)[C@H](O)[C@H](OC(C3=CC(O)=C(O)C(O)=C3)=O)[C@H](OC(C4=CC(O)=C(O)C(O)=C4C5=C(O)C(O)=C(O)C=C56)=O)[C@H]2COC6=O)=CC(O)=C1C(CCC7=CC=CC=C7)=O		PD	6-OHDA/zebrafish	Inhibit ferroptosis	KEAP1, NRF2, P62/SQSTM1	241
Hinokitiol	CC(C(C=C1O)=CC=CC1=O)C		PD	6-OHDA/PC12 cell lines	Inhibit ferroptosis	GPX4, NRF2, SLC7A11	242
HPPE	FC(F)(F)C1=CC(N=C(NC2=NC(C=CC(C(NCCOCCO)=O)=C3)=C3N2C)S4)=C4C=C1		PD	MPTP mice	Inhibit ferroptosis	BACH1–NRF2	243
Triacsin C	CCC/C=C/C/C=C/C=C/C=NNN=O		PD	MPP cells	Inhibit ferroptosis	ACSL4	244
Veliparib	O=C(N)C1=C2C(N=C([C@@]3(C)CCCN3)N2)=CC=C1		PD, Amyotrophic Lateral Sclerosis (ALS)	Rotenone-treated dopaminer	Inhibit parthanatos	PARP1, TFEB, NLRP3	245

NSA	O=C(/C=C/C1=CC=C([N+](=O)[O-])S1)NC(C=C2)=CC=C2S(NC3=NC=CN=C3OC)(=O)=O		PD	subacute MPTP mice	Inhibit necroptosis	MLKL, proinflammatory molecules	246
Pazopanib	CN(C1=CC=NC(NC2=CC=C(C(S(N)(=O)=O)=C2)C)=N1)C3=CC4=NN(C(C)=C4C=C3)C		PD	Adult male albino Wistar rats	Inhibit necroptosis	RIPK1/RIPK3/MLKL, Caspase8	247
Carveol	C=C(C)C1CC(O)C(C)=CC1		PD	Male albino mice	Inhibit pyroptosis	NRF2	23
BHB	CC(O)CC(O)=O		PD	C57BL/6 mice	Inhibit pyroptosis	STAT3, NLRP3, GSDMD	248
Baohuoside I	OC1=C(C(C=C(C)/C)C2=C(C(C(O[C@@H]3O[C@@H](C)[C@H](O)[C@@H](O)[C@H]3O)=C(C4=CC=C(OC)C=C4)O2)=O)C(O)=C1		PD	C57BL/6 mice	Inhibit pyroptosis	NFκB, NLRP3, ASC, Caspase1	249
Necrostatin-1	O=C(N1C)C(NC1=S)CC2=CNC3=C2C=CC=C3		PD	PC12 cells	Inhibit autophagic cell death	BCL2	131
6b	O=C(C1=CC=CC=N1)NC2=CC=CC(CCN3CCN(C4=CC=CC=C4)CC3)=C2		PD	SH-SY5Y cells	Inhibit autophagic cell death	AKT	250
O-Methylpara-cannabidiolquinone	CC1=C[C@@H](C2=C(OC)C(C(CCCC)=CC2=O)=O)[C@H](C(C)=C)CC1		AD, Huntington's disease (HD), Multiple sclerosis (MS)	HaCaT cell line	Inhibit ferroptosis	BACH1–NRFf2	251
MIND4	O=[N+]([O-])C1=C2C=CC=NC2=C(C=C1)SC3=NN=C(N3C4=CC=CC=C4)COC5=CC=CC=C5		HD	Rat embryonic striatal ST14A cells	Inhibit ferroptosis	NRF2	252
SIH	O=C(C1=CC=NC=C1)NN=CC2=CC=CC=C2O		ALS	*Sod1*(*G37R*) mice	Inhibit ferroptosis	GPX4, NRF2	253
VAR10303	OC1=C(N=CC=C2)C2=C(CCN(CC#C)C)C=C1		ALS	*Sod1*(*G93A*) mice	Inhibit ferroptosis	GPX4, NRF2, PGC1α	254
HBX	OC1=CC=CC=C1C2=NC3=CC=CC=C3O2		ALS	*Sod1(G93A)* mice	Inhibit ferroptosis	GPX4, NRF2	255
SAR443820	N#CC1=C2C(CN(C(C(C)(C)C)C(F)F)=O)CCO2)=CN=C1		ALS, MS	–	Inhibit necroptosis	RIPK1	256

n-BP	O=C1OC(C2=C1C=CC=C2)=CCCC		ALS	NSC34 cells, *SOD1*(*G93A*) mice	Inhibit autophagic cell death	ATG1, ATG5, mTOR	259
Trientine	NCCNCCNCCN		ALS	*Sod1*(*G93A*) mice	Inhibit cuproptosis	Cu^{2+}	24
Dabrafenib	CC(C)(C1=NC(C2=C(C(NS(=O)(C3=C(C=CC=C3F)F)=O)=CC=C2)F)=C(C4=NC(N)=NC=C4)S1)C		MS	C57BL/6 mice	Inhibit ferroptosis	AXL	260
UAMC-3203	O=S(C1=CC=C(C(NCC2=CC=CC=C2)=C1)NC3CCCCC3)(NCCN4CCNCC4)=O		MS	Biozzi ABH mice	Inhibit ferroptosis	GPX4	191
PJ34	O=C(CN(C)C)NC1=CC(C(C=CC=C2)=C2C(N3)=O)=C3C=C1		MS	C57BL/6 mice	Inhibit parthanatos	NFκB	261
Ketotifen	CN1CC/C(C1)=C2C3=C(C(CC4=CC=CC=C/24)=O)SC=C3		MS	C57BL/6 mice	Inhibit pyroptosis	NLPR3	263
Fingolimod	CCCCCCCCC1=CC=C(C=C1)CCC(CO)(CO)N		MS	–	Inhibit pyroptosis	NLRP3	264

used at a dose of 2400 mg/day in patients with PD. However, no results or updates from this trial were reported (NCT01892176).

6.3. *Clinical trials of non-apoptotic RCDs inhibitors in HD*

CBD has been shown in preclinical studies to alleviate ferroptosis in the treatment of HD *via* the Bach1/NRF2 pathway. In one clinical trial, HD patients were orally administered Sativex, a botanical extract containing delta-9-tetrahydrocannabinol (THC) and CBD, and a placebo served as a control. During 12 weeks of continuous treatment, the researchers assessed motor, cognitive, behavioral, and functional aspects of HD patients using the Unified Huntington's Disease Rating Scale (UHDRS) score. The results showed that patients in the test group did not show significant changes in their UHDRS scores. In terms of tolerability, there was one case of hematologic disease in each of the trial and placebo groups, which was considered acceptable. The difference in efficacy from the preclinical assessment may be due to the absence of treatment with CBD alone, which provides a potential direction for subsequent clinical trials. Alternatively, future designs may need to consider longer treatment periods and higher doses (NCT01502046).

6.4. *Clinical trials of non-apoptotic RCDs inhibitors in ALS*

SAR443820, a RIPK1 inhibitor with high brain permeability, was recognized as a neuroprotective agent for inhibiting necroptosis in preclinical studies in ALS. In a clinical trial of up to 110 weeks, SAR443820 demonstrated a favorable safety and tolerability profile, but did not show superior efficacy, possibly due to dose limitations. The ALS Functional Rating Scale-Revised (ALSFRS-R) is used to assess the functional status of patients with ALS. After 24 weeks of treatment, ALSFRS-R scores increased by 6.1 in the oral tablet SAR443820 group, but were only 0.2 higher than in the placebo group in a cross-sectional comparison. There was still no outstanding efficacy demonstrated at the 52-, 76-, and 104-week tests. The same results were reflected in tests of muscle strength, which may suggest that SAR443820 did not significantly improve symptoms in ALS patients. It is worth noting that although the most serious adverse reaction seen in the SAR443820 group was elevated liver enzymes (3.8%, $n = 79$), this statistic only included patients who completed the trial. However, there were a number of patients who withdrew early during the clinical trial due to other adverse reactions, and these data were not included in the final statistics. Therefore, a more rigorous safety and tolerability assessment is still needed for a larger dose of SAR443820 (NCT05237284).

6.5. *Clinical trials of non-apoptotic RCDs inhibitors in MS*

Fingolimod has been approved by the FDA for the treatment of RRMS, and in the previous summary, there have been preclinical studies demonstrating that the mechanism of action is inhibition of NLRP3 activation and thus pyroptosis. Several clinical studies have been conducted to evaluate the efficacy and safety of Fingolimod, including one trial using Fingolimod and placebo and ultimately assessed using the Annualized Relapse Rate (ARR). The results showed a significant reduction in ARR in the Fingolimod group compared to the placebo group at 24 and 54 months, with a reduction in the number of lesions observed by MRI. Interestingly, patients in the placebo group experienced a substantial reduction in the number of lesions with the use of 0.5 mg/day of Fingolimod in the later stages of the trial, reflecting the effectiveness of Fingolimod. The percentage of participants who were relapse-free by the end of the trial was also at least 14.76% higher than in the placebo group. In terms of adverse reactions, hematologic, vascular, psychiatric, and cardiac adverse reactions were predominant in the 1.25 mg/day Fingolimod group.

Table 4 Clinical trials of small molecule compounds targeting regulated cell deaths (RCDs) in neurodegenerative diseases (NDs).

Drug	Sponsor	Treatment	Disease	Phase	Status	Adverse reaction	Response	NCT Identifier
α-Lipoic acid	National Institute on Aging	Vitamin E, Vitamin C, α-lipoic acid, and coenzyme Q	Alzheimer's disease (AD)	Phase I	Completed	Adverse events occur independently of the drug	ADCS-ADL, MMSE mean scores reduction ($n = 28$)	NCT00117403
	Oregon Health and Science University	α-Lipoic acid and omega-3 fatty acids	AD	Phase I/II	Completed	Cardiac disorders (5.88%), gastrointestinal disorders (5.88%), nervous system disorders (8.82%)	Mean ADCS-ADL scores were equal to controls, and mean ADCS-cog scores were higher than controls ($n = 24$)	NCT01058941
Coenzyme Q	National Institute on Aging	Coenzyme Q	AD	Phase I	Completed	Adverse events occur independently of the drug	ADCS-ADL, MMSE mean scores equal to controls ($n = 25$)	NCT00117403
Eda	Treeway B.V.	Eda	AD	Phase II	Completed	–	–	NCT05323812
CBD	Sunnybrook Health Sciences Centre	CBD	AD	Phase II	Recruiting	–	–	NCT06014424
	Mclean Hospital	CBD and THC	AD	Early Phase I	Recruiting	–	–	NCT04075435
	University of Colorado	CBD	AD	Phase II	Recruiting	–	–	NCT05822362
Deferiprone	University Hospital, Lille	Deferiprone	Parkinson's disease (PD)	Phase II/III	Completed	Granulocyte deficiency (2.5%), neutropenia (5%), transient diarrhea (7.5%), transient headache (2.5%)	Decreased levels of iron in the substantia nigra and CSF and elevated levels of antioxidant markers and anti-ferroptosis markers. Decrease by 1.1 in the mean score of UPDRS ($n = 40$)	NCT00943748
Coenzyme Q	National Institute of Neurological Disorders and Stroke	Coenzyme Q	PD	Phase II	Completed	Adverse events occur independently of the drug	Mean UPDRS scores decreased by 3.18 in the 300 mg/d group ($n = 21$) and 5.3 in the 1200 mg/d group ($n = 23$)	NCT00004731
	National University Hospital, Singapore	Coenzyme Q	PD	Phase II/III	Completed	–	–	NCT01892176

CBD	Fundacion para la Investigacion Biomedica del Hospital Universitario Ramon y Cajal	CBD and THC	Huntington's disease (HD)	PhaseII	Completed	Dizziness and disturbance in attention (16%), self-limited microcytic anemia (8.3%)	UHDRS mean scores equal to controls ($n = 24$)	NCT01502046
SAR443820	Sanofi	Itraconazole, Erythromycin ethyl succinate, and SAR443820	Amyotrophic lateral sclerosis (ALS)	Phase I	Completed	–	–	NCT05797753
	Sanofi	SAR443820	ALS	Phase I	Completed	–	–	NCT05797701
	Sanofi	SAR443820	ALS	Phase I	Completed	–	–	NCT05795907
	Sanofi	SAR443820	ALS	Phase II	Completed	Elevated liver enzymes (3.8%), anemia (0.74%), cardiac disorders (0.96%), gastrointestinal disorders (1.54%)	ALSFRS-R and CAFS mean scores were equal to controls, with no significant change in muscle strength ($n = 84$)	NCT05237284
n-BP	Everfront Biotech Co., Ltd.	*n*-BP	ALS	Phase I	Active, not recruiting	–	–	NCT03651349
SAR443820	Sanofi	SAR443820	Multiple sclerosis (MS)	Phase I	Completed	–	–	NCT04982991
	Sanofi	SAR443820	MS	Phase II	Terminated	–	–	NCT05630547
Fingolimod	Novartis	Fingolimod	MS	Observational	Completed	–	–	NCT01281657
	Novartis	Fingolimod	MS	Phase III	Completed	Lymphopenia (8%), elevated alanine aminotransferase (8%), hypertension (9%), AV block (5%)	Reduced ARR, slower growth in the number of lesions, and a lower percentage of participants without recurrence ($n = 523$)	NCT00355134

Overall, adverse reactions occurred at a low rate and were not persistent, reflecting the good tolerability of Fingolimod (NCT00355134).

Overall, there is limited clinical trial data on small molecule compounds related to targeting RCDs for the treatment of NDs, and many of the completed clinical trials have not published results. Most importantly, the mechanism of action of the compounds is generally not emphasized in clinical trials, and we hope that future studies will complement these types of compound trials in order to provide additional direction for the treatment of NDs (Table 4).

7. Conclusions and future perspectives

Recent neurobiological advancements highlight the importance of non-apoptotic RCD pathways in NDs. These include ferroptosis, pyroptosis, necroptosis, parthanatos, and others, each characterized by unique biochemical and molecular mechanisms. For instance, ferroptosis involves lipid peroxidation mediated by iron-dependent pathways, while pyroptosis is driven by inflammasome activation and gasdermin-mediated membrane pore formation. These non-apoptotic RCDs contribute to the progression of chronic NDs such as AD and PD. In contrast, cell death in acute NDs like cerebral ischemia, brain injury, and epilepsy typically involves non-regulated cell death. This review comprehensively addresses neuronal death mediation and crosstalk mechanisms among non-apoptotic RCDs, emphasizing their interplay with NDs pathophysiology. Furthermore, emerging therapeutic strategies targeting these pathways enable innovative treatments.

The intricate crosstalk among non-apoptotic RCD pathways in NDs highlights their pivotal roles in driving neuronal loss and disease progression. Several key molecular hubs, such as ATG7, GBA1, and NLRP3, orchestrate the crosstalk among various non-apoptotic RCDs. They achieve this by modulating critical cellular processes, including organelle dynamics, metal homeostasis, and inflammatory signaling. Targeting these hubs, such as enhancing TFEB-mediated lysosomal function to mitigate ferroptosis or inhibiting NLRP3−cGAS−STING1 crosstalk to balance pyroptosis and necroptosis, offers promising therapeutic avenues. In addition, therapeutic strategies targeting these RCD pathways have gained traction, with several small molecule inhibitors showing promise in preclinical studies and clinical trials. Ferroptosis inhibitors, such as α-lipoic acid, necroptosis inhibitors like necrostatins, and PARP1 inhibitors, including Olaparib, represent some of the most advanced efforts. Drugs already on the market, such as Olaparib and clioquinol, originally developed to treat other diseases, have recently been discovered to target RCDs for treating NDs. Besides, metformin and trazodone, although their mechanisms do not specifically target RCDs, have recently been found to hold potential for treating NDs[264,265]. This phenomenon of repurposing existing drugs can significantly shorten the development cycle and offers high safety, potentially making it a highly advantageous research direction. The complexity of NDs has also led to the exploration of combination therapies, which aim to modulate multiple RCD pathways simultaneously. Such approaches are emerging as powerful tools to address the multifactorial nature of neurodegeneration, potentially improving therapeutic outcomes.

Despite these advances, significant challenges remain. The lack of reliable biomarkers for monitoring RCD activity in clinical settings hinders both diagnosis and therapeutic evaluation. Translational success is limited by factors such as poor blood−brain barrier permeability of therapeutic agents and off-target effects. Additionally, the temporal and spatial specificity of RCD activation in the brain remains underexplored, leaving gaps in our understanding of when and where these pathways dominate during disease progression. Future research should prioritize the development of highly specific inhibitors with improved blood−brain barrier permeability. Structure-based drug design and AI-driven approaches hold promise for accelerating this process. Given the interplay between RCD pathways, combinatorial therapeutic approaches that target multiple mechanisms simultaneously could yield superior clinical outcomes. For example, combining ferroptosis and pyroptosis inhibitors may address overlapping inflammatory and oxidative stress processes. Advances in proteomics and metabolomics should also be leveraged to identify reliable biomarkers capable of monitoring RCD activity and therapeutic responses in real time. Developing more physiologically relevant models, such as organoids or humanized animal models, will enhance translational research, while investigating the temporal dynamics of RCD activation across different stages of NDs could inform stage-specific therapeutic interventions. Certain protein aggregates may be by-products of cellular stress responses or play a protective role against cell death under specific circumstances. For example, in the conventional perception, Aβ accumulation is one of the major pathological hallmarks of AD and plays an important role in its pathogenesis. Novel evidence suggests that small amounts of Aβ aggregation may have antimicrobial and immune-enhancing effects and promote recovery after brain injury[266,267]. The same is true for Tau proteins, which attenuate neuronal damage induced by excess ROS or free radicals and promote healthy aging[225]. These examples may weaken the causal relationship between some traditionally considered pathogenic proteins and NDs, thereby elevating the difficulty of designing inhibitors for NDs. Consequently, targeting RCD while rationally preserving the protective effects caused by these protein aggregates becomes a future direction of drug design research.

Nanoparticles possess significant therapeutic potential for targeting RCD, particularly in precision interventions for disease models[268]. Their core strength lies in delivering drugs or nucleic acids and directly modulating signaling pathways, thereby mitigating side effects and enhancing efficacy[269]. Nanoparticles have demonstrated excellent BBB penetration in the delivery of therapeutic NDs, *e.g.*, PEG-PLL polymeric nano systems carry monoclonal antibodies targeting degradation of Aβ[270], PDMAEMA carries siRNA for silencing of BACE1[271], and PEI carries siRNA for silencing of α-syn[272]. Recently, nanoparticles have demonstrated the potential for targeting RCDs. β-LG nanoparticles were developed to deliver disulfiram to target cellular pyroptosis in brain injury, effectively inhibiting the release of inflammatory factors[269]. However, the mechanism of nanoparticle diffusion in CSF remains unclear. Currently, nanoparticles modulating RCDs are primarily used in antitumor therapy. In contrast, treating NDs often requires curtailing neuronal cell death, which opposes tumor therapy approaches. Nonetheless, nanoparticles enhance targeting and BBB penetration while reducing toxic side effects, and their potential to modulate RCDs in NDs is significant. Fusion protein technology, exemplified by fusing brain-targeted peptides with RCD-targeted small molecule compounds, demonstrates extraordinary potential in drug delivery. Engineered cytokines (*e.g.*, modified IL-10 or TGFβ) can be targeted to reduce pro-inflammatory factors (TNFα, IL-1β), thereby

blocking key necroptosis and pyroptosis pathways. These fusion proteins and engineered cytokines provide a novel strategy for treating NDs by precisely intervening in neuroinflammation, delivering neurotrophic factors, and directly inhibiting cell death pathways, potentially leading to important breakthroughs. Besides engineered cytokines, certain cytokines with radioprotective effects also ameliorate NDs. Radiation can trigger ferroptosis through radiolysis of cellular water and stimulation of oxidative enzymes to produce ROS such as oxygen free radicals and hydrogen peroxide[273]. Radiation can also trigger autophagic cell death, necroptosis, and pyroptosis through other complex mechanisms[274]. These radioprotective cytokines attenuate tissue damage from ionizing radiation by modulating cellular stress responses, DNA repair mechanisms, and antioxidant pathways. However, over-reliance on cytokines may accelerate certain death pathways (*e.g.*, TGF-β promotes glial cell activation and exacerbates inflammation in late-stage AD), and thus precise cytokine regulation is needed, which may become a new strategy for targeting both radiation damage and NDs.

In addition to the non-apoptotic RCDs mentioned in the text, a number of novel RCDs have recently been reported, which deserve to be explored for their association with neurodegenerative phenotypes. For example, triaptosis, a new type of RCD, has recently been reported. The precursor of vitamin K, menadione, was found to directly oxidize the essential cysteine residue on VPS34, thereby triggering triaptosis to mitigate prostate cancer progression. Consequently, in NDs, certain antioxidants may possess the potential for an opposite effect—targeting triaptosis to reduce neuronal death[275,276]. More than one novel oxidation-related RCD has demonstrated therapeutic potential for NDs. Oxeiptosis is induced by pathologic accumulation of intracellular ROS through the ROS receptor KEAP1, pro-apoptotic factor apoptosis-inducing factor mitochondria-associated 1, and the PGAM5-mediated caspase-independent RCD pathway. Critical oxidative stress processes in NDs suggest therapeutic potential for inhibiting oxeiptosis[277]. In addition, there is ammonium-induced death (AID), which has recently entered the researcher's field of vision. Ammonia accumulation was found to cause lysosomal and mitochondrial damage and lead to cell death based on effector T cells, accompanied by mitochondrial swelling. In liver failure, hyperammonemia inevitably develops, destroying astrocytes and other neuronal cells *via* AID, leading to hepatic encephalopathy. Considering the symptoms shared by hepatic encephalopathy and NDs, it implies our therapeutic potential to inhibit AID[278]. Entotic cell death is a form of cell death triggered by the invasion of adjacent cells, relying on intercellular adhesion molecules and cytoskeletal reorganization. The prolonged entotic cell death process is accompanied by the activation of inflammatory microglia and astrocytes. In aging or diseased neurons, impaired lysosomal function may lead to the accumulation of incompletely degraded entotic cell debris, forming "cellular remnants" that further activate inflammation. However, whether entotic cell death is a cause or consequence of NDs remains controversial, as it may merely represent a concomitant phenomenon of disease progression[279].

Non-apoptotic RCD pathways represent a double-edged sword in NDs, offering insights into disease mechanisms while posing therapeutic challenges. This review underscores the need for an integrative approach to understanding these pathways, emphasizing the development of targeted and combinatorial therapies. By addressing current limitations—including biomarker discovery, specificity of inhibitors, and temporal mapping—future research can unlock the full therapeutic potential of modulating RCDs in neurodegeneration.

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Author contributions

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used DeepL Write AI translation to polish some sentences. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflicts of interest

The authors declared no conflicts of interest.

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