



Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

Structures and functions of the MICOS: Pathogenesis and therapeutic implications in Alzheimer's disease



Zihan Wang^a, Kaige Zhang^a, Minghao Huang^a, Dehao Shang^a,
Xiaomin He^a, Zhou Wu^{b,c}, Xu Yan^{d,*}, Xinwen Zhang^{a,e,*}

^aDepartment of Oral Implantology, School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002, China

^bDepartment of Aging Science and Pharmacology, Faculty of Dental Science, Kyushu University, Fukuoka 812-8582, Japan

^cOBT Research Center, Faculty of Dental Science, Kyushu University, Fukuoka 812-8582, Japan

^dThe VIP Department, School and Hospital of Stomatology, China Medical University, Liaoning Provincial Key Laboratory of Oral Diseases, Shenyang 110002, China

^eLaboratory Animal Centre, School and Hospital of Stomatology, China Medical University, Shenyang 110002, China

Received 5 August 2024; received in revised form 30 November 2024; accepted 20 December 2024

KEY WORDS

Alzheimer's disease;
Mitochondria;
Cristae junctions;
MICOS complex;
MIC60;
MIC10;
CHCHD10;
CHCHD2

Abstract Mitochondrial dysfunction is a critical factor in the pathogenesis of Alzheimer's disease (AD). The mitochondrial contact site and cristae organizing system (MICOS) plays a pivotal role in shaping the inner mitochondrial membrane, forming cristae junctions and establishing interaction sites between the inner and outer mitochondrial membranes and thereby serving as a cornerstone of mitochondrial structure and function. In the past decade, MICOS abnormalities have been extensively linked to AD pathogenesis. In particular, dysregulated expression of MICOS subunits and mutations in MICOS-related genes have been identified in AD, often in association with hallmark pathological features such as amyloid- β plaque accumulation, neurofibrillary tangle formation, and neuronal apoptosis. Furthermore, MICOS subunits interact with several etiologically relevant proteins, significantly influencing AD progression. The intricate crosstalk between these proteins and MICOS subunits underscores the relevance of MICOS dysfunction in AD. Therapeutic strategies targeting MICOS subunits or their interacting

*Corresponding authors.

E-mail addresses: zhangxinwen@cmu.edu.cn (Xinwen Zhang), xyan@cmu.edu.cn (Xu Yan).

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

<https://doi.org/10.1016/j.apsb.2025.04.019>

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proteins may offer novel approaches for AD treatment. In the present review, we introduce current understanding of MICOS structures and functions, highlight MICOS pathogenesis in AD, and summarize the available MICOS-targeting drugs potentially useful for AD.

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1. Introduction

Alzheimer's disease (AD) is characterized by the neuronal accumulation of neurofibrillary tangles and amyloid- β (A β) plaques. Its hallmark symptoms include progressive cognitive impairment and severe neurobehavioral disturbances¹. AD accounts for nearly 80% of dementia cases worldwide and is estimated to affect approximately 50 million people globally, a number projected to triple by 2050^{1,2}.

Mitochondria are maternally inherited organelles essential for multiple cellular functions, including energy metabolism, second messenger signaling, and programmed cell death^{3,4}. Proper mitochondrial function depends on the integrity of the mitochondrial membrane and the dynamic regulation of inner membrane cristae. Structural defects in these components contribute to severe human diseases, including AD⁵. Mitochondrial abnormalities are now widely recognized as a fundamental aspect of AD pathology, with increasing evidence indicating mitochondrial dysfunction in the brains of AD patients^{1,6-8}. Consequently, therapeutic strategies aimed at restoring mitochondrial function may offer potential avenues for alleviating or even curing AD.

Localized to cristae junctions (CJs), the mitochondrial contact site and cristae organizing system (MICOS) functions as a conserved multi-subunit complex and is crucial for maintaining the normal architecture and function of mitochondria in multiple diseases including neurodegenerative diseases like AD, cancer, liver disease, Barth syndrome, obesity, insulin resistance and diabetes mellitus⁹⁻¹⁹. In the last decade, emerging evidence has indicated a non-negligible role of MICOS in AD pathogenesis (Fig. 1). A circular regulatory mechanism has been identified between MIC25 and amyloid precursor protein (APP) processing, in which APP processing promotes A β peptide production while inhibiting MIC25 expression¹⁹. Reduced MIC60 levels and epigenetic modifications affecting MIC60 expression have been observed in both AD patients and AD mouse models²⁰⁻²⁵. Furthermore, multiple mutations in the mitochondrial proteins CHCHD2 and CHCHD10 have been detected in AD²⁶⁻²⁹. Several disease-associated proteins, including heme-binding protein 1 (HEBP1)³⁰, the microprotein SHMOOSE³¹, and TOMM40 and TOMM22³², have been shown to interact with MIC60 and to thereby play crucial roles in AD progression through their associations with MICOS (Fig. 2). In addition, CHCHD10 accumulates and colocalizes with transactive response DNA-binding protein 43 (TDP-43) inclusions in AD-affected brains, suggesting that CHCHD10 mutations may influence AD progression *via* TDP-43³³. Emerging evidence also suggests potential links of MICOS with tau pathology, as well as with mitochondrial quality control mechanisms, particularly mitophagy.

Collectively, these findings stress that the MICOS complex, the essential structural and functional cornerstone of mitochondria, bridges AD pathogenesis and mitochondria, the energy factory that fuels the nervous system. Here, we summarize the current

understanding of MICOS structure and function, explore its involvement in AD pathogenesis, and discuss MICOS-targeting drugs with potential therapeutic implications for AD.

2. The MICOS complex: Structures and functions

The MICOS complex plays a fundamental role in maintaining the architecture of the inner mitochondrial membrane, facilitating the formation of CJs and mediating interactions between the inner and outer mitochondrial membranes. As a result, it is essential for efficient mitochondrial respiration, quality control, lipid metabolism, protein import, and mitochondrial DNA inheritance³⁴. In humans, the MICOS complex comprises seven primary subunits: MIC60, MIC10, MIC25, MIC26, MIC19, MIC13, and MIC27^{5,35}. Additionally, CHCHD2 and CHCHD10 have been proposed as potential MICOS subunits in recent studies³⁶⁻³⁸. Each subunit is designated as MIC“X”, where “X” represents the molecular weight of the subunit in kDa^{34,35}. While MICOS composition varies across species⁵, MIC60 and MIC10 are evolutionarily conserved in all eukaryotic cells containing cristae-bearing mitochondria and are thus regarded as core components^{39,40}. Deletion of MIC10 or MIC60 results in significant structural alterations in cristae and severe mitochondrial dysfunction, whereas the absence of other subunits has less pronounced effects^{17,41,42}. In parallel with their central roles, the MICOS complex consists of two subcomplexes, namely, the MIC60/MIC19/MIC25 subcomplex and the MIC10/MIC13/MIC26/MIC27 subcomplex, with MIC13 serving as a bridging component between the two (Figs. 1 and 2)⁴³⁻⁴⁵.

2.1. The MIC60/MIC19/MIC25 subcomplex

MIC60 plays a dual role in shaping CJs and establishing interaction sites between the inner and outer mitochondrial membranes. Downregulation of MIC60 reshapes the inner membrane into interconnected concentric layers, leading to the loss of discernible CJs, impaired oxidative phosphorylation, elevated membrane potential, and increased reactive oxygen species (ROS) production^{32,46,47}. F₁F₀-ATP synthase is another critical regulator of cristae biogenesis, and MIC60 functions as its antagonist to determine cristae architecture^{47,48}. Additionally, MIC60 also interacts with SAM50 (TOB55) and TOB38, two core subunits of the sorting and assembly machinery (SAM) complex, thereby stabilizing CJs near the outer membrane⁴⁹. In mammals, the SAM complex and MICOS complex constitute a supercomplex known as the mitochondrial intermembrane space bridging complex, which is also involved in mediating mitochondrial contact sites⁵⁰⁻⁵². Notably, the SAM50–MIC19–MIC60 pathway dominates the assembly of the mitochondrial intermembrane space bridging super-complex⁵⁰. Furthermore, MIC60 participates in the import of mitochondrial proteins through its interaction with the translocase of the outer mitochondrial membrane (TOMM) complex, which serves as the

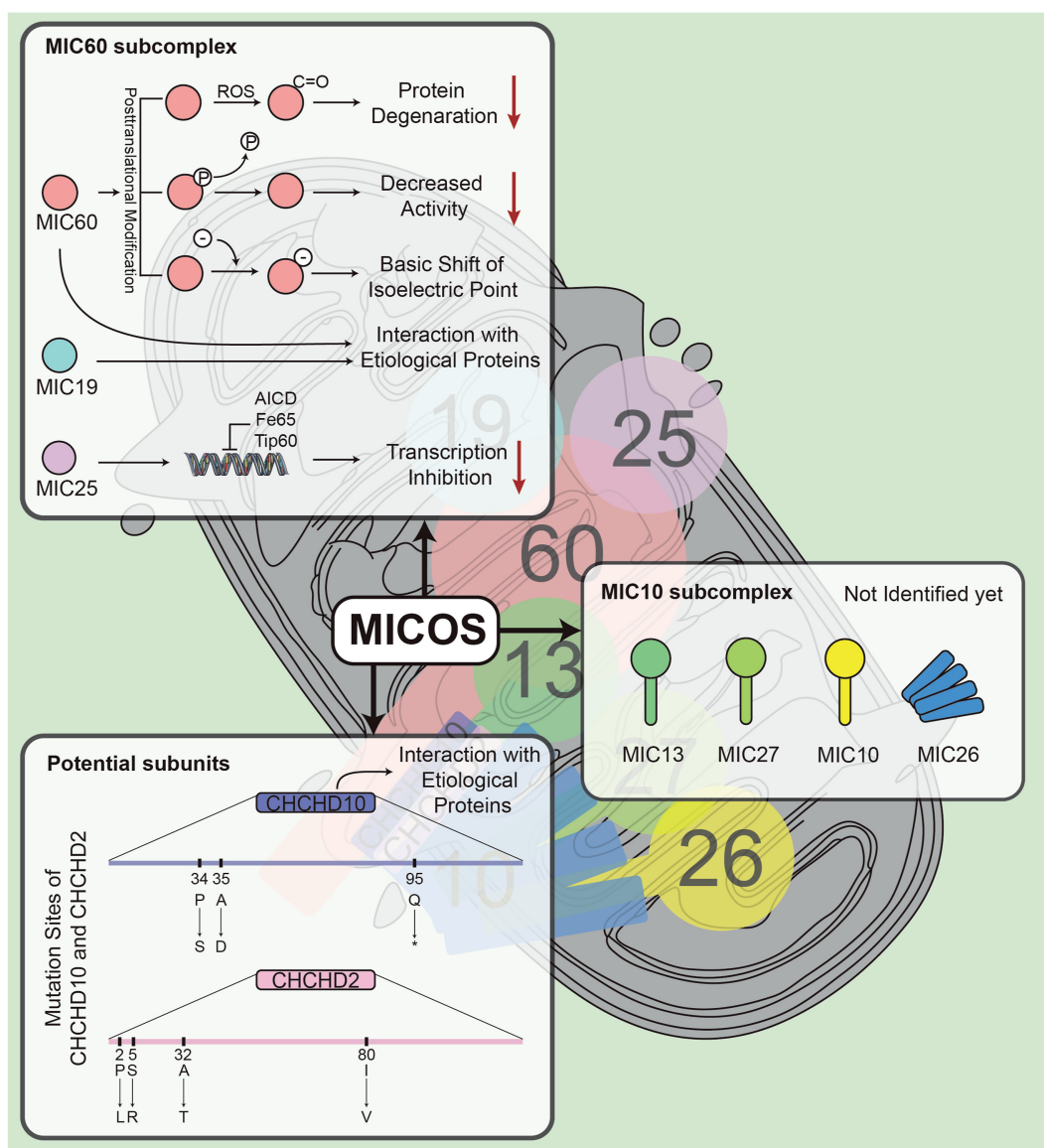


Figure 1 Alterations in MICOS subunits in AD. MIC60 subcomplex: post-translational modifications of MIC60, including increased carbonylation, decreased phosphorylation, and a basic shift in its isoelectric point, have been observed in AD. The transcription of MIC25 is inhibited by AICD, Fe65, and Tip60. Additionally, both MIC60 and MIC25 interact with disease-associated proteins, as detailed in Fig. 2. MIC10 subcomplex: no studies have reported the specific involvement of MIC13, MIC26, MIC27, or MIC10 in AD, highlighting an area for future investigation. Potential subunits: mutation sites in CHCHD10 and CHCHD2 are summarized. CHCHD10 also interacts with disease-associated proteins, as depicted in Fig. 2.

primary entry gateway for most mitochondrial precursor proteins^{32,50,51,53-55}.

MIC19, also known as CHCHD3, was initially identified as a substrate of cAMP-dependent protein kinase⁵⁶. By interacting with MIC60, MIC19 regulates the submitochondrial localization of MIC60, promotes its tetramerization, and preserves its membrane remodeling function^{18,41,45,57-60}. The MIC60/MIC19 subcomplex spans CJs as a molecular strut, a concept vividly illustrated by E. Werner in the CJ model⁶⁰. In mammals, MIC19 also functions as a “bridge” linking MIC60 and SAM50, forming the SAM50–MIC19–MIC60 axis, which is crucial for determining mitochondrial cristae architecture⁵⁰. Recently, the PERK–OGT axis, activated in response to cold stress, was reported to regulate cristae formation by inducing a post-

translational modification that modulates TOM70 activity during the import of MIC19. This finding highlights the role of MIC19 in cellular energetics and adaptive responses to stress conditions⁶¹.

MIC25, also known as CHCHD6, is a homolog of MIC19 (CHCHD3)⁵. Similar to MIC19, MIC25 interacts with MIC60 and SAM50⁵⁷. Although MIC19 (CHCHD3) and MIC25 (CHCHD6) are often regarded as twin proteins due to their similar molecular sizes and 36% sequence identity, further research is necessary to delineate their functional distinctions⁶².

2.2. The MIC10/MIC13/MIC26/MIC27 subcomplex

The MIC10 subcomplex consists of MIC10, MIC13, MIC26, and MIC27^{5,63,64}. In 2015, Barbot et al.⁶⁴ and Bohnert et al.¹⁷

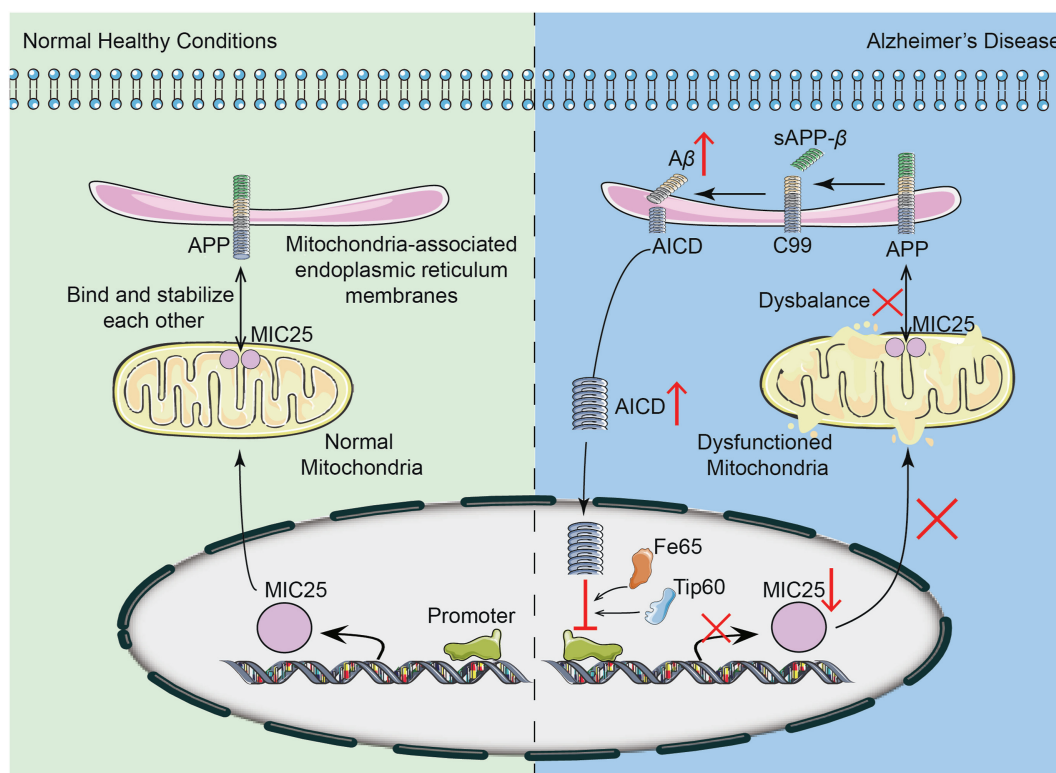


Figure 2 Interactors of the MICOS complex in AD and drugs targeting MICOS subunits. Solid arrows indicate physical interactions. MIC60 and MIC19 interact with SLC25A46, contributing to mitochondrial dynamics. MIC60 binds to TOM40/TOMM40 and TOM22/TOMM22, thereby influencing the mitochondrial accumulation of A β peptides. Decreased MIC60 levels release HEBP1 from mitochondria, increasing sensitivity to apoptosis triggers such as heme. MIC60 also binds to the microprotein SHMOOSE, which positively correlates with tau levels and counteracts A β pathology. Cardiolipin stabilizes MIC10 oligomers independently of MIC26 and MIC27. MIC10 binds to dimeric F₁F₀-ATP synthase, functioning as its interaction partner. Drugs targeting MICOS subunits are summarized in the right column, with their specific functions detailed in Table 2.

demonstrated that MIC10 is critical to the inner membrane curvature at CJs. MIC10 tends to form oligomers through a four-glycine motif, a structural feature initially identified in F₁F₀-ATP synthase^{17,65,66}. The conservation of glycine motifs in both MIC10 and F₁F₀-ATP synthase suggests a functional connection between these two proteins^{17,63,64}. The MICOS complex and oligomeric F₁F₀-ATP synthase represent two major cristae-shaping machineries, each localized at distinct sites within the mitochondrial inner membrane and associated with different membrane curvatures. However, their potential interaction has long been overlooked^{63,67-70}. Recent findings indicate that MIC10 directly binds to dimeric F₁F₀-ATP synthase and functions as its interacting partner, promoting inner membrane energization and facilitating respiratory growth^{63,67,68}. These observations suggest that the distinct roles of F₁F₀-ATP synthase and MICOS in mitochondrial function may necessitate direct physical interactions between MIC10 and ATP synthase. Thus, MIC10 serves dual roles in shaping the inner mitochondrial membrane and in regulating metabolic adaptation and respiratory growth, functions traditionally attributed to ATP synthase⁶³.

Within the MIC10 subcomplex, MIC26 and MIC27 regulate the oligomeric state of MIC10⁵. Notably, MIC27 stabilizes MIC10 oligomers, whereas MIC26 exerts a destabilizing effect^{5,17,43,71}. Cardiolipin (CL), a tetra-acylated diphosphatidylglycerol lipid, also plays a crucial role in stabilizing MIC10 oligomers independently of MIC26 and MIC27^{71,72}. The absence of both MIC27 and CL results in a more pronounced MIC10 oligomerization

defect⁷¹. MIC26 (also known as apolipoprotein O) and MIC27 (also known as apolipoprotein O-like) belong to the apolipoprotein O family and are believed to influence the lipid environment of the MICOS complex^{5,73,74}. MIC27 has been shown to bind CL *in vitro*; however, the effects of MIC26 and MIC27 on phospholipid regulation have yet to be demonstrated in organello^{5,73}.

MIC13 functions as a bridging component between the MIC10 and MIC60 subcomplexes through its interactions with MIC60 and MIC27, playing a fundamental role in MICOS integrity^{75,76}. Loss of MIC13 results in accumulation of the MIC60 subcomplex, destabilization of the MIC10 subcomplex, and, ultimately, MICOS disassembly, leading to CJ loss and the formation of concentric ring-like cristae^{44,76}. In addition to its structural role, MIC13 also contributes to the assembly of respiratory chain supercomplexes⁷⁵.

3. Circular loop of MIC25/CHCHD6 and APP processing in AD

Proteolysis of APP generates the neurotoxic A β peptide, a hallmark characteristic of AD^{19,77-79}. In 2018, an integrated proteomics study of postmortem brain tissue from 16 AD patients identified significant downregulation of MIC25 (CHCHD6) as a hub protein, revealing a previously unrecognized role of MIC25 in AD pathophysiology⁸⁰. Similarly, decreased MIC25 levels have been observed in AD cell and animal models, as well as in the hippocampus of AD patients^{19,81,82}.

However, the specific involvement of MIC25 in AD remained unclear until recent research demonstrated that MIC25 and APP form a regulatory feedback loop in neurons, with imbalances in this loop contributing to AD progression¹⁹. APP is primarily processed at mitochondria-associated endoplasmic reticulum membranes, whereas MIC25 is localized to the inner mitochondrial membrane^{5,83}. Under physiological conditions, MIC25 and APP stabilize each other¹⁹. In AD, the loss of MIC25 disrupts this balance, leading to enhanced APP processing at mitochondria-associated endoplasmic reticulum membranes and increased production of APP proteolytic fragments¹⁹. These fragments include the β -cleaved C-terminal fragment of APP (C99) and the APP intracellular domain (AICD)^{84–88}. The C99 fragment has been implicated in abnormal lipid homeostasis and has been shown to contribute to the accumulation of toxic cholesterol in the brain^{19,89,90}. Furthermore, elevated C99 levels correlate with cognitive impairment in AD patients⁸⁵. Meanwhile, AICD, in association with the cofactors Fe65 and Tip60, directly binds to the MIC25 promoter, downregulating MIC25 transcription and suppressing its activity¹⁹. Because MIC25 is essential for maintaining MICOS function, its depletion compromises cristae integrity, disrupts mitochondrial bioenergetics, and ultimately leads to neuronal death^{19,91}.

In summary, a circular feedback loop between MIC25 levels and APP processing has been established (Fig. 3). In AD neurons, reduced MIC25 expression enhances APP accumulation and accelerates its proteolysis, generating increased levels of neurotoxic products, including A β , AICD, and C99. In particular, AICD further suppresses MIC25 expression by binding to its promoter, exacerbating MIC25 depletion. This pathological cycle promotes mitochondrial dysfunction, neuronal cholesterol accumulation, amyloid pathology, and, ultimately, AD progression.

4. MIC60/mitofilin in AD

Abnormal protein phosphorylation, a major post-translational modification, is considered a key event in AD^{78,92}. Brain tissue from AD patients exhibits both decreased phosphorylation of MIC60 (also known as mitofilin) and reduced protein levels, suggesting an altered function of MIC60 in AD^{20,21}. In the hippocampus of Wistar rats injected with kainic acid, a neuroexcitotoxic and epileptogenic agent that induces A β aggregation and clinical symptoms resembling AD^{93,94}, MIC60 has been consistently found to undergo carbonylation, likely as a result of oxidative damage²⁴. Given the reported reduction in MIC60 phosphorylation in hippocampal specimens from AD patients, epigenetic modifications of MIC60 may be closely linked to AD pathogenesis²⁰. The slow Wallerian degeneration (*Wlds*) gene has neuroprotective effects in the central nervous system and is implicated in several neurodegenerative diseases, including AD^{95–97}. Notably, decreased MIC60 levels have been observed in isolated synaptic preparations from the striatum of *Wlds* mice, which exhibit the full *Wlds* phenotype²⁵. However, the relationship between *Wlds* and MIC60 in AD remains poorly understood and requires further investigation. The senescence-accelerated mouse prone 8 (SAMP8) strain, an AD mouse model derived from an AKR/J breeding colony^{98,99}, has also been used to study MIC60 alterations. In 6-month-old SAMP8 mice, MIC60 exists in four isoforms and demonstrates a consistent shift in isoelectric point compared to control SAMR1 mice, although no changes in total MIC60 protein levels have been detected²². Subsequent studies identified differential MIC60

expression in the hippocampus of 5-month-old and 15-month-old SAMP8 mice compared to age-matched SAMP1 mice²³. However, because no significant difference was observed between 5-month-old and 15-month-old SAMP8 mice, these findings suggest that genetic differences between SAMP8 and SAMP1 mice may underlie MIC60 variations rather than age-related changes²³.

Despite reports from AD patient samples and animal models suggesting a potential link between MIC60 and AD, the precise role of MIC60 in AD pathogenesis remains unclear. Nevertheless, emerging evidence indicates that MIC60 functions as a hub protein, interacting with multiple etiologically relevant proteins involved in AD (Fig. 2)^{30,31,100}. Further investigation of these interactions may help to elucidate the role of MIC60 in AD progression.

4.1. Disease-associated proteins interacting with MIC60 in AD

4.1.1. SHMOOSE microprotein

Microproteins are peptides encoded by small open reading frames. They have been rarely studied in the context of AD pathology and therapy due to technical limitations³¹. However, recent advances in proteomic techniques have led to the identification of thousands of microproteins, many of which were previously overlooked by earlier genomic and proteomic approaches^{31,101,102}. Among these, SHMOOSE, a previously unannotated mitochondrial microprotein, has been linked to AD. Importantly, SHMOOSE directly binds to the inner mitochondrial membrane protein MIC60, thereby regulating mitochondrial biology (Fig. 2)³¹.

Elevated levels of SHMOOSE have been detected in AD patients, and SHMOOSE levels in cerebrospinal fluid correlate positively with the levels of both total tau and phosphorylated tau 181³¹. *In vitro* experiments have shown that SHMOOSE protects against A β pathology³¹. Mass spectrometry analysis identified MIC60 as a top candidate among the 98 proteins that bind SHMOOSE³¹. Under normal conditions, SHMOOSE lowers mitochondrial superoxide levels; however, this effect is abolished when MIC60 is knocked down using siRNA³¹. The functional interaction between MIC60 and SHMOOSE suggests the possibility that SHMOOSE may be a component of a mitochondrial protein complex that includes MIC60 in the inner mitochondrial membrane. Nevertheless, whether SHMOOSE is a subunit of the MIC60 subcomplex or part of the MICOS complex remains to be explored. As the mitochondria-encoded microprotein identified by mass spectrometry, SHMOOSE may represent the first microprotein identified to bind MICOS.

4.1.2. Heme-binding protein 1

HEBP1, a key participant in heme metabolism, interacts with heme to regulate mitochondrial dynamics, which are disrupted in AD^{3,103,104}. Recent studies have identified HEBP1 as an important regulator of neuronal cell death and a potential marker of early AD pathogenesis^{30,103}. Elevated HEBP1 levels have been observed in patients with rapidly progressing AD and in 3 $\times$ Tg-AD transgenic mice, consistent with earlier reports of HEBP1 as a differentially expressed protein in the SAMP8 model of AD^{23,103,105}. Interestingly, components of the MICOS complex—specifically, MIC60, MIC25, and MIC19—have been found to be enriched in HEBP1 co-immunoprecipitation samples, with direct interaction between HEBP1 and MIC60 subsequently confirmed using immunoblotting³⁰. Additionally, outer mitochondrial membrane proteins, including SAMM50—a mammalian homolog of yeast SAM50 that physically binds MIC60—have also

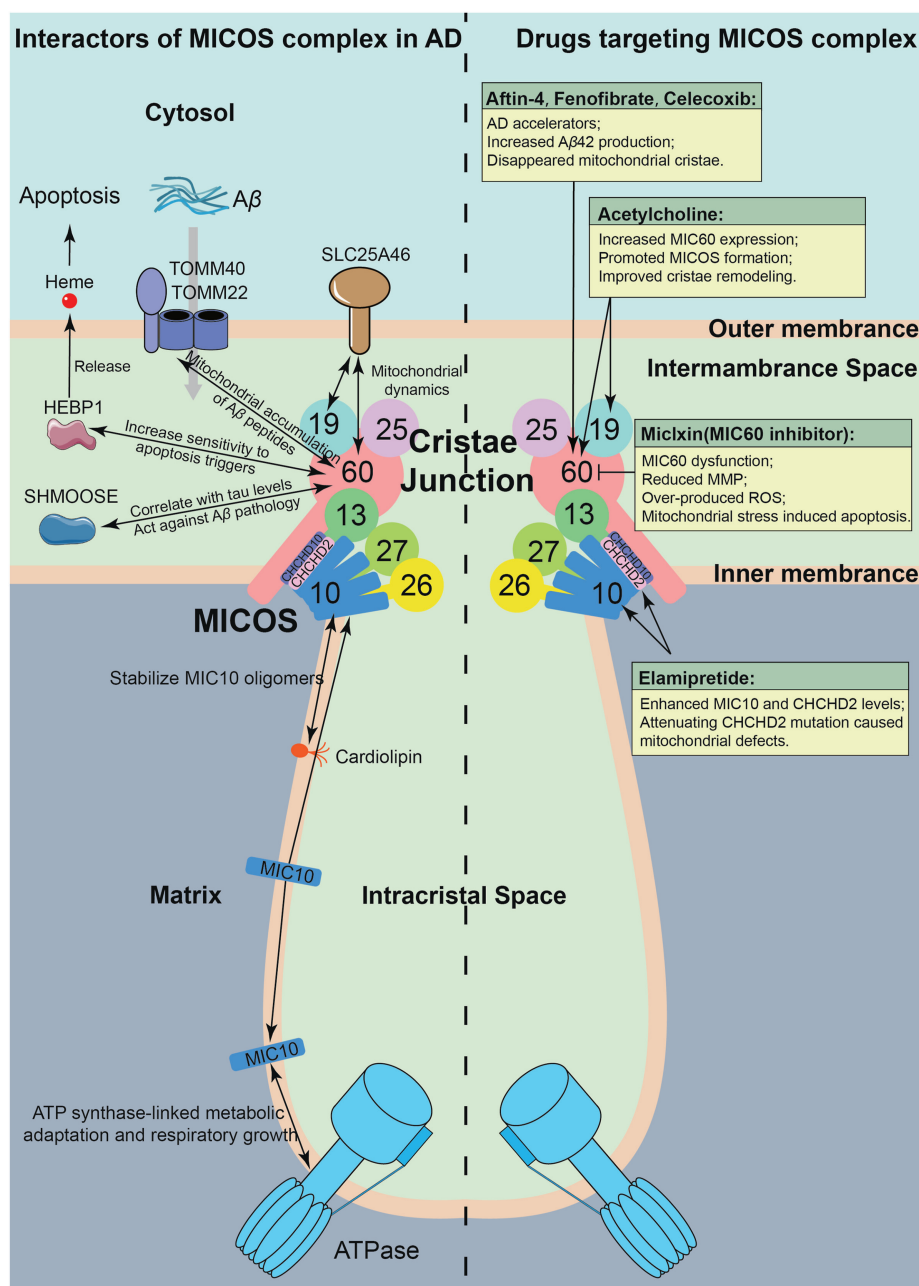


Figure 3 The MIC25–APP axis links amyloid pathology and mitochondrial dysfunction in AD. Under physiological conditions, MIC25 and APP interact and stabilize each other. In AD, the reduced levels of MIC25 disrupt this balance, leading to increased production of AICD, which cooperates with Fe65 and Tip60 to bind the MIC25 promoter and suppress MIC25 expression. This circular feedback loop exacerbates amyloid pathology while simultaneously contributing to mitochondrial dysfunction.

been detected in HEBP1 co-immunoprecipitation samples^{30,50,51}. Through its interaction with the MICOS complex, HEBP1 localizes to mitochondria. These findings suggest that HEBP1 may be positioned near the outer mitochondrial membrane, where it could associate with the MICOS complex, potentially *via* outer membrane proteins such as SAMM50.

Under exogenous heme exposure, normal neurons exhibit increased cell death, whereas HEBP1 deficiency confers protection against hemin-induced cytotoxicity³⁰. During this process, cytochrome *c* is released from mitochondria in both HEBP1-deficient and control neurons; however, MIC60 release from mitochondria is observed exclusively in HEBP1-deficient

cells³⁰. Because MIC60 depletion has previously been linked to cytochrome *c* release and increased sensitivity to apoptotic inducers¹⁰⁶, an underlying connection between MIC60 and HEBP1 may play a role in neuronal apoptosis in AD. Given the reported decrease in MIC60 protein levels in AD patients²¹, it is possible that MIC60 depletion alleviates its regulatory restriction on HEBP1, resulting in increased HEBP1 release from mitochondria. This, in turn, may enhance neuronal sensitivity to apoptosis-inducing factors such as heme, ultimately exacerbating AD pathology (Fig. 2). However, the complex crosstalk between MIC60 and HEBP1 in AD requires further investigation.

4.1.3. TOMM40 and TOMM22

The central receptor TOMM22 and the channel-forming protein TOMM40 are two core components of the TOMM complex (referred to as Tom in yeast and TOMM in humans)¹⁰⁷. In yeast, Tom40 and Tom22 physically interact with MIC60 (Fig. 2)³². During the mitochondrial accumulation of A β peptides, cytosolic A β is first recognized by TOMM22, subsequently translocated to TOMM40, and ultimately transported into mitochondria through the TOMM channel¹⁰⁰. Additionally, reduced TOMM40 expression has been observed in the blood of AD patients^{108–110}, and anti-TOMM40 antibody levels in blood have been strongly associated with cognitive impairment in AD patients¹¹¹. Although TOMM40 and TOMM22 have been extensively studied in AD, the specific role of their interaction with MIC60 in AD pathogenesis remains unexplored. Further investigation of this connection may provide new insights into the mitochondrial dysfunction associated with AD.

5. SLC25A46 and MIC60 and MIC19

SLC25A46, an integral outer mitochondrial membrane protein and a member of the mitochondrial metabolite carrier family, interacts with OPA1, MFN1, MFN2, and voltage-dependent anion channels and plays a crucial role in mitochondrial fission and fusion^{112–114}. Recently, SLC25A46 has been identified as a novel gene signature and predictive factor for AD¹¹⁵. As early as 2011, Ugo1, the yeast ortholog of SLC25A46, was co-isolated with MICOS components⁶⁶, suggesting a potential link between SLC25A46 and MICOS. More recently, studies on mitochondrial interactors of SLC25A46 have provided evidence that MICOS interacts with SLC25A46 and may significantly influence mitochondrial dynamics through their mutual crosstalk^{112–114,116}.

SLC25A46 functions upstream of the MICOS complex and is essential for maintaining proper cristae architecture. Immunoprecipitation studies have confirmed interactions among SLC25A46, MIC60, and MIC19 (Fig. 2)^{112,114,116}. Loss of SLC25A46 results in the disruption of mitochondrial cristae, a phenotype consistent with cells lacking a functional MICOS complex^{42,66,112}. Moreover, fibroblasts treated with SLC25A46 siRNA exhibit substantial reductions in the protein levels of MIC60 and MIC19 (MIC60 to 34% of control and MIC19 to 21%)¹¹², suggesting that SLC25A46 regulates MICOS complex stability. Meanwhile, MIC60 depletion significantly upregulates SLC25A46 levels, whereas MIC19 depletion does not affect SLC25A46 expression, indicating a specific regulatory relationship between MIC60 and SLC25A46¹¹². The upregulation of SLC25A46 in response to MIC60 depletion may serve as a compensatory mechanism to mitigate MICOS dysfunction. Collectively, these findings suggest functional interactions between SLC25A46 and the MICOS complex.

The MICOS complex contributes to mitochondrial dynamics through its interaction with SLC25A46. Unlike Ugo1, which plays a critical role in mitochondrial fusion, SLC25A46 promotes mitochondrial fission¹¹⁶. Loss of SLC25A46 function or its reduced expression leads to mitochondrial hyperfusion^{112,114}. Previous studies have demonstrated that depletion of MIC19 causes striking mitochondrial fission in HeLa cells, and mitochondria lacking MIC19 are considered fusion incompetent^{41,117}. Combined with the fact that depletion of MIC60 increases SLC25A46 levels, thereby promoting mitochondrial fission¹¹², it is reasonable to hypothesize that the MICOS complex participates

in mitochondrial dynamics, because downregulation of MIC60 or MIC19 similarly leads to mitochondrial fission while loss of SLC25A46 function completely suppresses this phenotype. As mentioned above, SLC25A46 functionally connects with the MICOS complex and the mitochondrial dynamics proteins. It seems that a more complex system containing these proteins indeed exists and their functional interactions remain to be explored.

6. Newly identified subunits of the MICOS and their pathogenesis in AD

6.1. Potential subunits of the MICOS complex: CHCHD10 and CHCHD2

CHCHD10 and CHCHD2 are suspected subunits of the MICOS complex, and mutations in these proteins have been identified in AD^{26–29,118}. Similar to the confirmed MICOS complex subunits MIC19 (CHCHD3) and MIC25 (CHCHD6), CHCHD10 and CHCHD2 also contain a CHCH domain^{91,119}. CHCHD2 possesses a single C-terminal CHCH domain and an N-terminal mitochondrial-targeting sequence, while CHCHD10, which shares 53% sequence identity with CHCHD2, also contains a C-terminal CHCH domain and is considered its homolog¹¹⁹. The functional connection between CHCHD10 and CHCHD2 has been demonstrated in multiple models, and they are likely to operate as a CHCHD10/CHCHD2 complex^{36,120,121}. In 2017, Meng et al.¹²² reported that CHCHD2 loss resulted in mild mitochondrial cristae distortion in *Drosophila*. In 2019, Zhou et al.¹²¹ observed that CHCHD2 knockdown led to mitochondrial cristae abnormalities and MICOS complex destabilization. Given the structural and functional similarities among CHCHD2, CHCHD10, and MICOS subunits, their potential roles in the MICOS complex remain an open question.

Over the past decade, multiple research groups have attempted to characterize the CHCHD10–MIC60 interaction using various experimental models. However, these efforts have not provided conclusive evidence supporting a direct interaction between CHCHD10 and the MICOS complex^{36,120,123}. In 2016, Genin et al.³⁷ reported that CHCHD10 colocalized with MIC60 and MIC19 and that CHCHD10 mutations in fibroblasts destabilized the MICOS complex and promoted the loss of CJs. Based on these findings, the researchers proposed that CHCHD10 was a component of MICOS, leading many to consider CHCHD10 to be a novel MICOS subunit. However, in 2018, Straub et al.³⁶, using fibroblast cell lysates similar to those in Genin's study³⁷, determined that neither CHCHD2 nor CHCHD10 co-migrated with MIC19 or MIC60. In contrast to Genin's findings, Straub et al. concluded that the CHCHD10/CHCHD2 complex does not associate with MICOS. At present, the available evidence remains insufficient to definitively classify CHCHD10 as a MICOS subunit, and further research is required to clarify its role.

In 2022, Lu et al.³⁸ provided a new perspective by reporting that CHCHD2 interacts with MIC10 in HeLa cells and contributes to MICOS complex stability. However, rather than proposing CHCHD2 as a structural MICOS component, Lu et al.³⁸ suggested that CHCHD2 interacts with MICOS without serving as one of its core subunits. These findings provide partial support for a subunit-like role of CHCHD2 in MICOS. However, the question of whether CHCHD2 and CHCHD10 are functionally integrated into the MICOS complex remains unresolved. Given the accumulating

evidence suggesting the existence of unrecognized MICOS components, additional subunits may yet be discovered. To systematically define new MICOS subunits, we propose the following criteria for classification: (a) a physical interaction between the candidate subunit and core MICOS components, specifically, MIC60 or MIC10; (b) an observable impact of the candidate subunit on MICOS complex stability and CJ formation when its expression is altered; and (c) reproducibility of the above criteria across multiple cell types and species, reflecting the conserved nature of MICOS subunits.

6.2. CHCHD2 and CHCHD10 mutations in AD

Mutations in CHCHD2 and CHCHD10 have been identified in AD (Table 1)^{26–29,118}. In 2015, the p.P34S variant of CHCHD10 was identified in two Caucasian AD patients; however, after comparison with control frequencies and database records, it was determined to be non-pathogenic¹¹⁸. This is thus far the only CHCHD10 mutation reported in a non-Chinese population. In 2017, Shen's group identified a p.A35D (c.104C > A) heterozygous mutation in a late-onset AD patient from a cohort of 484 AD patients²⁶. This mutation alters a conserved amino acid and is predicted to have a pathological effect based on *in silico* analysis. More recently, from a larger cohort of 1593 AD patients, the same group identified a nonsense mutation in CHCHD10 (c.283C > T, p.Q95) in two female AD patients²⁷.

Regarding CHCHD2 mutations in AD, two independent reports in 2018 identified four CHCHD2 mutations in Chinese populations. The 5C > T (p.P2L) variant was found in six unrelated AD patients, while 238A > G (p.I80V), c.15C > G (p.S5R), and c.94G > A (p.A32T) were each observed in separate male AD patients^{28,29}. The 5C > T (p.P2L) variant, which was identified in two separate studies, was predicted to be “probably damaging” by *in silico* analysis. However, Liu et al.²⁹ suggested that, although CHCHD2 may be associated with AD, it is unlikely to be a causative gene. The specific role of CHCHD2 in AD pathogenesis remains unclear, and further functional studies are needed to clarify its significance.

Most CHCHD10 and CHCHD2 mutations have been identified in Chinese populations, which may be due to genetic differences among ethnic groups. These mutations may play a more critical role in AD pathogenesis in Chinese individuals than in other populations. However, studies of CHCHD10 and CHCHD2 mutations in AD face several limitations. First, multicenter collaborations with larger cohorts are necessary to clarify the association of these variants with pathological and clinical phenotypes and, more importantly, to determine whether CHCHD10 and CHCHD2

are causative genes in AD. Second, functional studies are required to characterize the molecular alterations induced by these variants. Finally, bioinformatics predictions are dependent on existing databases, which may lead to inaccurate or incomplete conclusions. Further research integrating genomic, functional, and clinical data is essential to elucidate the precise role of CHCHD10 and CHCHD2 in AD.

6.3. CHCHD10 and TDP-43

TDP-43 is a DNA- and RNA-binding protein that plays a crucial role in RNA splicing, nuclear transcription, and metabolism^{124,125}. TDP-43 shuttles between the nucleus and cytoplasm, and its pathological aggregation is characterized by abnormal cytosolic TDP-43 inclusions and nuclear depletion¹²⁶. TDP-43 pathology has been identified in a significant proportion of AD patients, with some studies reporting a prevalence of up to 57%^{127,128}. Decreased TDP-43 levels in the frontal cortices of AD brains have been observed, and intracellular TDP-43 aggregation is often accompanied by tau pathology^{129,130}. Additionally, imaging evidence from tau-PET and volumetric MRI suggests that TDP-43 pathology contributes to the volume–uptake mismatch observed in older AD patients¹³¹. Given these findings, the targeting of abnormal TDP-43 production may offer a therapeutic avenue for preventing AD-related neurodegeneration.

CHCHD10, a potential subunit of the MICOS complex, has recently been found to colocalize and accumulate with phospho-TDP-43 inclusions in the brains of AD patients³³. Transgenic mice carrying CHCHD10 R15L or CHCHD10 S59L mutations exhibit phospho-TDP-43 pathology along with enhanced CHCHD10 aggregation³³. Additionally, CHCHD10 knockdown in cultured cells leads to disassembly of the OPA1/MIC60 complex and TDP-43 overexpression downregulates CHCHD10 levels and also promotes OPA1/MIC60 complex disassembly¹³². However, the CHCHD10 R15L and CHCHD10 S59L mutations have not been identified in AD, and whether AD-associated CHCHD10 mutations contribute to disease progression *via* TDP-43 remains unclear.

As highlighted above, further functional studies are necessary to elucidate the role of CHCHD10 in AD. Transgenic mouse models carrying CHCHD10-associated mutations may provide valuable insights into this interaction. Additionally, therapeutic strategies aimed at enhancing CHCHD10 activity or expression may prove beneficial in mitigating TDP-43-related neurodegenerative disorders, including AD.

7. Potential connections between MICOS and tau pathology

The deposition of phosphorylated tau aggregates is another pathological hallmark of AD¹³³. Emerging evidence suggests that MICOS abnormalities and MICOS-associated proteins may contribute to tau aggregation in AD. Here, we summarize the potential connections between MICOS and tau pathology.

The THY-Tau22 AD mouse model, widely used to study tau aggregation, develops a series of tau-related neuropathological changes¹³⁴. In 2024, Ali et al.¹³⁵ performed single-cell RNA sequencing in THY-Tau22 mice and highlighted sex-based differences in AD-associated gene activity. Among the differentially expressed genes, CHCHD2 in oligodendrocytes and CHCHD10 in astrocytes emerged as the top female-specific differentially expressed genes¹³⁵. While CHCHD10 and CHCHD2 mutations

Table 1 Summary of mutation sites of CHCHD2 and CHCHD10 in AD.

Gene	Mutation site	Genotype	Ethnicity	Ref.
CHCHD10	c.104C > A, p.A35D	+/-	Chinese	26
	c.283C > T, p.Q95*	+/-	Chinese	27
	c.100C > T, p.P34S	+/-	Caucasian	118
CHCHD2	c.5C > T, p.P2L	+/-	Chinese	28
	c.15C > G, p.S5R	+/-	Chinese	
	c.94G > A, p.A32T	+/-	Chinese	
	c.5C > T, p.P2L	+/-	Chinese	29
	c.238A > G, p.I80V	+/-	Chinese	

have been identified in AD patients^{26-29,118} and CHCHD10 may contribute to AD progression through its interaction with TDP-43³³. Ali's findings suggest a possible link between MICOS and tau pathology and identify candidate cell types for further investigation. Additionally, these results indicate that sex may influence MICOS subunit expression and related tau aggregation.

The p.T61I mutation in CHCHD2 was initially identified in Parkinson's disease¹³⁶. Accumulation of phosphorylated tau, neurofibrillary tangles, and A β was observed in the brain of a patient with the CHCHD2 p.T61I mutation, suggesting that this variant disrupts proteolytic pathways¹³⁶. Furthermore, studies in *Drosophila* have shown that the CHCHD2 p.T61I mutation impairs autophagy, leading to compensatory upregulation of proteasomes. This mutation has been extensively studied in Parkinson's disease pathogenesis¹³⁷⁻¹⁴¹ and has not yet been reported in AD patients. Given that CHCHD2 p.T61I induces mitochondrial dysfunction, impairs proteolysis, and promotes tau and A β pathology, it may directly contribute to AD pathogenesis, warranting further investigation.

As a novel therapeutic approach, the injection of stem cells from human exfoliated deciduous teeth (SHED) has been shown to improve cognitive function and alleviate tau pathology in the SAMP8 AD mouse model¹⁴². Proteomic analysis of the hippocampus indicated a strong link between these improvements and mitochondrial function, with MIC13 identified as a core target of SHED therapy¹⁴². However, an unexpected finding was that SHED treatment increased ATP production while simultaneously decreasing MIC13 levels (Table 2^{121,142-145}). Because MIC13 serves as a bridging component between the two MICOS subcomplexes⁴³⁻⁴⁵, its downregulation typically leads to MICOS abnormalities, impaired mitochondrial biogenesis, reduced ATP production, and diminished membrane potential^{44,76}. Resolving this apparent contradiction may enhance our understanding of the relationship between MIC13 dysregulation and tau pathology.

In summary, MIC13 downregulation in the hippocampus, increased CHCHD2 expression in oligodendrocytes, and elevated CHCHD10 expression in astrocytes may contribute to tau pathology and other hallmarks of AD. Additionally, we propose CHCHD2 p.T61I as a potential candidate mutation for promoting tau aggregation. Compared to the well-established role of MICOS in A β pathology, the involvement of MICOS in tau accumulation remains less understood and requires further investigation. Future studies should focus on elucidating the mechanisms linking MICOS dysfunction to tau pathology in AD.

8. MICOS in mitochondrial quality control mechanisms

Mitochondrial quality control mechanisms can be categorized into three levels: (a) maintaining mitochondrial protein import homeostasis at the molecular level; (b) altering morphology and repairing damage at the organelle level; and (c) removing damaged mitochondria *via* mitophagy at the cellular level¹⁴⁶⁻¹⁴⁹. Herein, we mainly focus on MICOS-related mitophagy in AD and its connections to other quality control mechanisms, including mitochondrial dynamics and mitochondrial transport, to provide a comprehensive perspective on the role of MICOS in mitochondrial quality control in AD.

Drosophila Miro (dMiro), an ortholog of human Miro¹⁵⁰, is an atypical mitochondrial GTPase involved in mitochondrial transport along intracellular filaments. The removal of dMiro from the outer mitochondrial membrane is a prerequisite for the mitophagy of impaired mitochondria¹⁵¹. Under oxidative stress, dMIC60 stabilizes dMiro, thereby inhibiting mitophagy^{151,152}. Pharmacological or genetic dissociation of the dMIC60/dMiro complex protects *Drosophila* from neurodegenerative aging, a significant risk factor for AD¹⁵¹⁻¹⁵³. Conversely, knockdown of MIC60, MIC13, or MIC26–MIC27 in *Drosophila* significantly increases mitophagy and disrupts the balance between mitochondrial fusion and fission¹⁵⁴. These findings suggest that MICOS plays an essential role in mitophagy and mitochondrial dynamics, both of which are implicated in AD pathology.

The SH-SY5Y neuroblastoma cell line is widely used as an *in vitro* model for AD¹⁵⁵⁻¹⁵⁹. Immunity-related GTPase M (IRGM), located in the inner mitochondrial membrane, regulates membrane remodeling events, particularly mitophagy^{160,161}. During carbonyl cyanide 3-chlorophenylhydrazone-induced mitophagy, IRGM levels increase, while IRGM-silenced SH-SY5Y cells exhibit impaired mitophagy, characterized by reduced PINK1 recruitment and increased MIC60 stability¹⁶¹. By downregulating MIC60, IRGM enhances PINK1–Parkin-mediated mitophagy¹⁶¹. Understanding the regulatory mechanisms of the IRGM–MIC60 axis in mitophagy may provide valuable insights into AD pathology.

MICOS may also regulate mitochondrial quality control mechanisms through interactions with MICOS subunit-associated proteins. MIC60 may influence mitochondrial transport *via* TOMM40 and TOMM22, core components of the TOMM complex responsible for mitochondrial protein import¹⁰⁷. In AD, TOMM40 and TOMM22 facilitate the mitochondrial accumulation of A β peptides¹⁰⁰, while interactions between MIC60,

Table 2 Summary of MICOS targeting drugs.

Drug	Target	Effects	Ref.
Elamipretide	MIC10, CHCHD2	Enhanced MIC10 and CHCHD2 levels; attenuating CHCHD2 mutation R145Q-caused mitochondrial defects	121
SHEDs	MIC13	Dysregulation of MIC13; enhanced ATP production, improved cognitive ability and alleviated tau pathology	142
Aftin-4 Fenofibrate Celecoxib Miclxin	MIC60	Increased A β_{42} production and disappeared mitochondrial cristae	143
Acetylcholine	MIC60, MIC19	MIC60 dysfunction, reduced mitochondrial membrane potential, production of reactive oxygen species and mitochondrial stress induced apoptosis Increased MIC60 expression and activation of AMP-activated protein kinase to form the MICOS complex through muscarinic ACh receptor, thus improving cristae remodeling	144 145

Tom40, and Tom22 have been identified in yeast³². Additionally, MIC60 and MIC19 may modulate mitochondrial fusion and fission through their interaction with SLC25A46, a key regulator of mitochondrial dynamics¹¹².

As the central hub for energy production and cellular metabolism, mitochondria have evolved multiple quality control systems, including mitophagy, mitochondrial dynamics, and mitochondrial transport, to maintain their functionality^{146–149}. Emerging reports suggest that MICOS is involved in these mitochondrial quality control mechanisms, necessitating a reevaluation of its role in AD from a broader perspective.

9. Drugs targeting MICOS

Clinical and pathological evidence supports the critical role of MICOS in AD, suggesting that therapeutic strategies targeting MICOS may offer new insights into AD prevention and treatment. This section summarizes the available drugs targeting MICOS and provides a novel perspective on their potential therapeutic applications (Fig. 2 and Table 2).

9.1. AD accelerators targeting MIC60: Aftin-4, fenofibrate, and celecoxib

Aftin-4, a purine derivative structurally related to roscovitine (a cyclin-dependent kinase inhibitor), functions as an AD accelerator^{143,162}. Unlike roscovitine, aftin-4 is kinase-inactive and selectively promotes A β ₄₂ peptide production in N2a cells stably expressing human APP695, as well as in primary neuronal cultures¹⁴³. Two-dimensional difference gel electrophoresis and mass spectrometry identified voltage-dependent anion channel 1 (VDAC1), prohibitin, and MIC60 as targets of aftin-4. Notably, all three proteins are predominantly localized to mitochondria, and aftin-4 treatment induces mitochondrial cristae loss, mirroring the pathology observed in AD patients. Additionally, aftin-4 has been suggested to act through a pathway influencing γ -secretase activity. As a core subunit of the MICOS complex, MIC60 is downregulated in the brains of AD patients^{20,21}. Moreover, MIC25, a subunit of the MIC60 subcomplex, has been implicated in a circular feedback loop with APP processing¹⁹. The effects of aftin-4 further support the involvement of MICOS in A β pathology, emphasizing its role in mitochondrial dysfunction in AD.

Celecoxib, a selective COX-2 inhibitor commonly used as a nonsteroidal anti-inflammatory drug, and fenofibrate, a peroxisome proliferator-activated receptor alpha agonist used to treat hypercholesterolemia, also increase A β ₄₂ levels^{143,163}. Interestingly, these compounds share a common mechanism with aftin-4: they target the VDAC1/prohibitin/MIC60 complex and similarly accelerate A β ₄₂ production while affecting mitochondrial cristae morphology. Of the three, aftin-4 is the most potent A β ₄₂ inducer with the lowest toxicity and has the most pronounced effect on mitochondrial cristae, making it a valuable tool for studying A β -related pathology in AD.

These findings have significant therapeutic implications. In particular, the results suggest that simple γ -secretase modulators designed to reduce A β ₄₂ production without addressing MICOS dysfunction and mitochondrial impairment are likely to fail as AD treatments. Identification of the pathological interactors of MICOS in AD has proven crucial^{50,108,111,112}. The involvement of VDAC1, prohibitin, and MIC60 suggests potential mechanistic pathways, such as the VDAC1–prohibitin/MIC60 axis or the

VDAC1–prohibitin–MIC60 pathway. Because VDAC1 is an essential outer mitochondrial membrane protein, while prohibitin and MIC60 are localized to the inner mitochondrial membrane^{164,165}, it is plausible that VDAC1 functions upstream of prohibitin and MIC60. Additional yet unidentified MIC60 interactors may serve as molecular bridges linking VDAC1 and prohibitin/MIC60. Research on aftin-4 and its effects in AD is ongoing^{166,167}, and future studies investigating its impact on the MICOS complex are anticipated.

9.2. The MIC60 inhibitor Miclxin

To our knowledge, Miclxin was the first compound identified as a MIC60 inhibitor. Its chemical structure was well characterized by Ikeda et al¹⁴⁴. Unlike previously reported compounds, Miclxin selectively induces β -catenin-dependent cell death^{144,168}. Under Miclxin treatment, β -catenin-mutated HCT116 cells exhibit mitochondrial dysfunction and undergo mitochondrial stress-mediated apoptosis. Cellular thermal shift assays and LC–MS/MS analyses confirmed that Miclxin interacts with MIC60 and inhibits its function, leading to reduced mitochondrial membrane potential, increased ROS production, and subsequent cell death. Notably, outer mitochondrial membrane proteins such as voltage-dependent anion channels, TOMM40, and TOMM22 also bind to Miclxin. It seems that Miclxin acts as a bridge connecting MIC60 and these proteins. Previously, MIC60 was demonstrated to bind TOM40 and TOM22 in yeast³². TOMM40-related pathologies are also found in AD patients^{108–111}. Additionally, aftin-4, another compound targeting MIC60, has been found to bind VDAC1, further hinting at a potential VDAC1–MIC60 pathway¹⁴³.

Taken together, these findings suggest that artificial compounds or unidentified proteins may mediate interactions between outer mitochondrial membrane proteins and the MICOS complex, playing critical roles in AD and other diseases. Therefore, the identification of novel MICOS interactors could provide deeper insights into MICOS-related mechanisms and accelerate the development of therapeutic strategies for AD.

9.3. Elamipretide increases MIC10 and CHCHD10 levels

Elamipretide, also known as SS-31, is a mitochondria-targeted tetrapeptide that binds to CL on the inner mitochondrial membrane. As a mitochondria-targeted antioxidant and protector, elamipretide promotes ATP synthesis, reduces ROS production, preserves mitochondrial cristae integrity, and enhances overall mitochondrial function^{121,169}. In clinical trials for mitochondrial diseases^{170–172}, elamipretide has demonstrated efficacy in multiple conditions, including heart failure, skeletal myopathy, and various neurodegenerative diseases^{173,174}. With its alternating aromatic and cationic group structure, elamipretide can freely cross the blood–brain barrier, making it a promising therapeutic candidate for central nervous system disorders¹⁷⁵. Indeed, elamipretide has recently been proposed as a potential therapy for AD^{176–179}. In APP transgenic mice, elamipretide treatment reduces A β production and mitigates A β -induced mitochondrial and synaptic toxicity associated with AD progression^{177,178}. Additionally, the combination of elamipretide and mitochondrial division inhibitor 1 has been suggested as an advanced therapeutic strategy for AD¹⁷⁶.

The MICOS complex and CL, both targets of elamipretide, are essential for shaping mitochondrial cristae^{5,180}. In 2019, elamipretide was reported to increase MIC10 and CHCHD2 levels in isogenic human embryonic stem cell lines harboring the CHCHD2

R145Q mutation¹²¹. As described in Table 1, while multiple CHCHD10 mutations have been identified in AD patients^{28,29}, the CHCHD2 R145Q mutation has not yet been reported in AD. In 2020, proteomic analysis identified mitochondrial protein interaction landscapes affected by elamipretide, linking its function to ATP production and 2-oxoglutarate metabolism¹⁸¹. These results suggested that MICOS subunits are unlikely to be direct interactors of elamipretide. Given that CL has been shown to stabilize MIC10 oligomers^{17,66}, elamipretide may exert its effects *via* CL, thereby upregulating MIC10 and CHCHD2 to enhance mitochondrial function and alleviate AD pathology. However, the specific mechanisms underlying elamipretide–MICOS crosstalk require further investigation. Elamipretide distinguishes itself as a low-toxicity compound with the ability to cross the blood–brain barrier and has been extensively studied in clinical trials^{170–172}. Given its mitochondrial–protective properties, elamipretide holds considerable potential to be included in AD clinical trials as the first MICOS-related therapeutic agent.

9.4. Acetylcholine upregulates MIC60 and enhances MICOS formation

Since the introduction of the “cholinergic hypothesis of AD”, which posits that memory and learning deficits in AD result from a loss of cholinergic innervation to the entorhinal cortex and hippocampus from basal forebrain nuclei^{182,183}, pharmaceutical companies have pursued therapies aimed at increasing acetylcholine (ACh) levels. These strategies include inhibiting ACh-catabolizing cholinesterases and developing ACh receptor agonists^{184–186}. In 2019, Xue et al.¹⁴⁵ reported that ACh increased MIC60 expression *via* the muscarinic ACh receptor and promoted the SAMM50–MIC60–MIC19 interaction, thereby enhancing cristae remodeling and improving mitochondrial function. The effects of ACh on MICOS were abolished upon AMP-activated protein kinase silencing, highlighting the role of the ACh–muscarinic ACh receptor–AMP-activated protein kinase–MICOS signaling pathway¹⁴⁵. These findings expand our understanding of the therapeutic mechanisms of ACh in AD. In addition to its well-established role in attenuating learning and memory deficits, elevated ACh levels may also enhance mitochondrial function *via* MICOS, suggesting a broader neuroprotective effect.

10. Discussion and future prospects

Compared to the MIC10 subcomplex, the MIC60 subcomplex appears to play a dominant role in AD pathogenesis (Table 3^{19–21,23–25,30–32,80,100,104,112}). Alterations in the epigenetic modifications of MIC60, along with decreased MIC60 and MIC25 levels, have been identified in AD patients and various AD models^{19–25,80–82}. Aftin-4, fenofibrate, and celecoxib—three compounds considered AD accelerators—target MIC60 and promote A β ₄₂ peptide production¹⁴³. Conversely, ACh, a neurotransmitter known to alleviate AD symptoms, upregulates MIC60 expression and enhances SAMM50–MIC60–MIC19 interactions¹⁴⁵. Additionally, an imbalance in the MIC25–APP processing loop leads to excessive A β peptide production and inhibits MIC25 expression *via* the AICD¹⁹. As a modular complex, MICOS comprises two subcomplexes: MIC60 and MIC10 subcomplex. Most studies implicating MICOS in AD focus on the MIC60 subcomplex, with little evidence linking the MIC10

subcomplex to AD. This specificity may be unique to AD pathogenesis, and further investigation of the potential involvement of MIC10 subunits in AD may provide novel insights.

The impact of MICOS in AD largely depends on its interactions with other mitochondrial proteins. MIC60 has been shown to functionally interact with HEBP1³⁰, the microprotein SHMOOSE³¹, and TOMM40 and TOMM22³² and to thereby contribute to neuronal apoptosis and tau- and A β -related pathologies. Furthermore, the MICOS complex may regulate mitochondrial dynamics through interactions among MIC60, MIC25, and the mitochondrial metabolite carrier protein SLC25A46¹¹². Additionally, CHCHD10 accumulates in and colocalizes with TDP-43 inclusions, suggesting that CHCHD10 mutations may influence AD progression *via* TDP-43³³. Several MICOS-targeting drugs interact with key mitochondrial proteins, such as voltage-dependent anion channels, TOMM40, and TOMM22^{143,144}. Given the subcellular localization of these proteins, it is worth considering whether they act as molecular “bridges” linking outer mitochondrial membrane proteins to MICOS. Based on these findings, we propose that MICOS may form higher-order complexes with other mitochondrial components to exert diverse functions in AD pathogenesis. The identification of novel etiological interactors of MICOS and elucidation of their mechanisms of action will likely become a key area of research.

The cellular basis of AD pathogenesis involves the progressive degeneration of neurons and dysregulation of glial cells, including astrocytes, microglia, and oligodendrocytes. In AD neurons, a circular feedback loop between MIC25 levels and APP processing has been identified. This loop leads to mitochondrial dysfunction and multiple AD hallmarks, particularly amyloid pathology¹⁹. Furthermore, aftin-4, fenofibrate, and celecoxib—three AD accelerators targeting MIC60—share a common mechanism of selectively promoting A β ₄₂ peptide production in neurons¹⁴³, further emphasizing the crucial role of neurons in MICOS-induced amyloid pathology. Additionally, decreased MIC60 levels in AD may reduce its regulatory restriction on HEBP1, increasing HEBP1 release from mitochondria and promoting neuronal apoptosis³⁰. MICOS abnormalities, including MIC60 haploinsufficiency, downregulation of MIC60, disruption of the SAM50–MIC19–MIC60 axis, CHCHD10 mutations, and CHCHD2 overexpression, have been implicated in various nervous system disorders, including mitochondrial encephalomyopathies¹⁸⁷, Parkinson’s disease¹⁸⁸, cerebral ischemia-reperfusion injury¹⁸⁹, and intracerebral hemorrhage¹⁹⁰. These findings align with our conclusions regarding the essential role of MICOS in maintaining neuronal function. Investigation of MICOS dysfunction in other neurological diseases may provide insights into AD pathogenesis.

The upregulation of CHCHD2 in oligodendrocytes and of CHCHD10 in astrocytes in female THY-Tau22 mice suggests that glial cells are deeply involved in MICOS-related AD pathology¹³⁴. Oligodendrocyte dysfunction or death leads to myelin degeneration and white matter loss, early events in AD that contribute to cognitive deficits¹⁶⁴. CHCHD2 upregulation is generally associated with enhanced mitochondrial function and may alleviate AD progression^{121,177,178}. However, its increased expression in the oligodendrocytes of female THY-Tau22 mice¹³⁴ appears contradictory. This discrepancy may reflect a compensatory mechanism to support oligodendrocyte function or a sex-specific genetic difference, although further investigation is required. In recent decades, astrocytes have emerged as key players in both normal brain function and neurodegenerative

Table 3 Summary of MICOS studies and important interactors of MICOS in AD.

Subunit		Pathological changes	Interactor	Study subject	Ref.
MIC60 subcomplex	MIC60	Downregulated phosphorylation of MIC60	\	Hippocampal specimens from AD patients	20
		Decreased MIC60	\	Frontal cortex of AD patients	21
		Differentially expressed MIC60	\	Hippocampus from SAMP8 mice	23
		Carbonylated MIC60	\	Hippocampus from kainic acid treated mice	24
		Decreased MIC60	\	Synapses of striatum from <i>Wlds</i> mice	25
		Decreased MIC60 may free its restriction on HEBP1, thus releasing more HEBP1 from the mitochondria and meanwhile increasing sensitivity to apoptosis triggers like hemes, and eventually aggravating AD.	HEBP1	Brains of 3 × Tg-AD mice and patients affected by rapidly progressing forms of AD	30
		MIC60 binds to microprotein SHMOOSE, which is elevated in AD, positively correlates with tau levels, and acts against A β pathology.	Microprotein SHMOOSE	Brain from AD patients	31
		MIC60 binds to TOM40/TOMM40 and TOM22/TOMM22, which participate in the mitochondrial accumulation of A β peptides.	TOMM40, TOMM22	Yeast	32,100
		MIC60 interacts with SLC25A46, which functions upstream of MICOS and is essential in the mitochondrial cristae architecture. Besides, MICOS may participate in mitochondrial dynamics <i>via</i> its impact on SLC25A46.	SLC25A46	Fibroblasts	104
		MIC25			
	MIC25	Reduced MIC25 enhances APP accumulation and accelerates APP processing.	\	Hippocampus from AD patients; Neuro2a cells stably expressing <i>APP^{swe}</i> ;	19
		AICD binds to MIC25 promoter and inhibit MIC25 expression		Hippocampus from <i>APP^{NL-G-F}</i> and <i>APP^{NL-F}</i> knock-in mice	
		Decreased MIC25	\	Postmortem brain tissue from AD patients	80
		MIC19			
	MIC19	MIC19 interacts with SLC25A46, similar to MIC60	SLC25A46	Fibroblasts	112
		MIC10			
		MIC27			
		MIC26			
MIC10 subcomplex	MIC13	Not available			
		Not available			

diseases, including AD. Astrocyte dysfunction has been shown to trigger or exacerbate tau and A β pathology¹⁹¹. Similarly, the increased expression of CHCHD10 in astrocytes of THY-Tau22 mice, potentially enhancing astrocyte function, raises important questions for future research¹³⁴.

Chronic inflammation involving astrocytes and microglia is an early event in many neurodegenerative diseases, including AD¹⁹². Although MIC60 downregulation has been associated with microglial inflammation during pregnancy¹⁹³, coenzyme Q10 has been shown to exert a protective role in optic nerve head astrocytes by upregulating MIC60¹⁹⁴, and MIC19 levels have been negatively correlated with motor function in GFAP-IL6 transgenic mice, a model characterized by astrocyte and microglial activation¹⁹⁵, few studies have directly examined the specific involvement of astrocytes and microglia in AD pathogenesis.

MICOS abnormalities may contribute to memory deficits in AD by impairing synaptic plasticity. Synaptic dysfunction is a key mechanism underlying memory impairment in AD^{164,196-198}.

Drosophila serves as an effective model system for investigating the functional consequences of MICOS subunit dysregulation in synaptic plasticity^{199,200}. A mutant allele of dMIC60 containing a PiggyBac transposable element insertion (LL02849) was identified and designated as *dMIC60^{mut}*²⁰¹. This mutation disrupts the structure and function of synapses at the neuromuscular junctions of *Drosophila* at the cellular level²⁰⁰.

Previous studies have identified interactions between CHCHD10 and phospho-TDP-43 in AD³³. Additionally, TDP-43 overexpression has been shown to downregulate CHCHD10 expression¹³². CHCHD10 has also been reported to play a protective role in maintaining synaptic integrity and retaining nuclear TDP-43²⁰², thereby establishing a pathological link between CHCHD10-associated synaptic dysfunction and cytoplasmic TDP-43 inclusions. These findings suggest that MICOS subunits may contribute to synaptic dysfunction through interactions with other disease-associated proteins, such as TDP-43. In postmortem hippocampal sections from AD patients, phospho-TDP-43

inclusions have been detected in astrocytic endfeet, potentially contributing to pathological changes in AD²⁰³. In mice over-expressing human APP with the Arctic and Swedish mutations, depletion of microglial TDP-43 facilitated amyloid clearance but also led to significant synapse loss²⁰⁴. Notably, even in the absence of A β , TDP-43 depletion resulted in intrinsic microglial dysregulation, which was sufficient to induce synapse loss. Although the underlying mechanisms remain unclear, further studies investigating the relationship between MICOS and TDP-43 may provide valuable insights. Here, we summarize the available evidence linking synaptic dysfunction, MICOS abnormalities, and TDP-43 pathology in AD-related memory impairment. We hope that this discussion will contribute to a better understanding of the role of MICOS in memory function and synaptic health in AD.

MICOS dysfunction in neurons and glial cells is an early event in the AD brain, capable of inducing abnormal APP processing and potentially leading to A β production. As a complex, MICOS subunits influence one another, affecting both the integrity of the complex and overall mitochondrial function^{17,41,42}. Mitochondrial dysfunction in neurons and glial cells, along with associated pathological changes—including chronic inflammation, demyelination, white matter loss, and neurological aging—occurs in the AD brain prior to A β pathology^{30,134,191,192,196–198}. Shang et al.¹⁹ demonstrated that AICD, a product of APP processing, transcriptionally inhibits MIC25 expression, thereby amplifying a pathological feedback loop that leads to sustained MIC25 downregulation and increased A β production. Given the circular nature of this mechanism, it remains unclear where the process originates. It is possible that MIC25 loss precedes AICD upregulation, a hypothesis that warrants further long-term investigation into AD progression, with a particular focus on MICOS subunits. Based on the available evidence, we propose that MICOS defects impair CJ function, thereby contributing to mitochondrial dysfunction at the early stages of AD.

Rather than general MICOS dysfunction, the dysregulation of specific MICOS subunits appears to be the key driver of abnormal APP processing in AD. Both widespread MICOS dysfunction and A β production may be downstream consequences of disruptions in particular MICOS subunits. The role of MIC25 in promoting abnormal APP processing has been elucidated¹⁹. In addition to MIC25 loss, MIC60 downregulation, epigenetically modified MIC60, and disease-associated proteins interacting with MIC60 have been associated with A β production in AD^{20,21,24,25}. Furthermore, MIC60-targeting drugs, including aftin-4, fenofibrate, and celecoxib, have been shown to promote A β production¹⁴³. These findings support the notion that specific MICOS subunits, particularly MIC25 and MIC60, drive abnormal APP processing. However, interventions targeting MIC60 could profoundly disrupt MICOS stability, cristae structure, and mitochondrial function. While MIC25 deletion generally has less severe effects on mitochondrial function than MIC60 deletion^{17,41,42}, MIC25 loss has nonetheless been implicated in neuronal mitochondrial dysfunction in AD¹⁹. Based on current reports, we conclude that dysregulation of specific MICOS subunits, rather than generalized MICOS dysfunction, promotes A β production. However, further studies are needed to elucidate the complex relationship between specific MICOS subunit dysregulation and broader MICOS dysfunction in abnormal APP processing and other AD-related pathological changes. Given the complexity of this interplay, it may be premature to draw definitive conclusions at this stage.

MICOS-associated metabolic disturbances, including impairments in energy, lipid, and heme metabolism, have been identified in AD^{19,30,63,67,68,103}. MICOS is essential for maintaining mitochondrial architecture and function, and its dysfunction significantly affects the metabolism of multiple biomolecules^{17,41,42}. As a functional partner of F₁F₀-ATP synthase, MIC10 plays a role in regulating mitochondrial energy metabolism^{63,67,68}. Additionally, by modulating MIC13, SHEDs may enhance ATP production in the SAMP8 AD mouse model¹⁴². Elamipretide has also been implicated in ATP and 2-oxoglutarate metabolic processes through its effects on MIC10 and CHCHD2 in AD^{121,181}. In AD neurons, MIC25 loss leads to the accumulation of toxic cholesterol¹⁹, aligning with a recent study reporting that MIC19 depletion impairs mitochondrial lipid metabolism and triggers liver disease²⁰⁵. This finding suggests a potential role for MICOS in lipid metabolism in AD. Given that lipid metabolism is a key mechanism underlying ferroptosis^{206,207}, it remains to be determined whether MICOS regulates ferroptosis in AD. Furthermore, MIC60 may participate in neuronal heme metabolism through its interaction with HEBP1^{3,30,103,104}. Because metabolic homeostasis is fundamental for normal brain function, elucidation of the mechanisms by which MICOS disruption affects metabolic balance may lead to novel therapeutic targets for AD treatment.

Although the debate over whether CHCHD10 and CHCHD2 function as MICOS subunits continues, we summarize the current understanding of CHCHD10 and CHCHD2 mutations in AD patients. Notably, nearly all reported mutations have been observed in Chinese populations, which may be attributable to genetic differences among ethnic groups. Multicenter studies and functional analyses of CHCHD10 and CHCHD2 mutations are necessary to identify additional variants and elucidate their underlying molecular mechanisms. Given the potential discovery of new MICOS subunits, we have also proposed criteria for their classification. The MICOS complex is fundamental for shaping mitochondrial architecture and plays a critical role in the pathogenesis of mitochondrial dysfunction-related AD. Restoring MICOS function may represent a promising therapeutic approach for mitigating or even reversing AD pathology.

Given the essential role of MICOS in AD, translating these findings into clinical practice could significantly benefit patients. However, several challenges remain. As an early event in AD, MICOS dysfunction holds promise as a potential biomarker for early screening and prevention. Further research is needed to identify MICOS dysfunction-specific markers in easily accessible samples, such as blood. Additionally, genetic screening for pathogenic MICOS subunit variants represents another promising avenue, requiring multicenter collaborations to elucidate the associations of variants with pathological and clinical phenotypes in AD.

MICOS subunits also serve as potential therapeutic targets in AD. Multiple drugs targeting MICOS subunits have been shown to either promote or alleviate AD-related pathological changes. Although these drugs may not be highly specific to MICOS, they remain valuable tools for elucidating MICOS-related mechanisms in AD. Furthermore, these compounds may provide a foundation for future drug design and synthesis. However, the specificity of currently available MICOS-targeting drugs requires further investigation. The development of highly selective MICOS-targeting drugs could have a profound impact on alleviating or even preventing AD in its early stages. Given that MICOS dysfunction is implicated in multiple neurodegenerative diseases, assessment of the therapeutic potential of MICOS-targeting

drugs could have broader implications beyond AD. From a long-term perspective, the development of small-molecule chemical compounds, peptide- or antibody-based drugs, and RNA-based modalities to regulate MICOS function or disrupt interactions between MICOS subunits and other disease-associated proteins may represent future directions in AD therapy.

This review has some limitations. MICOS abnormalities are early pathological events preceding A β and tau pathology in AD. Thus, compelling clinical evidence documenting MICOS defects in the brain during the early stages of AD is still needed. Because MICOS is a conserved complex, *Drosophila* serves as an effective model for studying MICOS-related AD pathogenesis, but findings from *Drosophila* require validation in mammalian AD models. We encourage researchers to remain attentive to advances in MICOS-related pathogenesis using *Drosophila*, as these studies may provide novel insights into MICOS function in AD. Compared to A β production, tau pathology appears to play a less dominant role in MICOS-mediated AD pathogenesis. We suggest THY-Tau22 mice as a valuable model for investigating MICOS-related tau pathology in AD. Mitochondrial quality control mechanisms are critical in neurodegeneration; this review primarily focuses on mitophagy in relation to MICOS, which may have led to the omission of other mitochondrial quality control pathways. Additionally, the specificity of the available MICOS-targeting drugs requires further validation. The development of highly selective MICOS-targeting drugs could represent a promising strategy for AD treatment.

Acknowledgments

This work was funded by the National Natural Science Foundation of China (No. 81500858 to Xinwen Zhang, No. 81700977 to Xu Yan), Natural Science Foundation of Liaoning Province (China) (No. 2022-MS-231 to Xinwen Zhang), the Science and Technology Planning Project of Shenyang (China) (No. 22-321-33-26 to Dehao Shang), Grants-in-Aid for Scientific Research (Japan) (No. 22K09927 to Zhou Wu).

Author contributions

Zihan Wang: Writing – review & editing, Writing – original draft, Conceptualization. Kaige Zhang: Writing – review & editing, Conceptualization. Minghao Huang: Writing – review & editing, Conceptualization. Dehao Shang: Writing – review & editing, Conceptualization. Xiaomin He: Writing – review & editing. Zhou Wu: Writing – review & editing, Conceptualization. Xu Yan: Writing – review & editing, Conceptualization. Xinwen Zhang: Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Conflicts of interest

The authors declare no conflicts of interest.

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