Acta Pharmaceutica Sinica B 2025;15(9):4582−4613

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

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

Nanomedicine strategies for cuproptosis: Metabolic reprogramming and tumor immunotherapy

Ruixuan Zhang[a,†], Yunfei Li[a,†], Hui Fu[b,†], Chengcheng Zhao[c], Xiuyan Li[d], Yuming Wang[a,*], Yujiao Sun[a,*], Yingpeng Li[a,*]

[a]*School of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China*
[b]*College of Integrated Chinese and Western Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China*
[c]*Experimental Teaching and Practical Training Center, Heilongjiang University of Chinese Medicine, Harbin 150040, China*
[d]*College of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin 150040, China*

Received 24 February 2025; received in revised form 7 April 2025; accepted 20 May 2025

KEY WORDS

Cuproptosis;
Immunotherapy;
Metabolic reprogramming;
Nanomedicine;
Cancer;
Tumor microenvironment;
Combination therapy;
Precision therapy

Abstract Cuproptosis, a recently discovered form of regulated cell death involving copper ion metabolism, has emerged as a promising approach for tumor therapy. This pathway not only directly eliminates tumor cells but also promotes immunogenic cell death (ICD), reshaping the tumor microenvironment (TME) and initiating robust anti-tumor immune responses. However, translating cuproptosis-based therapies into clinical applications is hindered by challenges, including complex metabolic regulation, TME heterogeneity, and the precision required for effective drug delivery. To address these limitations, nanoparticles offer transformative solutions by providing precise delivery of cuproptosis-inducing agents, controlled drug release, and enhanced therapeutic efficacy through simultaneous modulation of metabolic pathways and immune responses. This review systematically discusses recent advancements in nanoparticle-based cuproptosis delivery systems, highlighting nanoparticle design principles and their synergistic effects when integrated with other therapeutic modalities such as ICB, PTT, and CDT. Furthermore, we explore the potential of cuproptosis-based nanomedicine for personalized cancer treatment by emphasizing strategies for TME stratification and therapeutic optimization tailored to

*Corresponding authors.
E-mail addresses: wangyuming226@163.com (Yuming Wang), sunyujiao@tjutcm.edu.cn (Yujiao Sun), liyingpeng@tjutcm.edu.cn (Yingpeng Li).
†These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

http://dx.doi.org/10.1016/j.apsb.2025.07.007

patient profiles. By integrating current insights from metabolic reprogramming, tumor immunotherapy, and nanotechnology, this review aims to facilitate the clinical translation of cuproptosis nanomedicine and significantly contribute to the advancement of precision oncology.

1. Introduction

Cuproptosis, as an emerging form of regulated cell death, has garnered increasing attention in cancer therapy due to its distinctive biological mechanisms. Unlike traditional forms of cell death modalities, cuproptosis disrupts mitochondrial homeostasis through intracellular copper accumulation, triggering oxidative stress and leading to proteotoxicity[1]. Importantly, cuproptosis has been identified as a promoter of immunogenic cell death (ICD), facilitating tumor antigen release, reshaping the tumor immune microenvironment (TME), and initiating robust anti-tumor immune response[2]. Nevertheless, translating cuproptosis into clinical practice presents significant challenges, particularly in maximizing its immunostimulatory potential while preserving therapeutic safety and efficacy.

Tumor cells frequently exhibit metabolic reprogramming to adapt to the harsh microenvironment, enabling rapid proliferation and immune evasion[3]. By disrupting metabolic homeostasis—particularly mitochondrial function and glucose metabolism-cuproptosis propels tumor cells into a highly oxidised state[1]. This metabolic imbalance not only drives tumor cell death but also amplifies immune activation, suggesting that metabolic modulation could synergistically enhance cuproptosis-induced immune responses[4]. However, given the metabolic plasticity of tumor cells and the complexity inherent in the TME, effectively harnessing and modulating cuproptosis-induced metabolic disruptions remain significant obstacles[5].

Nanocarriers, with their unique physicochemical properties, offer promising solutions to address these therapeutic challenges[6]. Though precise drug delivery, controlled release, and modulation of the tumor microenvironment, nanoformulations enhance the efficacy of cuproptosis-targeted therapies and optimize immune activation[7]. Additionally, nanoparticles can synergize with immune checkpoint blockade (ICB)[8], photothermal therapy (PTT)[9], chemodynamic therapy (CDT)[10], and other therapeutic modalities, further amplifying anti-tumor efficacy[11,12]. Consequently, nanomedicine emerges as a crucial tool for cuproptosis-based immunotherapy, improving drug bioavailability, modulating tumor metabolism and reshaping immune responses (Fig. 1).

Building upon recent foundational reviews that detail the biological mechanisms, copper homeostasis, mitochondrial metabolism, and prognostic significance of cuproptosis across various cancers[13,14], this review expands the discussion toward the therapeutic potential of cuproptosis. Specifically, we emphasize its intrinsic relationship with tumor metabolism and immune regulation, two interdependent cancer hallmarks[15,16]. Notably, cuproptosis is distinct from other regulated cell death forms such as ferroptosis, disulfidptosis, and autophagy-dependent cell death, as it selectively targets mitochondrial lipoylated proteins, resulting in proteotoxic stress and enhanced immunogenicity[17]. Recognizing the tight interplay between metabolic pathways and immune activity, we propose a dual-track framework centered around metabolic reprogramming and immune activation to guide the rational development and application of nanomedicine in cuproptosis therapies. Furthermore, we highlight emerging innovations such as real-time treatment monitoring through liquid biopsy, aiming to accelerate the translation of mechanistic insights into clinically viable, personalized oncology strategies.

2. Major challenges in the development and immunological application of cuproptosis-related drugs

Cuproptosis shows considerable promise in tumor immunotherapy; however, numerous challenges persist in developing and applying its drugs, especially in achieving effective immunomodulatory outcomes and addressing the complexity of tumor metabolism. The distinct mechanisms of cuproptosis, including its capacity to induce oxidative stress and modulate the tumor immune microenvironment, offer potential to strengthen anti-tumor immunity. However, gaining a deeper understanding of these mechanisms-and designing drugs that precisely trigger cuproptosis while circumventing metabolic barriers-remains a major challenge.

2.1. Molecular mechanisms of cuproptosis and their immunological implications

Cuproptosis is a unique form of regulated cell death characterized primarily by mitochondrial dysfunction triggered by excessive copper accumulation. This accumulation impairs mitochondria respiration, reducing ATP synthesis, increasing reactive oxygen species (ROS) production, and promoting oxidative stress[18]. Under hypoxic conditions, this effect is further amplified by the activation of AMP-activated protein kinase (AMPK), which decreases cellular ATP levels and increases the AMP:ATP ratio[19]. Additionally, copper accumulation facilitates Fenton-like reactions, generating excessive ROS, exacerbating mitochondrial damage, and perpetuating a destructive cycle leading to cell death[20].

Beyond directly influencing tumor cell viability, cuproptosis holds significant implications for tumor immunology, notably through the induction of ICD. ICD results from the oxidative stress and extensive ROS production associated with cuproptosis[21], causing damage to critical cellular structures, including the endoplasmic reticulum and cell membrane. This cellular damage facilitates the release of danger-associated molecular patterns (DAMPs), such as HMGB1, ATP, and heat shock proteins (HSP70 and HSP90). These DAMPs are recognized by Pattern Recognition Receptors (PRRs) of innate immune cells, thereby initiating potent anti-tumor immune responses[2]. Furthermore, mitochondrial DNA (mtDNA) released into the cytoplasm due to mitochondrial disruption activates the cyclic GMP−AMP synthase (cGAS)−STING pathway[22]. Activation of this pathway triggers a phosphorylation cascade (TBK1→IRF3), leading to type I interferon secretion and dendritic cell (DC) maturation[23],

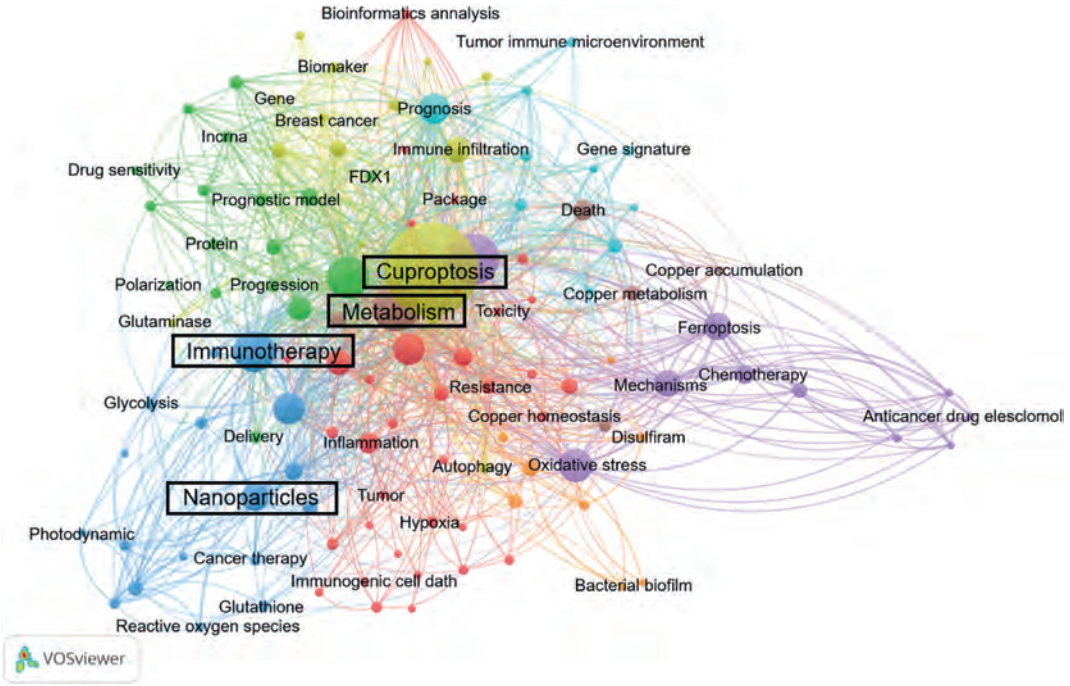

Figure 1 Term co-occurrence network analysis of cuproptosis-related research using VOSviewer. This visualization underscores the central role of cuproptosis in tumor metabolism and immunotherapy, emphasizing its links to nanoparticles, immunogenic cell death, and copper metabolism. The network uses color-coding to differentiate major thematic clusters: purple denotes molecular mechanisms of copper-induced cell death, blue centers on nanoparticle delivery systems and cancer therapy, green addresses metabolic reprogramming and immune responses, and yellow emphasizes bioinformatics and prognostic modeling in cancer research.

thus significantly enhancing their antigen-presenting ability and driving $CD8^+$ T cell infiltration into tumors[16]. In addition to its role in activating DCs and enhancing T-cell responses, cuproptosis reshapes the tumor microenvironment by modulating macrophage polarization[24]. Specifically, cuproptosis promotes the conversion of tumor-associated macrophages (TAMs) from an immunosuppressive M2 phenotype toward an immunostimulatory M1 phenotype. This repolarization significantly reduces the prevalence of myeloid-derived suppressor cells (MDSCs), further enhancing anti-tumor immune responses and improving the overall immune landscape of tumors (Fig. 2).

Interestingly, copper-induced oxidative stress can intersect with other cellular processes, especially ferroptosis. Copper and iron both contribute to ROS accumulation *via* similar Fenton reactions, thereby driving oxidative stress and cell death[25]. Growing evidence indicates that copper is involved in ferroptosis, especially under cuproptosis conditions. For instance, elesclomol-induced cuproptosis reportedly inhibits colorectal cancer (CRC) by targeting ATP7A and regulating ferroptosis[26]. Similarly, DSF/Cu triggers ferroptosis in nasopharyngeal carcinoma cells *via* ROS/MAPK and p53 pathways[27]. In hepatocellular carcinoma (HCC), DSF/Cu acts synergistically with sorafenib to inhibit NRF2 and MAPK kinase signaling, resulting in ferroptosis[28]. Notably, ferroptosis also initiates ICD, and its combination with cuproptosis represents a promising avenue for improving tumor immunotherapy[29].

2.2. *Progress in the development of drugs related to cuproptosis*

The development of therapeutic agents targeting copper metabolism for cancer treatment includes strategies designed either to reduce copper bioavailability or enhance copper accumulation within tumor cells, thus triggering cuproptosis. Copper chelators, such as D-penicillamine (D-Pen), tretinoin, and tetrathiomolybdate ammonium (TTM), have been investigated for their potential in regulating copper homeostasis and influencing cuproptosis. For instance, D-Pen attenuates copper-induced cytotoxicity by chelating copper ions and increases the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-23, which activate macrophages and augment autoimmune responses[30,31]. On the other hand, TTM binds to ATOX1 to form a complex that blocks the transport of copper to LOX and inhibits its activity, which leads to cell death[32]. TTM also induces autophagy by stimulating autophagosome formation through activation of the AMPK/mTOR/ULK1 signaling pathway, and enhances the antioxidant capacity of tumor cells by elevating NRF2 expression, indirectly influencing immune regulation by modulating copper metabolism[33]. Thus, the potential of these copper chelators in regulating copper homeostasis and immune responses provides strong support for an in-depth study of immune mechanisms induced by cuproptosis.

Cuproptosis-related drugs are generally classified into two main groups: copper-containing compounds and copper ion carriers, both capable of inducing cuproptosis by modulating copper metabolism within tumor cells (Table 1[21,34-57]). Copper-containing compounds directly release copper ions into the TME, thereby activating cuproptosis and stimulating anti-tumor immune responses. Among the copper ion carriers, disulfiram (DSF) and elesclomol (ES) have attracted substantial research interest. DSF, historically employed for alcohol dependence treatment, exhibits promising anti-tumor properties[58]. It is metabolized hepatically to produce DTC, which forms $Cu(DTC)_2$ complexes upon binding with copper ions, significantly enhancing anti-tumor effects[59]. However, endogenous copper concentrations in tumor tissues often remain insufficient to

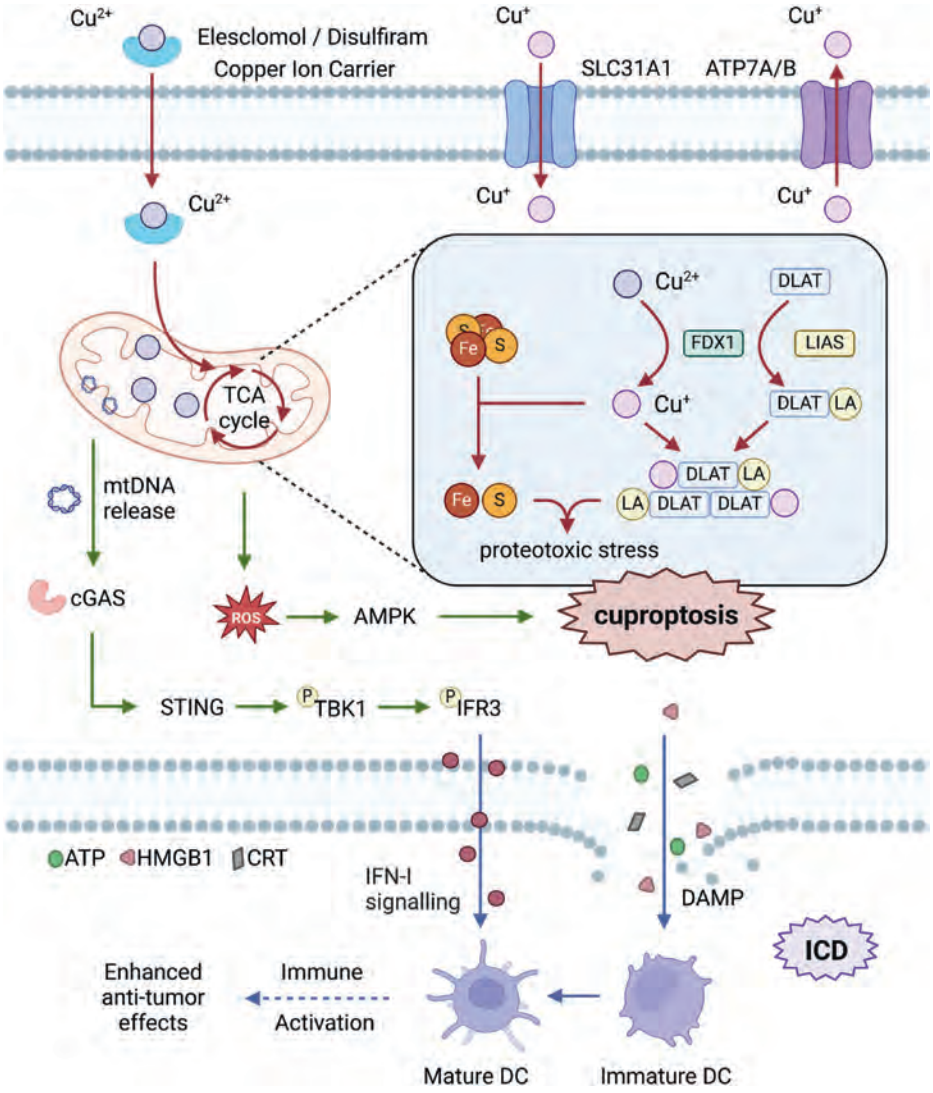

Figure 2 Biological mechanisms of cuproptosis and its effects on immune activation and ICD in tumor cells. Copper ion transport and accumulation result in cuproptosis, generating ROS, and activating the cGAS−STING and AMPK pathways. Subsequent proteotoxic stress drives immune activation by promoting DC maturation, which then augments the immune response and boosts anti-tumor efficacy. Red arrows signify cuproptosis mechanisms, green arrows depict metabolic process, and blue arrows represent immune pathways.

induce cuproptosis effectively. Consequently, separately delivering copper ions alongside DSF to form $Cu(DTC)_2$ complexes *in vivo* could substantially increase therapeutic efficacy[60].

ES represents another promising copper ion carrier, although its precise mechanism and impact on the tumor immune microenvironment require further clarification. ES targets mitochondria and facilitates cuproptosis through the formation of ES−Cu complexes[55]. Notably, melanoma cells lacking electron transport chain activity exhibit resistance to ES, indicating that the drug's effectiveness might depend upon mitochondrial functionality. This observation underscores the necessity for additional research to optimize ES's therapeutic potential, possibly through combination with other cuproptosis-inducing agents[61].

2.3. Challenges of cuproptosis in tumor metabolism and immune regulation

Tumor cells exhibit remarkable metabolic plasticity, allowing them to survive and proliferate despite harsh microenvironmental stresses, including those triggered by cuproptosis. This adaptive capacity involves enhancing antioxidant defenses[62], reprogramming glycolysis[63], and altering lipid metabolism[64] to withstand hypoxia and nutrient deprivation. These metabolic shifts collectively reduce the therapeutic effectiveness of cuproptosis-based treatments by helping tumor cells resist induced cell death. Additionally, excess copper ions used to trigger cuproptosis can accumulate in non-target organs such as the liver, kidney, and nervous system, resulting in systemic toxicity and further compromising the safety and efficacy of this therapeutic strategy[65].

Although cuproptosis has the potential to activate anti-tumor immune responses, its effectiveness is significantly limited by immunosuppressive components within the TME. Cells such as Tregs and MDSCs suppress immune activation[66], while inhibitory cytokines like TGF-β and IL-10 create an immunosuppressive milieu[67]. Furthermore, hypoxic and acidic conditions prevalent in the TME inhibit the activity and infiltration of immune effector cells. Tumor cells may also increase the expression of immune checkpoint proteins, such as PD-L1, facilitating immune escape

Table 1 Overview of drugs inducing cuproptosis: types, mechanisms, immunological effects, and clinical Applications.

Types	Drugs	Advantages	Immunological Effect	Limitations	Clinical Application
Copper compound	Copper nanoparticles ($CuCl_2$)	Direct supply of copper ions[34]	Upward revision of PD-L1[35], induction of ICD	Highly toxic; Lack of specific targeting[34]	Used in preclinical studies for the diagnosis and treatment of PCA[36], BC[37], GBM[38], etc.
	Copper oxide (CuO, Cu_2O, CuO_2)	High stability; release of copper ions in TME[21]	Cuproptosis-dependent macrophage death[39]	Poor solubility; release rate difficult to control; Uneven distribution of organisms[40]	Preclinical studies for the treatment of ccRCC[41], COAD[42], LC[43], etc.
	Copper-sulfur compounds ($Cu_{2-x}S$, $CuSO_4$, Cu_2Se)	Strong photothermal conversion capacity[44]	Photothermal response induced ICD[45]	Poor solubility and stability; Restrictions on direct application[46]	Preclinical studies for MEL[47], BC[48,49], etc.
Copper ion carrier	DSF	Targeted delivery of copper ions to the body; Exhibits anti-cancer properties; Suppression of stemness-associated transcription factors[50]; Activation of the MAPK signalling pathway[51]	Activation of T cell receptors enhances tumor immunity of $CD8^+$ T cells[52]; inhibition of the NF-κB/NLRP3 signalling pathway[53]	Short half-life; lacks tumor targeting ability; CuET poor solubility[54]	Clinical trials for MEL (NCT00256230), refractory sarcoma (NCT05210374), BC, (NCT03323346), glioma (NCT02678975)
	ES	Translocates copper ions to mitochondria[55]	Delivery of copper ions into mitochondria induces ICD[55]	High lipophilicity; short half-life; Cannot cause cuproptosis when used alone[56]	Clinical trials for MEL (NCT00522834) [57]

and further weakening the immune-mediated anti-tumor effects of cuproptosis[68]. Thus, strategies relying solely on cuproptosis induction may not achieve sufficient immune activation to fully control tumor progression.

In addition to biological challenges, the clinical translation of cuproptosis-inducing agents faces substantial hurdles related to drug delivery. Conventional cuproptosis inducers often undergo rapid metabolism and clearance *in vivo*, resulting in subtherapeutic concentrations in tumor tissues and unintended accumulation in healthy tissues, leading to off-target toxicities[69]. To overcome these issues, the development of advanced drug delivery systems is critical. Specifically, there is an urgent need for innovative delivery platforms that can enhance selective tumor targeting, precisely control drug release within the TME, and minimize systemic side effects, thereby significantly improving the therapeutic outcomes and clinical applicability of cuproptosis-based therapies.

3. Nanopreparations for cuproptosis: mechanisms of metabolic reprogramming and immune activation

Nanopreparations serve as powerful carrier systems that precisely regulate the onset of cuproptosis and modulate the tumor immune microenvironment through metabolic reprogramming. These nanoparticles can be engineered to target specific metabolic pathways in tumor cells, such as mitochondrial stress, glycolysis, lipid metabolism, and amino acid metabolism. By fine-tuning these processes, nanocarriers enhance copper accumulation, induce oxidative stress, and promote ICD, which collectively improve the anti-tumor immune response (Fig. 3).

3.1. Metabolic distinctions between cuproptosis, ferroptosis, and apoptosis

The core metabolic mechanism of cuproptosis lies in the fact that intracellular copper ion overload leads to abnormal aggregation of lipoylated proteins of DLAT, a key enzyme of the mitochondrial respiratory chain, which triggers a toxic gain of function[1]. Cuproptosis directly targets mitochondrial metabolism and is particularly advantageous for selective killing of tumor cells that rely on aerobic respiration. Notably, cuproptosis differs from ferroptosis and apoptosis in the mechanism of metabolic regulation (Table 2[1,70-72]). Ferroptosis is driven by iron-dependent lipid peroxidation involving ACSL4-mediated synthesis of polyunsaturated fatty acid phospholipids and failure of the GPX4 antioxidant system[73,74]. Whereas apoptosis is dependent on caspase protease cascade reactions and mitochondrial membrane permeabilization[75,76]. This is in contrast to cuproptosis, which disrupts energy metabolism by interfering with lipid acylation modifications.

For therapeutic applications, cuproptosis exhibits a unique window of metabolic vulnerability. Copper ion carriers synergistically target copper ions specifically to tumor cells, whereas normal cells can be less toxic due to the protective effect of the copper homeostasis regulatory proteins ATP7A/B[77]. In contrast, ferroptosis is susceptible to Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4) and ferroptosis suppressor protein 1 (FSP1)[78,79], whereas apoptosis is dependent on a protein hydrolysis cascade reaction in the death receptor or mitochondrial pathway[80,81]. In addition, cuproptosis activates anti-tumor immune responses through the release of DAMPs. Whereas a number of previous studies have suggested that ferroptosis belongs to the ICD, the characteristics of the ICD are questionable and more

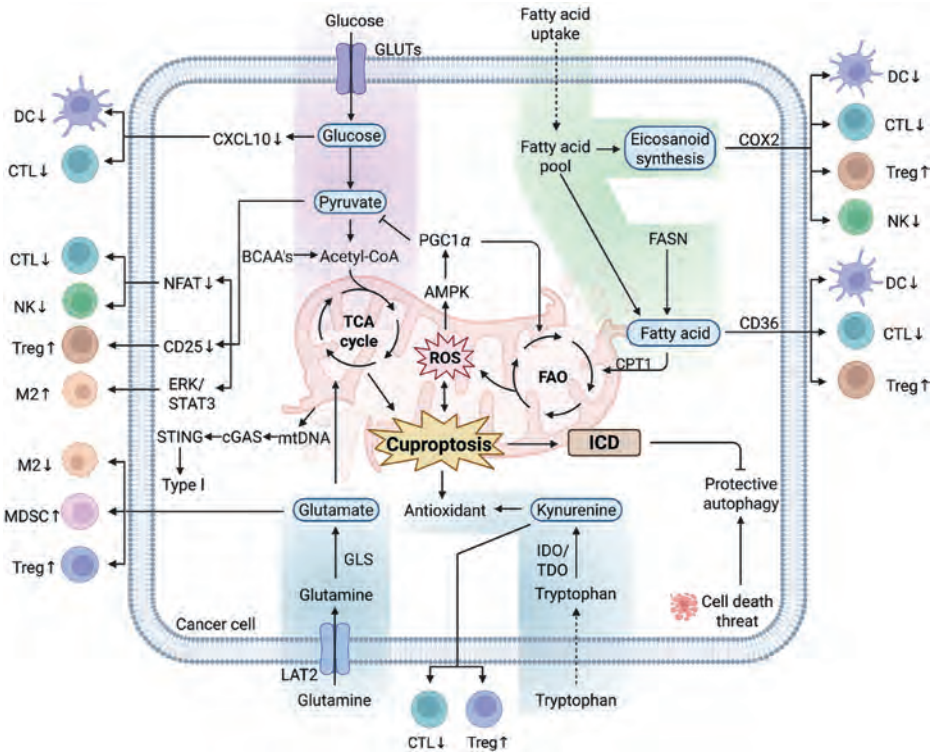

Figure 3 Metabolic reprogramming in tumor cells and immune microenvironment modulation *via* cuproptosis-induced cell death nanopreparations. Tumor cells produce immunosuppressive metabolites by metabolizing nutrients, thereby creating tumor-promoting conditions in the TME. Nanopreparations targeting cuproptosis can inhibit tumor growth and restore immune cell function by altering tumor cell metabolism. Cuproptosis is connected to three primary metabolic pathways: glucose metabolism (purple), lipid metabolism (green), and amino acid metabolism (blue).

Table 2 Comparison of cuproptosis, ferroptosis, and apoptosis in metabolic pathways and therapeutic implications.

Feature	Cuproptosis	Ferroptosis	Apoptosis
Core triggers	Copper ion-mediated disruption of the TCA cycle	Iron-dependent lipid peroxidation	Caspase activation
Morphological characteristics	Mitochondrial atrophy, membrane rupture	Mitochondrial shrinkage, cristae loss, membrane rupture	Cell membrane blebbing, apoptotic body formation
Key regulatory factors	FDX1, LIAS, DLAT	GPX4, ACSL4, FSP1, SLC7A11	BCL-2 family, caspases, APAF-1
Metabolic targeting	TCA cycle in mitochondria	Synthesis and peroxidation of polyunsaturated fatty acid-containing phospholipids	Mitochondrial membrane permeabilization, cytochrome *c* release
Potential for therapeutic applications	Targeting tumors with active mitochondrial metabolism	Targeting tumors with GPX4 deficiency or aberrant lipid metabolism	Broadly used to induce programmed tumor cell death
Immuno-activating properties	ICD *via* release of mitochondrial DAMPs	Controversial role in ICD induction	Generally considered immunologically silent
Ref.	1	70, 71	72

recent studies have suggested that it may suppress anti-tumor immunity[70]. Apoptosis usually mediates immune silencing through phosphatidylserine ectopics[82]. This immune-activating property provides a potential advantage for combined immunotherapeutic means of cuproptosis.

3.2. *Mitochondrial stress and immune activation*

Mitochondria are key sites for the initiation of cuproptosis. Copper accumulation leads to mitochondrial dysfunction, reducing ATP synthesis and increasing ROS production, which activates immune cells through PRRs[83]. This process promotes the maturation and antigen-presenting function of DC and activates the STING pathway *via* the release of mtDNA, further amplifying immune responses[22,84,85].

Nanopreparations can enhance mitochondrial stress by targeting mitochondria specifically. Mitochondria-targeted nanoparticles, such as those functionalized with triphenylphosphine (TPP), exploit the high lipophilicity and negative potential of the mitochondrial membrane, facilitating copper ion accumulation

and boosting ROS generation[86]. Additionally, mitochondria-targeted synthetic macrofractions such as OPDEA and mitochondria-targeted peptides[87], which can further enhance tumor permeability[88-90], allowing more efficient induction of cuproptosis and stronger immune activation.

This mitochondrial stress enhances immune responses by promoting the infiltration of effector T cells and suppressing MDSCs[91]. Moreover, ROS accumulation in the TME shifts immune cells from immunosuppressive (*e.g.*, Treg cells and M2-type macrophages) to immune-activating phenotypes (*e.g.*, M1 macrophages), significantly improving anti-tumor immunity[92,93]. Furthermore, the combination of cuproptosis inducers and immune checkpoint inhibitors (*e.g.*, anti-PD-1/PD-L1 antibodies) can counteract immune escape mechanisms, enhancing immune surveillance[94].

3.3. Glucose metabolism and immune effects

The core mechanism of cuproptosis lies in the binding of copper ions to lipoylated proteins in the mitochondrial TCA cycle, which inhibits their activity and triggers metabolic disorders[1]. FDX1 is closely related to glucose metabolism, and its high expression promotes oxidative phosphorylation (OXPHOS), which enhances the cellular susceptibility to cuproptosis[95]. As well as p53 inhibits PKM2 activity by up-regulating circ*FRMD4A* expression, shifting glycolytic metabolism to the TCA cycle, thereby increasing sensitivity to cuproptosis[96]. Cells dependent on mitochondrial respiration are more susceptible to cuproptosis than glycolytic cells, so in lung cancer cells, increased glucose uptake promotes glycolysis and inhibits cuproptosis[1].

Abnormal glucose metabolism in tumor cells contributes not only to rapid tumor growth but also to the establishment of an immunosuppressive TME[97]. The increased glucose uptake and glycolysis in tumor cells produce excess lactate, acidifying the TME, which inhibits $CD8^+$ T cell and DC function[98,99]. This low pH environment also stabilizes HIF-1α and arginase, polarizing tumor-associated TAMs to the M2 phenotype and promoting the differentiation of Treg cells, further promoting immune evasion[100,101].

Nanopreparations can target and modulate glucose metabolism in tumor cells, overcoming these metabolic barriers and enhancing immune response[102,103]. Binding of glucose oxidase (GOx) to cuproptosis nanopreparations depletes glucose and inhibits glycolysis, thereby enhancing cuproptosis. In addition, it can be combined with glycolysis inhibitors[87] or lactate oxidase (LOx)[41] to remodel tumor metabolism, shifting the energy production from glycolysis to OXPHOS[104]. This reduces lactate production, alleviates TME acidity, and restores immune cell function[105].

Surface modifications of nanocarriers can also enhance tumor-targeting specificity[106]. Ligands such as hyaluronic acid or folic acid can bind to overexpressed receptors (*e.g.*, CD44 or folate receptors) on tumor cells, increasing nanoparticle accumulation at the tumor site and enhancing the efficacy of metabolic modulation[107,108]. By targeting glucose metabolism directly, nanoparticles synergize with cuproptosis inducers, boosting immune activation and the release of DAMPs from cuproptosis.

3.4. The role of lipid metabolism in immune regulation

Lipid metabolism in tumor cells play a pivotal role in regulating immune responses and the TME. High cholesterol levels in the TME can induce $CD8^+$ T cell exhaustion, while fibroblast growth factor 21 (FGF21) secreted by tumor cells exacerbates cholesterol accumulation in $CD8^+$ T cells, leading to dysfunction[109]. Arachidonic acid metabolites also promote immune evasion by activating the PPARγ pathway, which increases PD-L1 expression on DC, supporting immune suppression[110,111].

During cuproptosis, lipid peroxidation and fatty acid oxidation (FAO) are promoted, generating large amounts of ROS[112]. These products, including lipid peroxides (LPO), act as danger signals to activate DC and effector T cells, enhancing the anti-tumor immune response[113,114]. Nanopreparations play a critical role in modulating lipid metabolism by targeting lipid metabolic pathways. Nanocarriers can enhance ROS generation through FAO and facilitate the upregulation of copper ions, which activates the AMPK−PGC1α−PPARα signalling pathway, promoting FAO and amplifying both cuproptosis and immune activation[115,116].

Nanoparticles such as copper metal−organic frameworks (Cu-MOFs), loaded with mitofloxacin and axitinib, can synergistically drive cuproptosis versus ferroptosis *via* Fenton-like reactions, generating hydroxyl radicals ($\cdot$OH) and enhancing the overall immunotherapeutic effect[117]. These nanoparticles precisely target lipid metabolism, increasing oxidative stress and potentiating both ICD and immune activation.

3.5. Amino acid metabolism and regulation of the immune microenvironment

Tumor cells regulate amino acid metabolism to support their growth and suppress immune responses, particularly through glutamine metabolism and tryptophan metabolism. Glutamine is converted to glutamate *via* glutaminase (GLS), which is further involved in the TCA cycle[118]. Cuproptosis indirectly affects glutamine metabolism by interfering with the TCA cycle. GLS acts as a negative regulator in the process of cuproptosis, and its high expression negatively correlates with the susceptibility to cuproptosis[119]. Additionally, glutamine promotes the differentiation of $CD4^+$ T cells into the Treg phenotype and $CD8^+$ T cells into the memory T cell phenotype, contributing to immune evasion[120].

Nanopreparations can target and modulate glutamine metabolism, enhancing immune responses in the TME. Copper-doped polypyrrole nanoparticles modified with PM-coated BPTES (a GLS inhibitor) have been shown to inhibit glutamine metabolism, increasing ROS production and enhancing ICD[121]. This not only enhances tumor cell death but also reduces MDSC recruitment and promotes macrophage M1 polarization, boosting the anti-tumor immune response[122].

Tryptophan metabolism has a potent immunosuppressive function, and its main metabolic pathway is the kynurenine (KYN) pathway[123]. Among them, the IDO1 enzyme catalyzes the degradation of tryptophan, generating KYN, a metabolite that inhibits T and NK cell activity and promotes the expansion of Treg cells, enhancing immunosuppression[124-126]. Studies have shown that kynurenine enzyme promotes gastric cancer cell proliferation, invasion and resistance to cuproptosis, and reduces cuproptosis sensitivity by down-regulating LIAS[127]. Moreover, tryptophan 2,3-dioxygenase (TDO2), the rate-limiting enzyme of the KYN pathway, is sensitive to oxidative stress[128], and its activity may be inhibited by cuproptosis induced oxidative stress, thereby restoring immune cell function.

In addition, branched-chain amino acids (BCAA) are converted to α-keto acids by branched-chain amino acid transaminase (BCAT) and enter the TCA cycle[129]. Increased BCAA catabolism

promotes M2 macrophage polarization, and its dysregulation hinders $CD8^+$ T cell function[130,131]. By interfering with the TCA cycle, cuproptosis may indirectly affect the utilization efficiency of BCAA metabolites. Nano-formulations aimed at modulating BCAA metabolism can shift immune cell polarization towards an immune-activated M1 phenotype, enhancing tumor immunotherapy, and can be used for BCAT1 inhibitor delivery to enhance antitumor function of $CD8^+$ T cells[132].

3.6. The role of autophagy in immune regulation

Autophagy plays a dual role in immune regulation by both suppressing and enhancing immune responses. In the TME, autophagy promotes tumor cell survival by activating AMPK under hypoxic conditions, and tumor cells can evade immune surveillance by degrading MHC class I molecules[133,134]. However, autophagy also enhances immune activation by promoting antigen presentation[135]. Autophagic vesicles process intracellular antigens and present them *via* MHC I and MHC II molecules, activating $CD8^+$ T cells[136].

Nanopreparations can modulate autophagy to enhance immunogenic cell death. By targeting autophagy pathways, nanocarriers can trigger ROS-induced autophagy, enhancing the release of DAMPs such as HMGB1 and ATP, which increase DC maturation and immune cell activation[137]. Copper-based nanoparticles, like the copper (II) complex (LCU) are able to effectively kill HeLa cells *via* the ROS-triggered autophagy pathway[138]. In addition, synergizing these nanoparticles with cuproptosis inducers enhance overall immune activation and improves the efficacy of cancer immunotherapy.

3.7. Summary of the differential impact of cuproptosis on tumor metabolism and immune activation

We explored the pivotal role of nanopreparations in mediating cuproptosis-induced metabolic reprogramming and immune activation. Nanocarriers target mitochondrial stress, glucose metabolism, lipid metabolism, amino acid metabolism, and autophagy to regulate the tumor microenvironment and promote immune responses. Cuproptosis enhances ROS generation *via* Fenton reaction, activates mitochondrial stress and promotes immune cell activation. Nano-formulations regulate glucose metabolism by inhibiting glucose transport or enhancing OXPHOS, etc., alleviating the acidic environment of TME and restoring immune cell function. Lipid metabolism further promotes immune response by inducing lipid peroxidation and activating NLRP3 inflammatory vesicles[139]. Regulation of amino acid metabolism further disrupts cellular antioxidant homeostasis and enhances cellular sensitivity to cuproptosis. Autophagy enhances antigen presentation and amplifies ICD, boosting tumor recognition and clearance by the immune system (Table 3[1,41,84,86,87,98,104, 114,117,121,130,131,133,138,140-150]).

While cuproptosis affects tumor cell metabolism, it also regulates immune cell function, especially TAM polarization and Treg metabolism. Cuproptosis affects TAM metabolic reprogramming and polarization through mitochondrial dysfunction and oxidative stress. M2-type TAM is dependent on OXPHOS and FAO[151], and accumulation of cuproptosis disrupts the function of OXPHOS and inhibits metabolic adaptations in M2-type TAM. The mtDNA released by cuproptosis activates the cGAS−STING pathway, induces type I IFN production, promotes M1 polarization, and remodels the immunosuppressive microenvironment[23,152]. In addition, TCA circulatory disorders and oxidative

Table 3 Impact of cuproptosis on tumor metabolism and immune regulation: mechanisms, nanopreparation strategies, and metabolic reprogramming effects.

Metabolic pathway	Affected mechanism	Impact on immune response	Key nanopreparation strategies	Metabolic reprogramming impact
Mitochondrial stress	Mitochondrial dysfunction, decreased ATP, increased ROS[1]	Enhanced DC maturation, T-cell infiltration, immune activation[84]	Targeting mitochondria (*e.g.* TPP)[86]	Mitochondrial dysfunction, increased ROS[1]
Glucose metabolism	Increased glucose uptake, lactic acid production, TME acidification[98]	Glucose inhibits CTL and DC function[140], lactate inhibits T cell and NK cell function[141], promotes Treg recruitment and macrophage M2 polarization[142,143]	Inhibits glucose uptake, inhibits glycolysis[87], depletes lactic acid[41]	Inhibits glycolysis, reduces lactic acid accumulation, promotes OXPHOS, restores immune cell function[104]
Lipid metabolism	Promotes FAO, fatty acid oxidation, increased ROS[114]	Fatty acids promote DC and CTL inactivation[144], increase Treg activity[145]	Inhibits cholesterol metabolism, promotes FAO[117]	Enhanced FAO, increased oxidative stress, enhanced DC activation and T cell function[114]
Amino acid metabolism	GLS metabolism, BCAA metabolism, Ido1 tryptophan metabolism, promoting immune escape[146]	Glu promotes Treg and MDCS recruitment[147], macrophage M2 polarization[148], Kyn promotes increased Treg[149], BCAA catabolism enhances M2 polarization and inhibits CD8+ T cell function[130,131]	Inhibits GLS activity, blocks glutamine[121], inhibits Ido1[150], inhibits BCAT activity	Breaks down immunosuppression, promotes T-cell activation, macrophage M1 polarization[146]
Autophagy	Facilitates tumor cell survival[133], modulates immune response[138]	Evasion of immune surveillance, protective autophagy[133]	Inhibits protective autophagy, promotes autophagic ICD[138]	Triggering autophagy-dependent cell death, enhancing tumor immunity[138]

stress triggered by cuproptosis can inhibit glutamine and kynurenine metabolism, which in turn inhibits Treg proliferation. Whereas Treg depends on lactate metabolism to maintain immunosuppression, its elevation promotes Treg proliferation[101]. The synergistic action of copper ions with LOx depletes lactate and impairs Treg function, enabling cuproptosis-immunotherapy[153].

The strategic combination of cuproptosis inducers with metabolic modulators and immune checkpoint inhibitors further strengthens immune responses, overcoming immune escape mechanisms. In a BC model, cuproptosis significantly increases $CD8^+$ T cell infiltration and enhances therapeutic efficacy by optimizing reprogramming of glucose metabolism and lipid metabolism in conjunction with PD-1 antibody[154]. Nanopreparations offer a promising therapeutic approach by precisely targeting these metabolic alterations, enhancing immune activation, and improving the overall efficacy of cancer immunotherapy.

4. Design of cuproptosis-based nanoparticles

Nanotechnology-based immunomodulatory nanopreparations for cuproptosis offer a promising strategy to enhance cuproptosis induction and immune responses in cancer therapy. These advanced delivery systems not only allow precise control over drug release but also enable the targeted delivery of cuproptosis inducers to the tumor site, increasing their efficacy while minimizing off-target effects. The ability of nanoparticles to modulate the TME and induce ICD presents a significant opportunity for improving tumor immunotherapy (Fig. 4).

4.1. *Organic nanoparticles*

Organic nanomaterials are particularly well-suited for promoting cuproptosis and enhancing immune responses due to their excellent biocompatibility, modifiable surface properties, and controlled drug release capabilities[155]. These nanoparticles can significantly increase the stability and efficacy of cuproptosis-inducing agents, reduce toxic side effects, and precisely regulate immune responses through metabolic reprogramming of tumor cells.

4.1.1. *Polymer nanoparticles*

Polymeric materials commonly used as nanoparticle coatings, such as polyethylene glycol (PEG)-modified polymers and polyvinyl alcohol (PVA), provide nanoparticles with 'stealth' characteristics. These stealth properties prevent rapid clearance by the immune system, thereby extending circulation times and enhancing drug bioavailability[156]. For instance, DSPE-PEG_{2000}-NH_2 can be stably encapsulated on the surface of ES/CuO nanoparticles through covalent bonding. This dual protection strategy not only improves biocompatibility but also prolongs nanoparticle circulation, creating favorable conditions for the effective inducting cuproptosis[21].

Moreover, polymeric nanoparticles can be designed to respond specifically to the oxidative stress generated during cuproptosis, primarily through Fenton-like reactions and associated ROS production. ROS-responsive polymers release additional copper ions under oxidative stress, enhancing copper accumulation in tumor cells and intensifying the cytotoxic effects associated with cuproptosis[24]. Polydopamine (PDA)-modified DTC nanoparticles

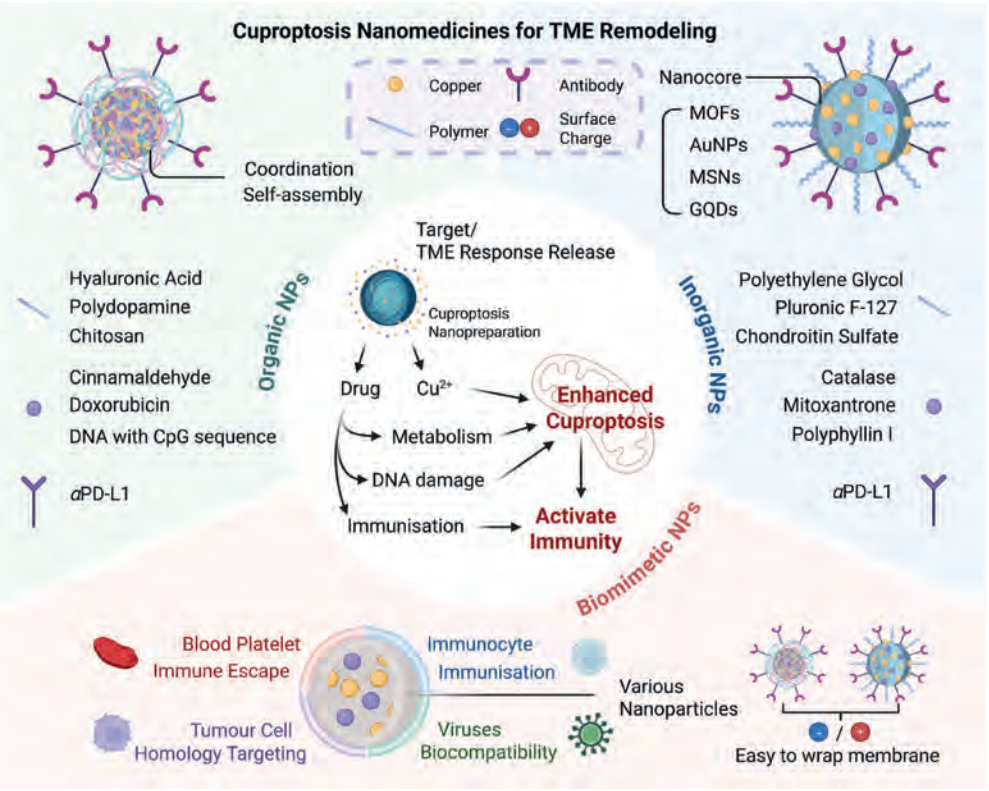

Figure 4 Cuproptosis nanoplatforms for TME modulation to enhance antitumor therapy. Cuproptosis nanoplatforms are carefully engineered to induce cuproptosis and reshape the immune microenvironment through multiple strategies, including targeted copper ion delivery, TME modulation, metabolic interference, and immune adjuvant integration.

can simultaneously accumulate copper within cells and inhibit copper export, significantly augmenting cuproptosis-mediated immunotherapy in 4T1 mouse BC model[157]. Similarly, hyaluronic acid (HA)-functionalized Cu-Pic nanopillars enhance the antitumor immune response by blocking polyamine synthesis and uptake, causing intracellular polyamine depletion, and thereby promoting both cuproptosis and pyroptosis (Fig. 5[158]).

Certain polymers also actively modulate immune response. For instance, polylactic acid-hydroxyacetic acid (PLGA) nanoparticles are efficiently internalized by antigen-presenting cells (APCs), leading to accumulation in peripheral immune organs such as lymph nodes. This accumulation facilitates the activation and differentiation of T cells[159]. Additionally, polymers like chitosan and sodium alginate assist in nanoparticle delivery to immune cells, stimulating cytokine and growth factor production[160-162]. These cytokines promote the differentiation and proliferation of $CD4^+$ and $CD8^+$ T cells, significantly enhancing antitumor immunity[163]. An illustrative example includes low molecular weight heparin tocopherol succinate nanoparticles loaded with chitosan and DSF, which activate the cGAS−STING signaling pathway upon inhalation. This activation promotes dendritic cell maturation and triggers potent antitumor immune responses driven by enhanced $CD8^+$ T-cell activity[164].

4.1.2. Liposomes

Liposomes are versatile, lipid bilayer-enclosed vesicles composed of amphiphilic lipids or phospholipids, enabling them to encapsulate bot hydrophilic and hydrophobic agents[165]. Their structural flexibility makes them ideal carriers for cuproptosis inducers, facilitating precise delivery to tumor cells. In particular, liposomes are well-suited for combination therapies, outperforming traditional carriers in targeting tumor sites more effectively[166]. For instance, during radiotherapy, tumor cells often exhibit varying degrees of damage, which can reduce uptake efficiency of conventional carriers. Liposomes, however, can fuse directly with cell membranes, enhancing drug internalization and ensuring efficient delivery to tumor cells[167]. Furthermore, liposomes co-loaded with copper ions and cinnamaldehyde exhibit photothermal properties and, upon light exposure, generate ROS. This promotes LPO and establishes a positive feedback loop of ROS production by mediating HSP suppression, ultimately contributing to ICD and strengthening the effects of immunotherapy[168].

Additionally, liposomes can be functionally modified to achieve targeted release of cuproptosis inducers. This can be accomplished through the B-cell/antibody recognition pathway or by leveraging cancer-specific peptides presented on MHC-I molecules for T cell targeting[169,170]. Such targeted strategies amplify

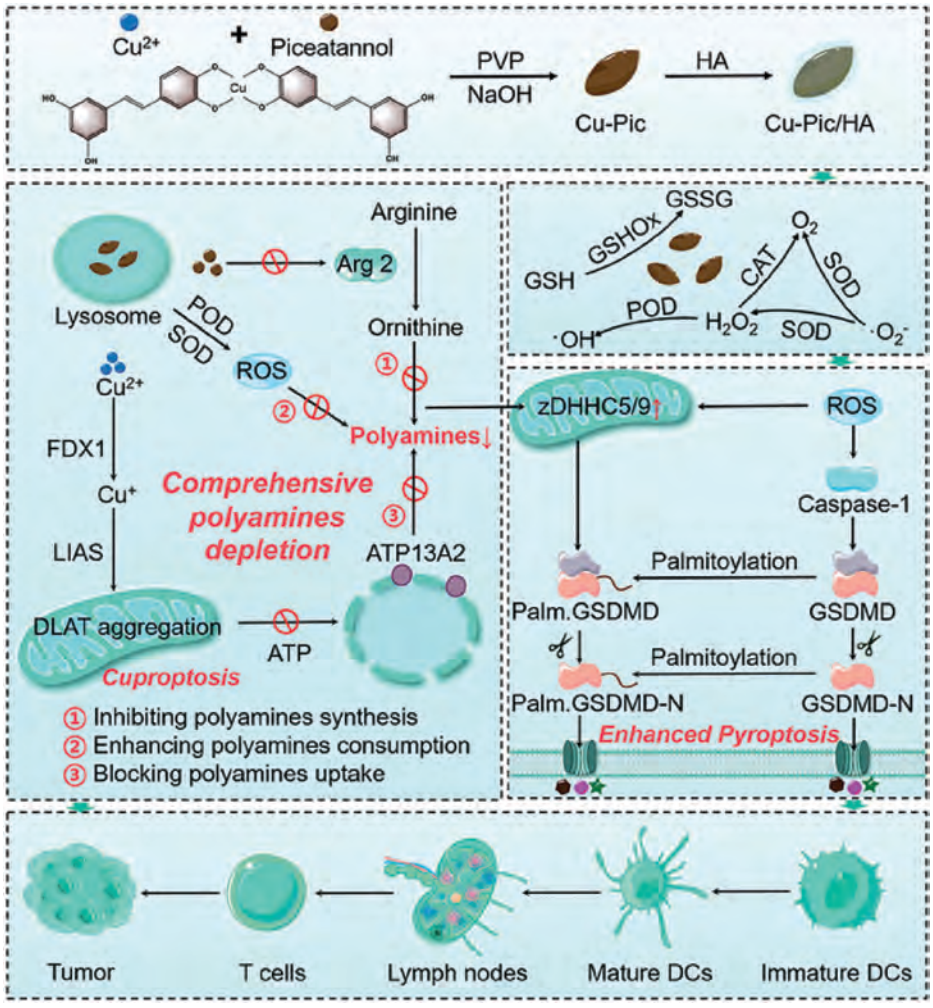

Figure 5 Schematic illustration of the mechanism by which Cu-Pic/HA nanoparticles enhance pyroptosis and cuproptosis *via* polyamine depletion and thereby activate tumor immune responses. Reprinted with the permission from Ref. 158. Copyright © 2024 Wiley Online Library.

the immune-activating of cuproptosis and enhance the overall efficacy of tumor immunotherapy. By improving both drug delivery precision and immune engagement, modified liposomes represent a promising nanoplatform for advancing cuproptosis-based combination therapies.

4.1.3. Polyelectrolyte complexes

Polyelectrolyte complexes are used to encapsulate copper ions, facilitating their prolonged circulation and enhancing their ability to trigger cuproptosis in tumor cells. The positively charged regions of these nanoparticles interact with the negatively charged cell membrane, promoting the uptake of the encapsulated drugs and enhancing copper ion delivery directly to the mitochondria of tumor cells.

In addition to their role in cuproptosis induction, polyelectrolyte complexes can be engineered for gene therapy. For example, delivery of STING agonists through these complexes activates dendritic cells and T cells, enhancing tumor immunogenicity while simultaneously promoting cuproptosis[171]. Similarly, the delivery of *p53* gene can regulate oxidative stress and increase the sensitivity of tumor cells to copper-induced death[172]. Polyelectrolyte complexes can also deliver long single-stranded DNA (PApt) containing multivalent epithelial cell adhesion molecule (EpCAM) aptamers, specifically targeting tumor cells and improving drug targeting[173]. Additionally, CpG sequence-based DNA can be delivered to activate TLR-9, increasing DC maturation, enhancing antigen presentation, and promoting T-cell activation, thereby potentiating the immune response triggered by cuproptosis[174].

4.2. Inorganic nanoparticles

Inorganic nanoparticles are particularly advantageous in cuproptosis-based therapy due to their high structural stability, optical and thermal properties, and catalytic activity. These properties make them ideal for both drug delivery and immune activation, especially in combination with photothermal and photodynamic therapies. The ability of metal nanoparticles to catalyze the Fenton reaction effectively promotes ICD, enhancing the anti-tumor immune response. Moreover, the integration of organic and inorganic materials through hybridization allows for multifunctional capabilities that improve drug efficacy and therapeutic outcomes.

4.2.1. Metal−organic frameworks (MOFs)

MOFs are a promising class of inorganic nanomaterials that can be engineered to load copper ions, cuproptosis inducers, and immunomodulatory agents, making them an effective platform for both drug delivery and immune system activation. MOFs can be synthesized using impregnation-phosphorylation, solvothermal, and electrochemical methods[175-177]. Making it loaded with copper ions with ES triggers cuproptosis by depleting FDX1 and increasing mitochondrial ROS in tumor cells. This leads to ICD, activation of DC, and increased infiltration of $CD8^+$ T cells, resulting in a systemic immune memory and enhanced tumor immune responses[178].

MOFs can be modified to optimize immune activation. Spike-like Cu-MOFs, for instance, can physically interact with the tumor cell membrane, triggering mechanical stimulation-sensitive cellular responses, including DNA damage and activation of the cGAS−STING pathway, which enhances immune system activation[179]. The structural defects in MOFs allow for the formation of electron-distributed single metal catalytic sites, which enhance enzyme-like catalytic activity and ROS generation, further accelerating cuproptosis and improving immune activation[180]. These modifications provide new strategies for effective cancer therapy by simultaneously enhancing oxidative stress and immune responses.

In addition, OPDEA coating can be performed outside the Cu-MOFs to increase the cell membrane affinity of the nanoparticles through surface modification and promote effective uptake by tumor cells[87]. Coating tumor cell membranes can likewise improve the biocompatibility of nanoparticles and enable homologous targeting[181]. Chondroitin sulphate (CS) can also be modified for CD44 receptor-mediated tumor-specific targeting and hyaluronidase-responsive charge reversal for effective cellular internalization (Fig. 6[182]). All of these strategies can enhance the cuproptosis effect and thus induce immune activation.

4.2.2. Mesoporous silica nanoparticles (MSNs)

MSNs are highly porous materials with large surface areas, making them ideal for drug delivery and immune modulation[183]. Their porous structure allows for efficient loading and controlled release of cuproptosis inducers. MSNs can be used to APCs and enhance immune responses, significantly improving Th1 and Th2 anticancer immunity *in vivo*, as well as effector memory T-cells[184].

In cuproptosis immunotherapy, MSNs can deliver CuO_2 and cisplatin (DDP), enhancing drug loading and prolonging the action of the drugs *in vivo*[185]. The acid-sensitive Si−O−Si bonds in MSNs enable them to respond to the acidic TME, facilitating the release of copper ions when the nanoparticles are exposed to low pH environments. Additionally, CuO_2-MSNs can decompose tannic acid (TA)-copper complexes at the TME, resulting in glutathione (GSH) depletion, inducing a severe redox imbalance, and significantly enhancing cuproptosis[186].

4.2.3. Layered inorganic nanoparticles

Layered inorganic nanoparticles, such as Cu-layered double hydroxides (LDHs), offer significant advantages in terms of high drug loading and cell surface affinity. The positively charged lamellar structure of Cu-LDHs facilitates interactions with negatively charged cell membranes, promoting effective cellular uptake. After internalization, it is suitable for causing copper ion release in the extremely acidic environment of lysosomes, triggering mitochondrial damage and enhancing the cuproptosis effect. Intratumoral administration can continuously acidify the tumor microenvironment, impede the lysosome-dependent autophagy process in tumor cells, and increase the number of anti-tumor TAMs and T cells, effectively inhibiting BC proliferation *in vivo*[187].

Layered inorganic nanoparticles (*e.g.*, MXenes) can be functionalized, *e.g.*, by binding targeting ligands (*e.g.*, aptamers, antibodies, etc.) to improve tumor targeting and enhance immunomodulation. Combining them with PD-L1 antibodies allows the materials to be preferentially enriched at the tumor site, blocking the PD-1/PD-L1 pathway, lifting immunosuppression, and promoting the activation and infiltration of effector T cells to further enhance the anti-tumor immune response[188].

4.2.4. Other inorganic nanoparticles

AuNPs have unique physicochemical properties that make them ideal carriers for cuproptosis inducers. AuNPs are capable of binding to copper ions and immunotherapeutic agents *via* electrostatic or covalent bonding, delivering a high concentration of immune adjuvants and antigens to tumor cells[189]. This enhances immune responses and facilitates tumor cell killing, while improving the therapeutic efficacy of cuproptosis-based therapies.

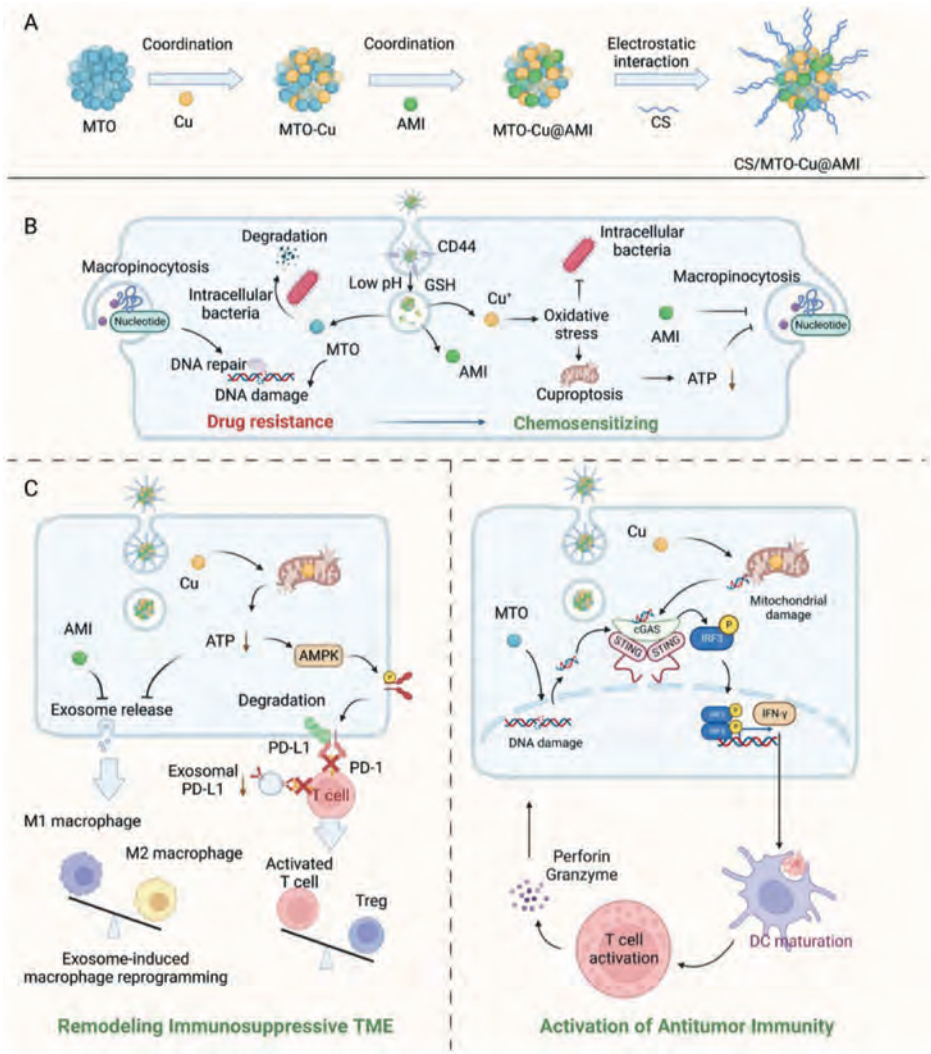

Figure 6 CS/MTO-Cu@AMI nano-adjuvant reverses chemoresistance and activates anti-tumor immunity through cuproptosis-induced mitochondrial damage, inhibition of megaloblast action and exosome release. Reprinted with the permission from Ref. 182. Copyright © 2023 Wiley Online Library.

The localized surface plasmon resonance (LSPR) effect of AuNPs plays a crucial role in immune activation. By absorbing specific wavelengths of light and converting them into thermal energy, AuNPs can induce ICD in tumor cells, activating the anti-tumor immune response[190]. Combining gold nanocages with Cu-HSA and exposing them to near-infrared (NIR) laser irradiation enhances ROS generation and drug loading, triggering a strong immune response[191]. In addition, compared to spherical DSF-loaded copper-doped mesoporous silica-shelled gold nanorods, such rod-shaped AuNPs exhibit higher uptake efficiencies, allowing them to be adapted to different therapeutic conditions and to enhance the efficacy of cancer immunotherapy[192].

Semiconducting ferroelectric materials combine ferroelectric and semiconducting properties to efficiently transport copper ions and catalyze ROS generation to promote cuproptosis. By introducing copper vacancies in Bi_2CuO_4, these materials enhance piezoelectric and ferroelectric catalytic properties, which help to induce ICD by decreasing mitochondrial ATP levels, inhibiting copper ion efflux, and facilitating the release of HMGB1. This process promotes dendritic cell maturation, M1-type macrophage polarization, and T-cell differentiation, which enhances immune memory and remodels the immune microenvironment. The synergistic effect of ferroelectricity and copper ion delivery provides a new strategy to overcome immunosuppression and enhance tumor immunotherapy (Fig. 7[193]).

Graphene quantum dots (GQDs) are stable *in vivo* and effectively protect Cu_2O from degradation, reducing side effects on normal cells. GQDs also target tumor DNA and inhibit topoisomerase I/II, leading to DNA damage. Z-type heterojunctions formed by GQDs with Cu_2O inhibit electron−hole pair complexation and enhance the acoustic kinetic activity of Cu_2O, making it efficient in generating ROS that Triggers cuproptosis and activates ICD, reverses immunosuppressive TME, and induces systemic immune responses[194].

4.3. *Biomimetic nanoparticles*

Biomimetic nanoparticles, which mimic the natural components of cell membranes, have emerged as a promising tool in cancer therapy. These nanoparticles take advantage of the unique properties of cells from various origins, allowing for targeted delivery and immune system evasion. By utilizing cell membranes or their

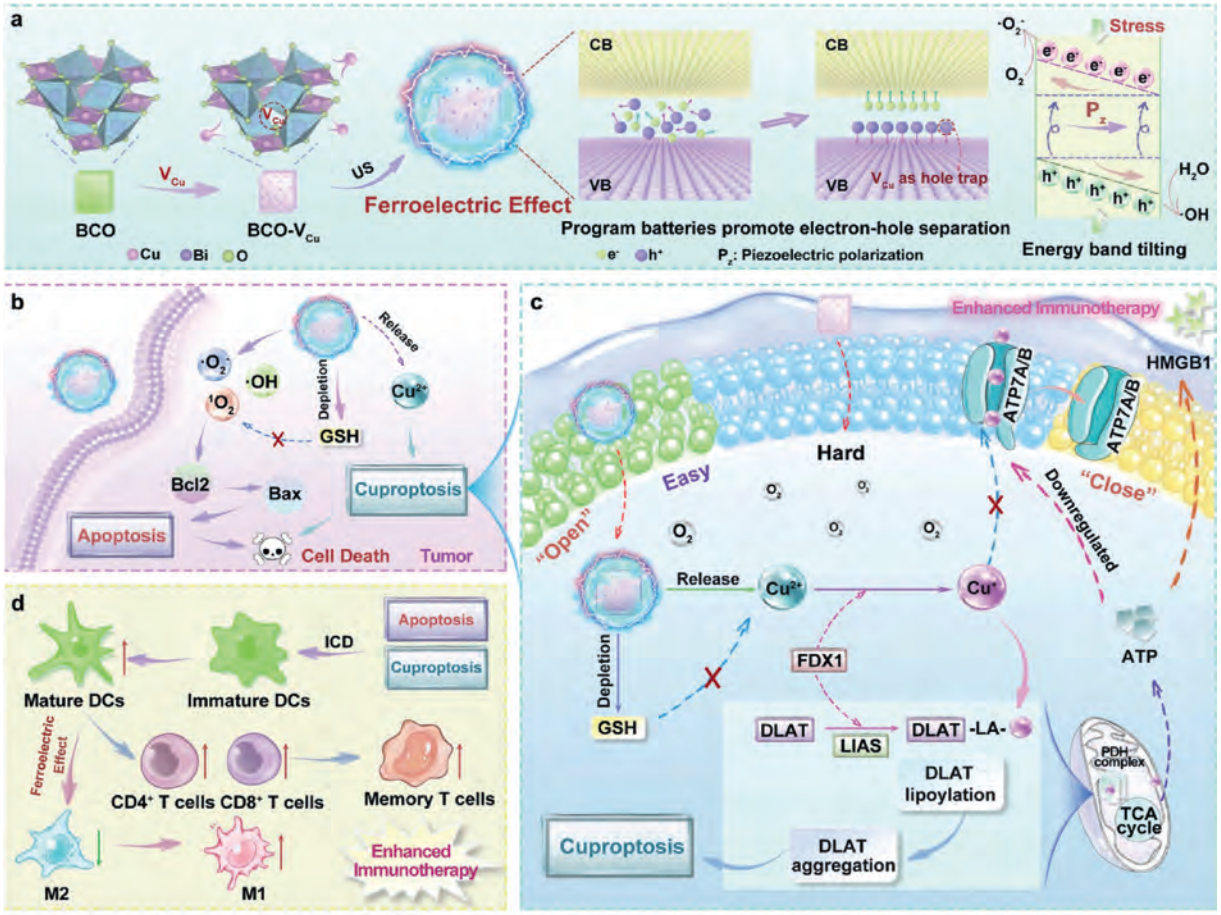

Figure 7 Schematic diagram of the ferroelectric effect of BCO−VCu and the mechanism of tumor immunotherapy. Reprinted with the permission from Ref. 193. Copyright © 2024 Wiley Online Library.

components, these nanoparticles can evade immune clearance, prolong circulation time, and enhance the efficacy of cuproptosis while simultaneously promoting immune activation.

4.3.1. Platelet membrane-camouflaged nanoparticles

Platelets naturally express surface proteins such as CD47, CD55, and CD59, which allow them to evade immune recognition and phagocytosis by macrophages[195,196]. By using platelet membrane-camouflaged nanoparticles, Cu_2O and TBP-2 can be modified to carry P-selectin proteins that specifically target CD44 receptors on tumor cells. This cell-mimetic design ensures that nanoparticles can evade the immune system and specifically target solid tumors, enhancing the delivery of cuproptosis inducers while protecting them from premature immune clearance[197].

4.3.2. Tumor cell membrane-camouflaged nanoparticles

Membranes derived from tumor cells offer superior protection against immune surveillance compared to platelet membranes, allowing for more efficient targeting of solid tumors. For example, $CuO@Gd_2O_3$ nanoparticles loaded with LOx can be camouflaged with Renca tumor cell membranes to selectively target renal clear cell tumors. This biomimetic design not only enhances the precision of copper-based cuproptosis induction but also activates immune responses by promoting antigen presentation and enhancing T cell infiltration into the tumor microenvironment (Fig. 8[41]). By utilizing tumor cell membranes, nanoparticles can homologously target cancer cells, improving the therapeutic efficacy and reducing off-target effects.

4.3.3. Microbial membrane-coated nanoparticles

Another innovative approach is the use of bacterial membranes for nanoparticle coating. *Escherichia coli*-based microbial nanohybrids, when combined with Cu_2O nanoparticles, have demonstrated good biocompatibility and the ability to accumulate at tumor sites. These microbial membrane-coated nanoparticles are capable of inducing cuproptosis upon intravenous injection, specifically targeting colon tumors and reversing immunosuppression in the tumor microenvironment[42]. This strategy allows for the targeted induction of cuproptosis and enhances the anti-tumor immune response by promoting immune cell activation and ROS generation.

4.3.4. Immune cell membrane-coated nanoparticles

Biomimetic nanoparticles coated with immune cell membranes offer another layer of specificity and immune activation. For example, T-cell membrane-coated nanosheets loaded with DSF/Cu^{2+} can mask PD-L1 overexpression triggered by DSF/Cu^{2+}, creating a positive feedback mechanism that enhances ICD and boosts tumor responsiveness to immunotherapy[188]. DC and natural killer (NK) cells can also be used as nanoparticle coatings, further enhancing immune activation[159,198]. Notably, NK cells and their surface proteins (*e.g.*, RANKL) can interact with

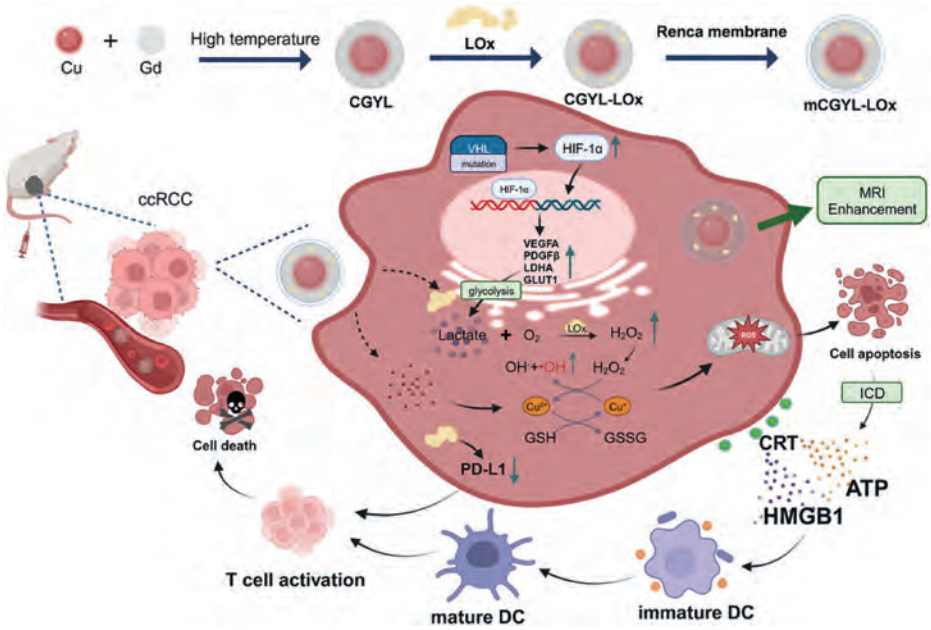

Figure 8 mCGYL-LOx exerts antitumor effects by inducing cuproptosis and CDT and is used in tumor immunotherapy. Reprinted with the permission from Ref. 41. Copyright © 2023 Wiley Online Library.

macrophage membranes to promote polarisation of pro-inflammatory M1 phenotypes and enhance tumor killing[199]. By integrating immune cell membranes, nanoparticles can trigger synergistic immune activation in addition to cuproptosis, improving the overall tumor immunotherapy efficacy.

4.4. Overview of nanopreparations for cuproptosis induction and immune modulation

Nanopreparations are crucial for enhancing cuproptosis and modulating immune responses in the TME. Various nanopreparations induce cuproptosis through multiple mechanisms, including ROS and copper ion release, each providing distinct benefits for targeted drug delivery and immune modulation (Table 4[24,41,158,167,168,174,179,180,182,185-188,190,191,197,200-217]). Organic nanoparticles (*e.g.*, polymer-based, liposomal) exhibit favorable biocompatibility and controlled release, whereas inorganic systems (*e.g.*, MOFs, gold nanoparticles) deliver enhanced catalytic activity and photothermal effects to boost ROS generation.

These diverse nanocarriers enhance drug delivery and immune activation, promoting antigen presentation and T-cell infiltration. The capacity to customize nanopreparations for specific tumor types and immune contexts underscores their promise in advancing personalized immunotherapy. Overall, incorporating these nanoparticles into cuproptosis-based treatment strategies offers a promising solution for overcoming tumor therapy challenges and enhancing clinical outcomes.

5. Synergistic application of cuproptosis nanopreparations with immunotherapy

Cuproptosis presents a promising avenue for tumor immunotherapy by triggering immune responses and enhancing the efficacy of traditional therapies. When combined with other therapeutic modalities, such as ICB, PTT, and sonodynamic therapy (SDT), cuproptosis has demonstrated synergistic effects, providing a more effective and personalized treatment strategy (Fig. 9).

5.1. Combination with immune checkpoint blockade (ICB)

In the TME, tumor cells inhibit T cell activation by expressing PD-L1, which binds to PD-1 on T cells[218]. ICB therapy lifts this immunosuppression, enhancing T cell recognition and killing of tumor cells. However, ICB monotherapy often faces challenges such as low tumor immunogenicity and insufficient T-cell infiltration[219]. As illustrated in Fig. 9, sustained elevation of copper ion levels can promote PD-L1 expression on tumor cells, thus laying the foundation for improving the effectiveness of anti-PD-L1 therapy[35]. In addition, cuproptosis further enhances the anti-tumor immune response by inducing mitochondrial damage, depriving energy supply, and then activating the AMPK pathway to promote PD-L1 degradation[182]. Therefore, the combination of cuproptosis and ICB not only promotes T-cell infiltration and activation, but also doubly regulates PD-L1 expression, thereby synergistically enhancing the efficacy of tumor immunotherapy[220].

Nanopreparations provide an efficient way to deliver both cuproptosis inducers and immune checkpoint inhibitors simultaneously. CuP/Er nanoparticles promote lipid peroxidation by inhibiting aerobic glycolysis, depleting GSH, and generating ROS, which induces cuproptosis along with ferroptosis[154]. By combining αPD-L1, the proliferation and activation of T cells can be enhanced, thus providing a more effective antitumor immunotherapy strategy.

Mitoxantrone was liganded with copper ions and loaded with amiloride for topical targeting of CS modification. Cu^{2+} triggered cuproptosis-induced mitochondrial dysfunction, which activated AMPK pathway-mediated degradation of PD-L1 proteins, and amiloride inhibited megaloblastoid action and exocytosis, thus effectively increasing the susceptibility to immunotherapy. In addition, dsDNA damaged during treatment activates the

Table 4 Comparison of various nanopreparations for cuproptosis induction and immunomodulation.

Type	Mechanism of cuproptosis induction	Type function characteristics	Disadvantages	Mechanisms of immunity	Clinical phase
Polymer nanoparticles	Targeted delivery of copper ions, interferes with copper metabolism[158]	High drug stability, biocompatibility, targeting and controlled release, immunomodulatory function[24,158]	Complex synthesis, potentially toxic[158]	Copper ions and ROS-induced ICD enhance immunity[24]	Albumin-bound paclitaxel Abraxane® for pancreatic cancer (NCT00691054) and metastatic BC (NCT00308178)[200]
Liposomes	Encapsulation of cuproptosis drugs, induction of oxidative stress and cell death[168]	Biocompatible, low immunogenicity, suitable for combination therapy[167]	Challenges to large-scale production, high preparation costs[167]	Avoid clearance by the immune system, combine with other therapies, enhance ICD[167]	Doxil® for recurrent ovarian cancer (NCT00248248) and human immunodeficiency virus-induced Kaposi's sarcoma (NCT05567601)[201,202], Marqibo against acute lymphoblastic leukaemia (NCT00495079)[203], Depcyte® against tumorous meningitis (NCT00854867)[204]
Polyelectrolyte complexes	Charge interactions promote drug uptake[174]	High transfection efficiency, easy functionalisation, enhanced immune system activation, combined with gene therapy[174]	More complex design, potentially higher immune response[174]	Combined gene therapy enhances immunisation[174]	Widely used in preclinical experiments such as mesothelioma[205], hepatocellular carcinoma[206]
Metal−organic frameworks	Porous structure efficiently loaded with copper ions, structural changes to promote uptake[179,180]	High surface area and structural tunability, good drug loading capacity and release control, significant immunomodulatory effect[179,182]	Complex preparation process, high production cost[180]	Structural adjustments to improve immune activation and high drug loads to promote immunological effects of cuproptosis[179,180]	Widely used in preclinical experiments, such as triple-negative BC[207], pancreatic cancer[208], rectal cancer[209]
Mesoporous silica nanoparticles	High cuproptosis death drug load, released under acidic conditions[186]	Large specific surface area with nanopores, TME responsiveness, as an immunoadjuvant[186]	Requires more complex surface modification and functionalization[186]	Enhances antigen presentation and T-cell activation, improve immune response[185]	In phase II clinical trials, cRGDY-PEG-Cy5.5-nanoparticles were used for head and neck melanoma sentinel lymph node detection (NCT02106598)[210]
Layered inorganic nanoparticles	Laminar patch structure promotes copper ion accumulation[211]	High aspect ratio, high surface area, high drug loading capacity, strong cell surface affinity[188]	Still need to optimize functionalization, complex synthesis process[188]	Promotes tumor cell uptake and enhances the immune effects of cuproptosis[187]	Widely used in preclinical experiments, such as BC[212], sarcoma osteoma[213]
Other (gold nanoparticles)	SPR effect generates thermal energy, activates copper ion release and triggers oxidative stress[191]	High biocompatibility, surface modifiable, flexible morphology control, photothermal effect[190,191]	High cost, lower productivity[191]	Photothermal and ROS effects promote immune activation[191]	Widely used in preclinical studies such as bladder cancer[214], cervical cancer[215]
Biomimetic nanoparticles	Mimics natural cells to promote drug uptake[197]	Mimics cellular components for precise targeted delivery, enhanced immune surveillance[41,188]	Complex preparation, high difficulty in large-scale production[188]	Enhance tumor cell uptake, activate and enhance immune cell function[41,188]	Widely used in preclinical experiments, such as BC[216], glioblastoma[217]

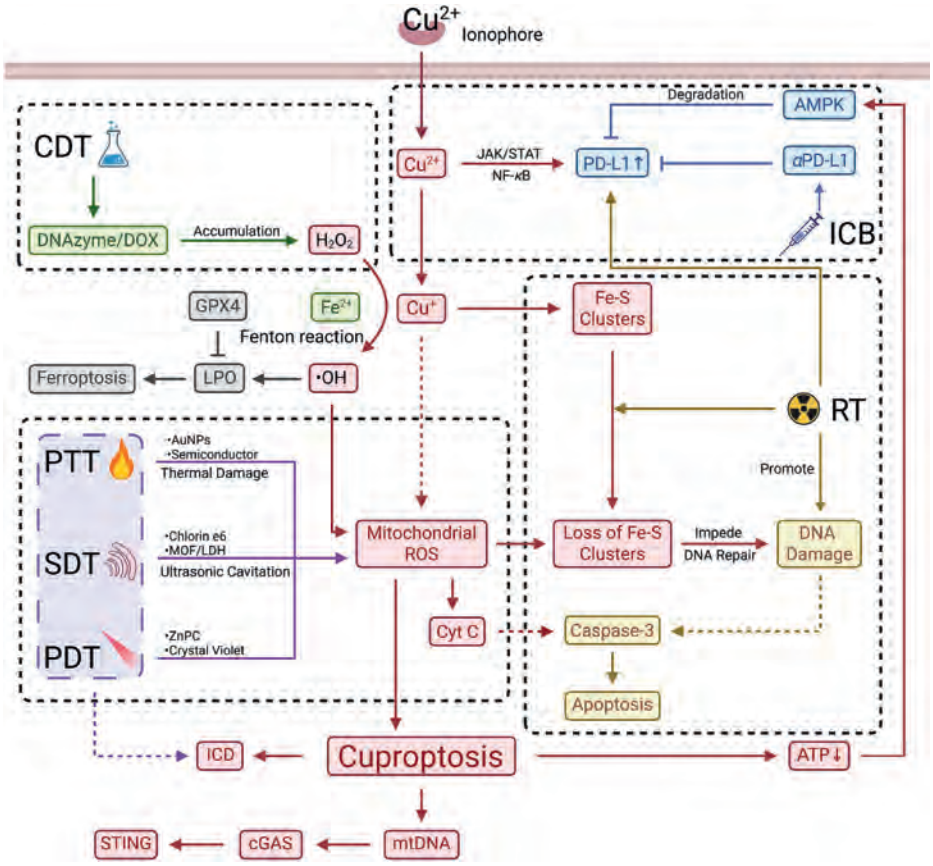

Figure 9 Synergistic mechanisms between cuproptosis and combined therapeutic modalities in enhancing anti-Tumor immunity. Multiple therapeutic strategies synergize with cuproptosis by elevating ROS levels, inducing oxidative stress, and disrupting organelle homeostasis (including mitochondria, nucleus, endoplasmic reticulum, and lysosomes). These effects collectively enhance tumor immunogenicity and relieve immunosuppression, thereby potentiating anti-tumor immune responses. (i) Chemodynamic therapy (CDT) synergizes with cuproptosis primarily through Fenton-like reactions, thereby enhancing tumor chemosensitivity. (ii) Photothermal therapy (PTT), sonodynamic therapy (SDT), and photodynamic therapy (PDT) synergize with cuproptosis by promoting mitochondrial ROS accumulation. (iii) Radiotherapy (RT) synergizes with cuproptosis by disrupting Fe−S clusters and activating caspase-3-mediated apoptosis. (iv) Immune checkpoint blockade (ICB) synergizes with cuproptosis through pathways such as JAK−STAT and NF-κB, enhancing immune activation.

cGAS−STING pathway, further stimulating anti-tumor immunity[182].

5.2. *Combination with photothermal therapy (PTT)*

PTT uses NIR light to generate heat, which induces tumor cell death by disrupting cellular structures. The thermal effect also activate immune responses by triggering heat shock protein (HSP) transcription and promoting NK recruitment[221,222]. However, the immunostimulatory effect of PTT itself is more limited. When combined with cuproptosis agents, as presented in Fig. 9, PTT enhances the release of ROS and promotes the release of copper ions from nanocarriers, which accelerates the onset of cuproptosis, thereby inducing ICD and enhancing anti-tumor immune responses. And tumors are more sensitive to heat and cuproptosis due to their hypoxic and weakly acidic microenvironment[223]. Thus, the combination therapy of PTT and cuproptosis is more effective in synergistically suppressing tumors by expanding ICD, increasing ROS accumulation, and disrupting tumor cell homeostasis.

Organic semiconductor polymers have high photothermal conversion efficiency, NIR-II ultra-small polymer dots (Pdots) bind to DOX and enhance cuproptosis and ICD effects through Cu (II)-mediated ligand self-assembly by utilizing the NIR-II absorption properties and releasing copper ions and ROS under laser irradiation. GSH depletion makes the tumor cells more sensitive to oxidative stress, and the synergistic effect of DOX Further enhancement of ICD, combined with αPD-L1 can activate the immune response and improve the therapeutic effect[224].

Copper-sulfur compounds and copper oxide are excellent photothermal materials but poorly water-soluble. Cu_2-xS nanopreparations were prepared by glucose-mediated biomineralization to target tumors using the high glucose metabolism of tumor cells, and NIR-II laser irradiation releases copper ions to react with GSH to generate ROS, induce ICD and activate systemic immune responses[225].

5.3. *Combination with chemodynamic therapy (CDT)*

CDT induces tumor cell death using Fenton or Fenton-like reactions to generate ·OH within the tumor[226]. However, low levels of H_2O_2 in the tumor may limit the effectiveness of CDT[227]. As shown in Fig. 9, H_2O_2 generation was promoted by the addition of drugs capable of generating H_2O_2, whereas copper ions, due to

their higher Fenton reaction rate and stability over a wide pH range, accelerated the decomposition of H_2O_2 and promoted the accumulation of ROS, thus enhancing oxidative stress and inducing cuproptosis[228]. Excess ROS generated during this process can deplete intracellular GSH, weakening the antioxidant defense of tumor cells and further exacerbating oxidative damage. Therefore, the combination of cuproptosis and CDT significantly enhances ROS generation, disrupts cellular homeostasis, promotes immune activation, and improves tumor therapeutic efficacy.

Copper nanoparticles, based on Fenton-like reactions, enhance the generation of hydroxyl radicals (−OH) and O_2, thereby amplifying oxidative stress. Disulfide-bonded hybrid copper/iron amorphous metal−organic framework (HaMOF), an amorphous MOF that lacks long-range ordering and has excellent catalytic activity, amplifies oxidative stress, increases H_2O_2 production, depletes GSH, and triggers cuproptosis, ferroptosis, and apoptosis[228].

The generation of Cu^{2+} and H_2O_2 by copper oxides in acidic tumor microenvironments further expands the application of CDT. Cu_2O nanocomplexes with ZIF-8 as a carrier, which adsorbed DNAzyme on its surface, enhanced the effect of cuproptosis by specifically cleaving CAT-associated RNA to increase intracellular H_2O_2 levels[229]. This combination enhances the immune response and promotes the synergistic effect of cuproptosis and CDT.

5.4. Combination with photodynamic therapy (PDT)

PDT kills tumor cells by generating singlet oxygen ($^1O_2$) through photosensitizers (PS) upon light activation. Although it has been used in clinical practice, its therapeutic effect is often limited by the hypoxia of the TME, and the shallower penetration depth of light in the tissue also affects its killing effect on deeper tumors[230]. Cuproptosis can form a synergy with PDT to compensate for these deficiencies. As depicted in Fig. 9, Copper ions enhance PDT-induced oxidative damage by enhancing the Fenton reaction to increase the efficiency of ROS generation and by triggering oxidative stress in the deeper layers of the tumor independently of the area of light exposure. In addition, PDT promotes the release of tumor antigens and immunostimulatory molecules, while cuproptosis also induces ICD, both of which work together to activate the immune system and further enhance anti-tumor therapeutic effects[231].

Some nanomaterials can be excellent photosensitizers in their own right. Nano-heterostructures consisting of heterogeneous carbon nitride nanosheets (HCN) and copper-loaded 1T-MoS_2 nanosheets (CuMS) have strong reducing properties with high specific surface area and sulfur-rich sites, and this structure enhances NIR light-induced catalytic activity and ROS generation, inducing potent cuproptosis[232].

MOF-derived materials, such as copper-loaded mesoporous structures, improve the efficiency of PDT by maximizing photosensitizer loading and enhancing ROS generation. Dispersion of single-atom nanoenzymes (SAzymes) in MOF maximizes catalytic activity and induces cuproptosis and ferroptosis, thereby reversing the TME[181]. By synergizing with cuproptosis, these agents can overcome the limitations of PDT, improve immune responses, and enhance the efficacy of cancer immunotherapy.

5.5. Combination with sonodynamic therapy (SDT)

SDT uses ultrasound (US) to activate acoustic sensitisers, which generate ROS and trigger a cavitation effect, thereby promoting tumor cell death. Although it has a similar mechanism of ROS generation as in PDT and the antitumor immune effects are also limited by the hypoxic conditions of TME, SDT has greater tissue permeability and catalytic properties[233]. As demonstrated in Fig. 9, after the synergistic application of SDT and cuproptosis, the cavitation effect of SDT can enhance the generation of ROS, and the stability and persistence of ROS can be improved by the Fenton reaction of cuproptosis, which can form a synergistic amplification effect[45,231]. Moreover, cuproptosis and SDT can jointly induce ICD and promote DC maturation and antigen presentation, thus enhancing anti-tumor immune response and therapeutic efficacy.

MOF-derived materials with high surface area and porous structure enhance the ultrasound cavitation effect, facilitating ROS generation under US irradiation. Cu_2-xSe@cMOF nanoparticles promote cuproptosis and selenium ion release under ultrasonic irradiation, selenium ion conversion to H_2Se, which further promotes cell death *via* gas therapy and further enhances immune response in combination with ICB therapy[45].

LDH due to its unique layered structure permits optimization of its acoustic-dynamic therapeutic properties through chemical composition and structural modulation. Copper-substituted ZnAl ternary LDH nanosheets (ZCA NS) exhibit a strong Jahn-Teller effect that provides additional active sites to promote ROS generation. ZCA NS exhibits excellent ICD properties under ultrasound irradiation and enhances immune effects by increasing cuproptosis and SDT sensitivity through GSH depletion (Fig. 10[211]).

5.6. Combination with radiotherapy (RT)

RT induces DNA damage by ionizing radiation, ultimately leading to apoptosis. Notably, the expression of cuproptosis-related proteins (FDX1 and LIAS) was up-regulated in residual tumor tissues after radiotherapy, increasing the sensitivity of tumor cells to cuproptosis[234]. As depicted in Fig. 9, Cu^+ in cuproptosis impairs cellular DNA repair by inhibiting the synthesis of Fe−S cluster proteins. Radiotherapy induced DNA damage is more difficult to repair in this situation, resulting in cells that are more sensitive to radiotherapy[235]. And RT was able to increase the expression of PD-L1 in tumor cells, which provided the basis for further combination therapy with ICB[236].

A copper-containing polymetallic oxygenate material (PWCu) was designed as a nanocapsule structure. Its ultra-high specific surface area of CuO_6 octahedron, which is highly susceptible to reduction by water-radiated reductants, releases Cu ions to induce cuproptosis when activated by X-ray irradiation, further stimulating immune responses and optimizing RT effects to improve tumor selectivity and killing efficiency[234].

PVP-coated copper (Cu^{2+}) and hafnium-doped nanoparticles amplify ROS generation, induce DNA damage, cuproptosis, and enhance immune response under radiation. This combination likewise optimizes the RT effect and improves tumor selectivity and killing efficiency[237].

5.7. Overview of synergistic strategies for cuproptosis-based immunotherapy

The clinical translation of cuproptosis nanopreparations still faces significant challenges, particularly regarding the long-term cumulative toxicity of metal ions. In healthy adults, serum copper levels typically range from 70 to 140 μg/dL[238], and prolonged exposure to elevated copper concentrations can result in metabolic

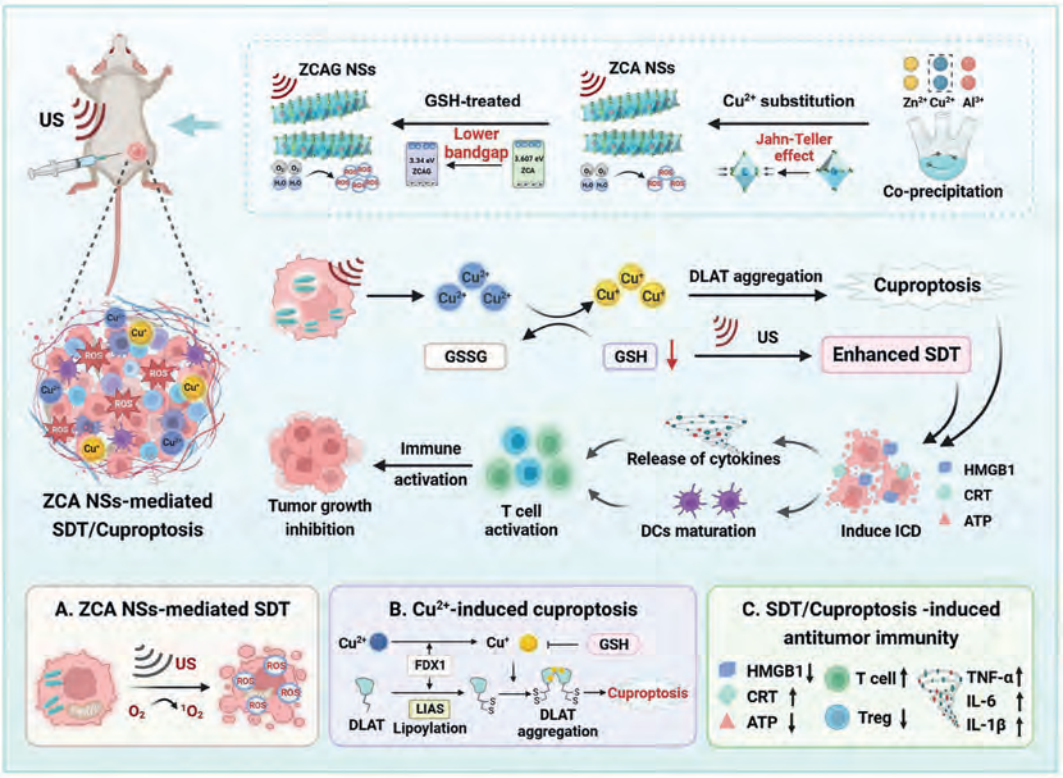

Figure 10 Schematic representation of the underlying mechanism of SDT/Cuproptosis tumor immunotherapy synergistic therapy mediated by ZCA NSs. Reprinted with the permission from Ref. 211. Copyright © 2024 American Chemical Society.

disorders, liver damage and even conditions such as Wilson's disease[20]. However, it is important to note that the mechanism underlying cuproptosis relies on mitochondrial proteolipid acylation and the destabilization of iron-sulfur cluster proteins, meaning that even small amounts of copper ions entering cells and accumulating in mitochondria are sufficient to induce cell death-thus reducing the need for large systemic copper large doses and minimizing toxicity risks[1]. Additionally, many nanomaterials used in cuproptosis delivery systems possess high biocompatibility and can effectively buffer copper-related toxicity, improving the overall safety of these therapies[239]. Despite these advantages, clinical studies investigating cuproptosis remain limited. To date, no clinical trials have specifically evaluated its application in cancer; the only registered trial involving cuproptosis focuses on acute myocardial infarction (NCT06833918). Current oncology-related studies explore the combined use of disulfiram (DSF) and copper in the treatment of refractory sarcoma and breast cancer (NCT05210374 and NCT03323346). While preclinical animal models have provided encouraging data, the absence of validation in human tissues remains a critical barrier to clinical translation.

Commonly used nanocarriers in these studies include polymeric nanoparticles and Cu-MOF, which enable controlled release and reduced systemic toxicity. Notably, most preclinical efforts favor combination therapies over monotherapies, leveraging synergistic mechanisms to enhance the efficacy of cuproptosis (Table 5[21,42,87,94,164,167,185,188,194,235,240-252]). For example, integrating cuproptosis with immune checkpoint blockade (ICB) has been shown to improve T-cell activation and tumor suppression, while photothermal therapy (PTT) and chemodynamic therapy (CDT) increase ROS production, facilitating immunogenic cell death (ICD) and further stimulating immune responses. Similarly, photodynamic therapy (PDT) and sonodynamic therapy (SDT) help overcome hypoxic limitations by enhancing ROS levels, making them particularly effective for deep-seated tumors. Radiotherapy (RT) can also augment immune responses by increasing tumor sensitivity to cuproptosis. Collectively, these combinatorial strategies not only enhance the therapeutic effectiveness of cuproptosis but also address persistent challenges in oncology, such as immune evasion and insufficient treatment precision. Therefore, the integration of cuproptosis with complementary therapies holds broad developmental potential and is anticipated to emerge as a clinically translatable anti-tumor strategy.

6. Perspectives of cuproptosis nanopreparations in the immune microenvironment and individualized therapy

Precision medicine has significantly advanced cancer therapies, particularly individualized tumor immunotherapy. However, variable copper metabolism among tumor cells creates challenges, affecting patient responses to cuproptosis-based therapies. Precise patient screening and tailored treatment regimens based on individual metabolic profiles are essential for maximizing the effectiveness of cuproptosis-mediated immunotherapy.

6.1. Metabolomics-guided precision therapy for cuproptosis and clinical translation

Metabolomics, as central tool in precision medicine, systematically analyzes dynamic metabolite changes in tissues and biofluids, capturing genome, environmental, and microbiome

Table 5 Comparison of cuproptosis combination therapies with immunotherapy.

Combination therapy	Therapeutic mechanism	Nanomedicine types	Cuproptosis reagents	Encapsulated drug	Immune pathways	Tested model	Ref.
Combination with ICB	Cuproptosis increases ROS and PD-L1 expression, enhances T cell responses and immune checkpoint inhibition	Polymer NPs	Cu^{2+}	DTPH, CaO_2, JQ-1, DSPE-PEG-FA	Glycolysis↓, ATP7B↓, reverse TIME, αPD-1↑	CT26 cell, CT26 hormonal mice	240
		Polymer NPs	Cu^{2+}, DSF	LMWH-TOS, chitosan	Augment cGAS-STING activity, mature DC↑, CTLs↑, NK↑, αPD-1↑, ATP7B↓	B16F10 cell, B16F10 hormonal mice	164
		Polymer NPs	Cu^{2+}, ES	Amphiphilic biodegradable polymer	Mature DC↑, $CD8^+$ T cells↑, reverse TIME, αPD-1↑	BIU-87 cell (human source), MB49 cell-hormonal mice	94
		Polymer NPs	CuO, ES	Glycol polymer	CTLs↑, reverse TIME, αPD-1↑	B16 cell, B16 hormonal mice	21
		Cu-MOF	Cu-based MOF of MOF-199	DDM	ATP7B↓, mature DC↑, $CD8^+$ T cells↑, reverse TIME, αPD-1↑	GL261 cells, GL261-luc hormonal mice	241
		Cu-MOF	$Cu(NO_3)_2$	OPDEA, 2-methylimidazole, Zn $(NO_3)_2 \cdot 6H_2O$, siPDK	Glycolysis↓, mature DC↑, $CD8^+$ T cells↑, reverse TIME, αPD-1↑	B16F10 cell, B16F10 hormonal mice	87
		Bionic NPs	Cu^{2+}	HPB, Au−Pt nanozymes, cancer cell membrane	Caspase-1, TNF-α, Calreticulin, HSP70, HSP90, ATP↑, PD-L1↓	CT26 cell, CT26 hormonal mice	235
Combination with PTT	Photothermal effect induces copper ion release, ROS generation, and promotes immune cell activation	Self-assembly NPs	Cu^{2+}	MoO_4^{2-}, SDS	Multienzyme activities↑, cooperative ferroptosis, reverse TIME	MCF-7 cell (human source), 4T1 hormonal mice	242
		Nanozymes	Cu−O_2/Cu−O_4	DMONs, phloretin	Glycolysis↓, ATP7B↓	CT26 cell, CT26 hormonal mice	243
		Nanozymes	Cu_2O	$Mn_3Cu_3O_8$	Multienzyme activities↑, cooperative ferroptosis, HSP70↑	CT26 cell, CT26 hormonal mice	244
		Bionic NPs	Cu^{2+}, DSF	PD-1 overexpressing T cell membrane, Mxene	Mature DC↑, $CD8^+$ T cells↑, reverse TIME, PD-L1↓	4T1 cell, 4T1 hormonal	188
Combination with CDT	Fenton reaction generates ROS, increases GSH consumption, and enhances ICD	Cu-MOF	Cu^{2+}	DOX, hyaluronate acid	ROS↑, mature DC↑, $CD8^+$ T cells↑	4T1 cell, 4T1 hormonal mice	245
		MSN	CuO_2	DDP, SiO_2	HIF-1↓, reverse TIME	H22 cell, H22 hormonal mice	185
		LDH	Copper −aluminum layered double	5-FU, hydroxide, hyaluronic acid	Reverse TIME, M1 phenotype↑, $CD4^+$ T cells↑, $CD8^+$ T cells↑	4T1 cell, 4T1 hormonal mice	246
Combination with PDT	Photosensitizer activation generates ROS and synergistically enhances ICD	Hydrogel	Cu^{2+}	Glycyrrhizic acid, norcantharidin	Reverse TIME	HepG2 cell (human source), Hepa 1−6 hormonal mice	247

Combination with SDT	High-frequency acoustic waves induce ROS generation and ultrasonic cavitation enhances ICD	Quantum dot	Cu_2O	GQD	ROS↑, reverse TME, DNA damage	4T1 cell, 4T1 hormonal mice	194
Combination with RT	Induces DNA damage, generates ROS, and enhances immune effects	Bionic NPs	Cu^{2+}	Capsaicin, Pdzyme, zeolitic imidazolate framework-8	Mature DC↑, $CD8^+$ T cells↑, reverse TIME	MC38 cell, MC38 hormonal mice	167
Combination with PTT and ICB	Increased temperature induces heat stress, relieves immunosuppression and promotes immune cell activation	Nanozymes	CuI	Bi_2Se_3	Multienzyme activities↑, mature DC↑, $CD8^+$ T cells↑, αPD-1↑	PC-3 cells, PC-3 hormonal mice (human source)	248
		Bionic NPs	Cu_2O	*E. coli*	Cooperative ferroptosis, mature DC↑, $CD8^+$ T cells↑, reverse TIME	MC38 cell, MC38 hormonal mice	42
Combination with PTT and CDT	Heating promotes catalytic reaction to produce ROS and exacerbates immune response	Cu-MOF	Cu^{2+}	H_3tbc-TEA, F-127	GSH↓, ATP7B↓, GSDME↓	CT26 cell, CT26 hormonal mice	249
Combination with PTT, CDT and ICB	Heating and catalysis promote ROS generation and release immunosuppression	Polymer NPs	Cu_2O, ES	PEG	Mature DC↑, $CD8^+$ T cells↑, reverse TIME	4T1 cell, 4T1 hormonal mice	250
		Self-assembly NPs	Cu^{2+}	ZnPc; thioketal, 1-MT, DOX	ROS↑, ATP7B↓, reverse TIME, αPD-1↑	PC-3 cells, PC-3 hormonal mice (human source)	251
Combination with PTT, CDT and PDT	Triple ROS generation for enhanced ICD	Hydrogel	$CuCl_2$	NAC, 4-mercaptobenzoic acid, $HAuCl_4$, NaOH, $NaBH_4$	Reverse TIME	HepG2 cell (human source), H22 hormonal mice	252

influences[253,254]. Tumor metabolic reprogramming is linked to drug resistance and immune evasion, and metabolomics can identify specific metabolic phenotypes to guide patient stratification and therapy[255]. In CAR-T therapies, metabolomics has identified metabolic signatures like low glutamate levels associated with rapid cytokine release syndrome[256], highlighting the shift from static genic profiling to dynamic phenotype analysis.

Cuproptosis disrupts the TCA cycle, induces lipid peroxidation, and collapses energy metabolism, producing unique metabolic fingerprints characterized by impaired TCA enzyme function, glutathione depletion, oxidative stress, and disrupted ATP synthesis[1]. These metabolic features provide a basis for patient stratification and support the clinical validation of cuproptosis. In hepatocellular carcinoma PDX models, epigallocatechin gallate combined with copper ion carriers significantly suppressed tumor growth, accompanied by HSP70 upregulation and ATP7B inhibition, confirming cuproptosis induction[257]. Similarly, in cervical cancer PDX models, tretinoin promoted copper accumulation *via* the XIAP/COMMD1/ATP7B axis and triggered depletion of FDX1 and DLAT, highlighting the potential of cuproptosis in precision therapy[258]. These signatures facilitate precise patient stratification and guide combination therapies due to cuproptosis-induced ICD[259]. Metabolomics thus offers two-dimensional insights into metabolism−immunity interactions, enhancing therapy personalization.

Humanized models are also essential for preclinical validation of cuproptosis nanoformulations, accurately replicating human immune environments and metabolic profiles[260]. In the Hu-PBL-CDX NSCLC model, the LDH inhibitor oxamate augments the anti-tumor efficacy of Pembrolizumab, increases $CD8^+$ T-cell infiltration, and improves NSCLC immunotherapy outcomes, thereby providing a preclinical rationale for combination therapy[261]. By integrating metabolomics data, researchers can dynamically track metabolic shifts and immune responses driven by cuproptosis, thereby elucidating the immunometabolic synergy of nanoformulations. Moving forward, combining multi-omics analysis with high-throughput screening in humanized mice is anticipated to overcome the limitations of conventional models and expedite the clinical translation of cuproptosis-based therapies[262].

6.2. *Patient screening based on tumor copper metabolic profile*

Copper metabolism biomarkers, including cuproptosis-related genes (CRGs, *e.g.*, FDX1, LIAS, DLAT)[1], copper transporters (*e.g.*, CTR1, ATP7A/B)[263], and long-stranded noncoding RNAs (lncRNAs) regulating cuproptosis[264], show notable prognostic and therapeutic potential across cancers (Table 6[265-274]). In triple-negative breast cancer (TNBC), elevated ATP7A and LIAS levels correlate with worse overall survival (OS), whereas high LIPT1 expression indicates a favorable prognosis[265]. In HCC, elevated expression of certain lncRNAs correlates with immunosuppression and chemotherapy resistance. Moreover, ATP7A/B directly mediates chemoresistance by binding and effluxing platinum drugs[267]. In NSCLC, high CTR1 expression increases the likelihood of benefiting from platinum-based chemotherapy[275], and targeting ATP7B regulated by miR139 reduces platinum resistance in ovarian cancer[276]. Collectively, these studies support individualized treatment approaches.

Tumors exhibiting abnormal copper metabolism (*e.g.*, HCC and TNBC) are potential candidates for cuproptosis-mediated immunotherapy. HCC displays copper accumulation, copper−protein complex formation, elevated copper-binding proteins (CBPs), and reduced copper transport proteins such as ATP7A/B and SLC31A1/2[277,278]. TNBC also exhibits similar copper metabolic abnormalities[279]. COX17 expression in HCC correlates with immune cell infiltration and immune checkpoint expression[280]. Tumors with abundant lipoylated proteins show heightened sensitivity to cuproptosis, and FDX1 expression correlates with the amount of these lipoylated proteins-providing a basis for metabolic typing of cuproptosis drugs[281]. The clinical value of these biomarkers can be validated using TCGA, GEO, and other multicenter cohort data, establishing a basis for precise screening and optimization of cuproptosis nanomedicines[282,283].

Beyond conventional biomarker testing, advanced imaging techniques like PET/CT are crucial for evaluating copper metabolism. PET/CT integrates functional and anatomical data to monitor tumor metabolism in real time[284]. The development of the PET copper ion probe ^{64}Cu-liposome, which functions as both a radiotracer and a targeted drug delivery system, has shown promise. In a hamster oral cancer model, this probe effectively identifies early lesions pre-metastasis and shows higher sensitivity to abnormal mucosa, facilitating early diagnosis[285]. This imaging approach could enable novel strategies for monitoring immune responses linked to cuproptosis. Despite its efficacy in animal models, clinical use of PET copper metabolism imaging is constrained by issues such as probe stability, resolution, and cost[286]. Future improvements in immune molecular probe design may bolster the precision and clinical feasibility of cuproptosis-based immunoassessment.

6.3. *Hierarchical modulation of the immune microenvironment and therapeutic optimization*

TME is a critical determinant of tumor immunotherapy efficacy. The TME's heterogeneity can markedly influence tumor responses, underscoring the need for precise environmental modulation in individualized therapy. In highly aggressive tumors (*e.g.*, breast and colorectal cancers), the TME often exhibits strong immunosuppression, marked by limited T-cell infiltration, elevated Treg and M2-type macrophage levels, and secretion of inhibitory factors (TGF-β, IL-10) that undermine anti-tumor immunity[287,288].

Cuproptosis helps counter these challenges by inducing oxidative stress in the TME, driving the of M2-to M1-macrophage polarization and bolstering anti-tumor immune responses[24]. Combining cuproptosis with ICB and Treg-targeted therapies can further restore immune function and bolster tumor suppression[21]. For highly immunogenic tumors, such as renal cell carcinoma and non-small cell lung cancer[289,290], cuproptosis can induce immunity *via* ICD. Moreover, adding immunostimulants (*e.g.*, STING or TLR agonists) can further amplify the immune response[174,179]. Tailoring TME modulation to each tumor's specific immune environment is vital for optimal therapeutic outcomes, enabling precise and individualized immunotherapy.

Additionally, tumors frequently experience hypoxia, which activates angiogenic factors (*e.g.*, VEGF) that drive tumor growth and metastasis. Tumors like lung cancer and BC often overexpress HIF-1α or VEGF, fostering tumor angiogenesis[291,292]. Anti-angiogenic therapies aimed at VEGF signaling can normalize tumor vasculature, thereby increasing immune cell infiltration, especially tumor-infiltrating lymphocytes (TILs)[293]. Combining anti-VEGF drugs (*e.g.*, axitinib) with cuproptosis inducers promotes vascular normalization, further inhibiting tumor growth and

Table 6 Clinical implications of cuproptosis-related biomarkers across different cancer types.

Cancer type	Biomarkers	Function in cuproptosis	Regulation direction	Clinical implication	Biomarker analysis	Ref.
TNBC	ATP7A, DLST, LIAS; LIPT1, PDHA1; LINC01614/miR-204-5p/SLC31A1 axis	Copper transport, copper metabolism, energy metabolism	ATP7A, DLST, LIAS; LIPT1, PDHA1 upregulated	Prognostic, Predictive	High ATP7A/DLST/LIAS expression → poor OS; high LIPT1/PDHA1 → better prognosis; SLC31A1 axis predicts immune cell infiltration & chemo-sensitivity	265, 266
HCC	ATP7A/B, SLC31A1/2; ATP7A mRNA, SLC31A1/2 mRNA	Copper transport	ATP7A/B, SLC31A1/2, SLC31A1/2 mRNA downregulated; ATP7A mRNA upregulated	Prognostic, Predictive	Decreased ATP7A/B, SLC31A1/2 linked to tumor progression and poor survival	267
LC	DLD, DLAT, PHDA1, PHDB, CDKN2A	Lipid metabolism, cell cycle	Upregulated	Prognostic	High DLD/DLAT/PDHA1/PHDB/CDKN2A → poor OS; DLD/DLAT/CDKN2A→ high risk indicator	268
SKCM	LIPT1, PDHA1, SLC31A1	Lipid metabolism, energy metabolism, copper transport	Upregulated	Prognostic, Immunologic	High LIPT1/PDHA1/SLC31A1 → better prognosis; high LIPT1 →increased PD-L1 expression and decreased Treg infiltration	269
ccRCC	ATP7B, DLAT, DLD, LIAS, SLC31A1, DBT, FDX1, PDHB	Copper transport, copper metabolism, energy metabolism	ATP7B, DLAT, DLD, LIAS, SLC31A1 upregulated; DBT, FDX1, PDHB downregulated	Prognostic, Immunologic	High DLAT and low DBT/PDHB → poor OS; ATP7B/DBT/DLAT/LIS/PDHB are associated with immune status	270
ESCA	SLC25A5, SLC23A2, PDHX, COX7B, PIH1D2, FDX1, ATP7A, NDUFB1	Copper transport, copper metabolism, energy metabolism	Upregulated	Prognostic, Immunologic	High SLC25A5/SLC23A2/PDHX/ATP7A/COX7B → poor OS and more immune infiltration; high PHID2 → long OS	271
COAD	FDX1; CKDN2A, SDHB, CCS, ULK1, CMC1	Copper metabolism, energy metabolism, cell cycle	Upregulated	Prognostic, Immunologic	FDX1 positively correlates with OS, TME remodeling and immune cell infiltration; CKDN2A, SDHB, CCS, ULK1, CMC1 predict prognosis by immunologic microenvironment	272, 273
CC	ATP7A, DBT, DLAT, FDX1, SLC31A1, GCSH, LIPT1, PDHA1, PDHB	Copper transport, copper metabolism, energy metabolism	ATP7A, DBT, DLAT, FDX1, SLC31A1 upregulated; GCSH, LIPT1, PDHA1, PDHB downregulated	Prognostic	DBT/FDX1/LIPT1/PDHA1 → positive prognosis; ATP7A/DLAT/GCSH → negative prognosis	274

augmenting the immunogenic response to cuproptosis[117]. This strategy not only refines the TME but also optimizes therapy, offering a robust avenue for individualized cancer treatment.

6.4. *AI-driven design of cuproptosis nanopreparations*

Artificial intelligence (AI) can synergize data-driven predictions with domain-specific knowledge to play a key role in the design of cuproptosis nano-formulations. Inspired by advanced platforms such as FormulationDT, researchers can use machine learning to analyze structural correlations between drug molecules and their formulation properties to optimize copper-based nanocarriers[294]. FormulationDT demonstrated how the PU-Decide framework can address the challenge of positive unlabeled learning in pharma datasets even with limited negative samples to build robust classification models (average ROC_AUC >0.91)[294]. This approach can be applied to cuproptosis formulations by training models for copper ion interactions, metabolic enzyme binding modes, and nanocarrier compatibility to identify the best drug candidates for enhanced tumor targeting.

These platforms are typically based on large amounts of drug formulation data for training and learning. The FormulationAI platform, for example, covers exhaustive data on six major drug formulation systems and can accurately predict a wide range of key properties of formulations[295]. For cuproptosis therapies, such systems can predict the suitability of nanocarriers based on copper chelation capacity, metabolic pathway regulation, and tumor microenvironment penetration. Simulation of absorption, distribution, metabolism and excretion (ADME) through hybrid models such as PBPK and Meta Tox, combined with the PASS (Prediction of Activity Spectrum of Substances) algorithm, enables prediction of the bioactivity profiles of compounds and their metabolites[296,297]. Artificial intelligence can optimize the pharmacokinetics of nanoparticles while minimizing off-target toxicity.

Artificial intelligence can also predict cell abundance within a wide range of tumors, using deep neural network (DNN) models to predict cell proportions by analyzing the gene expression profiles of tumor cells, thus providing a basis for targeted tumor therapy[298]. The use of SHAP analysis improves the interpretability of models, revealing the overall impact of molecular features on the design of formulation strategies, as well as key molecular features of immune activation[299]. This is consistent with the principle of "structure determines function" and enables tailored modifications to expand the ICD triggered by cuproptosis. In addition, AI-driven patient stratification based on a multimodal cancer treatment response prediction model that integrates clinical information, treatment history, genomic and imaging data, etc., may be able to identify patients who are the most responsive to the cuproptosis−immunotherapy combinations in the most responsive populations[300,301]. Artificial intelligence-driven design has the potential to overcome key barriers in metabolic regulation and immune activation, bringing us closer to optimizing the clinical application of cuproptosis nano-formulations.

6.5. *Cuproptosis and liquid biopsy: real-time monitoring and efficacy prediction*

Incorporating copper metabolic profiles with liquid biopsy offers a powerful approach to monitor the process of cuproptosis and evaluate its therapeutic efficacy in real time. By tracking copper ion levels in the bloodstream, liquid biopsies not only reflect the initiation of cuproptosis but also provide insight into changes in copper metabolism within tumor cells, especially in the context of sugar and lipid metabolism[302,303]. Modulating these metabolic

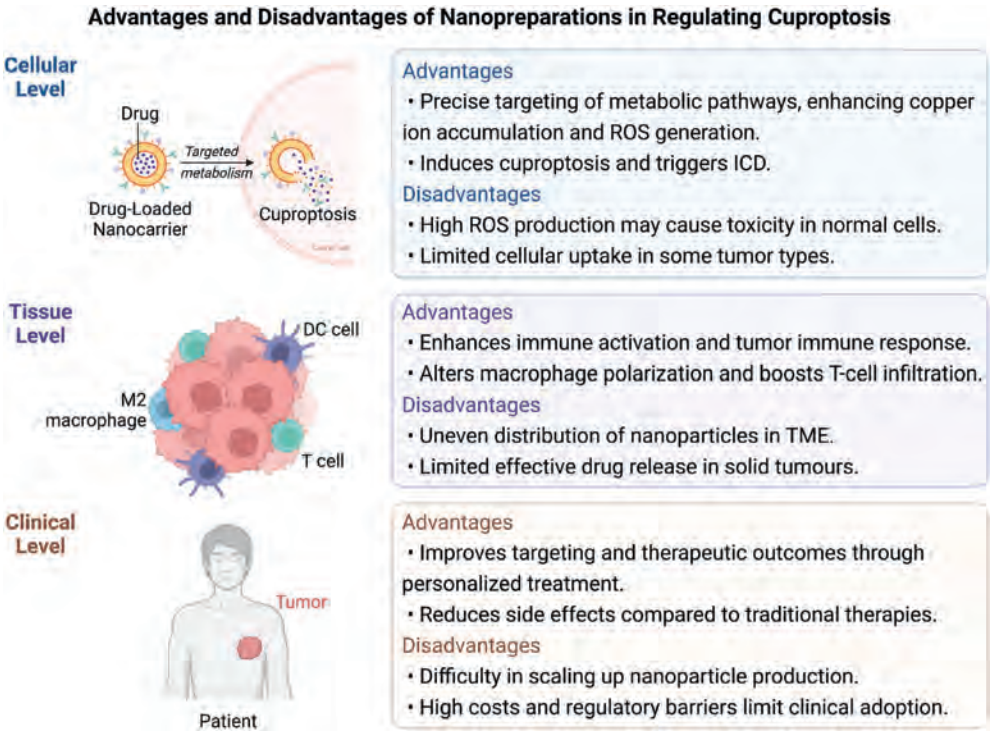

Figure 11 Advantages and disadvantages of nanopreparations in regulating cuproptosis-induced tumor metabolism and immunity at cellular, tissue, and clinical levels.

pathways induces an oxidative state in tumor cells, thereby accelerating cuproptosis and triggering immune responses. The levels of ROS and GSH during oxidative stress can serve as key indicators for monitoring cuproptosis progression.

Liquid biopsies can detect changes in DAMPs such as HMGB1 and ATP, which signal immune activation triggered by cuproptosis. Liquid biopsy also offers valuable information about immune responses by assessing the expression of immune cells like T cells, dendritic cells, and macrophages, as well as immune factors such as IFN-γ, TNF-α, and IL-2, which are indicative of immune infiltration[304]. Monitoring immune checkpoint molecules like PD-1 and PD-L1 is critical for identifying immune escape, which can provide a foundation for combining cuproptosis with ICB therapy[305].

Moreover, multidrug resistance (MDR), a common challenge in cancers such as hepatocellular carcinoma and pancreatic ductal adenocarcinoma, can be effectively addressed by liquid biopsy[306-308]. For instance, TPGS/CS-CA nanoparticles delivering ES-Cu complexes can bypass P-glycoprotein (P-gp)-mediated efflux and enhance cuproptosis immunotherapy in drug-resistant cancer cells. These nanoparticles also induce the polarization of macrophages towards the M1 phenotype, enhancing immune surveillance and clearance[309]. Liquid biopsy allows for early detection of drug resistance and enables the timely adjustment of treatment regimens by tracking biomarker changes over time[310]. This approach provides a comprehensive solution for the precision and individualization of future cancer treatments, supporting more targeted and effective therapeutic strategies based on real-time monitoring of cuproptosis, immune activation, and drug resistance.

In conclusion, cuproptosis-induced tumor immunotherapy holds great promise, particularly with the advancement of precision medicine. Nanopreparations play a key role in modulating copper metabolism and tumor immunity, offering targeted therapeutic benefits. These treatments can improve tumor immune responses by inducing ICD and reprogramming tumor metabolism, which enhances the effectiveness of immune therapies. Personalized treatment approaches, informed by individual tumor characteristics and copper metabolic profiles, are crucial for optimizing cuproptosis therapies. Technologies like liquid biopsies and AI-driven design can further refine these treatments. The advantages and limitations of nanopreparations in regulating cuproptosis and immune activation, underscore the need for tailored strategies to maximize treatment efficacy and improve clinical outcomes (Fig. 11).

7. Summary and outlook

The discovery of cuproptosis as a novel mode of cell death, first identified by Tsvetkov and colleagues[1] in 2022, has opened new avenues for cancer therapy. Distinct from traditional cell death mechanisms, cuproptosis uniquely combines tumor cell death with the activation of robust immune response, highlighting its promise for tumor immunotherapy. Its integration with various immunotherapeutic strategies, especially when facilitated by advances in nanotechnology, has demonstrated significant potential for enhancing treatment specificity and efficacy. Despite this promising outlook, several important challenges remain. Excessive copper accumulation, essential for initiating cuproptosis, can lead to tissue damage and oxidative stress, posing significant safety concerns for clinical applications. Consequently, rigorous biosafety studies-including thorough *ex vivo* and *in vivo* assessments-are necessary to precisely determine safe copper dosage ranges and minimize adverse off-target effects. Furthermore, while nanomedicines significantly improve copper ion delivery to tumors, additional optimization is required to achieve higher drug delivery efficiency and specificity, thereby enhancing therapeutic safety and effectiveness.

To realize the full potential of cuproptosis-based nanomedicine strategies, future research must address critical scientific questions and technical bottlenecks on multiple fronts. First, the mechanistic relationship between cuproptosis and immune regulation needs comprehensive and systematic analysis. Specifically, studies should clarify whether the metabolic signaling pathways directly influence immune cell phenotype remodeling or if their effects on the TME occur indirectly through mitochondrial and endoplasmic reticulum stress responses. Employing integrated multi-omics approaches will be essential for resolving these complexities. If non-metabolic regulatory pathways are involved this could affect the targeting strategies employed by nanomedicine formulations, necessitating reassessment of their therapeutic suitability. Second, translating cuproptosis-induced immune activation into effective anti-tumor responses remains challenging due to the involvement of complex molecular networks and signaling pathways. Thus, strategies to optimize cuproptosis-mediated immunomodulation through rational combination with other therapeutic modalities are essential for enhancing overall therapeutic efficacy. Finally, clinical validation of cuproptosis-related therapies is still in its infancy, and transitioning from fundamental research to large-scale clinical trials remains a significant hurdle. Consequently, future studies should prioritize mechanism elucidation, nanoformulation optimization, and rational combination therapies to expedite clinical translation.

In conclusion, cuproptosis presents an exciting and innovative strategy for advancing cancer immunotherapy. With ongoing technological improvements and deeper mechanistic insights, cuproptosis-mediated immunotherapies have substantial potential to evolve into more effective and personalized cancer treatments, ultimately benefiting patients through improved clinical outcomes.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82374050 and 82074030), the Faculty Development Research Project of Tianjin University of Traditional Chinese Medicine (Project No. Y-202506, China), and the Open Projects Fund of the Shandong Key Laboratory of Carbohydrate Chemistry and Glycobiology, Shandong University (Grant No. 2023CCG13, China).

Author contributions

Ruixuan Zhang, Yunfei Li and Hui Fu framed the synthesis. Chengcheng Zhao and Xiuyan Li collected literature and sifted through articles. Ruixuan Zhang, Yunfei Li and Hui Fu wrote the manuscript and draw diagrams. Yuming Wang, Yujiao Sun and Yingpeng Li proposed the project and revised the manuscript. All authors have contributed to the article and approved the submitted version.

Conflicts of interest

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 2022;**375**:1254−61.
2. Wu HY, Lu XY, Hu YH, Baatarbolat J, Zhang ZH, Liang YP, et al. Biomimic nanodrugs overcome tumor immunosuppressive microenvironment to enhance cuproptosis/chemodynamic-induced cancer immunotherapy. *Adv Sci* 2024;**12**:e2411122.
3. Mao YX, Xia ZY, Xia WJ, Jiang P. Metabolic reprogramming, sensing, and cancer therapy. *Cell Rep* 2024;**43**:115064.
4. Zhang XJ, Tang BF, Luo JH, Yang Y, Weng QY, Fang SJ, et al. Cuproptosis, ferroptosis and PANoptosis in tumor immune microenvironment remodeling and immunotherapy: culprits or new hope. *Mol Cancer* 2024;**23**:255.
5. Wang QH, Wu YJ, Jiang GM, Huang X. Galectin-3 induces pathogenic immunosuppressive macrophages through interaction with TREM2 in lung cancer. *J Exp Clin Cancer Res* 2024;**43**:224.
6. Wang J, Liao ZX. Research progress of microrobots in tumor drug delivery. *Food Med Homol* 2024;**1**:9420025.
7. Lin HM, Zhang PP, Yu J, Deng HP, Ge SF, Dou HJ, et al. Thermal-triggered mitochondrial oxidative phosphorylation-enhanced nanodrug sensitizes cuproptosis with amplified anti-tumor immunity. *Mater Today* 2025;**82**:12−31.
8. Zou JL, Jiang C, Hu QS, Jia XL, Wang SQ, Wan SY, et al. Tumor microenvironment-responsive engineered hybrid nanomedicine for photodynamic-immunotherapy *via* multi-pronged amplification of reactive oxygen species. *Nat Commun* 2025;**16**:424.
9. Xin YT, Yu YJ, Wu MD, Su MH, Elsabahy M, Qu XW, et al. Tumor and intratumoral pathogen cascade-targeting photothermal nanotherapeutics for boosted immunotherapy of colorectal cancer. *J Control Release* 2025;**379**:574−91.
10. Jiao YF, Wang HY, Wang H, Xie YM, Shang YX, Wu YS, et al. A DNA origami-based enzymatic cascade nanoreactor for chemodynamic cancer therapy and activation of antitumor immunity. *Sci Adv* 2025;**11**:eadr9196.
11. Hu C, He XQ, Chen YX, Yang XT, Qin L, Lei T, et al. Metformin mediated PD-L1 downregulation in combination with photodynamic-immunotherapy for treatment of breast cancer. *Adv Funct Mater* 2021;**31**:2007149.
12. Song YJ, Du YF, Hu C, Lei L, Yang LY, Wang XR, et al. Metformin-mediated immunosuppressive microenvironment remodeling in combination with chemotherapy *via* a spatial-specific multi-responsive carrier-free self-assembled nanoparticle. *Adv Funct Mater* 2024;**34**:2316145.
13. Liu WQ, Lin WR, Yan L, Xu WH, Yang J. Copper homeostasis and cuproptosis in cancer immunity and therapy. *Immunol Rev* 2024;**321**:211−27.
14. Wang L, Xiao K, Dong ZG, Meng T, Cheng XW, Xu YH. A novel copper-induced cell death-related lncRNA prognostic signature associated with immune infiltration and clinical value in gastric cancer. *J Cancer Res Clin Oncol* 2023;**149**:10543−59.
15. Liu JY, Bai Y, Li YG, Li XL, Luo K. Reprogramming the immunosuppressive tumor microenvironment through nanomedicine: an immunometabolism perspective. *EBioMedicine* 2024;**107**:105301.
16. Li YK, Shen XD, Ding HT, Zhang YX, Pan DY, Su LP, et al. Dendritic nanomedicine enhances chemo-immunotherapy by disturbing metabolism of cancer-associated fibroblasts for deep penetration and activating function of immune cells. *Acta Pharm Sin B* 2024;**14**:3680−96.
17. Jin X, Jin WK, Tong LL, Lin N, Zhang L, Zhao J. Therapeutic strategies of targeting non-apoptotic regulated cell death (RCD) with small-molecule compounds in cancer. *Acta Pharm Sin B* 2024;**14**:2815−53.
18. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. *Nat Rev Mol Cell Biol* 2020;**21**:85−100.
19. Liu J, Liu Y, Wang Y, Kang R, Tang DL. HMGB1 is a mediator of cuproptosis-related sterile inflammation. *Front Cell Dev Biol* 2022;**10**:996307.
20. Chen LY, Min JX, Wang FD. Copper homeostasis and cuproptosis in health and disease. *Signal Transduct Targeted Ther* 2022;**7**:378.
21. Lu XF, Chen XD, Lin CY, Yi YD, Zhao SS, Zhu BZ, et al. Elesclomol loaded copper oxide nanoplatform triggers cuproptosis to enhance antitumor immunotherapy. *Adv Sci* 2024;**11**:2309984.
22. Zhi H, Fu H, Zhang YX, Fan N, Zhao CC, Li YF, et al. Progress of cGAS−STING signaling pathway-based modulation of immune response by traditional Chinese medicine in clinical diseases. *Front Immunol* 2024;**15**:1510628.
23. Zhu CY, Li JL, Sun WY, Li DS, Wang YL, Shen XC. Signaling mechanism of cuproptosis activating cGAS−STING immune pathway. *JACS Au* 2024;**4**:3988−99.
24. Wu HY, Zhang ZH, Cao YN, Hu YH, Li Y, Zhang LY, et al. A self-amplifying ROS-responsive nanoplatform for simultaneous cuproptosis and cancer immunotherapy. *Adv Sci* 2024;**11**:2401047.
25. Chi H, Zhu G, Yin YL, Diao H, Liu ZC, Sun SB, et al. Dual-responsive multifunctional "core−shell" magnetic nanoparticles promoting Fenton reaction for tumor ferroptosis therapy. *Int J Pharm* 2022;**622**:121898.
26. Gao W, Huang Z, Duan JF, Nice EC, Lin J, Huang CH. Elesclomol induces copper-dependent ferroptosis in colorectal cancer cells *via* degradation of ATP7A. *Mol Oncol* 2021;**15**:3527−44.
27. Li YQ, Chen FF, Chen J, Chan S, He Y, Liu WL, et al. Disulfiram/Copper induces antitumor activity against both nasopharyngeal cancer cells and cancer-associated fibroblasts through ROS/MAPK and ferroptosis pathways. *Cancers* 2020;**12**:138.
28. Ren XY, Li YC, Zhou Y, Hu WY, Yang C, Jing QG, et al. Overcoming the compensatory elevation of NRF2 renders hepatocellular carcinoma cells more vulnerable to disulfiram/copper-induced ferroptosis. *Redox Biol* 2021;**46**:102122.
29. Wang J, Zhang W, Xie Z, Wang X, Sun J, Ran F, et al. NIR-responsive copper nanoliposome composites for cascaded ferrotherapy *via* ferroptosis actived ICD and IFN-γ released. *Biomaterials* 2024;**308**:122570.
30. Li JZ, Uetrecht JP. D-Penicillamine-induced autoimmunity: relationship to macrophage activation. *Chem Res Toxicol* 2009;**22**:1526−33.
31. Nagatani K, Abe Y, Homma T, Fujii J, Suzuki T. Copper chelation by D-penicillamine alleviates melanocyte death induced by rhododendrol without inhibiting tyrosinase. *Biochem Biophys Res Commun* 2023;**663**:71−7.
32. Alvarez HM, Xue Y, Robinson CD, Canalizo-Hernández MA, Marvin RG, Kelly RA, et al. Tetrathiomolybdate inhibits copper trafficking proteins through metal cluster formation. *Science* 2010;**327**:331−4.
33. Zhang ML, Qiu HM, Mao LJ, Wang B, Li N, Fan YZ, et al. Ammonium tetrathiomolybdate triggers autophagy-dependent NRF2 activation in vascular endothelial cells. *Cell Death Dis* 2022;**13**:733.
34. Ni C, Ou Yang ZJ, Li GM, Liu JJ, Cao XY, Zheng LF, et al. A tumor microenvironment-responsive core-shell tecto dendrimer nanoplatform for magnetic resonance imaging-guided and cuproptosis-promoted chemo-chemodynamic therapy. *Acta Biomater* 2023;**164**:474−86.
35. Voli F, Valli E, Lerra L, Kimpton K, Saletta F, Giorgi FM, et al. Intratumoral copper modulates PD-L1 expression and influences tumor immune evasion. *Cancer Res* 2020;**80**:4129−44.
36. Guerreiro J, Alves V, Abrunhosa A, Paulo A, Gil O, Mendes F. Radiobiological characterization of $^{64}CuCl_2$ as a simple tool for prostate cancer theranostics. *Molecules* 2018;**23**:2944.
37. Kim KI, Jang SJ, Park JH, Lee YJ, Lee TS, Woo KS, et al. Detection of increased ^{64}Cu uptake by human copper transporter 1 gene

overexpression using PET with $^{64}CuCl_2$ in human breast cancer xenograft model. *J Nucl Med* 2014;**55**:1692−8.
38. Pinto CIG, Branco ADM, Bucar S, Fonseca A, Abrunhosa AJ, Da Silva CL, et al. Evaluation of the theranostic potential of [^{64}Cu]$CuCl_2$ in glioblastoma spheroids. *EJNMMI Res* 2024;**14**:26.
39. Gupta G, Cappellini F, Farcal L, Gornati R, Bernardini G, Fadeel B. Copper oxide nanoparticles trigger macrophage cell death with misfolding of Cu/Zn superoxide dismutase 1 (SOD1). *Part Fibre Toxicol* 2022;**19**:33.
40. Miao LZ, Wang C, Hou J, Wang PF, Ao YH, Li Y, et al. Enhanced stability and dissolution of CuO nanoparticles by extracellular polymeric substances in aqueous environment. *J Nanopart Res* 2015; **17**:404.
41. Xu XT, Li HM, Tong BH, Zhang WJ, Wang XF, Wang Y, et al. Biomimetic nano-regulator that induces cuproptosis and lactate-depletion mediated ROS storm for metalloimmunotherapy of clear cell renal cell carcinoma. *Adv Healthcare Mater* 2024;**13**:2400204.
42. Ruan YH, Zhuang HL, Zeng XM, Lin LL, Wang XC, Xue PP, et al. Engineered microbial nanohybrids for tumor-mediated NIR II photothermal enhanced ferroptosis/cuproptosis and immunotherapy. *Adv Healthcare Mater* 2024;**13**:2302537.
43. Jiang TY, Jia TY, Yin YP, Li TY, Song XR, Feng W, et al. Cuproptosis-inducing functional nanocomposites for enhanced and synergistic cancer radiotherapy. *ACS Nano* 2025;**19**:5429−46.
44. Yue ZW, Zhou W, Ji XL, Wang YS, Guo F. Thermoelectric performance of hydrothermally synthesized micro/nano $Cu_{2-x}S$. *Chem Eng J* 2022;**449**:137748.
45. Zhao C, Tang XY, Chen XY, Jiang ZQ. Multifaceted carbonized metal-organic frameworks synergize with immune checkpoint inhibitors for precision and augmented cuproptosis cancer therapy. *ACS Nano* 2024;**18**:17852−68.
46. Kwon YT, Lim GD, Kim S, Ryu SH, Lim HR, Choa YH. Effect of localized surface plasmon resonance on dispersion stability of copper sulfide nanoparticles. *Appl Surf Sci* 2019;**477**:204−10.
47. Wang SH, Riedinger A, Li HB, Fu CH, Liu HY, Li LL, et al. Plasmonic copper sulfide nanocrystals exhibiting near-infrared photothermal and photodynamic therapeutic effects. *ACS Nano* 2015;**9**: 1788−800.
48. Lee SY, Seo JH, Kim S, Hwang C, Jeong DI, Park J, et al. Cuproptosis-inducible chemotherapeutic/cascade catalytic reactor system for combating with breast cancer. *Small* 2023;**19**:2301402.
49. Feng XL, Lin T, Chen D, Li ZY, Yang QP, Tian HT, et al. Mitochondria-associated ER stress evokes immunogenic cell death through the ROS−PERK−eIF2α pathway under PTT/CDT combined therapy. *Acta Biomater* 2023;**160**:211−24.
50. Liu P, Kumar IS, Brown S, Kannappan V, Tawari PE, Tang JZ, et al. Disulfiram targets cancer stem-like cells and reverses resistance and cross-resistance in acquired paclitaxel-resistant triple-negative breast cancer cells. *Br J Cancer* 2013;**109**:1876−85.
51. Xie JY, Liu J, Zhao M, Li XR, Wang YB, Zhao YL, et al. Disulfiram/Cu kills and sensitizes BRAF-mutant thyroid cancer cells to BRAF kinase inhibitor by ROS-dependently relieving feedback activation of MAPK/ERK and PI3K/AKT pathways. *Int J Mol Sci* 2023;**24**:3418.
52. Wang QL, Zhu T, Miao NJ, Qu YY, Wang ZN, Chao YN, et al. Disulfiram bolsters T-cell anti-tumor immunity through direct activation of LCK-mediated TCR signaling. *EMBO J* 2022;**41**:e110636.
53. Huang XT, Sun P, Qin YY, Wang XJ, Wang MY, Lin YT, et al. Disulfiram attenuates MCMV-Induced pneumonia by inhibition of NF-κB/NLRP3 signaling pathway in immunocompromised mice. *Int Immunopharmacol* 2022;**103**:108453.
54. Tang YX, Dang M, Li Y, Sha X, Xu ZQ, Zhang J, et al. *In situ* activatable disulfiram-rhodium(III) nanocomplex for Cu chelation and STAT3 inhibition to Potentiate photodynamic and immunotherapy. *Chem Eng J* 2025;**507**:160182.
55. Zhang HY, Xia J, Xie LL, Hao M, Liang WL, Wang SZ, et al. Mitochondria-and anaerobic glycolysis-targeted self-assembled copper complex nanoparticles for boosting cuproptosis-immunotherapy. *Adv Compos Hybrid Mater* 2025;**8**:45.
56. Nagai M, Vo NH, Shin Ogawa L, Chimmanamada D, Inoue T, Chu J, et al. The oncology drug elesclomol selectively transports copper to the mitochondria to induce oxidative stress in cancer cells. *Free Radical Biol Med* 2012;**52**:2142−50.
57. O'Day SJ, Eggermont AMM, Chiarion-Sileni V, Kefford R, Grob JJ, Mortier L, et al. Final results of phase III SYMMETRY study: randomized, double-blind trial of Elesclomol plus paclitaxel *versus* paclitaxel alone as treatment for chemotherapy-naive patients with advanced melanoma. *J Clin Oncol* 2013;**31**:1211−8.
58. Skrott Z, Mistrik M, Andersen KK, Friis S, Majera D, Gursky J, et al. Alcohol-abuse drug disulfiram targets cancer *via* p97 segregase adaptor NPL4. *Nature* 2017;**552**:194−9.
59. Kannappan V, Ali M, Small B, Rajendran G, Elzhenni S, Taj H, et al. Recent advances in repurposing disulfiram and disulfiram derivatives as copper-dependent anticancer agents. *Front Mol Biosci* 2021;**8**: 741316.
60. Wang CH, Yang XD, Dong CY, Chai KK, Ruan J, Shi S. Cu-related agents for cancer therapies. *Coord Chem Rev* 2023;**487**:215156.
61. Modica Napolitano JS, Bharath LP, Hanlon AJ, Hurley LD. The anticancer agent elesclomol has direct effects on mitochondrial bioenergetic function in isolated mammalian mitochondria. *Biomolecules* 2019;**9**:298.
62. He LX, Chen JX, Deng PW, Huang SM, Liu P, Wang CJ, et al. Lysosomal cyst(e)ine storage potentiates tolerance to oxidative stress in cancer cells. *Mol Cell* 2023;**83**:3502−19.e11.
63. Qiao QQ, Hu SF, Wang X. The regulatory roles and clinical significance of glycolysis in tumor. *Cancer Commun* 2024;**44**:761−86.
64. Wang Y, Guo ZJ, Isah AD, Chen SW, Ren YF, Cai HZ. Lipid metabolism and tumor immunotherapy. *Front Cell Dev Biol* 2023;**11**: 1187989.
65. Turnlund JR. Human whole-body copper metabolism. *Am J Clin Nutr* 1998;**67**:960−64S.
66. Du M, Sun L, Guo JS, Lv HN. Macrophages and tumor-associated macrophages in the senescent microenvironment: from immunosuppressive TME to targeted tumor therapy. *Pharmacol Res* 2024;**204**: 107198.
67. Watson MJ, Delgoffe GM. Fighting in a wasteland: deleterious metabolites and antitumor immunity. *J Clin Investig* 2022;**132**:e148549.
68. Yang Z, Liu XP, Zhu J, Chai YY, Cong BY, Li B, et al. Inhibiting intracellular CD28 in cancer cells enhances antitumor immunity and overcomes anti-PD-1 resistance *via* targeting PD-L1. *Cancer Cell* 2025;**43**:86−102.e10.
69. Zheng PJ, Zhou CT, Lu LY, Liu B, Ding YM. Elesclomol: a copper ionophore targeting mitochondrial metabolism for cancer therapy. *J Exp Clin Cancer Res* 2022;**41**:271.
70. Zheng YC, Sun LQ, Guo JM, Ma J. The crosstalk between ferroptosis and anti-tumor immunity in the tumor microenvironment: molecular mechanisms and therapeutic controversy. *Cancer Commun* 2023;**43**:1071−96.
71. Stockwell BR. Ferroptosis turns 10: emerging mechanisms, physiological functions, and therapeutic applications. *Cell* 2022;**185**: 2401−21.
72. Newton K, Strasser A, Kayagaki N, Dixit VM. Cell death. *Cell* 2024; **187**:235−56.
73. Yang X, Liu YQ, Wang Z, Jin Y, Gu W. Ferroptosis as a new tool for tumor suppression through lipid peroxidation. *Commun Biol* 2024;**7**: 1475.
74. Liu Y, Wan YC, Jiang Y, Zhang L, Cheng WJ. GPX4: the hub of lipid oxidation, ferroptosis, disease and treatment. *Biochim Biophys Acta Rev Cancer* 2023;**1878**:188890.
75. Nagata S. Apoptosis and clearance of apoptotic cells. *Annu Rev Immunol* 2018;**36**:489−517.
76. Dadsena S, King LE, García Sáez AJ. Apoptosis regulation at the mitochondria membrane level. *Biochim Biophys Acta Biomembr* 2021;**1863**:183716.

77. Furukawa T, Komatsu M, Ikeda R, Tsujikawa K, Akiyama Si. Copper transport systems are involved in multidrug resistance and drug transport. *Curr Med Chem* 2008;**15**:3268−78.
78. Huang Q, Ru Y, Luo YL, Luo XY, Liu DD, Ma YC, et al. Identification of a targeted ACSL4 inhibitor to treat ferroptosis-related diseases. *Sci Adv* 2024;**10**:eadk1200.
79. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature* 2019;**575**:688−92.
80. Green DR. The death receptor pathway of apoptosis. *Cold Spring Harbor Perspect Biol* 2022;**14**:a041053.
81. Green DR. The mitochondrial pathway of apoptosis: Part I: MOMP and beyond. *Cold Spring Harbor Perspect Biol* 2022;**14**:a041038.
82. Birge RB, Boeltz S, Kumar S, Carlson J, Wanderley J, Calianese D, et al. Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer. *Cell Death Differ* 2016; **23**:962−78.
83. McKernan DP. Pattern recognition receptors as potential drug targets in inflammatory disorders. *Adv Protein Chem Struct Biol* 2020;**119**: 65−109.
84. Man SM, Jenkins BJ. Context-dependent functions of pattern recognition receptors in cancer. *Nat Rev Cancer* 2022;**22**:397−413.
85. Dvorkin S, Cambier S, Volkman HE, Stetson DB. New frontiers in the cGAS−STING intracellular DNA-sensing pathway. *Immunity* 2024;**57**:718−30.
86. Li YY, Liu J, Weichselbaum RR, Lin WB. Mitochondria-targeted multifunctional nanoparticles combine cuproptosis and programmed cell death-1 downregulation for cancer immunotherapy. *Adv Sci* 2024;**11**:2403520.
87. Yan CZ, Liu Y, Zhao GZ, Yang HT, Lv HY, Li GJ, et al. Inhalable metal-organic framework-mediated cuproptosis combined with PD-L1 checkpoint blockade for lung metastasis synergistic immunotherapy. *Acta Pharm Sin B* 2024;**14**:2281−97.
88. Zhang L, Feng MW, Wang XJ, Zhang H, Ding JJ, Cheng ZJ, et al. Peptide Szeto-Schiller 31 ameliorates doxorubicin-induced cardiotoxicity by inhibiting the activation of the p38 MAPK signaling pathway. *Int J Mol Med* 2021;**47**:63.
89. Klimpel A, Neundorf I. Bifunctional peptide hybrids targeting the matrix of mitochondria. *J Control Release* 2018;**291**:147−56.
90. Qin JB, Gong NQ, Liao ZH, Zhang SW, Timashev P, Huo SD, et al. Recent progress in mitochondria-targeting-based nanotechnology for cancer treatment. *Nanoscale* 2021;**13**:7108−18.
91. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol* 2021;**21**:485−98.
92. Chávez MD, Tse HM. Targeting mitochondrial-derived reactive oxygen species in T cell-mediated autoimmune diseases. *Front Immunol* 2021;**12**:703972.
93. Yu WH, Wang X, Zhao JZ, Liu R, Liu JZ, Wang Z, et al. Stat2−Drp1 mediated mitochondrial mass increase is necessary for pro-inflammatory differentiation of macrophages. *Redox Biol* 2020;**37**: 101761.
94. Guo BD, Yang FY, Zhang LP, Zhao QX, Wang WK, Yin L, et al. Cuproptosis induced by ROS responsive nanoparticles with elesclomol and copper combined with αPD-L1 for enhanced cancer immunotherapy. *Adv Mater* 2023;**35**:e2212267.
95. Zhang ZY, Ma YR, Guo XL, Du YX, Zhu Q, Wang XB, et al. FDX1 can impact the prognosis and mediate the metabolism of lung adenocarcinoma. *Front Pharmacol* 2021;**12**:749134.
96. Liao Q, Deng J, Tong J, Gan Y, Hong WW, Dong HZ, et al. p53 induces circFRMD4A to suppress cancer development through glycolytic reprogramming and cuproptosis. *Mol Cell* 2025;**85**: 132−49.e7.
97. Liu JY, Li XL, Li YG, Gong QY, Luo K. Metformin-based nanomedicines for reprogramming tumor immune microenvironment. *Theranostics* 2025;**15**:993.
98. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, et al. Lactate metabolism in human lung tumors. *Cell* 2017;**171**:358−71.e9.
99. Peralta RM, Xie B, Lontos K, Nieves Rosado H, Spahr K, Joshi S, et al. Dysfunction of exhausted T cells is enforced by MCT11-mediated lactate metabolism. *Nat Immunol* 2024;**25**:2297−307.
100. Manoharan I, Prasad PD, Thangaraju M, Manicassamy S. Lactate-dependent regulation of immune responses by dendritic cells and macrophages. *Front Immunol* 2021;**12**:691134.
101. Ding R, Yu XY, Hu ZL, Dong Y, Huang HY, Zhang YR, et al. Lactate modulates RNA splicing to promote CTLA-4 expression in tumor-infiltrating regulatory T cells. *Immunity* 2024;**57**:528−40.e6.
102. Li XL, Duan ZY, Chen XT, Pan DY, Luo Q, Gu L, et al. Impairing tumor metabolic plasticity *via* a stable metal-phenolic-based polymeric nanomedicine to suppress colorectal cancer. *Adv Mater* 2023; **35**:2300548.
103. Hu TY, Liu CH, Lei M, Zeng QM, Li L, Tang H, et al. Metabolic regulation of the immune system in health and diseases: mechanisms and interventions. *Signal Transduct Targeted Ther* 2024;**9**:268.
104. Zhai XW, Yang RH, Chu QY, Guo ZH, Hou PJ, Li XX, et al. AMPK-regulated glycerol excretion maintains metabolic crosstalk between reductive and energetic stress. *Nat Cell Biol* 2025;**27**:141−53.
105. Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. *Nat Rev Mol Cell Biol* 2023;**24**:255−72.
106. Li X, Duan Z, Chen X, Pan D, Luo Q, Gu L, et al. Impairing tumor metabolic plasticity *via* a stable metal-phenolic-based polymeric nanomedicine to suppress colorectal cancer. *Adv Mater* 2023;**35**: 2300548.
107. Xu WJ, Wang YP, Hou GH, Wang JL, Wang TB, Qian JM, et al. Tumor microenvironment responsive hollow nanoplatform for triple amplification of oxidative stress to enhance cuproptosis-based synergistic cancer therapy. *Adv Healthcare Mater* 2023;**12**:2202949.
108. Xiao C, Wang X, Li SY, Zhang ZJ, Li JY, Deng QY, et al. A cuproptosis-based nanomedicine suppresses triple negative breast cancers by regulating tumor microenvironment and eliminating cancer stem cells. *Biomaterials* 2025;**313**:122763.
109. Hu CG, Qiao W, Li X, Ning ZK, Liu J, Dalangood S, et al. Tumor-secreted FGF21 acts as an immune suppressor by rewiring cholesterol metabolism of $CD8^+$ T cells. *Cell Metab* 2024;**36**:630−47.e8.
110. Alsalem M, Haddad M, Aldossary SA, Kalbouneh H, Azab B, Dweik A, et al. Effects of dual peroxisome proliferator-activated receptors α and γ activation in two rat models of neuropathic pain. *PPAR Res* 2019;**2019**:2630232.
111. Yin XZ, Zeng WF, Wu BW, Wang LY, Wang ZH, Tian HJ, et al. PPARα inhibition overcomes tumor-derived exosomal lipid-induced dendritic cell dysfunction. *Cell Rep* 2020;**33**:108278.
112. Yang K, Wang XK, Song CH, He Z, Wang RX, Xu YR, et al. The role of lipid metabolic reprogramming in tumor microenvironment. *Theranostics* 2023;**13**:1774−808.
113. Xiao LL, Xian M, Zhang CC, Guo Q, Yi Q. Lipid peroxidation of immune cells in cancer. *Front Immunol* 2024;**14**:1322746.
114. Li T, Wang DW, Meng M, Yang ZY, Luo ZM, Li Z, et al. Copper-coordinated covalent organic framework produced a robust fenton-like effect inducing immunogenic cell death of tumors. *Macromol Rapid Commun* 2023;**44**:2200929.
115. Gao Y, Song ZL, Jia L, Tang Y, Wang CC, Zhao XL, et al. Self-amplified ROS production from fatty acid oxidation enhanced tumor immunotherapy by atorvastatin/*PD-L1* siRNA lipopeptide nanoplexes. *Biomaterials* 2022;**291**:121902.
116. Xie LP, Yuan YM, Xu SM, Lu SJ, Gu JY, Wang YP, et al. Down-regulation of hepatic ceruloplasmin ameliorates NAFLD *via* SCO1−AMPK−LKB1 complex. *Cell Rep* 2022;**41**:111498.
117. Ji MS, Liu HB, Liang XX, Wei ML, Shi DM, Gou JX, et al. Tumor cells are under siege from all sides: tumor cell-mimic metal-organic framework nanoparticles triggering cuproptosis/ferroptosis/apoptosis for chemo-chemodynamic-photothermal-immunological synergistic antitumor therapy. *Chem Eng J* 2024;**485**:149640.
118. Chen L, Cui HM. Targeting glutamine induces apoptosis: a cancer therapy approach. *Int J Mol Sci* 2015;**16**:22830−55.
119. Ouyang Z, Zhang HY, Lin WR, Su J, Wang XG. Bioinformatic profiling identifies the glutaminase to be a potential novel

cuproptosis-related biomarker for glioma. *Front Cell Dev Biol* 2022; **10**:982439.
120. Madden MZ, Rathmell JC. The complex integration of T-cell metabolism and immunotherapy. *Cancer Discov* 2021;**11**:1636−43.
121. Zhang N, Ping W, Rao KX, Zhang ZL, Huang R, Zhu DM, et al. Biomimetic copper-doped polypyrrole nanoparticles induce glutamine metabolism inhibition to enhance breast cancer cuproptosis and immunotherapy. *J Control Release* 2024;**371**:204−15.
122. Cheng K, Cai N, Zhu JH, Yang X, Liang HF, Zhang WG. Tumor-associated macrophages in liver cancer: from mechanisms to therapy. *Cancer Commun* 2022;**42**:1112−40.
123. Bryleva EY, Brundin L. Kynurenine pathway metabolites and suicidality. *Neuropharmacology* 2017;**112**:324−30.
124. Schlichtner S, Yasinska IM, Klenova E, Abooali M, Lall GS, Berger SM, et al. L-Kynurenine participates in cancer immune evasion by downregulating hypoxic signaling in T lymphocytes. *OncoImmunology* 2023;**12**:2244330.
125. Chen EN, Wu JW, Huang JJ, Zhu WC, Sun HH, Wang XN, et al. FLI1 promotes IFN-γ-induced kynurenine production to impair anti-tumor immunity. *Nat Commun* 2024;**15**:4590.
126. Li YK, Wu YH, Fang ZX, Zhang YX, Ding HT, Ren L, et al. Dendritic nanomedicine with boronate bonds for augmented chemo-immunotherapy *via* synergistic modulation of tumor immune microenvironment. *Adv Mater* 2024;**36**:2307263.
127. Liu YD, Li CF, Cui XL, Liu C, Xiao PT, Yang W. Kynureninase induce cuproptosis resistance in gastric cancer progression through downregulating lipotic acid synthetase mediated non-canonical mechanism. *Cell Signal* 2025;**127**:111565.
128. Xue C, Li GL, Zheng QX, Gu XY, Shi QM, Su YS, et al. Tryptophan metabolism in health and disease. *Cell Metab* 2023;**35**:1304−26.
129. Qian L, Li N, Lu XC, Xu MD, Liu Y, Li KY, et al. Enhanced BCAT1 activity and BCAA metabolism promotes RhoC activity in cancer progression. *Nat Metab* 2023;**5**:1159−73.
130. Lu MX, Luo D, Zhang ZX, Ouyang F, Shi YH, Hu CY, et al. Branched-chain amino acid catabolism promotes M2 macrophage polarization. *Front Immunol* 2024;**15**:1469163.
131. Ericksen RE, Lim SL, McDonnell E, Shuen WH, Vadiveloo M, White PJ, et al. Loss of BCAA catabolism during carcinogenesis enhances mTORC1 activity and promotes tumor development and progression. *Cell Metab* 2019;**29**:1151−65.e6.
132. Lodi F, Certo M, Elkafrawy H, Li W, Vu HA, Gilbo K, et al. BCAT1 inhibition affects $CD8^+$ T cell activation, exhaustion, and tumoral immunity by altering iron homeostasis. *bioRxiv* 2023;**25**:530034.
133. Bi J, Guo QL, Gong YQ, Chen X, Wu HJ, Song L, et al. Troglitazone reduction of intracellular mycobacterium tuberculosis survival *via* macrophage Autophagy through LKB1−AMPKα signaling. *J Infect Dis* 2024;**231**:e553−65.
134. Herhaus L, Gestal-Mato U, Eapen VV, Mačinković I, Bailey HJ, Prieto-Garcia C, et al. IRGQ-mediated autophagy in MHC class I quality control promotes tumor immune evasion. *Cell* 2024;**187**: 7285−302.e29.
135. Patterson NL, Mintern JD. Intersection of autophagy with pathways of antigen presentation. *Protein Cell* 2012;**3**:911−20.
136. Merkley SD, Chock CJ, Yang XO, Harris J, Castillo EF. Modulating T cell responses *via* autophagy: the intrinsic influence controlling the function of both antigen-presenting cells and T cells. *Front Immunol* 2018;**9**:2914.
137. Ghislat G, Lawrence T. Autophagy in dendritic cells. *Cell Mol Immunol* 2018;**15**:944−52.
138. Guo WJ, Ye SS, Cao N, Huang J, Gao J, Chen QY. ROS-mediated autophagy was involved in cancer cell death induced by novel copper (II) complex. *Exp Toxicol Pathol* 2010;**62**:577−82.
139. Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production?. *Nat Rev Immunol* 2010;**10**:210−5.
140. Dong M, Lu LL, Xu H, Ruan ZY. DC-derived CXCL10 promotes CTL activation to suppress ovarian cancer. *Transl Res* 2024;**272**: 126−39.
141. Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab* 2016;**24**: 657−71.
142. Chirasani SR, Leukel P, Gottfried E, Hochrein J, Stadler K, Neumann B, et al. Diclofenac inhibits lactate formation and efficiently counteracts local immune suppression in a murine glioma model. *Int J Cancer* 2013;**132**:843−53.
143. Mu XM, Shi W, Xu Y, Xu C, Zhao T, Geng B, et al. Tumor-derived lactate induces M2 macrophage polarization *via* the activation of the ERK/STAT3 signaling pathway in breast cancer. *Cell Cycle* 2018;**17**: 428−38.
144. Xu S, Chaudhary O, Rodríguez Morales P, Sun X, Chen D, Zappasodi R, et al. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in $CD8^+$ T cells in tumors. *Immunity* 2021;**54**:1561−77.e7.
145. Wang HP, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, et al. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nat Immunol* 2020;**21**:298−308.
146. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. *Immunity* 2005;**22**:633−42.
147. Leone RD, Zhao L, Englert JM, Sun IM, Oh MH, Sun IH, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science* 2019;**366**:1013−21.
148. Oh MH, Sun IH, Zhao L, Leone RD, Sun IM, Xu W, et al. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. *J Clin Investig* 2020;**130**: 3865−84.
149. Chen W, Liang X, Peterson AJ, Munn DH, Bruce BR. The indoleamine 2,3-dioxygenase pathway is essential for human plasmacytoid dendritic cell-induced adaptive T regulatory cell generation. *J Immunol* 2008;**181**:5396−404.
150. Yeung AW, Lim YJ, Hastad M, Dang L, Örfi L, Szabadkai I, et al. Redox control of the critical immune regulatory enzyme indoleamine 2,3-dioxygenase by NADPH oxidase 2-derived reactive oxygen species in human monocytes. *Free Radic Biol Med* 2016;**100**:S62.
151. Yang H, Kim C, Zou WP. Metabolism and macrophages in the tumor microenvironment. *Curr Opin Immunol* 2024;**91**:102491.
152. Zhang WY, Huang X. Targeting cGAS−STING pathway for reprogramming tumor-associated macrophages to enhance anti-tumor immunotherapy. *Biomarker Res* 2025;**13**:43.
153. Yu NY, Zhou JH, Ding MB, Li M, Peng SJ, Li JC. Sono-triggered cascade lactate depletion by semiconducting polymer nanoreactors for cuproptosis-immunotherapy of pancreatic cancer. *Angew Chem Int Ed* 2024;**63**:e202405639.
154. Li YY, Liu J, Chen YM, Weichselbaum RR, Lin WB. Nanoparticles synergize ferroptosis and cuproptosis to potentiate cancer immunotherapy. *Adv Sci* 2024;**11**:2310309.
155. Abasian P, Ghanavati S, Rahebi S, Nouri Khorasani S, Khalili S. Polymeric nanocarriers in targeted drug delivery systems: a review. *Polym Adv Technol* 2020;**31**:2939−54.
156. Li SY, Ma YT, Cui JW, Caruso F, Ju Y. Engineering poly(ethylene glycol) particles for targeted drug delivery. *Chem Commun* 2024;**60**: 2591−604.
157. Chang J, Yin WM, Zhi H, Chen SY, Sun JY, Zhao YG, et al. Copper deposition in polydopamine nanostructure to promote cuproptosis by catalytically inhibiting copper exporters of tumor cells for cancer immunotherapy. *Small* 2024;**20**:2308565.
158. Zhu GQ, Xie YL, Wang JR, Wang M, Qian YR, Sun QQ, et al. Multifunctional copper-phenolic nanopills achieve comprehensive polyamines depletion to provoke enhanced pyroptosis and cuproptosis for cancer immunotherapy. *Adv Mater* 2024;**36**:2409066.
159. Ma XY, Kuang L, Yin Y, Tang L, Zhang Y, Fan Q, et al. Tumor-antigen activated dendritic cell membrane-coated biomimetic nanoparticles with orchestrating immune responses promote therapeutic efficacy against glioma. *ACS Nano* 2023;**17**:2341−55.

160. Ghattas M, Dwivedi G, Chevrier A, Horn Bourque D, Alameh MG, Lavertu M. Chitosan immunomodulation: insights into mechanisms of action on immune cells and signaling pathways. *RSC Adv* 2025;**15**: 896−909.
161. Huang C, Xie T, Liu YF, Yan S, OuYang FJ, Zhang HT, et al. A sodium alginate-based multifunctional nanoplatform for synergistic chemo-immunotherapy of hepatocellular carcinoma. *Adv Mater* 2023;**35**:2301352.
162. Zhang S, Ma DW, Yang X, Chen L, Xia H, Wang SK, et al. The effect of chitosan on blood lipids in patients with hypercholesterolemia and hyperlipidemia: a systematic review and meta-analysis. *Food Med Homol* 2024;**2**:9420061.
163. Ahmad K, Zhang YY, Chen P, Yang X, Hou H. Chitosan interaction with stomach mucin layer to enhances gastric retention and mucoadhesive properties. *Carbohydr Polym* 2024;**333**:121926.
164. Yan CZ, Lv HY, Feng YF, Li YH, Zhao ZX. Inhalable nanoparticles with enhanced cuproptosis and cGAS−STING activation for synergistic lung metastasis immunotherapy. *Acta Pharm Sin B* 2024;**14**: 3697−710.
165. Huang DD, Tang ZJ, Pu X, Wang TQ, Gao FY, Li C. A novel cabazitaxel liposomes modified with ginsenoside Rk1 for cancer targeted therapy. *Acupunct Herb Med* 2024;**4**:113.
166. Dymek M, Sikora E. Liposomes as biocompatible and smart delivery systems-the current state. *Adv Colloid Interface Sci* 2022;**309**:102757.
167. Li R, Zhao WH, Han Z, Feng N, Wu TT, Xiong HH, et al. Self-cascade nanozyme reactor as a cuproptosis inducer synergistic inhibition of cellular respiration boosting radioimmunotherapy. *Small* 2024;**20**:2306263.
168. Chen MY, Xu C, Wang CH, Huang N, Bian ZX, Xiao YX, et al. Three birds with one stone: copper ions assisted synergistic cuproptosis/chemodynamic/photothermal therapy by a three-pronged approach. *Adv Healthcare Mater* 2024;**13**:2401567.
169. Cheng WWK, Allen TM. Targeted delivery of anti-CD19 liposomal doxorubicin in B-cell lymphoma: a comparison of whole monoclonal antibody, Fab' fragments and single chain Fv. *J Control Release* 2008;**126**:50−8.
170. Shi CR, Zhang QY, Yao YY, Zeng FT, Du C, Nijiati S, et al. Targeting the activity of T cells by membrane surface redox regulation for cancer theranostics. *Nat Nanotechnol* 2023;**18**:86−97.
171. Li XF, Khorsandi S, Wang YF, Santelli JL, Huntoon K, Nguyen N, et al. Cancer immunotherapy based on image-guided STING activation by nucleotide nanocomplex-decorated ultrasound microbubbles. *Nat Nanotechnol* 2022;**17**:891−9.
172. Kong N, Tao W, Ling X, Wang JQ, Xiao YL, Shi SJ, et al. Synthetic mRNA nanoparticle-mediated restoration of p53 tumor suppressor sensitizes p53-deficient cancers to mTOR inhibition. *Sci Transl Med* 2019;**11**:eaaw1565.
173. Wang S, Liu XL, Wei DL, Zhou HY, Zhu JW, Yu Q, et al. Polyvalent aptamer nanodrug conjugates enable efficient tumor cuproptosis therapy through copper overload and glutathione depletion. *J Am Chem Soc* 2024;**146**:30033−45.
174. Huang YT, Liu XL, Zhu JW, Chen ZJ, Yu L, Huang X, et al. Enzyme core spherical nucleic acid that enables enhanced cuproptosis and antitumor immune response through alleviating tumor hypoxia. *J Am Chem Soc* 2024;**146**:13805−16.
175. Tang XR, Li N, Pang H. Metal-organic frameworks-derived metal phosphides for electrochemistry application. *Green Energy Environ* 2022;**7**:636−61.
176. Zhang YF, Bo XJ, Nsabimana A, Han C, Li M, Guo LP. Electrocatalytically active cobalt-based metal-organic framework with incorporated macroporous carbon composite for electrochemical applications. *J Mater Chem A* 2015;**3**:732−8.
177. Campagnol N, Souza ER, De Vos DE, Binnemans K, Fransaer J. Luminescent terbium-containing metal-organic framework films: new approaches for the electrochemical synthesis and application as detectors for explosives. *Chem Commun* 2014;**50**:12545−7.
178. Luo YL, Luo XY, Ru Y, Zhou XR, Liu DD, Huang Q, et al. Copper (II)-based nano-regulator correlates cuproptosis burst and sequential immunogenic cell death for synergistic cancer immunotherapy. *Biomater Res* 2024;**28**:39.
179. Xu M, Chen H, Zhu G, Zhu X, Gao R, Xu B, et al. Spiky metal-organic framework nanosystem for enhanced cuproptosis-mediated cancer immunotherapy. *Nano Today* 2024;**56**:102231.
180. Liu Y, Zhao H, Niu R, Zhang B, Lim BTG, Song SY, et al. Single-site nanozyme with exposed unsaturated Cu-O_2 sites for tumor therapy by coordinating innate immunity and vasculature normalization. *Chem* 2025;**11**:102297.
181. Yang LJ, Pan MM, Hu HF, Liu FR, Jiang M, Ning SW, et al. Bio-inspired bimetallic ions functionalized MOF SAzyme nanocomposites for synergistic ferroptosis/cuproptosis-enhanced immune checkpoint therapy. *bioRxiv* 2024;**12**:607118.
182. Tian HL, Duan JF, Li BW, Qin SY, Nice EC, Zhang W, et al. Clinical chemotherapeutic agent coordinated copper-based nanoadjuvants for efficiently sensitizing cancer chemo-immunotherapy by cuproptosis-mediated mitochondrial metabolic reprogramming. *Adv Funct Mater* 2023;**33**:2306584.
183. Ahmed H, Gomte SS, Prathyusha E, A P, Agrawal M, Alexander A. Biomedical applications of mesoporous silica nanoparticles as a drug delivery carrier. *J Drug Deliv Sci Technol* 2022;**76**:103729.
184. Gu B, Zhao Q, Ao YR. Advances in immunomodulatory mesoporous silica nanoparticles for inflammatory and cancer therapies. *Biomolecules* 2024;**14**:1057.
185. He XL, Li MJ, Fan SJ, Li YY, Fang L, Xiang GY, et al. Copper peroxide and cisplatin co-loaded silica nanoparticles-based trinity strategy for cooperative cuproptosis/chemo/chemodynamic cancer therapy. *Chem Eng J* 2024;**481**:148522.
186. Tian XJ, Xu H, Zhou FF, Gong XY, Tan SW, He YJ. An intelligent cupreous nanoplatform with self-supplied H_2O_2 and Cu^{2+}/Cu^{+} conversion to boost cuproptosis and chemodynamic combined therapy. *Chem Mater* 2024;**36**:815−28.
187. Zhu GQ, Wang M, Qiao LY, Xie YL, Wang JR, Li L, et al. Lysosomal rupture-mediated "Broken Window Effect" to amplify cuproptosis and pyroptosis for high-efficiency cancer immunotherapy. *Adv Funct Mater* 2024;**34**:2400496.
188. Liu TT, Zhou ZH, Zhang MX, Lang PX, Li J, Liu ZM, et al. Cuproptosis-immunotherapy using PD-1 overexpressing T cell membrane-coated nanosheets efficiently treats tumor. *J Control Release* 2023;**362**:502−12.
189. Liu YM, Shi DW, Ren YQ, Li L, Zhao YB, Zheng CS, et al. The immune-chemo-embolization effect of temperature sensitive gold nanomedicines against liver cancer. *Nano Res* 2023;**16**:2749−61.
190. Yan FH, Li RY, Liu JX, Yang LL, Liu HL, Zhu SC, et al. Hybrid near-infrared-activated luminescent gold nanoparticle platform for efficient cancer therapy. *Adv Compos Hybrid Mater* 2025;**8**:173.
191. Zafar H, Zhang J, Raza F, Pan XH, Hu ZW, Feng HX, et al. Biomimetic gold nanocages incorporating copper-human serum albumin for tumor immunotherapy *via* cuproptosis-lactate regulation. *J Control Release* 2024;**372**:446−66.
192. Zhou J, Yu Q, Song J, Li S, Li XL, Kang B, et al. Photothermally triggered copper payload release for cuproptosis-promoted cancer synergistic therapy. *Angew Chem Int Ed* 2023;**62**:e202213922.
193. Du YQ, Zhao XD, He F, Gong HJ, Yang JN, Wu LZ, et al. A vacancy-engineering ferroelectric nanomedicine for cuproptosis/apoptosis co-activated immunotherapy. *Adv Mater* 2024;**36**:2403253.
194. Yan L, Chang L, Tian YJ, Hu JY, Cao Z, Guo X, et al. Graphene quantum dot sensitized heterojunctions induce tumor-specific cuproptosis to boost sonodynamic and chemodynamic enhanced cancer immunotherapy. *Adv Sci* 2025;**12**:e2410606.
195. Placke T, Örgel M, Schaller M, Jung G, Rammensee HG, Kopp HG, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. *Cancer Res* 2012;**72**:440−8.
196. Tang MQ, Zhang ZJ, Wang P, Zhao F, Miao L, Wang YM, et al. Advancements in precision nanomedicine design targeting the anoikis-platelet interface of circulating tumor cells. *Acta Pharm Sin B* 2024;**14**:3457−75.

197. Ning SP, Lyu M, Zhu DM, Lam JWY, Huang QQ, Zhang TF, et al. Type-I AIE photosensitizer loaded biomimetic system boosting cuproptosis to inhibit breast cancer metastasis and rechallenge. *ACS Nano* 2023;**17**:10206−17.
198. Rao ZY, Kuang J, Pan T, Qin YT, Huang QX, Sun YL, et al. Cationic magnetic nanoparticles activate natural killer cells for the treatment of glioblastoma. *ACS Nano* 2025;**19**:649−61.
199. Wan L, Lin HJ, Huang CC, Chen YC, Hsu YA, Lin CH, et al. Galectin-12 enhances inflammation by promoting M1 polarization of macrophages and reduces insulin sensitivity in adipocytes. *Glycobiology* 2016;**26**:732−44.
200. Ding S, Xiong J, Lei D, Zhu X-l, Zhang H-j. Recombinant nanocomposites by the clinical drugs of Abraxane® and Herceptin® as sequentially dual-targeting therapeutics for breast cancer. *J Cancer* 2018;**9**:502.
201. Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A, et al. Pegylated-liposomal doxorubicin *versus* doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J Clin Oncol* 1998;**16**:2445−51.
202. Neale MH, Lamont A, Hindley A, Kurbacher CM, Cree IA. The *ex vivo* effect of high concentrations of doxorubicin on recurrent ovarian carcinoma. *Anti Cancer Drugs* 2000;**11**:865.
203. O'Brien S, Schiller G, Lister J, Damon L, Goldberg S, Aulitzky W, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol* 2013;**31**:676−83.
204. Murry DJ, Blaney SM. Clinical pharmacology of encapsulated sustained-release cytarabine. *Ann Pharmacother* 2000;**34**:1173−8.
205. Anderson CF, Singh A, Stephens T, Hoang CD, Schneider JP. Kinetically controlled polyelectrolyte complex assembly of microRNA peptide nanoparticles toward treating mesothelioma. *Adv Mater* 2024;**36**:2314367.
206. Ji F, Li JJ, Qin ZH, Yang BG, Zhang ES, Dong DY, et al. Engineering pectin-based hollow nanocapsules for delivery of anticancer drug. *Carbohydr Polym* 2017;**177**:86−96.
207. Zeng LJ, Ding SS, Cao YH, Li CL, Zhao B, Ma ZL, et al. A MOF-based potent ferroptosis inducer for enhanced radiotherapy of triple negative breast cancer. *ACS Nano* 2023;**17**:13195−210.
208. Wang JL, Wu CH, Wang YR, Shen YC, Wu KR, Shi YK, et al. Nano-enabled regulation of DNA damage in tumor cells to enhance neoantigen-based pancreatic cancer immunotherapy. *Biomaterials* 2024;**311**:122710.
209. Yang C, Ming H, Li BW, Liu SS, Chen LH, Zhang TT, et al. A pH and glutathione-responsive carbon monoxide-driven nano-herb delivery system for enhanced immunotherapy in colorectal cancer. *J Control Release* 2024;**376**:659−77.
210. Zanoni DK, Stambuk HE, Madajewski B, Montero PH, Matsuura D, Busam KJ, et al. Use of ultrasmall core-shell fluorescent silica nanoparticles for image-guided sentinel lymph node biopsy in head and neck melanoma. *JAMA Netw Open* 2021;**4**:e211936.
211. Tang W, Wu J, Wang L, Wei KL, Pei ZF, Gong F, et al. Bioactive layered double hydroxides for synergistic sonodynamic/cuproptosis anticancer therapy with elicitation of the immune response. *ACS Nano* 2024;**18**:10495−508.
212. Lin H, Wang XG, Yu LD, Chen Y, Shi JL. Two-dimensional ultrathin MXene ceramic nanosheets for photothermal conversion. *Nano Lett* 2017;**17**:384−91.
213. Li L, Zhang R, Gu WY, Xu ZP. Mannose-conjugated layered double hydroxide nanocomposite for targeted siRNA delivery to enhance cancer therapy. *Nanomedicine* 2018;**14**:2355−64.
214. Cao XQ, Yang CK, Zhu XD, Zhao MX, Yan YL, Huang ZN, et al. Synergistic enhancement of chemotherapy for bladder cancer by photothermal dual-sensitive nanosystem with gold nanoparticles and PNIPAM. *Chin Chem Lett* 2024;**35**:109199.
215. Guan YH, Tian M, Liu XY, Wang YN. Preparation of novel cisplatin-conjugated hollow gold nanospheres for targeting cervical cancer. *J Cell Physiol* 2019;**234**:16475−84.
216. Hu QY, Sun WJ, Qian CG, Wang C, Bomba HN, Gu Z. Anticancer platelet-mimicking nanovehicles. *Adv Mater* 2015;**27**:7043−50.
217. Fan Q, Kuang L, Wang BY, Yin Y, Dong ZF, Tian NX, et al. Multiple synergistic effects of the microglia membrane-bionic nanoplatform on mediate tumor microenvironment remodeling to amplify glioblastoma immunotherapy. *ACS Nano* 2024;**18**:14469−86.
218. Ai LY, Xu AT, Xu J. Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. In: Xu J, editor. *Regulation of cancer immune checkpoints*. Singapore: Springer Singapore; 2020. p. 33−59.
219. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. *Cell* 2021;**184**:5309−37.
220. Li PF, Sun Q, Bai SP, Wang HT, Zhao L. Combination of the cuproptosis inducer disulfiram and anti-PD-L1 abolishes NSCLC resistance by ATP7B to regulate the HIF-1 signaling pathway. *Int J Mol Med* 2023;**53**:19.
221. Wu JM, Liu TE, Rios Z, Mei QB, Lin XK, Cao SS. Heat shock proteins and cancer. *Trends Pharmacol Sci* 2017;**38**:226−56.
222. Gastpar R, Gehrmann M, Bausero MA, Asea A, Gross C, Schroeder JA, et al. Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells. *Cancer Res* 2005;**65**:5238−47.
223. Shang TY, Yu XY, Han SS, Yang B. Nanomedicine-based tumor photothermal therapy synergized immunotherapy. *Biomater Sci* 2020;**8**:5241−59.
224. Dai YN, Zhu LP, Li X, Zhang FJ, Chen K, Jiao GD, et al. A biomimetic cuproptosis amplifier for targeted NIR-II fluorescence/photoacoustic imaging-guided synergistic NIR-II photothermal immunotherapy. *Biomaterials* 2024;**305**:122455.
225. Zu H, Wu YX, Meng HZ, Cheng XJ, Wang YY, Zhang LW, et al. Tumor metabolism aiming $Cu_{2-x}S$ nanoagents mediate photothermal-derived cuproptosis and immune activation. *ACS Nano* 2024;**18**:23941−57.
226. Kong SZ, Zhang J, Ding BY, He CC, Zhang XJ. Nanoplatform-based synergistic cancer immuno-chemodynamic therapy. *Int J Pharm* 2024;**226**:124956.
227. Yu WJ, Jia F, Fu JZ, Chen YH, Huang Y, Jin Q, et al. Enhanced transcutaneous chemodynamic therapy for melanoma treatment through cascaded fenton-like reactions and nitric oxide delivery. *ACS Nano* 2023;**17**:15713−23.
228. Xu WJ, Qian JM, Hou GH, Wang TB, Wang JL, Wang YP, et al. A hollow amorphous bimetal organic framework for synergistic cuproptosis/ferroptosis/apoptosis anticancer therapy *via* disrupting intracellular redox homeostasis and copper/iron metabolisms. *Adv Funct Mater* 2022;**32**:2205013.
229. Yu Q, Zhou J, Liu Y, Li XQ, Li S, Zhou H, et al. DNAzyme-mediated cascade nanoreactor for cuproptosis-promoted pancreatic cancer synergistic therapy. *Adv Healthcare Mater* 2023;**12**:2301429.
230. Li XS, Lovell JF, Yoon JY, Chen XY. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat Rev Clin Oncol* 2020;**17**:657−74.
231. Zhang SW, Wang J, Kong ZQ, Sun XX, He ZG, Sun BJ, et al. Emerging photodynamic nanotherapeutics for inducing immunogenic cell death and potentiating cancer immunotherapy. *Biomaterials* 2022;**282**:121433.
232. Xia JC, Hu C, Ji YW, Wang M, Jin Y, Ye L, et al. Copper-loaded nanoheterojunction enables superb orthotopic osteosarcoma therapy *via* oxidative Stress and cell cuproptosis. *ACS Nano* 2023;**17**:21134−52.
233. Zhang QY, Bao CX, Cai XJ, Jin LW, Sun LL, Lang YH, et al. Sonodynamic therapy-assisted immunotherapy: a novel modality for cancer treatment. *Cancer Sci* 2018;**109**:1330−45.
234. Liao Y, Wang DM, Gu CL, Wang X, Zhu S, Zheng ZY, et al. A cuproptosis nanocapsule for cancer radiotherapy. *Nat Nanotechnol* 2024;**19**:1892−902.
235. Pei P, Wang YH, Shen WH, He Q, Han XM, Zhang CH, et al. Oxygen-driven cuproptosis synergizes with radiotherapy to potentiate tumor immunotherapy. *Aggregate* 2024;**5**:e484.

236. Deng LF, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Investig* 2014;**124**:687−95.
237. Jiang XH, Wang J, Huang WJ, Ma HW, Zhang SL, Cai ZH, et al. Tumor microenvironment reprogrammed bimetallic hybrid nanostimulator for triggering radio-cuproptosis-immunotherapy. *Adv Healthcare Mater* 2024;**13**:2401902.
238. Torkian S, Khanjani N, Mahmoodi MR, Khosravi V. A review of copper concentrations in Iranian populations. *Environ Monit Assess* 2019;**191**:1−10.
239. Song YB, Tan KB, Zhou SF, Zhan GW. Biocompatible copper-based nanocomposites for combined cancer therapy. *ACS Biomater Sci Eng* 2024;**10**:3673−92.
240. Jin XK, Liang JL, Zhang SM, Huang QX, Zhang SK, Liu CJ, et al. Orchestrated copper-based nanoreactor for remodeling tumor microenvironment to amplify cuproptosis-mediated anti-tumor immunity in colorectal cancer. *Mater Today* 2023;**68**:108−24.
241. Huang QX, Liang JL, Chen QW, Jin XK, Niu MT, Dong CY, et al. Metal-organic framework nanoagent induces cuproptosis for effective immunotherapy of malignant glioblastoma. *Nano Today* 2023;**51**:101911.
242. Zhang JZ, Peng LQ, Hao YJ, Yang HN, Zhao WB, Mao C. Biodegradable $CuMoO_4$ nanodots with multienzyme activities for multimodal treatment of tumor. *Adv Healthcare Mater* 2023;**12**:e2300167.
243. Zhang WY, Wang MF, Liu B, Chen H, Tan J, Meng Q, et al. Glutathione induced *in situ* synthesis of Cu single-atom nanozymes with anaerobic glycolysis metabolism interference for boosting cuproptosis. *Angew Chem Int Ed* 2024;**63**:e202402397.
244. Chen W, Xie WY, Gao ZM, Lin C, Tan ML, Zhang YR, et al. Mild-photothermal effect induced high efficiency ferroptosis-boosted-cuproptosis based on $Cu_2O@Mn_3Cu_3O_8$ nanozyme. *Adv Sci* 2023;**10**:2303694.
245. Du C, Guo X, Qiu XL, Jiang WX, Wang XT, An HJ, et al. Self-reinforced bimetallic mito-jammer for Ca^{2+} overload-mediated cascade mitochondrial damage for cancer cuproptosis sensitization. *Adv Sci* 2024;**11**:2306031.
246. Xia Y, Gu MG, Wang JY, Zhang XQ, Shen TY, Shi XY, et al. Tumor microenvironment-activated, immunomodulatory nanosheets loaded with copper(II) and 5-FU for synergistic chemodynamic therapy and chemotherapy. *J Colloid Interface Sci* 2024;**653**:137−47.
247. Pi WM, Wu LY, Lu JH, Lin XY, Huang XM, Wang ZJ, et al. A metal ions-mediated natural small molecules carrier-free injectable hydrogel achieving laser-mediated photo-Fenton-like anticancer therapy by synergy apoptosis/cuproptosis/anti-inflammation. *Bioact Mater* 2023;**29**:98−115.
248. Hu PC, Li YX, Zhang LC, Lan XP, Ren XC, Liang WL, et al. Defect-engineered photothermal nanozyme with NIR-II absorption induces cuproptosis-apoptosis for synergized cancer immunotherapy and fast wound healing. *Mater Des* 2024;**237**:112568.
249. Xiao WT, Qu KM, Zhang W, Lai LH, He L, Cheng F, et al. High immunogenic cuproptosis evoked by *in situ* sulfidation-activated pyroptosis for tumor-targeted immunotherapy of colorectal cancer. *Small Sci* 2024;**4**:2300164.
250. Li W, Xiao Y, Guo GH, Peng JX, Zhu N, Chen ZK, et al. Cuprous oxide nanocomposites with photothermal (PTT) and chemical dynamics (CDT) effects induce cuproptosis in breast cancer using the strategy of increasing inflow and reducing outflow. *Nano Today* 2024;**56**:102223.
251. Liang WL, Han C, Zhang DL, Liu CL, Zhu MH, Xu FJ, et al. Copper-coordinated nanoassemblies based on photosensitizer-chemo prodrugs and checkpoint inhibitors for enhanced apoptosis-cuproptosis and immunotherapy. *Acta Biomater* 2024;**175**:341−52.
252. Yang Z, Zhao Z, Cheng HL, Shen YH, Xie AJ, Zhu MZ. *In-situ* fabrication of novel Au nanoclusters-Cu^{2+}@sodium alginate/hyaluronic acid nanohybrid gels for cuproptosis enhanced photothermal/photodynamic/chemodynamic therapy *via* tumor microenvironment regulation. *J Colloid Interface Sci* 2023;**641**:215−28.
253. Schmidt JC, Dougherty BV, Beger RD, Jones DP, Schmidt MA, Mattes WB. Metabolomics as a truly translational tool for precision medicine. *Int J Toxicol* 2021;**40**:413−26.
254. Cao B, Li YY, Lin MM, Xu J, Li TF, Fei XF, et al. Integrated analysis of metabolomic and gut microbiota reveals idiosyncratic drug-induced liver injury resulting from the combined administration of bavachin and icariside II. *Acupunct Herb Med* 2024;**4**:222−33.
255. Ghini V, Laera L, Fantechi B, Del Monte F, Benelli M, McCartney A, et al. Metabolomics to assess response to immune checkpoint inhibitors in patients with non-small-cell lung cancer. *Cancers* 2020;**12**:3574.
256. Jalota A, Hershberger CE, Patel MS, Mian A, Faruqi A, Khademi G, et al. Host metabolome predicts the severity and onset of acute toxicities induced by CAR T-cell therapy. *Blood Adv* 2023;**7**:4690−700.
257. Fu YH, Hou LR, Han K, Zhao C, Hu HB, Yin ST. Epigallocatechin gallate promotes cuproptosis *via* the MTF1/ATP7B axis in hepatocellular carcinoma. *Cells* 2025;**14**:391.
258. Xiao YX, Yin JM, Liu P, Zhang X, Lin YJ, Guo J. Triptolide-induced cuproptosis is a novel antitumor strategy for the treatment of cervical cancer. *Cell Mol Biol Lett* 2024;**29**:113.
259. Chen XX, Sun M, Yang ZB. Single cell mass spectrometry analysis of drug-resistant cancer cells: metabolomics studies of synergetic effect of combinational treatment. *Anal Chim Acta* 2022;**1201**:339621.
260. Allen TM, Brehm MA, Bridges S, Ferguson S, Kumar P, Mirochnitchenko O, et al. Humanized immune system mouse models: progress, challenges and opportunities. *Nat Immunol* 2019;**20**:770−4.
261. Qiao TY, Xiong YL, Feng YB, Guo WW, Zhou YS, Zhao JB, et al. Inhibition of LDH-A by oxamate enhances the efficacy of anti-PD-1 treatment in an NSCLC humanized mouse model. *Front Oncol* 2021;**11**:632364.
262. Jonas O, Oswald E, Lashuk K, Ahn S, Schuler J. A high-throughput *in situ* screen to identify synergistic combinations of immune-oncology drugs with targeted and cytotoxic agents in a patient-derived humanized mouse model of renal cancer. *J Immunother Cancer* 2021;**9**:A585.
263. Zhao QW, Qi TG. The implications and prospect of cuproptosis-related genes and copper transporters in cancer progression. *Front Oncol* 2023;**13**:1117164.
264. Bhat AA, Afzal M, Moglad E, Thapa R, Ali H, Almalki WH, et al. lncRNAs as prognostic markers and therapeutic targets in cuproptosis-mediated cancer. *Clin Exp Med* 2024;**24**:226.
265. Sha SN, Si LY, Wu XR, Chen YB, Xiong H, Xu Y, et al. Prognostic analysis of cuproptosis-related gene in triple-negative breast cancer. *Front Immunol* 2022;**13**:922780.
266. Wu JH, Cheng TC, Zhu B, Gao HY, Zheng L, Chen WX. Identification of cuproptosis-related gene *SLC31A1* and upstream lncRNA−miRNA regulatory axis in breast cancer. *Sci Rep* 2023;**13**:18390.
267. Davis CI, Gu X, Kiefer RM, Ralle M, Gade TP, Brady DC. Altered copper homeostasis underlies sensitivity of hepatocellular carcinoma to copper chelation. *Metallomics* 2020;**12**:1995−2008.
268. Hu Q, Wang RT, Ma HY, Zhang ZW, Xue Q. Cuproptosis predicts the risk and clinical outcomes of lung adenocarcinoma. *Front Oncol* 2022;**12**:922332.
269. Lv HZ, Liu X, Zeng XH, Liu YT, Zhang CJ, Zhang Q, et al. Comprehensive analysis of cuproptosis-related genes in immune infiltration and prognosis in melanoma. *Front Pharmacol* 2022;**13**:930041.
270. Mei WL, Liu X, Jia XY, Jin L, Xin SY, Sun XC, et al. A cuproptosis-related gene model for predicting the prognosis of clear cell renal cell carcinoma. *Front Genet* 2022;**13**:905518.
271. Jiang RM, Huan Y, Li Y, Gao XY, Sun Q, Zhang F, et al. Transcriptional and genetic alterations of cuproptosis-related genes correlated to malignancy and immune-infiltrate of esophageal carcinoma. *Cell Death Discov* 2022;**8**:370.

272. Wang LZ, Cao Y, Guo W, Xu JY. High expression of cuproptosis-related gene FDX1 in relation to good prognosis and immune cells infiltration in colon adenocarcinoma (COAD). *J Cancer Res Clin Oncol* 2022;**149**:15−24.
273. Luo BX, Lin JW, Ni AQ, Cai W, Yu XB, Wang ML. A novel defined cuproptosis-related gene signature for predicting the prognosis of colon adenocarcinoma. *Front Oncol* 2022;**12**:927028.
274. Lei L, Tan L, Sui L. A novel cuproptosis-related gene signature for predicting prognosis in cervical cancer. *Front Genet* 2022;**13**:957744.
275. Chen HHW, Yan JJ, Chen WC, Kuo MT, Lai YH, Lai WW, et al. Predictive and prognostic value of human copper transporter 1 (hCtr1) in patients with stage III non-small-cell lung cancer receiving first-line platinum-based doublet chemotherapy. *Lung Cancer* 2012; **75**:228−34.
276. Xiao F, Li YR, Wan YJ, Xue M. MircroRNA-139 sensitizes ovarian cancer cell to cisplatin-based chemotherapy through regulation of ATP7A/B. *Cancer Chemother Pharmacol* 2018;**81**:935−47.
277. Haratake J, Horie A, Takeda S. Histochemical and ultrastructural study of copper-binding protein in hepatocellular carcinoma. *Cancer* 1987;**60**:1269−74.
278. Davis CI, Gu XX, Kiefer RM, Ralle M, Gade TP, Brady DC. Altered copper homeostasis underlies sensitivity of hepatocellular carcinoma to copper chelation. *Metallomics* 2020;**12**:1995−2008.
279. Ramchandani D, Berisa M, Tavarez DA, Li ZN, Miele M, Bai Y, et al. Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis. *Nat Commun* 2021;**12**:7311.
280. Wang XQ, Chen DF, Shi YM, Luo JM, Zhang YQ, Yuan XH, et al. Copper and cuproptosis-related genes in hepatocellular carcinoma: therapeutic biomarkers targeting tumor immune microenvironment and immune checkpoints. *Front Immunol* 2023;**14**:1123231.
281. Zhang C, Zeng YX, Guo XC, Shen HJ, Zhang JH, Wang KK, et al. Pan-cancer analyses confirmed the cuproptosis-related gene FDX1 as an immunotherapy predictor and prognostic biomarker. *Front Genet* 2022;**13**:923737.
282. Wang FW, Lin HS, Su QS, Li CQ. Cuproptosis-related lncRNA predict prognosis and immune response of lung adenocarcinoma. *World J Surg Oncol* 2022;**20**:275.
283. Ma C, Gu ZY, Ding WZ, Li F, Yang Y. Crosstalk between copper homeostasis and cuproptosis reveals a lncRNA signature to prognosis prediction, immunotherapy personalization, and agent selection for patients with lung adenocarcinoma. *Aging (Albany NY)* 2023;**15**: 13504.
284. Knaup H, Weindler J, van Heek L, Voltin CA, Fuchs M, Borchmann P, et al. PET/CT reconstruction and its impact on [Measures of] metabolic tumor volume. *Acad Radiol* 2024;**31**: 3020−5.
285. Mahakian LM, Farwell DG, Zhang H, Seo JW, Poirier B, Tinling SP, et al. Comparison of PET imaging with ^{64}Cu-Liposomes and ^{18}F-FDG in the 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced hamster buccal pouch model of oral dysplasia and squamous cell carcinoma. *Mol Imag Biol* 2014;**16**:284−92.
286. Hicks RJ, Ware RE, Callahan J. Total-body PET/CT: pros and cons. *Semin Nucl Med* 2025;**55**:11−20.
287. Hu HH, Zhu HX, Zhan WD, Hao B, Yan T, Zhang JD, et al. Integration of multiomics analyses reveals unique insights into CD24-mediated immunosuppressive tumor microenvironment of breast cancer. *Inflamm Res* 2024;**73**:1047−68.
288. Acha-Sagredo A, Andrei P, Clayton K, Taggart E, Antoniotti C, Woodman CA, et al. A constitutive interferon-high immunophenotype defines response to immunotherapy in colorectal cancer. *Cancer Cell* 2025;**43**:292−307.e7.
289. Braun DA, Moranzoni G, Chea V, McGregor BA, Blass E, Tu CR, et al. A neoantigen vaccine generates antitumour immunity in renal cell carcinoma. *Nature* 2025;**639**:474−82.
290. Seto T, Nosaki K, Shimokawa M, Toyozawa R, Sugawara S, Hayashi H, et al. Phase II study of atezolizumab with bevacizumab for non-squamous non-small cell lung cancer with high PD-L1 expression (@Be Study). *J Immunother Cancer* 2022;**10**:e004025.
291. Hung MS, Chen IC, Lin PY, Lung JH, Li YC, Lin YC, et al. Epidermal growth factor receptor mutation enhances expression of vascular endothelial growth factor in lung cancer. *Oncol Lett* 2016; **12**:4598−604.
292. Bahamin N, Rafieian-Kopaei M, Ahmadian S, Karimi I, Doustimotlagh AH, Mobini G, et al. Combined treatment with Alhagi maurorum and docetaxel inhibits breast cancer progression *via* targeting HIF-1α/VEGF mediated tumor angiogenesis *in vivo*. *Heliyon* 2023;**9**:e16292.
293. Waldner MJ, Neurath MF. Targeting the VEGF signaling pathway in cancer therapy. *Expert Opin Ther Targets* 2012;**16**:5−13.
294. Wang NN, Dong J, Ouyang DF. AI-directed formulation strategy design initiates rational drug development. *J Control Release* 2025; **378**:619−36.
295. Dong J, Wu Z, Xu HL, Ouyang DF. FormulationAI: a novel web-based platform for drug formulation design driven by artificial intelligence. *Briefings Bioinf* 2023;**25**:bbad419.
296. Domínguez-Romero E, Mazurenko S, Scheringer M, Martins Dos Santos VAP, Evelo CT, Anton M, et al. Making PBPK models more reproducible in practice. *Briefings Bioinf* 2024;**25**:bbae569.
297. Rudik AV, Bezhentsev VM, Dmitriev AV, Druzhilovskiy DS, Lagunin AA, Filimonov DA, et al. MetaTox: web application for predicting structure and toxicity of xenobiotics' metabolites. *J Chem Inf Model* 2017;**57**:638−42.
298. Xiong X, Liu YR, Pu DD, Yang Z, Bi ZD, Tian L, et al. DeSide: a unified deep learning approach for cellular deconvolution of tumor microenvironment. *Proc Natl Acad Sci U S A* 2024;**121**:e2407096121.
299. Ye GC, Wu GY, Qi Y, Li K, Wang ML, Zhang CY, et al. Non-invasive multimodal CT deep learning biomarker to predict pathological complete response of non-small cell lung cancer following neoadjuvant immunochemotherapy: a multicenter study. *J Immunother Cancer* 2024;**12**:e009348.
300. Chen ZF, Chen Y, Sun Y, Tang L, Zhang L, Hu YJ, et al. Predicting gastric cancer response to anti-HER2 therapy or anti-HER2 combined immunotherapy based on multi-modal data. *Signal Transduct Targeted Ther* 2024;**9**:222.
301. Xiang JX, Wang XY, Zhang XM, Xi YH, Eweje F, Chen YJ, et al. A vision-language foundation model for precision oncology. *Nature* 2025;**638**:769−78.
302. Gu Y, Zhang TT, Huang ZF, Hu SW, Zhao W, Xu JJ, et al. An exploration of nucleic acid liquid biopsy using a glucose meter. *Chem Sci* 2018;**9**:3517−22.
303. Guo W, Ying PY, Ma RY, Jing ZQ, Ma G, Long J, et al. Liquid biopsy analysis of lipometabolic exosomes in pancreatic cancer. *Cytokine Growth Factor Rev* 2023;**73**:69−77.
304. Schumacher TN, Scheper W. A liquid biopsy for cancer immunotherapy. *Nat Med* 2016;**22**:340−1.
305. Fatima S, Ma Y, Safrachi A, Haider S, Spring KJ, Vafaee F, et al. Harnessing liquid biopsies to guide immune checkpoint inhibitor therapy. *Cancers* 2022;**14**:1669.
306. Chen SY, Meng T, Zheng XW, Cai JX, Zhang WP, You HS, et al. Contribution of nucleophosmin overexpression to multidrug resistance in breast carcinoma. *J Drug Target* 2018;**26**:27−35.
307. Shao YY, Su RR, Wang Y, Yin SS, Pu WL, Koo S, et al. Drug co-administration in the tumor immune microenvironment of hepatocellular carcinoma. *Acupunct Herb Med* 2023;**3**:189.
308. Zhao BB, Qin C, Li ZR, Wang YY, Li TH, Cao HT, et al. Multidrug resistance genes screening of pancreatic ductal adenocarcinoma based on sensitivity profile to chemotherapeutic drugs. *Cancer Cell Int* 2022;**22**:374.
309. Wang Q, Huang CH, Wibowo FS, Amin R, Shen JZ, Li F, et al. Elesclomol-copper nanoparticles overcome multidrug resistance in cancer cells. *ACS Appl Mater Interfaces* 2024;**16**:13509−24.
310. Parikh AR, Corcoran RB. Monitoring resistance through liquid biopsy. *Ann Oncol* 2018;**29**:8−11.