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REVIEW

Mechanism and role of regulated cell death in tumor immunity and immunotherapy

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Abstract

Cancer immune checkpoint inhibitors (ICIs) have brought breakthroughs, but only about one-third of cancer patients benefit from ICIs. In recent years, targeting non-apoptotic regulated cell death (RCD) subtypes, such as ferroptosis, necroptosis, autophagy, cuproptosis, and pyroptosis, has emerged as a novel strategy in cancer therapy due to their ability to release damage-associated molecular patterns (DAMPs), enhance antigen presentation, and remodel the tumor immune microenvironment, thereby activating anti-tumor immune responses. A number of studies have shown that precise induction of these pathways by small molecules or nanoparticles can reverse the resistance to chemoradiotherapy and ICIs, promote the transformation of "cold tumors" to "hot tumors," and ultimately establish durable immune memory. This article systematically reviewed the key mechanisms and immunomodulatory functions of five types of non-apoptotic RCD (ferroptosis, necroptosis, autophagy, cuproptosis, and pyroptosis), discussed the related treatment strategies, and prospects for the future application in combination with existing immunotherapy.

KEYWORDS
regulated cell death, tumor immune microenvironment, tumor immunity, tumor immunotherapy

List of Abbreviations: 15-HETE, 15-Hydroxyeicosanotetraenoic acid; 5-FU, 5-fluorouracil; 5-HT, 5-hydroxytryptamine; 5-HT1A, 5-hydroxytryptamine 1A; 8-OHG, 8-hydroxyguanosine; A-TEA, α-tocopherol ether-linked acetic acid; A20, Cylindromatosis Tumor Necrosis Factor Alpha-Induced Protein 3; AA, Arachidonic acid; AAK1, Adaptor-associated protein kinase 1; ACD, Accidental cell death; ACSL4, Acyl-CoA synthetase long-chain family member 4; AdA, Adrenic acid; AGER, Receptor for advanced glycation end products; AI, Artificial intelligence; AIM2, Absent in melanoma 2; ALOX15, Arachidonate 15-lipoxygenase; AMPKα1, AMP-activated protein kinase α1 subunit; APCs, Antigen-presenting cells; ARG, Arginine; ASC, Apoptosis-associated speck-like protein; ATG4B, Autophagy-related protein 4 homolog B; ATG101, Autophagy-related protein 101; ATP, Adenosine Triphosphate; ATP7A, ATPase Copper Transporting Alpha; B3GNT3, β1, 3-N-acetylglucosamine transferase-3; BECN1, Beclin 1; BLCA, Bladder cancer; BNIP3, BCL2 interacting protein 3; BNIP3L, BCL2 interacting protein 3 like; CAFs, Cancer-associated fibroblasts; CAR-T, Chimeric antigen receptor T cells; CARD, Caspase recruitment domain; CARS1, Cysteinyl transferase synthetase 1; CBP, CREB-binding protein; ccRCC, Clear cell renal carcinoma; c-Myc, Cellular myelocytomatosis viral oncogene; CCL2, C-C class chemokine ligand 2; CCL5, C-C class chemokine ligand 5; CD36, Cluster of differentiation 36; CD70, Cluster of differentiation antigens 70; cDC1s, Conventional type 1 DCs; CDKN1B, Cyclin-dependent kinase inhibitor 1B; CDKN2A, Cyclin-dependent kinase inhibitor 2A; CDT, Chemodynamic therapy; cIAP1, Cellular inhibitor of apoptosis protein 1; CMA, Chaperone-mediated autophagy; COX-2, Cyclooxygenase-2; CQ, Chloroquine; CRC, Colorectal cancer; CRG, Cuproptosis-related gene; CRS, Cytokine release syndrome; CRT, Calreticulin; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTLs, Cytotoxic T lymphocytes; Cu, Copper; CXCL1, C–X–C motif chemokine ligand 1; CYLD, Cylindromatosis; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; DHA, Dihydroartemisinin; DLAT, Dihydrolipoamide transacetylase; DLD, Dihydrolipoic amide dehydrogenase; dsDNA, Double-stranded DNA; EGFR, Epidermal growth factor receptor; EIF2AK2, Eukaryotic translation initiation factor 2-alpha kinase 2; EMT, Epithelial-to-mesenchymal transition; ER, Endoplasmic reticulum; ESCC, Esophageal squamous cell carcinoma; FADD, Fas-associated Death Domain protein; FAO, Fatty acid oxidation; FAS, Fas cell surface death receptor; Fas, Factor associated suicide ligand; FasL, Fas Ligand; FDX1, Ferredoxin 1; FGFR2, Fibroblast growth factor receptor 2; FPN, Ferroportin; FIN56, Ferroptosis-inducing compound; FIP200, FAK family kinase-interacting protein of 200 kDa; FTH/FTL, Ferritin heavy chain/ferritin light chain; Fe-S, Iron–sulfur cluster proteins; GBM, Glioblastoma; GEM, Gemcitabine; GLS, Glutaminase; GO, Graphene oxide; GPX4, Glutathione peroxidase 4; GSDM, Gasdermin; GSH, Glutathione; GSSG, Oxidized glutathione; GZMB, Granzyme B; HAMP, Heparin antimicrobial peptide; HCC, Hepatocellular carcinoma; HCQ, Hydroxychloroquine; H-FIRE, High-frequency irreversible electroporation; HMGB1, High mobility group box 1; HNSCC, Head and neck squamous cell carcinoma; HSP70/90, Heat shock protein 70/90; HSPA1A, Heat shock protein family A member 1A; LA, Lipoic acid; ICAM1, Intercellular adhesion molecule 1; ICB, Immune checkpoint blockade; ICD, Immunogenic cell death; ICIs, Immune checkpoint inhibitors; IFN, Interferon; IFNR, Interferon receptor; LIAS, Lipoic acid synthase; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-12, Interleukin-12; iNOS, Inducible nitric oxide synthase; IRP1/2, Iron regulatory protein 1 / 2; Irgm1, Immune-related guanosine triphosphatase M protein; KRASG12D, Kirsten rat sarcoma virus oncogene homolog with G12D mutation; LAMP2, Recombinant lysosomal associated membrane protein 2; LC3, Microtubule-associated protein light chain 3; LCSC, Lung cancer stem cell; LIP, Labile iron pool; LIPT1, Lipoyltransferase 1; LOXL4, Lysyl oxidase-like protein 4; LOXs, Lipoxygenase; LPCAT3, Lysophosphatidylcholine acyltransferase 3; LPS, Lipopolysaccharide; LPO, Lipid peroxides; LTB4, Leukotriene B4; MDSCs, Myeloid-derived suppressor cells; MHC, Major histocompatibility complex; MLKL, Mixed-lineage kinase domain-like protein; MPR, Mannose-6-phosphate receptor; MSCs, Mesenchymal stroma/stem cells; MST1, Macrophage stimulating 1; MT2A, Metallothionein 2A; MTF1, Metal-regulatory transcription factor 1; mTOR, Mechanistic (formerly "mammalian") target of rapamycin; mTORC1, Mechanistic target of rapamycin complex 1; MTX, Mitoxantrone; MUFA, Monounsaturated fatty acids; NBIF, Neosporin isoflavone; NBR1, Neighbor of BRCA1 gene 1; NF-κB, Nuclear factor-κB; NK cell, Natural killer cell; NKTs, Natural killer T cells; NLRP3, NOD-like receptor family, pyrin domain containing 3; NLRC4, NOD-like receptor family CARD domain-containing protein 4; NOS2, Nitric oxide synthase 2; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; Nrf2, Nuclear factor E2-related factor 2; OS, Overall survival; P2×7, Purinergic receptors; P300, E1A binding protein p300; PAMPs, Pathogen-associated molecular patterns; PC, Pancreatic cancer; PCA, Principal component analysis; PD-1, Programmed death-1; PDAC, Pancreatic ductal adenocarcinoma; PDHA1, Pyruvate dehydrogenase E1 subunit α1; PDHB, Pyruvate dehydrogenase E1 subunit β; PDK1/3, Pyruvate dehydrogenase kinase 1/3; PD-L1, Programmed death-ligand 1; PDT, Photodynamic therapy; PE, Phosphatidylethanolamine; PGE2, Prostaglandin E2; PI3K, Phosphatidylinositol 3-kinase; PIP2, Phosphatidylinositol diphosphate; PPAR, Peroxisome proliferator-activated receptor; PPRs, Pattern recognition receptors; PtdIns3K, Phosphatidylinositol 3-kinase; PTT, Photothermal therapy; PUFAs, Polyunsaturated fatty acids; PYD, Pyrophilin structural domains; RARRES3, Retinoic acid receptor responder 3; RCC, Renal cell carcinoma; RCD, Regulated cell death; RIG-I, retinoic acid-inducible gene I; RIPK1, Receptor-interacting protein kinase 1; RIPK3, Receptor-interacting protein kinase 3; ROS, Reactive oxygen species; RSL3, RAS-selective lethal small molecule 3; RT, Radiation therapy; SAP130, Splicing factor-associated protein of 130 kDa; SAPE-OOH, Stearoyl-arachidonoyl-phosphatidylethanolamine hydroperoxide; SAS, Sulfasalazine; SLC3A2, Solute carrier family 3 member 2; SLC7A11, Solute carrier family 7 member 11; SMAC, Second mitochondrial-derived activator of caspases; STAT3, Signal transducer and activator of transcription 3; STEAP3, Six transmembrane epithelial antigen of the prostate 3; STING, Stimulator of interferon genes; System Xc−, Cystine–glutamate antiporter; TAAs, Tumor-associated antigen; TAMs, Tumor-associated macrophages; TCA, Tricarboxylic acid cycle; TFR1, Cell membrane transferrin receptor 1; TGF-β, Transforming growth factor beta; TGM2, Transglutaminase 2; Th1, Type 1 T helper cell; TIDE, Tumor immune dysfunction and exclusion; TIM-3, T cell immunoglobulin and mucin-domain containing protein 3; TIM-4, T cell immunoglobulin and mucin-domain containing protein 4; TIME, Tumor immune microenvironment; TLR4, Toll-like receptor 4; TMAO, Trimethylamine N-oxide; TNF-α, Tumor necrosis factor-alpha; TNBC, Triple-negative breast cancer; TNFR1, Human tumor necrosis factor receptor 1; TNFRSF1A, Tumor necrosis factor receptor superfamily member 1A; TRADD, Tumor necrosis factor receptor-associated death domain protein.; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R, TNF-related apoptosis-inducing ligand receptor; TRAF2, TNF receptor-associated factor 2; Tregs, Regulatory T cells; TME, Tumor microenvironment; TYRO3, Protein tyrosine kinases; XCL1, X-C motif chemokine ligand 1; ULK1, Unc-51-like autophagy activating kinase 1;

1 | INTRODUCTION

Cell death is indispensable for eliminating damaged cells and maintaining physiological homeostasis. Fundamentally, cancer development is characterized by evasion of cell death [1]. Cell death itself can be categorized as accidental cell death (ACD) and regulated cell death (RCD) [2]. RCD differs from uncontrolled accidental cell death and is controlled by signal-directed cascades that are critical for organismal development, immunity, and stress adaptation [3]. Although apoptosis historically dominated RCD paradigms, emerging research has unveiled critical non-apoptotic forms, including ferroptosis, necroptosis, autophagy, cuproptosis, and pyroptosis, which exhibit complex immunobiological functions [4].

The tumor microenvironment (TME) orchestrates a dynamic interplay between innate and adaptive immunity. It can mediate immune elimination, immune balance, and immune escape [5]. The advent of tumor immunotherapy, particularly ICIs, has revolutionized cancer treatment by reactivating T cell-mediated tumor elimination, taking research and therapy to new heights [6–8]. However, RCD within the TME exhibits a dual role in both tumor progression and the response to treatment [9], and there is a key limitation: because of the complexity of tumor-cell and immune-cell interactions within the TME, only a minority of patients can achieve effective treatment [10, 11]. This limitation stems largely from the existence of distinct TME phenotypes: immunodeficient or even immunologically quiescent "cold" tumors, and immunologically infiltrated "hot" tumors, which critically influence treatment resistance [12–14]. However, traditional therapeutic strategies centered on inducing apoptosis may be inherently limited by two key challenges: (1) tumor evasion of apoptosis leads to resistance to apoptosis [15], and (2) compensatory reduction of immunogenicity and promotion of immunosuppressive network disruption of therapeutic efficacy [16]. Therefore, inducing immunogenic cell death (ICD) has emerged as a promising strategy to enhance immunotherapeutic efficacy by activating the tumor immune microenvironment (TIME) [17]. What's more, ICD is closely related to tumor immunity and the TIME. It's an umbrella term representing different cell death modes such as ferroptosis, pyroptosis, autophagy, cuproptosis, and necroptosis [18]. These different forms of ICD may alter the TME through the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), type I interferon responses, and the production of pathogen-responsive-like chemokines [19]. Furthermore, the complex crosstalk between these death pathways offers potential targets to overcome tumor resistance [20]. However, non-apoptotic RCD often exhibits a dualistic nature in TME reprogramming. They can also drive immunosuppression through recruiting myeloid cells or upregulation of checkpoints [21]. Their efficacy is influenced by the spatial heterogeneity and temporal evolution of TME.

This review systematically deconstructed five non-apoptotic RCD patterns and dissected their molecular mechanisms, dichotomous immunomodulatory functions, and therapeutic targeting potential. By constructing the selective immunomodulation profile of RCD and building a new understanding of the classical ICD concept, this review elucidated new therapeutic potential for the precise intervention of refractory malignant tumors.

2 | FERROPTOSIS

First described by Brent Stockwell in 2012, ferroptosis is an iron-dependent non-apoptotic RCD induced by erastin [22]. It is characterized by iron-dependent reactive oxygen species (ROS) accumulation, lipid peroxidation, and iron overload [23]. It is suppressible via iron chelation or lipophilic antioxidant administration [24], the sensitivity can vary with the cell type, cell state, and the response to host environmental changes [25]. As a novel RCD distinct in morphology, biochemistry, and genetics [26], ferroptosis involves three core pathways: the iron metabolism pathway [27], lipid oxidation pathway [28], and glutathione metabolism pathway [29]. Ferroptosis participates in diverse pathologies, including cancer [30], neurodegeneration [31, 32], and organ injury [33]. Critically, it functions as an ICD mode [34] underpinning its dual anti-tumor mechanisms: intrinsic suppression via iron/lipid peroxidation-driven cytotoxicity [35] and immune-mediated regression through the release of DAMPs and T-cell activation [36]. Consequently, inducing ferroptosis not only synergizes with ICIs to enhance immunotherapy efficacy [37] but also overcomes therapy resistance in refractory malignancies [38, 39].

2.1 | Regulatory mechanisms (Figure 1)

2.1.1 | Glutathione metabolic pathway

Glutathione peroxidase 4 (GPX4), a glutathione-dependent selenoenzyme, is the central regulator of ferroptosis [40]. GPX4 activity requires glutathione (GSH), a glutamate-glycine-cysteine tripeptide [41, 42]. GPX4 inhibits lipid peroxidation by detoxifying polyunsaturated

UCN3, Urothelin 3; USP8, Ubiquitin-specific peptidase 8; ZBP1, Z-DNA binding protein 1.

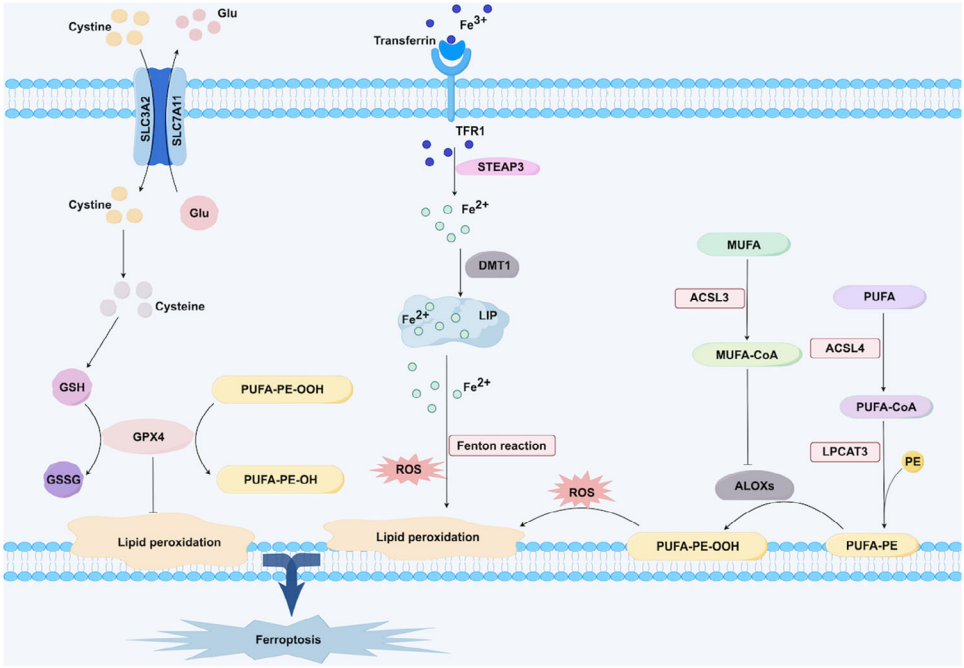


FIGURE 1 Mechanisms of ferroptosis. Ferroptosis is regulated through glutathione metabolism, iron metabolism, and lipid oxidation pathways. Glutathione metabolism (left): GPX4 is a key regulator of ferroptosis, and its activity is controlled by the amount of glutathione. The production of glutathione depends on the cysteine-glutamic acid antitransporter (Xc^- system), which consists of SLC3A2 and SLC7A11. The Xc^- system mediates the extracellular cystine import and excrete Glu, and intracellular cystine is reduced to cysteine for the synthesis of GSH. GSH is utilized as a substrate by GPX4 to reduce PUFA-PE-OOH to PUFA-PE-OH, and in the process, it is oxidized to GSSG. thereby inhibiting lipid peroxidation. Iron metabolism (middle): Fe^{3+} binds to transferrin and enters the cell via TFR1, then Fe^{3+} is reduced to Fe^{2+} by STEAP3, which is finally released into the LIP. Excess ferrous iron in the iron pool mediates the production of reactive ROS through the Fenton reaction, which promotes lipid peroxidation and induces ferroptosis. Lipid oxidation (right): ACSL4 catalyzes the combination of free PUFA and CoA to form PUFA-CoA. LPCAT3 esterifies PUFA-CoA into PE to form PUFA-PE, which is then catalyzed by ALOXs to generate PUFA-PE-OOH, resulting in membrane lipid peroxidation. MUFA can be doped into the membrane by ACSL3 to replace PUFA, reducing the sensitivity to peroxidation. Abbreviations: ACSL3, acyl-CoA synthetase long-chain family member 3; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX, arachidonate lipoxygenase; CoA, coenzyme A; Fe^{2+}, ferrous iron; Fe^{3+}, ferric iron; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; Glu, glutamate; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; MUFA, monounsaturated fatty acid; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acid; PUFA-PE-OOH, polyunsaturated fatty acid-phosphatidylethanolamine hydroperoxide; PUFA-PE-OH, polyunsaturated fatty acid-phosphatidylethanolamine alcohol; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; TFR1, transferrin receptor 1; Xc^-, system Xc^- transporter.

fatty acid-phosphatidylethanolamine hydroperoxide (PUFA-PE-OOH) to their corresponding alcohols, polyunsaturated fatty acid-phosphatidylethanolamine alcohol (PUFA-PE-OH) [43, 44], and in this reaction, two molecules of GSH provide reducing equivalents and are concomitantly oxidized to form one molecule of oxidized glutathione (GSSG) [45]. GSH synthesis depends on cystine uptake via the system Xc^- transporter composed of solute carrier family 3 member 2 (SLC3A2) and solute carrier family 7 member 11 (SLC7A11) [46], which imports extracellular cystine while exporting intracellular glutamate [47]. The imported cystine is reduced to cysteine for GSH production. Cysteine depletion impairs GSH synthesis, inactivating GPX4 and triggering ferroptosis [48, 49]. Compounds (e.g., erastin, sulfasalazine, sorafenib, and high-concentration glutamate) that inhibit the Xc^- system transporter, depleting intracellular GSH and suppressing GPX4 activity, thereby inducing ferroptosis [50, 51]. Additionally, interferon-gamma (IFN-γ) downregulates SLC7A11 or SLC3A2, affecting cystine uptake in tumor cells and promoting lipid peroxidation and ferroptosis [52]. In addition, direct GPX4 inhibitors, such as RAS-selective lethal small molecule 3 (RSL3) and ferroptosis-inducing compound 56 (FIN56), induce ferroptosis by binding to GPX4 and blocking its enzymatic activity [23, 53]. Studies have shown that GSH metabolism negatively correlates with $CD8^+$ T cells (CD, cluster of differentiation) and M1 macrophagesbut positively with M2 macrophages and resting mastocytes [54]. Renal *GPX4* gene deletion leads to the release of DAMPs, macrophage recruitment, mass death

of renal tubules, and renal failure [55]. Complementarily reduced GPX4 activity generates pro-inflammatory lipids, specifically 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB4), which drive ferroptosis-associated T cell responses [56, 57].

2.1.2 | Iron metabolism

Dysregulated iron homeostasis is a central driver of ferroptosis, characterized by abnormalities in iron uptake, storage, utilization, or efflux that elevate the labile iron pool (LIP). This process triggers ferroptosis through Fenton reaction-mediated ROS generation [42, 57, 58]. The iron cycle initiates with systemic Fe^{3+} binding to transferrin [59], forming a complex with transferrin receptor 1 (TFR1) [58], which then enters the cell via endocytosis [60]. Within endosomes, six-transmembrane epithelial antigen of the prostate 3 (STEAP3) catalyzes the reduction of Fe^{3+} to Fe^{2+} [61], and the reduced iron is subsequently released into the LIP [62]. Dysregulated iron homeostasis, prevalent in malignancies such as breast, ovarian, renal, and lung cancers [63], drives aberrant iron accumulation in cancer cells relative to normal counterparts [64]. For example, in renal cancer, tumor-associated macrophages (TAMs) maintain an iron-releasing phenotype through upregulation of ferroportin (FPN) and M2 polarization, which promotes tumor proliferation and dissemination [65]. Consequently, dysregulated iron homeostasis drives iron overload, potentiating oxidative stress that facilitates malignant transformation, cancer progression, therapeutic resistance, and immune evasion through pathological iron recycling pathways [66, 67].

2.1.3 | Lipid oxidation metabolism

Ferroptosis is driven by the lethal buildup of lipid peroxides, notably from polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA) and adrenic acid (AdA), whose diallylic hydrogen atoms are especially prone to ROS attack [68, 69].

Although free PUFAs alone cannot initiate iron-dependent lipid peroxidation, acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the esterification of free PUFAs to their CoA derivatives (PUFA-CoAs) [70]. Subsequently, lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates these PUFA-CoAs into phosphatidylethanolamine (PE) phospholipids, including arachidonic acid-phosphatidylethanolamines (AA-PE) and adrenic acid-phosphatidylethanolamines (AdA-PE) [71, 72]. Finally, arachidonate lipoxygenases (ALOXs) peroxidize AA-PE and AdA-PE to generate hydroperoxy derivatives (AA-PE-OOH and AdA-PE-OOH), which execute ferroptosis by propagating membrane lipid peroxidation [73]. ACSL4 promotes tumor progression, while AA supplementation enhances ferroptosis and immunotherapy [74].

Compared with PUFA, monounsaturated fatty acids (MUFA) inhibit ferroptosis by displacing PUFAs in membranes via ACSL3 [75]. Lipid accumulation generally immunosuppresses immune cells [76]. For example, long-chain fatty acid metabolism enhances the suppressive effect of TAMs on tumor immune surveillance [77].

2.2 | Ferroptosis and tumor immune microenvironment (Figure 2)

This section examines the context-dependent roles of ferroptosis in shaping the TIME, highlighting how iron-dependent lipid peroxidation can both potentiate anti-tumor immunity and, paradoxically, drive immune suppression and tumor progression. Ferroptosis exhibits dual roles in cancer, influencing epithelial-to-mesenchymal transition (EMT) [78], immune response, and drug resistance [79]. It may improve the efficacy of immunotherapy and enhance anti-tumor immune responses [35]. However, ferroptosis can paradoxically promote tumor growth through inflammation-driven immunosuppression within the TME [80]. Resolving this context-dependent duality represents a critical frontier for clinical translation.

2.2.1 | Ferroptosis in immune cells

Here, we surveyed how ferroptosis affects key immune cell subsets—T cells, dendritic cells, macrophages, and NK cells, thereby modulating anti-tumor responses within the TME.

T Cells

In the adaptive immune system, cytotoxic T cells (CTL, also known as $CD8^+$ T cells) directly kill tumor cells, while T helper cells (Th, also known as $CD4^+$ T cells), such as type 1 T helper cells (Th1), secrete IFN-γ to attack tumors and activate $CD8^+$ T cells [81–84]. Iron overload disrupts Th1/Th2 differentiation and induces the expression of negative checkpoints, such as T cell immunoglobulin mucin-3 (TIM-3), on $CD4^+$ T cells, thereby suppressing IFN-γ production [85].

$CD8^+$ T cells upregulate the lipid transporter CD36 promoting intracellular lipid peroxidation and triggering ferroptosis. This ferroptosis-mediated cell death impairs

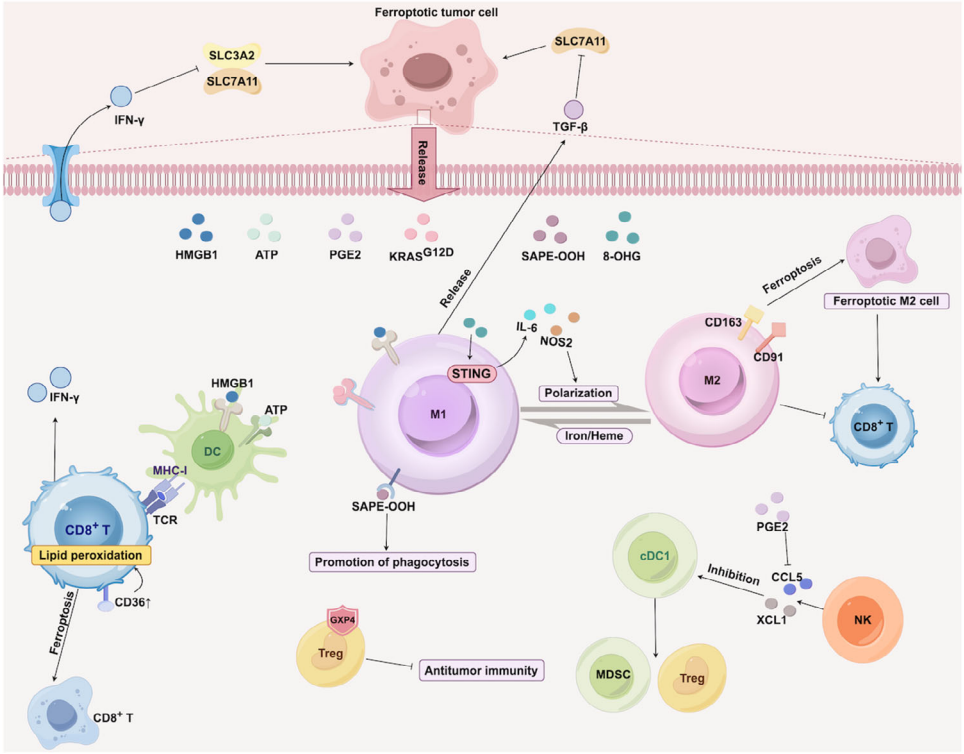


FIGURE 2 Ferroptosis and tumor immunity. Ferroptotic cancer cell release HMGB1, ATP, PGE2, $KRAS^{G12D}$, 8-OHG, etc. DC cells recognize HMGB1 and ATP to promote antigen presentation to $CD8^+$ T cells. $CD8^+$ T cells upregulate the lipid transporter CD36, promoting intracellular lipid peroxidation and triggering ferroptosis. Surviving T cells secrete IFN-γ to promote ferroptosis in tumor cells by reducing the expression of cystine transporters (SLC7A11/SLC3A2). In contrast, GPX4 on the surface of Treg cells maintains their homeostasis, is resistant to ferroptosis, and inhibits anti-tumor immunity. The 8-OHG and $KRAS^{G12D}$ released by ferroptotic cancer cells promote the polarization of the M1 phenotype to the M2 phenotype. The 8-OHG promotes the release of cytokines such as IL-6 and NOS2 through the STING pathway, induces adaptive immunosuppression, and stimulates tumor growth. M2-type TAMs highly express clearance rate receptors such as CD163 and CD91, and exert a promoting effect on cancer by suppressing $CD8^+$ T cell function. Iron or heme exposure reprograms TAMs to the M1 phenotype, inhibiting SLC7A11 and enhancing anti-tumor immunity by releasing TGF-β; SAPE-OOH acts as an "eat me" signal to activate macrophage phagocytic function. PGE2 inhibits cDC1 by suppressing the secretion of CCL5 and XCL1 by NK cells, thereby activating immunosuppressive cells such as MDSCs and Tregs. Abbreviations: 8-OHG, 8-Hydroxyguanosine; ATP, adenosine triphosphate; cDC1, conventional type 1 dendritic cell; CD36, cluster of differentiation 36 (fatty acid translocase); CD91, cluster of differentiation 91; CD163, cluster of differentiation 163 (hemoglobin scavenger receptor); DC, dendritic cell; GPX4, glutathione peroxidase 4; HMGB1, high mobility group box 1; IFN-γ, interferon gamma; IL-6, interleukin-6; KRASG12D, kirsten rat sarcoma viral oncogene homolog G12D mutant; MDSC, myeloid-derived suppressor cell; MHC-I, major histocompatibility complex class I; NOS2, nitric oxide synthase 2; PGE2, prostaglandin E2; SAPE-OOH, stearoyl-arachidonoyl-phosphatidylethanolamine hydroperoxide; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STING, stimulator of interferon genes; TAM, tumor-associated macrophage; TGF-β, transforming growth factor beta; Treg, regulatory T cell; XCL1, X-C motif chemokine ligand 1.

cytotoxic function, an effect rescued by *GPX4* overexpression [86–88]. Conversely, IFN-γ released by surviving $CD8^+$ T cells downregulates SLC7A11and SLC3A2 in tumor cells, and induces ferroptosis [89].

Regulatory T cells (Tregs), a specialized T lymphocyte subpopulation, exhibit high ferroptosis resistance that sustains their immunosuppressive function. This contrasts with $CD8^+$ T cells' tumoricidal activity [76, 90]. GPX4 sustains Treg homeostasis [91]; GPX4 deficiency induces ferroptosis and interleukin-1 beta (IL-1β) release, promoting Th17 responses [92] that disrupt Treg-mediated immunosuppression [93]. Targeting Treg ferroptosis resistance could potentiate adoptive T cell therapies.

Dendritic cells

As central regulators of anti-tumor immunity, dendritic cells (DCs) initiate and sustain immune responses by modulating the TME and activating anti-tumor T cells [94, 95]. However, DCs are vulnerable to ferroptosis [96]. Pharmacological inhibition of GPX4 (e.g., RSL3) directly triggers ferroptosis in DCs, impairing their antigen uptake and presentation capacity. Consequently, DCs lose the ability to

activate $CD8^+$ T cells for IFN-γ production [97]. Protecting DCs from ferroptosis may improve cancer vaccine efficacy.

Tumor-associated macrophages

TAMs exhibit divergent ferroptosis sensitivities and iron-handling phenotypes that shape their pro- or anti-tumor functions. TAMs are mainly classified into M1 and M2 types. M1-type TAMs sequester iron by upregulating ferritin heavy and light chains (FTH and FTL) and hepcidin antimicrobial peptide (HAMP), while downregulating FPN and iron regulatory protein 1/2 (IRP1/2). Conversely, M2-type TAMs adopt an iron-releasing phenotype characterized by elevated FPN and scavenger receptors (CD163, CD91). This phenotype facilitates tissue repair processes and promotes tumor cell growth [98, 99] through CTL inhibition [100], ultimately exerting pro-tumorigenic effects [101]. Acute iron overload induces macrophage M1-polarization through ROS-mediated activation of E1A binding protein p300 (p300) and CREB-binding protein (CBP), and acetylation of umor protein p53 (p53), upregulating pro-inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and IL-1β, while suppressing M2 markers, transglutaminase 2 (TGM2) [102, 103]. Conversely, chronic iron overload inactivates macrophages, characterized by diminished expression of TNF-α, IL-6, interleukin-12 (IL-12), major histocompatibility complex class II (MHC-II), intercellular adhesion molecule 1 (ICAM1), and inducible nitric oxide synthase (iNOS) [104, 105]. Early tumors employ M1-like iron sequestration for defense, while chronic inflammation drives M2-like iron release to accelerate progression [106].

Natural killer cells

Natural killer (NK) cells effectively eliminate malignant cells evading $CD8^+$ T cell surveillance and enhancing antibody-dependent cellular cytotoxicity and T cell responses [107]. Their anti-tumor function exhibits iron-dependent duality: systemic iron deficiency impairs NK activity [108], yet within breast TME, localized iron restriction correlates with enhanced NK-mediated tumor killing [67]. Conversely, in ovarian cancer, tumor-associated NK cells display attenuated cytotoxicity due to elevated lipid peroxidation and ferroptosis susceptibility [109].

2.2.2 | Ferroptosis in tumor cells

DAMP release and immune recognition

Ferroptotic cancer cells release DAMPs into the TME [110], including high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), Kirsten rat sarcoma virus oncogene homolog with G12D mutation ($KRAS^{G12D}$), heat shock protein 70/90 (HSP 70/90), and calreticulin (CRT) [111]. These DAMPs activate immune recognition through pattern recognition receptors (PPRs), such as Toll-like receptor 4 (TLR4) and purinergic receptor (P2×7) [57, 112], with HMGB1 serving as a signature nuclear DAMP that undergoes autophagy-dependent release [61, 113]. Critically, HMGB1's redox state dictates immunogenic outcomes: reduced HMGB1 activates anti-immunity, while oxidized HMGB1 suppresses it [114, 115]. Besides, the receptor for advanced glycation end products (AGER) is a key recognition molecule of HMGB1, which can activate immune cells, promote the release and expansion of proinflammatory cytokines, and regulate the local immune microenvironment [116]. Thus, monitoring HMGB1 redox transitions may predict immunotherapy efficacy.

Bidirectional regulation of macrophage polarization

Ferroptotic tumor cells orchestrate macrophage polarization through context-dependent signaling cascades that drive divergent immune outcomes. In pancreatic cancer (PC), ferroptotic cancer cells recruit macrophages via C-C motif chemokine ligand 2 (CCL2) and secrete cytokines such as IL-6 and IL-1β, exacerbating tissue inflammation [78]. GPX4-deficient ferroptotic cancer cells release 8-hydroxyguanosine (8-OHG) to activate macrophage stimulator of interferon genes (STING) signaling, inducing IL-6 and nitric oxide synthase 2 (NOS2)-dependent cytokine release that generates a protumor inflammatory microenvironment [92, 117]. Concurrently, ferroptotic PC cells release $KRAS^{G12D}$, which undergoes AGER-mediated internalization by macrophages [118], thereby reprogramming them from the M1 to M2 phenotype [119]. Resulting M2-TAMs stimulate tumor growth via adaptive immunosuppression mediated by arginine (ARG), interleukin-10 (IL-10), and transforming growth factor-beta (TGF-β) [120].

The impact of ferroptosis on TAMs exhibits cancer-type specificity. In breast cancer models, ferroptotic tumor cells induce M2-TAMs to release DAMPs that enhance T cell responses [121]. Conversely, glioma ferroptosis drives M2-TAMs polarization, establishing an immunosuppressive microenvironment that confers resistance to immunotherapy [48, 122]. Notably, lung adenocarcinoma demonstrates beneficial outcomes: ferroptosis-correlated accumulation of anti-tumor M1-TAMs associates with improved patient survival [65]. Beyond cancer-type specificity, fundamental mechanisms exist: iron or heme exposure universally repolarizes TAMs toward tumoricidal phenotypes capable of direct tumor killing [123].

Ferroptosis also facilitates immune cell localization through "find-me" signals [124]. This signal involves lipid mediators and helps immune cells localize dead or dying iron cells [125]. Specifically, stearoyl-arachidonoyl-

phosphatidylethanolamine hydroperoxide (SAPE-OOH) released by ferroptotic cells acts as an "eat-me" signal, activating macrophage phagocytosis and immunomodulation [120]. Harnessing these signals could enhance phagocyte-mediated tumor clearance.

Inhibition of T cell activity

To support their rapid proliferation, cancer cells need to maintain a high metabolic state, a process that is accompanied by an increase in the production of reactive ROS [126, 127]. Therefore, elevated ROS, as an intrinsic hallmark of tumors, disrupts the formation of T cell receptor-major histocompatibility complex (TCR-MHC) antigen complexes, thereby impairing T cell activation and proliferation and suppressing antitumor immunity [128]. Prostaglandin E2 (PGE2) released by ferroptotic cancer cells has immunosuppressive activity [129]. It induces $CD14^+$ monocytes to express the cell surface nucleases CD39 and CD73, leading to the production of adenosine. As a degradation product of ATP, adenosine promotes tumor progression and mediates immunosuppression [130], hereby amplifying the immunosuppressive microenvironment established by tumor-derived metabolic factors. Cyclooxygenase-2 (COX-2) and PGE2 blockade may reverse ferroptosis-driven T cell exhaustion.

Impact on the function of DC and NK cells

The release of HMGB1 from ferroptotic cancer cells attracts DCs, promotes antigen presentation by DCs to T cells, and ultimately stimulates CTL responses to clear tumor cells [131, 132]. Furthermore, autophagy inhibition achieved through genetic knockdown of autophagy genes or pharmacological treatment with chloroquine enhances $CD8^+$ T cell responses by upregulating MHC-I molecules on DCs [133]. In early cancer stages, ferroptosis triggers ICD, promoting the activation and maturation of bone marrow-derived dendritic cells (BMDCs). This subsequently induces a vaccine-like immune response [134]. Notably, immunogenicity is strongly associated with time-dependent ATP and HMGB1 release [135]. However, when exposed to ferroptotic cancer cells, BMDCs exhibit impaired capacity to induce antigen-specific T cell proliferation [38]. Furthermore, ferroptotic cells generate abundant oxidized phospholipids [136]. These lipids potently suppress antigen-presenting cells (APCs) by diminishing DCs' phagocytosis and cross-presentation capacity [137], potentially facilitating tumor immune escape. Collectively, oxidized lipid metabolites from ferroptotic cells modulate immune cell function.

Ferroptosis triggers the metabolic conversion of AA into signature eicosanoids and derivatives. These include PGE2, the ferroptosis-specific phospholipid peroxidation product 15-hydroperoxy-eicosatetraenoic acid phosphatidylethanolamine (15-HpETE-PE), and hydroxyeicosatetraenoic acids (15-HETE, 12-HETE, and 5-HETE). These lipid mediators are subsequently released into the TME [138]. Specific eicosanoids (e.g., 5-HETE, 11-HETE, 15-HETE) deplete *GPX4*, thereby compromising anti-tumor immunity [57]. This lipid overload also directly impacts immune cells: DCs exposed to high lipid concentrations exhibit reduced antigen-processing capacity [77].

PGE2 broadly suppresses anti-tumor immunity by directly impairing NK cells, DCs, and CTLs [139, 140]. This prostaglandin specifically disrupts conventional type 1 DCs (cDC1s) through the downregulation of chemokine receptors [141] while simultaneously suppressing NK cell secretion of the C-C chemokine ligand 5 (CCL5) and X-C motif chemokine ligand 1 (XCL1) [142]. Together, these effects create an immunosuppressive cascade: impaired cDC1s recruitment to tumors, activation of MDSCs and Tregs, and ultimately systemic immune evasion [143]. Moreover, cancer cells with dysregulated iron metabolism release PGE2 that targets NK cells and cDC1s, subverting innate anti-tumor immunity and accelerating colon cancer progression [140].

CRT, which is normally an endoplasmic reticulum (ER)-resident chaperone protein, undergoes stress-induced translocation to the plasma membrane during immunogenic cell death such as ferroptosis [29, 144, 145]. This surface-exposed CRT serves as an "eat-me" signal for phagocytes, including macrophages, neutrophils, and DCs. Engulfment of CRT-marked dying cells subsequently triggers antigen cross-presentation to cytotoxic T cells and promotes Th17 cell activation [146].

2.3 | Applications of ferroptosis in tumor immunotherapy

Despite ICIs' success in solid tumors, low response rates persist due to insufficient T cell infiltration [15]. Therefore, how to rationally and effectively enhance, expand, and predict the clinical response to anti- programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) therapy has become a key issue in the field of cancer immunology and immunotherapy [147].

Ferroptosis-inducing agents can enhance immunotherapy through different mechanisms. The combination of ubiquitin-specific peptidase 8 (USP8) inhibition with the ferroptosis inducer sulfasalazine (SAS) significantly delayed tumor growth, promoted $CD8^+$ T cell infiltration, and enhanced the efficacy of anti-PD-1 immunotherapy [148]. Besides, TYRO3 protein tyrosine kinase (TYRO3) inhibition restores anti-PD-1 sensitivity by blocking ferroptosis resistance [149], positioning TYRO3 as a promising

therapeutic target for overcoming anti-PD-1 resistance in immunotherapy. The study by Ma *et al.* revealed a positive feedback loop between carnitine palmitoyltransferase 1A (CPT1A), a key rate-limiting enzyme in the fatty acid oxidation (FAO) metabolic pathway, and cellular myelocytomatosis viral oncogene homolog (c-Myc). Targeting CPT1A (e.g., etomoxir + anti-PD-1) triggers ferroptosis in lung cancer stem cells, achieving a 2.3-fold increase in tumor inhibition efficacy compared to anti-PD-1 monotherapy [150]. Additionally, ferroptotic cells secrete Galectin-13, which attenuates SLC7A11 membrane localization via CD44 binding, establishing "wave-like" death propagation. The Galectin-13 mimetic peptide enhances sensitivity to ferroptosis inducers by 3-fold compared to monotherapy with ferroptosis inducers alone, establishes long-term immune memory in melanoma models, and potentiates the responses to ferroptosis inducers, radiotherapy, and immunotherapy [151]. Collectively, these findings demonstrate that ferroptosis not only overcomes cellular resistance to death but also reshapes the TIME, thereby enhancing the efficacy of immunotherapies. Therefore, ferroptosis represents a promising anti-tumor strategy.

Ferroptosis induction by diverse cancer therapies, including sorafenib, cisplatin, and radiotherapy, may enhance tumor immunogenicity and immune infiltration to potentiate checkpoint inhibitor responses. However, these effects show marked heterogeneity across tumor immune landscapes. In MDSC-rich tumors where ferroptosis-resistant MDSCs deplete cystine to inhibit T cells [152], the use of ferroptosis inducers may not be advisable. Here, inhibitors such as ferrostatin-1 offer clinical value: they preserved $CD8^+$ T cells by blocking CD36-mediated ferroptosis while stimulating IFN-γ production and proliferation, thereby enhancing ICI efficacy [87]. Therapies such as erastin demonstrate clinical potential by promoting Th17 differentiation and $CD8^+$ T cell enhancement [153]. Similarly, sorafenib-triggered ferroptosis in hepatocellular carcinoma (HCC) can enhance anti-tumor immunity [154], and dihydroartemisinin (DHA)-induced ferroptosis via p53-ALOX12 in PC remodels the TME by suppressing M2 macrophages while expanding $CD8^+$ T, NK, and natural killer T (NKT) cells [155].

Critically, ferroptosis immunogenicity is temporally regulated. Early-stage ferroptotic cells robustly activate adaptive immunity, unlike late-stage cells (>24 h post-induction) [135]. We hypothesize that monitoring ferroptosis kinetics by means of lipid peroxidation imaging may optimize the timing of therapy in future trials.

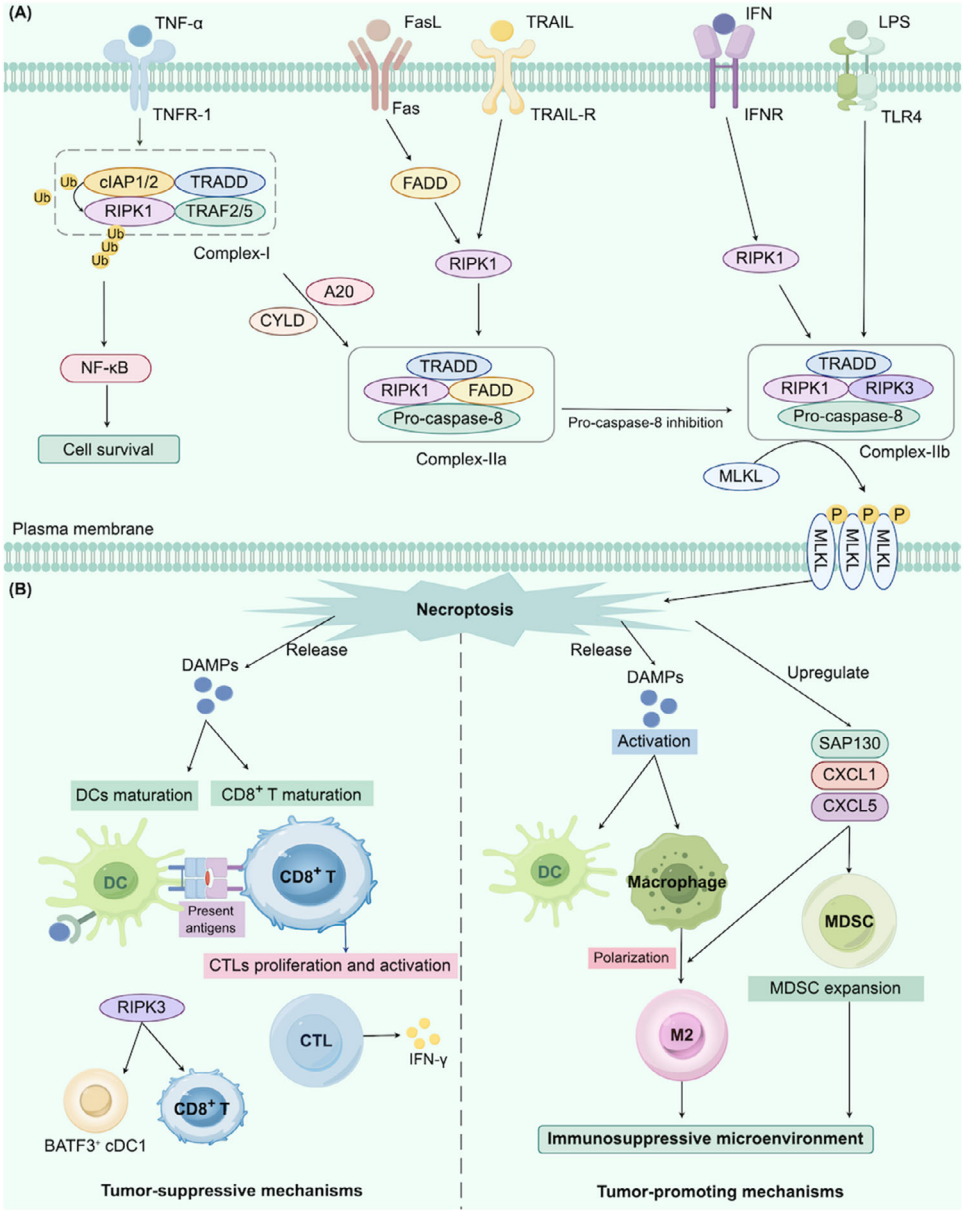
Nanomaterials enable tumor-selective ferroptosis induction while sparing immune cells. For instance, zero-valent iron nanoparticles (ZVI-NP) promote M2 to M1 macrophage polarization, reduce Treg populations, and downregulate PD-L1 on tumor cells alongside PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on $CD8^+$ T cells, amplifying anti-tumor immunity [156]. Ce6-PEG-HKN15 nanoparticles utilize a transferrin receptor (TFR)-targeting peptide (HKN15) to deliver the photosensitizer Chlorin e6 (Ce6), enabling tumor-specific photodynamic therapy that synergistically induces ferroptosis [157], while Fe_3O_4-siPD-L1@M-BV2 creates self-amplifying ferroptosis-immunity cycles via IFN-γ feedback [158]. Two distinct biomimetic nanoplatforms demonstrate ferroptosis-mediated TME remodeling: The biomimetic nanoplatform IMP@CM-PEP20 nanoparticles (NPs) synergize sonodynamic therapy (SDT)-activated ferroptosis with CD47 blockade to transform immunologically "cold" tumors into immune-active states [159]; cRGD/RBCM dual target head nanoparticles (GEM + siCTRP6@RBCM/crGd-phlips) deliver gemcitabine (GEM) and target the CTRP6 gene to activate the nuclear factor erythroid 2-related factor 2 (NRF2) and signal transducer and activator of transcription 3 (STAT3) pathway, inducing ferroptosis and potentiating PD-L1 antibody efficacy [160].

Ferroptosis therapy has developed from a single induction of lipid peroxidation to a multi-dimensional treatment mode integrating metabolic intervention and nano-precision regulation. Future research may exploit multidimensional ferroptosis therapies, combining metabolic modulation and nanoprecision, to develop spatiotemporal-specific activators that synergize with immune cells to overcome resistance to traditional therapies.

3 | NECROPTOSIS

3.1 | Regulatory mechanisms

Necroptosis is a caspase-independent form of RCD [161], implicated in ischemia/reperfusion injury, inflammation, autoimmune disorders, and cancer [162–165]. This process requires three core executors: receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed spectrum kinase domain-like pseudokinase (MLKL). It can be triggered by death receptors (e.g., fas cell surface death receptor [Fas] and tumor necrosis factor receptor superfamily member 1A [TNFRSF1A]); toll-like receptors (TLRs [e.g., TLR3 and TLR4]; nucleic acid sensors (e.g., Z-DNA binding protein 1 [ZBP1], retinoic acid-inducible gene I [RIG-I], retinoic acid receptor responder 3 [RARRES3]); STING or adhesion receptors [115, 166–168]. Unlike immunologically silent



apoptosis, necroptosis is immunogenic and can elicit anti-tumor responses [169], making it an attractive therapeutic target.

The process of necroptosis involves three central stages (Figure 3A): complex I assembly, complex II formation, and necrotic vesicle generation [170]. The tumor necrosis factor (TNF) signaling pathway is one of the most intensively studied necroptotic programmed death signaling pathways [171]. TNF-α serves as a trigger for the regulation of cell death, activating both caspase-dependent apoptosis and caspase-independent necroptosis [172]. TNF-α binding recruits cellular inhibitor of apoptosis protein 1/2 (cIAP1/2), TNF receptor-associated death domain protein (TRADD), RIPK1, and TNF receptor-associated factor 2/5 (TRAF2/5) to assemble complex I at the plasma membrane [173]. cIAP1/2-mediated ubiquitination of RIPK1 is the linchpin that locks TNF signaling into a pro-survival trajectory by sterically hindering death complex assembly while licensing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation [174]. Subsequently, ubiquitin editing by cylindromatosis (CYLD) or tumor necrosis factor alpha-induced protein 3 (A20) deubiquitinates RIPK1 [175], triggering dissociation of TRADD and RIPK1 from complex I and enabling their recruitment into complex IIa with fas-associated death domain protein (FADD) and pro-caspase-8. This complex activates caspase-8, finally inducing cell apoptosis. However, if caspase-8 is inhibited, RIPK1 engages RIPK3 recruits FADD to form complex IIb (necrosome) [176]. Within this complex, RIPK3 phosphorylates MLKL [177], which

oligomerizes, translocates to the plasma membrane, and disrupts membrane integrity to execute necroptosis [178, 179]. Notably, necroptosis can bypass complex I entirely through direct activation by: death receptors (such as Fas activated by Fas Ligand (FasL), or TNF-related apoptosis-inducing ligand receptor [TRAIL-R] engaged by TRAIL); cytokine signaling (e.g., interferon receptors [IFNR] stimulated by IFNs), or pattern recognition sensors like ZBP1 (activated by viral nucleic acids), which directly nucleate the formation of complex IIa or IIb. Exogenous stimuli such as lipopolysaccharide (LPS), which activates TLR4, may also directly initiate complex IIb assembly and induce necroptosis [180–182].

3.2 | Dual roles in tumor immunity (Figure 3B)

Necroptosis exhibits a dual role in tumor immunity. On one hand, plasma membrane rupture releases cytokines, chemokines, and DAMPs. This creates an immunogenic environment capable of driving antitumor immunity. By disrupting the plasma membrane, it releases cytokines, chemokines, and DAMPs, creating an immunogenic foundation that can drive antitumor immunity [183, 184]. However, conversely, necroptosis can also promote tumor progression through myeloid cell-mediated immunosuppression [185].

3.2.1 | Mechanisms of anti-tumor immunity promotion

Necroptosis can initiate potent adaptive anti-tumor immunity through activating specific immune cells [186]. Tumor cell necroptosis disrupts the plasma membrane, releasing immunostimulatory molecules, including autophagy-mediated DAMPs (e.g., HMGB1, C-X-C motif chemokine ligand 1 [CXCL1]) [187], and pro-inflammatory cytokines/chemokines [188]. These signals serve dual functions: 1) They directly stimulate immune responses [187]; and 2) Crucially, they promote DCs and $CD8^+$ T lymphocyte maturation [189]. Mature DCs efficiently present tumor antigens to $CD8^+$ T cells, driving CTLs activation and proliferation [190]. Effective priming of antigen-specific CTLs requires both DAMP release and RIPK1-mediated NF-κB activation to generate essential pro-inflammatory signals [191]. Activated CTLs produce IFN-γ, further amplifying the anti-tumor immune response and enhancing tumor cell clearance [188, 190], ultimately leading to tumor growth suppression.

Clinically, chemotherapy- or radiotherapy-induced acute necroptosis promotes DC-mediated antigen presentation and T cell activation, driving cytotoxic T cell infiltration into the TME for tumor elimination [192]. Similarly, immunogenic Mito + oHSV-1 (Mitoxantrone + Oncolytic herpes simplex virus type 1) therapy triggers necroptosis-dependent inflammation characterized by

FIGURE 3 Mechanisms of necroptosis and its relation to tumor immunity. (A) The regulatory mechanism of necroptosis involves three stages: complex I formation, complex II assembly, and necrotic vesicle formation. After TNF-α binds to TNFR1, RIPK1, TRADD, cIAP1/2, and TRAF2/5 are recruited to the cell membrane to form complex I; cIAP1/2 mediated RIPK1 ubiquitination not only prevents the assembly of apoptotic complexes but also promotes the activation of the NF-κB pathway, achieving cell survival. In the presence of A20 and CYLD, TRADD, RIPK1, FADD, and pro-caspase-8 form complex IIa. Blocked caspase-8 activity leads to RIPK1 assembly with RIPK3 and FADD to form complex IIb. Subsequently, RIPK3 phosphorylates MLKL, promoting the oligomerization of MLKL and its transfer to the plasma membrane, which triggers membrane rupture and necrotic apoptosis of cells. In addition, Fas, TRAIL-R, IFNR and TLR4 respectively recognize FasL, TRAIL, IFN and LPS, all of which can bypass complex I and directly trigger the formation of complex IIa/IIb, initiating necroptosis. (B) Necroptosis plays a dual role in tumor immunity. *Tumor suppression mechanism*. Necroptotic tumor cells release DAMPs, promoting the maturation of DCs and $CD8^+$ T cells. Mature DCs efficiently present tumor antigens to $CD8^+$ T cells, driving the activation and proliferation of CTLs. Activated CTLs secrete IFN-γ, further amplifying the anti-tumor immune response and enhancing tumor cell clearance, ultimately inhibiting tumor growth. Exogenous RIPK3 activation enhances $BATF3^+$ cDC1 and $CD8^+$ T cell-dependent anti-tumor immunity by strengthening antigen presentation and immune stimulation. *Tumor-promoting mechanism*. DAMPs released by ruptured tumor cells activate macrophages and DCs. Necrotic apoptosis upregulates SAP130, CXCL1 and CXCL5. In PDAC, the release of SAP130, CXCL1 and CXCL5 promotes the expansion of MDSCs and the M2 polarization of macrophages, restricting the infiltration of immune cells while increasing MDSCs and TAMs, thus forming an immunosuppressive microenvironment. Abbreviations: cIAP1/2: cellular inhibitor of apoptosis protein 1/2; cDC1: conventional type 1 dendritic cell; CTL: cytotoxic T lymphocyte; CYLD: cylindromatosis; CXCL1: C-X-C motif chemokine ligand 1; DAMP: damage-associated molecular pattern; DC: dendritic cell; FADD: fas-associated death domain protein; Fas, factor associated suicide; FasL, fas ligand; GBM: glioblastoma; HMGB1: high mobility group box 1; IFN, interferon; IFNR: interferon- receptor; LPS: lipopolysaccharide; MDSC: myeloid-derived suppressor cell; MLKL: mixed-lineage kinase domain-like protein; NF-κB: nuclear factor kappa B; PDAC: pancreatic ductal adenocarcinoma; RIPK1: receptor-interacting protein kinase 1; SAP130: spliceosome-associated protein 130 kDa; TAM: tumor-associated macrophage; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor-alpha; TNFR1: TNF receptor 1; TRAIL: TNF-related apoptosis-inducing ligand; TRAIL-R: TNF-related apoptosis-inducing ligand receptor; TRADD: TNF receptor-associated death domain; TRAF2/5: TNF receptor-associated factor 2/5.

pro-inflammatory cytokine/chemokine profiles, myeloid cell recruitment, and cytotoxic T cell infiltration, limiting tumor progression [193]. PolyI: C-induced necroptosis in cervical cancer cells releases immunostimulatory substances that promote DC-derived IL-12 production, boosting anti-tumor immunity [194, 195].

However, tumors frequently evade this immunogenic pathway. RIPK3 downregulation or loss is a common occurrence across multiple cancer cell lines and primary human tumors [196–198], including melanoma, where it correlates with poor prognosis [199, 200]. This functional loss is pro-tumorigenic: RIPK3 knockout mice have increased susceptibility to colorectal cancer (CRC), and their TME contains more pro-oncogenic factors [201]. Conversely, ectopic RIPK3 activation enhances $BATF3^+$ cDC1 and $CD8^+$ T cell-dependent antitumor immunity via improved antigen presentation and immunostimulation [202]. The frequent loss of RIPK3 in tumors suggests it acts as a tumor suppressor in specific contexts, making its restoration or bypass a compelling therapeutic avenue. Consequently, strategies to restore necroptotic signaling (e.g., RIPK3 reactivation or bypass) represent a compelling therapeutic avenue for cancer immunotherapy.

3.2.2 | Mechanisms of anti-tumor immunity suppression

Necroptosis suppresses anti-tumor immunity through multiple interconnected mechanisms. Initially, DAMPs released from ruptured tumor cells activate macrophages and DCs, increase the levels of proinflammatory factors such as IL-1, and induce chronic inflammation [203, 204]. This process not only accelerates tumor progression [205] but also induces T cell death [206], directly compromising adaptive immunity. The immunosuppressive effects extend further through chemokine signaling: necroptosis upregulates splicing factor-associated protein of 130 kDa (SAP130), CXCL1, and C-X-C motif chemokine ligand 5 (CXCL5) [207]. In pancreatic ductal adenocarcinoma (PDAC), the release of SAP130, CXCL1, and CXCL5 promotes MDSCs expansion and macrophage M2 polarization, limiting immune cell infiltration while promoting MDSCs and TAMs, forming an immunosuppressive microenvironment [208].

The roles of key necroptosis mediators are highly context-dependent. For instance, RIPK3-mediated necroptosis exhibits a dual role in tumorigenesis, influenced by tumor type and microenvironmental context [209]. In CRC, RIPK3 deficiency promotes tumor growth by accumulating MDSCs [210]; its restoration enhances anti-tumor immunity via dendritic cell activation [202]. Conversely, elevated RIPK1 correlates with poor prognosis in glioblastoma (GBM) [170], not primarily through necroptosis execution, but via NF-κB-driven pro-survival signaling that suppresses p53 and accelerates proliferation [211]. Similarly, increased MLKL phosphorylation is linked to poor prognosis and reduced survival in colon and esophageal cancer patients [212]. TNF-driven RIPK3-dependent necroptosis may remodel TIME and inhibit tumor growth [213].

Therapeutically, reversing necroptosis-driven immunosuppression reveals three promising avenues: Counteracting potassium ion-mediated T-cell dysfunction in melanoma, where necrotic tumor cells inhibit $CD4^+/CD8^+$ T-cell activity to block anti-tumor immunity [214]; reprogramming TAMs through RIPK1 inhibition, which shifts them toward an immunogenic phenotype to promote Th1/Th17 responses [215]; and blocking metastatic vascular manipulation, wherein tumor-induced endothelial necroptosis releases ATP to disrupt endothelial junctions and facilitate extravasation—a process suppressed by the RIPK1 inhibitor necrostatin-1 [2, 165, 216].

3.3 | Applications of necroptosis in tumor immunotherapy

In recent years, researchers have successfully transformed "cold" tumors into highly immunogenic therapeutic targets by inducing necroptosis in tumor cells through a variety of methods. Targeted regulation of the RIPK1/RIPK3/MLKL pathway or combined immunotherapy can reshape the immune microenvironment and enhance the anti-tumor effect. Therapeutic approaches fall into four interconnected categories.

The first category is immunization strategies and gene-directed platforms, which involve using necroptotic cells as vaccines [217] or employing gene therapy to trigger necroptosis directly within the tumor to stimulate an immune response. For example, prophylactic vaccination with RIPK3-induced cancer cells in mice successfully cross-activates $CD8^+$ T cells, elicits IFN-γ, and confers resistance against tumor engraftment [218]. Building on this principle, gene-directed platforms enable localized immunogenic death: intratumoral delivery of mRNA encoding MLKL triggers in situ necroptotic death, engages $BATF3^+$ cDC1 and type I IFN signaling, and drives potent $CD4^+$ and $CD8^+$ T-cell responses that synergize with immune checkpoint blockade (ICB) drugs to suppress melanoma and colon carcinoma growth [219]. Similarly, adeno-associated virus-mediated RIPK3 gene delivery induces tumor-specific necroptosis and enhances durable clearance when combined with checkpoint inhibitors [202].

The second category is small-molecule and biological approaches, which use pharmaceuticals like second mitochondrial-derived activator of caspases (SMAC) mimetics and kinase inhibitors to target and reactivate the necroptosis pathway in tumors where it is deficient. Loss of RIPK3 expression or inhibition of MLKL phosphorylation is present in many solid tumors, and small-molecule and biological approaches targeting the regulation of necrosis pathways can compensate for this deficiency [220]. SMAC mimetics (SMs) activate RIPK1-dependent necroptosis in apoptosis-resistant tumors, while concomitant NF-κB signaling in dying cells enhances cross-presentation of tumor antigens to $CD8^+$ T cells [221]. Complementary to these, caspase-8 inhibitor zVAD-fmk redirects radiotherapy-, chemotherapy- and hyperthermia-induced cell death toward necroptosis, reducing intratumoral Tregs while increasing dendritic cell and $CD8^+$ T-cell infiltration and markedly inhibiting tumor growth in mouse models [222]. Novel kinase inhibitors further expand this arsenal: fibroblast growth factor receptor 2 (FGFR2) inhibitor AZD4547 induced RIP3-independent necroptosis by activating macrophage stimulating 1 (MST1)-MLKL phosphorylation and FGFR2-NF2-YAP signaling axis, and combined treatment with PD-L1 inhibitor significantly inhibited the growth of esophageal squamous cell carcinoma (ESCC) [223].

The third category is conventional chemotherapy drugs. Classic DNA-damaging chemotherapy drugs can also trigger necroptosis and exhibit the characteristics of ICD: mitoxantrone (MTX) can restore anti-cancer immune surveillance by inducing necroptosis [224]. Besides, paclitaxel, etoposide, and 5-fluorouracil (5-FU) [225, 226] can enhance anti-tumor immunity by inducing necroptosis, have been widely used in a variety of cancer treatments [227].

The fourth category is emerging modalities and nanotechnology strategies, encompassing newer physical methods like photothermal therapy (PTT), chemodynamic therapy (CDT), and necroptosis, dependent on TNF-α and RIPK3-MLKL pathways can also be used to enhance anti-tumor immune responses through nanotechnology strategies [228].

Together, these strategies illustrate the versatility of necroptosis induction—whether by cell-based "vaccines", small molecules, conventional therapies, or novel delivery systems—to elicit potent antitumor immunity. The key to clinical translation will be refining tumor specificity, controlling off-target inflammation, and rationally combining necroptosis induction with existing immunotherapies.

4 | AUTOPHAGY

4.1 | Regulatory mechanisms (Figure 4)

Autophagy is a lysosomal degradation process, basally regulated but stress-activated (e.g., by inflammation, hypoxia, or ROS) [229]. It comprises three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [230, 231], progressing through initiation, elongation, maturation, fusion, and degradation.

Under basal conditions, the mechanistic target of rapamycin complex 1 (mTORC1) suppresses autophagy by inhibiting the Unc-51-like autophagy activating kinase 1 (ULK1) complexes, which is composed of ULK1, autophagy-related protein 101 (ATG101), ATG13, and FAK family kinase-interacting protein of 200 kDa (FIP200) [232, 233]. Upon mTORC1 inhibition or AMP-activated protein kinase (AMPK) activation, the ULK1 complex initiates macroautophagy [234]. The process involves phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which leads to the recruitment of the phosphatidylinositol 3-kinase (PI3K) complex containing Beclin1 (BECN1) and vacuolar protein sorting 34 (VPS34) to phagophore membranes, a step critical for autophagy initiation [235, 236]. The elongation phase of autophagy is driven by two ubiquitin-like systems: In the first system, ATG7 and ATG10 mediate ATG12-ATG5 conjugation to form the ATG12-ATG5-ATG16L1 complex. Simultaneously, the second system processes microtubule-associated protein light chain 3 (LC3, also known as ATG8): ATG4 cleaves pro-LC3 to generate LC3-I, which is then conjugated to PE through sequential actions of ATG7 and ATG3, forming membrane-anchored LC3-II. These systems operate synergistically, with the ATG12-ATG5-ATG16L1 complex functioning as an E3 ligase to facilitate LC3-II formation. The resulting LC3-II integration drives phagophore expansion, leading to autophagosome maturation. Finally, mature autophagosomes fuse with lysosomes for cargo degradation, completing the process [237].

4.2 | Dual effects on tumor immunity

Autophagy critically regulates immunomodulation and is essential for initiating anti-tumor innate/intrinsic immunity [238]. Its role in tumorigenesis and progression is complex and context-dependent, exerting either anti- or pro-tumor effects influenced by tumor type, model, and TME metabolic dynamics [239, 240]. Consequently,

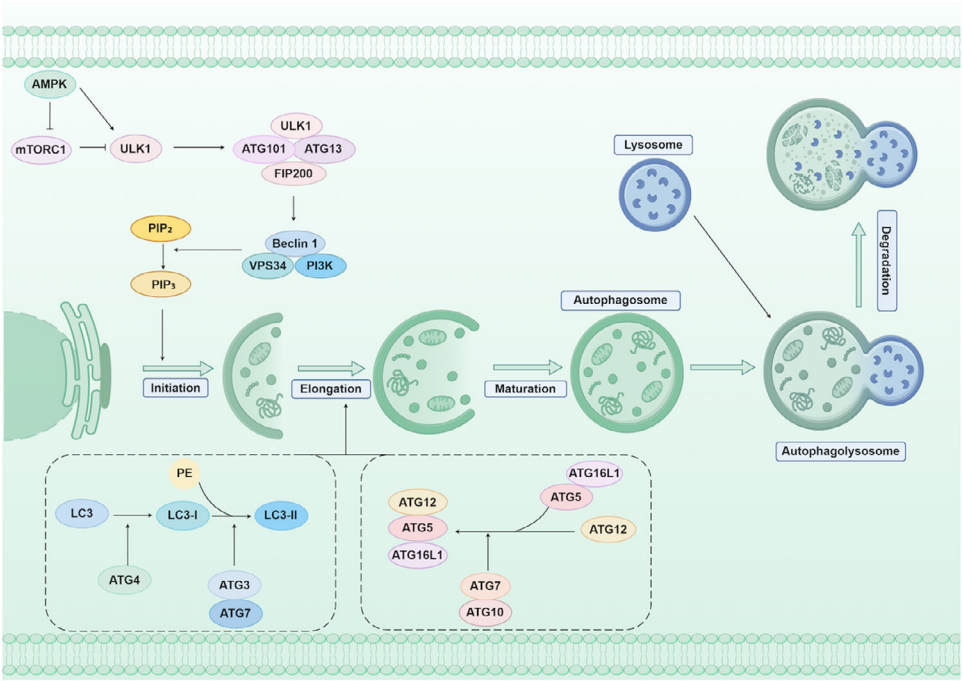


FIGURE 4 Mechanisms of autophagy. Under basic conditions, mTORC1 inhibits autophagy by suppressing the ULK1 complex (ULK1/ATG101/ATG13/FIP200). After mTORC1 inhibition or AMPK activation, the released ULK1 complex is recruited to the phagocytic cell membrane through PIP_2-PIP_3 phosphorylation and the PI3K complex (Beclin1/VPS34/PI3K) to initiate autophagy. The biogenesis of autophagosomes occurs through two synergistic ubiquitin-like coupling systems: (1) the ATG12-ATG5 system. ATG7, and ATG10 couple ATG12 with ATG5 to form the ATG12-ATG5-ATG16L1 complex. (2) LC3 esterification: ATG4 converts pro-LC3 to LC3-I; ATG7 and ATG3 combine LC3-I with PE to form membrane-anchored LC3-II. The ATG12-ATG5-ATG16L1 complex acts as an E3 ligase to accelerate the formation of LC3-II. LC3-II integration drives the phagosome to expand into a mature autophagosome, which then fuses with lysosomes to degrade cargo. Abbreviations: AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; ATG3, autophagy-related protein 3; ATG4, autophagy-related protein 4; ATG5, autophagy-related protein 5; ATG7, autophagy-related protein 7; ATG10, autophagy-related protein 10; ATG12, autophagy-related protein 12; ATG13, autophagy-related protein 13; ATG16L1, autophagy-related protein 16-like 1; ATG101, autophagy-related protein 101; FIP200, FAK family kinase-interacting protein of 200 kDa; LC3-I, microtubule-associated protein 1A/1B-light chain 3-I (cytosolic form); LC3-II, microtubule-associated protein 1A/1B-light chain 3-II (phosphatidylethanolamine-conjugated); mTORC1, mechanistic target of rapamycin complex 1; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; ULK1, unc-51-like autophagy activating kinase 1; VPS34, vacuolar protein sorting 34.

targeting autophagy represents a promising cancer therapy strategy [241], with autophagy inhibitors or activators emerging as novel therapeutic approaches.

4.2.1 | Tumor cell-autonomous autophagy (Figure 5)

Autophagy maintains metabolic and genomic stability by scavenging damaged cellular components (e.g., proteins, organelles, DNA, ROS), and plays a tumor suppressor role in the early stage of tumors [242, 243]. Genetic evidence shows that defective autophagy significantly increases the risk of tumorigenesis [244]. For example, autophagy-deficient tumor cells accumulate p62 protein under stress, and then abnormally activate the NF-κB pathway to drive carcinogenesis [245]. Key studies reinforce this protective role: in the mouse mammary tumor virus-polyoma middle t antigen (MMTV-PyMT) mouse breast cancer model, deletion of the mitophagy hub protein BCL2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3) hindered mitochondrial renewal, resulting in abnormal activation of ROS-HIF-1α signaling and accelerated tumor growth [246]; in addition, defects in the key autophagy protein BECN1 are associated with increased cancer susceptibility [247, 248]; consistent with this, BECN1 heterozygous mice developed spontaneous lung and HCC [249], and BECN1-deficient epithelial cells had a significantly enhanced tumorigenic ability in vivo [250].

Paradoxically, advanced tumors exploit autophagy for progression: it recycles intracellular components to fuel metabolic demands [251–253], inhibits immune

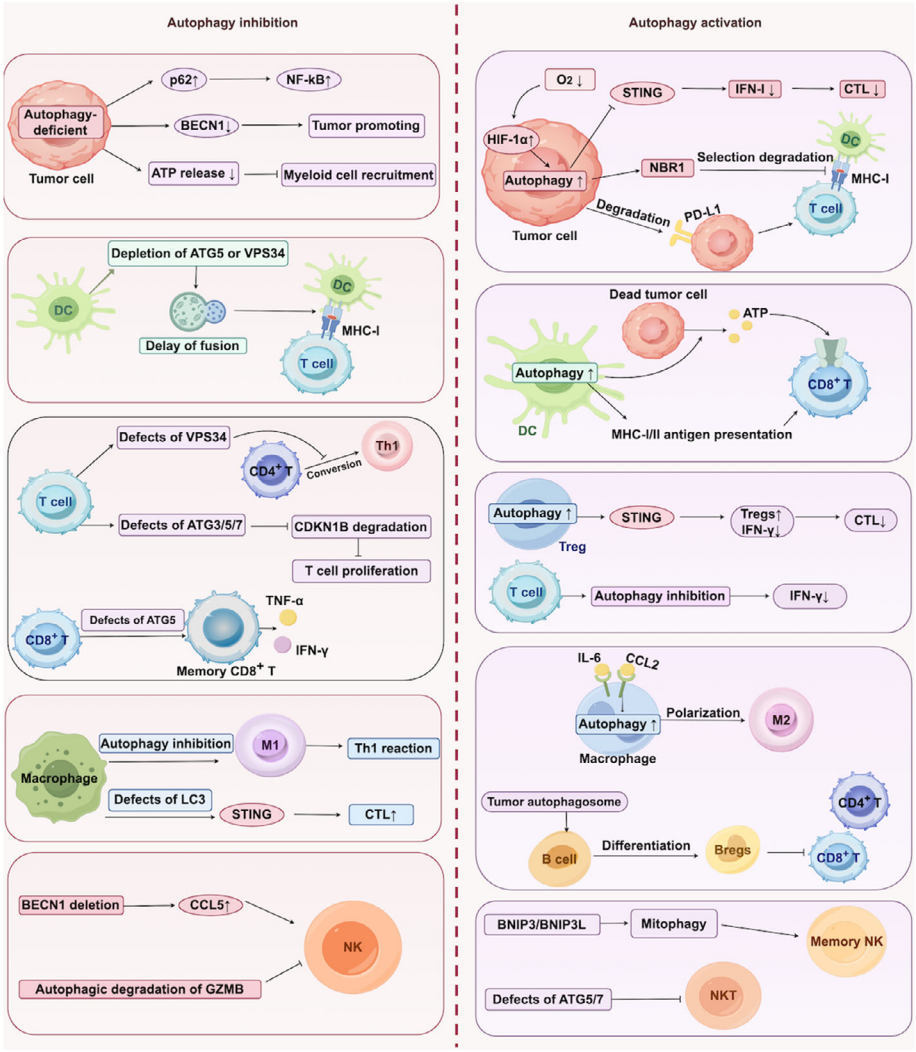


FIGURE 5 Autophagy and tumor immunity. *Autophagy inhibition*: Inhibiting autophagy in tumor cells leads to the accumulation of p62, activation of the NF-κB pathway, and promotion of tumorigenesis. Deficiency of the key autophagy protein BECN1 is associated with increased cancer susceptibility. Malignant cells with autophagy deficiency cannot release ATP during chemotherapy, which hinders the anti-cancer immune response. Although the deletion of ATG5 or VPS34 in DCs delays the phagosome-lysosomal fusion, it increases the level of MHC-I on the surface of DCs. In T cells, the absence of VPS34 hinders the differentiation of $CD4^+$ T cells into Th1. The absence of ATG3/5/7 inhibits the clearance of CDKN1B (also known as p27), thereby suppressing T cell infiltration. ATG5-deficient $CD8^+$ T cells promote differentiation into memory cells, generating high levels of IFN-γ and TNF-α, thereby enhancing anti-tumor activity. Macrophage autophagy blockade makes TAM biased towards M1-like, supporting the Th1 response. Knockdown of LC3 in TAM enhances anti-tumor CTL activity by activating the STING pathway. BECN1 deficiency attracts NK cell infiltration by up-regulating CCL5, and autophagy-degrading granzyme B weakens the lysis ability of NK cells. *Autophagy activation*: Hypoxia enhances autophagy in tumors by degrading STING-dependent type I interferon signaling and weakening CTL. NBR1 degrades MHC-I, impairs antigen presentation. Additionally, autophagy can mediate the degradation of PD-L1 and enhance T-cell toxicity. DC autophagy enhances the presentation of MHC-I/II antigens and ATP release, jointly activating $CD8^+$ T cells to promote anti-tumor immune responses. Treg cell autophagy enhances Treg activation by inhibiting the STING pathway and reduces the production of IFN-γ, thereby suppressing anti-tumor immune responses and further leading to the exhaustion of $CD8^+$ and $CD4^+$ T cells. IL-6 and CCL2 in the tumor microenvironment promote M2 polarization through autophagy. Tumor autophagosomes stimulate the development of B cells into Bregs and inhibit the function of $CD8^+$ and $CD4^+$ T cells. BNIP3/BNIP3L-dependent mitochondrial autophagy promotes memory formation in NK cells. The absence of ATG5/7 inhibits the function of NKT cells. Abbreviations: ATG3, autophagy-related protein 3; ATG5, autophagy-related protein 5; ATG7, autophagy-related protein 7; BECN1, Beclin 1; BNIP3, BCL2 interacting protein 3; BNIP3L, BCL2 interacting protein 3 like; CCL2, C–C motif chemokine ligand 2; CCL5, C–C motif chemokine ligand 5; CDKN1B, cyclin-dependent kinase inhibitor 1B (p27);; CTL, ccytotoxic T lymphocyte; DC, dendritic cell; IFN-I, type I interferon; IFN-γ, interferon gamma; IL-6, interleukin-6; LC3, microtubule-associated protein 1A/1B-light chain 3; MHC-I, major histocompatibility complex class I; NBR1, neighbor of BRCA1 gene 1; NF-κB, nuclear factor kappa B; NK, natural killer cell; NKT, natural killer T cell; p62, sequestosome-1; PD-L1, programmed death-ligand 1; STING, stimulator of interferon genes; TAM, tumor-associated macrophage; Th1, type 1 T helper cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; VPS34, vacuolar protein sorting 34.

infiltration [254], supports tumor progression, and promotes tumor metastasis [255]. Hypoxia-induced autophagy exemplifies this pro-tumor shift—in ESCC, HIF-1α activates autophagy via p27-E2F1 to enhance proliferation [256], while in breast cancer, autophagy reduces NK cell sensitivity [257], thereby suppressing anti-tumor immunity. Molecular studies reveal that autophagy mediates immunosuppression through multiple mechanisms: autophagy degrades the STING-dependent type I interferon signaling pathway, thereby weakening CTL immunogenicity [258]; it disrupts immune synapse stability, reducing the cytolytic effects of NK cells and CTLs [259, 260]; and the 5-hydroxytryptamine (5-HT)/5-hydroxytryptamine 1A (5-HT_{1A}) receptor axis enhances resistance to CTL killing in non-small cell lung cancer via autophagy-mediated STAT3 activation [261].

This spatiotemporal functional shift reveals autophagy's dual role in cancer: defective autophagy initiates tumors (e.g., *ATG5* deletion accelerates *KRAS*-driven lung carcinogenesis [262]), whereas advanced tumors exploit intact autophagy to sustain their malignant (e.g., liver-specific *ATG7* knockout limits HCC malignancy [263]). Tissue-specific *ATG5* inactivation experiments further demonstrate this dichotomy—accelerating the development of $KRAS^{G12D}$-driven lung cancer while blocking its progression [262]. At the immune interface, ATG16L1 and immunity-related GTPase family M member 1 (IRGM1) deficiency in DC cells enhances Th17 response by stabilizing DC-T cell interaction [264], suggesting that the dynamic regulation of immune synapse by autophagy may constitute a new mechanism of tumor immune editing.

4.2.2 | The autophagy of immune cells

APCs

Autophagy dynamically regulates immune cell function, shaping anti-tumor responses [236, 265]. T cell-driven immune responses rely on specialized APCs [266], especially the presentation and induction of antigenic peptides by DCs. APCs exert a dualistic control over tumor immunity by both promoting and restraining antigen display. On one hand, autophagy enhances MHC-I/II antigen presentation [267, 268] and DAMP release (e.g., ATP) [269], which collectively prime $CD8^+$ T lymphocytes and recruit myeloid effectors to tumor sites [270]. Induction of autophagy in tumor cells can enhance their ability to be phagocytosed and cross-presented by MHC-I molecules [271, 272], while the knockdown of autophagy genes (e.g., *ATG5*, *ATG7*, and *BECN1*) can weaken the release of DAMPs from cancer cells killed by mitoxantrone or oxaliplatin, resulting in weakened anti-tumor immunity [273, 274]

Interestingly, depletion of ATG5 or VPS34, although delaying phagosome fusion with lysosomes, significantly increased the surface MHC-I level of DCs through the recruitment of adaptor-associated protein kinase 1 (AAK1) by LC3-II lipolization [133, 275]. This seemingly paradoxical phenomenon reveals the delicacy of autophagy regulation: the balance between excessive degradation and moderate presentation needs to be maintained. In addition, autophagy can also mediate the degradation of immune checkpoint proteins, such as PD-L1, in tumor cells, thereby enhancing the cytotoxicity of T cells and improving the effect of immunotherapy [276]. Conversely, autophagy defects stimulate PD-L1 expression, which may promote immunosuppressive TME, as demonstrated in pancreatic ductal adenocarcinoma [277]. In breast cancer, epidermal growth factor receptor (EGFR) upregulates β1, 3-N-acetylglucosamine transferase-3 (B3GNT3), which mediates PD-L1 glycosylation. This modification blocks the autophagic degradation of PD-L1, revealing a new mechanism of tumor immune escape [278]. In contrast, in PDAC, selective autophagy degrades MHC-I through the receptor neighbor of BRCA1 gene 1 (NBR1), impairing antigen presentation to T cells and enabling immune evasion [279, 280]. Parallel studies reveal that macrophage or DC autophagy activation accelerates lysosomal antigen degradation, which suppresses T-cell cytotoxicity and accelerates MC38 colon cancer progression [281]. Crucially, chloroquine (CQ)-mediated autophagy inhibition reverses this immunosuppression, significantly enhancing $CD8^+$ T cell-mediated killing of colon cancer cells [282].

T cells

In T cell populations, autophagy is a central mechanism for maintaining energetic homeostasis and functional differentiation [19, 283]. The absence of autophagy-related molecules, such as ATG3, ATG5, ATG7, BECN1, and phosphatidylinositol 3-kinase (PtdIns3K), severely weakens the ability of T cells to survive, activate, proliferate, and differentiate [284, 285]. This imbalance is reflected at the molecular level by the fact that VPS34 deficiency induces mitochondrial metabolic collapse, preventing the conversion of $CD4^+$ T cells to Th1 cells [286]. It is worth noting that the role of autophagy in $CD4^+$ T cell subsets is complex. Although its inhibitory effect is beneficial to Th2 and Th9, it is unfavorable to Th1 and Th17 subsets [287], revealing the precise control of the autophagic network in the immune response.

In autophagy-deficient models, the number of peripheral T cells, especially CTLs, is significantly reduced [288, 289], and the defects of ATG3, ATG5, and ATG7 hinder the degradation of cyclin-dependent kinase inhibitor 1B (CDKN1B), thus inhibiting the proliferation efficiency of T cells [290]. Moreover, autophagy sustains

cellular metabolism and organelle homeostasis in $CD8^+$ T cells, enabling the generation and long-term persistence of memory populations essential for adaptive immunity [291]. This characteristic suggests that clinical interventions need to distinguish between the effector phase and the memory maintenance phase. The former can moderately enhance autophagy to expand the number of CTL, and the latter needs to maintain the base autophagy level to protect the mitochondrial mass of memory T cells.

$CD4^+$ Treg cell-mediated anti-tumor immunosuppression is a major mechanism of tumor immune escape and immunotherapy resistance [126]. Autophagy plays an important role in maintaining the survival, lineage stability, and integrity of immunosuppressive function of $CD4^+$ Tregs [292]. For example, in HCC, autophagy inhibits antitumor immune responses by inhibiting the STING pathway to enhance Treg activation and reduce IFN-γ production. This inhibitory effect further leads to depletion of $CD8^+$ and $CD4^+$ T cells, providing favorable conditions for tumor growth [293]. Meanwhile, in a $KRAS^{G12D}$-driven lung cancer model, *ATG5*-dependent autophagy not only conferred a significant survival advantage to cancer cells but also accelerated tumor progression by increasing the oncogenic effects of regulatory T cells [289]. In contrast, defective autophagy due to ATG5 or ATG7 deficiency upregulates the metabolic regulators mTORC1 and c-Myc and activates glycolysis, which ultimately leads to defective Treg function [292, 294]. Given the differences in the autophagy requirements of T cells at different stages, adoptive cell therapy or vaccination should consider the sequential regulation of autophagy levels to optimize the therapeutic effect.

NK cells and macrophages

In NK cells and macrophages, autophagy also determines antitumor effects and polarization. NK cells play an antitumor role through a variety of mechanisms, such as direct cell killing, inducing cell apoptosis, secreting IFN-γ, and inhibiting tumor metabolism. BCL2 interacting protein 3 (BNIP3) and BCL2 interacting protein 3 like (BNIP3L)-dependent mitophagy is indispensable for the memory and cytotoxic function of NK cells [295, 296], but in the hypoxic microenvironment of breast cancer, autophagic degradation of granzyme B impairs the tumor lytic ability of NK cells [257]. In melanoma, BECN1 deletion attracts NK cell infiltration by upregulating CCL5, contributing to the inhibition of tumor growth and improved prognosis [297].

In addition to NK cells, autophagy actively supports the development and survival of NKT cells. Deletion of ATG5 or ATG7 during NKT cell maturation significantly impaired their development [298], while autophagy inhibition reduced T cell tumor killing with a concomitant decrease in IFN-γ expression [248]. Nevertheless, in some models, ATG5-deficient $CD8^+$ T cells, despite having a reduced total population, are more likely to differentiate into effector memory cells producing high levels of IFN-γ and TNF-α, resulting in enhanced antitumor activity [248, 299]. Notably, hypoxia-induced autophagy reduces the sensitivity of lung cancer cells to CTLs by modulating the STAT3 pathway [281, 300]. Impaired autophagosome maturation without lysosomal-associated membrane protein 2 (LAMP2) also disrupts $CD4^+$ T cell function [301], and autophagy activated by the T cell immunoglobulin and mucin-domain containing protein 4 (TIM-4) and AMP-activated protein kinase α1 subunit (AMPKα1) pathway impairs antigen presentation and weakens immune responses [302].

Autophagy inhibition in macrophages promotes TAM polarization to the M1 phenotype and activates the inflammasome, supporting the Th1 response [303]. Conversely, IL-6 and CCL2 trigger autophagy by binding to their corresponding receptors [304], which polarizes macrophages to an immunosuppressive M2 phenotype [305]. Chloroquine lysosomal inhibitors can reverse M2 to M1 [306]. In addition, tumor-derived autophagosomes can drive the differentiation of B cells into $CD1d^+CD5^+IL\text{-}10^+$ regulatory B cells and inhibit the function of $CD8^+$ and $CD4^+$ T cells in the spleen [307], revealing a new escape mechanism. Finally, transient inhibition of autophagy by carrying a dominant negative mutant of autophagy-related protein 4 homolog B (ATG4B) in tumors enhanced macrophage infiltration [308], while knockdown of LC3-related phagocytic genes in TAMs greatly enhanced antitumor T cell activity through the cGAS-STING-type I IFN pathway [309]. This further demonstrates the potential of precise intervention of autophagy subprocesses against tumor immunotherapy.

4.3 | Applications of autophagy in tumor immunotherapy

The dual function of autophagy in the TIME directly affects the fate of tumor cells while dynamically reshaping the immune response, thereby establishing its therapeutic value. Strategic targeting of autophagy pathways in malignant cells or immune cells could address key resistance barriers and enhance the efficacy of immunotherapy.

Small-molecule or gene interventions can precisely regulate autophagy activity to enhance the efficacy of chemotherapy, radiotherapy, and immunotherapy. This therapeutic strategy is exemplified by CQ, a lysosomal autophagy inhibitor that demonstrates context-dependent benefits: In immunotherapy, CQ enhances high-dose

IL-2 efficacy while reducing toxicity in melanoma/renal cancer by suppressing Treg expansion and stabilizing effector T cells [269]. Concurrently, in chemotherapy, CQ synergizes with 5-FU to trigger mitochondrial DNA release and DAMPs that activate $CD8^+$ T cell priming via the cGAS-STING pathway in CRC [310]. Inhibition of autophagy by genetic or pharmacological means can also effectively enhance the cytotoxicity of chemotherapeutic drugs to tumors [311]. Complementary strategies further demonstrate autophagy modulation in cancer therapy: ULK1 inhibitor combined with cisplatin significantly improved the sensitivity of non-small cell lung cancer to chemotherapy [312] while rapamycin and hydroxychloroquine (HCQ) combinations reprogram TAMs toward M1-like polarization, thereby disrupting the CD47-SIRPα checkpoint axis and potentiating phagocytic clearance of tumor cells [313]. Other therapeutic strategies leverage autophagy's immunostimulatory properties. The small-molecule autophagy inducer ABTL0812 demonstrated favorable safety and tolerability in a first-in-human Phase I trial (NCT02201823) involving advanced solid tumors [314]. Autophagy induced by radiotherapy or chemotherapy promotes the binding of the mannose-6-phosphate receptor (MPR) and its ligands to CTL-produced granzyme B through the mechanism of lattice protein-encapsulated vesicles, which enhances the sensitivity of tumor cells to CTLs, thereby increasing the effectiveness of immunotherapy [315, 316]. In addition, α-tocopherol ether-linked acetic acid (α-TEA), a semi-synthetic vitamin E derivative, enhances the cross-presentation of DC to MHC-I tumor antigens by activating autophagy in lung cancer cells, providing a new adjuvant strategy for immunotherapy [317, 318].

Immunotherapy combinations further leverage autophagy modulation. The combination of ICB and autophagy inhibitors can neutralize pro-tumorigenic autophagic effects [319]. Furthermore, a chemical agent such as cordycepin induces autophagic cancer cell death by inactivating the PI3K/ Ak strain transforming (Akt)/mTOR signaling pathway and enhances the anticancer activity of chemotherapeutic agents like cisplatin and paclitaxel [320]. In the PC model, CQ blocks cancer-associated fibroblasts (CAFs) autophagy, downregulates IL-6 secretion, and inhibits USP14-mediated PD-L1 deubiquitination, transforming "immune desert type" (type IV) tumors into type II tumors sensitive to PD-1 antibody, which can enhance ICB efficacy [321].

The development of nanomedicine has provided new tools for autophagy regulation [322]. Graphene oxide (GO) activates TLR4/9-dependent autophagy systemically, enhancing antitumor immunity [323], while titanium dinitride (Ti_2N_X) nanoparticles generate self-assembling "Self-NCAP" vaccines that quadruple $CD8^+$ T-cell infiltration and establish durable memory [324].

In summary, by fine-tuning on or off the autophagy "switch", it can cooperate with chemotherapy, radiotherapy, ICB, and nanocarriers to maximize the dual effects of tumor cell apoptosis and immune activation, which provides rich ideas and paths for clinical translation.

5 | CUPROPTOSIS

5.1 | Regulatory mechanisms (Figure 6)

Cuproptosis is a copper-dependent cell death pathway driven by mitochondrial copper accumulation [325], primarily occurring in oxidative phosphorylation-dependent cells [326]. Extracellular Cu^{2+} is reduced to Cu^+ and flows into the cell via the copper transporter SLC31A1. It can also be delivered to mitochondria as a Cu^{2+}-elesclomol complex. Concurrently, the depletion of the endogenous copper chelator GSH collectively elevates intracellular bioavailable copper levels. Ferridoxin 1 (FDX1) reduces Cu^{2+} in mitochondria to more reactive Cu^+, enhancing its binding ability to target proteins, and simultaneously regulates the lipoylation of dihydrolipoic amide acetyltransferase (DLAT) together with lipoic acid synthase (LIAS). The accumulated Cu^+ disrupts mitochondrial metabolism by targeting the lipoic acid (LA) biosynthesis pathway. Cu^+ directly binds to the LA moiety attached to the key tricarboxylic acid cycle (TCA) enzyme DLAT. The Cu^+-mediated disruption triggers the abnormal aggregation of DLAT and leads to the destabilization and loss of iron-sulfur cluster (Fe-S) proteins. This cascade ultimately induces severe proteotoxic stress and results in cell death [166].

Genome-wide CRISPR/Cas9 loss-of-function screening identified ten core cuproptosis regulatory genes: The upregulated genes were *FDX1*, lipoyltransferase 1 (*LIPT1*), *LIAS*, dihydrolipoic amide dehydrogenase (*DLD*), *DLAT*, pyruvate dehydrogenase E1 subunit α1 (*PDHA1*), and pyruvate dehydrogenase E1 subunit β (*PDHB*), whereas downregulated genes include metal-regulatory transcription factor 1 (*MTF1*), glutaminase (*GLS*), and cyclin-dependent kinase inhibitor 2A (*CDKN2A*). [327]. In addition, copper transporters SLC31A1 take copper as input, ATPase copper transporting alpha (ATP7A) and ATP7B output copper [328], six-transmembrane epithelial antigen of the prostate (STEAP) promotes the absorption and utilization of copper ions [329], further modulating cuproptosis. Collectively, these 13 genes constitute cuproptosis-related genes (CRGs).

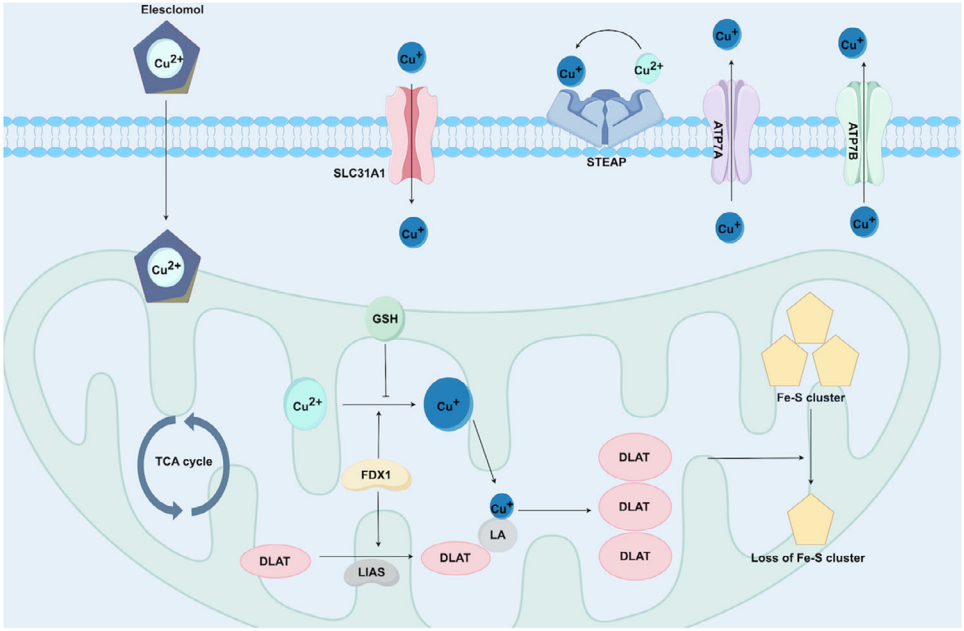


FIGURE 6 Mechanisms of cuproptosis. Extracellular Cu^{2+} is reduced to Cu^{+} and flows into the cell via the copper transporter SLC31A1. It can also be delivered to mitochondria as a Cu^{2+}-elesclomol complex. Concurrent depletion of the endogenous copper chelator GSH elevates intracellular copper levels. Within mitochondria, FDX1 reduces Cu^{2+} to highly reactive Cu^{+}, enhancing its binding affinity to target proteins, while coordinating with LIAS to regulate lipoylation of DLAT. Accumulated Cu^{+} directly binds to the LA moiety attached to the key TCA cycle enzyme DLAT, triggering abnormal aggregation of DLAT and leading to instability and loss of Fe-S proteins, ultimately triggering irreversible proteotoxic stress and cell death. Copper homeostasis is further modulated by efflux transporters ATP7A/ATP7B and the STEAP family, which reduces Cu^{2+} to Cu^{+} to promote copper absorption and utilization. Abbreviations: ATP7A, ATPase copper transporting alpha; ATP7B, ATPase copper transporting beta; DLAT, dihydrolipoamide transacetylase; FDX1, ferredoxin 1; Fe-S, iron-sulfur cluster proteins; GSH, glutathione; LA, lipoic acid; LIAS, lipoic acid synthetase; SLC31A1, solute carrier family 31 member 1; STEAP, six-transmembrane epithelial antigen of the prostate; TCA, tricarboxylic acid cycle.

5.2 | Cuproptosis modulates tumor immunity through microenvironment remodeling

Copper homeostasis exhibits a dualistic influence on tumor immunity, where both excess and deficiency disrupt immune function. Elevated intratumoral copper concentrations promote angiogenesis and foster immunosuppressive microenvironments that facilitate immune escape and metastasis [330, 331], while copper deficiency impairs IL-2-driven T cell proliferation and depletes $CD4^{+}$ and $CD8^{+}$ T cell populations [332, 333], yet paradoxically constrains immune evasion by inhibiting lysyl oxidase-like protein 4 (LOXL4)-mediated PD-L1 presentation on macrophages [334]. This dualism may imply a copper equilibrium threshold where deviations disrupt immune function—a balance exploitable for therapeutic intervention.

CRGs further reprogram immune landscapes across malignancies. In triple-negative breast cancer (TNBC), CRGs significantly reshape the immune infiltration profile [335]. The elevated copper death score was quantified by principal component analysis (PCA) of the CRGs expression profile, showing a positive correlation with activated memory $CD4^{+}$ T cells, eosinophils, and myeloid dendritic cells, while inverse associations with immunosuppressive Tregs, resting NK cells, and M0 macrophages [336] (Figure 7A). This indicates that there is enhanced anti-tumor immunity in the high-scoring TNBC microenvironment. Transition to CRC, prognostic models reveal cancer-specific biomarker implications: overexpression of heat shock protein family A member 1A (HSPA1A) and CDKN2A correlates with poor survival, reflecting dysregulated stress response and cell-cycle control. Conversely, elevated urothelin 3 (UCN3) is linked to improved prognosis and may be achieved through enhanced energy homeostasis [337]. In HCC, the role of copper metabolism is markedly different. Elevated expression of the copper-related enzyme DLAT leads to the recruitment of $CD49d^{+}$ Tregs, a specific subset of immunosuppressive cells, which in turn accelerates tumor progression [338] (Figure 7B). In melanoma, patients exhibit prolonged overall survival (OS) with high expression of CRGs [339]. Furthermore, the CRG LIPT1 exemplifies a complex mechanism in this context, as it enhances PD-L1 expression while simultaneously

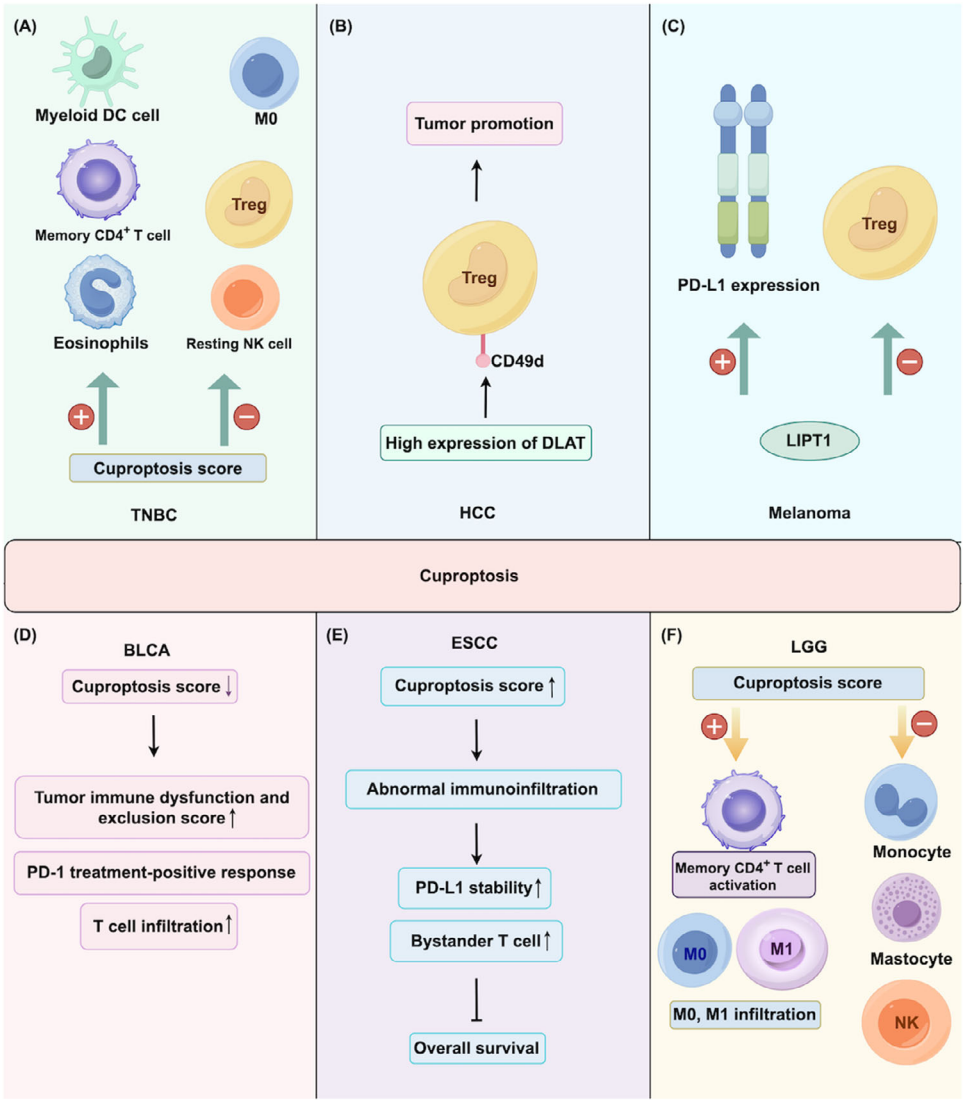


FIGURE 7 Cuproptosis and tumor immunity. (A) In TNBC, the cuprotosis score was significantly positively correlated with specific immune cell subsets (such as eosinophils, memory CD4$^+$ T cells and bone marrow dendritic cells), and significantly negatively correlated with Tregs, resting NK cells, M0 macrophages, etc. (B) In HCC, the high expression of DLAT promotes the infiltration of Tregs in the tumor microenvironment, which is related to the typical phenotypic marker CD49d of Tregs, and thereby promotes the occurrence and development of tumors. (C) In melanoma, LIPT1 is positively correlated with PD-L1 expression and negatively correlated with regulatory T cell infiltration. (D) In BLCA, patients with a low cuprotosis score had a higher TIDE score, a stronger positive response to PD-1 treatment, and a higher T-cell infiltration level than patients with a high cuprotosis score; (E) In ESCC, high cuprotosis score leads to an increase in immune abnormal infiltration, an increase in PD-L1 stability, an increase in the proportion of bystander T cells, and is significantly associated with poor overall survival rate; (F) In LGG, higher cuprotosis score is positively correlated with the infiltration of macrophages M0 and M1 and the activation of memory CD4$^+$ T cells, and negatively correlated with the activation of mastocyte, monocytes and NK cells. Abbreviations: BLCA, bladder cancer; CD49d, cluster of differentiation 49d; CRG, cuproptosis-related gene; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DLAT, dihydrolipoamide transacetylase; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; LGG, low-grade glioma; LIPT1, lipoyltransferase 1; M0 macrophage, non-polarized macrophage; NK cell, natural killer cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophage; TIDE, tumor immune dysfunction and exclusion; TIME, tumor immune microenvironment; TNBC, triple-negative breast cancer; Treg, regulatory T cell.

suppressing Tregs infiltration [340] (Figure 7C), suggesting a multifaceted role in the TIME. Clear cell renal carcinoma (ccRCC) cuproptosis scores strongly correlate with diverse immune infiltrates [341], while bladder cancer (BLCA) patients with low cuproptosis scores had high tumor immune dysfunction and exclusion (TIDE) scores as well as stronger positive responses to PD-1 therapy compared to patients with high scores, and the low-scoring group consistently had higher levels of T-cell infiltration [342] (Figure 7D). Dysregulated copper transport via ATP7A

mediates tumor immune escape and invasion by altering immune cell infiltration and checkpoint expression [343].

These CRG-driven immune alterations generate paradoxical survival outcomes, revealing the intricate duality of cuproptosis in tumor immunity. ESCC with high CRGs demonstrate poorer survival despite increased immune infiltration, attributed to PD-L1 stabilization and dysfunctional T cell activity [344] (Figure 7E). In LGG, higher CRG scores were positively associated with macrophage M0 and M1 infiltration, memory $CD4^+$ T cell activation, and negatively associated with monocyte, mastocyte, and NK cell activation [345] (Figure 7F), while CRC's CHS3 subtype (cuproptosis/hypoxia signatures) accumulates immunosuppressive MDSCs and CAFs that override antitumor immunity [346]. Similarly, in HCC, cuproptosis cluster B shows significant infiltration of multiple immune cell types, particularly Tregs and $CD56^{bright}$ NK cells, yet correlates with poor survival via Kaplan-Meier analysis [347]. Glioma studies similarly show that high cuproptosis aligns with enhanced immune infiltration yet poor prognosis because of dominant immunosuppressive elements, including elevated checkpoints, cytokines, CAFs, and TIDE scores [348]. In addition, it has been suggested that the prognosis of high cuproptosis may be associated with low stromal infiltration and low immunosuppressive status [349]. Stromal cells critically regulate antitumor immunity by physically blocking immune cell access to tumor parenchyma. When T cells infiltrate the microenvironment, stromal encapsulation functionally neutralizes their effector responses [350]. Together, these findings unravel the intricate interplay between cuproptosis-related genes and tumor immunity, offering fresh insights into immune escape mechanisms and potential immunotherapeutic strategies.

5.3 | Applications of cuproptosis in tumor immunotherapy

Copper homeostasis maintains cellular equilibrium under physiological conditions, but exceeding concentration thresholds activates copper-induced lethality. This metabolic dysregulation fuels tumor proliferation, dissemination, and drug adaptation through complex oncogenic networks [351], positioning copper-targeting agents as emerging strategic interventions. Primary approaches include copper ionophores to induce mitochondrial overload and copper chelators to deplete oncogenic copper pools, with advanced nanoplatforms enhancing both strategies.

Copper ionophores exemplify targeted cuproptosis induction. Elesclomol delivers copper to mitochondria, triggering DLAT aggregation and ROS-mediated cuproptosis [331]. To address its rapid clearance, nanotechnological innovations improve tumor targeting. For example, a copper oxide nano platform (notated as ES@CuO) containing elesclomol was able to directly target mitochondria and induce the aggregation of DLAT, ultimately inhibiting the growth of melanoma cells [352]. Similarly, photothermally responsive gold mesoporous silica platforms (Au@MSN-Cu/PEG/DSF) release disulfiram to form cytotoxic CuET, promoting mitochondrial protein aggregation, synergizing with photothermal ablation against resistant tumors [228]. Chlorogenic acid-copper self-assembled nanoparticles (ChA-Cu NPs) further demonstrate dual-path activation: they simultaneously trigger Gasdermin D-mediated pyroptosis and mitochondrial DLAT oligomerization in acidic TME, doubling dendritic cell maturation compared to single-path approaches and suppressing colon cancer [353]. Biomimetic nanomedicine (ECNM) carriers extend this paradigm by co-delivering elesclomol-Cu^{2+} with IDO1 inhibitors to simultaneously induce cuproptosis and reverse immunosuppression, achieving metabolic-immune co-modulation [354].

Complementary approaches employ copper chelators to remodel tumor immunity. Notably, certain chelators promote PD-L1 degradation via ubiquitination pathways, increasing T/NK cell infiltration [355]. Additionally, pyrithione-copper complexes are capable of inhibiting 19S proteasome deubiquitinating enzymes, and combining them with Cu(II) has been shown to kill cancer cells more effectively than treatment alone [352]. These mechanisms converge in chemosensitization strategies: For instance, DSF/Cu complexes overcome cisplatin resistance in cervical cancer by suppressing cancer stemness and inducing S-phase arrest [356], while elesclomol reverses radioresistance across models by increasing copper uptake and radiosensitivity [357]. Furthermore, the copper chelator tetrathiomolybdate was able to inhibit the expression of ATP7B in head and neck squamous cell carcinoma (HNSCC) cells, which enhanced the accumulation of cisplatin in tumor cells and ultimately enhanced the anti-tumor effect of cisplatin [358].

Advanced nanoplatforms integrate these mechanisms for synergistic therapy. exemplified by copper-manganese oxide nanocomposites (Cu_2O-MnO@PEG) directly trigger cuproptosis while enhancing anti-tumor immunity and synergizing with PD-L1 blockade to sustain therapeutic efficacy [359].

Despite reshaping paradigms of metal-ion mediated cell death and tumor metabolism-immunity crosstalk, clinical translation faces biological barriers. Critically, HIF-1α can construct a copper death resistance barrier by activating pyruvate dehydrogenase kinase 1/3 (PDK1/3) phosphorylation to degrade DLAT and up-regulating

metallothionein 2A (MT2A) to chelate free copper [360], which weakens the therapeutic effect. Future development should prioritize precision delivery systems, potent combination regimens (e.g., cuproptosis inducers with checkpoint inhibitors), and biomarker-guided patient stratification to overcome these limitations and advance personalized therapeutic applications.

6 | PYROPTOSIS

Pyroptosis is a pro-inflammatory programmed cell death mediated by gasdermin (GSDM) proteins, characterized by pore formation, cell swelling, membrane rupture, and release of inflammatory mediators. Humans express five gasdermin family proteins (GSDMA, GSDMB, GSDMC, GSDMD, and GSDME), while mice possess multiple gasdermin genes encoding homologous proteins, including *Gsdma*, *Gsdmc*, *Gsdmd*, and *Gsdme*. Pyroptosis occurs through classical caspase-1-dependent or non-classical caspase-4/5/11-mediated pathways [361].

6.1 | Activation pathways

6.1.1 | Classical inflammatory vesicle pathways (Figure 8A)

Inflammatory vesicles are composed of multiple components, including nucleotide-binding oligomerization structural domain (NOD)-like receptor (NLR) family (e.g., NLR pyrin domain containing 3 [NLRP3], NLRP1, pyrin proteins, melanoma 2 (AIM2), or NLR family CARD domain-containing protein 4 [NLRC4]). These inflammasomes function as crucial intracellular sensors that recognize PAMPs and DAMPs through specific structural domains—such as the NLR family proteins, which contain caspase recruitment domain (CARD) and pyrin structural domains (PYD), thereby initiating downstream inflammatory signaling pathways [362]. For instance, the NLRP1 inflammasome is activated in response to Toxoplasma gondii infection and anthrax lethal toxin. The Pyrin inflammasome senses modifications in host Rho GTPases caused by various bacterial toxins or effectors. The AIM2 inflammasome detects cytosolic double-stranded DNA (dsDNA) derived from pathogens. Finally, the NLRC4 inflammasome recognizes specific bacterial components, including flagellin and subunits of the type III secretion system [363]. Activated sensors recruit apoptosis-associated speck-like protein (ASC), which cleaves pro-caspase-1 to caspase-1. Activated caspase-1 converts pro-IL-1 and pro-IL-18 to IL-1 and IL-18, respectively [364]. These pro-inflammatory factors are then released through the membrane necrotic pore generated by GSDMD-N, ultimately leading to cellular pyroptosis. This initiates inflammatory cascades that recruit immune cells and amplify systemic inflammation [365]. NLRC4 specifically recruits pro-caspase-1 without forming ASCs.

6.1.2 | Non-classical inflammatory vesicle pathway (Figure 8B)

Human caspases 4 and 5 and mouse caspase 11 bind directly to lipid fragments of LPS via their CARDs [366]. These changes lead to oligomerization of their CARD domains and cleavage of the GSDMD, generating the N-terminal structural domains and disrupting the extracellular barrier, which induces cellular death [367]. Unlike the classical pathway, this non-classical pathway releases IL-1α and HMGB1, and does not mature pro-IL-1β directly but regulates IL-1β secretion by activating the NLRP3/ASC/caspase-1 pathway [368].

6.1.3 | Alternative pathways (Figure 8C)

Furthermore, other alternative pathways can induce cellular pyroptosis. For example, lymphocyte-derived granzymes can directly trigger pyroptosis. Granzyme B (GZMB) and granzyme A (GZMA), released by NK cells and CTLs, induce pyroptosis through distinct Gasdermin pathways. GZMA cleaves GSDMB, generating the pore-forming N-terminal fragment (GSDMB-N), which directly causes pore formation, cellular swelling, and lysis. Conversely, GZMB directly cleaves GSDME to trigger pyroptosis independently of caspase-3 [369]. In addition, caspase-8 can also indirectly participate in the activation of GSDME by directly cleaving GSDMC [370] or by activating downstream caspase-3 in the death receptor signaling pathway [371], further expanding the immune activation effect of pyroptosis. IFN-γ further upregulates GSDMB to enhance this process. GZMB-mediated GSDME activation in tumor cells promotes their phagocytosis and boosts infiltration and activation of NK and $CD8^+$ T cells [372]. Likewise, CAR-T cells deliver granzyme to target cells, activate caspase-3/GSDME, and induce widespread pyroptosis in B leukemia cells and other target cells [373]. Such granzyme-driven pyroptosis amplifies inflammatory signals in the TME, recruiting additional immune effectors and promoting anti-tumor immunity.

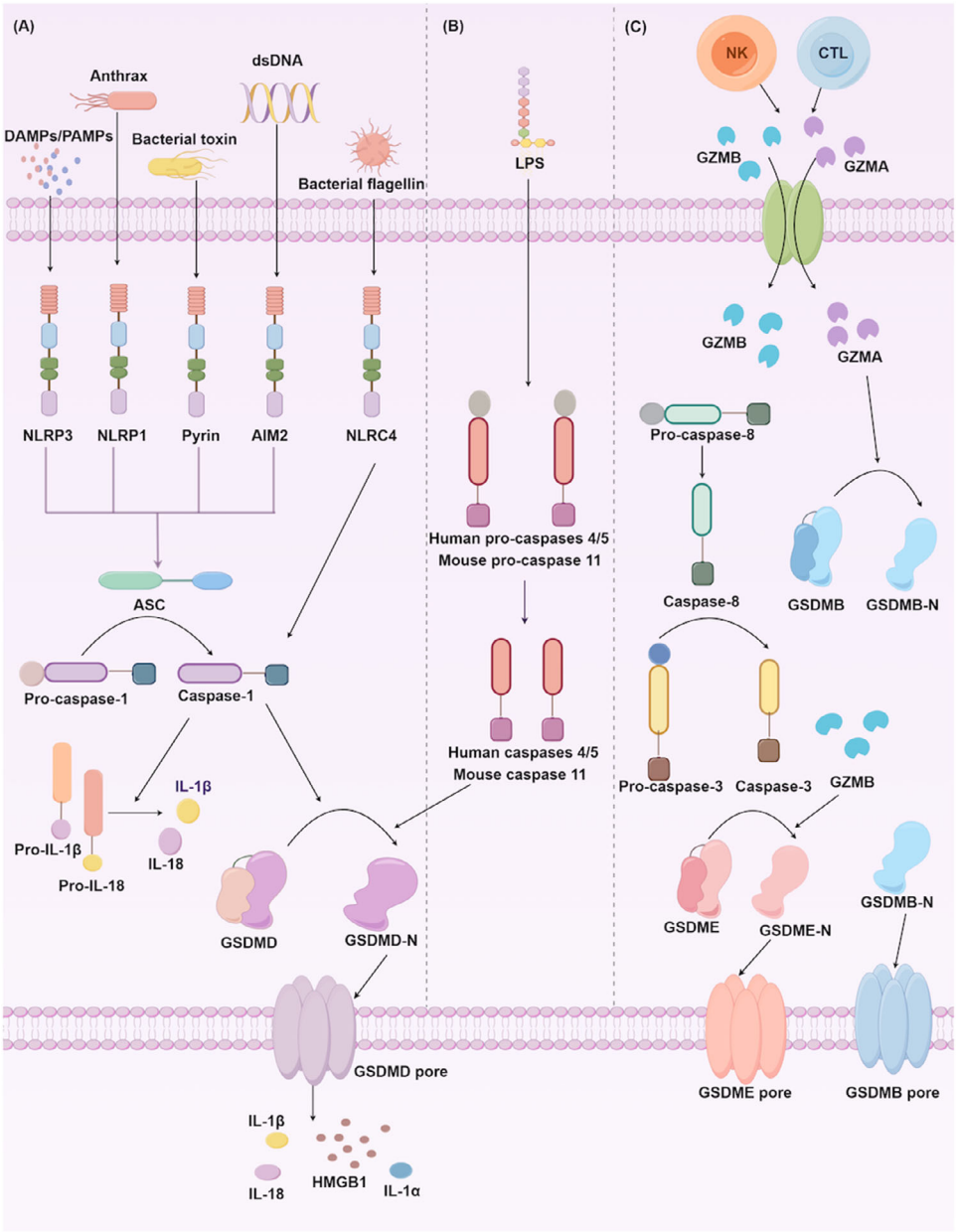


FIGURE 8 Mechanisms of pyroptosis. The regulatory mechanisms of pyroptosis mainly include the classical inflammasome pathway, non-classical pathway, and alternative pathways. (A) In the classical inflammasome pathway, inflammasomes (such as NLRP3, NLRP1, pyrin, AIM2, and NLRC4) act as intracellular sensor molecules capable of detecting PAMPs and DAMPs. The NLRP1 inflammasome recognizes anthrax toxin, the pyrin inflammasome recognizes certain bacterial toxins, the AIM2 inflammasome recognizes cytoplasmic dsDNA, the NLRC4 inflammasome recognizes bacterial flagellin, and the activated sensor recruits ASC (except NLRC4, which directly binds to pro-caspase-1), cutting pro-caspase-1 into active caspase-1. Caspase-1 processes pro-IL-1β and pro-IL-18 into mature cytokines and cleaves GSDMD, releasing its N-terminal pore-forming domain (GSDMD-N). GSDMD-N forms plasma membrane pores, promoting the release of IL-1β/IL-18 and the rupture of permeable cells, resulting in pyroptosis. (B) The non-classical pathway is directly activated by human caspase 4 and caspase 5 or mouse caspase 11 in combination with LPS, cleaving GSDMD to release IL-1α and HMGB1. (C) The alternative pathway is mediated by granzymes from cytotoxic lymphocytes: granzyme B, released by NK cells and CTL, cleaves GSDME, while granzyme A cleaves GSDMB. This processing generates N-terminal pore-forming domains and insert into the plasma membrane, thereby inducing pyroptosis in tumor cells. In addition, caspase-8 can also participate in GSDME activation in the death receptor signaling pathway by indirectly activating downstream caspase-3, further amplifying the pyroptosis-induced immune activation effect. Abbreviations: AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CTL, cytotoxic T lymphocyte; DAMP, damage-associated molecular pattern; dsDNA, double-stranded DNA; GSDM, gasdermin; GZMA, granzyme A; GZMB, granzyme B; HMGB1, high mobility group box 1; IL, interleukin; LPS, lipopolysaccharide; NLR, NOD-like receptor; NLRC4, NLR family CARD domain-containing Protein 4; NLRP, NLR pyrin domain-containing; PAMP, pathogen-associated molecular pattern.

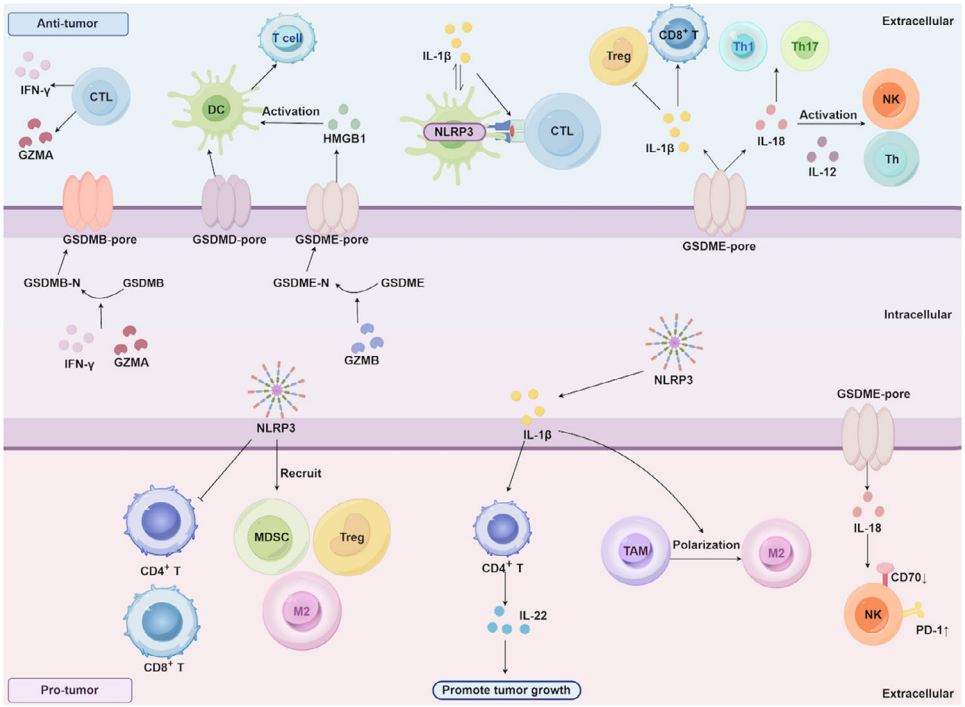


FIGURE 9 Pyroptosis and tumor immunity. Pyroptosis exhibits a context-dependent duality in tumor immunity. Anti-tumor effects: The granzyme GZMA and cytokine IFN-γ released by CTL can cleave GSDMB, producing GSDMB-N that triggers membrane pore formation and cell lysis, establishing a dual induction pathway against tumors. In gastric cancer, GSDMD-mediated pyroptosis increases tumor immunogenicity and promotes DCs maturation, while GSDME-mediated pyroptosis releases HMGB1 and other pro-inflammatory signals that activate DCs and ultimately drive T-cell proliferation. In DCs, NLRP3 activation induces IL-1β release, which enhances antigen presentation and elicits robust CTL responses, thereby facilitating tumor clearance. The pro-inflammatory cytokines IL-1β and IL-18 are released through GSDM-mediated pore formation during pyroptosis. IL-1β, when released in a controlled manner, promotes DCs maturation, activates $CD8^+$ T cells, and suppresses Tregs. Similarly, IL-18, under appropriate spatial and temporal conditions, favors Th1/Th17 differentiation and cooperates with IL-12 to activate NK cells and Th cells, thereby strengthening cytotoxic responses.Pro-tumor effects: In certain contexts, NLRP3 activation recruits MDSCs, Tregs and M2-type TAMs, and suppresses $CD8^+$ and $CD4^+$ T-cell functions. NLRP3-driven IL-1β can promote M2 TAM polarization and induce $CD4^+$ T cells to secrete IL-22, which supports tumor growth and metastasis. In gastrointestinal tumors, IL-18 can impair NK-cell cytotoxicity by upregulating PD-1 and downregulating CD70. Overall, gasdermins, inflammasomes and associated cytokines can exert opposing immunological effects depending on tissue context, timing and genetic background. Abbreviations: CD70, cluster of differentiation 70; CTL, cytotoxic T lymphocyte; DC, dendritic cell; GSDMB, gasdermin B; GSDMB-N, GSDMB N-terminal domain; GSDMD, gasdermin D; GSDME, gasdermin E; GZMA, granzyme A; GZMB, granzyme B; HMGB1, high mobility group box 1; IFN-γ, interferon gamma; IL-1β, interleukin-1 beta; IL-12, interleukin-12; IL-18, interleukin-18; IL-22, interleukin-22; MDSC, myeloid-derived suppressor cell; NK cell, natural killer cell; NLRP3, NOD-like receptor family pyrin domain containing 3; PD-1, programmed cell death protein 1; TAM, tumor-associated macrophage; Th, T helper cell; Th1, type 1 T helper cell; Th17, type 17 T helper cell; Treg, regulatory T cell.

6.2 | Key molecules in anti-tumor immunity (Figure 9)

Cellular pyroptosis demonstrates context-dependent roles in tumor immunity, shaped by genetic background, cell type, and duration of induction [374]. As a pro-inflammatory cell death mechanism, it can rupture the immunosuppressive TME by releasing DAMPs, tumor antigens, and cytokines that amplify anti-tumor responses [375]. Paradoxically, sustained pyroptotic inflammation may foster tumor progression by remodeling immune evasion pathways [376]. This functional duality underscores the need to dissect the contributions of core molecular components governing pyroptosis, including gasdermins, inflammasomes, and key cytokines, which collectively bridge cell death execution to immune modulation. The roles of these specific molecules in shaping anti-tumor immunity are detailed below.

6.2.1 | Gasdermin proteins

The GSDM family orchestrates pyroptotic outcomes with therapeutic implications. GSDMA activation via nutrient

stress-induced ULK1 phosphorylation releases immunogenic DAMPs (e.g., creatine) to stimulate type I interferon pathways [377]. Using bioorthogonal chemistry, Wang's team delivered active GSDMA into tumor cells and demonstrated that targeting <15% of cells sufficed for complete 4T1 tumor regression—but only in immunocompetent hosts [378]. These results suggest that GSDMA-induced pyroptosis contributes to the enhancement of anti-tumor immunity.

The expression of GSDMB protein is mainly concentrated in the gastrointestinal tract, and its mechanism of inducing tumor cell pyroptosis is complex and diverse. Although CTL-derived GZMA or IFN-γ induces GSDMB to establish an anti-tumor dual induction pathway [379], its pro-metastatic role in $HER2^+$ breast cancer exemplifies tissue-specific functionality [380].

The role of GSDMD in cancer is context-dependent and exhibits dual functions. In gastric cancer, GSDMD promotes immunogenic cell death by enhancing tumor immunogenicity and facilitating DCs maturation [381]. Paradoxically, downregulation of GSDMD can also accelerate tumor progression through activation of the PI3K/Akt signaling pathway [367]. Further underscoring its complex role, high GSDMD expression in lung adenocarcinoma is associated with poor prognosis, suggesting that its effects may vary by tumor stage or type [382]. Moreover, pharmacological inhibition of GSDMD has been shown to activate the mitochondrial apoptosis pathway and suppress the EGFR/Akt signaling axis, thereby inhibiting tumor growth [383].

GSDME, as an important member of the GSDM family, has the unique ability to convert apoptosis into cancer cell death [384], thereby activating anti-tumor immunity and contributing to cancer treatment [385]. This conversion mechanism enables cytotoxic lymphocytes (NK and $CD8^+$ T cells) to deliver (GZMB to GSDME-expressing tumor cells, cleaving GSDME to trigger pyroptosis, caspase-3 amplifies this process, and the ensuing pyroptosis in turn activates the killer cell-mediated anti-tumor response [369]. Moreover, GSDME cleavage and HMGB1 release activate DCs, ultimately driving T-cell proliferation and establishing a self-amplifying cycle of tumor killing [386]. Critically, GSDME-deficient models exhibit diminished immune infiltration in TNBC microenvironments [372], confirming that its tumor-suppressive function depends on pyroptosis-driven immune activation. Beyond transforming "cold" tumors into immunogenic "hot" niches, GSDME further enhances immune cell recruitment via EIF2AK2 signaling [384], potentially synergizing with anti-PD-1 therapy by overcoming T-cell exclusion [387].

However, scientists have reported that GSDME is highly expressed in only 10% of tumor cells, but 60% of normal human cells exhibit abundant GSDME expression [388]. Pyroptosis may be a potential source of toxic side effects of chemotherapeutic agents. Alarmingly, uncontrolled GSDME activation may even trigger cytokine release syndrome (CRS), as observed in CAR-T therapy [389]. These findings highlight a fundamental challenge: without a precise grasp of the degree of activation of GSDME, its role as an immune amplifier cannot be exploited. Future strategies may require tumor-selective GSDME activation or concurrent cytoprotection of normal tissues to safely develop its proimmunogenicity.

6.2.2 | Inflammasomes

NLRP3 inflammasome, as a key intracellular multiprotein complex, modulates the innate immune response by regulating pro-inflammatory cytokine production [390]. Its role in cancer exhibits context-dependent duality, balancing anti-tumor and immunosuppressive functions. In DCs, activation of the NLRP3 inflammasome triggers IL-1β release, leading to DC hyperactivation, robust CTL responses, and tumor elimination in vivo [391]. However, in HCC, NLRP3 expression is reduced compared with adjacent non-tumorous tissue and correlates with advanced disease stage and poor prognosis [380]. NLRP3 signaling often recruits immunosuppressive MDSCs, Tregs, and M2 TAMs while depleting $CD8^+$ T and $CD4^+$ T cells [392]. Inhibition of NLRP3 in such contexts may restore tumor sensitivity to PD-1 blockade by altering PD-L1 dynamics [393]. Paradoxically, PD-1 inhibition itself can activate NLRP3-mediated polymorphonuclear MDSCs (PMN-MDSCs) recruitment, blunting therapeutic efficacy [394]. This functional dichotomy extends across tumor types: NLRP3 drives IL-1β-dependent M2 TAM polarization and metastasis in breast cancer [395], subverts DC vaccines via MDSCs recruitment in melanoma [396], and establishes immunosuppressive microenvironments in PC [397]. Notably, NLRP3-induced IL-1β also provokes $CD4^+$ T cells to secrete pro-tumorigenic IL-22 [398]. Collectively, these findings highlight NLRP3's paradoxical capacity to either enhance or undermine anti-tumor immunity, emphasizing the need for context-specific therapeutic strategies.

6.2.3 | Cytokines

IL-18 exemplifies the paradoxical nature of tumor immunity, where context dictates function. Elevated IL-18 levels often promote tumor progression by stimulating angiogenesis, invasion, and metastasis, correlating with poor prognosis [399, 400]. Conversely, this cytokine simultaneously activates potent anti-tumor responses. It enhances

Th1/Th17 cell differentiation [401] and synergizes with IL-12 to activate Th cells and NK cells [402]. However, in gastrointestinal tumors, IL-18 paradoxically suppresses NK cell cytotoxicity by upregulating PD-1 and downregulating CD70 [403]. Low IL-18 levels further disrupt NK cell surveillance through increased PD-1 expression [404], while optimal concentrations recruit NK cells, T cells, and monocytes to inhibit tumor progression [405]. Notably, in colitis-associated colon cancer, IL-18 boosts IFN-γ production by Th cells and macrophages, amplifying NK and $CD8^+$ T cell cytotoxicity [406].

Mirroring this context-dependent duality, IL-1β bridges innate and adaptive immunity [407] with profound contextual duality. In anti-tumor mode, IL-1β matures DCs, activates $CD8^+$ T cells, recruits Th1-type $CD4^+$ T cells, suppresses Treg differentiation, and mobilizes NK cells [408, 409]. Pretreatment with IL-1β even enhances metastatic T cell homing and survival [410], supporting its potential as an adjuvant for adoptive cell therapies. Yet in established TME, particularly during chronic inflammation, IL-1β drives tumor development and progression by interfering with different mechanisms [411]. NLRP3 inflammasome-derived IL-1β in gastrointestinal TMEs recruits MDSCs that secrete immunosuppressive cytokines and induce Tregs, while fibroblast-secreted IL-1β promotes metastasis via endothelial adhesion molecules and invasive markers [412]. In addition, IL-1β also drives $CD4^+$ T cells into the TME and induces the release of IL-22, thus supporting a pro-tumorigenic microenvironment [403].

Collectively, both cytokines demonstrate that their therapeutic harnessing requires precise contextual control—suppressing pro-tumor functions while leveraging immunostimulatory potential.

6.3 | Applications of pyroptosis in tumor immunotherapy

Pyroptosis enhances antitumor immunity by releasing DAMPs that promote DC maturation and $CD8^+$ T cell activation, and synergize with ICIs or CAR-T therapies [217]. However, since pyroptotic effectors exist in normal tissues, achieving tumor-specific targeting remains a fundamental challenge.

Multiple small molecules demonstrate anti-tumor efficacy through selective pyroptosis induction. For instance, anthocyanins trigger oral squamous cell carcinoma death [413], neosporin isoflavone (NBIF) upregulates Tom20 to activate calpain I/GSDME in HCC [414], diosgenin drives GSDME-dependent pyroptosis in osteosarcoma to inhibit tumor growth [415], and simvastatin activates NLRP3/caspase-1 to induce pyroptosis and inhibit NSCLC migration [139].

Beyond direct cytotoxicity, pyroptosis remodels immune landscapes. RIG-I agonists induce GSDMD-dependent cellular pyroptosis to reduce breast cancer migration and growth [416], while trimethylamine N-oxide (TMAO) induces PERK-mediated pyroptosis to amplify $CD8^+$ T cell responses [417]. Sorafenib induces macrophage pyroptosis to mobilize NK cells against HCC [418].

Combining pyroptosis inducers with other therapies further magnifies antitumor immunity. The combination of BRAF inhibitors and MEK inhibitors enhanced GSDME cleavage and HMGB1 release, driving DC and activated $CD4^+$ and $CD8^+$ T cell infiltration [419]; radiotherapy synergizes with pyroptosis to stimulate DC maturation and $CD8^+$ T cell recruitment via cytokine (TNF-α/IFN-γ) release [420]; chimeric co-stimulatory switching receptor-engineered NK92 cells reverse PD-1-mediated suppression to rapidly induce GSDME-dependent pyroptosis in lung cancer [390]. Physical modalities like high-frequency irreversible electroporation (H-FIRE) combine necrosis/pyroptosis to polarize the TME toward inflammation [421].

Epigenetic strategies demonstrate innovative synergy. Decitabine upregulates GSDME, enabling cisplatin-loaded nanoliposomes to activate calpain I-mediated pyroptosis and increase CTL ($CD3^+$, $CD8^+$) infiltration and DC maturation ($CD11c^+$, $CD80^+$, $CD86^+$) in draining lymph nodes [422], which effectively activated the systemic immune response. Similarly, the apoptosis-pyroptosis switch (PL@SD) co-delivers decitabine and SN38 to upregulate GSDME and activate the Caspase-3/cGAS-STING pathway, promoting tumor DNA release, enhancing DC maturation and NK cell recruitment, and inhibiting breast cancer metastasis [423]. In addition, pyroptosis can propagate GSDMD pores through extracellular vesicles to bystander cells, amplifying anti-tumor effects [424].

Nanotechnology addresses targeting challenges through innovative delivery: zirconia nanoparticles (ZrNPs) elevate ROS to activate caspase-1/GSDMD and enhance DC and T cell proliferation [425]; ROS/GSH dual-responsive nanoplatforms (MCPP NPs) achieved co-delivery of the cytotoxic reagent PTX and the phototoxic reagent P18 to induce pyroptosis that boosts anti-PD-1 efficacy via DAMPs-driven DC and T cell activation [426]. The AIE-based photosensitizer TBD-3C induces PDT-triggered pyroptosis, polarizes macrophages to M1, matures DCs, and activates $CD8^+$ CTLs to suppress both primary and distant pancreatic tumors [427]. Notably, the siRNAPD-L1@HA-ZIF-8 system achieves pH-responsive Zn^{2+} release for caspase-1 activation while silencing PD-L1, yielding 4-fold increased $CD8^+$ T cell infiltration [428]. Similarly, mRNA-LNP delivery of the GSDMB-NT domain can directly trigger pyroptosis without protease cleavage and significantly enhance anti-PD-1 efficacy [429].

Collectively, these approaches demonstrate pyroptosis's therapeutic potential across diverse modalities. Tumor-selective strategies leveraging metabolic vulnerabilities, epigenetic dysregulation, or nanocarrier targeting provide promising pathways to minimize off-tumor toxicity, though clinical translation requires further optimization of specificity and safety.

7 | CONCLUSIONS AND PERSPECTIVES

RCD serves as a critical guardian of physiological homeostasis and a decisive factor in tumor development and treatment. Although ICIs have redefined cancer immunotherapy, their effectiveness remains constrained by tumor adaptability and the complex TME. Traditional therapies centered on apoptosis continue to struggle against drug-resistant cancers, which has prompted a renewed attention to other RCD pathways, namely ferroptosis, necroptosis, autophagy, cuproptosis, and pyroptosis, as well as their unique interactions with anti-tumor immunity.

Our analysis systematically examined five non-apoptotic RCD pathways (i.e., ferroptosis, necroptosis, autophagy, cuproptosis, and pyroptosis), focusing on their molecular mechanisms and dual roles in tumor immunity. These death modalities function not merely as cytotoxicity mechanisms but as dynamic immune regulators exhibiting context-dependent duality. For example, ferroptosis inducers may enhance radiotherapy through lipid peroxidation but risk polarizing immunosuppressive TAMs. Pyroptosis can recruit T cells via inflammasome activation, yet may inadvertently expand MDSCs that drive treatment resistance. Similarly, autophagy enhancement improves antigen presentation but may sustain Tregs survival in nutrient-deprived niches. Collectively, this duality underscores a fundamental principle: successful therapy requires not only inducing tumor cell death but also precisely managing the resulting immune cascade.

Current interventions, including small molecules, nanodrug delivery systems, and gene therapies, demonstrate preclinical promise in enhancing treatment sensitivity and establishing durable anti-tumor immunity. Future efforts should focus on achieving precision and coordination in manipulating these death pathways. Nanotechnology offers spatiotemporal control to deliver "death signals" specifically to tumor compartments, maximizing immune activation while minimizing damage to healthy tissues and immunosuppressive consequences. Strategic cross-application of RCD modalities, such as initiating T cell infiltration through pyroptosis followed by ferroptosis-mediated elimination of residual cells, could overcome adaptive resistance. Such approaches may synergize effectively with checkpoint inhibitors to extend therapeutic responses.

Treatment personalization represents another critical frontier. Artificial intelligence (AI) could enable "death response prediction models" that analyze individual tumor metabolism and clinical profiles to identify optimal RCD modalities, thereby avoiding empirical treatment approaches. Realizing this potential requires a deeper understanding of stage-specific RCD functions across tumor types, elucidation of key regulatory nodes, and rational design of interventions that convert tumor cell death into predictable immune activation. Through these advances, we may ultimately overcome refractory malignancies and achieve sustained, controllable anti-tumor immunity.

AUTHOR CONTRIBUTIONS

Luqing Zhao provided direction and guidance throughout the preparation of this manuscript. Jingwen Hu completed the writing of the manuscript and the drawing of the pictures. Yan Li revised and improved the figure and checked the revised manuscript. Bingjie Lian checked and corrected the grammar problems. Yitao Mao reviewed and made significant revisions to the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

2. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018;25(3):486-541.
3. Peng F, Liao M, Qin R, Zhu S, Peng C, Fu L, et al. Regulated cell death (RCD) in cancer: key pathways and targeted therapies. Signal Transduct Target Ther. 2022;7(1):286.
4. Nagata S, Tanaka M. Programmed cell death and the immune system. Nat Rev Immunol. 2017;17(5):333-40.
5. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer. 2006;6(1):24-37.
6. Phillips R. CD38hiCD8+ T cells characterize ICI-mediated arthritis. Nat Rev Rheumatol. 2023;19(10):605.
7. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65(3):1089-96.
8. Szeto GL, Finley SD. Integrative Approaches to Cancer Immunotherapy. Trends Cancer. 2019;5(7):400-10.
9. Wang W, Li T, Wu K. Cell death in tumor microenvironment: an insight for exploiting novel therapeutic approaches. Cell Death Discov. 2025;11(1):93.
10. Lv B, Wang Y, Ma D, Cheng W, Liu J, Yong T, et al. Immunotherapy: Reshape the Tumor Immune Microenvironment. Front Immunol. 2022;13:844142.
11. Hinshaw DC, Shevde LA. The Tumor Microenvironment Innately Modulates Cancer Progression. Cancer Res. 2019;79(18):4557-66.
12. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017;541(7637):321-30.
13. Gao C, Zhang H, Wang X. Current advances on the role of ferroptosis in tumor immune evasion. Discov Oncol. 2024;15(1):736.
14. Yuen VW-H, Chiu DK-C, Law C-T, Cheu JW-S, Chan CY-K, Wong BP-Y, et al. Using mouse liver cancer models based on somatic genome editing to predict immune checkpoint inhibitor responses. J Hepatol. 2023;78(2):376-89.
15. O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. Nat Rev Clin Oncol. 2019;16(3):151-67.
16. Bagchi S, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. Annu Rev Pathol. 2021;16:223-49.
17. Li Z, Lai X, Fu S, Ren L, Cai H, Zhang H, et al. Immunogenic Cell Death Activates the Tumor Immune Microenvironment to Boost the Immunotherapy Efficiency. Adv Sci Weinh Baden-Wurtt Ger. 2022;9(22):e2201734.
18. Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology. 2014;3(9):e955691.
19. Liu J, Hong M, Li Y, Chen D, Wu Y, Hu Y. Programmed Cell Death Tunes Tumor Immunity. Front Immunol. 2022;13:847345.
20. He R, Liu Y, Fu W, He X, Liu S, Xiao D, et al. Mechanisms and cross-talk of regulated cell death and their epigenetic modifications in tumor progression. Mol Cancer. 2024;23(1):267.
21. Hänggi K, Ruffell B. Cell death, therapeutics, and the immune response in cancer. Trends Cancer. 2023;9(5):381-96.
22. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060-72.
23. Wang Y, Zheng L, Shang W, Yang Z, Li T, Liu F, et al. Wnt/beta-catenin signaling confers ferroptosis resistance by targeting GPX4 in gastric cancer. Cell Death Differ. 2022;29(11):2190-202.
24. Sanz AB, Sanchez-Niño MD, Ramos AM, Ortiz A. Regulated cell death pathways in kidney disease. Nat Rev Nephrol. 2023;19(5):281-99.
25. Lee WC, Dixon SJ. Mechanisms of ferroptosis sensitization and resistance. Dev Cell. 2025;60(7):982-93.
26. Wang L, Wang H. The putative role of ferroptosis in gastric cancer: a review. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP. 2023;32(6):575-83.
27. Li J, He D, Li S, Xiao J, Zhu Z. Ferroptosis: the emerging player in remodeling triple-negative breast cancer. Front Immunol. 2023;14:1284057.
28. Kennedy L, Sandhu JK, Harper M-E, Cuperlovic-Culf M. Role of Glutathione in Cancer: From Mechanisms to Therapies. Biomolecules. 2020;10(10):1429.
29. Sacco A, Battaglia AM, Botta C, Aversa I, Mancuso S, Costanzo F, et al. Iron Metabolism in the Tumor Microenvironment-Implications for Anti-Cancer Immune Response. Cells. 2021;10(2):303.
30. Ali SL, Ali A, Khan A. Identification and assessment of ferroptosis-related genes and their implication as therapeutic agents for pancreatic ductal adenocarcinoma. Ann Pancreat Cancer. 2025;8(0):6.
31. Nguyen TPM, Alves F, Lane DJR, Bush AI, Ayton S. Triggering ferroptosis in neurodegenerative diseases. Trends Neurosci. 2025;S0166-2236(25)00138-9.
32. Otasevic V, Vucetic M, Grigorov I, Martinovic V, Stancic A. Ferroptosis in Different Pathological Contexts Seen through the Eyes of Mitochondria. Oxid Med Cell Longev. 2021;2021:5537330.
33. Gao M, Jiang X. To eat or not to eat-the metabolic flavor of ferroptosis. Curr Opin Cell Biol. 2018;51:58-64.
34. Gong C, Ji Q, Wu M, Tu Z, Lei K, Luo M, et al. Ferroptosis in tumor immunity and therapy. J Cell Mol Med. 2022;26(22):5565-79.
35. Zhang D, Man D, Lu J, Jiang Y, Ding B, Su R, et al. Mitochondrial TSPO Promotes Hepatocellular Carcinoma Progression through Ferroptosis Inhibition and Immune Evasion. Adv Sci Weinh Baden-Wurtt Ger. 2023;10(15):e2206669.
36. Riegman M, Sagie L, Galed C, Levin T, Steinberg N, Dixon SJ, et al. Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture. Nat Cell Biol. 2020;22(9):1042-8.
37. Song G, Li M, Fan S, Qin M, Shao B, Dai W, et al. Boosting synergism of chemo- and immuno-therapies via switching paclitaxel-induced apoptosis to mevalonate metabolism-triggered ferroptosis by bisphosphonate coordination lipid nanogranules. Acta Pharm Sin B. 2024;14(2):836-53.
38. Wiernicki B, Maschalidi S, Pinney J, Adjemian S, Vanden Berghe T, Ravichandran KS, et al. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor immunity. Nat Commun. 2022;13(1):3676.

39. He Y, Ling Y, Zhang Z, Mertens RT, Cao Q, Xu X, et al. Butyrate reverses ferroptosis resistance in colorectal cancer by inducing c-Fos-dependent xCT suppression. Redox Biol. 2023;65:102822.
40. Yan H-F, Zou T, Tuo Q-Z, Xu S, Li H, Belaidi AA, et al. Ferroptosis: mechanisms and links with diseases. Signal Transduct Target Ther. 2021;6(1):49.
41. Xu Q, Zhan G, Zhang Z, Yong T, Yang X, Gan L. Manganese porphyrin-based metal-organic framework for synergistic sonodynamic therapy and ferroptosis in hypoxic tumors. Theranostics. 2021;11(4):1937-52.
42. Chen X, Kang R, Kroemer G, Tang D. Ferroptosis in infection, inflammation, and immunity. J Exp Med. 2021;218(6):e20210518.
43. Zhou Q, Li T, Qin Q, Huang X, Wang Y. Ferroptosis in lymphoma: Emerging mechanisms and a novel therapeutic approach. Front Genet. 2022;13:1039951.
44. Proneth B, Conrad M. Ferroptosis and necroinflammation, a yet poorly explored link. Cell Death Differ. 2019;26(1):14-24.
45. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. 2009;30(1-2):1-12.
46. Li R, Ning Y, Yuan Y, Yang X. Molecular mechanisms of ferroptosis and its effects on bladder cancer. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2024;49(2):286-95.
47. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, et al. Ferroptosis: process and function. Cell Death Differ. 2016;23(3):369-79.
48. Dang Q, Sun Z, Wang Y, Wang L, Liu Z, Han X. Ferroptosis: a double-edged sword mediating immune tolerance of cancer. Cell Death Dis. 2022;13(11):925.
49. Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, et al. CD8+ T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;569(7755):270-4.
50. Sato M, Kusumi R, Hamashima S, Kobayashi S, Sasaki S, Komiyama Y, et al. The ferroptosis inducer erastin irreversibly inhibits system xc- and synergizes with cisplatin to increase cisplatin's cytotoxicity in cancer cells. Sci Rep. 2018;8(1):968.
51. Del Re DP, Amgalan D, Linkermann A, Liu Q, Kitsis RN. Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease. Physiol Rev. 2019;99(4):1765-817.
52. Du W, Frankel TL, Green M, Zou W. IFNγ signaling integrity in colorectal cancer immunity and immunotherapy. Cell Mol Immunol. 2022;19(1):23-32.
53. Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, et al. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. Nature. 2017;551(7679):247-50.
54. Yang F, Xiao Y, Ding J-H, Jin X, Ma D, Li D-Q, et al. Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy. Cell Metab. 2023;35(1):84-100.e8.
55. Talty R, Bosenberg M. The role of ferroptosis in melanoma. Pigment Cell Melanoma Res. 2022;35(1):18-25.
56. Matsushita M, Freigang S, Schneider C, Conrad M, Bornkamm GW, Kopf M. T cell lipid peroxidation induces ferroptosis and prevents immunity to infection. J Exp Med. 2015;212(4):555-68.
57. Jiang M, Qiao M, Zhao C, Deng J, Li X, Zhou C. Targeting ferroptosis for cancer therapy: exploring novel strategies from its mechanisms and role in cancers. Transl Lung Cancer Res. 2020;9(4):1569-84.
58. Han C, Liu Y, Dai R, Ismail N, Su W, Li B. Ferroptosis and Its Potential Role in Human Diseases. Front Pharmacol. 2020;11:239.
59. Bell HN, Stockwell BR, Zou W. Ironing out the role of ferroptosis in immunity. Immunity. 2024;57(5):941-56.
60. Pandrangi SL, Chittineedi P, Chikati R, Lingareddy JR, Nagoor M, Ponnada SK. Role of dietary iron revisited: in metabolism, ferroptosis and pathophysiology of cancer. Am J Cancer Res. 2022;12(3):974-85.
61. Yapici FI, Bebber CM, von Karstedt S. A guide to ferroptosis in cancer. Mol Oncol. 2024;18(6):1378-96.
62. Friedmann Angeli JP, Krysko DV, Conrad M. Ferroptosis at the crossroads of cancer-acquired drug resistance and immune evasion. Nat Rev Cancer. 2019;19(7):405-14.
63. El Hout M, Dos Santos L, Hamaï A, Mehrpour M. A promising new approach to cancer therapy: Targeting iron metabolism in cancer stem cells. Semin Cancer Biol. 2018;53:125-38.
64. Torti SV, Torti FM. Iron and cancer: more ore to be mined. Nat Rev Cancer. 2013;13(5):342-55.
65. DeRosa A, Leftin A. The Iron Curtain: Macrophages at the Interface of Systemic and Microenvironmental Iron Metabolism and Immune Response in Cancer. Front Immunol. 2021;12:614294.
66. Estêvão D, daCruz-Ribeiro M, Cardoso AP, Costa ÂM, Oliveira MJ, Duarte TL, et al. Iron metabolism in colorectal cancer: a balancing act. Cell Oncol Dordr Neth. 2023;46(6):1545-58.
67. Brown RAM, Richardson KL, Kabir TD, Trinder D, Ganss R, Leedman PJ. Altered Iron Metabolism and Impact in Cancer Biology, Metastasis, and Immunology. Front Oncol. 2020;10:476.
68. Zhao X, Lian X, Xie J, Liu G. Accumulated cholesterol protects tumours from elevated lipid peroxidation in the microenvironment. Redox Biol. 2023;62:102678.
69. Yang WS, Stockwell BR. Ferroptosis: Death by Lipid Peroxidation. Trends Cell Biol. 2016;26(3):165-76.
70. Dixon SJ, Winter GE, Musavi LS, Lee ED, Snijder B, Rebsamen M, et al. Human Haploid Cell Genetics Reveals Roles for Lipid Metabolism Genes in Nonapoptotic Cell Death. ACS Chem Biol. 2015;10(7):1604-9.
71. Zhang H, Zhang J, Dong H, Kong Y, Guan Y. Emerging field: O-GlcNAcylation in ferroptosis. Front Mol Biosci. 2023;10:1203269.
72. Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, Croix CS, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017;13(1):81-90.
73. Sun Y, Xia X, Basnet D, Zheng JC, Huang J, Liu J. Mechanisms of Ferroptosis and Emerging Links to the Pathology of Neurodegenerative Diseases. Front Aging Neurosci. 2022;14:904152.
74. Liao P, Wang W, Wang W, Kryczek I, Li X, Bian Y, et al. CD8+ T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. Cancer Cell. 2022;40(4):365-378.e6.
75. Huang Y, Li X, Zhang Z, Xiong L, Wang Y, Wen Y. Photodynamic Therapy Combined with Ferroptosis Is a Synergistic Antitumor Therapy Strategy. Cancers. 2023;15(20):5043.
76. Wang X, Zhou L, Wang H, Chen W, Jiang L, Ming G, et al. Metabolic reprogramming, autophagy, and ferroptosis: Novel arsenals to overcome immunotherapy resistance in gastrointestinal cancer. Cancer Med. 2023;12(21):20573-89.

77. Wu H, Han Y, Rodriguez Sillke Y, Deng H, Siddiqui S, Treese C, et al. Lipid droplet-dependent fatty acid metabolism controls the immune suppressive phenotype of tumor-associated macrophages. EMBO Mol Med. 2019;11(11):e10698.
78. Zhuo S, Yang L, Chen S, Tang C, Li W, Gao Z, et al. Ferroptosis: A potential opportunity for intervention of pre-metastatic niche. Front Oncol. 2022;12:980620.
79. Chen X, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. Nat Rev Clin Oncol. 2021;18(5):280-96.
80. Li S, Huang Y. Ferroptosis: an iron-dependent cell death form linking metabolism, diseases, immune cell and targeted therapy. Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex. 2022;24(1):1-12.
81. Rochette L, Dogon G, Rigal E, Zeller M, Cottin Y, Vergely C. Lipid Peroxidation and Iron Metabolism: Two Corner Stones in the Homeostasis Control of Ferroptosis. Int J Mol Sci. 2022;24(1):449.
82. Ghiringhelli F, Ménard C, Terme M, Flament C, Taieb J, Chaput N, et al. CD4+CD25+ regulatory T cells inhibit natural killer cell functions in a transforming growth factor-beta-dependent manner. J Exp Med. 2005;202(8):1075-85.
83. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med. 2004;10(9):942-9.
84. Kwon ED, Hurwitz AA, Foster BA, Madias C, Feldhaus AL, Greenberg NM, et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. Proc Natl Acad Sci U S A. 1997;94(15):8099-103.
85. Pfeifhofer-Obermair C, Tymoszuk P, Nairz M, Schroll A, Klais G, Demetz E, et al. Regulation of Th1 T Cell Differentiation by Iron via Upregulation of T Cell Immunoglobulin and Mucin Containing Protein-3 (TIM-3). Front Immunol. 2021;12:637809.
86. Sun L-L, Linghu D-L, Hung M-C. Ferroptosis: a promising target for cancer immunotherapy. Am J Cancer Res. 2021;11(12):5856-63.
87. Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, et al. CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. Cell Metab. 2021;33(5):1001-1012.e5.
88. 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(7):1561-1577.e7.
89. Wawrzyniak P, Hartman ML. Dual role of interferon-gamma in the response of melanoma patients to immunotherapy with immune checkpoint inhibitors. Mol Cancer. 2025;24(1):89.
90. Yang C, Dong Q, Bao H, Ge Y, Xu Z, Li J, et al. Ferroptosis: New Strategies and Ideas for the Treatment of Pancreatic Ductal Adenocarcinoma. Front Biosci Landmark Ed. 2024;29(1):45.
91. Xu C, Sun S, Johnson T, Qi R, Zhang S, Zhang J, et al. The glutathione peroxidase Gpx4 prevents lipid peroxidation and ferroptosis to sustain Treg cell activation and suppression of antitumor immunity. Cell Rep. 2021;35(11):109235.
92. Gu X, Liu Y, Dai X, Yang Y-G, Zhang X. Deciphering the potential roles of ferroptosis in regulating tumor immunity and tumor immunotherapy. Front Immunol. 2023;14:1137107.
93. Diao J, Jia Y, Dai E, Liu J, Kang R, Tang D, et al. Ferroptotic therapy in cancer: benefits, side effects, and risks. Mol Cancer. 2024;23(1):89.
94. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20(1):7-24.
95. Zhu Z, Wu X, Zhang J, Zhu M, Tian M, Zhao P. Advances in understanding ferroptosis mechanisms and their impact on immune cell regulation and tumour immunotherapy. Discov Oncol. 2025;16(1):153.
96. Giuliani C. The Flavonoid Quercetin Induces AP-1 Activation in FRTL-5 Thyroid Cells. Antioxid Basel Switz. 2019;8(5):112.
97. Han L, Bai L, Qu C, Dai E, Liu J, Kang R, et al. PPARG-mediated ferroptosis in dendritic cells limits antitumor immunity. Biochem Biophys Res Commun. 2021;576:33-9.
98. Mertens C, Schnetz M, Rehwald C, Grein S, Elwakeel E, Weigert A, et al. Iron-Bound Lipocalin-2 from Tumor-Associated Macrophages Drives Breast Cancer Progression Independent of Ferroportin. Metabolites. 2021;11(3):180.
99. Recalcati S, Gammella E, Buratti P, Doni A, Anselmo A, Locati M, et al. Macrophage ferroportin is essential for stromal cell proliferation in wound healing. Haematologica. 2019;104(1):47-58.
100. Wang D, Qiu G, Zhu X, Wang Q, Zhu C, Fang C, et al. Macrophage-inherited exosome excise tumor immunosuppression to expedite immune-activated ferroptosis. J Immunother Cancer. 2023;11(5):e006516.
101. Vassiliou E, Farias-Pereira R. Impact of Lipid Metabolism on Macrophage Polarization: Implications for Inflammation and Tumor Immunity. Int J Mol Sci. 2023;24(15):12032.
102. Soh J, Lim ZX, Lim EH, Kennedy BK, Goh J. Ironing out exercise on immuno-oncological outcomes. J Immunother Cancer. 2022;10(9):e002976.
103. Yang Y, Wang Y, Guo L, Gao W, Tang T-L, Yan M. Interaction between macrophages and ferroptosis. Cell Death Dis. 2022;13(4):355.
104. Oexle H, Kaser A, Möst J, Bellmann-Weiler R, Werner ER, Werner-Felmayer G, et al. Pathways for the regulation of interferon-gamma-inducible genes by iron in human monocytic cells. J Leukoc Biol. 2003;74(2):287-94.
105. Melillo G, Taylor LS, Brooks A, Musso T, Cox GW, Varesio L. Functional requirement of the hypoxia-responsive element in the activation of the inducible nitric oxide synthase promoter by the iron chelator desferrioxamine. J Biol Chem. 1997;272(18):12236-43.
106. Cronin SJF, Woolf CJ, Weiss G, Penninger JM. The Role of Iron Regulation in Immunometabolism and Immune-Related Disease. Front Mol Biosci. 2019;6:116.
107. Shimasaki N, Jain A, Campana D. NK cells for cancer immunotherapy. Nat Rev Drug Discov. 2020;19(3):200-18.
108. Littwitz-Salomon E, Moreira D, Frost JN, Choi C, Liou KT, Ahern DK, et al. Metabolic requirements of NK cells during the acute response against retroviral infection. Nat Commun. 2021;12(1):5376.
109. Poznanski SM, Singh K, Ritchie TM, Aguiar JA, Fan IY, Portillo AL, et al. Metabolic flexibility determines human NK cell functional fate in the tumor microenvironment. Cell Metab. 2021;33(6):1205-1220.e5.

110. Wang F, He J, Xing R, Sha T, Sun B. Molecular mechanisms of ferroptosis and their role in inflammation. Int Rev Immunol. 2023;42(1):71-81.
111. Chattopadhyay S, Hazra R, Mallick A, Gayen S, Roy S. A review on comprehending immunotherapeutic approaches inducing ferroptosis: Managing tumour immunity. Immunology. 2024;172(4):547-65.
112. Wan C, Sun Y, Tian Y, Lu L, Dai X, Meng J, et al. Irradiated tumor cell-derived microparticles mediate tumor eradication via cell killing and immune reprogramming. Sci Adv. 2020;6(13):eaay9789.
113. Chen X, Comish PB, Tang D, Kang R. Characteristics and Biomarkers of Ferroptosis. Front Cell Dev Biol. 2021;9:637162.
114. Tang D, Kang R, Zeh HJ, Lotze MT. The multifunctional protein HMGB1: 50 years of discovery. Nat Rev Immunol. 2023;23(12):824-41.
115. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019;29(5):347-64.
116. Chen X, Li J, Kang R, Klionsky DJ, Tang D. Ferroptosis: machinery and regulation. Autophagy. 2021;17(9):2054-81.
117. Dai E, Han L, Liu J, Xie Y, Zeh HJ, Kang R, et al. Ferroptotic damage promotes pancreatic tumorigenesis through a TMEM173/STING-dependent DNA sensor pathway. Nat Commun. 2020;11(1):6339.
118. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy. 2020;16(11):2069-83.
119. Wen Q, Liu J, Kang R, Zhou B, Tang D. The release and activity of HMGB1 in ferroptosis. Biochem Biophys Res Commun. 2019;510(2):278-83.
120. Gao W, Wang X, Zhou Y, Wang X, Yu Y. Autophagy, ferroptosis, pyroptosis, and necroptosis in tumor immunotherapy. Signal Transduct Target Ther. 2022;7(1):196.
121. Hua Y, Yang S, Zhang Y, Li J, Wang M, Yeerkenbieke P, et al. Modulating ferroptosis sensitivity: environmental and cellular targets within the tumor microenvironment. J Exp Clin Cancer Res CR. 2024;43(1):19.
122. Liu T, Zhu C, Chen X, Guan G, Zou C, Shen S, et al. Ferroptosis, as the most enriched programmed cell death process in glioma, induces immunosuppression and immunotherapy resistance. Neuro-Oncol. 2022;24(7):1113-25.
123. Consonni FM, Bleve A, Totaro MG, Storto M, Kunderfranco P, Termanini A, et al. Heme catabolism by tumor-associated macrophages controls metastasis formation. Nat Immunol. 2021;22(5):595-606.
124. Trzeciak A, Wang Y-T, Perry JSA. First we eat, then we do everything else: The dynamic metabolic regulation of efferocytosis. Cell Metab. 2021;33(11):2126-41.
125. Klöditz K, Fadeel B. Three cell deaths and a funeral: macrophage clearance of cells undergoing distinct modes of cell death. Cell Death Discov. 2019;5:65.
126. Bardelčíková A, Šoltys J, Mojžiš J. Oxidative Stress, Inflammation and Colorectal Cancer: An Overview. Antioxid Basel Switz. 2023;12(4):901.
127. Ojo OA, Grant S, Nwafor-Ezeh PI, Maduakolam-Aniobi TC, Akinborode TI, Ezenabor EH, et al. Ferroptosis as the new approach to cancer therapy. Cancer Treat Res Commun. 2025;43:100913.
128. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. Immunity. 2015;42(3):406-17.
129. Jinesh GG, Brohl AS. Classical epithelial-mesenchymal transition (EMT) and alternative cell death process-driven blebbishield metastatic-witch (BMW) pathways to cancer metastasis. Signal Transduct Target Ther. 2022;7(1):296.
130. Johnson AM, Kleczko EK, Nemenoff RA. Eicosanoids in Cancer: New Roles in Immunoregulation. Front Pharmacol. 2020;11:595498.
131. Dong H, Zhang L, Liu S. Targeting HMGB1: An available Therapeutic Strategy for Breast Cancer Therapy. Int J Biol Sci. 2022;18(8):3421-34.
132. Yamazaki T, Hannani D, Poirier-Colame V, Ladoire S, Locher C, Sistigu A, et al. Defective immunogenic cell death of HMGB1-deficient tumors: compensatory therapy with TLR4 agonists. Cell Death Differ. 2014;21(1):69-78.
133. Loi M, Müller A, Steinbach K, Niven J, Barreira da Silva R, Paul P, et al. Macroautophagy Proteins Control MHC Class I Levels on Dendritic Cells and Shape Anti-viral CD8(+) T Cell Responses. Cell Rep. 2016;15(5):1076-87.
134. Wang G, Xie L, Li B, Sang W, Yan J, Li J, et al. A nanounit strategy reverses immune suppression of exosomal PD-L1 and is associated with enhanced ferroptosis. Nat Commun. 2021;12(1):5733.
135. Efimova I, Catanzaro E, Meeren LV der, Turubanova VD, Hammad H, Mishchenko TA, et al. Vaccination with early ferroptotic cancer cells induces efficient antitumor immunity. J Immunother Cancer. 2020;8(2):e001369.
136. Blüml S, Zupkovitz G, Kirchberger S, Seyerl M, Bochkov VN, Stuhlmeier K, et al. Epigenetic regulation of dendritic cell differentiation and function by oxidized phospholipids. Blood. 2009;114(27):5481-9.
137. Demuynck R, Efimova I, Naessens F, Krysko DV. Immunogenic ferroptosis and where to find it?. J Immunother Cancer. 2021;9(12):e003430.
138. Liu Y, Duan C, Dai R, Zeng Y. Ferroptosis-mediated Crosstalk in the Tumor Microenvironment Implicated in Cancer Progression and Therapy. Front Cell Dev Biol. 2021;9:739392.
139. Tong X, Tang R, Xiao M, Xu J, Wang W, Zhang B, et al. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. J Hematol OncolJ Hematol Oncol. 2022;15(1):174.
140. Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell. 2018;172(5):1022-1037.e14.
141. Wang D, DuBois RN. Immunosuppression associated with chronic inflammation in the tumor microenvironment. Carcinogenesis. 2015;36(10):1085-93.
142. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, et al. Regulation of Ferroptotic Cancer Cell Death by GPX4. Cell. 2014;156(1-2):317-31.
143. Finetti F, Travelli C, Ercoli J, Colombo G, Buoso E, Trabalzini L. Prostaglandin E2 and Cancer: Insight into Tumor Progression and Immunity. Biology. 2020;9(12):434.

144. Yu B, Choi B, Li W, Kim D-H. Magnetic field boosted ferroptosis-like cell death and responsive MRI using hybrid vesicles for cancer immunotherapy. Nat Commun. 2020;11(1):3637.
145. Yue W, Chen L, Yu L, Zhou B, Yin H, Ren W, et al. Checkpoint blockade and nanosonosensitizer-augmented noninvasive sonodynamic therapy combination reduces tumour growth and metastases in mice. Nat Commun. 2019;10(1):2025.
146. Pawaria S, Binder RJ. CD91-dependent programming of T-helper cell responses following heat shock protein immunization. Nat Commun. 2011;2:521.
147. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016;8(328): 328rv4.
148. Li H, Sun Y, Yao Y, Ke S, Zhang N, Xiong W, et al. USP8-governed GPX4 homeostasis orchestrates ferroptosis and cancer immunotherapy. Proc Natl Acad Sci U S A. 2024;121(16):e2315541121.
149. Jiang Z, Lim S-O, Yan M, Hsu JL, Yao J, Wei Y, et al. TYRO3 induces anti-PD-1/PD-L1 therapy resistance by limiting innate immunity and tumoral ferroptosis. J Clin Invest. 2021;131(8):e139434, 139434.
150. Ma L, Chen C, Zhao C, Li T, Ma L, Jiang J, et al. Targeting carnitine palmitoyl transferase 1A (CPT1A) induces ferroptosis and synergizes with immunotherapy in lung cancer. Signal Transduct Target Ther. 2024;9(1):64.
151. Zhang H-L, Guo Y-Q, Liu S, Ye Z-P, Li L-C, Hu B-X, et al. Galectin-13 reduces membrane localization of SLC7A11 for ferroptosis propagation. Nat Chem Biol. 2025.
152. Srivastava MK, Sinha P, Clements VK, Rodriguez P, Ostrand-Rosenberg S. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res. 2010;70(1):68-77.
153. Tang B, Zhu J, Li J, Fan K, Gao Y, Cheng S, et al. The ferroptosis and iron-metabolism signature robustly predicts clinical diagnosis, prognosis and immune microenvironment for hepatocellular carcinoma. Cell Commun Signal CCS. 2020;18(1): 174.
154. Tong R, Feng X, Sun J, Ling Z, Wang J, Li S, et al. Co-Delivery of siNRF2 and Sorafenib by a "Click" Dual Functioned Hyperbranched Nanocarrier for Synergistically Inducing Ferroptosis in Hepatocellular Carcinoma. Small. 2024;20(21):2307273.
155. Zhang H, Zhuo Y, Li D, Zhang L, Gao Q, Yang L, et al. Dihydroartemisinin inhibits the growth of pancreatic cells by inducing ferroptosis and activating antitumor immunity. Eur J Pharmacol. 2022;926:175028.
156. Hsieh C-H, Hsieh H-C, Shih F-S, Wang P-W, Yang L-X, Shieh D-B, et al. An innovative NRF2 nano-modulator induces lung cancer ferroptosis and elicits an immunostimulatory tumor microenvironment. Theranostics. 2021;11(14):7072-91.
157. Zhu L, You Y, Zhu M, Song Y, Zhang J, Hu J, et al. Ferritin-Hijacking Nanoparticles Spatiotemporally Directing Endogenous Ferroptosis for Synergistic Anticancer Therapy. Adv Mater Deerfield Beach Fla. 2022;34(51):e2207174.
158. Liu B, Ji Q, Cheng Y, Liu M, Zhang B, Mei Q, et al. Biomimetic GBM-targeted drug delivery system boosting ferroptosis for immunotherapy of orthotopic drug-resistant GBM. J Nanobiotechnology. 2022;20(1):161.
159. Liao H, Chen M, Liao Z, Luo Y, Chen S, Tan W, et al. Sonodynamic therapy-boosted biomimetic nanoplatform targets ferroptosis and CD47 as vulnerabilities for cancer immunotherapy. J Nanobiotechnology. 2025;23(1):432.
160. Cai S, Huang J, Fan H, Sui Z, Huang C, Deng Y, et al. Targeted tumor cell-intrinsic CTRP6 biomimetic codelivery synergistically amplifies ferroptosis and immune activation to boost anti-PD-L1 immunotherapy efficacy in lung cancer. J Nanobiotechnology. 2025;23(1):409.
161. DeAntoneo C, Danthi P, Balachandran S. Reovirus Activated Cell Death Pathways. Cells. 2022;11(11):1757.
162. Khan M, Lin J, Wang B, Chen C, Huang Z, Tian Y, et al. A novel necroptosis-related gene index for predicting prognosis and a cold tumor immune microenvironment in stomach adenocarcinoma. Front Immunol. 2022;13:968165.
163. Liu C, Zhang K, Shen H, Yao X, Sun Q, Chen G. Necroptosis: A novel manner of cell death, associated with stroke (Review). Int J Mol Med. 2018;41(2):624-30.
164. Kinoshita Y, Saeki H. A Review of the Pathogenesis of Toxic Epidermal Necrolysis. J Nippon Med Sch Nippon Ika Daigaku Zasshi. 2016;83(6):216-22.
165. Strilic B, Yang L, Albarrán-Juárez J, Wachsmuth L, Han K, Müller UC, et al. Tumour-cell-induced endothelial cell necroptosis via death receptor 6 promotes metastasis. Nature. 2016;536(7615):215-8.
166. Wendlocha D, Kubina R, Krzykawski K, Mielczarek-Palacz A. Selected Flavonols Targeting Cell Death Pathways in Cancer Therapy: The Latest Achievements in Research on Apoptosis, Autophagy, Necroptosis, Pyroptosis, Ferroptosis, and Cuproptosis. Nutrients. 2024;16(8):1201.
167. Yu Z, Jiang N, Su W, Zhuo Y. Necroptosis: A Novel Pathway in Neuroinflammation. Front Pharmacol. 2021;12:701564.
168. Holler N, Zaru R, Micheau O, Thome M, Attinger A, Valitutti S, et al. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. Nat Immunol. 2000;1(6):489-95.
169. Xiao H, Jensen PE, Chen X. Elimination of Osteosarcoma by Necroptosis with Graphene Oxide-Associated Anti-HER2 Antibodies. Int J Mol Sci. 2019;20(18):4360.
170. Sun C, Zhan J, Li Y, Zhou C, Huang S, Zhu X, et al. Non-apoptotic regulated cell death mediates reprogramming of the tumour immune microenvironment by macrophages. J Cell Mol Med. 2024;28(8):e18348.
171. Lu JV, Chen HC, Walsh CM. Necroptotic signaling in adaptive and innate immunity. Semin Cell Dev Biol. 2014;35:33-9.
172. Ang RL, Ting AT. Tumor necrosis factor-driven cell death in donor organ as a barrier to immunological tolerance. Curr Opin Organ Transplant. 2019;24(1):12-9.
173. Micheau O, Tschopp J. Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes. Cell. 2003;114(2):181-90.
174. Mahoney DJ, Cheung HH, Mrad RL, Plenchette S, Simard C, Enwere E, et al. Both cIAP1 and cIAP2 regulate TNFalpha-mediated NF-kappaB activation. Proc Natl Acad Sci U S A. 2008;105(33):11778-83.
175. Zhou J, Xu J, Li P, Sun S, Kadier Y, Zhou S, et al. Necroptosis and Viral Myocarditis: Tumor Necrosis Factor α as a Novel Biomarker for the Diagnosis of Viral Myocarditis. Front Cell Dev Biol. 2022;10:826904.

176. Wang X, Yousefi S, Simon H-U. Necroptosis and neutrophil-associated disorders. Cell Death Dis. 2018;9(2):111.
177. Riley JS, Malik A, Holohan C, Longley DB. DED or alive: assembly and regulation of the death effector domain complexes. Cell Death Dis. 2015;6(8):e1866.
178. Zhao J, Jitkaew S, Cai Z, Choksi S, Li Q, Luo J, et al. Mixed lineage kinase domain-like is a key receptor interacting protein 3 downstream component of TNF-induced necrosis. Proc Natl Acad Sci U S A. 2012;109(14):5322-5327.
179. Cai Z, Jitkaew S, Zhao J, Chiang H-C, Choksi S, Liu J, et al. Plasma membrane translocation of trimerized MLKL protein is required for TNF-induced necroptosis. Nat Cell Biol. 2014;16(1):55-65.
180. Jiao H, Wachsmuth L, Kumari S, Schwarzer R, Lin J, Eren RO, et al. Z-nucleic-acid sensing triggers ZBP1-dependent necroptosis and inflammation. Nature. 2020;580(7803):391-395.
181. Dillon CP, Weinlich R, Rodriguez DA, Cripps JG, Quarato G, Gurung P, et al. RIPK1 blocks early postnatal lethality mediated by caspase-8 and RIPK3. Cell. 2014;157(5):1189-1202.
182. He S, Liang Y, Shao F, Wang X. Toll-like receptors activate programmed necrosis in macrophages through a receptor-interacting kinase-3-mediated pathway. Proc Natl Acad Sci U S A. 2011;108(50):20054-20059.
183. Krysko O, Aaes TL, Kagan VE, D'Herde K, Bachert C, Leybaert L, et al. Necroptotic cell death in anti-cancer therapy. Immunol Rev. 2017;280(1):207-19.
184. Annibaldi A, Meier P. Checkpoints in TNF-Induced Cell Death: Implications in Inflammation and Cancer. Trends Mol Med. 2018;24(1):49-65.
185. Ocansey DKW, Qian F, Cai P, Ocansey S, Amoah S, Qian Y, et al. Current evidence and therapeutic implication of PANoptosis in cancer. Theranostics. 2024;14(2):640-61.
186. Chen D, Yu J, Zhang L. Necroptosis: an alternative cell death program defending against cancer. Biochim Biophys Acta. 2016;1865(2):228-36.
187. Kaczmarek A, Vandenabeele P, Krysko DV. Necroptosis: The Release of Damage-Associated Molecular Patterns and Its Physiological Relevance. Immunity. 2013;38(2):209-23.
188. Jinushi M, Hodi FS, Dranoff G. Enhancing the clinical activity of granulocyte-macrophage colony-stimulating factor-secreting tumor cell vaccines. Immunol Rev. 2008;222:287-98.
189. Hsu S-K, Li C-Y, Lin I-L, Syue W-J, Chen Y-F, Cheng K-C, et al. Inflammation-related pyroptosis, a novel programmed cell death pathway, and its crosstalk with immune therapy in cancer treatment. Theranostics. 2021;11(18):8813-35.
190. Aaes TL, Kaczmarek A, Delvaeye T, De Craene B, De Koker S, Heyndrickx L, et al. Vaccination with Necroptotic Cancer Cells Induces Efficient Anti-tumor Immunity. Cell Rep. 2016;15(2):274-87.
191. Gao L, Shay C, Teng Y. Cell death shapes cancer immunity: spotlighting PANoptosis. J Exp Clin Cancer Res CR. 2024;43(1):168.
192. Lu J, He R, Liu Y, Zhang J, Xu H, Zhang T, et al. Exploiting cell death and tumor immunity in cancer therapy: challenges and future directions. Front Cell Dev Biol. 2024;12:1416115.
193. Workenhe ST, Nguyen A, Bakhshinyan D, Wei J, Hare DN, MacNeill KL, et al. De novo necroptosis creates an inflammatory environment mediating tumor susceptibility to immune checkpoint inhibitors. Commun Biol. 2020;3:645.
194. Meng M-B, Wang H-H, Cui Y-L, Wu Z-Q, Shi Y-Y, Zaorsky NG, et al. Necroptosis in tumorigenesis, activation of anti-tumor immunity, and cancer therapy. Oncotarget. 2016;7(35):57391-413.
195. Schmidt SV, Seibert S, Walch-Rückheim B, Vicinus B, Kamionka E-M, Pahne-Zeppenfeld J, et al. RIPK3 expression in cervical cancer cells is required for PolyIC-induced necroptosis, IL-1α release, and efficient paracrine dendritic cell activation. Oncotarget. 2015;6(11):8635-47.
196. Xin J, You D, Breslin P, Li J, Zhang J, Wei W, et al. Sensitizing acute myeloid leukemia cells to induced differentiation by inhibiting the RIP1/RIP3 pathway. Leukemia. 2017;31(5):1154-65.
197. Nugues A-L, El Bouazzati H, Hétuin D, Berthon C, Loyens A, Bertrand E, et al. RIP3 is downregulated in human myeloid leukemia cells and modulates apoptosis and caspase-mediated p65/RelA cleavage. Cell Death Dis. 2014;5(8):e1384.
198. He S, Wang L, Miao L, Wang T, Du F, Zhao L, et al. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF-alpha. Cell. 2009;137(6):1100-11.
199. Moriwaki K, Bertin J, Gough PJ, Orlowski GM, Chan FKM. Differential roles of RIPK1 and RIPK3 in TNF-induced necroptosis and chemotherapeutic agent-induced cell death. Cell Death Dis. 2015;6(2):e1636.
200. Hartman ML. Non-Apoptotic Cell Death Signaling Pathways in Melanoma. Int J Mol Sci. 2020;21(8):2980.
201. Bozec D, Iuga AC, Roda G, Dahan S, Yeretssian G. Critical function of the necroptosis adaptor RIPK3 in protecting from intestinal tumorigenesis. Oncotarget. 2016;7(29):46384-400.
202. Snyder AG, Hubbard NW, Messmer MN, Kofman SB, Hagan CE, Orozco SL, et al. Intratumoral activation of the necroptotic pathway components RIPK1 and RIPK3 potentiates antitumor immunity. Sci Immunol. 2019;4(36):eaaw2004.
203. Orozco S, Oberst A. RIPK3 in cell death and inflammation: the good, the bad, and the ugly. Immunol Rev. 2017;277(1):102-12.
204. Martin SJ. Cell death and inflammation: the case for IL-1 family cytokines as the canonical DAMPs of the immune system. FEBS J. 2016;283(14):2599-615.
205. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.
206. Ando Y, Ohuchida K, Otsubo Y, Kibe S, Takesue S, Abe T, et al. Necroptosis in pancreatic cancer promotes cancer cell migration and invasion by release of CXCL5. PloS One. 2020;15(1):e0228015.
207. Molnár T, Mázló A, Tslaf V, Szöllősi AG, Emri G, Koncz G. Current translational potential and underlying molecular mechanisms of necroptosis. Cell Death Dis. 2019;10(11):860.
208. Seifert L, Werba G, Tiwari S, Giao Ly NN, Alothman S, Alqunaibit D, et al. The necrosome promotes pancreatic oncogenesis via CXCL1 and Mincle-induced immune suppression. Nature. 2016;532(7598):245-9.
209. Yan J, Wan P, Choksi S, Liu Z-G. Necroptosis and tumor progression. Trends Cancer. 2022;8(1):21-7.
210. Yan G, Zhao H, Zhang Q, Zhou Y, Wu L, Lei J, et al. A RIPK3-PGE2 Circuit Mediates Myeloid-Derived Suppressor Cell-Potentiated Colorectal Carcinogenesis. Cancer Res. 2018;78(19):5586-99.

211. Park S, Hatanpaa KJ, Xie Y, Mickey BE, Madden CJ, Raisanen JM, et al. The receptor interacting protein 1 inhibits p53 induction through NF-kappaB activation and confers a worse prognosis in glioblastoma. Cancer Res. 2009;69(7):2809-16.
212. Liu X, Zhou M, Mei L, Ruan J, Hu Q, Peng J, et al. Key roles of necroptotic factors in promoting tumor growth. Oncotarget. 2016;7(16):22219-33.
213. Kearney CJ, Cullen SP, Tynan GA, Henry CM, Clancy D, Lavelle EC, et al. Necroptosis suppresses inflammation via termination of TNF- or LPS-induced cytokine and chemokine production. Cell Death Differ. 2015;22(8):1313-27.
214. Vodnala SK, Eil R, Kishton RJ, Sukumar M, Yamamoto TN, Ha N-H, et al. T cell stemness and dysfunction in tumors are triggered by a common mechanism. Science. 2019;363(6434):eaau0135.
215. Scarpitta A, Hacker UT, Büning H, Boyer O, Adriouch S. Pyroptotic and Necroptotic Cell Death in the Tumor Microenvironment and Their Potential to Stimulate Anti-Tumor Immune Responses. Front Oncol. 2021;11:731598.
216. Tan Y, Chen Q, Li X, Zeng Z, Xiong W, Li G, et al. Pyroptosis: a new paradigm of cell death for fighting against cancer. J Exp Clin Cancer Res CR. 2021;40(1):153.
217. Tang R, Xu J, Zhang B, Liu J, Liang C, Hua J, et al. Ferroptosis, necroptosis, and pyroptosis in anticancer immunity. J Hematol OncolJ Hematol Oncol. 2020;13(1):110.
218. Yatim N, Jusforgues-Saklani H, Orozco S, Schulz O, Barreira da Silva R, Reis e Sousa C, et al. RIPK1 and NF-κB signaling in dying cells determines cross-priming of $CD8^+$ T cells. Science. 2015;350(6258):328-34.
219. Van Hoecke L, Van Lint S, Roose K, Van Parys A, Vandenabeele P, Grooten J, et al. Treatment with mRNA coding for the necroptosis mediator MLKL induces antitumor immunity directed against neo-epitopes. Nat Commun. 2018;9(1):3417.
220. Koo G-B, Morgan MJ, Lee D-G, Kim W-J, Yoon J-H, Koo JS, et al. Methylation-dependent loss of RIP3 expression in cancer represses programmed necrosis in response to chemotherapeutics. Cell Res. 2015;25(6):707-25.
221. Messmer MN, Snyder AG, Oberst A. Comparing the effects of different cell death programs in tumor progression and immunotherapy. Cell Death Differ. 2019;26(1):115-29.
222. Gong Y, Fan Z, Luo G, Yang C, Huang Q, Fan K, et al. The role of necroptosis in cancer biology and therapy. Mol Cancer. 2019;18(1):100.
223. Chen D, Zhao Z, Hong R, Yang D, Gong Y, Wu Q, et al. Harnessing the FGFR2/NF2/YAP signaling-dependent necroptosis to develop an FGFR2/IL-8 dual blockade therapeutic strategy. Nat Commun. 2025;16(1):4128.
224. Zhu F, Zhang W, Yang T, He S-D. Complex roles of necroptosis in cancer. J Zhejiang Univ Sci B. 2019;20(5):399-413.
225. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013;13(10):714-26.
226. Wang T, Jin Y, Yang W, Zhang L, Jin X, Liu X, et al. Necroptosis in cancer: An angel or a demon?. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2017;39(6):1010428317711539.
227. Zhao D, Zhang H, Tao W, Wei W, Sun J, He Z. A rapid albumin-binding 5-fluorouracil prodrug with a prolonged circulation time and enhanced antitumor activity. Biomater Sci. 2017;5(3):502-10.
228. Li Y, Guo Y, Zhang K, Zhu R, Chen X, Zhang Z, et al. Cell Death Pathway Regulation by Functional Nanomedicines for Robust Antitumor Immunity. Adv Sci Weinh Baden-Wurtt Ger. 2024;11(3):e2306580.
229. deGonçalves R C, Freire PP, Coletti D, Seelaender M. Tumor Microenvironment Autophagic Processes and Cachexia: The Missing Link?. Front Oncol. 2020;10:617109.
230. Wen X, Klionsky DJ. An overview of macroautophagy in yeast. J Mol Biol. 2016;428(9 Pt A):1681-99.
231. Feng Y, Chen Y, Wu X, Chen J, Zhou Q, Liu B, et al. Interplay of energy metabolism and autophagy. Autophagy. 2024;20(1):4-14.
232. Peña-Oyarzún D, Reyes M, Hernández-Cáceres MP, Kretschmar C, Morselli E, Ramirez-Sarmiento CA, et al. Role of Autophagy in the Microenvironment of Oral Squamous Cell Carcinoma. Front Oncol. 2020;10:602661.
233. Ahsan N, Shariq M, Surolia A, Raj R, Khan MF, Kumar P. Multipronged regulation of autophagy and apoptosis: emerging role of TRIM proteins. Cell Mol Biol Lett. 2024;29(1):13.
234. Sanchez-Garrido J, Shenoy AR. Regulation and repurposing of nutrient sensing and autophagy in innate immunity. Autophagy. 2021;17(7):1571-91.
235. Giansanti M, Theinert T, Boeing SK, Haas D, Schlegel P-G, Vacca P, et al. Exploiting autophagy balance in T and NK cells as a new strategy to implement adoptive cell therapies. Mol Cancer. 2023;22(1):201.
236. Jiang G-M, Tan Y, Wang H, Peng L, Chen H-T, Meng X-J, et al. The relationship between autophagy and the immune system and its applications for tumor immunotherapy. Mol Cancer. 2019;18(1):17.
237. Lavallard VJ, Gual P. Autophagy and non-alcoholic fatty liver disease. BioMed Res Int. 2014;2014:120179.
238. Patel NH, Sohal SS, Manjili MH, Harrell JC, Gewirtz DA. The Roles of Autophagy and Senescence in the Tumor Cell Response to Radiation. Radiat Res. 2020;194(2):103-15.
239. Singh SS, Vats S, Chia AY-Q, Tan TZ, Deng S, Ong MS, et al. Dual role of autophagy in hallmarks of cancer. Oncogene. 2018;37(9):1142-58.
240. You L, Jin S, Zhu L, Qian W. Autophagy, autophagy-associated adaptive immune responses and its role in hematologic malignancies. Oncotarget. 2017;8(7):12374-88.
241. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;132(1):27-42.
242. Hernandez GA, Perera RM. Autophagy in cancer cell remodeling and quality control. Mol Cell. 2022;82(8):1514-27.
243. Cordani M, Strippoli R, Trionfetti F, Barzegar Behrooz A, Rumio C, Velasco G, et al. Immune checkpoints between epithelial-mesenchymal transition and autophagy: A conflicting triangle. Cancer Lett. 2024;585:216661.
244. Gerada C, Ryan KM. Autophagy, the innate immune response and cancer. Mol Oncol. 2020;14(9):1913-29.
245. Ren Y, Wang R, Weng S, Xu H, Zhang Y, Chen S, et al. Multifaceted role of redox pattern in the tumor immune microenvironment regarding autophagy and apoptosis. Mol Cancer. 2023;22(1):130.
246. Chourasia AH, Tracy K, Frankenberger C, Boland ML, Sharifi MN, Drake LE, et al. Mitophagy defects arising from BNip3 loss promote mammary tumor progression to metastasis. EMBO Rep. 2015;16(9):1145-63.

247. Zheng X, Qian Y, Fu B, Jiao D, Jiang Y, Chen P, et al. Mitochondrial fragmentation limits NK cell-based tumor immunosurveillance. Nat Immunol. 2019;20(12):1656-67.
248. DeVorkin L, Pavey N, Carleton G, Comber A, Ho C, Lim J, et al. Autophagy Regulation of Metabolism Is Required for CD8+ T Cell Anti-tumor Immunity. Cell Rep. 2019;27(2):502-513.e5.
249. Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest. 2003;112(12):1809-20.
250. Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature. 2008;451(7182):1069-75.
251. White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer. 2012;12(6):401-10.
252. Reyes-Castellanos G, Abdel Hadi N, Carrier A. Autophagy Contributes to Metabolic Reprogramming and Therapeutic Resistance in Pancreatic Tumors. Cells. 2022;11(3):426.
253. Guo JY, White E. Autophagy, Metabolism, and Cancer. Cold Spring Harb Symp Quant Biol. 2016;81:73-8.
254. Amaravadi R, Kimmelman AC, White E. Recent insights into the function of autophagy in cancer. Genes Dev. 2016;30(17):1913-30.
255. Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. Mol Cancer. 2020;19(1):12.
256. Wang P, Long M, Zhang S, Cheng Z, Zhao X, He F, et al. Hypoxia inducible factor-1α regulates autophagy via the p27-E2F1 signaling pathway. Mol Med Rep. 2017;16(2):2107-12.
257. Baginska J, Viry E, Berchem G, Poli A, Noman MZ, van Moer K, et al. Granzyme B degradation by autophagy decreases tumor cell susceptibility to natural killer-mediated lysis under hypoxia. Proc Natl Acad Sci U S A. 2013;110(43):17450-5.
258. Luo X, Qiu Y, Dinesh P, Gong W, Jiang L, Feng X, et al. The functions of autophagy at the tumour-immune interface. J Cell Mol Med. 2021;25(5):2333-41.
259. Folkerts H, Hilgendorf S, Vellenga E, Bremer E, Wiersma VR. The multifaceted role of autophagy in cancer and the microenvironment. Med Res Rev. 2019;39(2):517-60.
260. Larabi A, Barnich N, Nguyen HTT. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. Autophagy. 2020;16(1):38-51.
261. Liu Y, Zhang H, Wang Z, Wu P, Gong W. 5-Hydroxytryptamine1a receptors on tumour cells induce immune evasion in lung adenocarcinoma patients with depression via autophagy/pSTAT3. Eur J Cancer Oxf Engl 1990. 2019;114:8-24.
262. Rao S, Tortola L, Perlot T, Wirnsberger G, Novatchkova M, Nitsch R, et al. A dual role for autophagy in a murine model of lung cancer. Nat Commun. 2014;5:3056.
263. Takamura A, Komatsu M, Hara T, Sakamoto A, Kishi C, Waguri S, et al. Autophagy-deficient mice develop multiple liver tumors. Genes Dev. 2011;25(8):795-800.
264. Wildenberg ME, Vos ACW, Wolfkamp SCS, Duijvestein M, Verhaar AP, Te Velde AA, et al. Autophagy attenuates the adaptive immune response by destabilizing the immunologic synapse. Gastroenterology. 2012;142(7):1493-1503.e6.
265. Lei Y, Zhang E, Bai L, Li Y. Autophagy in Cancer Immunotherapy. Cells. 2022;11(19):2996.
266. Mah LY, Ryan KM. Autophagy and cancer. Cold Spring Harb Perspect Biol. 2012;4(1):a008821.
267. Duan Y, Tian X, Liu Q, Jin J, Shi J, Hou Y. Role of autophagy on cancer immune escape. Cell Commun Signal CCS. 2021;19(1):91.
268. Ma Y, Galluzzi L, Zitvogel L, Kroemer G. Autophagy and cellular immune responses. Immunity. 2013;39(2):211-27.
269. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 2011;334(6062):1573-7.
270. Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymeric L, Yang H, et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity. 2013;38(4):729-41.
271. Pishesha N, Harmand TJ, Ploegh HL. A guide to antigen processing and presentation. Nat Rev Immunol. 2022;22(12):751-64.
272. Xia H, Green DR, Zou W. Autophagy in tumour immunity and therapy. Nat Rev Cancer. 2021;21(5):281-97.
273. Lee HK, Mattei LM, Steinberg BE, Alberts P, Lee YH, Chervonsky A, et al. In vivo requirement for Atg5 in antigen presentation by dendritic cells. Immunity. 2010;32(2):227-39.
274. Oh DS, Lee HK. Autophagy protein ATG5 regulates CD36 expression and anti-tumor MHC class II antigen presentation in dendritic cells. Autophagy. 2019;15(12):2091-106.
275. Parekh VV, Wu L, Boyd KL, Williams JA, Gaddy JA, Olivares-Villagómez D, et al. Impaired autophagy, defective T cell homeostasis, and a wasting syndrome in mice with a T cell-specific deletion of Vps34. J Immunol Baltim Md 1950. 2013;190(10):5086-101.
276. Gou Q, Dong C, Xu H, Khan B, Jin J, Liu Q, et al. PD-L1 degradation pathway and immunotherapy for cancer. Cell Death Dis. 2020;11(11):955.
277. An CH, Kim MS, Yoo NJ, Park SW, Lee SH. Mutational and expressional analyses of ATG5, an autophagy-related gene, in gastrointestinal cancers. Pathol Res Pract. 2011;207(7):433-7.
278. Li C-W, Lim S-O, Chung EM, Kim Y-S, Park AH, Yao J, et al. Eradication of Triple-Negative Breast Cancer Cells by Targeting Glycosylated PD-L1. Cancer Cell. 2018;33(2):187-201.e10.
279. Yamamoto K, Venida A, Yano J, Biancur DE, Kakiuchi M, Gupta S, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. Nature. 2020;581(7806):100-5.
280. Görgülü K, Diakopoulos KN, Ai J, Schoeps B, Kabacaoglu D, Karpathaki A-F, et al. Levels of the Autophagy-Related 5 Protein Affect Progression and Metastasis of Pancreatic Tumors in Mice. Gastroenterology. 2019;156(1):203-217.e20.
281. Baghdadi M, Yoneda A, Yamashina T, Nagao H, Komohara Y, Nagai S, et al. TIM-4 glycoprotein-mediated degradation of dying tumor cells by autophagy leads to reduced antigen presentation and increased immune tolerance. Immunity. 2013;39(6):1070-81.
282. Zamame Ramirez JA, Romagnoli GG, Falasco BF, Gorgulho CM, Sanzochi Fogolin C, Dos Santos DC, et al. Blocking drug-induced autophagy with chloroquine in HCT-116 colon cancer cells enhances DC maturation and T cell responses induced by tumor cell lysate. Int Immunopharmacol. 2020;84:106495.

283. Amaravadi RK, Kimmelman AC, Debnath J. Targeting Autophagy in Cancer: Recent Advances and Future Directions. Cancer Discov. 2019;9(9):1167-81.
284. Pan H, Chen L, Xu Y, Han W, Lou F, Fei W, et al. Autophagy-associated immune responses and cancer immunotherapy. Oncotarget. 2016;7(16):21235-46.
285. Jin X, You L, Qiao J, Han W, Pan H. Autophagy in colitis-associated colon cancer: exploring its potential role in reducing initiation and preventing IBD-Related CAC development. Autophagy. 2024;20(2):242-58.
286. Gettinger S, Choi J, Hastings K, Truini A, Datar I, Sowell R, et al. Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. Cancer Discov. 2017;7(12):1420-35.
287. Xia R, Yang M, Fu X, Du W, Gao X, Li G, et al. Differential Requirement of Beclin 1 for Regulating the Balance of Naïve and Activated CD4+ T Cells. Front Cell Dev Biol. 2020;8:834.
288. Puleston DJ, Zhang H, Powell TJ, Lipina E, Sims S, Panse I, et al. Autophagy is a critical regulator of memory CD8(+) T cell formation. eLife. 2014;3:e03706.
289. Pua HH, Guo J, Komatsu M, He Y-W. Autophagy is essential for mitochondrial clearance in mature T lymphocytes. J Immunol Baltim Md 1950. 2009;182(7):4046-55.
290. Jia W, He M-X, McLeod IX, Guo J, Ji D, He Y-W. Autophagy regulates T lymphocyte proliferation through selective degradation of the cell-cycle inhibitor CDKN1B/p27Kip1. Autophagy. 2015;11(12):2335-45.
291. Xu X, Araki K, Li S, Han J-H, Ye L, Tan WG, et al. Autophagy is essential for effector CD8(+) T cell survival and memory formation. Nat Immunol. 2014;15(12):1152-61.
292. Wei J, Long L, Yang K, Guy C, Shrestha S, Chen Z, et al. Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis. Nat Immunol. 2016;17(3):277-85.
293. Poillet-Perez L, Sharp DW, Yang Y, Laddha SV, Ibrahim M, Bommareddy PK, et al. Autophagy promotes growth of tumors with high mutational burden by inhibiting a T-cell immune response. Nat Cancer. 2020;1(9):923-34.
294. Duan Z, Shi Y, Lin Q, Hamaï A, Mehrpour M, Gong C. Autophagy-Associated Immunogenic Modulation and Its Applications in Cancer Therapy. Cells. 2022;11(15):2324.
295. O'Sullivan TE, Johnson LR, Kang HH, Sun JC. BNIP3- and BNIP3L-Mediated Mitophagy Promotes the Generation of Natural Killer Cell Memory. Immunity. 2015;43(2):331-42.
296. López-Soto A, Bravo-San Pedro JM, Kroemer G, Galluzzi L, Gonzalez S. Involvement of autophagy in NK cell development and function. Autophagy. 2017;13(3):633-6.
297. Mgrditchian T, Arakelian T, Paggetti J, Noman MZ, Viry E, Moussay E, et al. Targeting autophagy inhibits melanoma growth by enhancing NK cells infiltration in a CCL5-dependent manner. Proc Natl Acad Sci U S A. 2017;114(44):E9271-9.
298. Pei B, Zhao M, Miller BC, Véla JL, Bruinsma MW, Virgin HW, et al. Invariant NKT cells require autophagy to coordinate proliferation and survival signals during differentiation. J Immunol Baltim Md 1950. 2015;194(12):5872-84.
299. Yang H, Ma Y, Chen G, Zhou H, Yamazaki T, Klein C, et al. Contribution of RIP3 and MLKL to immunogenic cell death signaling in cancer chemotherapy. Oncoimmunology. 2016;5(6):e1149673.
300. Aita VM, Liang XH, Murty VV, Pincus DL, Yu W, Cayanis E, et al. Cloning and genomic organization of beclin 1, a candidate tumor suppressor gene on chromosome 17q21. Genomics. 1999;59(1):59-65.
301. Rodrigues PM, Sousa LG, Perrod C, Maceiras AR, Ferreirinha P, Pombinho R, et al. LAMP2 regulates autophagy in the thymic epithelium and thymic stroma-dependent CD4 T cell development. Autophagy. 2023;19(2):426-39.
302. Bates JP, Derakhshandeh R, Jones L, Webb TJ. Mechanisms of immune evasion in breast cancer. BMC Cancer. 2018;18(1):556.
303. Saitoh T, Fujita N, Jang MH, Uematsu S, Yang B-G, Satoh T, et al. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature. 2008;456(7219):264-8.
304. Műzes G, Sipos F. Autoimmunity and Carcinogenesis: Their Relationship under the Umbrella of Autophagy. Biomedicines. 2023;11(4):1130.
305. Li N, Qin J, Lan L, Zhang H, Liu F, Wu Z, et al. PTEN inhibits macrophage polarization from M1 to M2 through CCL2 and VEGF-A reduction and NHERF-1 synergism. Cancer Biol Ther. 2015;16(2):297-306.
306. Chen D, Xie J, Fiskesund R, Dong W, Liang X, Lv J, et al. Chloroquine modulates antitumor immune response by resetting tumor-associated macrophages toward M1 phenotype. Nat Commun. 2018;9(1):873.
307. Murakami Y, Saito H, Shimizu S, Kono Y, Shishido Y, Miyatani K, et al. Increased regulatory B cells are involved in immune evasion in patients with gastric cancer. Sci Rep. 2019;9(1):13083.
308. Russell RC, Guan K-L. The multifaceted role of autophagy in cancer. EMBO J. 2022;41(13):e110031.
309. Cunha LD, Yang M, Carter R, Guy C, Harris L, Crawford JC, et al. LC3-Associated Phagocytosis in Myeloid Cells Promotes Tumor Immune Tolerance. Cell. 2018;175(2):429-441.e16.
310. Sasaki K, Tsuno NH, Sunami E, Tsurita G, Kawai K, Okaji Y, et al. Chloroquine potentiates the anti-cancer effect of 5-fluorouracil on colon cancer cells. BMC Cancer. 2010;10(1):370.
311. Carew JS, Nawrocki ST, Kahue CN, Zhang H, Yang C, Chung L, et al. Targeting autophagy augments the anticancer activity of the histone deacetylase inhibitor SAHA to overcome Bcr-Abl-mediated drug resistance. Blood. 2007;110(1):313-22.
312. Dou C, Ding N, Zhao C, Hou T, Kang F, Cao Z, et al. Estrogen Deficiency-Mediated M2 Macrophage Osteoclastogenesis Contributes to M1/M2 Ratio Alteration in Ovariectomized Osteoporotic Mice. J Bone Miner Res Off J Am Soc Bone Miner Res. 2018;33(5):899-908.
313. Kuo W-T, Chang J-M, Chen C-C, Tsao N, Chang C-P. Autophagy drives plasticity and functional polarization of tumor-associated macrophages. IUBMB Life. 2022;74(2):157-69.
314. Vidal L, Victoria I, Gaba L, Martín MG, Brunet M, Colom H, et al. A first-in-human phase I/Ib dose-escalation clinical trial of the autophagy inducer ABTL0812 in patients with advanced solid tumours. Eur J Cancer. 2021;146:87-94.
315. Ramakrishnan R, Huang C, Cho H-I, Lloyd M, Johnson J, Ren X, et al. Autophagy induced by conventional chemotherapy mediates tumor cell sensitivity to immunotherapy. Cancer Res. 2012;72(21):5483-93.

316. Shen T, Zhu W, Yang L, Liu L, Jin R, Duan J, et al. Lactosylated N-Alkyl polyethylenimine coated iron oxide nanoparticles induced autophagy in mouse dendritic cells. Regen Biomater. 2018;5(3):141-9.
317. Li Y, Hahn T, Garrison K, Cui Z-H, Thorburn A, Thorburn J, et al. The vitamin E analogue α-TEA stimulates tumor autophagy and enhances antigen cross-presentation. Cancer Res. 2012;72(14):3535-45.
318. Hahn T, Akporiaye ET. α-TEA as a stimulator of tumor autophagy and enhancer of antigen cross-presentation. Autophagy. 2013;9(3):429-31.
319. Dikic I, Elazar Z. Mechanism and medical implications of mammalian autophagy. Nat Rev Mol Cell Biol. 2018;19(6):349-64.
320. Chen Y-Y, Chen C-H, Lin W-C, Tung C-W, Chen Y-C, Yang S-H, et al. The Role of Autophagy in Anti-Cancer and Health Promoting Effects of Cordycepin. Mol Basel Switz. 2021;26(16):4954.
321. Zhang X, Lao M, Yang H, Sun K, Dong Y, He L, et al. Targeting cancer-associated fibroblast autophagy renders pancreatic cancer eradicable with immunochemotherapy by inhibiting adaptive immune resistance. Autophagy. 2024;20(6):1314-34.
322. Kumar S, Sánchez-Álvarez M, Lolo F-N, Trionfetti F, Strippoli R, Cordani M. Autophagy and the Lysosomal System in Cancer. Cells. 2021;10(10):2752.
323. Stolz A, Ernst A, Dikic I. Cargo recognition and trafficking in selective autophagy. Nat Cell Biol. 2014;16(6):495-501.
324. Huang W-Q, You W, Zhu Y-Q, Gao F, Wu Z-Z, Chen G, et al. Autophagosomes coated in situ with nanodots act as personalized cancer vaccines. Nat Nanotechnol. 2025;20(3):451-62.
325. Li C, Wu C, Ji C, Xu G, Chen J, Zhang J, et al. The pathogenesis of DLD-mediated cuproptosis induced spinal cord injury and its regulation on immune microenvironment. Front Cell Neurosci. 2023;17:1132015.
326. Miao M, Cao S, Tian Y, Liu D, Chen L, Chai Q, et al. Potential diagnostic biomarkers: 6 cuproptosis- and ferroptosis-related genes linking immune infiltration in acute myocardial infarction. Genes Immun. 2023;24(4):159-70.
327. 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(6586):1254-61.
328. Xie J, Yang Y, Gao Y, He J. Cuproptosis: mechanisms and links with cancers. Mol Cancer. 2023;22(1):46.
329. Cai Q, Jing C, Wang X, Xing X, Liu W. STEAP Proteins: Roles in disease biology and potential for therapeutic intervention. Int J Biol Macromol. 2025;309(Pt 1):142797.
330. Ge EJ, Bush AI, Casini A, Cobine PA, Cross JR, DeNicola GM, et al. Connecting copper and cancer: from transition metal signalling to metalloplasia. Nat Rev Cancer. 2022;22(2):102-13.
331. Zhong Y, Zeng W, Chen Y, Zhu X. The effect of lipid metabolism on cuproptosis-inducing cancer therapy. Biomed Pharmacother Biomedecine Pharmacother. 2024;172:116247.
332. Prohaska JR, Lukasewycz OA. Copper deficiency suppresses the immune response of mice. Science. 1981;213(4507):559-61.
333. Tan H-Y, Wang N, Zhang C, Chan Y-T, Yuen M-F, Feng Y. Lysyl Oxidase-Like 4 Fosters an Immunosuppressive Microenvironment During Hepatocarcinogenesis. Hepatology. 2021;73(6):2326.
334. Chen HHW, Song I-S, Hossain A, Choi M-K, Yamane Y, Liang ZD, et al. Elevated glutathione levels confer cellular sensitization to cisplatin toxicity by up-regulation of copper transporter hCtr1. Mol Pharmacol. 2008;74(3):697-704.
335. Sha S, Si L, Wu X, Chen Y, Xiong H, Xu Y, et al. Prognostic analysis of cuproptosis-related gene in triple-negative breast cancer. Front Immunol. 2022;13:922780.
336. Qin Y, Liu Y, Xiang X, Long X, Chen Z, Huang X, et al. Cuproptosis correlates with immunosuppressive tumor microenvironment based on pan-cancer multiomics and single-cell sequencing analysis. Mol Cancer. 2023;22(1):59.
337. Huang Y-Y, Bao T-Y, Huang X-Q, Lan Q-W, Huang Z-M, Chen Y-H, et al. Machine learning algorithm to construct cuproptosis- and immune-related prognosis prediction model for colon cancer. World J Gastrointest Oncol. 2023;15(3):372-88.
338. Yang Q, Zeng S, Liu W. Roles of cuproptosis-related gene DLAT in various cancers: a bioinformatic analysis and preliminary verification on pro-survival autophagy. PeerJ. 2023;11:e15019.
339. Chrzan N, Hartman ML. Copper in melanoma: At the crossroad of protumorigenic and anticancer roles. Redox Biol. 2025;81:103552.
340. Lv H, Liu X, Zeng X, Liu Y, Zhang C, Zhang Q, et al. Comprehensive Analysis of Cuproptosis-Related Genes in Immune Infiltration and Prognosis in Melanoma. Front Pharmacol. 2022;13:930041.
341. Fei C, Zhen X, Shiqiang Z, Jun P. Frontier knowledge and future directions of programmed cell death in clear cell renal cell carcinoma. Cell Death Discov. 2024;10(1):113.
342. Song Q, Zhou R, Shu F, Fu W. Cuproptosis scoring system to predict the clinical outcome and immune response in bladder cancer. Front Immunol. 2022;13:958368.
343. Mo J-Q, Zhang S-Y, Li Q, Chen M-X, Zheng Y-Q, Xie X, et al. Immunomodulation of cuproptosis and ferroptosis in liver cancer. Cancer Cell Int. 2024;24(1):22.
344. Jiang R, Huan Y, Li Y, Gao X, 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(1):370.
345. Bao J-H, Lu W-C, Duan H, Ye Y-Q, Li J-B, Liao W-T, et al. Identification of a novel cuproptosis-related gene signature and integrative analyses in patients with lower-grade gliomas. Front Immunol. 2022;13:933973.
346. Jiang P-C, Fan J, Zhang C-D, Bai M-H, Sun Q-Q, Chen Q-P, et al. Unraveling Colorectal Cancer and Pan-cancer Immune Heterogeneity and Synthetic Therapy Response Using Cuproptosis and Hypoxia Regulators by Multi-omic Analysis and Experimental Validation. Int J Biol Sci. 2023;19(11):3526-43.
347. Wang G, Xiao R, Zhao S, Sun L, Guo J, Li W, et al. Cuproptosis regulator-mediated patterns associated with immune infiltration features and construction of cuproptosis-related signatures to guide immunotherapy. Front Immunol. 2022;13:945516.
348. Feng S, Zhang Y, Zhu H, Jian Z, Zeng Z, Ye Y, et al. Cuproptosis facilitates immune activation but promotes immune escape, and a machine learning-based cuproptosis-related signature is identified for predicting prognosis and immunotherapy response of gliomas. CNS Neurosci Ther. 2024;30(2):e14380.

349. Wu C, Tan J, Wang X, Qin C, Long W, Pan Y, et al. Pan-cancer analyses reveal molecular and clinical characteristics of cuproptosis regulators. iMeta. 2023;2(1):e68.
350. Nishio N, Diaconu I, Liu H, Cerullo V, Caruana I, Hoyos V, et al. Armed oncolytic virus enhances immune functions of chimeric antigen receptor-modified T cells in solid tumors. Cancer Res. 2014;74(18):5195-205.
351. Ghosh P, Vidal C, Dey S, Zhang L. Mitochondria Targeting as an Effective Strategy for Cancer Therapy. Int J Mol Sci. 2020;21(9):3363.
352. Huang X-Y, Shen J-Y, Huang K, Wang L, Sethi G, Ma Z. Cuproptosis in cancers: Function and implications from bench to bedside. Biomed Pharmacother Biomedecine Pharmacother. 2024;176:116874.
353. Zhou Y, Wang Q, Wang Q, Zhou Z, Peng X, Qu B, et al. Self-assembled copper chlorogenic acid nanoparticles: Inducing pyroptosis and cuproptosis to activate antitumor immunity. J Control Release Off J Control Release Soc. 2025;384:113941.
354. Wu H, Lu X, Hu Y, Baatarbolat J, Zhang Z, Liang Y, et al. Biomimic Nanodrugs Overcome Tumor Immunosuppressive Microenvironment to Enhance Cuproptosis/Chemodynamic-Induced Cancer Immunotherapy. Adv Sci Weinh Baden-Wurtt Ger. 2025;12(5):e2411122.
355. Kciuk M, Gielecińska A, Kałuzińska-Kołat Ż, Yahya EB, Kontek R. Ferroptosis and cuproptosis: Metal-dependent cell death pathways activated in response to classical chemotherapy - Significance for cancer treatment?. Biochim Biophys Acta Rev Cancer. 2024;1879(4):189124.
356. Cao C, Wang X, Yang N, Song X, Dong X. Recent advances of cancer chemodynamic therapy based on Fenton/Fenton-like chemistry. Chem Sci. 2022;13(4):863-89.
357. Lei G, Sun M, Cheng J, Ye R, Lu Z, Horbath A, et al. Radiotherapy promotes cuproptosis and synergizes with cuproptosis inducers to overcome tumor radioresistance. Cancer Cell. 2025;43(6):1076-1092.e5.
358. Li Y, Fang M, Xu Z, Li X. Tetrathiomolybdate as an old drug in a new use: As a chemotherapeutic sensitizer for non-small cell lung cancer. J Inorg Biochem. 2022;233:111865.
359. Xie L, Gong J, He Z, Zhang W, Wang H, Wu S, et al. A Copper-Manganese Based Nanocomposite Induces Cuproptosis and Potentiates Anti-Tumor Immune Responses. Small Weinh Bergstr Ger. 2025;21(12):e2412174.
360. Yang Z, Su W, Wei X, Pan Y, Xing M, Niu L, et al. Hypoxia inducible factor-1α drives cancer resistance to cuproptosis. Cancer Cell. 2025;43(5):937-954.e9.
361. Al Mamun A, Shao C, Geng P, Wang S, Xiao J. The Mechanism of Pyroptosis and Its Application Prospect in Diabetic Wound Healing. J Inflamm Res. 2024;17:1481-501.
362. Aachoui Y, Sagulenko V, Miao EA, Stacey KJ. Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection. Curr Opin Microbiol. 2013;16(3):319-26.
363. Qian Z, Zhao Y, Wan C, Deng Y, Zhuang Y, Xu Y, et al. Pyroptosis in the Initiation and Progression of Atherosclerosis. Front Pharmacol. 2021;12:652963.
364. Wang K, Sun Q, Zhong X, Zeng M, Zeng H, Shi X, et al. Structural Mechanism for GSDMD Targeting by Autoprocessed Caspases in Pyroptosis. Cell. 2020;180(5):941-955.e20.
365. Ni L, Chen D, Zhao Y, Ye R, Fang P. Unveiling the flames: macrophage pyroptosis and its crucial role in liver diseases. Front Immunol. 2024;15:1338125.
366. Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. Nature. 2014;514(7521):187-92.
367. Yang J, Jiang J. Gasdermins: a dual role in pyroptosis and tumor immunity. Front Immunol. 2024;15:1322468.
368. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature. 2015;526(7575):666-71.
369. Ouyang X, Zhou J, Lin L, Zhang Z, Luo S, Hu D. Pyroptosis, inflammasome, and gasdermins in tumor immunity. Innate Immun. 2023;29(1-2):3-13.
370. Zhang J, Zhou B, Sun R, Ai Y, Cheng K, Li F, et al. The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. Cell Res. 2021;31(9):980-97.
371. Liu M, Chen J, Sun Y. Mechanistic insights into elevated caspase-8 expression driving caspase-3 activation and Gasdermin E-dependent pyroptosis in Alzheimer's disease. Exp Cell Res. 2025;449(1):114594.
372. Zhang Z, Zhang Y, Xia S, Kong Q, Li S, Liu X, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature. 2020;579(7799):415-20.
373. You H-M, Wang L, Meng H-W, Huang C, Fang G-Y, Li J. Pyroptosis: shedding light on the mechanisms and links with cancers. Front Immunol. 2023;14:1290885.
374. Huang C, Li J, Zhang C. What role does pyroptosis play in cancer?. Mol Metab. 2022;65:101587.
375. Choi M, Shin J, Lee C-E, Chung J-Y, Kim M, Yan X, et al. Immunogenic cell death in cancer immunotherapy. BMB Rep. 2023;56(5):275-86.
376. Li L, Jiang M, Qi L, Wu Y, Song D, Gan J, et al. Pyroptosis, a new bridge to tumor immunity. Cancer Sci. 2021;112(10):3979-94.
377. Li X, Li X, Xiang C, Cao J, Guo J, Zhu S, et al. Starvation-induced phosphorylation activates gasdermin A to initiate pyroptosis. Cell Rep. 2024;43(9):114728.
378. Wang Q, Wang Y, Ding J, Wang C, Zhou X, Gao W, et al. A bioorthogonal system reveals antitumour immune function of pyroptosis. Nature. 2020;579(7799):421-6.
379. Zhang L, Bai H, Zhou J, Ye L, Gao L. Role of tumor cell pyroptosis in anti-tumor immunotherapy. Cell Insight. 2024;3(3):100153.
380. Lu X, Guo T, Zhang X. Pyroptosis in Cancer: Friend or Foe?. Cancers. 2021;13(14):3620.
381. Li M, Jiang P, Yang Y, Xiong L, Wei S, Wang J, et al. The role of pyroptosis and gasdermin family in tumor progression and immune microenvironment. Exp Hematol Oncol. 2023;12(1):103.
382. Wang L, Qin X, Liang J, Ge P. Induction of Pyroptosis: A Promising Strategy for Cancer Treatment. Front Oncol. 2021;11:635774.
383. Gao J, Qiu X, Xi G, Liu H, Zhang F, Lv T, et al. Downregulation of GSDMD attenuates tumor proliferation via the intrinsic mitochondrial apoptotic pathway and inhibition of EGFR/Akt signaling and predicts a good prognosis in non-small cell lung cancer. Oncol Rep. 2018;40(4):1971-84.

384. Hu Y, Liu Y, Zong L, Zhang W, Liu R, Xing Q, et al. The multifaceted roles of GSDME-mediated pyroptosis in cancer: therapeutic strategies and persisting obstacles. Cell Death Dis. 2023;14(12):836.
385. Liao X-X, Dai Y-Z, Zhao Y-Z, Nie K. Gasdermin E: A Prospective Target for Therapy of Diseases. Front Pharmacol. 2022;13:855828.
386. Kong Q, Zhang Z. Cancer-associated pyroptosis: A new license to kill tumor. Front Immunol. 2023;14:1082165.
387. Hu J, Pei W, Jiang M, Huang Y, Dong F, Jiang Z, et al. DFNA5 regulates immune cells infiltration and exhaustion. Cancer Cell Int. 2022;22(1):107.
388. Wang Y, Gao W, Shi X, Ding J, Liu W, He H, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. Nature. 2017;547(7661):99-103.
389. Tsuchiya K. Switching from Apoptosis to Pyroptosis: Gasdermin-Elicited Inflammation and Antitumor Immunity. Int J Mol Sci. 2021;22(1):426.
390. Moossavi M, Parsamanesh N, Bahrami A, Atkin SL, Sahebkar A. Role of the NLRP3 inflammasome in cancer. Mol Cancer. 2018;17(1):158.
391. Zhivaki D, Borriello F, Chow OA, Doran B, Fleming I, Theisen DJ, et al. Inflammasomes within Hyperactive Murine Dendritic Cells Stimulate Long-Lived T Cell-Mediated Anti-tumor Immunity. Cell Rep. 2020;33(7):108381.
392. Faria SS, Fernando AJ, de Lima VCC, Rossi AG, de Carvalho JMA, Magalhães KG. Induction of pyroptotic cell death as a potential tool for cancer treatment. J Inflamm Lond Engl. 2022;19(1):19.
393. Wu J, Wang L, Xu J. The role of pyroptosis in modulating the tumor immune microenvironment. Biomark Res. 2022;10(1):45.
394. Lu F, Zhao Y, Pang Y, Ji M, Sun Y, Wang H, et al. NLRP3 inflammasome upregulates PD-L1 expression and contributes to immune suppression in lymphoma. Cancer Lett. 2021;497:178-89.
395. Wu L, Lu H, Pan Y, Liu C, Wang J, Chen B, et al. The role of pyroptosis and its crosstalk with immune therapy in breast cancer. Front Immunol. 2022;13:973935.
396. van Deventer HW, Burgents JE, Wu QP, Woodford R-MT, Brickey WJ, Allen IC, et al. The inflammasome component NLRP3 impairs antitumor vaccine by enhancing the accumulation of tumor-associated myeloid-derived suppressor cells. Cancer Res. 2010;70(24):10161-9.
397. Wang B, Wang L, Shang R, Xie L. MDSC suppresses T cell antitumor immunity in CAC via GPNMB in a MyD88-dependent manner. Cancer Med. 2024;13(1):e6887.
398. Lillo S, Saleh M. Inflammasomes in Cancer Progression and Anti-Tumor Immunity. Front Cell Dev Biol. 2022;10:839041.
399. Kang JS, Bae SY, Kim HR, Kim YS, Kim DJ, Cho BJ, et al. Interleukin-18 increases metastasis and immune escape of stomach cancer via the downregulation of CD70 and maintenance of CD44. Carcinogenesis. 2009;30(12):1987-96.
400. Park S, Cheon S, Cho D. The dual effects of interleukin-18 in tumor progression. Cell Mol Immunol. 2007;4(5):329-35.
401. Huang H, Weng Y, Tian W, Lin X, Chen J, Luo L. Molecular mechanisms of pyroptosis and its role in anti-tumor immunity. Int J Biol Sci. 2023;19(13):4166-80.
402. Du T, Gao J, Li P, Wang Y, Qi Q, Liu X, et al. Pyroptosis, metabolism, and tumor immune microenvironment. Clin Transl Med. 2021;11(8):e492.
403. Arrè V, Scialpi R, Centonze M, Giannelli G, Scavo MP, Negro R. The 'speck'-tacular oversight of the NLRP3-pyroptosis pathway on gastrointestinal inflammatory diseases and tumorigenesis. J Biomed Sci. 2023;30(1):90.
404. Terme M, Ullrich E, Aymeric L, Meinhardt K, Desbois M, Delahaye N, et al. IL-18 Induces PD-1–Dependent Immunosuppression in Cancer. Cancer Res. 2011;71(16):5393-9.
405. Ji F, Shi C, Shu Z, Li Z. Nanomaterials Enhance Pyroptosis-Based Tumor Immunotherapy. Int J Nanomedicine. 2024;19:5545-79.
406. Novick D, Kim S, Kaplanski G, Dinarello CA. Interleukin-18, more than a Th1 cytokine. Semin Immunol. 2013;25(6):439-48.
407. Chao L, Zhang W, Feng Y, Gao P, Ma J. Pyroptosis: a new insight into intestinal inflammation and cancer. Front Immunol. 2024;15:1364911.
408. Zhang M, Dang P, Liu Y, Qiao B, Sun Z. Noncoding RNAs in pyroptosis and cancer progression: Effect, mechanism, and clinical application. Front Immunol. 2022;13:982040.
409. Wang W, Zhang L, Sun Z. Eliciting pyroptosis to fuel cancer immunotherapy: mechanisms and strategies. Cancer Biol Med. 2022;19(7):948-64.
410. Lee P-H, Yamamoto TN, Gurusamy D, Sukumar M, Yu Z, Hu-Li J, et al. Host conditioning with IL-1β improves the antitumor function of adoptively transferred T cells. J Exp Med. 2019;216(11):2619-34.
411. Urwanisch L, Luciano M, Horejs-Hoeck J. The NLRP3 Inflammasome and Its Role in the Pathogenicity of Leukemia. Int J Mol Sci. 2021;22(3):1271.
412. Sallman DA, List A. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. Blood. 2019;133(10):1039-48.
413. Xia X, Wang X, Cheng Z, Qin W, Lei L, Jiang J, et al. The role of pyroptosis in cancer: pro-cancer or pro-"host"? Cell Death Dis. 2019;10(9):650.
414. Li Y, Zhao R, Xiu Z, Yang X, Zhu Y, Han J, et al. Neobavaisoflavone induces pyroptosis of liver cancer cells via Tom20 sensing the activated ROS signal. Phytomedicine Int J Phytother Phytopharm. 2023;116:154869.
415. Ohashi K, Wang Z, Yang YM, Billet S, Tu W, Pimienta M, et al. NOD-like receptor C4 Inflammasome Regulates the Growth of Colon Cancer Liver Metastasis in NAFLD. Hepatol Baltim Md. 2019;70(5):1582-99.
416. Liu W, Peng J, Xiao M, Cai Y, Peng B, Zhang W, et al. The implication of pyroptosis in cancer immunology: Current advances and prospects. Genes Dis. 2023;10(6):2339-50.
417. Wang A, Wang Y, Du C, Yang H, Wang Z, Jin C, et al. Pyroptosis and the tumor immune microenvironment: A new battlefield in ovarian cancer treatment. Biochim Biophys Acta Rev Cancer. 2024;1879(2):189058.
418. Qi S, Wang Q, Zhang J, Liu Q, Li C. Pyroptosis and Its Role in the Modulation of Cancer Progression and Antitumor Immunity. Int J Mol Sci. 2022;23(18):10494.
419. Erkes DA, Cai W, Sanchez IM, Purwin TJ, Rogers C, Field CO, et al. Mutant BRAF and MEK Inhibitors Regulate the Tumor

Immune Microenvironment via Pyroptosis. Cancer Discov. 2020;10(2):254-69.
420. Li H, Yang T, Zhang J, Xue K, Ma X, Yu B, et al. Pyroptotic cell death: an emerging therapeutic opportunity for radiotherapy. Cell Death Discov. 2024;10(1):32.
421. Ringel-Scaia VM, Beitel-White N, Lorenzo MF, Brock RM, Huie KE, Coutermarsh-Ott S, et al. High-frequency irreversible electroporation is an effective tumor ablation strategy that induces immunologic cell death and promotes systemic anti-tumor immunity. EBioMedicine. 2019;44:112-25.
422. Fan J-X, Deng R-H, Wang H, Liu X-H, Wang X-N, Qin R, et al. Epigenetics-Based Tumor Cells Pyroptosis for Enhancing the Immunological Effect of Chemotherapeutic Nanocarriers. Nano Lett. 2019;19(11):8049-58.
423. Zhong Y-T, Qiu Z-W, Zhang K-Y, Lu Z-M, Li Z-F, Nie J-M, et al. Chemotherapeutics-enabled apoptosis-pyroptosis switch to trigger adaptive and innate immunity for metastatic breast cancer immunotherapy. Mater Today. 2025;83:263-83.
424. Wright SS, Kumari P, Fraile-Ágreda V, Wang C, Shivcharan S, Kappelhoff S, et al. Transplantation of gasdermin pores by extracellular vesicles propagates pyroptosis to bystander cells. Cell. 2025;188(2):280-291.e17.
425. Yin Q, Song S-Y, Bian Y, Wang Y, Deng A, Lv J, et al. Unlocking the potential of pyroptosis in tumor immunotherapy: a new horizon in cancer treatment. Front Immunol. 2024;15:1381778.
426. Xiao Y, Zhang T, Ma X, Yang Q-C, Yang L-L, Yang S-C, et al. Microenvironment-Responsive Prodrug-Induced Pyroptosis Boosts Cancer Immunotherapy. Adv Sci Weinh Baden-Wurtt Ger. 2021;8(24):e2101840.
427. Wang M, Wu M, Liu X, Shao S, Huang J, Liu B, et al. Pyroptosis Remodeling Tumor Microenvironment to Enhance Pancreatic Cancer Immunotherapy Driven by Membrane Anchoring Photosensitizer. Adv Sci Weinh Baden-Wurtt Ger. 2022;9(29):e2202914.
428. Gong L, Liu Y, Feng J, Xiao C, Liu C, Chen B, et al. An immune activator encapsulating PD-L1 siRNA for augmented immune checkpoint blockade immunotherapy through Zn2+ overload triggered pyroptosis. J Nanobiotechnology. 2025;23(1):447.
429. Li F, Zhang X-Q, Ho W, Tang M, Li Z, Bu L, et al. mRNA lipid nanoparticle-mediated pyroptosis sensitizes immunologically cold tumors to checkpoint immunotherapy. Nat Commun. 2023;14(1):4223.

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