Review

Tumor metabolism-ferroptosis pathway regulating tumor-associated macrophage polarization: Research progress and therapeutic prospects

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Abstract

Tumor metabolic reprogramming serves as a fundamental driver of malignancy, fueling cancer cell growth while reshaping the immune landscape through metabolite accumulation. Ferroptosis, an iron-dependent form of regulated cell death, is intricately linked to these metabolic shifts. In the tumor microenvironment, tumor-associated macrophages (TAMs) are pivotal in modulating immune evasion and therapeutic resistance based on their polarization states. Emerging evidence suggests that metabolic alterations can dictate TAM functional plasticity by intersecting with ferroptosis-related pathways. However, the precisely orchestrated mechanisms within the “tumor metabolism-ferroptosis-TAM” axis remain to be fully integrated. This article systematically reviews the progress of tumor metabolic reprogramming and its impact

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on ferroptosis and TAM polarization. We specifically focus on the molecular crosstalk by which metabolic-ferroptosis signaling drives macrophage phenotypic shifts and discuss potential combinatorial strategies targeting this regulatory axis. In addition, we address critical challenges regarding safety, patient stratification, and clinical translation. A comprehensive understanding of this interplay will offer novel theoretical frameworks and identify promising intervention targets for enhancing the efficacy of targeted immunotherapy.

Keywords: Ferroptosis, tumor metabolic reprogramming, tumor-associated macrophages, macrophage polarization, tumor microenvironment, immunotherapy

INTRODUCTION

The proliferation of malignant tumor cells necessitates metabolic reprogramming, typified by the Warburg effect, dysregulated lipid metabolism, and aberrant amino acid catabolism. Rather than merely fulfilling the bioenergetic and synthetic demands of neoplastic cells, this metabolic rewiring establishes nutrient gradients and localized acidosis that structurally alter the tumor microenvironment (TME)[1]. This microenvironment forms a “cold tumor” ecological niche through nutrient competition and accumulation of immunosuppressive metabolites, depleting effector immune cells, while immunosuppressive cells exhibit strong metabolic adaptability, thereby reinforcing the immunosuppressive environment[2]. Delineating the precise mechanisms by which metabolic aberrations orchestrate immune evasion remains an essential prerequisite for optimizing oncological interventions.

Concurrently, ferroptosis functions as a distinct form of regulated cell death (RCD) driven by iron-dependent lipid peroxidation[3]. The initiation of this pathway is contingent upon a shift in the equilibrium between iron homeostasis, lipid remodeling, and cellular antioxidant networks. Beyond executing direct cytotoxicity, ferroptosis modifies the immune microenvironment via the extrusion of damage-associated molecular patterns (DAMPs)[4]. Consequently, ferroptosis functions as a mechanistic

nexus intertwining metabolic alterations with immune remodeling, presenting a critical variable in assessing tumor immune heterogeneity.

TAMs represent the predominant immunoregulatory infiltrating cell population in the TME of most solid tumors. Subject to environmental plasticity, TAMs polarize between pro-inflammatory (M1-like) and pro-tumorigenic (M2-like) phenotypes depending on localized biochemical cues. In established malignancies, TME conditions predominantly facilitate an M2-like polarization, which subsequently supports angiogenesis, extracellular matrix remodeling, and the restriction of cytotoxic T-cell functionality[5]. Current data suggest that tumor-derived metabolites function as primary signaling conduits regulating this polarization. Thus, targeting TAM metabolism or harnessing ferroptosis to reverse immunosuppression and overcome therapeutic resistance represents a emerging therapeutic strategy.

Although extant literature has independently characterized tumor metabolic reprogramming, the mechanisms of ferroptosis, and the immunometabolic dynamics of TAMs, a systematic and critical synthesis of their tripartite interaction remains structurally incomplete. Specifically, the regulatory axis of “tumor metabolism-ferroptosis-TAM polarization” requires critical evaluation, as the exact parameters dictating whether ferroptosis triggers immunogenic activation or paradoxically induces inflammation-associated immunosuppression remain poorly defined. Furthermore, the mechanistic variability of this axis across distinct histological subtypes introduces complexities that challenge its universal clinical applicability. To address this paradigm, we searched the PubMed database for the latest advances in the research fields of ferroptosis, TAMs, tumor immune microenvironment, and immunometabolism. This review systematically dissects the aforementioned axis. We evaluate how specific metabolic perturbations dictate ferroptotic susceptibility and critically appraise the resulting immunological consequences, focusing on the capacity of specific metabolites, ferroptosis regulators, and signaling modalities to mediate TAM reprogramming. Finally, we analyze the translational feasibility of targeting this axis,

evaluating the pharmacokinetic and physiological barriers that currently impede its integration into clinical practice.

INTERPLAY BETWEEN TUMOR METABOLIC REPROGRAMMING AND FERROPTOSIS

The execution of ferroptosis is inherently linked to metabolic dysregulation, provided that the accumulation of lipid peroxides exceeds the threshold of cellular homeostatic buffering capacity. Consequently, the specific metabolic configurations of neoplastic cells determine their baseline susceptibility to ferroptotic induction.

Aberrant glucose metabolism and ferroptosis

Despite sufficient oxygen availability, malignant cells frequently maintain continuous lactate extrusion via aerobic glycolysis. In neoplastic populations overexpressing SLC7A11, maintaining cystine uptake necessitates substantial glucose consumption to support NADPH biosynthesis via the pentose phosphate pathway. Although this adaptation sustains glutathione (GSH) synthesis, it inadvertently establishes a strict glucose dependency[6]. Consequently, intense intercellular glucose competition within the TME limits NADPH regeneration rates. This microenvironmental deprivation, combined with metabolic acidosis, destabilizes redox equilibrium, facilitating the lipid peroxidation cascade when reactive oxygen species (ROS) accumulation surpasses antioxidant thresholds[7]. Evidence indicates that restricting glucose transport or inhibiting key glycolytic enzymes compromises tumor cells' redox buffering capacity, thereby lowering the threshold for ferroptosis induction[8].

Lipid metabolic reprogramming and ferroptosis

Lipid metabolic rewiring functions as a primary determinant of ferroptotic vulnerability. While neoplastic cells frequently upregulate *de novo* fatty acid synthesis, polyunsaturated fatty acids (PUFAs) (the principal substrates for oxidation) determine cellular ferroptosis sensitivity based on their integration rate into cellular phospholipids[9]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) regulates

the esterification of PUFAs into membrane phospholipids, indicating that its relative expression alters the probability of ferroptotic lipid damage[10]. Conversely, the incorporation of exogenous monounsaturated fatty acids (MUFAs) or the upregulation of stearoyl-CoA desaturase 1 (SCD1) modulates membrane lipidomic profiles, elevating the MUFA/PUFA ratio and establishing a biochemical resistance mechanism that impedes lipid peroxide propagation[11].

Iron dyshomeostasis and ferroptosis

Disruption of cellular iron homeostasis is a core driver and key permissive factor for ferroptosis. Tumor cells frequently exhibit elevated iron reliance, increasing iron influx via transferrin receptor (TfR1) upregulation while restricting ferritin-mediated sequestration. This imbalance generates an expanded intracellular labile iron pool (Fe^{2+})[12]. The availability of free Fe^{2+} catalyzes lipid peroxidation via Fenton chemistry. In scenarios where endogenous antioxidant defenses are compromised, the accumulation of these oxidized lipids results in structural membrane destabilization, facilitating ferroptotic cell death[13].

MOLECULAR MECHANISMS OF FERROPTOSIS AND ITS DICHOTOMOUS ROLE IN TUMOR IMMUNOMODULATION

Ferroptosis operates under the regulation of distinct intracellular defense networks. The activation specificities of these networks introduce dichotomous effects on tumor immunity, indicating that therapeutic efficacy depends on resolving the temporal and spatial dynamics of these immunomodulatory signals.

Distinctive hallmarks of ferroptosis

Ferroptosis represents a regulated mechanism distinct from apoptosis, necroptosis, and autophagy regarding morphological, biochemical, and genetic criteria[14]. Its pathway relies on the accumulation of iron-dependent lipid peroxides exceeding cellular tolerance limits—a process subject to inhibition by specific iron chelators or radical-trapping antioxidants[15]. Morphologically, it involves condensed mitochondrial

membrane densities and diminished cristae; biochemically, it requires iron-dependent ROS propagation and specific oxidized phospholipids[3]. The cellular response to this process is mediated by parallel antioxidant networks.

Principal intracellular ferroptosis defense networks

There are three core ferroptosis defense pathways within cells:

First, the System Xc^--GSH-GPX4 axis, where the cystine/glutamate antiporter regulates cystine import for GSH biosynthesis. Glutathione Peroxidase 4 (GPX4) utilizes GSH to reduce phospholipid hydroperoxides to corresponding lipid alcohols, functioning as the primary mechanism for maintaining membrane integrity[16].

Second, the FSP1-CoQ10 system, which operates independently in various membrane compartments. FSP1 interfaces with membrane-embedded CoQ10 to generate an extramitochondrial antioxidant rheostat, scavenging lipid peroxyl radicals[17].

Third, the GCH1-BH4 signaling node, which synthesizes endogenous antioxidants (BH4 and BH2) and specifically shields di-polyunsaturated fatty acid (di-PUFA)-tailed phospholipids from oxidative degradation, thus modifying the lipidome[18].

The dependency on these respective networks is highly lineage-specific and subject to microenvironmental pressure. This heterogeneity accounts for the differential sensitivities between neoplastic and immune populations under identical metabolic stress, highlighting the necessity for calibrated therapeutic targeting.

Ferroptosis as a conditional regulator of tumor immunity

The initiation of ferroptosis is coupled with the disruption of redox homeostasis, meaning tumor cells undergo regulated ferroptotic cell death rather than passively undergoing cytolysis[19]. Thus, ferroptosis modifies tumor immunity through inherently conflicting mechanisms.

Initially, early-stage ferroptotic cancer cells release specific DAMPs capable of initiating immunogenic responses[20]. However, this effect is frequently counteracted as surviving neoplastic populations develop adaptive resistance through SLC7A11 up-regulation, NRF2 activation, or lipidomic restructuring, thereby maintaining tumor viability under persistent therapeutic pressure[21].

Concurrently, the ferroptotic process generates secondary signaling cues. The release of oxidized phospholipids and metabolic intermediates like extracellular glutamate establishes a paracrine gradient that conditionally activates or suppresses adjacent leukocytes depending on localized concentrations[22]. In the context of the TME, these specific chemical outputs directly influence the polarization of infiltrating TAMs, complicating the assumption that ferroptosis acts uniformly as a tumor-suppressive event.

THE CONDITIONAL REGULATORY NEXUS: TUMOR METABOLISM, FERROPTOSIS, AND TAM PHENOTYPIC REPROGRAMMING

Metabolic variance within the TME interfaces continuously with the ferroptotic signaling cascade, collectively dictating the phenotypic polarization of TAMs. Rather than operating as isolated occurrences, this remodeling relies on a tripartite regulatory structure. The direct modulation of macrophage ferroptotic thresholds by local metabolites, the intrinsic expression dependency of ferroptosis-regulating enzymes, and the paracrine re-education of macrophages by signaling cues extruded from ferroptotic neoplastic cells[23]. These mechanisms form an integrated, context-dependent network, demonstrating that signals derived from dying cells can structurally redefine the local immune topography, provided specific metabolic constraints are met. [Figure 1]

Metabolic drivers of the ferroptosis-polarization axis

The epigenetic and transcriptional modulation by lactate

Lactate, proceeding from aerobic glycolysis (the Warburg effect), accumulates sequentially within the TME, functioning less as a passive byproduct and more as a

primary structural variable regulating TAM polarization[24]. Upon being internalized via MCT-mediated H^+/lactate symport, lactate prevents the degradation of hypoxia-inducible factor-1α (HIF-1α), stabilizing its functional concentration. This stabilization subsequently transactivates specific M2-associated markers (e.g., *Arg1*, *Fizz1*), directing TAMs toward an immunoregulatory configuration. This structural shift ultimately supports VEGF-dependent neoangiogenesis and promotes neoplastic proliferation via ARG1-mediated pathways[24].

Concurrently, local lactate concentrations alter the baseline sensitivity of TAMs to ferroptotic execution. Elevated lactate levels precipitate targeted epigenetic modifications, specifically driving histone H3K18 lactylation, which actively correlates with an acquired ferroptosis-resistant phenotype in exposed macrophages[25]. Furthermore, adjusting to lactate-rich conditions necessitates alternative metabolic processing, which potentially depletes requisite redox cofactors, including NADPH. This competitive expenditure neutralizes the baseline antioxidant buffering capacity of macrophages, lowering their defense threshold against sporadic lipid peroxidation events.

Lipid metabolic reprogramming and ferroptotic vulnerability

The spatial rewiring of lipid metabolism dictates tumor immune circumvention strategies. Specifically, the processing efficiency and integration rate of PUFAs stringently dictate cellular execution thresholds for ferroptosis[9]. Evidence corroborates that ambient PUFA availability alters macrophage survival parameters, primarily because PUFAs function as the obligate structural substrates for iron-dependent peroxidation. The efficiency of their oxidative modification establishes the rate-limiting step for this localized cell death modality[26]. Consequently, within the hypoxic and nutrient-restricted TME, intercellular competition for lipid precursors continually forces macrophages into severe metabolic adaptations. This environmental pressure structurally coerces their polarization trajectory, adjusting their corresponding

immunological capabilities and dictating their susceptibility to consequent ferroptotic stress.

Direct intrinsic regulation of TAM polarization by ferroptosis executors

The intracellular transcriptional levels of core ferroptosis parameters (GPX4 and ACSL4) functionally adjudicate the survival and polarization potential of TAMs. Rather than operating uniformly, these enzymes exhibit distinct activity kinetics among disparate macrophage phenotypes.

Ferroptosis regulators modulate macrophage homeostasis

GPX4 functions as the primary enzymatic defense against lipid peroxidation. Within macrophages, maintaining functional GPX4 levels is obligatory for preserving general cellular homeostasis[27]. However, under specific inflammatory contingencies, the conditional restriction of GPX4 impairs antioxidant defenses, forcing macrophages to adopt a pro-inflammatory (M1-like) phenotype characterized by the sustained extrusion of cytokine mediators[28].

Conversely, ACSL4 governs the esterification of activating PUFAs into membrane phospholipids, presenting a direct variable for ferroptotic susceptibility. Under the constraints of an inflammatory microenvironment, upregulated ACSL4 actively drives lipid peroxidation within macrophages. This pathway drives M1-type repolarization, linking sustained, localized inflammation with ACSL4-mediated lipid processing[29]. Operating together, this expression axis establishes a regulatory feedback loop managing local inflammatory tone.

System Xc^--mediated metabolic competition

Neoplastic cells take up cystine via System Xc^- and excrete glutamate. The process induces marked local cystine depletion coupled with glutamate accumulation. Pharmacological interventions (e.g., Gigantol targeting SLC7A11) successfully restrict tumor cystine influx, thereby exhausting intracellular GSH reserves and triggering

tumor ferroptosis[30]. However, this nutritional disruption generates secondary systemic consequences. This metabolic "tug-of-war" deprives adjacent macrophages of the environmental cystine obligatory for their own GSH biosynthesis. Confronted with this limitation, TAMs must shift their functional parameters, frequently increasing their vulnerability to oxidative stress, which subsequently consolidates the prevailing immunosuppressive milieu[31].

The IGSF9-IL-6/STAT3 axis and the senescence phenotype

Beyond direct oxidative distress, tumor-derived structures dictate alternative macrophage states. Neoplastic immunoglobulin superfamily member 9 (IGSF9) dynamically crosslinks with TMUB1 presented on the TAM surface, accelerating the IL-6/STAT3 signaling cascade to instigate a senescence-associated secretory phenotype (SASP)[32]. This acquired structural senescence drives a functional atrophy of normal phagocytic capacity while simultaneously promoting the output of specific immunoregulatory factors. These secreted components paralyze local T effector cell proliferation and activation, defining the primary mechanism by which IGSF9 secures immune circumvention[32].

TME remodeling via ferroptotic neoplastic cues

Tumor cells undergoing ferroptotic disruption continually extrude a distinct sequence of DAMPs and oxidized lipid mediators. However, assuming these components function solely as immunological activators ignores their capacity to inadvertently drive immunosuppression depending on receptor interaction and microenvironmental conditions.

Contextual DAMP signaling and paracrine immunosuppression

During continuous ferroptosis, compromised cells release established DAMPs, including high mobility group box 1 (HMGB1) and specific oxidized phospholipids (e.g., SAPE-OOH). Upon ligating TLR2 and RAGE receptors situated on TAMs, these mediators stimulate the NF-κB transcription pathway. Rather than uniformly triggering

anti-tumor immunity, this activation frequently directs TAMs toward a regulatory (Reg-TAM) or classical M2 state, utilizing oxidized phospholipids as "eat-me" resolution signals[33]. These repolarized TAMs subsequently upregulate ARG1 and IL-10, enacting organized suppression of $CD8^+$ T-cell efficacy[33].

Simultaneously, mutated KRASG12D (frequently associated with autophagy-dependent ferroptosis) becomes actively compartmentalized into exosomes prior to extracellular shedding[34]. Following exosomal internalization by TAMs, KRASG12D initiates localized STAT3 phosphorylation, transactivating critical fatty acid oxidation (FAO) genes (e.g., CPT1A, ACADM). This metabolic recalibration further establishes the M2 phenotype[34]. Consequently, ferroptotic events within resident myeloid populations (including PMN-MDSCs) generate PGE2, establishing a reinforcing suppression loop whereby initial cell-death events precipitate localized immune paralysis rather than tumor resolution[35].

The dichotomous role of oxidized phospholipids

Evaluating the role of oxidized phospholipids (e.g., oxidized phosphatidylethanolamine) demands recognizing their dichotomous physiological capability. When recognized by scavenger receptors like CD36, these moieties precipitate metabolic shifts that, under precise conditions, direct TAMs toward an M1 or Mox inflammatory phenotype, marked by NF-κB engagement and localized IL-1β liberation[36].

The trajectory of TAM remodeling following ferroptosis remains heavily contingent upon multiple intersecting variables: the absolute concentration of released lipid signals, the spatial cytokine topography (baseline interferon-γ [IFN-γ] availability), and the concurrent deployment of interventional therapies. For instance, when synchronized with immune checkpoint blockade (e.g., anti-PD-1 modalities), pro-ferroptotic interventions facilitate heightened tumor immunogenicity, prompting T cells to elaborate IFN-γ. Provided that this specific cytokine threshold is met, IFN-γ synergizes with extruded DAMPs to overcome intrinsic M2 tendencies, coercing a functional M1

shift to restore $CD8^+$ cytotoxicity[37]. Without this external recalibration, ferroptosis alone may inadvertently consolidate tumor tolerance.

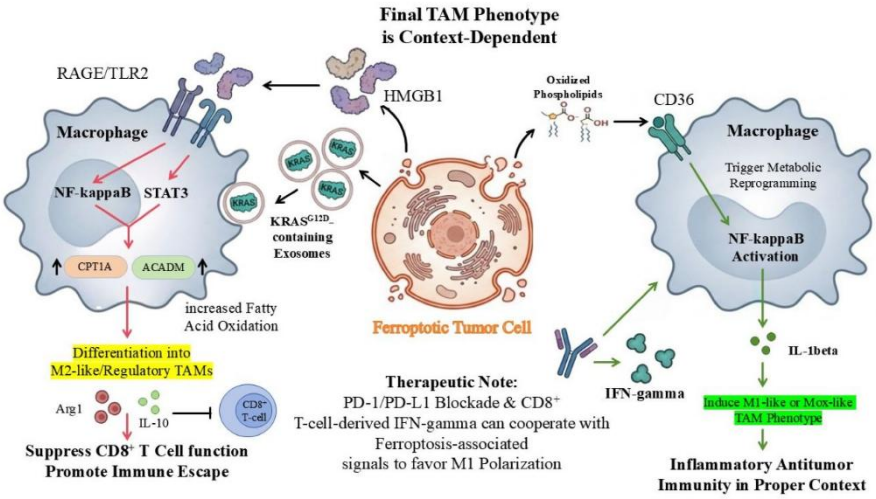

Figure 1. Ferroptotic tumor cells release exosomes harboring mutant KRAS (KRASG12D) and oxidized phospholipids (OxPLs). These two classes of signaling molecules exert context-dependent regulatory effects on the polarization of tumor-associated macrophages (TAMs) via two distinct functional pathways:

Left pathway (immunosuppressive arm)

Upon internalization by macrophages, KRAS-bearing exosomes activate the NF-κB/STAT3 signaling cascade, upregulate the expression of key fatty acid oxidation (FAO)-related enzymes (CPT1A and ACADM), and drive macrophage differentiation toward an M2-like/regulatory phenotype. These polarized TAMs are characterized by high expression of Arg1 and IL-10, which suppress the effector function of $CD8^+$ T cells and thereby promote tumor immune evasion.

Right pathway (anti-tumor immunity arm)

Oxidized phospholipids are recognized by macrophages via the CD36 receptor, which triggers metabolic reprogramming and NF-κB activation, induces IL-1β secretion, and drives macrophage polarization into an M1-like/Mox-like phenotype, thus eliciting an inflammatory anti-tumor immune response. Furthermore, PD-1/PD-L1 blockade,

together with interferon-γ (IFN-γ) secreted by $CD8^+$ T cells, can synergize with ferroptotic signals to further skew macrophage polarization toward the pro-inflammatory M1 phenotype.

Histotype-specific heterogeneity of the regulatory axis

The topological network composed of metabolite availability, intrinsic enzyme dependence, and extracellular signaling gradients forms the operational "tumor metabolism-ferroptosis-TAM" axis. Nevertheless, applying this model universally overlooks pronounced histotype-specific heterogeneity. Tumors derived from distinct ontogenetic origins maintain unique metabolic setpoints: Hepatocellular Carcinoma (HCC) dictates baseline activity through hyper-dysregulated lipid restructuring, whereas Pancreatic Ductal Adenocarcinoma (PDAC) operates on glycolytic dominance coupled with persistent lactate saturation[38,39]. These fundamental disparities establish widely divergent ferroptotic resistance thresholds prior to any pharmacological intervention.

Concurrently, the derivation pattern of TAM populations further dictates mechanistic susceptibility. In Glioblastoma (GBM), the TAM compartment involves dual ontogeny: sessile brain-resident microglia integrating via LOX signals, countered by peripheral monocytes recruited via tumor-derived CCN1[2]. The differing hypoxic exposure histories and cytokine proximities associated with these differing ontogenies strictly restrict how each subset responds to induced metabolic stress. Similarly, breast carcinoma models demonstrate that spatially localized glycolytic variance precisely correlates with regional variations in M2-macrophage density[40].

Consequently, presuming uniform efficacy for generalized pro-ferroptotic strategies contradicts the inherent metabolic diversity of solid tumors. Clinical implementation demands precise pretreatment stratification detailing the tumor's distinct lipidomic status and the localized TAM polarization spectrum. Calibrating ferroptosis induction alongside agents targeting discrete TAM signaling parameters remains a rigorous

prerequisite for circumventing the functional limitations of existing monotherapies and securing durable combinatory responses[41]. [Table 1]

Table 1. Main components of the tumor metabolism-ferroptosis-TAM polarization axis.

Component	Main description in this review	Related effect on TAMs
Tumor metabolic reprogramming	Malignant proliferation is associated with the Warburg effect, dysregulated lipid fluxes, and aberrant amino acid catabolism. These changes establish nutrient gradients and localized acidosis in the TME.	These alterations shape an immunosuppressive TME, which impairs the antitumor capacity of effector immune cells and drives TAM polarization towards an immunosuppressive phenotype.
Local metabolites	Local metabolites directly modulate macrophage ferroptotic thresholds.	They contribute to the phenotypic polarization of TAMs in a context-dependent manner.
Ferroptosis-regulating enzymes	GPX4 functions as a primary enzymatic defense against lipid peroxidation, whereas ACSL4 governs the esterification of activating PUFAs into membrane phospholipids.	Functional GPX4 helps maintain macrophage homeostasis. Under inflammatory conditions, GPX4 restriction may promote a pro-inflammatory M1-like phenotype, while ACSL4

		affects ferroptotic susceptibility.
Cystine and GSH	Nutritional disruption can exhaust intracellular GSH reserves and induce tumor ferroptosis. This nutritional disruption also deprives adjacent macrophages of environmental cystine required for GSH biosynthesis.	TAMs exhibit increased vulnerability to oxidative stress, which may consolidate the immunosuppressive milieu.
Ferroptotic neoplastic cues	Ferroptotic tumor cells extrude DAMPs and oxidized lipid mediators.	These signals may act as immunological activators but can also drive immunosuppression depending on receptor interaction and microenvironmental conditions.
IGSF9-IL-6/STAT3 axis	Tumor-derived IGSF9 crosslinks with TMUB1 on the TAM surface and accelerates the IL-6/STAT3 signaling cascade.	This induces SASP, reduces normal phagocytic capacity, promotes immunoregulatory factors, and inhibits local T effector cell proliferation and activation.

TAM: Tumor-Associated Macrophages; GPX4: Glutathione Peroxidase 4; SLC7A11: Solute Carrier Family 7 Member 11; GSH: Glutathione; DAMPs: Damage-Associated Molecular Patterns; HIF-1α:

Hypoxia-Inducible Factor-1α; NF-κB: Nuclear Factor kappa B; STAT3: Signal Transducer and Activator of Transcription 3.

THERAPEUTIC INTERVENTIONS TARGETING THE "tumor metabolism-ferroptosis-TAM reprogramming" AXIS

Strategies evaluating this regulatory axis suggest theoretical utility for redefining TME interactions. However, the objective of precipitating tumor-specific ferroptosis while avoiding immunoregulatory interference relies heavily on maintaining rigorous target specificity. [Figure 2]

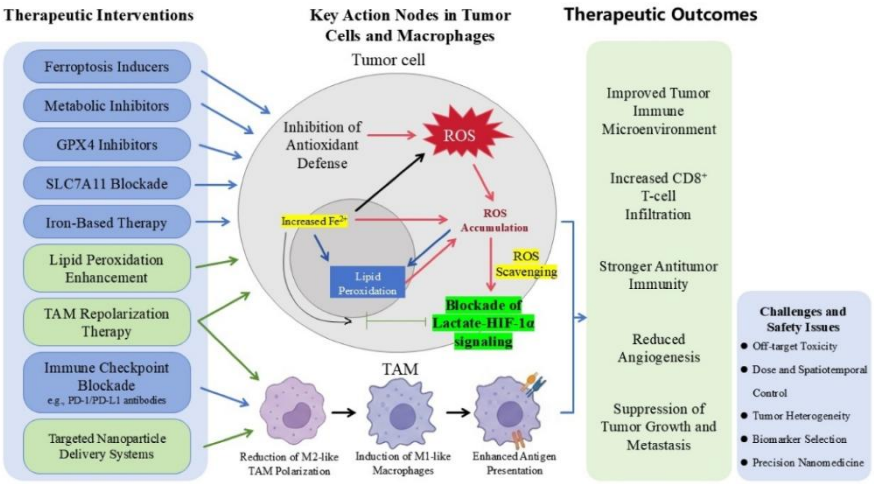

Figure 2. This figure depicts the mechanisms of action and corresponding therapeutic outcomes of multiple therapeutic interventions, including ferroptosis inducers, metabolic inhibitors, GPX4/SLC7A11 inhibitors, iron-based therapies, immune checkpoint blockade (ICB), and targeted nano-delivery systems, following their delivery into the tumor microenvironment (TME). TAM, ROS,

Pharmacological interventions and efficacy bottlenecks

Current ferroptosis inducers (FINs) typically utilize three mechanisms: (1) System Xc^- antagonism, (2) direct GPX4 inhibition, and (3) indirect orchestrators (e.g., Fenton reaction manipulation). While *in vitro* applications demonstrate efficient cytolysis, their clinical translation is challenged by critical limitations[42]. First, FINs display

substantive pharmacokinetic restrictions, specifically regarding the metabolic instability and aqueous limits of agents like erastin[42]. Second, the non-specific induction of lipid peroxidation corresponds to documented systemic toxicities in the central nervous system and renal parenchyma[43]. Third, neoplastic adaptation to FIN exposure frequently involves upregulation of compensatory mechanisms including the FSP1-CoQ10 system or SCD1 over-expression combined with reduced PUFA integration, mathematically diminishing susceptibility over successive treatment cycles[17,42].

Contextual modulations with immune checkpoint blockade

The simultaneous application of FINs with immune checkpoint inhibitors (ICIs) seeks to link adaptive immunity activation with cytolytic ferroptosis. Mechanistically, ICI-stimulated $CD8^+$ T cells release IFN-γ, which systematically represses SLC3A2 and SLC7A11 transcription, theoretically compounding lipid peroxidation vulnerabilities[44]. Preclinical melanoma models demonstrate numerical tumor suppression compared to monotherapies. However, this synergy assumes that ferroptosis-derived DAMPs act preferentially to sustain anti-tumor immunity without triggering compensatory M2 polarization[44].

Furthermore, within untreated niches, M2-TAMs transfer specific metabolites like taurine to tumor cells, which subsequently limits oxidative collapse via LXRα/SCD1 activation[45]. Establishing an effective FIN/ICI response requires specific disruption of this pathway to favor M1-like transitions[46]. However, this objective remains complicated by the intrinsic dichotomy of the immune response: lipid damage within activated $CD8^+$/NK cells themselves establishes secondary immunosuppressive boundaries[22]. Current developmental strategies propose targeted nanomedicine platforms to isolate these variables[33,47]. Early evidence involving attenuated tumoral SLC3A2 expression in patients responsive to nivolumab provides initial correlations[44], yet achieving reliable clinical modulation remains contingent upon rigorous patient stratification.

Systemic safety and translational challenges

Translating these combined paradigms entails confronting the aforementioned dual-effect paradox: inducing sufficient systemic lipid dysregulation for tumor cytolysis without simultaneously paralyzing infiltrating leukocyte populations or inducing hyperinflammatory pathologies[35,48]. Variations in baseline tumor lipid composition signify that lipid-enriched models (e.g., HCC) may demonstrate sensitivity, while tumors lacking sufficient PUFA densities (e.g., specific gliomas) inherently resist treatment due to substrate limitation alone[49]. Resolving these issues necessitates the deployment of targeted nanocarriers to isolate the intervention alongside rigorously validated predictive biomarkers (e.g., intracellular ferritin, 4-hydroxynonenal, or the ACSL4/GPX4 transcriptomic ratio)[49]. At present, the reliance on these proposed biomarkers requires rigorous multivariable prospective validation before stratifying clinical cohorts.

CONCLUSION

Tumor metabolic reprogramming structurally establishes the necessary biochemical conditions for subsequent ferroptosis signaling. The ensuing ferroptotic progression interlinks with expelled secondary molecular cues to conditionally regulate TAM polarization depending on existing microenvironmental gradients, highlighting a mechanistic explanation for variable therapeutic sensitivities[23]. Validating the “tumor metabolism-ferroptosis-TAM polarization” axis acknowledges significant histotype-specific heterogeneity, indicating that combinatorial therapeutic strategies must account for highly disparate baseline metabolic profiles rather than assuming universal applicability.

Currently, the literature structurally derives from preclinical murine models and *in vitro* conditions, exhibiting a deficit of human *in situ* validation. The understanding of spatial interactions mapping ferroptotic events directly to immune modifications remains fundamentally incomplete. Progressive resolutions to this investigative gap

require incorporating high-dimensional evaluation modalities, such as spatial transcriptomics and single-cell RNA sequencing, to rigorously establish localized concentration thresholds across actual human TMEs[50]. Concurrently, addressing the delivery and distribution limitations of existing FIN compounds is a critical priority to advance their clinical translation. Ultimately, ascertaining whether ferroptosis acts as a reliable clinical adjunct hinges upon empirical confirmation of systemic safety and validated pharmacological stratification, without which the broader integration of combinatory "ferroptosis-immunotherapy" regimens remains conjectural.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and framework design of the review, literature retrieval, screening and systematic collation of relevant studies, evidence summary, mechanistic analysis, figure production, and original manuscript drafting: HC.H;

Participated in study conception, literature organization and mechanistic analysis, made substantial contributions to content supplementation, manuscript revision and polishing, and revised and approved the manuscript: YQ.M.

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Consent for publication

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