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Tumor Microenvironment REVIEW

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Iron-based materials for sequential tumor microenvironment reprogramming: From mechanical decompression to immune remodeling

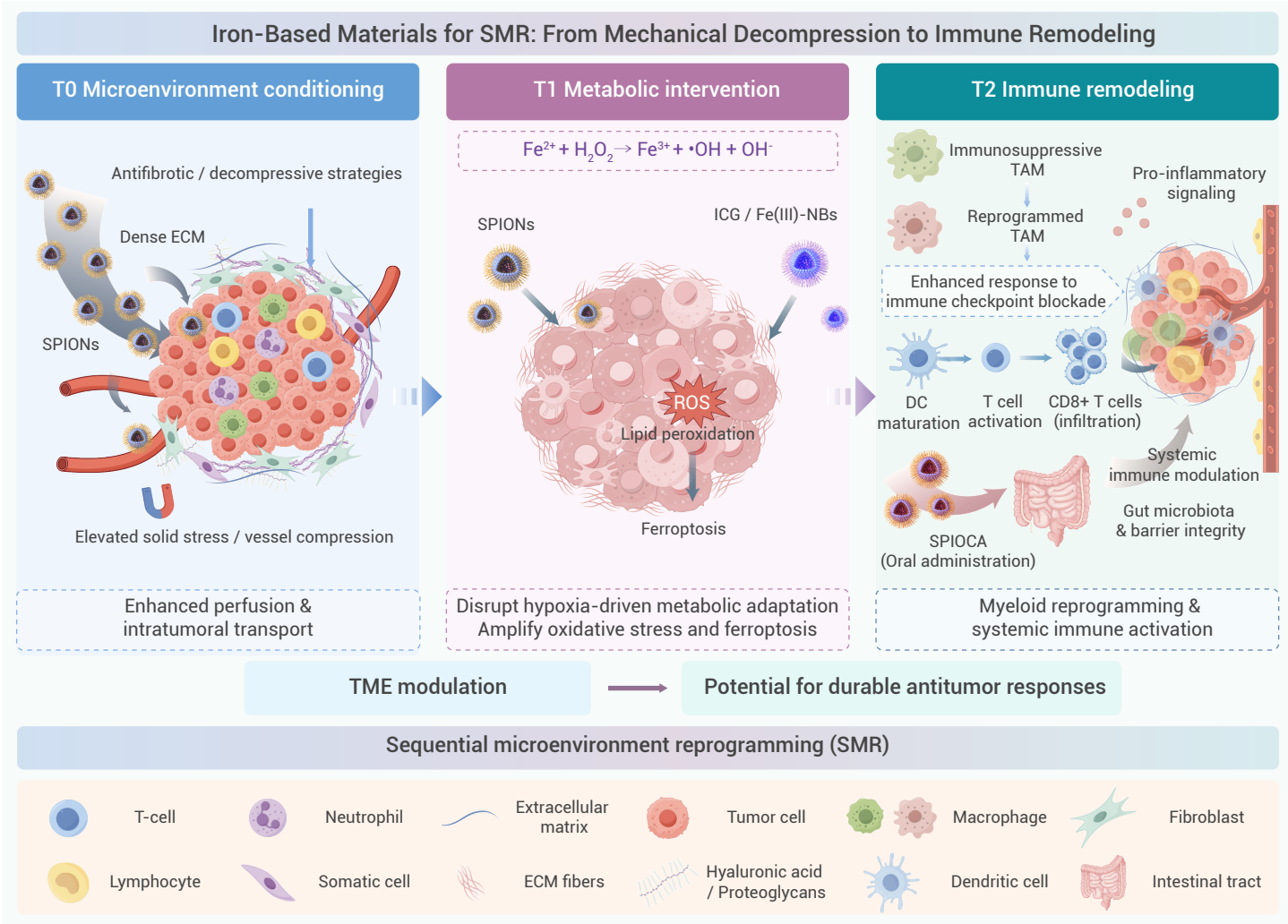
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The tumor microenvironment creates physical, metabolic, and immune barriers that limit cancer therapy.
- Iron-based materials offer magnetic, catalytic, and immune-regulating functions to address these barriers.
- Sequential microenvironment reprogramming (SMR) links three stages, from transport to immune remodeling.
- Rather than following a fixed sequence, SMR guides interventions based on biological responses.
- Its clinical potential requires reliable biomarkers, patient stratification, and rigorous validation.

REVIEW Tumor Microenvironment

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Iron-based materials for sequential tumor microenvironment reprogramming: From mechanical decompression to immune remodeling

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The tumor microenvironment (TME) is a dynamic ecosystem in which abnormal vasculature, stromal fibrosis, metabolic adaptation, and immune suppression collectively undermine the effectiveness of cancer therapy. Although iron-based materials have traditionally been developed as imaging agents or drug carriers, their magnetic responsiveness, catalytic activity, and immunomodulatory properties now provide opportunities to intervene in multiple components of the TME. We adapt and formalize sequential microenvironment reprogramming (SMR) as a framework that integrates the functions of iron-based materials across three interconnected intervention tiers (T0–T2). T0 represents baseline microenvironment conditioning, improving perfusion and intratumoral transport through magnetically assisted delivery together with antifibrotic or decompressive strategies. This creates a more permissive environment for T1, in which iron-catalyzed redox reactions and ferroptosis are exploited to disrupt tumor metabolic adaptation. T2 extends these local effects toward myeloid remodeling and regional immune activation to support more durable antitumor responses. SMR provides a framework for interpreting current evidence and identifying stage-specific therapeutic opportunities. Transitions between intervention tiers are guided by biological prerequisites rather than a fixed treatment sequence. We discuss the major challenges that remain, including biomarker-guided stage switching, patient stratification, translational feasibility, and the need for rigorous experimental validation of this staged therapeutic strategy.

INTRODUCTION

For decades, improving intratumoral drug delivery has been a central objective of cancer nanomedicine. Despite substantial advances in nanoparticle design, clinical translation has remained disappointing.[1,2] A major conceptual foundation of cancer nanomedicine was established in 1986, when *Yasuhiro Matsumura* and *Hiroshi Maeda*[3] first described the phenomenon that later became known as the enhanced permeability and retention (EPR) effect, establishing the physiological basis for the preferential accumulation of macromolecules and nanoparticles in solid tumors. Over the following decade, research focused primarily on enhancing tumor accumulation through active targeting and stimuli-responsive delivery, leading to the rapid development of liposomal, polymeric, and inorganic nanoplatforms.[4] However, in 2016, *Wilhelm* and colleagues reported that the median tumor accumulation of intravenously administered nanoparticles was only 0.7% of the injected dose, highlighting that the major obstacle to clinical translation lies not only in nanoparticle design but also in the dynamic and adaptive nature of the TME.[5] This finding underscores that multiple biological barriers continuously restrict nanoparticle transport and therapeutic efficacy.

Therapeutic resistance within the TME arises from multiple, interconnected biological barriers. Vascular abnormalities are among the earliest obstacles to effective therapy. Tumor vessels are structurally irregular, excessively permeable, and poorly covered by mural cells, leading to heterogeneous perfusion and elevated interstitial fluid pressure (IFP).[6,7] Jain's vascular normalization hypothesis proposed that antiangiogenic therapy can transiently restore vascular function, although this therapeutic window is often narrow and short-lived.[8] Beyond the vasculature, stromal remodeling limits drug transport. Cancer-associated fibroblasts (CAFs) and excessive extracellular matrix (ECM) deposition increase tissue stiffness and solid stress, which not only compress blood vessels but also promote malignant progression through mechanotransduction signaling.[9-11] These physical barriers are accompanied by profound metabolic adaptation. Hypoxia activates HIF-dependent transcriptional programs that enhance glycolysis, lactate production, and therapeutic tolerance.[12,13] Metabolic reprogramming is now recognized as a hallmark of cancer, extending beyond tumor cells to stromal and immune compartments through altered fatty acid and nutrient metabolism.[14,15] Such metabolic changes also reshape the immune landscape. An acidic, lactate-rich microenvironment suppresses the activity of effector T cells and natural killer (NK) cells while promoting immunosuppressive phenotypes in myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs).[16,17] Consistent with this concept, the tumor immune microenvironment (TIME) framework emphasizes that immune-cell composition and spatial organization are major determinants of therapeutic response.[18]

These barriers do not operate in isolation. Fibrosis compresses the tumor vasculature, impaired perfusion exacerbates hypoxia, and hypoxia further promotes extracellular matrix remodeling and immune suppression, creating a self-reinforcing cycle that progressively limits therapeutic access.[19] This interdependence has gradually reshaped the goals of cancer nanomedicine. Improving nanoparticle delivery alone is unlikely to produce durable therapeutic benefit unless the underlying microenvironment that drives adaptive resistance is also addressed. As a result, increasing attention has shifted from passive drug delivery toward active modulation of the TME. The key question is no longer simply how to enhance drug accumulation, but how to restore transport, disrupt metabolic adaptation, and create conditions that support sustained antitumor immunity.[20,21] Recent studies suggest that nanomedicine may offer benefits beyond increasing drug exposure. Remodeling the local tumor microenvironment may create a therapeutic window that enhances subsequent immunotherapy.[22]

Against this background, this Review adapts and formalizes SMR as a conceptual framework for organizing the emerging roles of iron-based materials in staged tumor microenvironment intervention. We summarize the current evidence supporting each therapeutic tier, discuss the biological rationale for stage-specific intervention, and highlight the key translational challenges and research priorities for future development.

RELATIONSHIP BETWEEN THE SMR FRAMEWORK AND EXISTING THERAPEUTIC STRATEGIES

Sequential treatment is not a new concept in oncology. Rather, many established therapeutic strategies rely on the deliberate timing of different interventions to maximize efficacy. Neoadjuvant chemotherapy followed by surgery represents one of the earliest clinical examples, while antiangiogenic therapy has been used to create a transient vascular normalization window that improves the delivery of subsequent treatment.[23] Similarly, radiotherapy-induced immunogenic cell death (ICD) can enhance the response to immune checkpoint blockade (ICB), illustrating how an initial intervention may reshape the tumor microenvironment to increase the effectiveness of later therapies.[24] This principle has also influenced the design of nanomedicine. As early as 2005, *Sengupta* et al.[25] developed a temporally programmed nanocarrier in

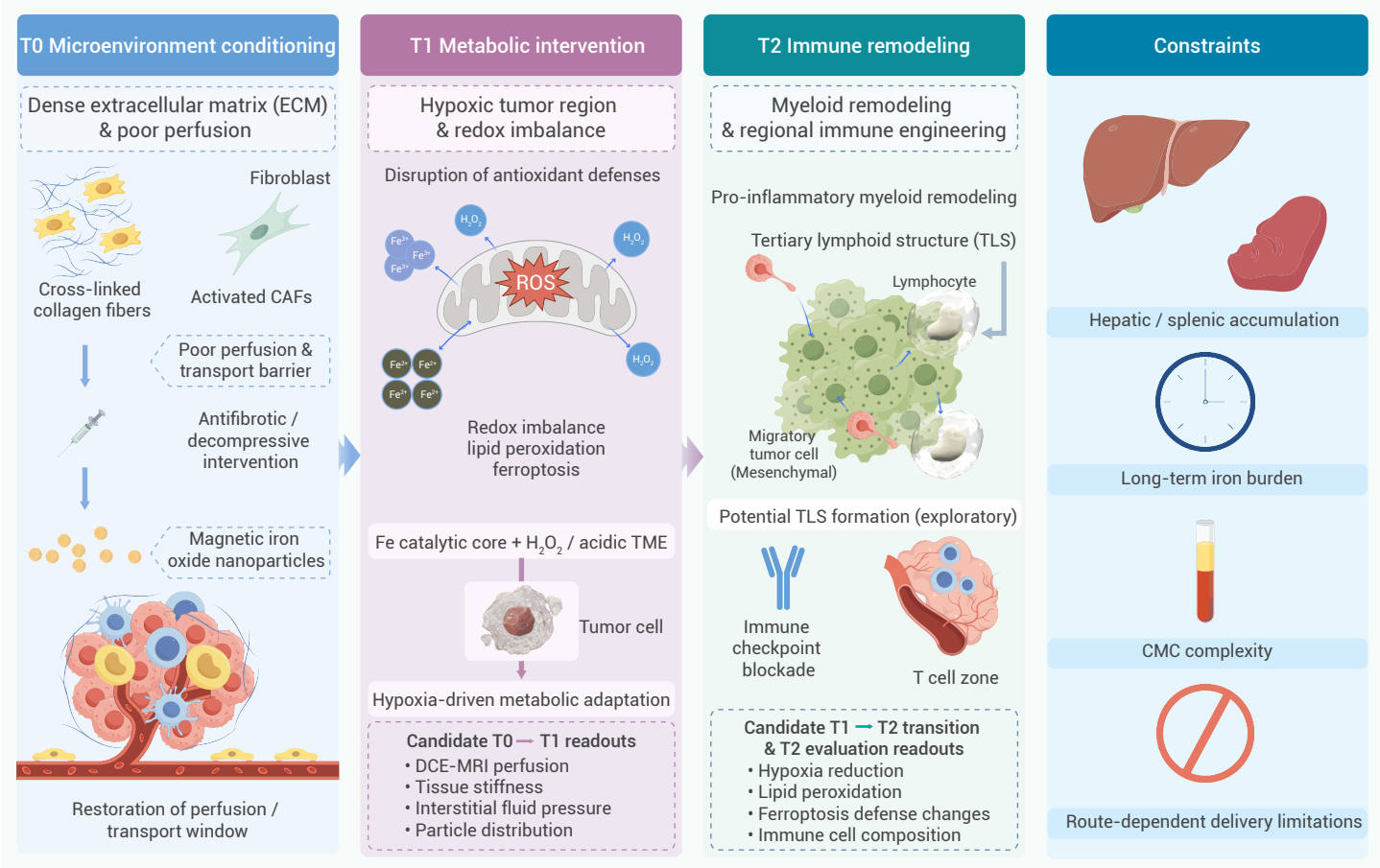


Figure 1. Conceptual framework of SMR (T0-T2) by iron-based nanomaterials T0 aims to establish a functional transport window through controlled stromal modulation and magnetically assisted delivery; T1 exploits iron-catalyzed redox sensitization and ferroptosis; and T2 extends these effects toward myeloid remodeling and immune engagement. Major translational constraints are summarized in the right panel. Created using Figdraw.

which a phospholipid shell released combretastatin A4 phosphate before the PLGA core subsequently released doxorubicin, achieving greater antitumor efficacy than concurrent drug administration in both B16/F10 melanoma and Lewis lung carcinoma models. More recently, *Mpekris* et al.[26,27] demonstrated that combining microenvironment normalization with immune checkpoint therapy markedly increased intratumoral $CD8^+$ T-cell infiltration and prolonged survival in a breast cancer lung metastasis model.

The SMR framework builds on existing concepts of sequential and cascade therapy but differs in both its biological rationale and therapeutic objective. SMR organizes microenvironmental interventions based on the evolving biological state of the tumor, rather than a predefined treatment sequence. This concept is supported by recent nanomedicine studies, including the sequential tumor microenvironment-reprogramming platform reported by *Yu* et al.,[28] which demonstrated that appropriately timed microenvironmental modulation can enhance therapeutic efficacy. Our framework extends this concept by focusing specifically on iron-based materials.

SMR differs from conventional sequential or cascade strategies in three key aspects. First, it organizes the diverse functions of iron-based materials into stage-specific microenvironmental interventions. Second, transitions between stages are guided by biological responses rather than predefined treatment intervals. Candidate indicators include perfusion recovery, reduced tissue stiffness, improved material distribution, hypoxia relief, lipid peroxidation, and myeloid remodeling. The MRI/MPI capabilities of iron oxide platforms may enable longitudinal monitoring and image-guided stage switching, although this approach remains insufficiently validated *in vivo*.[29,30] Third, the evidence supporting each stage remains uneven. T1 has the strongest experimental support, particularly for iron-catalyzed therapy and ferroptosis-based interventions.[22,31-37] T0 is mainly supported by magnetic targeting and antifibrotic delivery studies, with limited evidence for direct iron-mediated stromal remodeling.[38-45] T2 is supported primarily by myeloid remodeling studies,[46-50] whereas durable immune homeostasis reconstruction and mature tertiary lymphoid structures (TLS) remain largely speculative.[51-56] The causal continuity of T0-T1-T2 has yet to be demonstrated within a unified experimental system. Taken together, these considerations indicate that SMR is best regarded as a staged framework for organizing microenvironment-directed intervention. Its applicability is also likely to depend on tumor-specific features, including vascular architecture, stromal composition, iron metabolism, immune contexture, and the barriers to nanoparticle delivery (Figure 1).

TUMOR MICROENVIRONMENTAL ABNORMALITIES AND IRON-BASED MATERIAL INTERVENTION

Fibrosis, hypoxia, and immunosuppression constitute interconnected barriers

The major barriers to therapy in solid tumors arise from a closely interconnected microenvironment. Fibrotic ECM and activated CAFs increase tissue stiffness and generate solid stress, which can mechanically compress intratumoral blood vessels. In mouse tumor models, *Stylianopoulos* et al.[10] demonstrated that growth-induced solid stress may reach 10-100 mmHg and correlates with both tumor volume and collagen density, providing direct evidence that stromal remodeling can impair vascular function. Reduced perfusion subsequently aggravates local hypoxia, activating HIF-dependent programs that promote glycolysis, acidification, angiogenesis, and extracellular matrix remodeling, thereby reinforcing the physical and metabolic barriers to treatment.[12,13,57] These changes also reshape the immune microenvironment. Lactate accumulation and extracellular acidification suppress the activity of effector T cells and NK cells while favoring immunosuppressive myeloid phenotypes, ultimately creating conditions that support tumor persistence and therapeutic resistance.[17,58]

Suitability of iron-based materials

Iron-based materials are particularly well suited to the SMR framework because they combine magnetic responsiveness, catalytic activity, imaging capability, and immunomodulatory potential. These properties allow the same material family to support transport optimization during T0, catalytic intervention during T1, and immune regulation during T2. Surface engineering has expanded these functions, enabling iron oxide nanoparticles to evolve from passive carriers into active mediators of microenvironmental remodeling.[22,33,40,47,59-61]

Collectively, these studies indicate that iron oxides possess therapeutic functions that extend beyond drug delivery. Depending on the biological context, they may exert antitumor effects indirectly by reprogramming TAMs or directly by targeting tumor cells with impaired iron homeostasis. Importantly, these mechanisms are not universally applicable but depend on the cellular composition and metabolic characteristics of the local tumor microenvironment. Beyond their therapeutic activity, iron oxide platforms also offer a unique advantage for longitudinal imaging. Their intrinsic MRI/MPI visibility provides an opportunity to monitor particle distribution and microenvironmental changes throughout sequential intervention.[29,30,62,63] Since the introduction of magnetic particle imaging (MPI) by *Gleich* and *Weizenecker* in 2005,[64] growing evidence has demonstrated its potential for quantitative tracking of iron-based materials *in vivo*. *Makela* et al.[65] showed that MPI enables more direct and quantitative detection of iron-labeled tumor-associated macrophages than conventional MRI, highlighting its value for monitoring myeloid-cell dynamics during therapy. More recently, *Park* et al.[66] demonstrated sustained MPI visualization of superparamagnetic iron oxide nanoparticles (SPIONs) in CT26 and MC38 tumor models for up to seven days after administration, supporting the use of MPI for longitudinal assessment of intratumoral particle distribution and retention. Advances in particle engineering have improved imaging performance. *Dadfar* et al.[67] reported that size-selected SPIONs exhibited enhanced MRI, MPI, and magnetic hyperthermia performance compared with polydisperse formulations, indicating that structural optimization can simultaneously improve diagnostic and therapeutic capabilities. Most recently, *Kumar* et al.[68] developed iron oxide nanochains with enhanced MPI sensitivity for cancer detection, further illustrating that rational nanoparticle engineering can improve *in vivo* tracking of iron-based systems. Collectively, these advances suggest that iron oxide platforms are evolving from passive imaging probes toward monitorable theranostic systems capable of supporting longitudinal evaluation of material delivery, microenvironmental remodeling, and potentially stage-specific intervention within the SMR framework. Within the SMR framework, this capability could support assessment of T0 delivery, T1 material localization, and the identification of candidate stage-transition biomarkers.

Systematic classification of iron-based materials

Iron-based materials encompass a diverse range of platforms with distinct physicochemical characteristics, including superparamagnetic iron oxide nanoparticles (SPIONs), Fe-based metal-organic frameworks (Fe-MOFs), zero- or low-valent iron nanoparticles, iron-based metallic alloys and amorphous systems, iron coordination polymers, iron-polyphenol networks, as well as more recently developed iron-doped composites, nanozymes, and single-atom catalysts (Table 1). These materials differ substantially in their biological functions and translational potential.[69]

Among them, SPIONs remain the most clinically mature owing to their established imaging capability and translational experience. SPIONs are most closely aligned with T0. By contrast, Fe-MOFs, low-valent iron systems, amorphous iron materials, iron-polyphenol assemblies, and iron-based nanozymes are more closely associated with catalytic intervention during T1. In particular, zero- and low-valent iron systems provide a more efficient source of catalytic Fe^{2+} through Fe^{0}/Fe^{2+} oxidation and continuous Fe^{2+}/Fe^{3+} redox cycling than conventional Fe^{3+}-dominant oxides.[70] However, their biological stability, oxidation kinetics, protein-corona formation, degradation behavior, and long-term safety remain insufficiently characterized. Their contribution to T2 is less established and is currently supported mainly by evidence of myeloid uptake, macrophage remodeling, and the immune consequences of ferroptotic stress.

Iron-based materials nevertheless represent only one component of the broader metal-based nanomedicine landscape. Manganese-based systems can support oxygen modulation and cGAS-STING activation, whereas copper-based systems provide Fenton-like catalytic activity and can induce cuproptosis.[71-74] Gold nanomaterials are particularly suited to photothermal intervention, while calcium-based systems provide an alternative strategy based on intracellular calcium overload and mitochondrial disruption.[75,76] These mechanisms may complement iron-mediated intervention, but direct efficacy ranking is not currently justified because the available studies differ substantially in material composition, tumor model, administration route, treatment schedule, and experimental endpoint. Table 2 provides a functional positioning of these material families.

T0: ESTABLISHING PHYSICAL ACCESS WINDOWS WITH IRON-BASED MATERIALS

From ECM degradation to controlled mechanical decompression

Early stromal-targeting strategies largely focused on degrading collagen or hyaluronic acid to improve drug penetration. However, subsequent studies demonstrated that the ECM is not merely a physical barrier but also contributes to tissue integrity and can restrain tumor dissemination.[77-79] Recent evidence indicates that fibrosis promotes immune suppression, vascular compression, and metastasis. These findings highlight the need for controlled stromal remodeling.[80] Within the SMR framework, T0 aims to relieve solid stress and transport barriers to improve tumor perfusion and intratumoral delivery.[10,80]

The primary role of iron-based materials is to facilitate localized intervention. SPIONs can be magnetically guided to enhance local accumulation and improve the spatial precision of therapeutic delivery. *Liu* et al.[41] demonstrated that optimized magnetic field configurations significantly increased both nanoparticle accumulation and intratumoral penetration, supporting the use of magnetic iron oxide systems as delivery platforms . Nevertheless, magnetic targeting remains constrained by lesion depth, blood-flow dynamics, and the rapid attenuation of magnetic-field gradients, making current applications more suitable for superficial tumors or regional delivery strategies.[40,41]

Current evidence also suggests that cell-level magnetomechanical effects should not be equated with tissue-level stromal decompression. Although magnetic vortex microdisks and rotating magnetic particles can disrupt cell membranes and cytoskeletal organization,[42-44] direct evidence that iron nanoparticles alone reduce collagen density, relieve solid stress, restore perfusion, or remodel tumor stroma *in vivo* remains limited. A more realistic strategy is therefore to combine iron-based platforms with established antifibrotic interventions.

Restoration of perfusion and convective transport

The primary objective of T0 is to restore effective perfusion and facilitate intratumoral transport. Elevated interstitial fluid pressure (IFP), together with vascular compression, abolishes transvascular pressure gradients and severely limits convective drug delivery, forcing therapeutic agents to rely predominantly on diffusion.[81] Strategies that relieve vascular compression can therefore improve the distribution of both nanoparticles and conventional therapeutics. For example, angiotensin inhibition has been shown to decompress tumor vessels and enhance intratumoral delivery of chemotherapeutic agents and nanomaterials.[82] Within the SMR framework, iron-based platforms may support these interventions by enabling localized delivery and longitudinal monitoring, thereby creating more favorable conditions for the catalytic reactions and immune-cell infiltration required in T1 and T2.

This concept is closely related to *Jain*'s theory of vascular normalization, which emphasizes that transient restoration of vascular function can improve the efficacy of subsequent therapies.[8] More recent studies suggest that vascular normalization and immune reprogramming are mutually reinforcing processes, and that combining antifibrotic intervention with correction of vascular abnormalities enhances the response to immunotherapy.[26,27,83] These findings support the view that T0 functions primarily as a preparatory stage that establishes a transport-permissive microenvironment.

Successful T0 intervention should be evaluated using functional indicators. These include improved perfusion assessed by DCE-MRI, reduced interstitial fluid pressure and tissue stiffness, and more homogeneous intratumoral

Table 1. Representative iron-based materials and their stage-specific suitability within the SMR framework.

Material platform	Representative systems	Principal SMR role	Functional rationale	Translational status	Major limitations	Refs
SPIONs	Fe_3O_4 and γ-Fe_2O_3 nanoparticles; ferumoxytol	Primarily T0 and T2; supportive role in T1	Strong magnetic responsiveness enables magnetic enrichment, image-guided delivery, and longitudinal MRI/MPI tracking. Preferential myeloid uptake may support macrophage-oriented intervention, whereas catalytic activity generally depends on the generation of bioavailable Fe^{2+}.	Most clinically mature iron-based platform; ferumoxytol provides established clinical experience in systemic iron administration and off-label MRI.	Limited intrinsic catalytic efficiency; liver and spleen accumulation; formulation-dependent magnetic and biological behavior; repeated-dose safety requires evaluation.	29,30,40,41,47,61,65–68,172–174–181
Fe-MOFs	MIL-53, MIL-88, MIL-100 and MIL-101 derivatives	Primarily T1	High iron content, tunable porosity and stimulus-responsive degradation facilitate iron release, drug loading and ferroptosis-oriented catalytic therapy.	Extensive preclinical development, but no established clinical precedent for cancer treatment.	Variable degradation kinetics; uncertain long-term biosafety; batch reproducibility, scale-up and regulatory characterization remain unresolved.	36,98,101
Zero- or low-valent iron systems	Fe^0 nanoparticles, amorphous iron nanometallic glasses and Fe-based alloys	Primarily T1	Rapid Fe^{2+} generation and sustained $Fe^0/Fe^{2+}/Fe^{3+}$ redox cycling can enhance Fenton-like reactions under mildly acidic conditions.	Early preclinical stage with limited imaging or clinical experience.	Rapid oxidation and passivation; poorly defined degradation products; protein-corona effects and *in vivo* stability remain insufficiently characterized.	70
Iron coordination polymers and iron-polyphenol networks	Fe^{3+}-tannic acid assemblies and related coordination networks	Material-design precedent for T1; exploratory role in T2	Fe(III)-polyphenol coordination enables rapid, pH-responsive assembly and disassembly with adaptable surface coating; downstream therapeutic functions depend on the incorporated components.	Foundational materials chemistry is established, whereas oncology applications remain preclinical.	Weak magnetic responsiveness; limited imaging capability; biological effects depend strongly on ligand composition and degradation behavior.	69
Iron-doped composites, nanozymes and single-atom catalysts	Fe-N-C sites, Fe-doped mesoporous materials and iron single-atom catalysts	Primarily T1; exploratory role in T2	High catalytic-site exposure and enzyme-like activity can improve reactive oxygen species generation and redox intervention, including under near-neutral conditions.	Rapidly expanding preclinical field without established clinical translation.	Active-site heterogeneity; uncertain *in vivo* degradation and excretion; limited magnetic tracking; manufacturing and scale-up remain challenging.	99,100,111

Note. Iron-based platforms are classified by their predominant functions within the SMR framework. Each platform may contribute to multiple intervention stages. T0 denotes transport conditioning and image-guided delivery, T1 denotes iron-catalyzed redox intervention and ferroptosis sensitization, and T2 denotes myeloid remodeling and immune engagement. Stage assignments reflect the current evidence base and should not be interpreted as validated clinical indications.

particle distribution. Together, these measures provide more informative evidence of transport-window formation than ECM reduction alone.[84] These parameters may also facilitate the transition from T0 to T1 by identifying when sufficient transport-window formation has been achieved.

Risks of tumor dissemination and re-fibrosis

Although transient stromal decompression may improve drug transport, excessive disruption of the extracellular matrix also carries potential risks. Excessive or indiscriminate stromal depletion may disrupt tissue-restraining stromal functions and, in selected tumor contexts, promote immune suppression or more aggressive tumor behavior.[85,86] In addition, the benefits of decompression are often short-lived, as tumors can rapidly restore a fibrotic microenvironment through TGF-β signaling, CAF reactivation, and collagen redeposition.[9,87,88] The growing recognition of CAF heterogeneity suggests that distinct fibroblast subsets may respond differently to antifibrotic intervention, making indiscriminate stromal depletion an increasingly less attractive therapeutic strategy. Clinical and preclinical evidence further supports the need for caution during T0 intervention. Although hyaluronan depletion with PEGPH20 can reduce interstitial pressure and improve perfusion and intratumoral drug distribution, clinical outcomes have been inconsistent, suggesting that stromal modulation alone is insufficient to achieve durable therapeutic benefit.[89,90] These findings highlight the need for controlled, transient microenvironmental modulation during T0 while avoiding excessive stromal disruption. Emerging ECM-responsive nanoplatforms capable of releasing immunomodulatory agents may strengthen the connection between T0 and T2 by simultaneously improving transport and alleviating immune suppression in highly fibrotic tumors such as pancreatic ductal adenocarcinoma (PDAC).[91]

As illustrated in Figure 2, the purpose of T0 is the establishment of a functional transport window that enables the subsequent redox and immune-oriented interventions of SMR.

T1: IRON-CATALYSIS-DRIVEN REDOX DESTABILIZATION AND METABOLIC SENSITIZATION

T1 aims to disrupt hypoxia-driven metabolic adaptation

Hypoxia limits cancer therapy not only by restricting oxygen availability but, more importantly, by activating HIF-dependent adaptive programs that promote metabolic rewiring, therapeutic tolerance, and immune escape.[12,13]

Table 2. Functional positioning of representative metal-based material platforms in relation to the SMR framework.

Material platform	Distinctive properties	Principal relevance to SMR	Translational position	Major limitations	Refs
Iron-based materials	Magnetic responsiveness, MRI/MPI visibility, Fe^{2+}/Fe^{3+} redox cycling and preferential uptake by myeloid cells	Potentially spans T0 magnetic guidance and imaging, T1 catalytic redox intervention, and selected T2 myeloid-remodeling functions	SPIONs and ferumoxytol provide comparatively mature imaging and systemic-exposure experience; more complex catalytic platforms remain preclinical	T0 and T2 evidence is less mature than T1 evidence; catalytic activity, biodistribution and safety vary substantially among formulations	29,30,32,36,41,46,47,49,50,65–68,153,172,174–180
Manganese-based materials	Mn^{2+}-responsive MRI, oxygen modulation and enhancement of cGAS-STING signaling	Most relevant to T1 hypoxia modulation and T2 innate immune activation	Predominantly preclinical in oncology	manganese release, dose-dependent toxicity, and systemic exposure require careful control	71,72
Copper-based materials	Cu^{+}/Cu^{2+} redox cycling, Fenton-like catalysis and induction of cuproptosis	Primarily relevant to T1 catalytic intervention and metal-dependent cell death	Predominantly preclinical, without established oncological nanomedicine precedent	Limited intrinsic imaging capability; copper homeostasis, off-target toxicity and mechanistic heterogeneity complicate translation	73,74
Gold-based materials	Efficient photothermal conversion, surface functionalization and photoacoustic/CT-related imaging	Provides externally triggered local ablation that may complement T0 delivery or T1 tumor-cell injury, but does not reproduce iron-dependent ferroptotic mechanisms	Predominantly preclinical in oncology; clinical translation remains limited.	Limited intrinsic redox catalysis and no magnetic responsiveness; tissue persistence and treatment-depth constraints remain concerns	75
Calcium-based materials	Intracellular calcium overload and mitochondrial disruption	Provides an alternative ion-overload strategy for T1-like metabolic injury	Early preclinical development	Limited imaging and magnetic functionality; evidence for staged microenvironmental reprogramming remains sparse	76

Note. The table classifies metal-based material platforms by their functions without ranking their therapeutic efficacy. Cross-platform comparisons should be interpreted cautiously because the available studies differ in material composition, tumor model, administration route, treatment schedule, and experimental endpoint. T0 denotes transport conditioning and image-guided delivery, T1 denotes redox or metabolic intervention, and T2 denotes immune and myeloid remodeling.

Within the SMR framework, T1 therefore aims to disrupt hypoxia-driven adaptation. For most iron-based systems, this objective cannot be achieved by the catalytic core alone. Catalytic iron is commonly integrated with oxygen-generating or peroxide-producing components to sustain local redox reactions under hypoxic conditions. Representative examples include oxygen carriers for photodynamic therapy, H_2O_2-responsive oxygen-generating nanocarriers, catalase-loaded radiosensitizing nanosheets, and self-supplying nanocatalytic systems capable of generating both O_2 and H_2O_2.[92–96] Similar strategies have also been incorporated into iron-based platforms by combining catalytic iron with oxygen-releasing units, heme-mimetic structures, or oxygen carriers.[97]

The effectiveness of this strategy is constrained by the chemical requirements of iron-catalyzed reactions. Classical Fenton chemistry is most efficient under strongly acidic conditions (pH 2.5-4.0), whereas the tumor microenvironment is only mildly acidic (approximately pH 6.2-6.8).[33] This discrepancy has driven extensive efforts to improve catalytic activity under physiologically relevant conditions. Current approaches broadly follow three directions: enhancing Fe^{2+} release within acidic intracellular compartments such as endosomes and lysosomes,[98] engineering highly active catalytic centers such as Fe-N_x single-atom catalysts,[99,100] and developing functional material platforms, including amorphous iron nanoglasses that provide redox-active iron and MOF-based nanocarriers that enable drug loading and controlled release.[70,101] A recent example is the ICG/Fe(III)-oxygen nanobubble system, in which oxygen nanobubbles simultaneously improved oxygen availability and stabilized the ICG/Fe(III) complex, while Fe(III)-mediated hydroxyl-radical generation cooperated with photodynamic ROS production to disrupt tumor redox homeostasis and induce ferroptosis.[97]

T1 intervention requires coordination between oxygen availability and catalytic efficiency. Oxygen supplementation may support oxygen-dependent therapeutic processes, whereas iron-catalyzed reactions depend on local peroxide availability, iron speciation, and pH. T1 platforms should therefore optimize oxygen-release kinetics, iron availability, and local redox conditions according to their specific catalytic mechanisms.[102]

Iron catalysis is centered on amplifying oxidative damage rather than simply generating ROS

The T1 stage is currently supported by the most substantial body of evidence within the SMR framework. Its objective is not simply to increase ROS levels, but to intensify oxidative stress until it exceeds the metabolic adaptability and antioxidant buffering capacity of tumor cells. Accordingly, therapeutic efficacy depends less on the absolute amount of ROS generated than on the coordinated regulation of iron redox cycling, reaction kinetics, substrate availability, and antioxidant defenses to destabilize intracellular redox homeostasis.[103] This concept is consistent with growing evidence that redox-active nanozymes can not only catalyze ROS generation but also reprogram tumor metabolism, thereby increasing cellular vulnerability to oxidative damage. Studies of lipid metabolism indicate that lipid availability, membrane PUFA composition, and the extent of lipid peroxidation collectively determine cellular susceptibility to ferroptosis and other forms of oxidative injury.[15,104,105]

Current strategies to enhance T1 sensitization can be broadly grouped into four complementary approaches: expanding the intracellular iron pool, increasing the availability of peroxidation substrates, weakening antioxidant defenses, and improving catalytic-site accessibility through material engineering (Table 3). Among these, inhibition of GPX4 has received the greatest attention because of its central role in ferroptosis. GPX4 also plays an essential antioxidant role in normal tissues. Its systemic or nonselective inhibition may cause off-target tissue damage. Tumor-selective and spatially controlled interventions are therefore needed to minimize these risks.[31]

Recent studies further suggest that ferroptosis sensitization extends beyond direct GPX4 inhibition. Regulation of PRDX6 and depletion of intracellular GSH can influence GPX4 localization and activity, thereby enhancing ferroptotic susceptibility.[106,107] In parallel, the FSP1 and DHODH pathways have emerged as complementary defense systems that preserve redox

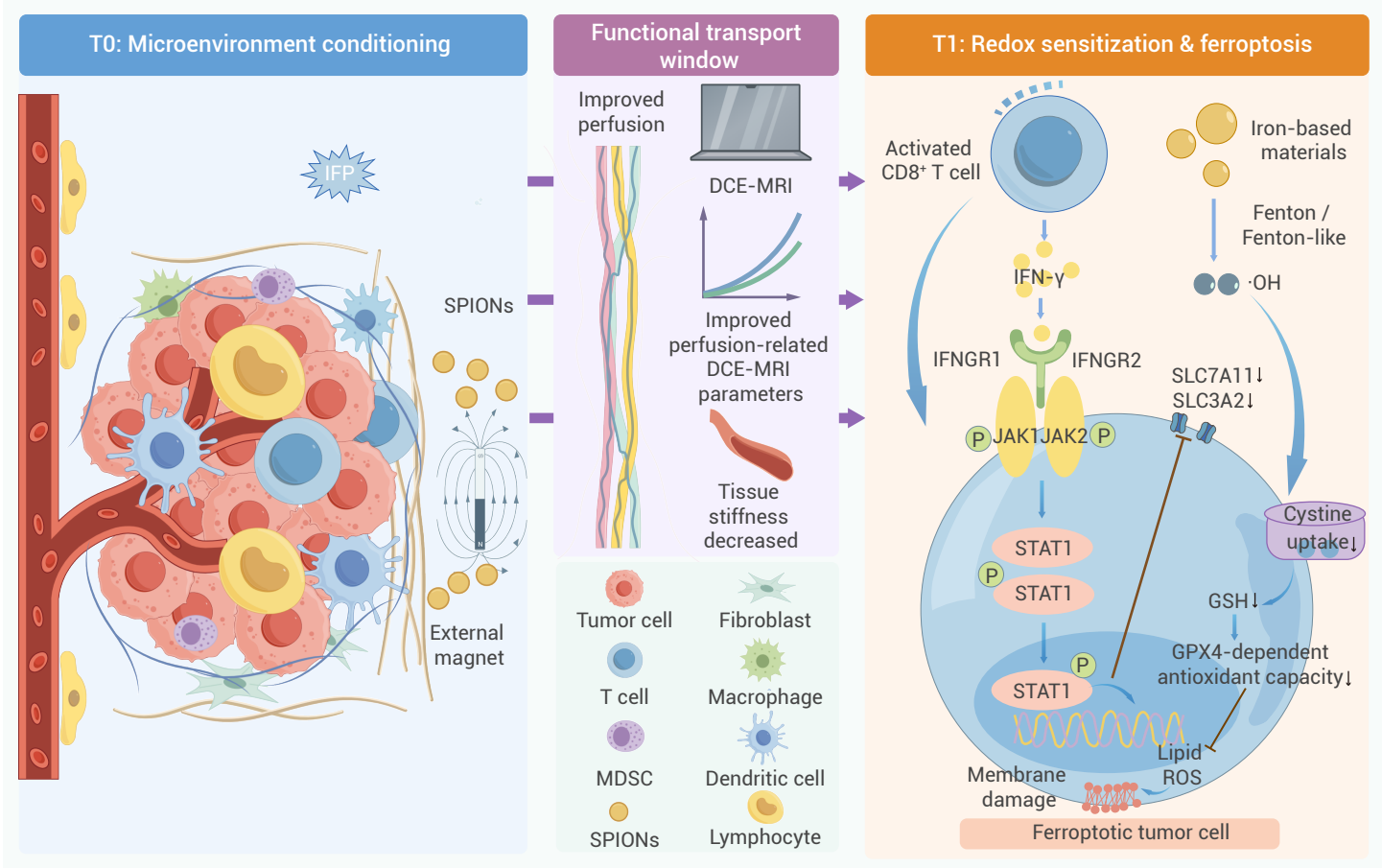


Figure 2. T0-T1 SMR mediated by iron-based nanomaterials T0 represents the fibrotic tumor stroma before intervention, where controlled stromal modulation is intended to improve perfusion and establish a functional transport window. T1 illustrates iron-catalyzed redox sensitization and ferroptosis induction through enhanced lipid peroxidation and disruption of antioxidant defenses. Created using Figdraw.

homeostasis independently of GPX4.[108,109] Metabolic regulation also contributes to this network, as suppression of the pentose phosphate pathway may weaken FSP1/DHODH-dependent antioxidant defenses.[110] Together, these findings support a network-based model of T1 intervention in which multiple ferroptosis-defense pathways are targeted simultaneously rather than through inhibition of a single antioxidant enzyme.

Beyond these biological defense mechanisms, material architecture is another critical determinant of T1 efficacy. Mesoporous engineering, for example, can improve the accessibility of reactants to catalytic sites, thereby enhancing catalytic efficiency and ferroptosis induction.[111] Effective T1 design requires coordinated optimization of catalytic activity, peroxidizable substrate availability, antioxidant defenses, and tumor-specific redox vulnerability. Optimizing individual material properties alone is insufficient.

Ferroptosis is a representative endpoint of T1, but its effective window must be defined

Ferroptosis is a promising therapeutic endpoint for iron-based materials because it may overcome apoptosis resistance in selected tumor contexts. Certain therapy-resistant and persister-like tumor cells exhibit increased ferroptosis susceptibility.[33,34,112-117] Recent advances in nanomedicine have further expanded its translational potential through biomimetic delivery systems, two-dimensional materials, and metabolically engineered nanoplatforms that improve tumor selectivity and therapeutic efficacy.[118,119] Material-mediated ferroptosis has shown synergistic effects with radiotherapy, photodynamic therapy, and metabolic intervention, among which radiosensitization currently has the substantial preclinical support.[46,120-124]

Reliable identification of ferroptosis requires multiple complementary readouts rather than ROS accumulation alone, including lipid peroxidation measured by C11-BODIPY or 4-HNE, changes in GPX4 and related defense pathways, expansion of the labile iron pool, and pharmacological rescue using ferrostatin-1, liproxstatin-1, or deferoxamine.[112,125-127] The kinetics of iron release, lipid peroxidation, tumor-cell death, and immune-cell responses vary according to material composition, dose, administration route, tumor model, and sampling strategy. T1-to-T2 transition should therefore be defined by longitudinal evidence of adequate tumor-selective ferroptotic stress together with preservation of dendritic cells, $CD8^+$ T cells, vascular integrity, and other components required for subsequent immune reprogramming, rather than by a fixed post-treatment interval.[128-133]

T2: FROM FERROPTOSIS-ASSOCIATED SIGNALING TO IMMUNE HOMEOSTASIS RECONSTRUCTION

The complex relationship between ferroptosis and immune activation

The transition from T1 to T2 represents the central biological assumption of the SMR framework: that localized oxidative injury can, under appropriate conditions, be converted into productive antitumor immunity. However, current evidence indicates that ferroptosis is neither intrinsically immunogenic nor uniformly beneficial. Rather, its immune consequences depend on the timing, intensity, and microenvironmental context of cell death.[134] Within an appropriate therapeutic window, ferroptotic tumor cells may release danger-associated signals, including ATP and HMGB1, that promote dendritic-cell recruitment, antigen presentation, and subsequent T-cell priming.[24,135-138] Activated $CD8^+$ T cells can amplify this process by increasing ferroptotic susceptibility through IFN-γ-dependent suppression of SLC7A11 and ACSL4-mediated enrichment of membrane polyunsaturated fatty acids.[139,140] Together, these findings suggest that ferroptosis can reinforce antitumor immunity when oxidative injury is spatially restricted and appropriately controlled.[141]

The transition from T1 to T2 represents a context-dependent biological window, not an automatic consequence of tumor-cell death. Candidate indicators include tumor-cell lipid peroxidation, early ICD-associated signals, and

Table 3. Representative strategies and mechanistic targets for enhancing ferroptosis susceptibility during the T1 stage of the SMR framework.

T1 sensitization strategy	Representative approach	Key evidence	Implication for SMR	Major limitation	Refs
Increase the available iron pool	GOx + ultrasmall Fe_3O_4 @mesoporous silica	~68.89% tumor inhibition in 4T1 tumors after intratumoral injection.	Demonstrates coupling of substrate generation with iron-catalyzed activation.	Requires intratumoral delivery; non-selective glucose consumption.	32
	NMIL-100@GOx@C	~92.4% tumor inhibition in 4T1 tumors after intravenous administration.	Fe-MOFs provide higher iron loading and tunable catalytic architecture.	Long-term biosafety remains unclear.	36
Increase lipid substrate availability	ACSL4-related mechanistic studies	ACSL4 knockout markedly increased resistance to ferroptosis.	Identifies membrane PUFA availability as a T1 design target.	Mechanistic evidence only; no material validation.	104
	Oxidative lipidomics	AA-PE-OOH and AdA-PE-OOH identified as execution lipids.	Defines lipid species that should be amplified by iron catalysis.	In vitro evidence only.	105
Weaken antioxidant buffering	Disulfide-containing Zn-MOF loaded with Ce6	~70% GSH depletion; ~3-fold MDA increase.	GSH depletion and GPX4 inactivation, leading to endogenous iron-dependent ferroptosis and enhanced PDT-induced apoptosis.	Long-term safety unknown.	107
	Fe-DOX@amorphous $CaCO_3$	Synergistic ferroptosis with pH modulation.	Illustrates multi-module synergy during T1.	High formulation complexity.	37
	PRDX6-GPX4 regulation	Targeting PRDX6 enhances ferroptosis-mediated tumor suppression.	Extends T1 beyond direct GPX4 inhibition.	Not yet translated into iron-material design.	106
	FSP1/DHODH pathways	Alternative ferroptosis-defense pathways identified.	Broadens T1 sensitization beyond GPX4.	Limited validation in iron-material systems.	108–110
	Mesoporous catalytic engineering	Enhanced ferroptosis induction.	Highlights catalytic-site accessibility as a determinant of T1 efficacy.	Early-stage strategy.	111

Note. Representative studies are reorganized according to the biological logic of T1 sensitization.

preserved immune-cell fitness. These combined readouts may be more informative than ROS accumulation or tumor-cell death alone. Ferroptosis resistance and immune evasion can arise from shared microenvironmental programs. Hypoxia, lactate accumulation, macrophage polarization, and metabolic adaptation may suppress both ferroptosis and antitumor immunity.[142-145]

T1-to-T2 coordination requires limiting excessive or prolonged oxidative injury while preserving immune-cell function. This may create favorable conditions for myeloid remodeling and adaptive immune activation. Catalytic nanozymes may support such coordination through their emerging roles in tumor immune microenvironment regulation.[146]

Myeloid remodeling in relation to iron metabolism

Among the biological events proposed for T2, myeloid remodeling currently has the strongest experimental support. Macrophages are central regulators of both iron homeostasis and immune function, making them a natural point of convergence between iron metabolism and immune reprogramming.[48,59,60] Earlier studies demonstrated that inflammatory and immunoregulatory macrophage states differ markedly in iron handling, suggesting that local iron metabolism is closely coupled to myeloid-cell function (Table 4).[48]

This concept is supported by several lines of evidence. Ferumoxytol preferentially accumulates in TAMs and promotes a pro-inflammatory phenotype associated with tumor suppression in murine tumor models.[46,47] Similar findings have been reported for both ionic and nanoparticle iron, although their biological effects vary according to iron speciation, material composition, release kinetics, and the activation state of the target macrophages.[49,50] These observations indicate that the immunological effects of iron-based materials arise from context-dependent interactions. More direct evidence is now emerging to connect ferroptosis with myeloid remodeling. Ferroptotic debris can reshape macrophage metabolism and promote pro-inflammatory reprogramming,[46] while ferroptosis itself may amplify antitumor immunity through myeloid activation.[147] However, the opposite outcome is also possible, as macrophages may protect tumor cells from ferroptotic injury or contribute to immune suppression depending on the surrounding microenvironment.[148] Shared regulatory circuits, such as the $IL4I1^+$ macrophage-$TDO2^+$ myofibroblast axis, further illustrate that ferroptosis resistance and immunosuppressive remodeling often arise from the same microenvironmental programs.[149]

These findings also underscore the limitations of the traditional M1/M2 paradigm. Myeloid populations differ according to ontogeny, spatial location, and treatment history, resulting in distinct responses to iron metabolism, oxidized lipids, and ferroptotic stress.[150-152] Spatial transcriptomics and other high-dimensional approaches therefore provide a more informative framework for interpreting myeloid remodeling than static phenotypic markers alone. Within SMR, successful T2 intervention should be evaluated by disruption of the suppressive myeloid-stromal-metabolic network. Successful remodeling depends on maintaining a balance between immune activation and immune injury. Excessive oxidative stress may impair immune-cell viability and reinforce suppressive clearance programs, whereas insufficient stimulation fails to disrupt the immunosuppressive niche. The objective of T2 is therefore not to convert all macrophages into an M1-like phenotype, but to re-establish a myeloid ecosystem that supports adaptive immunity while overcoming ferroptosis resistance.

Beyond direct intratumoral myeloid regulation, recent evidence suggests that iron oxide nanomaterials may also influence antitumor immunity through systemic microenvironmental axes. He et al. demonstrated that orally administered superparamagnetic iron oxide nanoparticle assemblies (SPIOCAs) restored gut microbial homeostasis and intestinal barrier integrity in lung tumor-bearing mice, accompanied by increased intratumoral $CD8^+$ T-cell and dendritic-cell infiltration and restored responsiveness to PD-1 blockade. This finding broadens the potential scope of T2 from local myeloid remodeling to host-level immune conditioning.[153]

Ferroptosis-ICB combination therapy links T1 injury to T2 immunity

The interaction between ferroptosis and ICB provides one of the strongest

Table 4. Core evidence supporting iron-associated myeloid remodeling during the T2 stage of the SMR framework.

Iron-based stimulus/material	Representative evidence	Mechanistic insight	Implication for SMR	Major limitation	Refs
Ferumoxytol	Promoted M1-like TAM polarization (iNOS↑, CD206↓), suppressed tumor growth and reduced liver metastasis.	Lysosomal iron release induces Fenton-type ROS and pro-inflammatory signaling, favoring macrophage reprogramming.	Provides the strongest *in vivo* evidence supporting T2 myeloid remodeling by iron oxide nanoparticles.	Mainly demonstrated in breast cancer-related models; durability and broader applicability remain uncertain.	47
Ferrous ammonium sulfate and Ferumoxytol	In vitro macrophage studies showed increased iNOS expression and TNF-α secretion after iron exposure.	Iron stimulates macrophage activation through iNOS/NO-related pathways; ionic and nanoparticle iron differ in activity.	Supports iron-induced pro-inflammatory macrophage activation as a potential T2 mechanism.	In vitro evidence only.	49
Fe_3O_4 vs. α-Fe_2O_3	Fe_3O_4 (magnetite) versus α-Fe_2O_3 (hematite) showed different macrophage-polarization efficacy.	Magnetite promoted M1 polarization more effectively than hematite; magnetite-associated IRF5 signaling and reduced arginase-1 were reported.	Indicates that iron oxide composition may influence T2 outcomes and material selection.	No direct *in vivo* comparison of TAM remodeling.	50
Ferroptotic lysates + iron nanoparticles	Ferroptosis-associated signals promoted TAM remodeling in vitro and *in vivo*.	Links ferroptosis-derived signals with downstream myeloid reprogramming.	Provides experimental support for T1→T2 coupling.	Short observation period; preformed lysates rather than endogenous real-time ferroptosis.	46
Ferroptosis-associated remodeling signals	Emerging studies suggest bidirectional interactions between ferroptosis, macrophage remodeling and suppressive stromal circuits (including IL4I1$^+$ macrophage-TDO2$^+$ myofibroblast axes).	Myeloid remodeling and ferroptosis resistance form a context-dependent regulatory network.	Highlights that successful T2 depends on both the myeloid niche and stromal context.	Heterogeneous evidence across tumor models; long-term validation is still lacking.	147–149

Note. Studies are reorganized according to their contribution to T2 myeloid remodeling within the SMR framework.

biological links between T1 and T2 within the SMR framework. Increasing evidence suggests that ferroptosis and antitumor immunity reinforce one another through reciprocal regulation. Activated CD8$^+$ T cells promote ferroptotic susceptibility through IFN-γ-dependent suppression of SLC7A11 and ACSL4-mediated remodeling of membrane lipid composition,[139,140] indicating that adaptive immunity actively shapes the metabolic vulnerability of tumor cells rather than simply responding to ferroptotic injury. The reciprocal nature of this interaction is supported by studies showing that ferroptosis sensitizes tumors to anti-PD-L1 therapy, whereas pre-existing T-cell immunity amplifies ferroptotic cell death.[154,155] These findings argue against a simple "damage first, immunity later" model and instead support a positive feedback loop in which metabolic injury and immune activation mutually reinforce therapeutic efficacy. This also explains why ferroptosis induction alone rarely produces durable responses in several preclinical models, whereas combination with immune checkpoint blockade is generally more effective.

Nanomaterial-based studies support this concept. Recent work demonstrates that co-delivery of sorafenib and an FSP1 inhibitor enhances ferroptotic vulnerability in both tumor cells and immunosuppressive macrophages, thereby strengthening the overall response to immunotherapy.[156] Such findings suggest that T1 and T2 may overlap biologically rather than being separated by a strict sequential boundary. Localized nanoplatforms capable of integrating ferroptosis induction with immune activation therefore provide a practical strategy for coordinating these two intervention stages. Although coupling ferroptosis with cGAS-STING signaling or other regional immune-engineering strategies may strengthen antitumor immunity,[109] excessive or prolonged ferroptosis can simultaneously damage infiltrating immune cells and reinforce immunosuppressive programs.[129-132,142,143,149] Consequently, the T1-to-T2 transition requires precise temporal and spatial control, allowing metabolic disruption to initiate immune activation while avoiding persistent oxidative injury to immune populations. As illustrated in Figure 3, ferroptosis-ICB combination therapy should therefore be viewed as a biologically regulated transition.

TLSs as an exploratory endpoint of interest

TLSs are increasingly recognized as indicators of effective local immune activation and are associated with improved responses to ICB and favorable clinical outcomes in multiple tumor types.[51,52,54,55] Within the SMR framework, TLSs should be regarded as exploratory downstream consequences of successful T2 remodeling. At present, convincing evidence that iron-based materials reproducibly induce mature TLSs remains limited. Consequently, myeloid remodeling, dendritic-cell activation, CD8$^+$ T-cell infiltration, and IFN-γ-related immune signatures remain more reliable readouts of T2 activity. When TLS formation is evaluated, lymphocyte aggregation alone should not be interpreted as evidence of functional TLS development. Mature TLSs require coordinated B-cell follicles, T-cell zones, mature dendritic cells, follicular dendritic-cell networks, high endothelial venules, and characteristic chemokine programs.[157] Accordingly, multiplex imaging, spatial transcriptomics, and conventional histopathology should be integrated to distinguish mature TLSs from immature lymphoid aggregates and to evaluate their spatial organization and functional relevance.

Growing evidence indicates that TLS formation is regulated by coordinated interactions among stromal cells, vascular remodeling, chemokine gradients, and tissue metabolism.[158-163] These observations reinforce the view that TLSs should be interpreted as spatially organized immune ecosystems rather than isolated histological structures. The biological significance of TLSs also depends on the surrounding immune context. Iron-rich and ferroptosis-associated microenvironments may reshape the abundance and function of myeloid-derived suppressor cells (MDSCs) and Tregs, thereby influencing whether local lymphoid organization supports effective antitumor immunity or remains functionally suppressed.[16-18,164,165] Importantly, monocytic and polymorphonuclear MDSCs differ substantially in lineage, metabolic adaptation, and suppressive mechanisms,[17,18] while hypoxia, lactate accumulation, lipid metabolism, and oxidative stress further influence Treg stability and function.[12,13,15-17]

SURROGACY, MONITORING, AND TRANSLATIONAL BOUNDARIES IN SEQUENTIAL INTERVENTION

Compensatory responses must be addressed in SMR

A defining feature of SMR is that each intervention stage can trigger compensatory responses that reshape the tumor microenvironment. Conse-

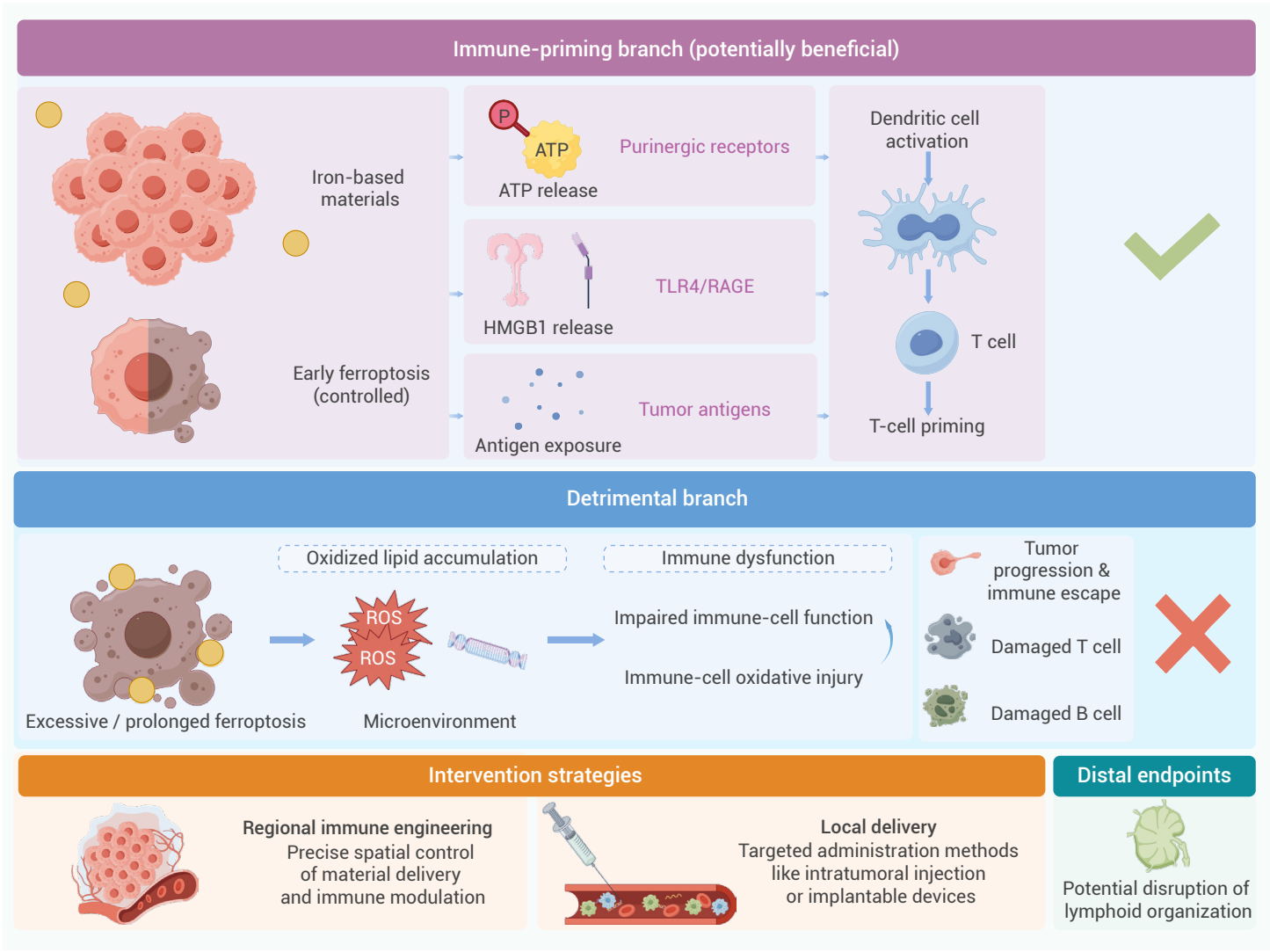


Figure 3. Beneficial and detrimental outcomes of ferroptosis during SMR Early, controlled ferroptotic stress may promote immunogenic signaling, dendritic-cell recruitment, T-cell priming, and regional immune activation, thereby supporting antitumor immunity. In contrast, excessive or prolonged ferroptotic stress may impair dendritic-cell and T-cell function, disrupt immune organization, and thereby limit durable antitumor immunity. Created using Figdraw.

quently, successful sequential intervention depends not only on advancing from T0 to T2, but also on anticipating and intercepting the dominant escape mechanisms that emerge during each stage. In this sense, SMR should be regarded as an adaptive therapeutic framework.[166-168]

Compensatory responses differ across stages. During T0, improved perfusion and matrix decompression may be followed by rapid re-establishment of stromal barriers through renewed angiogenesis, CAF reactivation, and collagen deposition.[9,87] By contrast, T1 is characterized primarily by metabolic adaptation. In response to oxidative stress, tumor cells may activate ferroptosis-defense pathways together with coordinated metabolic, epigenetic, and immune programs involving hypoxia signaling, lactate accumulation, and immune escape.[142-144,169] Importantly, these compensatory programs are not restricted to tumor cells. Stromal and myeloid populations actively participate in adaptive resistance. IL4I1^{+} macrophage-TDO2^{+} myofibroblast circuits, for example, simultaneously promote ferroptosis resistance and immunosuppression,[149] whereas controlled ferroptosis can conversely redirect myeloid remodeling toward a more inflammatory state.[147,156] These observations indicate that increased immune pressure may be counterbalanced by renewed myeloid suppression, maintenance of regulatory T cells, checkpoint upregulation, and impaired antigen presentation.[167,170] These findings emphasize that durable immune activation requires continuous suppression of compensatory pathways.

Accordingly, the purpose of SMR is not merely to coordinate sequential interventions but to integrate stage-specific therapy with stage-specific interception of adaptive resistance. This concept has practical implications for platform design: T0 should minimize re-fibrosis, T1 should combine catalytic intervention with inhibition of ferroptosis-defense or metabolic escape pathways, and T2 should reinforce immune activation through myeloid reprogramming, checkpoint blockade, or regional immune engineering. Only by coupling stage progression with compensatory interception can SMR evolve from a conceptual framework into a clinically testable therapeutic strategy.

Functional biomarkers for stage switching

A defining feature of SMR is that progression from one stage to the next should be guided by biological readiness. This requires biomarkers that reflect functional changes within the tumor microenvironment instead of isolated molecular events. Accordingly, candidate biomarkers can be organized into three complementary categories: mechanistic validation markers, stage-switching indicators, and stage-evaluation endpoints (Table 5). Successful transition from T0 to T1 depends on whether a functional transport window has been established. Defining the transition from T1 to T2 is inherently more challenging because it requires balancing metabolic disruption with preservation of immune competence. At the T2 stage, evaluation shifts from metabolic remodeling to reconstruction of the local immune ecosystem. At present, the goal is not to establish a fully autonomous T0-T1-T2 control system, but to develop an integrated framework that combines imaging, tissue-based, and molecular readouts to determine when the tumor microenvironment is biologically prepared for the next intervention stage. In

Table 5. Candidate functional readouts for stage assessment in the SMR framework

SMR stage	Candidate biomarker	Role in SMR	Measurement	Clinical feasibility	Key rationale	Refs
T0 → T1	Improved DCE-MRI perfusion	Switching indicator	Dynamic contrast-enhanced MRI	High	Indicates restoration of functional perfusion and transport; predicts treatment response.	84
	Reduced interstitial fluid pressure (IFP)	Switching / mechanistic validation	Wick-in-needle or catheter measurement	Low	Functional indicator of transport-window formation.	81,82
	More homogeneous intratumoral particle distribution	Candidate switching indicator	MRI/MPI or tracer mapping	Moderate	Evaluates delivery efficiency and transport-window establishment.	29,65–68,181
T1 → T2	Lipid peroxidation	Mechanistic validation	4-HNE, MDA, C11-BODIPY	Moderate	Core execution event of ferroptosis.	34,35,112,126
	GPX4/FSP1/DHODH	Mechanistic validation	IHC, Western blot, enzyme assays	Moderate	Reflects ferroptosis-defense status.	31,35,106,108–110,112,113,115,126
	Labile iron pool (LIP)	Mechanistic validation	FerroOrange or other validated intracellular Fe^{2+}-sensitive probes	Low	Provides a preclinical readout of intracellular redox-active Fe^{2+}; not validated for clinical stage switching.	127
	Early ICD-related signals	Candidate stage-readiness marker	CRT, ATP, HMGB1 assays	Low	Supports transition from local injury to immune activation.	24,134–138
T2 evaluation	DC maturation	Stage endpoint	Flow cytometry	Moderate	Indicates antigen-presenting activation.	24,134,138
	$CD8^+$ T-cell infiltration	Stage endpoint	Multiplex IF / IHC	High	Reflects adaptive immune activation.	26,27,139,140,153
	TAM remodeling	Stage endpoint	Flow cytometry / spatial profiling	Moderate	Evaluates myeloid reprogramming.	46,47,49,50,147–151
	IFN-γ-related signature	Stage endpoint	RNA-seq / NanoString	Moderate-High	Associated with response to ICB.	139,140
	TLS-associated histologic features	Exploratory endpoint	H&E plus IHC	Moderate-High	Represents higher-order immune organization.	52–56,157–159

Note. Biomarkers are organized according to the sequential logic of SMR (T0→T1→T2). None of these readouts has been prospectively validated as a stage-switching criterion for SMR.

this sense, SMR should be regarded as a semi-closed-loop strategy that can be progressively refined as biomarker technologies mature.

Safety and chemistry, manufacturing, and controls (CMC) are realistic bottlenecks

The major translational challenge for multifunctional SMR platforms is the reproducible manufacture and regulatory characterization of increasingly complex nanomedicines. Increasing structural and functional complexity expands the number of critical quality attributes that must be controlled, including particle-size distribution, surface properties, payload content and release, physical stability, and batch-to-batch consistency.[171] These manufacturing parameters must also remain stable under biologically relevant conditions.

Regulatory considerations further increase translational complexity. Multifunctional SMR systems frequently combine therapeutic, imaging, and device-related functions, meaning that their regulatory pathway may depend on the primary mode of action while still requiring coordinated evaluation of drug, device, and imaging components. For iron-based platforms, this includes assessment of particle specifications, magnetic-field geometry, imaging performance, drug release, and device-particle reproducibility.[172] Consequently, regulatory challenges arise not only from material safety but also from defining the identity and intended function of the final product.[173]

Safety is likewise stage dependent. Following intravenous administration, SPIONs and related iron oxide nanoparticles preferentially accumulate in the liver and spleen through uptake by the reticuloendothelial system (RES).[174-177] Although this biodistribution supports myeloid-targeted imaging and immunomodulation, it also raises concerns regarding hepatic and splenic accumulation, repeated-dose toxicity, and off-target oxidative injury. Released iron subsequently enters endogenous pathways involving ferritin storage, transferrin transport, and hepcidin-ferroportin-regulated recycling, providing a biological basis for the clinical familiarity of several iron oxide formulations. However, when iron release exceeds local buffering capacity, expansion of the labile iron pool may promote Fenton chemistry, lipid peroxidation, and secondary tissue injury. This risk is particularly relevant in RES-rich organs and during repeated dosing. Accordingly, safety assessment should consider biodistribution, degradation, iron recycling, dosing interval, and potential indicators of tissue iron accumulation in a stage- and dose-dependent manner. Clinically established iron formulations provide practical entry points for translation. Ferumoxytol, for example, offers substantial clinical experience regarding pharmacokinetics, MRI applications, and safety assessment.[178,179] Likewise, engineered iron oxide nanoplatforms and injectable hydrogels illustrate how imaging, regional drug delivery, and immune modulation may eventually be integrated, but their manufacturability, biodistribution, and long-term safety remain to be established.[180]

From a translational perspective, future SMR development should prioritize disease-specific biological problems rather than increasingly complex material architectures. Highly fibrotic and immune-excluded tumors such as PDAC provide a representative example, where the immediate objective is not maximal cytotoxicity but reproducible improvement in perfusion and particle deposition, together with reduced transport heterogeneity before subsequent metabolic or immune intervention.[181] Ultimately, successful SMR platforms will be judged not only by mechanistic sophistication but also by manufacturability, reproducibility, biodistribution, repeated-dose safety, and clinical practicality.

CONCLUSION

This Review adapts and formalizes SMR as a framework for coordinating iron-based interventions against physical, metabolic, and immune barriers in

the tumor microenvironment. Current evidence is strongest for T1 iron-catalyzed redox intervention and ferroptosis sensitization. T2 myeloid remodeling has emerging experimental support, whereas direct validation of T0 transport-window establishment remains limited. SMR therefore represents a testable conceptual framework rather than an established therapeutic paradigm.

Several critical questions remain unresolved. Direct evidence linking T0-mediated transport improvement to enhanced T1 catalytic efficacy within a unified platform is lacking. The ability of ferroptotic injury to generate durable immune remodeling, mature tertiary lymphoid structures, and long-term immune memory also requires validation. Moreover, the biological conditions governing stage transitions and their applicability across tumor types remain poorly defined.

Future research should prioritize four objectives. First, multimodal imaging, spatial omics, and tissue-based analyses should be integrated to identify and validate stage-switching biomarkers. Second, longitudinal studies using unified material platforms and tumor models are needed to establish causal relationships between T0, T1, and T2. Third, modular iron-based systems with clearly defined functions should be developed to improve manufacturing reproducibility and regulatory feasibility. Finally, disease-specific studies should determine whether SMR provides therapeutic advantages in tumors characterized by severe fibrosis, hypoperfusion, and immune exclusion.

The translational value of SMR lies in coordinating transport restoration, metabolic sensitization, and immune engagement according to biological responses. Progress will depend on reliable monitoring, tumor-selective interventions, manageable material complexity, and long-term safety. These advances may enable the gradual development of SMR into a clinically testable strategy for precision microenvironmental therapy.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors used AI-assisted language editing to polish the language and improve readability and grammar. All scientific content, arguments, evidence interpretation, literature citations, figure and table data, and translational conclusions were independently developed by the authors and were manually reviewed and revised as needed after AI-assisted language polishing. The use of the AI tool was strictly limited to language refinement and did not extend to scientific judgment or content generation. The authors take full responsibility for the scientific accuracy and originality of the manuscript.

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AUTHOR CONTRIBUTIONS

Shiyin Chen, Hao Wang and Yiling Gan contributed equally to this work and carried out most of the literature collection, synthesis, and manuscript drafting. Wencheng Zhao, Huixian Zhang, Xuyang Chen, Wengang Zhang, Xinyue Liu, Yujin Liu, Yujie Li, Runze Huang, Jialin Zeng, and Yuhang Li assisted with literature screening, section drafting, and manuscript revision. Ning Gu and Yayi He conceived the topic, provided overall supervision, and critically revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

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