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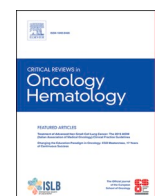
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TREM2⁺ tumor-associated macrophages in cancer: Context-dependent biology, biomarkers, and precision immunotherapy

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ABSTRACT

Tumor-associated macrophages (TAMs) are abundant and functionally important components of the tumor microenvironment (TME), yet the molecular programs that distinguish pathogenic macrophage states from tissue-adaptive populations remain incompletely defined. Triggering receptor expressed on myeloid cells 2 (TREM2) has emerged as a key marker of specialized immunoregulatory macrophage states across multiple solid tumors. Accumulating evidence links TREM2⁺ macrophages to metabolic adaptation, immune evasion, and impaired antitumor immunity, although their biological functions vary substantially across tumor types, tissue niches, and disease settings. In this review, we synthesize current understanding of TREM2-associated immunobiology, including ligand recognition, signaling architecture, immunometabolic adaptation, and macrophage functional heterogeneity. We critically evaluate conflicting findings across tumor types and discuss how tissue context, macrophage ontogeny, and microenvironmental cues shape immune evasion, therapeutic responsiveness, and clinical outcomes. We further examine emerging therapeutic strategies targeting TREM2-associated myeloid programs, including antibody-based approaches, macrophage reprogramming, pathway modulation, and rational combination immunotherapy, while highlighting translational challenges, safety considerations, and biomarker-guided opportunities. Building on previous reviews of TREM2 signaling and tumor-associated myeloid biology, this review proposes a context-dependent framework integrating macrophage heterogeneity, immunometabolism, spatial biology, biomarker development, and therapeutic decision-making to advance precision immunotherapy.

1. Introduction

Tumor-associated macrophages (TAMs) are among the most abundant and functionally influential immune cell populations within the tumor microenvironment (TME), where they regulate tumor progression, immune evasion, therapeutic resistance, and metastatic dissemination (Wang and Ma, 2025). Beyond their classical roles in phagocytosis and tissue homeostasis, TAMs orchestrate immunosuppressive ecosystems by limiting cytotoxic T-cell infiltration, impairing antigen presentation, remodeling the extracellular matrix, promoting angiogenesis, and adapting to the profound metabolic stress characteristic of solid tumors. Accumulating clinical and experimental evidence identifies TAMs as important mediators of resistance to immune

checkpoint blockade (ICB), cytotoxic therapies, and targeted agents, underscoring the need to define the molecular programs that govern their functional diversity and context-specific activities (Wang et al., 2024).

Within this evolving landscape, triggering receptor expressed on myeloid cells 2 (TREM2) has emerged as a key marker and functional regulator of specialized immunoregulatory macrophage states across multiple solid tumors (Huang and Fang, 2025). Single-cell and spatial profiling studies have consistently identified TREM2⁺ macrophage subsets enriched in advanced tumor ecosystems, where they are frequently associated with immune exclusion, therapeutic resistance, and adverse clinical outcomes (Wu et al., 2026). Beyond serving as a phenotypic marker, TREM2 influences macrophage behavior through ligand

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sensing, immunometabolic adaptation, and downstream signaling pathways that shape macrophage function within the TME.

Importantly, the biological functions of TREM2 are highly context dependent. In peripheral solid tumors, TREM2⁺ TAMs are generally associated with immunosuppressive myeloid programs and tumor progression, whereas in central nervous system (CNS) malignancies, TREM2 signaling may exert more complex or even tissue-protective effects depending on macrophage ontogeny, disease stage, and the local immune microenvironment (Zhong et al., 2024). These divergent observations caution against viewing TREM2 as a uniformly protumorigenic molecule and instead suggest that its biological significance is determined by tissue context, ligand availability, and macrophage state plasticity (Feiten et al., 2026).

This biological complexity raises an important translational question: when should TREM2 be therapeutically inhibited, when might macrophage reprogramming represent a more appropriate strategy, and under what circumstances could TREM2-directed intervention introduce unintended risks? Addressing these questions has become increasingly important with the rapid expansion of single-cell technologies, spatial profiling, and translational immuno-oncology.

Previous studies and reviews have established the molecular biology of TREM2, characterized TREM2-associated macrophage states in cancer, and highlighted their potential as therapeutic targets (Huang and Fang, 2025; Khantakova et al., 2022; Molgora et al., 2023). However, an increasingly important challenge is to reconcile apparently divergent TREM2 functions across tumor types and translate this heterogeneity into rational therapeutic decisions. Rather than treating TREM2⁺ TAMs as a uniform immunosuppressive population, the present review integrates macrophage ontogeny, immunometabolic adaptation, spatial organization, and tumor-specific functional states with biomarker development and therapeutic benefit-risk considerations. This framework is intended to distinguish contexts in which TREM2 represents a causal and therapeutically actionable macrophage dependency from those in which it may primarily mark an adaptive state or contribute to tissue-protective functions.

As a critical narrative review, our literature coverage emphasizes peer-reviewed mechanistic and translational studies of TREM2 and TREM2⁺ macrophages in cancer, particularly recent single-cell, spatial, immunometabolic, biomarker, and therapeutic studies. Selected non-cancer studies are included where they provide essential mechanistic context.

Accordingly, we provide a critical and translational synthesis of TREM2-associated macrophage biology in cancer. We examine the molecular basis of TREM2 ligand recognition and signaling, followed by its roles in macrophage functional heterogeneity, tumor- and tissue-specific biology, immune evasion, therapeutic targeting, and biomarker development. Emphasis is placed on conflicting tumor-specific evidence, the distinction between TREM2 expression and functional dependency, and the need to match therapeutic modality and intensity to biological context. Finally, we propose a context-dependent framework for interpreting TREM2 biology and discuss its implications for biomarker-guided precision immunotherapy.

2. Molecular and signaling basis of TREM2 function in myeloid cells

Understanding how TREM2 shapes macrophage behavior within the TME requires examination of both its ligand landscape and downstream signaling architecture (Li, A. et al., 2025). Unlike classical immune receptors that primarily recognize pathogen-associated molecular patterns, TREM2 functions as a context-responsive sensor of tissue stress, lipid remodeling, and metabolic disturbance, translating extracellular environmental cues into intracellular programs that regulate macrophage survival, metabolism, and immune function (Guan et al., 2025).

2.1. Ligands and receptor complexes

TREM2 recognizes a diverse spectrum of endogenous ligands, many of which are enriched in tissue injury, lipid dysregulation, and tumor-associated stress states. Among the best-characterized ligand classes are phospholipid-associated structures, oxidized lipoproteins, and apolipoproteins. Phosphatidylserine (PS), exposed on apoptotic cells and membrane debris, represents one of the best-characterized candidate ligands associated with TREM2-mediated recognition of damaged cellular material (Chu et al., 2025). Oxidized lipids, including oxidized low-density lipoprotein (oxLDL), as well as apolipoproteins (Apo) such as ApoE, have also been implicated in modulating TREM2-dependent macrophage responses, particularly in lipid-rich pathological microenvironments (Xing et al., 2026). Additional candidate ligands include phosphatidylethanolamine, oxidized phosphatidylcholine, sulfatides, and selected damage-associated molecular patterns, although ligand specificity and functional relevance may vary substantially across biological contexts (Choi and Kagan, 2025).

Recent structural studies have further refined understanding of ligand recognition by TREM2 (Colonna, 2023; Huang and Fang, 2025). The extracellular immunoglobulin-like ectodomain of TREM2 contains a ligand-binding interface capable of interacting with lipid-associated and anionic molecular structures, providing structural insight into its preferential engagement within metabolically stressed or degenerative tissue environments. These structural observations support the concept that TREM2 functions less as a classical binary receptor and more as a context-responsive environmental sensor whose activation may depend on ligand composition, availability, and tissue context (Greven et al., 2025).

Importantly, not all tumor-associated factors linked to TREM2⁺ macrophage enrichment should be interpreted as direct receptor ligands (Huang and Fang, 2025; Wang et al., 2025). Metabolic features of the TME, including hypoxia, lipid remodeling, oxidative stress, apoptotic turnover, extracellular vesicle exchange, and altered metabolite accumulation, may instead shape the abundance, activation state, or functional persistence of TREM2⁺ TAM populations through indirect contextual mechanisms rather than direct receptor binding (Yang et al., 2025). Distinguishing bona fide ligand engagement from broader microenvironmental association is therefore essential for mechanistic interpretation and therapeutic targeting.

Structurally, TREM2 lacks intrinsic intracellular signaling capability and instead requires association with the adaptor protein DNAX-activating protein of 12 kDa (DAP12, also known as TYROBP) for signal transduction (Colonna, 2023). Ligand engagement promotes phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) within DAP12, enabling recruitment of proximal signaling mediators including spleen tyrosine kinase (SYK). This obligate receptor-adaptor architecture places TREM2 within a broader family of myeloid immunoregulatory receptors while maintaining signaling flexibility through context-dependent ligand engagement and environmental modulation (Peshoff et al., 2024). Candidate ligand and tumor-associated contextual factors linked to TREM2⁺ TAM biology are summarized in Table 1.

2.2. Downstream signaling pathways

Upon ligand engagement and DAP12 phosphorylation, TREM2 signaling recruits signaling molecules including spleen tyrosine kinase (SYK), which functions as an important signaling hub linking receptor activation to downstream metabolic and transcriptional programs. Among the best-characterized downstream pathways, TREM2-associated signaling has been linked to PI3K-AKT-mTOR activation, a signaling axis implicated in macrophage survival, nutrient sensing, anabolic metabolism, and adaptation to metabolic stress (Guan et al., 2025; Joshi, 2024). These pathways may contribute to the maintenance of lipid-associated and metabolically adapted macrophage states

Table 1
Candidate TREM2 ligands and tumor microenvironmental factors associated with TREM2⁺ TAM enrichment and function.

Category	Representative ligands or signals	Relationship to TREM2	TME source	Functional consequences for TREM2 ⁺ TAMs	Biological significance in tumor context	References
Phospholipids and membrane components	Phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine	Candidate/direct ligand interactions	Apoptotic tumor cells, necrotic debris, damaged cell membranes	Ligand engagement supports phagocytic activation, lipid uptake, and metabolic adaptation	Enables clearance of apoptotic material while reinforcing immunoregulatory macrophage states	(Li et al., 2026)
Oxidized lipids and lipoproteins	Oxidized low-density lipoprotein (oxLDL), lipid peroxidation products	Candidate/direct ligand interactions	Oxidative stress within hypoxic tumor regions; dysfunctional tumor vasculature	Associated with lipid accumulation, foam-cell-like phenotype, and enhanced fatty acid oxidation (FAO)	Supports survival of macrophages in lipid-rich and metabolically stressed tumor niches	(Governa et al., 2024)
Apolipoproteins	ApoE, ApoA1, ApoC family proteins	Candidate/direct or ligand-associated interactions	Tumor-associated stromal cells, dying tumor cells, extracellular lipid transport	Stabilizes TREM2 receptor engagement and amplifies downstream signaling	Supports lipid sensing and is associated with immunosuppressive macrophage states	(Dong et al., 2026)
Tumor-derived metabolic products	Lactate, free fatty acids, cholesterol metabolites	Indirect contextual/metabolic factors	Aerobic glycolysis (Warburg metabolism), aberrant lipid metabolism in tumor cells	Associated with metabolic reprogramming toward oxidative and anabolic pathways	Links tumor metabolism to macrophage functional polarization	(Wang et al., 2023)
Apoptotic and necrotic cell debris	Damage-associated molecular patterns (DAMPs), fragmented cellular components	Mixed/indirect context; may contain candidate ligands	High tumor cell turnover, therapy-induced cell death	Sustained TREM2 activation and phagolysosomal activity	Maintains macrophage persistence in highly degenerative tumor environments	(Wang et al., 2025)
Hypoxia-associated stress signals	Hypoxia-induced lipid remodeling, oxidative stress mediators	Indirect contextual factor	Poor vascularization and oxygen deprivation in solid tumors	Promotes lipid accumulation and metabolic stress adaptation	Favors enrichment of TREM2 ⁺ TAMs in hypoxic tumor regions	(Dong et al., 2025)
Extracellular vesicles and lipid particles	Tumor-derived exosomes, lipid droplets, membrane vesicles	Indirect/contextual; potential carrier of candidate ligands	Active tumor secretion and intercellular communication	May support lipid transfer and signaling amplification	Supports intercellular metabolic coupling within the TME	(Xu and Xu, 2025)
Apoptosis-associated metabolic stress	Reactive oxygen species (ROS), mitochondrial debris	Indirect contextual/stress factor	Therapy response, immune attack, metabolic imbalance	Reinforces survival signaling and immunoregulatory gene programs	Sustains macrophage adaptation under chronic cellular stress	(Momcilovic et al., 2025)

Note: Candidate/direct ligands indicate molecules for which direct or putative receptor interaction has been reported, whereas indirect contextual factors denote metabolic, inflammatory, or microenvironmental conditions associated with the enrichment or functional programming of TREM2⁺ TAMs without implying direct TREM2 binding. Classification reflects the current evidence and does not establish equivalent ligand-binding strength or functional relevance across tumor contexts.

observed in multiple tumor settings (Bharadwaj et al., 2024; Li et al., 2026).

Beyond proximal metabolic signaling, TREM2 has also been associated with broader modulation of inflammatory and interferon-related programs, including context-dependent effects on STAT1- and STAT3-linked transcriptional programs. However, the directionality, mechanistic intermediates, and biological consequences of these interactions appear to vary substantially across tumor models, macrophage subsets, and experimental systems. Accordingly, these pathways should be interpreted as context-associated regulatory networks rather than universal linear signaling cascades.

Similarly, TREM2 signaling may intersect with NF- κ B-associated inflammatory programs in a context-dependent manner (Huang and Fang, 2025; Zhang et al., 2025). Rather than functioning as a classical inflammatory switch, TREM2 appears to fine-tune the amplitude and qualitative features of myeloid immune responses according to ligand composition, tissue environment, and metabolic stress conditions (Huang and Fang, 2025). This regulatory flexibility likely contributes to the heterogeneous phenotypes observed among TREM2⁺ macrophage populations across tumor types (Huang and Fang, 2025; Yang et al., 2025).

Collectively, current evidence supports a model in which TREM2 functions as a context-responsive signaling integrator that links environmental sensing to immunometabolic adaptation in macrophages. Rather than functioning as a simple on/off switch, TREM2 appears to

calibrate macrophage functional states according to tissue context, ligand availability, cellular ontogeny, and microenvironmental stress. These interconnected signaling relationships are conceptually summarized in Fig. 1.

TREM2 signaling engages multiple interconnected metabolic and immunoregulatory pathways that shape macrophage function within tumors. These major signaling modules and their biological consequences are summarized in Table 2.

3. TREM2⁺ TAMs as distinct functional and metabolic macrophage states

Accumulating evidence indicates that TREM2⁺ TAMs represent specialized macrophage states rather than simply an expanded population of canonical macrophages. Single-cell and spatial profiling studies have consistently identified TREM2 expression as a recurrent feature of macrophage populations associated with lipid adaptation, altered immunoregulatory programs, and tumor-associated microenvironmental remodeling (Mei et al., 2025; Zhang et al., 2025).

3.1. Metabolic reprogramming and immunosuppressive output

A defining feature of TREM2⁺ TAMs is their close association with lipid metabolism. Across multiple tumor settings, these cells frequently display transcriptional and functional characteristics resembling lipid-

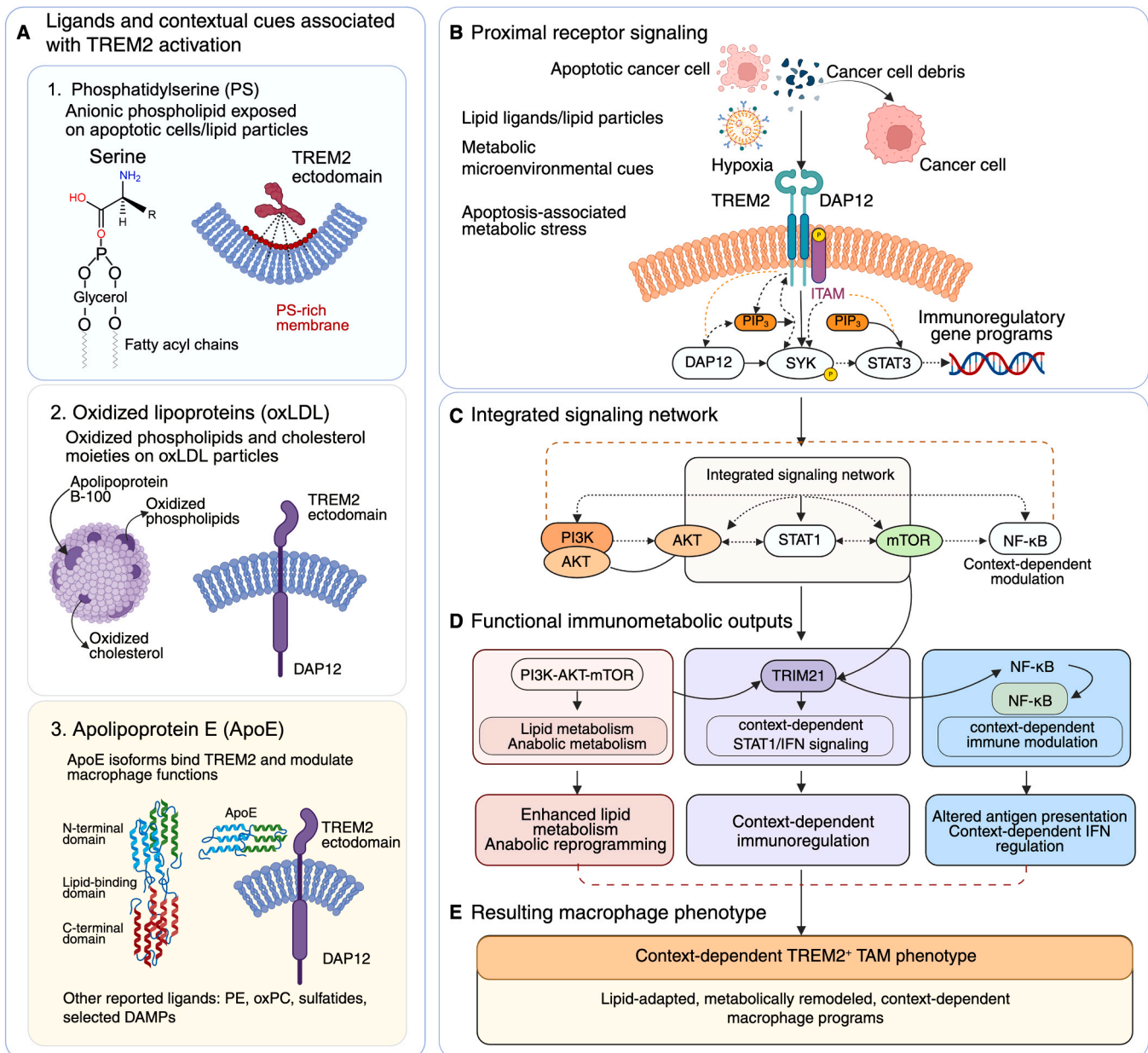


Fig. 1. TREM2 integrates ligand sensing, receptor signaling, and immunometabolic programming in TAMs. (A) TREM2 recognizes diverse endogenous ligands enriched within the TME, including phosphatidylserine (PS), oxidized lipoproteins (e.g., oxLDL), apolipoproteins (e.g., ApoE), and other lipid-associated or damage-associated molecules. (B) Ligand engagement activates TREM2 through the adaptor protein DAP12 (TYROBP), leading to ITAM phosphorylation, SYK recruitment, and downstream signaling. (C) TREM2 interfaces with interconnected signaling pathways, including PI3K-AKT-mTOR, STAT-associated signaling, and NF-κB modulation, forming regulatory networks rather than linear signaling cascades. (D) These pathways coordinate lipid metabolism, immunometabolic adaptation, antigen presentation, and immunoregulatory remodeling. (E) Integrated signaling supports specialized TREM2⁺ TAM phenotypes characterized by metabolic adaptation and immunoregulatory functions that may contribute to immune evasion and therapeutic resistance.

associated macrophages (LAMs), including elevated expression of genes involved in lipid uptake, intracellular storage, cholesterol handling, and fatty acid catabolism (Li et al., 2026; Shi et al., 2025b). Within lipid-rich TME, particularly those shaped by hypoxia, necrosis, oxidative stress, and aberrant tumor cell metabolism, TREM2⁺ TAMs appear positioned to sense and respond to excess phospholipids, oxidized lipoproteins, and lipid-associated environmental cues (Zhou et al., 2025).

Metabolically, TREM2⁺ TAMs exhibit substantial bioenergetic plasticity, with evidence supporting dynamic engagement of both glycolysis and lipid oxidative programs depending on tissue context and microenvironmental constraints. Glycolytic activity may facilitate short-term adaptation to hypoxia and nutrient stress, whereas enhanced fatty acid oxidation (FAO), lipid utilization, and mitochondrial metabolic

remodeling have been associated with sustained macrophage persistence and immunoregulatory adaptation. Emerging evidence further suggests that these metabolic programs may intersect with immune regulatory function, including altered antigen presentation capacity, reshaping of inflammatory signaling, and modulation of effector T-cell responsiveness. Hypoxia and metabolic stress may further reinforce these adaptive programs by stabilizing transcriptional and metabolic states favorable to macrophage persistence in hostile tumor ecosystems.

3.2. Transcriptional and epigenetic features

Single-cell RNA sequencing (scRNA-seq) studies across multiple tumor types have identified TREM2-associated macrophage populations

Table 2
Major downstream signaling pathways and functional consequences associated with TREM2 signaling in TAMs.

Signaling pathway	Core molecular components	Primary cellular function	Immunological consequences	TME impact	Therapeutic relevance	Representative evidence	References
DAP12-SYK activation axis	TREM2-DAP12 (TYROBP), ITAM phosphorylation, SYK recruitment	Initiates proximal intracellular signal transduction following ligand binding	Activates downstream immunoregulatory and metabolic signaling programs	Supports macrophage functional adaptation within tumor niches	Central proximal signaling node for therapeutic modulation	Genetic and pharmacologic inhibition studies in preclinical tumor models	(Karimova et al., 2025)
PI3K-AKT-mTOR metabolic pathway	PI3K, PIP3, AKT, mTOR complex 1	Regulates nutrient sensing, anabolic metabolism, and macrophage survival	Supports metabolically adapted macrophage states in selected tumor contexts	Supports lipid utilization and adaptation to metabolically stressed TME	Potentially targetable through PI3K/mTOR directed strategies	Metabolic profiling and pathway perturbation studies	(Chen et al., 2023)
STAT-associated signaling pathways	STAT1, STAT3 upstream regulatory mediators	Context-dependent transcriptional regulation of inflammatory and immunoregulatory programs	Associated with immunoregulatory transcriptional remodeling	May influence macrophage immune activation states depending on biological context	Potential relevance for rational combinatorial immune modulation	Transcriptomic and mechanistic studies across tumor models	(Shao et al., 2023)
STAT1/IFN-associated regulatory pathways	STAT1-associated signaling regulators, interferon response mediators, antigen presentation machinery	Context-dependent regulation of inflammatory and antigen presentation programs	May influence interferon signaling and immune responsiveness	Potential contribution to altered antigen presentation in selected tumor settings	Possible relevance for immune sensitization strategies	Mechanistic studies of interferon and antigen presentation regulation	(Canel et al., 2023)
NF-κB context-dependent modulation	NF-κB signaling intermediates (IKK complex, transcriptional regulators)	Context-dependent regulation of inflammatory gene expression	May contribute to immunoregulatory remodeling depending on tumor context	Influences macrophage inflammatory adaptation within the TME	Potential target for inflammatory reprogramming approaches	Cytokine profiling and macrophage functional studies	(De Vos et al., 2026)
Immunometabolism integration network	Crosstalk among PI3K-AKT-mTOR, STAT, and NF-κB-linked pathways	Coordinates metabolic adaptation with immune regulation	Supports functional plasticity of TREM2-associated macrophage states	Enables persistence of metabolically adapted macrophage populations	May require systems-level combinatorial therapeutic targeting	Multi-omic and systems biology analyses	(Xu et al., 2025)

Note: Pathways shown represent signaling mechanisms reported or implicated in TREM2-associated macrophage biology. Their activation, directionality, and functional consequences may vary according to tumor type, macrophage state, and microenvironmental context and should not be interpreted as uniformly direct or linear downstream effects of TREM2 signaling.

with transcriptional features that distinguish them from classical inflammatory or monocyte-like macrophage states. These populations frequently exhibit coordinated expression of genes linked to lipid metabolism, phagocytic activity, immune regulation, and tissue remodeling, consistent with specialized adaptation to tumor-associated microenvironmental pressures (Huang et al., 2026). In several malignancies, the abundance and transcriptional composition of TREM2⁺ macrophage populations have been associated with tumor progression, immune exclusion, and adverse clinical outcome, although these relationships remain context dependent (Wu et al., 2026; Zhang et al., 2025).

Ontogenetically, TREM2⁺ TAM populations may derive from both recruited circulating monocytes and tissue-resident macrophage compartments, with relative contributions influenced by tumor type, anatomical site, and local immune ecology (Park et al., 2023). Persistent exposure to tumor-derived inflammatory, metabolic, and stromal signals may further promote epigenetic remodeling that stabilizes adaptive macrophage programs over time, potentially contributing to resistance to functional reprogramming or therapeutic intervention. This interplay between developmental origin and microenvironmental conditioning highlights the plastic yet potentially durable nature of TREM2-associated macrophage states within tumors (Dolci et al., 2026; Wang et al., 2025). Representative conceptual models derived from published single-cell and spatial profiling studies are summarized in Fig. 2.

3.3. Soluble versus membrane-bound TREM2

In addition to membrane-bound TREM2, soluble TREM2 (sTREM2) generated through proteolytic shedding has emerged as a potentially relevant component of TREM2 biology with possible immunoregulatory implications within the TME (Dong et al., 2026; Nada et al., 2026). Although the precise biological functions of sTREM2 remain incompletely defined, emerging evidence suggests that it may influence macrophage activation states, ligand competition, or availability, and intercellular communication in a context-dependent manner. However, its mechanistic role in cancer remains substantially less well characterized than that of membrane-associated TREM2.

Circulating or tissue-associated sTREM2 levels have been explored as potential biomarkers of myeloid activation and disease-associated immune remodeling in both malignant and non-malignant inflammatory conditions (Bharadwaj et al., 2024; Filippello et al., 2022). Nevertheless, the specificity, biological interpretation, and translational robustness of sTREM2 as a cancer biomarker remain to be fully established, particularly given the heterogeneity of myeloid populations across disease contexts.

The biological distinction between membrane-bound TREM2 and sTREM2 adds a further complexity to the interpretation of TREM2-associated macrophage biology, with potential implications for biomarker development, therapeutic monitoring, and target selection. Whereas membrane-associated TREM2 functions as a proximal environmental sensor linked to intracellular signaling and immunometabolic adaptation, sTREM2 may instead reflect dynamic remodeling of the myeloid compartment and evolving inflammatory states during disease

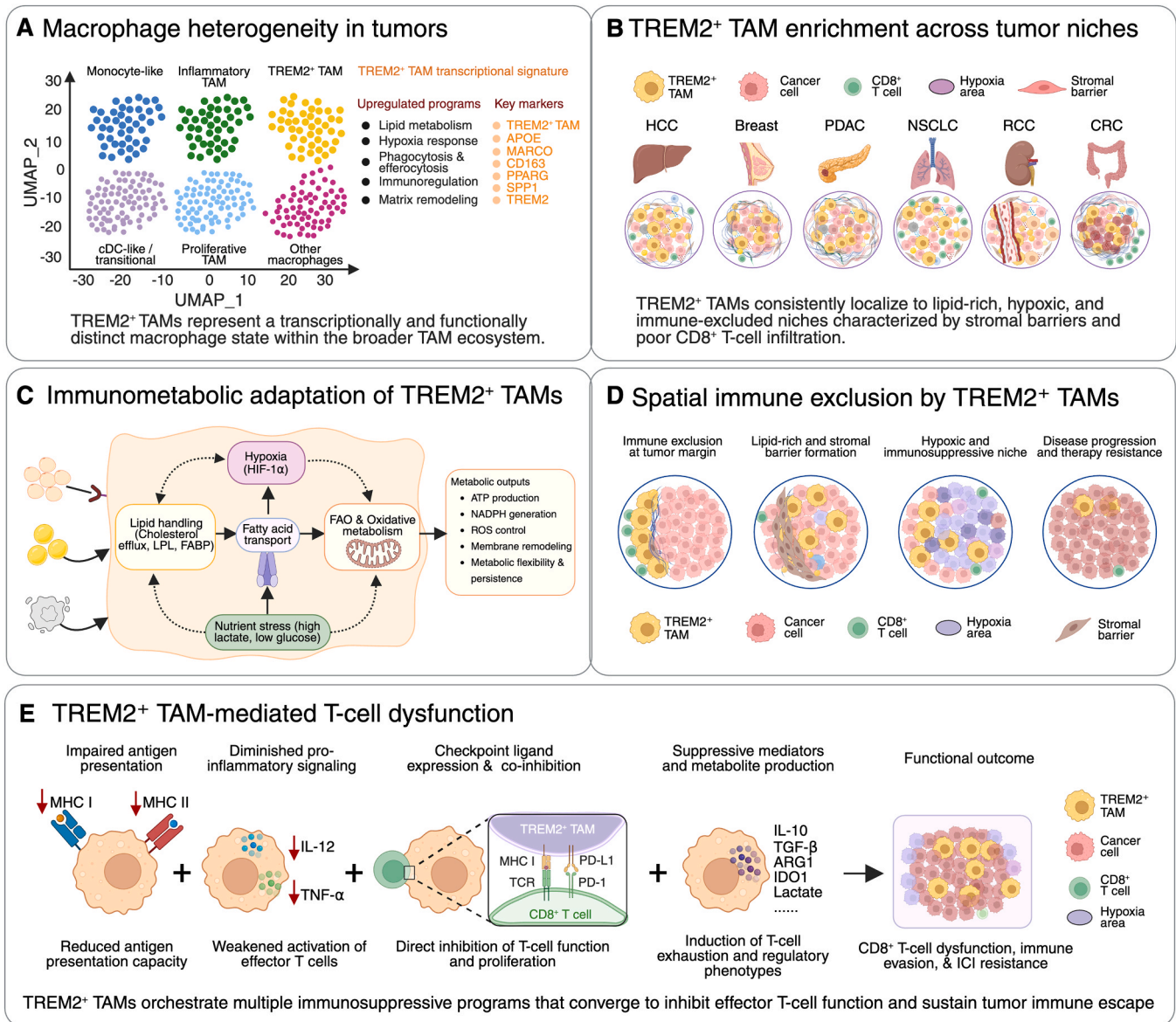


Fig. 2. Transcriptional identity, immunometabolic adaptation, spatial organization, and immunoregulatory functions of TREM2⁺ TAMs in solid tumors. (A) Conceptual single-cell RNA sequencing (scRNA-seq) landscape illustrating major macrophage states within tumors. TREM2⁺ TAMs exhibit a distinct transcriptional program enriched for lipid metabolism, hypoxia response, phagocytosis/effectorcytosis, immune regulation, and matrix remodeling, together with expression of markers such as TREM2, APOE, MARCO, CD163, PPARG, and SPP1. (B) TREM2⁺ TAMs preferentially accumulate in lipid-rich, hypoxic, and immune-excluded niches across multiple solid tumors, including hepatocellular carcinoma (HCC), breast cancer, PDAC, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and colorectal cancer (CRC). (C) Tumor-derived lipids, modified lipoproteins, and metabolic stress promote lipid uptake, fatty acid oxidation (FAO), metabolic flexibility, and long-term persistence of TREM2⁺ TAMs. (D) TREM2⁺ TAMs localize to stromal and hypoxic regions, where they contribute to immune exclusion and the establishment of suppressive tumor niches with limited CD8⁺ T-cell infiltration. (E) TREM2⁺ TAMs suppress antitumor immunity through impaired antigen presentation, reduced pro-inflammatory cytokine production, checkpoint-mediated inhibition, and secretion of immunosuppressive mediators, collectively promoting CD8⁺ T-cell dysfunction, immune evasion, and resistance to immune checkpoint inhibitor (ICI)-based therapies.

progression or therapeutic intervention (Huang and Fang, 2025).

Current evidence indicates that TREM2⁺ macrophages constitute metabolically adaptive and transcriptionally specialized myeloid states whose functions are shaped by developmental origin, tissue context, and dynamic microenvironmental conditioning (Tang et al., 2025).

4. Tumor- and tissue-specific roles of TREM2⁺ macrophages

Although TREM2-associated macrophage populations share recurring features of metabolic adaptation and immunoregulatory remodeling, their biological roles in cancer are strongly shaped by tissue context, tumor origin, macrophage ontogeny, and local microenvironmental

conditions (Salmaninejad et al., 2026). Differences in developmental origin, ligand availability, stromal architecture, metabolic stress, inflammatory tone, and therapeutic background may substantially alter the functional consequences of TREM2 signaling, resulting in immunosuppressive, tissue protective, or mixed phenotypic outcomes. Recognizing this context dependence is essential for reconciling apparently conflicting observations across tumor types and for guiding biologically rational, tissue-specific therapeutic strategies.

4.1. Gastrointestinal malignancies

In gastrointestinal cancers, including HCC, pancreatic ductal

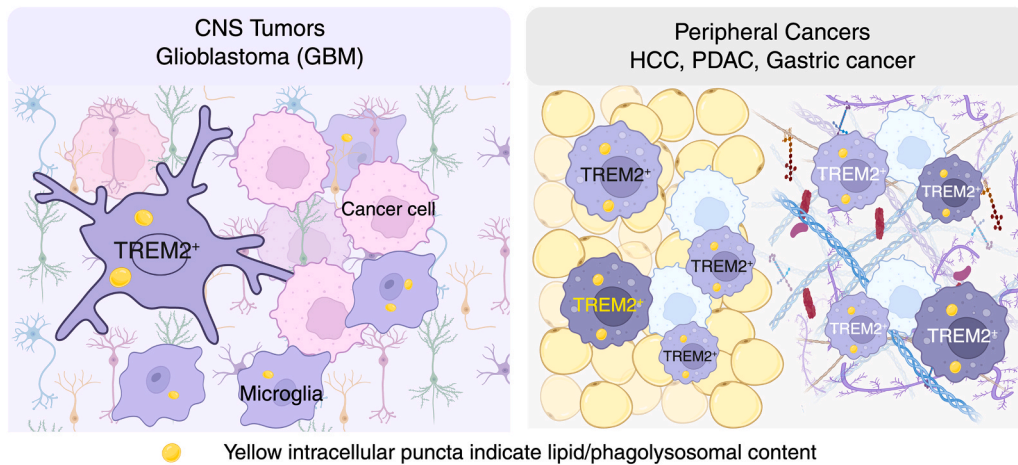
adenocarcinoma (PDAC), and gastric cancer, TREM2-associated macrophage populations have frequently been linked to immunoregulatory remodeling and adverse immune phenotypes, although the magnitude and functional consequences of these associations appear context dependent (Guo et al., 2025).

In HCC, TREM2⁺ macrophages are enriched in metabolically stressed and inflammatory tumor niches and have been closely associated with impaired T-cell infiltration, altered immune activation, and immunoregulatory remodeling. These associations may be particularly relevant in the setting of metabolic liver disease, where the nonalcoholic steatohepatitis (NASH)-HCC axis creates a chronic inflammatory and lipid-rich environment favoring accumulation of lipid-adapted macrophage states (Shi et al., 2025b; Xie et al., 2024). Within this context, TREM2 may function as an integrator of metabolic stress and inflammatory cues

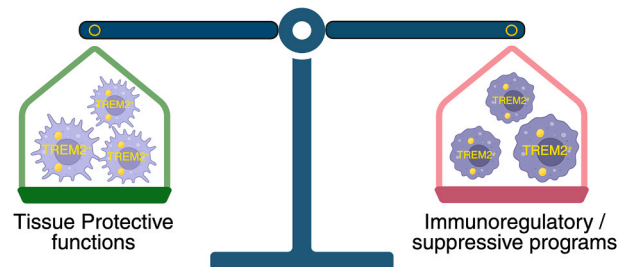
that shape macrophage adaptation and immune dysfunction.

Among gastrointestinal malignancies, PDAC illustrates perhaps the greatest biological complexity. Multiple studies have associated TREM2⁺ macrophage populations with fibrotic stromal remodeling, immune exclusion, and resistance to immunotherapy, consistent with the profoundly hypoxic, desmoplastic, and metabolically stressed nature of PDAC (Liang et al., 2026; Zhang et al., 2025). However, emerging evidence also indicates that TREM2 depletion may produce paradoxical consequences in selected biological contexts. Notably, a recent spontaneous PDAC model reported enrichment of IL-1 β ⁺ pro-inflammatory macrophages following TREM2 loss, accompanied by exacerbated pathological inflammation and accelerated tumor progression, highlighting potential safety concerns surrounding indiscriminate TREM2 inhibition (Yang et al., 2025). These observations suggest that TREM2

A Context-dependent roles of TREM2 in CNS versus peripheral tumors



B Functional bias of TREM2 signaling



C Context-specific determinants of TREM2 function

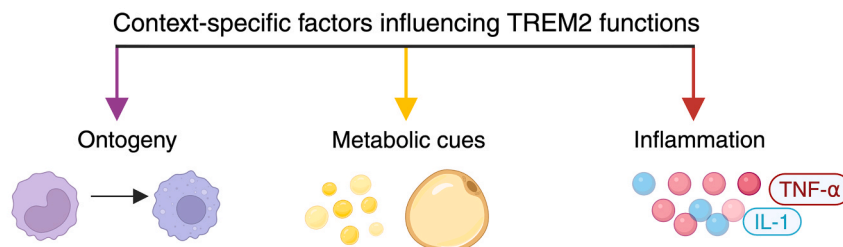


Fig. 3. Context-dependent roles of TREM2 across CNS versus peripheral tumor environments. (A) Conceptual comparison of TREM2-associated myeloid populations in CNS tumors and peripheral solid malignancies. In glioblastoma (GBM), TREM2 is predominantly expressed by microglia and macrophage-like myeloid cells within the neural microenvironment, where it has been implicated in phagocytic clearance, tissue remodeling, and context-dependent immune regulation. In peripheral tumors, including HCC, PDAC, and gastric cancer, TREM2-associated macrophage populations are commonly enriched within metabolically stressed, lipid-rich, hypoxic, and stromal-remodeled tumor microenvironments. Yellow intracellular puncta denote lipid-associated or phagolysosomal content. (B) Conceptual illustration of context-dependent functional bias in TREM2 signaling. Depending on cellular origin, tissue architecture, and local microenvironmental cues, TREM2 signaling may promote either tissue-protective adaptation or immunoregulatory and immunosuppressive macrophage programs. (C) Representative determinants of context-dependent TREM2 function, including macrophage ontogeny (microglia versus monocyte-derived macrophages), metabolic cues, inflammatory mediators, and tissue-specific microenvironmental signals that collectively shape downstream signaling, macrophage phenotype, and biological function.

function in PDAC may extend beyond immunosuppressive macrophage maintenance and may, in certain settings, restrain maladaptive inflammatory injury. Therapeutic targeting in PDAC therefore requires biological caution and context-aware patient stratification.

In gastric cancer, TREM2-associated macrophage populations have similarly been linked to metabolically adapted immunoregulatory states, immune exclusion, and advanced disease features, although mechanistic evidence remains less mature than in selected other tumor contexts (Cao et al., 2025; Zhang et al., 2025). Collectively, gastrointestinal malignancies illustrate how metabolic stress, stromal architecture, and inflammatory background shape TREM2-associated macrophage biology while underscoring the risks of overly generalized therapeutic assumptions. Fig. 3 summarizes the major determinants of TREM2 function across distinct tissue contexts.

Reported tumor-specific microenvironmental factors, biological associations, and potential therapeutic considerations related to TREM2-associated myeloid populations across major cancer types are summarized in Table 3.

4.2. CNS tumors

In CNS malignancies, the biological role of TREM2-associated myeloid populations appears particularly complex and strongly dependent on cellular origin and disease context. While some studies have associated TREM2 expression with immunoregulatory or tumor-supportive myeloid phenotypes in gliomas, other experimental observations suggest that disruption of TREM2 signaling in selected GBM models may exacerbate inflammatory injury and accelerate disease progression (Ghosh and Rothlin, 2024; Zhong et al., 2024). These divergent findings highlight fundamental differences between CNS and peripheral tumor biology, including tissue homeostasis, immune compartmentalization, and specialized macrophage adaptation within the neural microenvironment.

A major determinant of TREM2 function in brain tumors is macrophage ontogeny. Resident microglia and infiltrating monocyte-derived macrophages differ substantially in developmental origin, transcriptional identity, metabolic programming, and responses to local signaling cues, all of which may influence the biological consequences of TREM2 activity (Li, J. et al., 2025). In certain contexts, TREM2 signaling in resident microglia may contribute to phagocytic clearance, tissue adaptation, or regulation of neuroinflammatory stress, whereas in other settings, TREM2-associated myeloid populations may participate in immunoregulatory remodeling that could favor tumor persistence. These distinctions reinforce that therapeutic strategies targeting TREM2 in CNS tumors cannot be directly extrapolated from peripheral cancers.

4.3. Other solid tumors

Beyond gastrointestinal and CNS malignancies, TREM2-associated macrophage populations have also been identified across a broad spectrum of solid tumors, including lung, breast, prostate, and CRC. Although their abundance, transcriptional programs, and functional significance vary among tumor types, these populations consistently exhibit features of metabolic adaptation and immunoregulatory remodeling, frequently accompanied by altered T-cell interactions and immune-excluded phenotypes (Huang and Fang, 2025; Wang et al., 2025; Zhang et al., 2025). Across these tumor contexts, TREM2 expression frequently marks metabolically adapted macrophage populations shaped by local microenvironmental pressures, although the precise biological consequences appear to vary by tumor type and disease setting (Huang and Fang, 2025; Pierro et al., 2025). Tumor-specific signals may further diversify these macrophage states, contributing to distinct transcriptional and functional phenotypes (Chu et al., 2025). In prostate cancer, for example, endocrine signaling may influence macrophage specialization, with emerging evidence suggesting cross-talk between androgen-regulated pathways and macrophage

Table 3
Context-dependent roles of TREM2-associated myeloid populations across major cancer types.

Tumor type	Dominant TREM2-associated myeloid population	Microenvironmental context	Reported biological associations	Clinical associations	Therapeutic considerations	References
GBM	Microglia-like TREM2 ⁺ myeloid cells and infiltrating macrophages	Neural tissue signals, lipid debris, hypoxia, neuroinflammation	Phagocytic remodeling, context-dependent immune regulation, tissue adaptation	Variable associations depending on cellular composition and disease context	Potential need to preserve protective CNS myeloid functions	(Yu et al., 2025)
HCC	Lipid-associated TREM2 ⁺ macrophage populations	Steatosis, chronic inflammation, NASH-associated metabolic stress	Immune remodeling, altered T-cell infiltration, metabolically adapted macrophage states	Frequently associated with immunoregulatory TME features	Potential context-specific combination with immunotherapy	(Parseas et al., 2025)
PDAC	Stroma-associated TREM2 ⁺ macrophage populations	Dense desmoplasia, hypoxia, metabolic stress, inflammatory remodeling	Immune exclusion, stromal adaptation, context-dependent inflammatory regulation	Associated with therapy resistance in selected studies; conflicting biology reported	Requires caution due to paradoxical inflammatory consequences in some settings	(Liang et al., 2026)
Gastric cancer	Metabolically adapted TREM2 ⁺ associated macrophage populations	Hypoxia, altered lipid metabolism, chronic inflammation	Immunoregulatory macrophage remodeling	Associated with advanced disease features in selected studies	Potential biomarker candidate requiring validation	(Saha et al., 2024)
NSCLC	Monocyte-derived TREM2 ⁺ associated macrophage populations	Inflammatory cytokines, metabolic stress, tumor-derived signaling	Immune remodeling and altered T-cell interactions	Associated with immune-excluded phenotypes in selected cohorts	Potential combination immunotherapy targeting	(Wei et al., 2025)
Breast cancer	Lipid-adapted TREM2 ⁺ associated macrophage populations	Lipid metabolism, hypoxia, inflammatory cytokines	Immunoregulatory remodeling and macrophage adaptation	Associated with aggressive immune microenvironment features	Exploratory therapeutic target requiring further validation	(Yang et al., 2025)
CRC	Metabolically adapted TREM2 ⁺ associated macrophage populations	Microbial signals, inflammation, hypoxia	Context-dependent immune regulation	Variable associations depending on tumor context	Potential biomarker and therapeutic relevance under investigation	(Guo et al., 2025)

Note: The biological and clinical associations summarized here reflect currently available evidence and may vary according to macrophage ontogeny, disease stage, treatment context, and analytical platform. Therapeutic considerations are hypothesis-generating and should not be interpreted as established clinical indications.

immunobiology (Li, C. et al., 2025).

Additional complexity arises in tumor ecosystems where macrophages adopt less conventional adaptive phenotypes (Li, C. et al., 2025; Momcilovic et al., 2025). In selected experimental contexts, TREM2-associated macrophage populations have been reported to acquire neuron-like transcriptional or functional characteristics, potentially contributing to tumor-associated pain signaling and broader neuroimmune interactions that extend beyond classical immunoregulatory roles (Li, H. et al., 2025). All these observations remain relatively early; they highlight the plasticity of macrophage adaptations across distinct tumor ecosystems.

These studies reinforce the concept that TREM2 biology is highly tumor- and tissue-context dependent. The biological consequences associated with TREM2 expression in myeloid populations should not be uniformly generalized across cancer types but must instead be interpreted in the context of macrophage ontogeny, metabolic adaptation, tissue architecture, and local signaling networks (Qian et al., 2024).

5. TREM2⁺ macrophages and immune evasion in the TME

A defining feature of TREM2-associated macrophage populations is their frequent association with immunosuppressive TMEs that constrain effective antitumor immunity (Wang et al., 2025; Wang et al., 2026). Through coordinated regulation of immune-cell recruitment, activation, metabolic adaptation, and tissue organization, TREM2-associated macrophages have emerged as key contributors to immune evasion across multiple solid tumor types (Lei et al., 2024; Peshoff et al., 2024).

One of the most prominent observed associations is altered CD8⁺ T-cell infiltration and function in tumors enriched for TREM2⁺ macrophage populations (Tan et al., 2023; Wang et al., 2025). In several tumor settings, increased TREM2-associated abundance has been linked to reduced cytotoxic T-cell infiltration, immune exclusion, or enrichment of dysfunctional or exhausted T-cell states (Huang and Fang, 2025; Li et al., 2023). Mechanistically, these observations may reflect multiple non-mutually exclusive processes, including production of immunoregulatory mediators, disruption of chemokine gradients relevant to T-cell trafficking, and metabolic competition within the TME that constrains effector lymphocyte fitness (Binnewies et al., 2021; Huang and Fang, 2025; Wang et al., 2025). These interacting mechanisms may contribute to reduced responsiveness to ICB in selected contexts.

TREM2-associated macrophage programs have also been linked to altered antigen presentation capacity and modulation of interferon-associated immune signaling (Huang and Fang, 2025; Liu et al., 2025; Zhang et al., 2025). In some experimental settings, reduced expression of major histocompatibility complex (MHC) molecules, co-stimulatory programs, or interferon-responsive pathways has been observed in TREM2-enriched macrophage populations, potentially compromising both innate immune activation and adaptive T-cell priming (Lin et al., 2025). However, these effects appear context dependent and should not be interpreted as universal consequences of TREM2 signaling across all tumor settings (Vanmeerbeek et al., 2026).

Beyond direct interactions with lymphocytes, TREM2-associated macrophages participate in multicellular communication networks that coordinate stromal remodeling and myeloid-cell function within the TME (Binnewies et al., 2021). Interactions with myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs) have been proposed in selected tumor contexts, where reciprocal signaling, metabolic cooperation, extracellular matrix remodeling, or stromal barrier formation may further restrict immune access to malignant cells (Dash et al., 2026; Wang et al., 2025). These multicellular interactions likely contribute to stabilization of immune-restricted tumor niches in a context-dependent manner (Zhou et al., 2024).

TREM2-associated macrophages have also been linked to extracellular matrix remodeling and vascular remodeling in certain tumor settings (Dolci et al., 2026). Through production of matrix-modifying enzymes, pro-angiogenic mediators, and stromal regulatory signals,

these populations may contribute to stromal and vascular remodeling that impairs immune surveillance while supporting tumor adaptation (Lee et al., 2025). In selected contexts, such remodeling may reinforce hypoxia, immune exclusion, and metabolically restrictive tumor conditions (Shi et al., 2025a).

Current evidence therefore supports the view that TREM2-associated macrophage populations participate in multiple interconnected mechanisms of immune evasion, integrating cellular, metabolic, stromal, and structural dimensions of tumor immune regulation (Lei et al., 2024; Molgora et al., 2023; Wang et al., 2025).

6. Therapeutic strategies targeting TREM2-associated macrophages

Given their recurrent association with immunoregulatory remodeling, immune exclusion, and therapeutic resistance in selected tumor contexts, TREM2-associated macrophage populations have emerged as biologically attractive but mechanistically complex therapeutic targets in cancer (Binnewies et al., 2021; Guo et al., 2025; Lei et al., 2024). Preclinical studies and early clinical investigations suggest that modulation of TREM2 signaling may reshape macrophage behavior and alter tumor immune architecture; however, the context-dependent biology of TREM2, including its tissue-protective roles in selected settings, necessitates cautious and biologically calibrated therapeutic strategies (Binnewies et al., 2021; Huang and Fang, 2025; Nada et al., 2026). Fig. 4 provides a conceptual framework summarizing current therapeutic strategies and context-dependent translational considerations for targeting TREM2-associated macrophage populations.

Therapeutic strategies targeting TREM2⁺ TAMs, along with their mechanisms of action and key translational considerations, are summarized in Table 4.

6.1. Therapeutic modulation of TREM2 signaling

Therapeutic targeting of TREM2 has largely focused on antibody-based strategies designed to modulate receptor signaling, alter macrophage functional states, or reduce the abundance of TREM2⁺ macrophage populations within tumors (Fuchs et al., 2025; Huang and Fang, 2025). Current therapeutic strategies broadly include functional modulation of TREM2 signaling and antibody-mediated targeting of TREM2-expressing macrophages (Wang et al., 2025). Modulation of TREM2 signaling may reshape macrophage behavior through effects on phagocytic function, metabolic adaptation, and phenotypic state, whereas blocking or depleting antibodies, such as PY314, are intended to disrupt TREM2-associated immunoregulatory programs or reduce selected TREM2⁺ macrophage populations within the TME (Yeku et al., 2025).

Preclinical studies across multiple tumor models suggest that modulation of TREM2 may alter macrophage composition, influence T-cell infiltration, and enhance responses to ICB in selected experimental settings (Mateus-Tique et al., 2026). Translation into humans, however, remains at an early stage. Early-phase studies of TREM2-directed antibodies have primarily established clinical feasibility, safety, and pharmacodynamic activity rather than definitive antitumor efficacy (Vanmeerbeek et al., 2026). Accordingly, the magnitude and durability of therapeutic benefit, optimal dose and schedule, biomarker-guided patient selection, and long-term safety remain to be established.

The principal challenge is therefore not simply whether TREM2 can be pharmacologically targeted, but whether the appropriate TREM2-dependent macrophage state can be modulated without disrupting beneficial myeloid functions. The context-dependent biology of TREM2 raises particular concerns regarding excessive depletion or inappropriate modulation of tissue-adaptive macrophage populations, particularly in tumors where TREM2 may contribute to inflammatory restraint, immune homeostasis or tissue protection (Huang and Fang, 2025). These considerations favor therapeutic strategies capable of calibrating

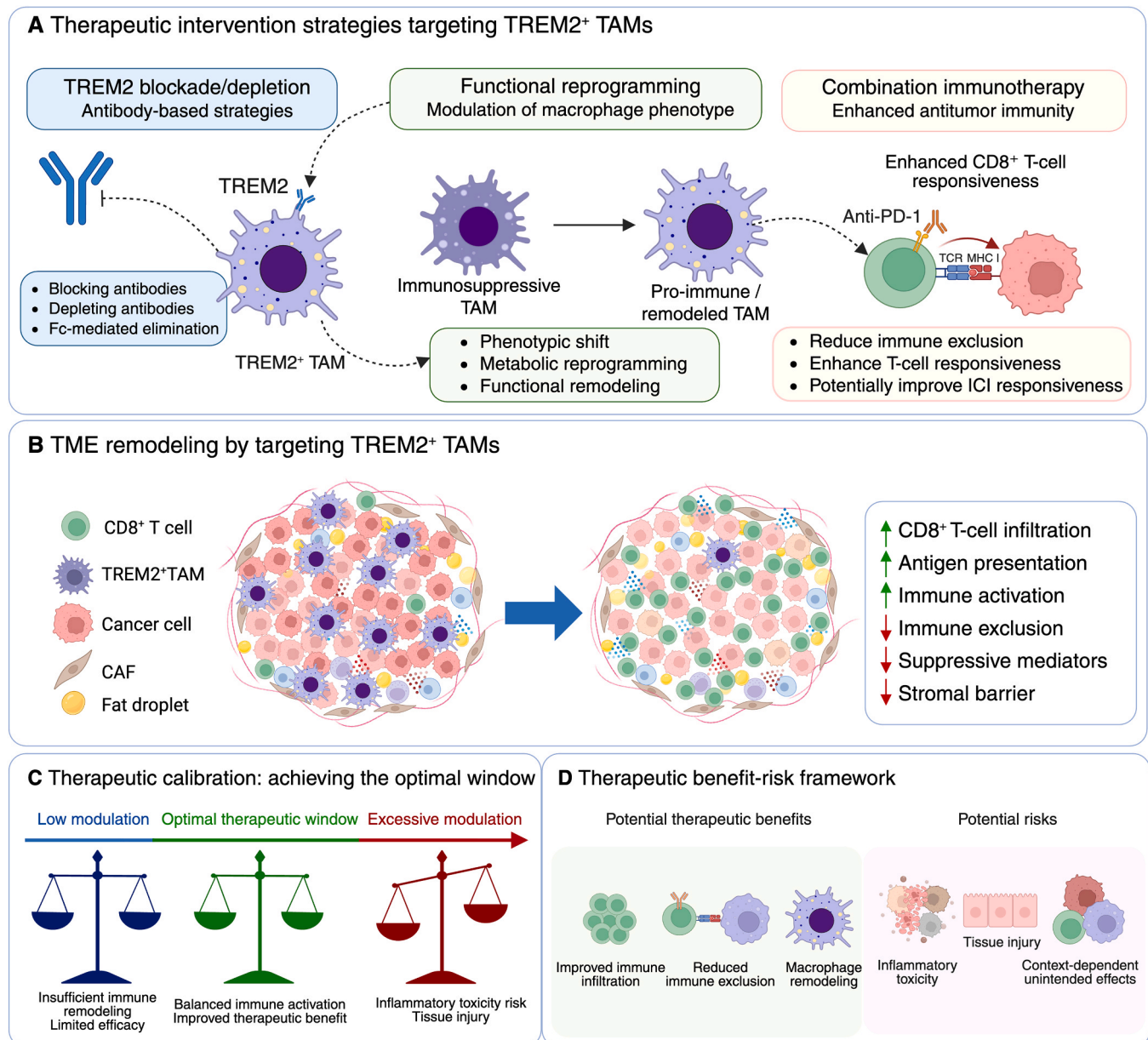


Fig. 4. Therapeutic strategies targeting TREM2⁺ TAMs and context-dependent translational considerations. (A) Therapeutic intervention strategies. Antibody-based approaches may modulate TREM2 signaling or reduce TREM2⁺ macrophage populations through blockade, depletion, or Fc-mediated elimination. Functional reprogramming strategies aim to shift immunosuppressive TAMs toward pro-immune phenotypes through metabolic and phenotypic remodeling. Combination immunotherapy, particularly with ICB, may enhance CD8⁺ T-cell activity, reduce immune exclusion, and improve responses to ICIs. (B) TME remodeling. Targeting TREM2⁺ TAMs may reshape the TME by increasing CD8⁺ T-cell infiltration, antigen presentation, and immune activation, while reducing immune exclusion, suppressive mediators, stromal barriers, and immunosuppressive macrophage niches. (C) Therapeutic calibration. Because TREM2 functions are context dependent, therapeutic benefit likely depends on achieving an optimal intervention window. Insufficient modulation may yield limited efficacy, whereas excessive targeting may provoke inflammatory toxicity or tissue injury. Biomarker-guided calibration and patient stratification may improve therapeutic precision. (D) Therapeutic benefit-risk framework. Potential benefits include improved immune infiltration, reduced immune exclusion, and macrophage remodeling that supports antitumor immunity. Potential risks include inflammatory toxicity, tissue injury, and context-dependent unintended effects, highlighting the need for tumor-specific therapeutic calibration.

rather than indiscriminately eliminating TREM2-associated macrophage activity and reinforce the need for tumor-specific functional biomarkers.

In addition, the structural complexity and promiscuity of TREM2 ligand recognition present additional challenges for rational drug development (Nada et al., 2026; Sigalov, 2024). Emerging advances in structural biology, computational modeling, and AI-assisted protein prediction may facilitate the development of more selective TREM2 modulators. Small-molecule agonists provide emerging proof that TREM2 can potentially be pharmacologically modulated beyond

antibody-based approaches, although their relevance to cancer remains to be established. Other strategies, including proximity-inducing technologies such as proteolysis-targeting chimeras (PROTACs) or molecular glues, remain speculative for TREM2 and should presently be regarded as future drug-development concepts rather than established therapeutic approaches. Progress will require improved structural characterization together with robust functional assays capable of determining how specific modes and degrees of TREM2 modulation reshape macrophage states across different tumor contexts.

Table 4

Therapeutic strategies targeting TREM2-associated macrophage populations: mechanisms, translational rationale, and limitations.

Strategy class	Intervention approach	Proposed mechanism	Potential TME impact	Key risks/limitations	Development stage	References
TREM2 signaling modulation	Antibody-mediated modulation of TREM2-associated signaling pathways	Functional modulation of TREM2-associated macrophage programs, including phagocytic activity, metabolic adaptation, and phenotypic remodeling	Potential remodeling of macrophage activation states and immune interactions	May reinforce tissue-adaptive programs in selected settings; uncertain tumor-specific consequences	Early clinical	(Yeku et al., 2025)
TREM2 blockade / depletion	TREM2-targeting blocking or depleting antibodies	Interference with TREM2-associated macrophage survival or signaling	Potential reduction of immune exclusion and altered T-cell accessibility	Risk of inflammatory dysregulation or loss of protective myeloid function	Early clinical	(Lei et al., 2024)
Combination immunotherapy	TREM2 modulation + PD-1/PD-L1 or CTLA-4 blockade	Concurrent targeting of macrophage-associated immune restriction and adaptive checkpoint resistance	Potential enhancement of antitumor immune responsiveness	Context-dependent efficacy; Patient selection needed	Preclinical-early clinical	(Xiang et al., 2021)
Innate immune activation	STING agonists ± TREM2 modulation	Promotion of innate immune activation and macrophage inflammatory reprogramming	Potential enhancement of antigen presentation and immune priming	Systemic inflammatory toxicity; delivery challenges	Preclinical	(Deng et al., 2025)
Targeted delivery platforms	Nanoparticle-based or macrophage-directed delivery systems	Localized modulation of TREM2-associated myeloid populations	Reduced systemic exposure; improved spatial targeting	Manufacturing complexity; biodistribution limitations	Preclinical	(Wang et al., 2026)
Engineered cellular / biologic strategies	CAR-based or scFv-directed macrophage targeting approaches	Direct depletion or functional modulation of suppressive myeloid populations	Potential remodeling of macrophage-dominant suppressive niches	Safety concerns, trafficking limitations, and off-tumor myeloid targeting	Translational	(Chen et al., 2023)
Precision biomarker-guided strategies	Spatial profiling and scRNA signatures; sTREM2-informed stratification	Context-aware therapeutic calibration and patient selection	Potential optimization of therapeutic window	Biomarker standardization lacking	Translational / emerging	(Tan et al., 2023)

Note: Development stages reflect the overall maturity of the therapeutic strategy based on currently available evidence and may vary among individual agents or platforms. Therapeutic approaches and biomarker strategies remain investigational, and their efficacy, safety, and optimal patient-selection criteria require prospective clinical validation.

6.2. Combination therapeutic strategies

Given the multifaceted and context-dependent role of TREM2⁺ macrophages in tumor immune regulation, combination strategies are increasingly being investigated to maximize therapeutic efficacy beyond the limits of single-agent interventions (Di Luccia et al., 2024; Lei et al., 2024). Preclinical studies suggest that TREM2 modulation may cooperate with ICB in selected tumor settings, where targeting TREM2⁺ macrophages can partially alleviate immune exclusion and improve responsiveness to PD-1 or CTLA-4 inhibition (Di Luccia et al., 2024; Huang and Fang, 2025). These observations support the concept that macrophage-directed interventions may complement adaptive immune reactivation by reshaping suppressive features of the TME.

Additional combination approaches aim to enhance innate immune activation while limiting macrophage-associated immunoregulatory programs (Hu et al., 2024). Activation of the stimulator of interferon genes (STING) pathway has shown potential to promote proinflammatory macrophage remodeling and augment interferon-associated immune activation, particularly when combined with TREM2-targeted strategies (Singhai et al., 2026). Nanoparticle-based delivery systems may further enable spatially restricted modulation of macrophage phenotypes, thereby enhancing tumor specificity while minimizing systemic toxicity and off-target immune effects (Wu et al., 2026).

Emerging cellular engineering approaches further broaden the therapeutic landscape for targeting TREM2-associated macrophages. Experimental platforms including CAR-M, other CAR-based platforms, and single-chain variable fragment (scFv)-directed strategies have been investigated for selective targeting of TREM2⁺ macrophages directly or delivery of immune-modulating payloads within the TME. Although these innovative approaches remain largely preclinical, they highlight the expanding landscape of macrophage-centered immunotherapeutic engineering and the growing interest in precision modulation of tumor-associated myeloid populations.

6.3. Risks, paradoxes, and safety considerations

Despite their therapeutic potential, interventions targeting TREM2⁺ macrophages also present important biological and translational challenges (Tang et al., 2025). In selected tumor contexts, depletion or inhibition of TREM2 signaling may provoke pathogenic inflammation, exacerbate tissue injury, or produce paradoxical tumor-promoting effects (Yang et al., 2025). Such observations appear particularly relevant in settings where TREM2 contributes to tissue adaptation, inflammatory restraint, or maintenance of local immune homeostasis (Huang and Fang, 2025). Accordingly, the therapeutic consequences of TREM2 inhibition are likely to depend on the functional state of the targeted macrophage population rather than on TREM2 expression alone.

PDAC provides a particularly important example of this paradox. Although TREM2⁺ macrophages are frequently interpreted as immunosuppressive and therefore therapeutically undesirable, TREM2 depletion in PDAC has been shown to enrich pathogenic IL-1β⁺ macrophages, intensify inflammatory signaling, and accelerate tumor progression (Yang et al., 2025). This finding indicates that removal of a TREM2-dependent macrophage program may not simply reverse immunosuppression but can redirect the myeloid compartment toward an alternative tumor-promoting inflammatory state. The PDAC findings therefore challenge a universal TREM2-blockade strategy and emphasize the need to determine whether TREM2 functions as a dominant immunosuppressive driver, a compensatory regulator of inflammation, or both within a particular tumor ecosystem.

Additional complexity arises from substantial heterogeneity across tumor types and tissue environments. Differences in macrophage ontogeny, ligand availability, metabolic stress, stromal composition, and inflammatory signaling may all influence therapeutic responses to TREM2 modulation, potentially leading to divergent or unpredictable biological outcomes (Rannikko and Hollmen, 2024). Patients whose tumors contain abundant TREM2⁺ macrophages with demonstrable immunosuppressive activity, spatial association with immune exclusion, and evidence of TREM2-dependent resistance may be more plausible

candidates for inhibitory strategies. In contrast, tumors in which TREM2⁺ macrophages retain tissue-protective or inflammation-restraining functions, or in which TREM2 loss promotes compensatory inflammatory macrophage states, may require alternative approaches such as partial pathway modulation or functional reprogramming rather than broad depletion or blockade. These considerations also caution against extrapolating therapeutic benefit from one tumor type to another without tumor-specific functional validation.

Therapeutic-window calibration should therefore incorporate both evidence of target dependency and evidence of biological risk. Biomarker-guided patient stratification should extend beyond TREM2 abundance to include macrophage transcriptional and metabolic state, spatial relationships with tumor and lymphoid cells, inflammatory cytokine programs, and, where feasible, pharmacodynamic evidence that TREM2 modulation produces the intended macrophage transition (Binnewies et al., 2021; Huang and Fang, 2025; Liang et al., 2026). Longitudinal monitoring may be particularly important for detecting compensatory myeloid reprogramming or inflammatory activation after treatment. Ultimately, successful clinical translation will require identifying not only patients most likely to benefit from TREM2-directed therapy, but also those in whom disruption of TREM2-dependent macrophage homeostasis could narrow or reverse the therapeutic window.

7. TREM2⁺ macrophages as biomarkers of tumor immune status and therapeutic response

Beyond their functional roles in shaping the TME, TREM2⁺ macrophages have emerged as promising biomarkers of tumor immune status, therapeutic responsiveness, and disease progression (Pierro et al., 2025). Their recurrent enrichment across diverse malignancies suggests that TREM2-associated macrophage states may provide clinically relevant information for patient stratification, prognosis, and therapeutic decision-making (Huang and Fang, 2025; Khantakova et al., 2022). Importantly, the clinical utility of TREM2-associated biomarkers is unlikely to depend on TREM2 expression alone but rather on their integration with the broader cellular and spatial context of the tumor microenvironment.

Across several cancer types, increased infiltration of TREM2⁺ macrophages has been associated with adverse clinical features, including reduced overall survival, shortened progression-free survival, immune exclusion, stromal remodeling, and resistance to therapy (Huang and Fang, 2025; Lei et al., 2024; Tang et al., 2025). Studies in HCC, PDAC, lung cancer, CRC, and glioma have reported correlations between TREM2⁺ macrophage abundance and immunosuppressive tumor features, although the magnitude and prognostic direction of these associations can vary substantially according to tumor type, tissue context, disease stage, and analytical methodology (Yang et al., 2025; Zhang et al., 2025). Of particular translational interest is the enrichment of TREM2-associated macrophage states in immune-cold or immune-excluded tumors, in which cytotoxic lymphocytes are sparse, spatially restricted, or functionally impaired. However, these associations should not be interpreted as evidence that TREM2 expression alone causes immune exclusion. Rather, TREM2⁺ macrophages may constitute one component of a broader suppressive ecosystem involving stromal barriers, altered chemokine signaling, metabolic constraints, and additional myeloid populations. Collectively, these observations suggest that TREM2-associated macrophage states may serve as context-dependent biomarkers of immunoregulatory tumor ecosystems rather than universal indicators of adverse prognosis.

In addition to potential prognostic value, TREM2⁺ macrophages have also been investigated as candidate predictive biomarkers for immunotherapy responsiveness (Huang and Fang, 2025; Yuan et al., 2026). Tumors enriched in TREM2⁺ macrophages frequently display reduced T-cell infiltration and impaired responsiveness to ICB in selected clinical and preclinical settings (Binnewies et al., 2021; Wang et al., 2026).

Evidence from functional perturbation studies further suggests that TREM2-associated macrophage programs can contribute to immune restriction in selected tumor models: genetic or therapeutic modulation of TREM2 has been associated with changes in myeloid composition, increased lymphocyte accessibility or activity, and improved responses to checkpoint blockade (Liu et al., 2025; Yu et al., 2022). These findings strengthen the biological link between TREM2-associated macrophage states and immune exclusion but do not establish a uniform causal relationship across tumor types. Accordingly, a TREM2-high/immune-excluded phenotype may be more informative than TREM2 abundance alone when considering macrophage-directed therapeutic combinations. Nevertheless, the predictive utility of TREM2-based biomarkers remains incompletely validated and requires further prospective clinical investigation.

Recent advances in spatial transcriptomics, multiplex imaging, and single-cell profiling have substantially expanded the biomarker potential of TREM2⁺ macrophages (Feiten et al., 2026). These approaches enable detailed mapping of TREM2⁺ macrophage localization relative to tumor cells, stromal compartments, vasculature, and infiltrating immune populations, revealing spatial architectures associated with immune exclusion and therapeutic resistance (Binnewies et al., 2021; Xia et al., 2026). Such spatial information may be particularly important for distinguishing immune-desert tumors, in which lymphocytes are globally scarce, from immune-excluded tumors, in which immune cells are present but fail to penetrate tumor nests. Single cell analyses further demonstrate marked heterogeneity within TREM2⁺ macrophage populations, identifying distinct transcriptional subclusters with potentially different biological and prognostic relevance (Mei et al., 2025; Wei et al., 2024).

Circulating sTREM2 has emerged as a candidate noninvasive biomarker. Plasma or serum sTREM2 levels may reflect systemic myeloid activation, inflammatory remodeling, and tumor-associated immune dynamics, thereby complementing tissue-based assessments (Ferri et al., 2020). Although the clinical utility of sTREM2 remains to be fully established, its accessibility makes it an attractive candidate for longitudinal monitoring of disease progression and therapeutic response (Colonna and Wang, 2016).

Collectively, current evidence supports the potential of TREM2-associated macrophages as integrated biomarkers of tumor immune remodeling, therapeutic responsiveness, and disease progression. Rather than serving as a single prognostic indicator, TREM2-associated biomarkers are likely to derive their greatest clinical value when combined with spatial, transcriptional, and functional profiling to enable context-aware patient stratification and precision immunotherapy. Continued prospective validation and biomarker standardization will be essential for translating these insights into routine clinical practice (Yuan et al., 2026).

8. Unresolved questions and future directions

Despite substantial progress in defining TREM2⁺ macrophage states in cancer, several mechanistic and translational questions remain unresolved. Foremost is what determines whether TREM2 signaling supports tumor-promoting immunosuppression or tissue-adaptive functions in a given setting. Macrophage ontogeny, tissue-specific metabolic constraints, inflammatory tone, stromal composition, disease stage, and local ligand availability may all contribute to these divergent outcomes, but their relative importance remains incompletely defined (Huang and Fang, 2025). Resolving these determinants will be essential for predicting when TREM2-directed intervention is likely to provide therapeutic benefit and when it may instead disrupt protective macrophage functions.

A related uncertainty concerns TREM2 ligand biology within tumors. Although phospholipid-associated structures, oxidized lipoproteins, apolipoproteins, and other candidate ligands have been implicated in TREM2 signaling, their generation, spatial distribution, temporal

dynamics, and functional relevance within individual tumor ecosystems remain poorly characterized (Greven et al., 2025; Huang and Fang, 2025; Qian et al., 2024). Importantly, direct receptor-ligand interactions must be distinguished from indirect metabolic and microenvironmental conditions that favor TREM2⁺ macrophage enrichment. Defining these relationships may reveal both more selective approaches to TREM2 modulation and opportunities to alter TREM2-associated macrophage states indirectly through metabolic or microenvironmental intervention.

The optimal therapeutic modality also remains uncertain. TREM2⁺ macrophages can potentially be targeted through receptor blockade, selective depletion, functional reprogramming, metabolic intervention, or combination strategies (Binnewies et al., 2021; Khantakova et al., 2022; Molgora et al., 2020; Rannikko and Hollmen, 2024). These approaches are unlikely to be interchangeable across tumor types. In settings where TREM2⁺ macrophages exert predominantly immunosuppressive functions, inhibition or depletion may be advantageous, whereas functional reprogramming or partial pathway modulation may be preferable when tissue-adaptive macrophage functions need to be preserved. Future studies should therefore define not only whether TREM2 is therapeutically actionable, but also which mode and intensity of intervention is appropriate for a specific biological context.

Progress toward such precision will require biomarkers that capture macrophage functional state rather than TREM2 expression alone. Integration of single-cell and spatial profiling, multiplex imaging, and computational pathology may enable assessment of TREM2⁺ macrophage ontogeny, metabolic programs, spatial relationships with tumor and immune cells, and association with immune exclusion or treatment resistance (Coulton et al., 2024; Mei et al., 2025). These approaches should be complemented by functional assays and clinically relevant models capable of testing TREM2-dependent responses across tumor types. Together, such platforms may help distinguish causal TREM2-dependent biology from transcriptional association and improve biomarker-guided patient stratification.

Additional variables that remain insufficiently studied should also be incorporated into future experimental design. Aging is particularly relevant because age-associated changes in macrophage metabolism, inflammatory signaling, tissue repair, and immune surveillance may alter both TREM2⁺ macrophage states and response to immunotherapy (Huang and Fang, 2025; Lei et al., 2024). Similarly, longitudinal studies are needed to determine how TREM2⁺ macrophage states evolve during tumor progression and under therapeutic pressure rather than relying predominantly on static pretreatment measurements.

Ultimately, advancing TREM2 from a descriptive macrophage marker to a clinically actionable target will require convergence of mechanistic, spatial, functional, and translational evidence. The key question is therefore no longer simply whether TREM2⁺ macrophages can be targeted, but which TREM2-associated macrophage state should be targeted, in which tumor context, by which therapeutic strategy, and at what stage of disease. Answering these questions will be central to developing context-aware TREM2-directed precision immunotherapy.

9. Critical view

The rapid expansion of TREM2-focused cancer research has established TREM2⁺ macrophages as a recurrent feature of multiple tumor ecosystems, but the strength of evidence supporting their functional and therapeutic significance remains uneven. Much of the field is still based on associations between TREM2 expression, macrophage transcriptional states, immune suppression, and adverse clinical features. Single-cell and spatial studies have greatly refined the phenotypic resolution of these populations, yet identification of a TREM2⁺ macrophage state does not by itself establish that TREM2 signaling is responsible for that state. This distinction between biomarker, mediator, and therapeutic dependency is fundamental. Functional perturbation studies provide stronger evidence for causality but remain limited to selected tumor types and experimental systems. Accordingly, TREM2 expression should

not automatically be interpreted as evidence of a therapeutically actionable TREM2 dependency.

A second limitation is the substantial heterogeneity of experimental models used to define TREM2 function. Murine tumors, genetically engineered models, human tumor specimens, organoid or coculture systems, and computational analyses capture different dimensions of macrophage biology and are not necessarily interchangeable. Macrophage ontogeny represents an additional source of uncertainty because tissue-resident macrophages and monocyte-derived TAMs may converge transcriptionally while retaining distinct functional properties. Moreover, commonly used experimental perturbations, including genetic deletion, antibody-mediated targeting, and macrophage depletion, can produce biological effects that extend beyond selective modulation of a disease-associated TREM2⁺ state. Greater use of lineage-resolved models, spatially informed functional assays, and human tumor systems will therefore be necessary to distinguish TREM2-dependent mechanisms from broader consequences of macrophage perturbation.

The most consequential challenge is cross-tumor extrapolation. In several cancers, TREM2⁺ TAMs are associated with immunosuppressive programs, restricted lymphocyte activity, treatment resistance, or tumor progression, supporting therapeutic inhibition or reprogramming. However, the PDAC paradox, in which TREM2 loss can promote pathogenic inflammation and accelerate tumor progression, demonstrates that the direction of therapeutic benefit cannot be inferred from TREM2 expression alone. Such findings should not be treated as isolated exceptions to an otherwise universal model; rather, they indicate that TREM2 function emerges from interactions among macrophage ontogeny, tissue physiology, inflammatory state, metabolic stress, ligand availability, and therapeutic pressure. Consequently, evidence supporting TREM2 inhibition in one tumor type should not be generalized to another without tumor-specific functional validation.

These limitations also redefine the requirements for clinical translation. Patient selection based solely on TREM2 abundance is unlikely to be sufficient. A clinically useful biomarker strategy will probably need to integrate TREM2 expression with macrophage functional state, spatial localization, immune-cell composition, metabolic features, and evidence of treatment-associated immune exclusion or resistance. Similarly, therapeutic development should move beyond the binary question of whether to inhibit TREM2. Depending on biological context, receptor blockade, selective depletion, partial pathway modulation, or functional reprogramming may produce substantially different outcomes. Early clinical studies should therefore incorporate pharmacodynamic measurements capable of determining whether an intervention has altered the intended macrophage state without provoking compensatory inflammation, loss of tissue-protective functions, or other unintended immune effects.

From our perspective, the field should therefore adopt a higher evidentiary threshold before designating TREM2 as a precision therapeutic target. Convincing translation will require concordant evidence that TREM2 identifies a reproducible macrophage state, contributes causally to the relevant tumor-promoting phenotype, predicts therapeutic vulnerability, and can be modulated within an acceptable biological and clinical therapeutic window. This framework shifts the central question from whether TREM2⁺ macrophages are generally “good” or “bad” to whether a specific TREM2-dependent macrophage program represents a causal and safely actionable vulnerability in a defined tumor ecosystem. Establishing that distinction will determine whether TREM2 ultimately becomes a broadly useful biomarker, a context-restricted therapeutic target, or both.

Abbreviations

AI	artificial intelligence
ApoE	apolipoprotein E
CAF	cancer-associated fibroblast
CAR	chimeric antigen receptor

CAR-M	chimeric antigen receptor macrophage
CAR-NK	chimeric antigen receptor natural killer
CAR-T	chimeric antigen receptor T cell
CRC	colorectal cancer
GBM	glioblastoma
HCC	hepatocellular carcinoma
ICB	immune checkpoint blockade
ICI	immune checkpoint inhibitor
MARCO	macrophage receptor with collagenous structure
MDSC	myeloid-derived suppressor cell
MHC	major histocompatibility complex
NSCLC	non-small cell lung cancer
oxLDL	oxidized low-density lipoprotein
PDAC	pancreatic ductal adenocarcinoma
PS	phosphatidylserine
RCC	renal cell carcinoma
ROS	reactive oxygen species
sTREM2	soluble triggering receptor expressed on myeloid cells 2
SYK	spleen tyrosine kinase
TAM	tumor-associated macrophage
TGF- β	transforming growth factor- β
TME	tumor microenvironment
TREM2	triggering receptor expressed on myeloid cells 2

CRedit authorship contribution statement

X.G. and W.M. conceptualized, drafted, reviewed, and edited the manuscript. J.Y., X.L., and Z.Q. contributed to literature collection and preparation of the initial draft. W.M. created all figures and the graphical abstract, supervised the project, provided critical scientific input, and was responsible for the comprehensive revision, refinement, and finalization of both the manuscript and the figures. All authors actively participated in revising the manuscript, critically reviewed the final version, and approved it for submission.

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