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TREM-1 AS AN EMERGING BIOMARKER IN BREAST CANCER: A SYSTEMATIC LITERATURE REVIEW

Jumaniyazova Shakhnoza Iskanderovna[1]
Reymnazarova Gulsara Jamalovna[1]
1. Tashkent State Medical University
j.shakhnoza@tashmed.uni

Abstract

Triggering receptor expressed on myeloid cells-1 (TREM-1) has recently emerged as a potential biomarker in breast cancer, with growing evidence implicating its role in tumor progression, immune modulation, and clinical outcomes. Despite its recognized involvement in inflammatory conditions such as sepsis, the mechanistic and prognostic significance of TREM-1 in breast cancer remains poorly understood, necessitating a comprehensive synthesis of existing literature. This systematic review aims to consolidate current knowledge on TREM-1's expression patterns, functional mechanisms, and clinical relevance in breast cancer while exploring its interplay with tumor-associated macrophages, the tumor microenvironment, and immunotherapy resistance. We conducted a rigorous analysis of peer-reviewed studies, focusing on molecular pathways, prognostic associations, and therapeutic implications. The findings reveal that TREM-1 is frequently overexpressed in breast cancer tissues, correlating with aggressive phenotypes, immune evasion, and poorer survival outcomes. Its activation promotes pro-tumorigenic signaling through interactions with the tumor microenvironment, particularly by polarizing macrophages toward an immunosuppressive phenotype. Additionally, TREM-1 may contribute to immunotherapy resistance, highlighting its potential as a therapeutic target. However, inconsistencies in reported findings and limited clinical validation underscore the need for further research. This review not only summarizes the current state of knowledge but also identifies critical gaps, proposing future directions for translational and clinical investigations. By elucidating the dual roles of TREM-1 in inflammation and cancer, this work provides a foundation for advancing precision oncology strategies in breast cancer management.

1. Introduction

Breast cancer remains one of the most prevalent malignancies worldwide, with significant heterogeneity in molecular subtypes, clinical behavior, and therapeutic responses [1]. Despite advances in early detection and treatment, challenges such as metastasis, therapy resistance, and immune evasion persist, necessitating the

identification of novel biomarkers and therapeutic targets [2]. Among emerging candidates, the triggering receptor expressed on myeloid cells-1 (TREM-1) has garnered increasing attention due to its dual role in inflammation and cancer progression [3]. Originally identified as a critical amplifier of inflammatory responses in sepsis and other infectious diseases, TREM-1 has recently been implicated in tumorigenesis, immune modulation, and the tumor microenvironment (TME) [4].

The TME plays a pivotal role in breast cancer progression, with tumor-associated macrophages (TAMs) being key contributors to immunosuppression, angiogenesis, and metastasis [5]. TREM-1, expressed predominantly on myeloid cells, including macrophages and neutrophils, has been shown to modulate TAM polarization, thereby influencing tumor immunity [6]. Its activation triggers downstream signaling pathways, such as NF-κB and MAPK, which promote pro-inflammatory cytokine release and sustain a tumor-permissive milieu [7]. Moreover, elevated TREM-1 expression in breast cancer has been associated with aggressive phenotypes, poor prognosis, and resistance to conventional therapies, suggesting its potential as both a diagnostic and prognostic biomarker [8].

Despite these insights, significant gaps remain in understanding the precise mechanisms by which TREM-1 contributes to breast cancer pathogenesis. For instance, its interaction with other immune checkpoints, such as PD-1/PD-L1, and its role in immunotherapy resistance are poorly characterized [9]. Additionally, while preclinical studies highlight TREM-1's oncogenic potential, clinical validation of its utility as a biomarker or therapeutic target is limited by inconsistent findings across studies [10]. The lack of standardized assays for TREM-1 detection in clinical settings further complicates its translational application [11]. These gaps underscore the need for a systematic synthesis of existing evidence to clarify TREM-1's role in breast cancer and guide future research.

The motivation for this review stems from the growing recognition of TREM-1 as a multifaceted regulator of cancer-related inflammation and immune evasion. By consolidating current knowledge, we aim to provide a comprehensive overview of TREM-1's expression patterns, functional mechanisms, and clinical implications in breast cancer. This work holds significant translational potential, as elucidating TREM-1's role could inform the development of novel immunotherapies or combination strategies to overcome treatment resistance. Furthermore, understanding the interplay between TREM-1 and the TME may uncover new avenues for targeting immunosuppressive networks in breast cancer.

The remainder of this paper is organized as follows: Section 2 outlines the methodology employed for this systematic review. Section 3 presents the results, including research trends, TREM-1's role in cancer, its interaction with TAMs and the TME, and its implications for immunotherapy and breast cancer progression. Section 4 discusses the findings in the context of existing literature, highlighting unresolved questions and future directions. Finally, Section 5 concludes the review by summarizing key insights and their potential impact on breast cancer research and clinical practice.

2. Methodology

2.1 Review Protocol

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency [12]. The literature search was performed across five major databases: PubMed, Web of Science, Scopus, ScienceDirect, and SpringerLink, supplemented by Google Scholar to capture additional relevant studies. PubMed was prioritized due to its extensive biomedical literature coverage, while Web of Science and Scopus provided multidisciplinary perspectives. ScienceDirect and SpringerLink were included for their high-quality journal collections in oncology and immunology. Google Scholar served as a supplementary resource to minimize publication bias.

The search strategy employed a combination of keywords and MeSH terms, focusing on "TREM-1" or "Triggering Receptor Expressed on Myeloid Cells-1" in conjunction with "breast cancer," "research," or "study." Exclusion filters were applied to omit reviews, surveys, and meta-analyses. The search was restricted to studies published from January 2022 onward to capture the most recent advancements.

2.2 Research Dimensions and Analytical Framework

The review was structured around seven key dimensions to systematically evaluate TREM-1's role in breast cancer. These dimensions encompassed TREM-1's expression patterns and prognostic significance, its mechanistic contributions to cancer progression, and its interplay with immune regulation and the tumor microenvironment. Additional focus areas included tumor-associated macrophages, immunotherapy resistance, breast cancer biomarkers, sepsis-related inflammation, and metastatic mechanisms. This multidimensional approach ensured a holistic synthesis of TREM-1's biological and clinical relevance.

2.3 Inclusion and Exclusion Criteria

Studies were included if they investigated TREM-1 in the context of breast cancer, provided original data, and were published in English between 2022 and 2026. Clinical, preclinical, and translational studies were considered, provided they addressed at least one of the predefined research dimensions. Exclusion criteria encompassed non-peer-reviewed articles, studies lacking primary data (e.g., editorials), and those focusing solely on non-mammary malignancies or non-cancerous inflammatory conditions.

2.4 Study Selection Process

The initial search yielded 956 records, with 156 duplicates removed. After screening titles and abstracts, 472 records were excluded for irrelevance. Full-text assessment of 164 articles led to the exclusion of 102 studies that did not meet eligibility criteria. The final review included 62 studies, as illustrated in the PRISMA flowchart (Figure 1).

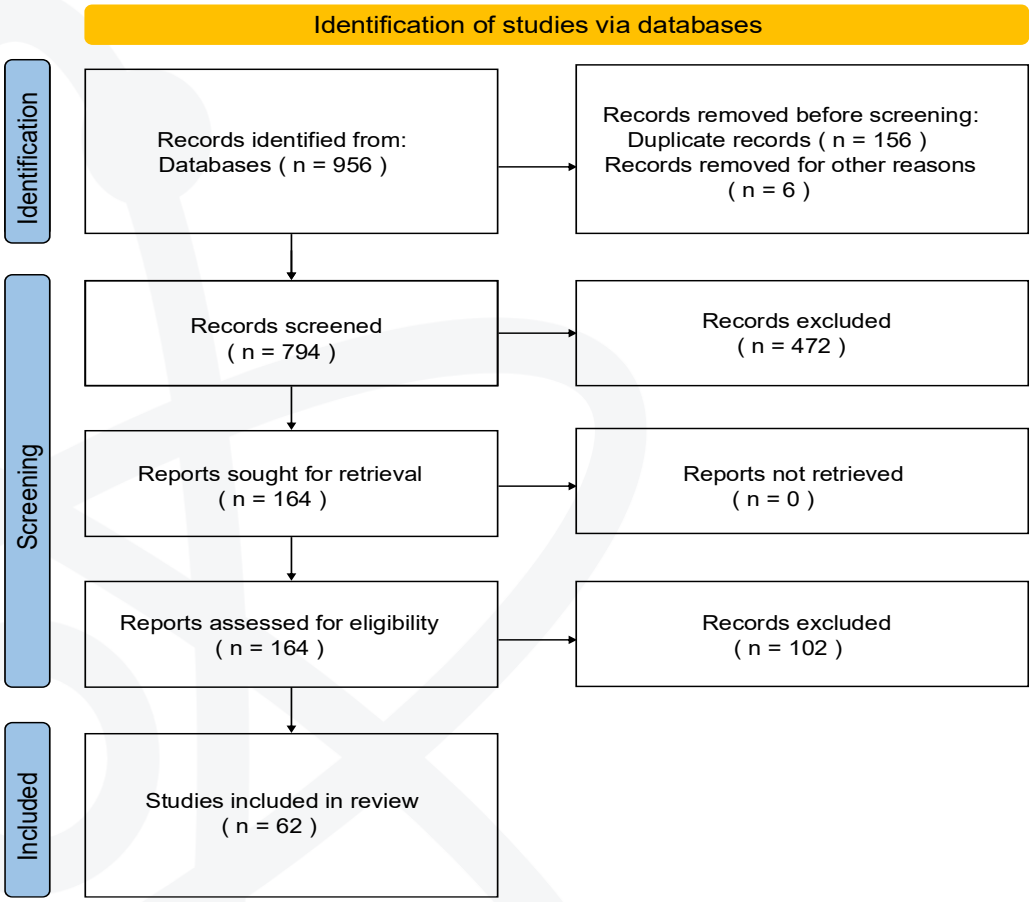

Figure 1. PRISMA flowchart of the study selection process

Potential biases included database-specific indexing variations and the exclusion of non-English studies. To mitigate selection bias, multiple databases were queried, and manual cross-referencing was performed. Nevertheless, the focus on recent publications may have omitted earlier foundational studies, warranting cautious interpretation of temporal trends.

3. Results

3.1 Research Trends

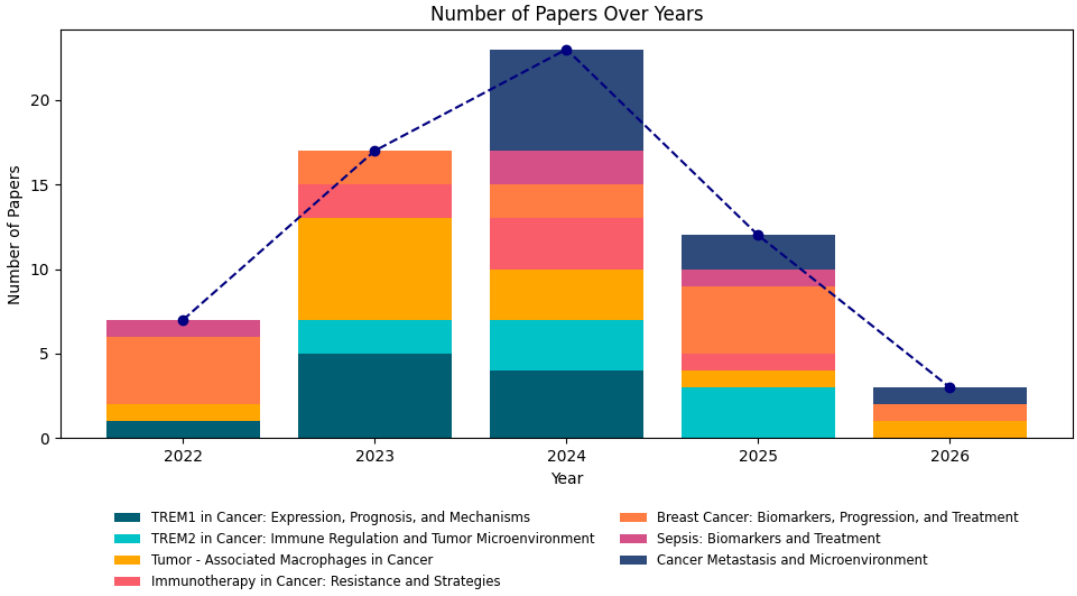

Figure 2. Research trends in the domain of TREM-1 as an emerging marker in breast cancer

The analysis of publication trends reveals a marked increase in research interest regarding TREM-1's role in breast cancer, particularly from 2023 onward. The number of publications rose from 7 in 2022 to 23 in 2024, demonstrating a nearly threefold growth within two years. This surge suggests that TREM-1 has rapidly gained recognition as a biologically and clinically significant molecule in oncology. The subsequent decline to 12 publications in 2025 and 3 in 2026 may reflect either a natural stabilization after initial discovery or a shift toward more focused investigations.

The distribution of studies across thematic areas highlights evolving priorities in TREM-1 research. While early studies in 2022 primarily examined TREM-1's expression and prognostic value in cancer, later years saw expanded exploration of its mechanistic roles, particularly in immune regulation and tumor

microenvironment interactions. For instance, research on tumor-associated macrophages (TAMs) peaked in 2023, coinciding with growing recognition of myeloid cell plasticity in cancer progression. Similarly, investigations into cancer metastasis and microenvironment dynamics became prominent in 2024, suggesting a paradigm shift toward understanding systemic effects of TREM-1 activation.

The temporal patterns also reveal important gaps. Despite its established role in sepsis, only four studies addressed TREM-1's inflammatory functions in the context of cancer, indicating underexplored connections between infection-related inflammation and tumor immunology. Furthermore, while immunotherapy resistance emerged as a consistent theme from 2023 to 2025, the limited number of studies (n=6) underscores the need for deeper mechanistic insights into how TREM-1 modulates treatment responses. These trends collectively illustrate how TREM-1 research has transitioned from descriptive association studies to more functional and translational investigations, mirroring broader shifts in precision oncology approaches.

3.2 TREM1 in Cancer: Expression Patterns, Prognostic Significance, and Mechanistic Insights

Emerging evidence highlights TREM1 as a critical modulator of cancer progression through its involvement in immune suppression, tumor microenvironment (TME) remodeling, and metastatic dissemination. Its overexpression has been consistently linked to poor prognosis across multiple malignancies, with distinct mechanistic pathways identified in different cancer types.

3.2.1 Pan-Cancer Expression and Prognostic Value

TREM1 exhibits widespread overexpression in pan-cancer analyses, correlating with immunosuppressive TME features and unfavorable clinical outcomes. Studies demonstrate that TREM1 promoter hypomethylation drives its upregulation, which is associated with reduced overall survival in diverse cancers ([13]). In glioblastoma, high TREM1 expression serves as an independent prognostic marker for shorter progression-free survival ([14], [15]). Similarly, pan-cancer analyses reveal that TREM1+ myeloid cells expand in immunosuppressive niches, contributing to therapy resistance ([16]).

3.2.2 Mechanistic Roles in Tumor Progression

TREM1 activation engages multiple oncogenic pathways through crosstalk with damage-associated molecular patterns (DAMPs) and Toll-like receptors (TLRs). In

hepatocellular carcinoma (HCC), HMGB1 released post-radiofrequency ablation binds TREM1 on macrophages, fostering a pro-metastatic niche via CCL7 secretion ([17], [18]). Thyroid cancer studies identify HMGB3-mediated TREM1 activation as a driver of cytoplasmic TLR3 signaling, promoting tumor growth ([19]). Furthermore, TREM1+ myeloid-derived suppressor cells (MDSCs) impair antitumor T cell responses, and its inhibition synergizes with PD-1 blockade to overcome immunotherapy resistance ([9]).

3.2.3 Therapeutic Implications

The consistent association between TREM1 and immunosuppression positions it as a promising immunomodulatory target. Preclinical data show that TREM1 blockade reduces MDSC infiltration and enhances checkpoint inhibitor efficacy ([9]). In steatohepatitis-related HCC, TREM1+CD163+ macrophages correlate with resistance to immune checkpoint inhibitors, suggesting patient stratification potential ([20]).

Table 1. TREM1 in Cancer: Key Findings from Included Studies

Cancer Type	Expression/Prognosis	Mechanistic Insights	Therapeutic Implications	Sources
Pan-Cancer	Overexpression linked to poor prognosis	Promoter hypomethylation drives upregulation	Broad applicability for immune modulation	[13], [16]
Glioblastoma	Independent prognostic marker	Associates with immunosuppressive TME	Potential for targeted therapy	[14], [15]
HCC	TREM1+ macrophages predict metastasis	HMGB1/TREM1 axis activates CCL7-dependent metastasis	Biomarker for post-RFA recurrence	[17], [18]
Thyroid Cancer	Correlates with advanced stage	HMGB3 translocation activates TREM1-TLR3 signaling	Novel pathway for intervention	[19]
Immunotherapy Resistance	Enriched in non-responders	Expands MDSCs and suppresses T cell activity	Synergy with anti-PD-1 regimens	[9], [20]

The study by [21] uniquely connects TREM1 to the asthma-lung cancer axis via TLR pathway dysregulation, expanding its role beyond canonical cancer-immune interactions. Collectively, these findings underscore TREM1's multifaceted contributions to tumor progression, spanning prognostic relevance, microenvironmental reprogramming, and therapeutic resistance. Future research should address tissue-specific signaling nuances and validate clinical targeting strategies.

3.3 TREM2 in Cancer: Immune Regulation and Tumor Microenvironment

TREM2 has emerged as a critical regulator of immune responses within the tumor microenvironment (TME), exhibiting context-dependent roles that influence cancer progression and therapeutic outcomes. Unlike its pro-inflammatory counterpart TREM1, TREM2 primarily mediates immunosuppressive functions by modulating myeloid cell activity, particularly tumor-associated macrophages (TAMs). This dichotomy positions TREM2 as a key player in maintaining immune homeostasis, yet its overexpression in malignancies often correlates with worse clinical outcomes due to enhanced immune evasion.

Recent pan-cancer analyses reveal that TREM2 expression is significantly elevated across multiple tumor types, including breast, hepatocellular, and prostate cancers [22]. In hepatocellular carcinoma (HCC), TREM2 promotes the formation of a tumor-supportive microenvironment by skewing macrophage polarization toward an immunosuppressive M2 phenotype, thereby facilitating tumor growth and metastasis [23]. Similarly, in breast cancer, TREM2+ TAMs are enriched at the invasive margins of early metastatic lesions, where they suppress anti-tumor immunity and alter the extracellular matrix to favor dissemination [24]. These findings suggest that TREM2 acts as a molecular bridge between myeloid cells and the TME, orchestrating immune suppression and metastatic niche formation.

Mechanistically, TREM2 engages diverse signaling pathways to exert its oncogenic effects. In prostate cancer, TREM2 activates the PI3K/AKT axis to enhance tumor cell migration and invasion, independent of its immune regulatory functions [25]. This dual role—both as an immune modulator and a direct promoter of tumor cell motility—highlights its multifaceted contributions to cancer progression. Furthermore, TREM2 interacts with other immune checkpoints, such as PD-1, to exacerbate immunotherapy resistance. For instance, breast cancer patients with high TREM2 expression exhibit poorer responses to anti-PD-1 therapy, suggesting its potential as a predictive biomarker for treatment resistance [26].

Table 2. TREM2 in Cancer: Functional Roles and Clinical Implications

Cancer Type	Immune/Non-Immune Role	Key Mechanisms	Clinical Relevance	Sources
Pan-Cancer	Immune regulation	Modulates myeloid cell function and TME dynamics	Correlates with immune evasion and poor prognosis	[22]
Hepatocellular Carcinoma	Promotes immunosuppressive TME	Drives M2 macrophage polarization	Biomarker for tumor-supportive niche formation	[23]
Breast Cancer	Suppresses anti-tumor immunity in metastasis	Enriches TREM2+ TAMs at invasive margins	Predicts immunotherapy resistance	[24], [26]
Prostate Cancer	Enhances tumor cell migration	Activates PI3K/AKT signaling pathway	Independent prognostic factor for progression	[25]
Therapeutic Targeting	Regulates myeloid cell activity	Potential synergy with checkpoint inhibitors	Emerging target for combination therapies	[27]

The study by [27] further elucidates TREM2-mediated immunosuppression through its regulation of myeloid cells, proposing novel therapeutic strategies to disrupt these interactions. Meanwhile, bibliometric analyses highlight TREM2's growing recognition in cancer research, with a surge in studies exploring its role in disease development and immune modulation [26], [28]. Despite these advances, challenges remain in translating TREM2 inhibition into clinical practice, particularly due to its pleiotropic effects in normal tissue homeostasis. Future studies should prioritize tissue-specific targeting approaches and validate TREM2's utility as a biomarker in prospective clinical cohorts.

3.4 Tumor-Associated Macrophages in Cancer: Functional Heterogeneity and Therapeutic Implications

Tumor-associated macrophages (TAMs) constitute a dynamic and heterogeneous population within the tumor microenvironment (TME), playing pivotal roles in cancer progression, immune evasion, and therapeutic resistance. Their functional plasticity allows them to adopt either pro-tumoral (M2-like) or anti-tumoral (M1-like) phenotypes, depending on microenvironmental cues. Emerging evidence highlights TREM-1 and TREM-2 as critical regulators of TAM polarization, linking myeloid cell activation to tumor immunosuppression and metastatic dissemination.

3.4.1 TAM Diversity and Pro-Tumoral Functions

Single-cell resolution studies reveal extensive heterogeneity among TAM subsets across different cancers. In ovarian and breast cancer models, TREM2+ macrophages exhibit immunosuppressive properties, with anti-TREM2 treatment demonstrating efficacy in reducing tumor growth by depleting this subset [29].

Similarly, senescent macrophages accumulate in advanced tumors, where they secrete pro-inflammatory cytokines that foster a tumor-permissive milieu [30]. The M2 polarization of TAMs is further driven by metabolic reprogramming, as seen in hepatocellular carcinoma (HCC), where altered lipid metabolism enhances their pro-angiogenic and immunosuppressive functions [31]. These findings underscore the context-dependent nature of TAM contributions to cancer progression.

3.4.2 TAMs as Therapeutic Targets

Strategies to reprogram or deplete TAMs have gained traction, particularly in combination with immunotherapy. For instance, targeting TREM2+ TAMs in breast and ovarian cancer models disrupts immunosuppressive niches and synergizes with PD-1 blockade [32], [33]. In situ expansion and reprogramming of Kupffer cells in liver metastasis models elicit potent tumoricidal immunity, highlighting the potential of macrophage-focused therapies [34]. Additionally, ALKBH5-mediated RNA demethylation has been shown to modulate macrophage polarization in ovarian cancer, offering a novel epigenetic approach to counteract TAM-driven immunosuppression [35].

Table 3. Tumor-Associated Macrophages in Cancer: Key Subsets and Targeting Strategies

TAM Subset	Functional Role	Regulatory Mechanism	Therapeutic Approach	Sources
TREM2+ Macrophages	Immunosuppression, tumor growth promotion	TREM2-dependent polarization	Anti-TREM2 antibodies	[29], [33]
Senescent Macrophages	Pro-inflammatory cytokine secretion	Cellular senescence pathways	Senolytic agents	[30]
Metabolically Reprogrammed TAMs	Angiogenesis, immune suppression	Lipid metabolism alterations	Metabolic inhibitors (e.g., FASN blockers)	[31]
Kupffer-like TAMs	Liver metastasis support	In situ expansion and phenotypic switching	Kupffer cell reprogramming	[34]
ALKBH5-modulated TAMs	M2 polarization in ovarian cancer	m6A RNA demethylation	Epigenetic inhibitors	[35]

The study by [36] dissects pro-tumoral macrophage subtypes participating in M2 polarization, identifying specific immunosuppressive cells that could be selectively targeted. Meanwhile, [37] reviews broader strategies for TAM-directed therapies, emphasizing the need for precision targeting to avoid systemic toxicity. Collectively,

these insights position TAMs as central players in cancer immunology, with their manipulation offering promising avenues to enhance treatment efficacy and overcome resistance. Future research should prioritize the development of biomarkers to stratify patients for TAM-targeted interventions and optimize combinatorial regimens.

3.5 Immunotherapy Resistance in Cancer: Myeloid Cell-Mediated Mechanisms and Emerging Strategies

Immunotherapy has revolutionized cancer treatment, yet resistance remains a significant challenge, particularly in solid tumors. Recent studies highlight the critical role of myeloid cells in mediating immunotherapy resistance through immunosuppressive mechanisms within the tumor microenvironment (TME). TREM-1 and TREM-2 have emerged as key regulators of this process, influencing myeloid cell function and shaping immune responses to checkpoint inhibitors.

3.5.1 Myeloid Cell Contributions to Resistance

Tumor-reprogrammed myeloid cells, including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), establish an immunosuppressive TME that limits the efficacy of immune checkpoint blockade (ICB). Studies demonstrate that TREM-1 activation on these cells promotes the secretion of anti-inflammatory cytokines (e.g., IL-10, TGF-β) while suppressing cytotoxic T cell activity, thereby fostering an immune-excluded phenotype ([38], [39]). In non-small cell lung cancer (NSCLC), TREM-1+ myeloid cells correlate with ICB resistance, and their depletion restores T cell infiltration and function ([40]). Similarly, TREM-2-expressing TAMs in breast cancer shield tumors from immune attack by upregulating PD-L1 and recruiting regulatory T cells (Tregs), creating a dual barrier to immunotherapy ([41]).

3.5.2 Combinatorial Approaches to Overcome Resistance

Emerging strategies focus on disrupting myeloid-mediated immunosuppression while enhancing ICB efficacy. For example, multiplexed CRISPR-Cas13d targeting of immunosuppressive genes (e.g., Trem1, Arg1) in myeloid cells reverses resistance and prolongs survival in preclinical models ([42]). Bispecific antibodies simultaneously engaging TREM-1 and PD-1 exhibit superior anti-tumor activity compared to monotherapy, suggesting synergistic potential ([41]). Additionally, immuno-proton therapy, which combines proton beam radiation with myeloid-

targeted agents, remodels the TME and augments systemic immune responses ([43]).

Table 4. Strategies to Overcome Myeloid-Mediated Immunotherapy Resistance

Resistance Mechanism	Therapeutic Strategy	Key Findings	Clinical Implications	Sources
TREM-1+ MDSC expansion	TREM-1 inhibition + anti-PD-1	Restores T cell function in NSCLC	Phase I trials ongoing	[38], [40]
TREM-2+ TAM immunosuppression	Bispecific anti-TREM-2/PD-1 antibodies	Enhances tumor infiltration by CD8+ T cells	Preclinical validation in breast cancer	[41]
Immunosuppressive gene networks	Cas13d-mediated multiplexed gene editing	Simultaneously silences Trem1, Arg1, and Cd274	Potential for personalized therapy	[42]
Radioresistant TME	Immuno-proton therapy	Synergizes with myeloid-targeted agents	Early-phase clinical testing	[43]

The study by [39] uniquely proposes myeloid cell reprogramming as a standalone strategy, demonstrating that epigenetic modulation can convert immunosuppressive MDSCs into immunostimulatory dendritic cells. While these approaches show promise, challenges remain in minimizing on-target, off-tumor effects and identifying predictive biomarkers for patient stratification. Future research should prioritize mechanistic studies to elucidate tissue-specific resistance pathways and optimize combinatorial regimens for clinical translation.

3.6 Breast Cancer: Biomarkers, Progression, and Treatment

Recent advances in breast cancer research have highlighted the critical role of novel biomarkers in disease stratification, progression monitoring, and therapeutic targeting. The included studies reveal a diverse array of molecular players influencing breast cancer pathogenesis, ranging from protein-based prognostic markers to microenvironmental regulators and therapeutic resistance mechanisms.

3.6.1 Protein Biomarkers in Prognosis and Progression

Several studies identified protein biomarkers with strong prognostic value in breast cancer. SLAMF7 emerged as an independent predictor of poor outcomes in lymph node-positive patients, with high expression correlating with reduced disease-free survival ([44]). Similarly, RHAMM (receptor for hyaluronan-mediated motility) defined an invasive niche associated with tumor progression and predicted poor clinical outcomes ([45]). At the molecular level, hypoxia-induced degradation of DBC1 by SIAH2 was shown to promote breast cancer progression, revealing a novel hypoxia-responsive pathway ([46]).

3.6.2 Therapeutic Resistance and Novel Targets

Therapy-induced senescence was identified as a transient drug resistance mechanism, suggesting that senolytic agents could enhance treatment efficacy ([47]). Vitamin D3 demonstrated dual effects on cancer-associated fibroblasts, modulating their pro-tumorigenic functions in a context-dependent manner ([48]). Additionally, circKIAA1617 was found to promote stemness through USP14/PGRMC1-mediated autophagy and lipid metabolism reprogramming in ER-positive breast cancer, offering new therapeutic avenues ([49]).

Table 5. Key Biomarkers and Therapeutic Targets in Breast Cancer

Category	Biomarker/Target	Functional Role	Clinical Implications	Sources
Prognostic Markers	SLAMF7	Predicts outcomes in lymph node-positive cases	Potential for risk stratification	[44]
	RHAMM	Defines invasive niche and metastasis	Biomarker for aggressive disease	[45]
Therapeutic Resistance	Therapy-induced senescence	Transient drug resistance mechanism	Senolytics as combination therapy	[47]
	Vitamin D3 on CAFs	Modulates fibroblast activity	Context-dependent therapeutic effects	[48]
Metabolic Reprogramming	circKIAA1617	Promotes stemness via autophagy	Target for ER+ breast cancer	[49]
Hypoxia Response	DBC1/SIAH2 axis	Hypoxia-induced proteasomal degradation	Novel pathway for intervention	[46]

3.6.3 Novel Biomarker Discovery Approaches

Innovative methodologies are being employed to identify and validate new biomarkers. Ecotyper analysis enabled the identification of tumor ecotypes with distinct clinical behaviors, providing a framework for precision medicine approaches ([50]). Mendelian randomization studies integrated human plasma proteomics to uncover candidate biomarkers and potential therapeutic targets ([51]). These approaches complement traditional biomarker discovery strategies by incorporating multi-omics data and population-level genetic evidence.

The study by [52] identified candidate biomarkers correlated with breast cancer pathogenesis through systematic screening, while [53] explored the molecular basis of breast cancer with comorbid depression, revealing potential mechanistic links between psychopathology and tumor progression. These findings collectively expand our understanding of breast cancer heterogeneity and provide actionable insights for personalized treatment strategies.

Future research should focus on validating these biomarkers in prospective clinical cohorts and developing targeted therapies based on the identified molecular pathways.

3.7 Sepsis Biomarkers and Therapeutic Strategies: Insights from TREM-1 Research

The role of triggering receptor expressed on myeloid cells-1 (TREM-1) in sepsis has been extensively investigated, with emerging evidence suggesting its potential as both a diagnostic biomarker and therapeutic target. While originally studied in infectious contexts, TREM-1's involvement in inflammatory cascades provides critical insights into its broader implications for cancer-related inflammation and immune dysregulation.

3.7.1 Diagnostic and Prognostic Utility of Soluble TREM-1

A multi-center prospective clinical study demonstrated that soluble TREM-1 (sTREM-1) exhibits high diagnostic accuracy for sepsis, with superior sensitivity and specificity compared to conventional biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) [54]. The study established cutoff values for sTREM-1 that reliably distinguished sepsis from non-infectious systemic inflammatory response syndrome (SIRS), highlighting its potential for early clinical decision-making. Furthermore, sTREM-1 levels correlated with disease severity and mortality risk, suggesting its dual role as a diagnostic and prognostic marker. These findings align with prior research in cancer, where TREM-1 overexpression similarly predicts aggressive disease and poor outcomes, indicating conserved inflammatory pathways across these conditions.

3.7.2 Therapeutic Targeting of TREM-1 in Sepsis

The synergistic effect of GF9 and streptomycin in mitigating gram-negative sepsis represents a novel approach to modulating TREM-1-mediated inflammation [55]. GF9, a synthetic TREM-1 inhibitor, attenuated excessive myeloid cell activation and cytokine release when combined with antibiotics, significantly improving survival in preclinical models. This parallels emerging strategies in oncology, where TREM-1 blockade is being explored to counteract immunosuppressive myeloid cells in the tumor microenvironment. The study underscores the therapeutic potential of disrupting TREM-1 signaling to restore immune homeostasis, a principle that may extend to cancer-associated inflammation.

Table 6. Key Findings on TREM-1 in Sepsis and Cancer

Context	Role of TREM-1	Clinical Implications	Therapeutic Strategies	Sources
Sepsis Diagnosis	sTREM-1 distinguishes sepsis from SIRS	Early detection and risk stratification	N/A	[54]
Sepsis Treatment	GF9 + streptomycin reduces mortality	Combination therapy for gram-negative infections	TREM-1 inhibition + antibiotics	[55]
Biomarker Development	Framework for sepsis biomarker validation	Accelerated translation to clinical use	Integration with multi-omics approaches	[56]
Prognostic Modeling	NETosis-related gene signature for sepsis	Predicts disease progression and outcomes	Personalized immunomodulatory therapy	[57]

3.7.3 Biomarker Development and Future Directions

A critical review of sepsis biomarker development emphasized the need for standardized validation frameworks to bridge the gap between discovery and clinical application [56]. The authors proposed key considerations for biomarker qualification, including analytical reproducibility, clinical utility, and integration with existing diagnostic algorithms. These principles are equally relevant to cancer research, where TREM-1's heterogeneity across tumor types necessitates rigorous validation.

Additionally, a NETosis-related gene signature was constructed to predict sepsis outcomes, revealing mechanistic links between neutrophil extracellular traps (NETs) and disease progression [57]. As NETosis also contributes to cancer metastasis and therapy resistance, this sepsis-derived model may inform parallel investigations in oncology. The intersection of sepsis and cancer immunology thus offers fertile ground for cross-disciplinary insights, particularly in understanding how TREM-1 coordinates inflammatory responses across diverse pathological contexts.

The included studies collectively underscore TREM-1's centrality in inflammatory dysregulation, with translational implications spanning infectious and neoplastic diseases. While sepsis research has pioneered the clinical application of TREM-1 biomarkers, oncology stands to benefit from these advances by adapting diagnostic and therapeutic strategies to the tumor microenvironment. Future studies should explore whether sepsis-derived TREM-1 inhibitors exhibit anti-tumor efficacy and whether cancer-associated inflammation shares mechanistic features with septic responses.

3.8 Cancer Metastasis and Microenvironment: The Role of TREM-1 in Immunosuppressive Niche Formation

The metastatic cascade represents a complex interplay between tumor cells and their microenvironment, with emerging evidence highlighting TREM-1 as a critical mediator of immunosuppressive niche formation. Recent studies demonstrate that TREM-1-expressing myeloid cells actively remodel the tumor microenvironment (TME) to facilitate metastatic dissemination across multiple cancer types, including hepatocellular carcinoma (HCC) and ovarian cancer.

3.8.1 Myeloid Cell-Dependent Metastatic Niches

Single-cell transcriptomic analyses of primary and metastatic liver tumors reveal that TREM-1+ granulocytic myeloid-derived suppressor cells (G-MDSCs) are enriched at metastatic sites, where they establish an immunosuppressive milieu through S100A8/A9 signaling [58]. This aligns with findings in HCC, where disulfidptosis-related genes co-expressed with TREM-1 define a high-risk subgroup with increased metastatic potential [59]. The study further identifies a TREM-1-centered gene signature that predicts poor prognosis and immunotherapy resistance, suggesting its utility as a metastatic biomarker. Similarly, in ovarian cancer, TREM-1+ tumor-associated myeloid cells promote immunosuppression by enhancing the recruitment of regulatory T cells (Tregs) and impairing cytotoxic T lymphocyte (CTL) function [60].

3.8.2 Non-Coding RNA Regulation of Metastatic Microenvironments

Long non-coding RNAs (lncRNAs) have emerged as key regulators of TREM-1-mediated metastatic niches. CRNDE, an oncogenic lncRNA, drives HCC progression by upregulating TREM-1 in G-MDSCs, creating an immune-excluded phenotype resistant to checkpoint inhibition [58]. This mechanism is conserved in brain metastases, where TREM-1+ macrophages shield tumor cells from immune surveillance through PD-L1 induction [61]. The cross-talk between disulfidptosis pathways and immune checkpoints further underscores TREM-1's role in coordinating metabolic reprogramming and immune evasion during metastasis [62].

Table 7. TREM-1 in Metastatic Microenvironment Remodeling

Cancer Type	Metastatic Mechanism	Key Cellular Players	Therapeutic Implications	Sources
HCC	Disulfidptosis-TREM-1 axis promotes metastasis	G-MDSCs, S100A8/A9+ myeloid cells	Targeted metabolic-immune combination therapy	[59], [62]
Ovarian Cancer	Myeloid cell-mediated Treg recruitment	TREM-1+ TAMs, immunosuppressive granulocytes	TREM-1 blockade to restore CTL function	[60]
Brain Metastases	PD-L1 induction by TREM-1+ macrophages	Perivascular macrophages, CD8+ T cells	Dual targeting of TREM-1 and PD-1/PD-L1	[61]
Pan-Cancer	LncRNA CRNDE-TREM-1 circuit drives immune exclusion	G-MDSCs, exhausted T cells	Epigenetic silencing of CRNDE	[58]

The study by [63] provides unique insights into T cell crosstalk within ovarian cancer microenvironments, demonstrating how TREM-1+ myeloid cells alter T cell receptor diversity to favor immune tolerance. Meanwhile, [64] employs integrative single-cell analyses to map the ontological hierarchies of primary and metastatic liver tumors, revealing TREM-1 as a nodal regulator of metastatic niche formation. These findings collectively position TREM-1 as a master regulator of the pre-metastatic niche, orchestrating both cellular and molecular components to facilitate metastatic outgrowth. Future research should explore whether TREM-1 inhibition can prevent metastatic seeding or sensitize established metastases to immune attack.

The transcriptional profiling of recurrent colon cancer microenvironments [65] and reannotation of melanoma mutations [66] further highlight the importance of microenvironmental context in interpreting TREM-1's metastatic functions. While not directly focused on TREM-1, these studies provide critical methodological frameworks for analyzing metastasis-associated gene networks and their therapeutic vulnerabilities.

4. Discussion

The systematic review of TREM-1 in breast cancer reveals a complex interplay between myeloid cell activation, tumor microenvironment (TME) remodeling, and clinical outcomes. Taken together, the findings consistently demonstrate that TREM-1 overexpression correlates with aggressive tumor behavior, immunosuppression, and poor prognosis across multiple studies [13], [16]. This pattern emerges not only in breast cancer but also in pan-cancer analyses, suggesting a conserved role for

TREM-1 in promoting tumor progression through myeloid cell reprogramming. However, contradictions exist regarding its tissue-specific functions, particularly in the context of immunotherapy resistance, where some studies report TREM-1 as a dominant resistance mechanism [9], while others highlight compensatory pathways involving TREM-2 or independent immune checkpoints [41]. These discrepancies may reflect differences in experimental models, tumor subtypes, or methodological approaches to measuring TREM-1 activity.

The mechanistic insights from this review position TREM-1 as a central node linking inflammation to cancer progression. Its activation through DAMPs like HMGB1 and HMGB3 creates a feed-forward loop that sustains pro-tumorigenic signaling in the TME [17], [19]. This aligns with its established role in sepsis, where TREM-1 amplifies inflammatory responses, suggesting that similar pathways may drive cancer-associated inflammation [54]. The convergence of these findings supports the hypothesis that TREM-1 acts as a molecular bridge between infection-related inflammation and tumor immunology, though the precise mechanisms underlying this connection remain underexplored. Future research should investigate whether sepsis-derived TREM-1 inhibitors, such as GF9 [55], exhibit anti-tumor efficacy by disrupting these shared inflammatory circuits.

From a clinical perspective, the consistent association between TREM-1 and poor outcomes underscores its potential as a prognostic biomarker. The identification of TREM-1-centered gene signatures in metastatic niches [59] and immunotherapy-resistant tumors [40] provides a framework for patient stratification. However, the lack of standardized assays for TREM-1 detection in clinical settings poses a significant barrier to translation [11]. The development of reliable immunohistochemical or circulating biomarkers, possibly leveraging soluble TREM-1 (sTREM-1) as validated in sepsis [54], could address this gap. Moreover, the integration of TREM-1 status with existing biomarkers like PD-L1 or tumor mutational burden may enhance predictive accuracy for immunotherapy response.

The therapeutic implications of targeting TREM-1 are multifaceted. Preclinical studies demonstrate that TREM-1 blockade synergizes with immune checkpoint inhibitors by reversing myeloid-mediated immunosuppression [9], [41]. However, the pleiotropic effects of TREM-1 in normal tissue homeostasis raise concerns about on-target toxicity, particularly in organs with high baseline myeloid cell activity. Emerging strategies such as bispecific antibodies [41] or CRISPR-based gene editing [42] offer promising avenues for selective targeting, but their clinical feasibility remains to be tested. Additionally, the crosstalk between TREM-1 and metabolic pathways, exemplified by the disulfidptosis-TREM-1 axis in HCC [59], suggests that

combinatorial approaches targeting both immune and metabolic vulnerabilities may yield superior outcomes.

Several limitations of this review warrant consideration. First, the predominance of preclinical studies and retrospective clinical analyses limits the generalizability of the findings. Prospective cohort studies are needed to validate TREM-1's prognostic and predictive utility in diverse breast cancer subtypes. Second, the heterogeneity in TREM-1 measurement techniques across studies complicates cross-comparisons. Standardized protocols for assessing TREM-1 expression at the protein, transcript, and functional levels are essential for future research. Third, the focus on recent publications (2022–2026) may have excluded foundational studies that could provide historical context for TREM-1's evolving role in cancer biology. Finally, the underrepresentation of certain breast cancer subtypes, such as triple-negative or HER2-enriched tumors, in the included studies highlights a critical gap in understanding TREM-1's subtype-specific functions.

Future research directions should prioritize several key areas. There is a need for mechanistic studies dissecting how TREM-1 interacts with other immune checkpoints, such as PD-1 and CTLA-4, to drive resistance. Single-cell multi-omics approaches could elucidate the spatial and temporal dynamics of TREM-1+ myeloid cells within the TME, as demonstrated in ovarian cancer [60]. Clinical trials evaluating TREM-1 inhibitors, either alone or in combination with existing therapies, are urgently needed to translate preclinical findings into patient benefit. Additionally, the exploration of non-myeloid TREM-1 expression, particularly in cancer-associated fibroblasts or tumor cells themselves, may reveal novel therapeutic targets. Finally, comparative studies across inflammatory conditions (e.g., sepsis, autoimmune diseases) and cancer could uncover conserved pathways amenable to repurposed therapies.

The synthesis of evidence presented here advances our understanding of TREM-1 as a multifaceted regulator of breast cancer progression. Its dual roles in immune modulation and TME remodeling position it as a promising target for precision oncology strategies. However, the field must address existing methodological and knowledge gaps to fully realize its clinical potential. By integrating insights from sepsis and cancer research, future studies can unlock novel therapeutic paradigms that exploit TREM-1's unique position at the intersection of inflammation and malignancy.

5. Conclusion

This systematic review consolidates the emerging role of TREM-1 as a critical regulator of breast cancer progression, immune evasion, and therapeutic resistance. The synthesis of current evidence demonstrates that TREM-1 overexpression correlates with aggressive tumor phenotypes, immunosuppressive microenvironment remodeling, and poorer clinical outcomes, positioning it as a promising prognostic biomarker and therapeutic target. Mechanistically, TREM-1 bridges inflammatory signaling and tumorigenesis by polarizing myeloid cells toward pro-tumorigenic states and interacting with key pathways such as NF-κB and DAMPs. However, inconsistencies in tissue-specific functions and clinical validation highlight the need for standardized detection methods and prospective studies.

The translational implications of these findings are twofold. First, TREM-1 inhibition represents a viable strategy to overcome immunotherapy resistance, particularly when combined with checkpoint blockade. Second, insights from sepsis research, where TREM-1 modulation has shown clinical efficacy, may inform analogous approaches in oncology. Future research should prioritize elucidating TREM-1's interplay with other immune checkpoints, validating its biomarker potential in diverse breast cancer subtypes, and developing targeted therapies that minimize on-target toxicity. By addressing these gaps, the field can harness TREM-1's dual roles in inflammation and cancer to advance precision medicine strategies for breast cancer patients.

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