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Review

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Macrophages in Lymphoma: Advances in Biology and Treatment

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Abstract: The tumor microenvironment (TME) is now recognized as a crucial factor in the development of cancer, impacting treatment strategies and resistance mechanisms. Current research indicates that the TME plays a significant role in various types of lymphoma. The diversity and prevalence of immune cells in the TME can vary greatly, and their composition and activity are believed to be key factors influencing disease progression. Emerging evidence indicates that tumor-associated macrophages (TAMs) are an important component of the TME and play a significant role in angiogenesis, extracellular matrix remodeling, tumor proliferation and metastasis, immunosuppression, resistance to chemotherapeutic agents and immune checkpoint blockade therapy. Molecules have been developed to target TAMs to treat lymphoma, and several clinical studies have investigated the safety and efficacy of targeted macrophage therapies. In this review, we summarize the roles of macrophages; elucidate distinct types of macrophage-targeted strategies that have been used to address lymphoma in preclinical experiments and clinical trials, and outline therapeutic approaches that are currently under development.

Keywords: tumor microenvironment; tumor-associated macrophages; lymphoma; therapeutic targets

1. Introduction

The TME is a highly dynamic and complex ecosystem that critically regulates tumor initiation, progression, and therapeutic response [1,2]. Among its cellular components, TAMs represent a dominant and functionally versatile immune population in both solid and hematologic malignancies, including lymphoma [3,4]. TAMs exhibit remarkable plasticity, exerting context-dependent anti- or pro-tumor functions [5,6]. While early-stage macrophages can mediate tumor clearance through antibody-dependent cellular phagocytosis (ADCP) and cytotoxic activity, they predominantly acquire a pro-tumorigenic phenotype during disease progression, promoting tumor cell survival, angiogenesis, immune evasion, and therapeutic resistance.

Lymphoma comprises a heterogeneous group of B-, T-, or NK-cell malignancies with diverse clinical behaviors and therapeutic responses [7,8]. Despite advances in immunotherapy, including monoclonal antibodies, CAR-T cells, and bispecific antibodies, relapse and resistance remain major clinical challenges.

Emerging evidence highlights TAMs as key regulators of lymphoma progression and treatment outcomes [9]. However, the precise mechanisms underlying TAM heterogeneity and their context-specific roles across lymphoma subtypes remain incompletely defined. Addressing this knowledge gap is essential for the rational development of macrophage-targeted therapies and for improving clinical efficacy in lymphoma.

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2. Macrophage Heterogeneity in the Initiation and Progression of Lymphoma

During the development and progression of lymphoma, TAMs do not constitute a homogeneous population but rather represent a highly heterogeneous and dynamic cellular ensemble. Although the classical M1/M2-like dichotomy has facilitated the conceptualization of macrophage functional polarization, it is increasingly insufficient to account for the complex and context-dependent roles of TAMs across distinct lymphoma subtypes. Recent advances in single-cell sequencing technologies have revealed that TAMs exhibit substantial diversity at multiple levels, including ontogeny (tissue-resident versus monocyte-derived), phenotype, metabolic state, and spatial distribution [10]. This heterogeneity is shaped by the coordinated influence of malignant cells, stromal components, and cytokine networks, thereby endowing TAMs with pronounced functional plasticity and the capacity for dynamic reprogramming during tumor progression [11].

Collectively, macrophage heterogeneity represents a multidimensional and highly integrated network governed by phenotypic, spatial, and developmental determinants, playing a pivotal regulatory role in lymphoma pathogenesis and progression, while also providing a critical foundation for the development of precision-targeted therapeutic strategies (Figure 1).

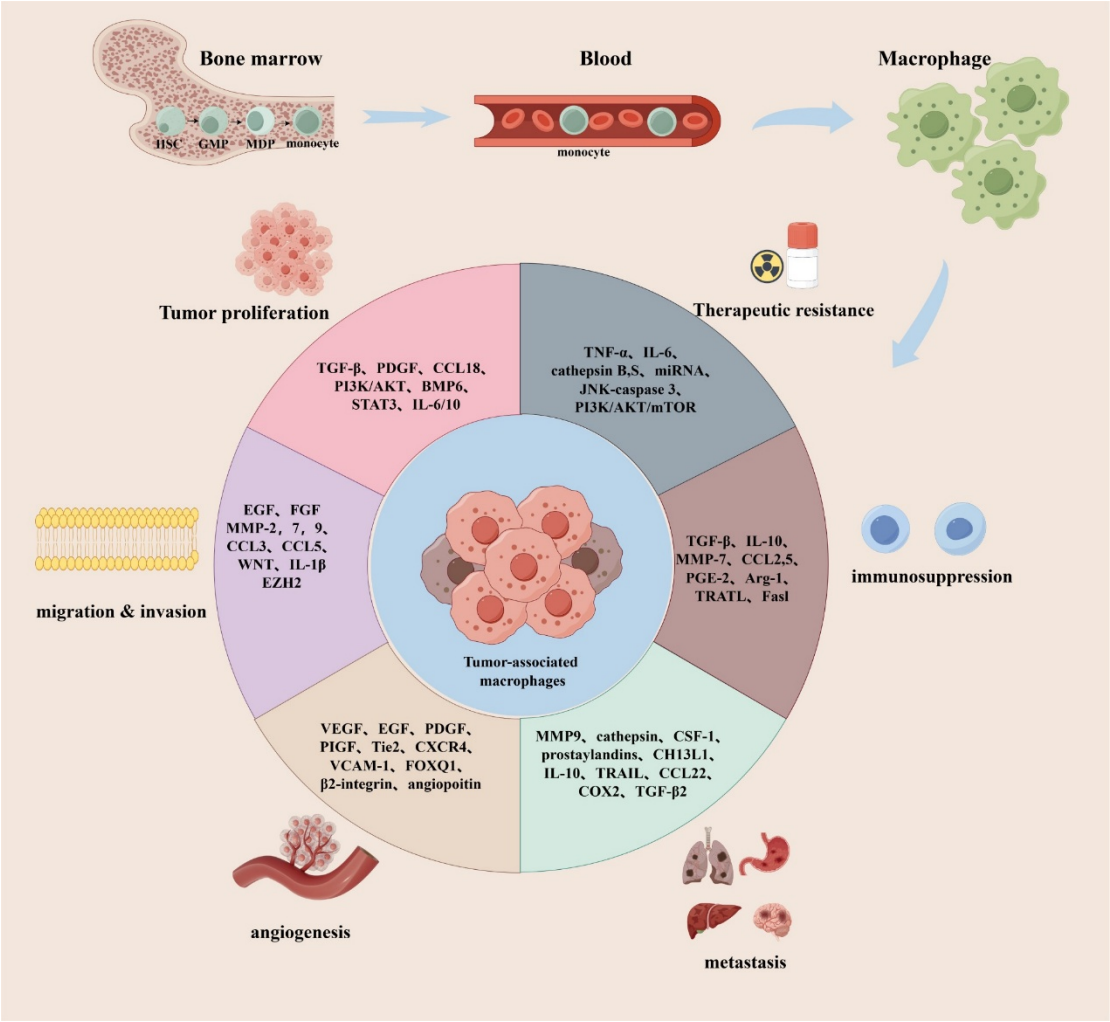

Figure 1. Mechanisms of TAMs in tumor metastasis. TAMs affect virtually almost every step of tumor cells metastasis, including angiogenesis, extracellular matrix remodeling, tumor proliferation and metastasis, immunosuppression, and resistance to chemotherapeutic agents and in immune checkpoint blockade therapy.

2.1. The Proliferation and Survival of Lymphoma Mediated by Macrophages

During lymphoma initiation and progression, TAMs provided essential trophic support for malignant cells by promoting proliferation, enhancing survival signaling, and maintaining stem-like tumor niches. Rather than acting through isolated pathways, TAM-mediated survival signals are closely interconnected with immunosuppressive and stromal remodeling programs within the TME [12].

In diffuse large B-cell lymphoma (DLBCL), TAMs promote tumor progression by secreting pleiotrophin (PTN), which activates β-catenin signaling pathway and increases the proportion of cancer stem-like cells, thereby enhancing tumor growth and self-renewal capacity [13]. This finding highlights that TAMs not only support lymphoma cell proliferation directly but also sustain long-term tumor maintenance through stemness regulation. Similarly, in classical Hodgkin lymphoma (cHL), increased infiltration of $CD68^+$ and $CD163^+$ macrophages is strongly associated with treatment failure and inferior overall survival, supporting their role in promoting tumor cell survival and resistance to apoptosis [14,15]. In mantle cell lymphoma (MCL), reciprocal interactions between lymphoma cells and macrophages induce a tumor-supportive macrophage phenotype, which further activates pro-survival pathways such as NF-κB signaling and facilitates tumor expansion [16]. In follicular lymphoma (FL), although the prognostic significance of TAMs abundance varies across treatment settings, TAMs consistently contribute to lymphoma cell survival through modulation of the germinal center-like microenvironment [17].

Collectively, these findings indicate that TAMs function not merely as passive stromal components, but as active regulators of lymphoma cell fitness by integrating survival signaling, stemness maintenance, and microenvironmental support.

2.2. Angiogenesis Yielded by Macrophages

In addition to directly supporting lymphoma cell survival, TAMs actively remodel the vascular microenvironment and promote angiogenesis, thereby facilitating nutrient supply, tumor expansion, and dissemination.

Within the lymphoma TME, TAMs promote neovascularization primarily through secretion of pro-angiogenic mediators, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinase-9 (MMP9). These factors stimulate endothelial cell migration, extracellular matrix remodeling, and vascular permeability, ultimately contributing to aggressive tumor behavior [18]. Moreover, TAMs preferentially accumulate in hypoxic tumor regions, where hypoxia-driven signaling further amplifies angiogenic activity through enhanced VEGF-A and MMP9 production [19]. In cHL, $CD68^+$ TAM density positively correlates with microvessel density, indicating a direct role for macrophages in vascular remodeling and disease progression [20,21]. Similarly, in peripheral T-cell lymphoma (PTCL), increased TAMs infiltration is associated with elevated VEGF expression and poor clinical outcomes, supporting a VEGF-dependent mechanism of tumor progression [22]. In FL and DLBCL, TAMs are frequently enriched at the invasive tumor front, where they coordinate angiogenesis and stromal remodeling through the secretion of chemokines and matrix-remodeling enzymes [18,23].

Importantly, angiogenic remodeling mediated by TAMs not only supports tumor growth but also establishes permissive conditions for lymphoma dissemination and therapeutic resistance.

2.3. Macrophage-Mediated Lymphoma Invasion and Metastasis

Through coordinated regulation of extracellular matrix remodeling, angiogenesis, and tumor cell motility, TAMs further promote lymphoma dissemination and tissue invasion [24–26].In DLBCL, TAM-derived PTN activates β-catenin signaling and enhances stem-like features associated with tumor invasiveness [13]. Meanwhile, reciprocal crosstalk between TAMs and lymphoma cells strengthens tumor–stromal interactions and promotes migratory capacity [27]. In cHL, increased infiltration of $CD163^+$ and $CD206^+$ macrophages correlates with advanced Ann Arbor stage and skeletal involvement, suggesting a role for TAMs in disease dissemination [28]. In FL and other indolent lymphomas, TAM-derived chemokines and stromal remodeling signals facilitate lymphoma cell trafficking and retention within supportive lymphoid niches [29].

2.4. Macrophage-Mediated Immunosuppression

Beyond their trophic and angiogenic functions, TAMs are central orchestrators of immune evasion in lymphoma. Through coordinated regulation of immune checkpoints, cytokine networks, and suppressive immune cell populations, TAMs establish an immunologically tolerant TME that limits effective antitumor responses [29–31].

In cHL, 9p24.1 amplification in Reed–Sternberg (RS) cells induces marked programmed death-ligand 1 (PD-L1) overexpression, while PD-L1 expression on TAMs further reinforces the immune escape mechanisms within the TME [32]. In DLBCL and cutaneous DLBCL, tumor-derived interleukin-10 (IL-10) promotes macrophage polarization toward an immunosuppressive phenotype and activates STAT3-dependent survival pathways, thereby suppressing cytotoxic T-cell activity and enhancing tumor immune evasion [33,34]. Similarly, in primary central nervous system lymphoma (PCNSL), TAMs cooperate with regulatory T cells and IDO-associated pathways to establish a highly suppressive immune milieu linked to unfavorable prognosis [14]. Likewise, in cutaneous T-cell lymphoma (CTCL) and MCL, accumulation of $CD163^+$ or programmed death-1^+ ($PD\text{-}1^+$) macrophages further

contributes to sustained immunosuppression and tumor progression [35,36]. Rather than functioning through a single suppressive pathway, TAMs generate a multidimensional immunoregulatory network involving IL-10, transforming growth factor-beta (TGF-β), PD-L1, and metabolic immune suppression, collectively constituting a major mechanism of lymphoma immune escape [37].

Notably, these immunosuppressive programs are closely linked to resistance to both chemotherapy and immunotherapy, highlighting the functional overlap between immune evasion and treatment adaptation.

2.5. Macrophage-Induced Lymphoma Treatment Resistance

TAMs-mediated immunosuppression and survival signaling substantially contribute to therapeutic resistance in lymphoma. Rather than representing an independent biological process, resistance frequently emerges as a downstream consequence of TAMs-driven immune remodeling and tumor-supportive signaling networks [38].

In DLBCL and primary cutaneous DLBCL, IL-10-mediated macrophage polarization is associated with reduced sensitivity to R-CHOP and enhanced resistance to doxorubicin [33,39]. Similarly, in PCNSL, increased TAMs infiltration and elevated cerebrospinal fluid IL-10 levels correlate with inferior progression-free survival [40]. These findings suggest that macrophage-associated cytokine programs contribute to diminished therapeutic efficacy across multiple lymphoma subtypes. Importantly, emerging studies indicates that targeting TAMs, such as through colony stimulating factor-1 Receptor (CSF-1R) inhibition or IL-10R blockade, can partially restore therapeutic sensitivity by reprogramming the TME, supporting TAMs-targeted interventions as a promising strategy to overcome treatment resistance.

Taken together, TAMs support lymphoma progression through highly interconnected mechanisms involving tumor survival, angiogenesis, immune suppression, therapeutic adaptation, and tissue dissemination. These processes are not independent events, but rather components of an integrated macrophage-driven network that dynamically shapes lymphoma evolution and treatment response.

3. Therapeutic Strategies to Target Macrophages in Lymphoma

3.1. Phagocytosis-Based Treatment Strategies

Within the landscape of lymphoma immunotherapy, phagocytosis-based strategies, such as CD47/SIRPα blockade, have emerged as a promising approach. Their central mechanism involves restoring or enhancing the phagocytic capacity of TAMs while concurrently reprogramming the tumor immune microenvironment (Figure 2).

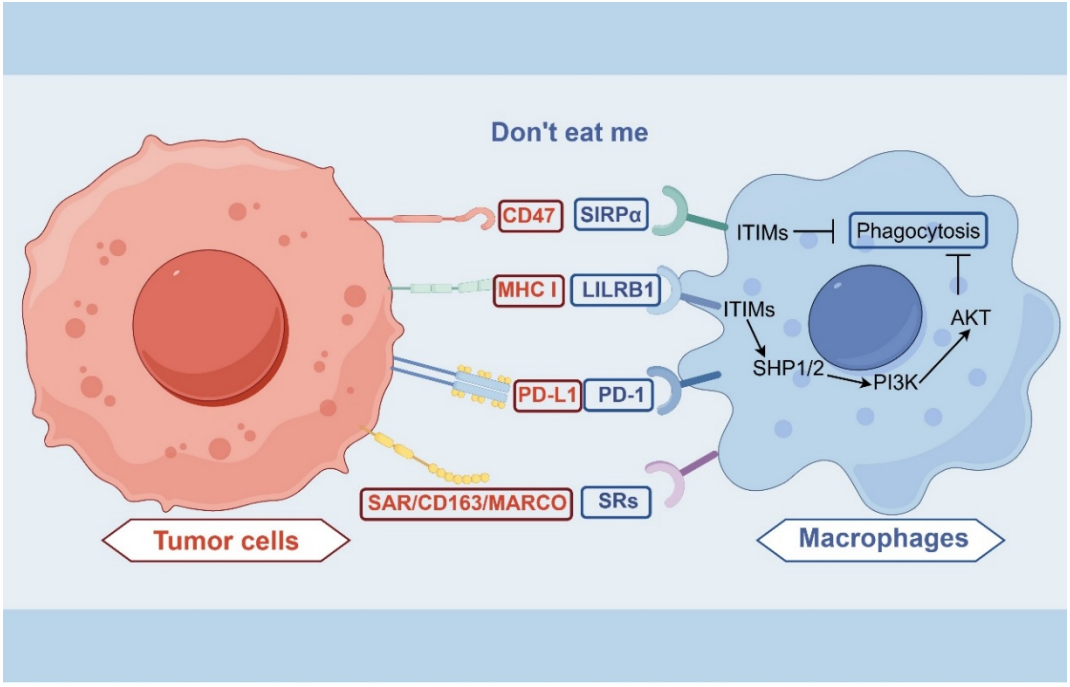

Figure 2. The major " Don't eat me" signals identified so far: the CD47 / SIRP α axis, the PD-1/PD-L1 axis, the MHC-I/LILRB1 axis, and the Scavenger Receptors all play important roles in inhibiting phagocytosis of cancer cells, and disrupting these interactions enhances phagocytosis by macrophages.

3.1.1. CD47-SIRPα Axis-Based Monoclonal Antibodies

The CD47-SIRPα axis has emerged as a widely studied innate immune checkpoint and plays a central role in immune evasion in lymphoma. CD47, a ubiquitously expressed transmembrane protein, interacts with SIRPα on macrophages to deliver a "don't eat me" signal, thereby inhibiting phagocytosis and promoting tumor cell survival [41,42]. In multiple lymphoma subtypes, CD47 is frequently overexpressed and correlates with poor prognosis, providing a strong rationale for therapeutic targeting [41,43].

Mechanistically, CD47-SIRPα engagement activates downstream phosphatases such as SHP-1/2, leading to inhibition of cytoskeletal rearrangement and blockade of macrophage-mediated phagocytosis. Disruption of this axis relieves inhibitory signaling, restores macrophage phagocytic activity, and enhances antigen presentation, thereby promoting adaptive immune activation [42]. This dual immunostimulatory effect positions the CD47-SIRPα pathway as a critical bridge between innate and adaptive immunity.

Based on this rationale, anti-CD47 monoclonal antibodies have become a major focus of investigation. Magrolimab (Hu5F9-G4), a representative agent, enhances macrophage-mediated ADCP by blocking CD47-SIRPα interactions. In lymphoma models, CD47 blockade not only directly promotes tumor cell clearance but also synergizes with other therapeutic antibodies, such as anti-CD20 agents, to enhance antitumor efficacy [44]. Clinical studies further support its translational potential. In relapsed or refractory indolent B-cell lymphomas, magrolimab combined with anti-CD20 antibodies and the BCL2 inhibitor venetoclax has demonstrated high complete response rates and promising antitumor activity [45].

However, accumulating clinical evidence indicates that CD47 monotherapy generally produces limited and often non-durable responses, suggesting that blockade of the CD47-SIRPα axis alone may be insufficient to fully reverse the highly immunosuppressive lymphoma microenvironment. Recent studies further suggest that therapeutic responsiveness is strongly influenced by TAMs heterogeneity, Fcγ receptor variability, compensatory immune checkpoint signaling, and context-dependent macrophage polarization states [46,47]. Current evidence suggests that CD47-targeted therapies demonstrate greater efficacy when incorporated into rational combination regimens rather than as monotherapies. Combination strategies involving rituximab, chemotherapy, immune checkpoint inhibitors, or CAR-T therapy may simultaneously enhance macrophage phagocytosis and remodel the immunosuppressive TME, thereby improving therapeutic responses [48]. Despite its promise, several challenges remain. Because CD47 is also widely expressed on normal cells, particularly erythrocytes, treatment is often associated with dose-dependent anemia; however, this toxicity can be partially mitigated through strategies such as priming doses [42]. In addition, the high abundance of CD47 on circulating red blood cells generates a substantial "antigen sink" effect that reduces antibody bioavailability and compromises effective tumor targeting. This phenomenon represents a major obstacle limiting the clinical efficacy and therapeutic window of systemic CD47 blockade [46]. Moreover, increasing evidence suggests that concurrent immunosuppressive pathways within the TME, including PD-1/PD-L1 signaling, TGF-β-mediated immune suppression, and immunosuppressive TAMs subsets, may contribute to adaptive resistance following CD47 blockade. Therefore, future development of CD47-targeted therapies will likely require biomarker-guided patient stratification and next-generation strategies capable of improving tumor selectivity while minimizing systemic toxicity [46,47].

To overcome these limitations, several next-generation CD47-targeted approaches are currently under development, including bispecific antibodies, SIRPα-Fc fusion proteins, tumor-selective CD47 inhibitors, and nanoparticle-based delivery systems designed to reduce erythrocyte binding and improve pharmacokinetic profiles.

3.1.2. CD47-SIRPα Axis-Based Bispecific Antibodies (BsABs)

To overcome immune evasion mediated by the CD47-SIRPα axis, BsAbs have been developed to enhance antitumor activity while improving target selectivity. Compared with conventional anti-CD47 monoclonal antibodies, BsAbs simultaneously bind CD47 and tumor-associated antigens (e.g., CD20 or CD19), enabling preferential targeting of malignant cells. This design allows effective blockade of the "don't eat me" signal while minimizing off-tumor effects on normal cells [49,50].

Mechanistically, CD47-SIRPα engagement suppresses macrophage phagocytosis through recruitment of SHP-1/2 phosphatases, a pathway initially elucidated in seminal studies [51]. Subsequent work has shown that CD47 blockade not only restores macrophage-mediated phagocytosis but also enhances antigen presentation, thereby promoting T cell mediated adaptive immune responses and generating coordinated innate-adaptive antitumor immunity [52]. Building on this, BsAbs incorporate tumor antigen–binding domains that drive preferential accumulation on tumor cells and potentiate Fc receptor–mediated ADCP.

Preclinical studies have demonstrated the advantages of this strategy in lymphoma. For instance, a CD47×CD20 BsAb developed by Piccione et al. selectively targets B-cell lymphoma cells, significantly enhances macrophage phagocytosis, and reduces binding to erythrocytes [53]. Further engineering approaches, such as reducing CD47-binding affinity, have been shown to mitigate the antigen sink effect and improve pharmacokinetics, thereby enhancing in vivo efficacy and safety [54]. Importantly, these next-generation BsAb designs were developed largely in response to the clinical limitations observed with first-generation CD47 monoclonal antibodies, particularly anemia, antigen sink effects, and insufficient tumor selectivity [46]. From a translational perspective, CD47-targeting BsAbs are advancing into clinical development, with common formats including CD47×CD20 and CD47×CD19 constructs. Functionally, these molecules recapitulate the synergy observed with CD47 blockade combined with anti-CD20 antibodies (e.g., rituximab), while achieving spatially restricted activity within a single agent, thereby improving the therapeutic index. Early clinical evidence further supports this rationale: in non-Hodgkin lymphoma, CD47 blockade combined with anti-CD20 therapy has demonstrated high response rates, providing a strong foundation for BsAb development [55]. Importantly, BsAbs offer potential safety advantages over conventional anti-CD47 antibodies. Given the widespread expression of CD47 on normal cells, particularly erythrocytes, traditional approaches are often associated with dose-limiting anemia. In contrast, the dual-targeting mechanism of BsAbs reduces nonspecific binding to normal tissues. Moreover, retention of the Fc domain enables robust activation of macrophage effector functions, further amplifying antitumor immunity [52]. Nevertheless, several challenges remain, including the structural complexity of BsAbs, optimization of affinity balance, and variability in tumor antigen expression. Furthermore, heterogeneity of the lymphoma immune microenvironment and dynamic changes in TAMs functional states may substantially influence therapeutic responsiveness. Consequently, not all patients may benefit equally from CD47-targeted BsAbs, further highlighting the importance of biomarker-guided patient selection and precision immunotherapy approaches.

3.1.3. The LILRB Family

The leukocyte immunoglobulin-like receptor subfamily B (LILRB) comprises inhibitory receptors expressed on myeloid cells, including macrophages, that mediate negative immune regulation through recognition of major histocompatibility complex class I (MHC-I) molecules. This pathway has been identified as an important innate immune checkpoint [56,57]. Within the lymphoma microenvironment, the MHC-I/LILRB1 axis directly suppresses macrophage effector function.

Mechanistically, MHC-I molecules on tumor cells engage LILRB1 on macrophages in a β2-microglobulin–dependent manner, thereby inhibiting phagocytosis. Seminal studies have demonstrated that either β2-microglobulin deletion or LILRB1 blockade significantly enhances macrophage-mediated phagocytosis and promotes tumor clearance in vivo, establishing this axis as a key negative regulator of macrophage activity [56].

In lymphoma models, this pathway shows clear functional relevance. LILRB1 blockade enhances macrophage-mediated ADCP and exhibits synergistic effects when combined with CD47 inhibition, markedly increasing the clearance of lymphoma cells. Moreover, LILRB1 inhibition promotes sustained phagocytic activity and augments macrophage function across different polarization states, indicating a broad and potent suppressive role of this checkpoint [58].

Importantly, the MHC-I/LILRB1 axis may represent a complementary immune checkpoint pathway that partially compensates for incomplete responses to CD47 blockade. This observation highlights the broader concept that macrophage immune checkpoints function within interconnected regulatory networks rather than as isolated inhibitory pathways [59]. However, the translational relevance of LILRB1-targeted therapies in lymphoma remains incompletely defined. Since MHC-I molecules are also essential for antigen presentation and adaptive immune surveillance, excessive disruption of MHC-I dependent signaling could theoretically alter T-cell mediated immunity or immune homeostasis. Therefore, achieving sufficient macrophage activation while preserving adaptive immune function may represent an important therapeutic balance in future clinical development. In addition, the efficacy of LILRB1 blockade is likely to depend on tumor specific immune context, including MHC-I expression levels and the composition of the surrounding myeloid microenvironment. These findings suggest that patient selection strategies based on immune profiling may be required to optimize clinical responsiveness to LILRB-targeted therapies.

3.1.4. Scavenger Receptors

Scavenger receptors (SRs) are a class of pattern recognition receptors predominantly expressed on macrophages, where they regulate ligand clearance, lipid metabolism, and immune responses. Within the TME,

SRs have been directly implicated in the functional reprogramming of TAMs and contribute to immunosuppression across multiple malignancies, including lymphoma [60,61].

In terms of expression, SR family members such as CD163, CD68, and SR-A (CD204) are consistently detected in macrophage populations within lymphoma tissues. CD163, a monocyte/macrophage-restricted receptor, is widely used as a TAMs marker in various lymphoma subtypes [62]. Similarly, SR-A is predominantly expressed by tissue-resident macrophages rather than circulating monocytes in cHL, suggesting a direct role in local immune regulation [63]. Functional evidence in lymphoma further supports these roles. In MCL, spatial transcriptomic and functional analyses demonstrate that $CD163^+$ macrophages are enriched within tumor regions and contribute to microenvironmental remodeling by activating MAPK-related signaling pathways and inducing immunosuppressive mediators [35]. In FL, clinical studies show that $CD163^+$ macrophage abundance correlates with patient survival, with its prognostic significance modulated in the context of rituximab therapy, indicating a role in therapeutic response [64]. Beyond CD163, other SR family members also participate in tumor regulation. SR-A has been shown to suppress antigen presentation and impair T-cell activation, thereby directly attenuating antitumor immunity. In addition, MARCO is highly expressed on TAMs, and its blockade can reprogram macrophages and enhance antitumor immune responses [61].

Collectively, these findings indicate that SRs are not merely phenotypic markers but active regulators of immunosuppressive functions. Accordingly, they represent promising targets for macrophage-directed therapies: SRs such as CD163 and MARCO can enable selective targeting of immunosuppressive TAM subsets, while modulation of SR-associated signaling pathways offers a strategy to reprogram macrophage polarization and restore antitumor immunity.

Despite these observations, the clinical applicability of SR-targeted therapies remains at an early stage. One major challenge is that many SRs are broadly expressed across tissue-resident macrophage populations, raising concerns regarding target specificity and potential disruption of physiological macrophage functions. Moreover, the biological significance of SR expression appears highly context-dependent. For example, the prognostic impact of $CD163^+$ macrophages differs across lymphoma subtypes and treatment settings, suggesting that SR expression alone may not uniformly predict therapeutic vulnerability. Accordingly, SR-targeted approaches will likely require integration with functional or spatial biomarkers to improve patient stratification and therapeutic precision.

3.1.5. PD-1/PD-L1 Signaling Pathway

The PD-1/PD-L1 signaling pathway not only regulates T-cell function but also exerts direct immunosuppressive effects in macrophages, with clear evidence in the lymphoma microenvironment [65]. Recent studies further demonstrate that macrophages themselves can express PD-1 and PD-L1, thereby directly participating in tumor immune regulation.

In T-cell lymphomas (T-NHL), high PD-1 expression on TAMs is significantly associated with poor patient survival and is accompanied by reduced phagocytic capacity and enhanced immunosuppressive function, indicating a direct inhibitory role of PD-1 in TAMs activity. In DLBCL, PD-L1 is predominantly expressed on tumor-associated myeloid cells rather than malignant cells, and its expression correlates with macrophage gene signatures and STAT3 signaling, highlighting a central role of the PD-1/PD-L1 axis in TAM-mediated immune regulation [66].

Similarly, in aggressive B-cell lymphomas such as primary testicular lymphoma, $PD\text{-}L1^+$ macrophages positively correlate with $PD\text{-}1^+$ tumor-infiltrating lymphocytes, suggesting a critical role for this pathway in orchestrating immune cell interactions within the TME [67]. Moreover, recent reviews indicate that TAMs contribute to immune evasion by upregulating PD-L1 and secreting immunosuppressive factors, forming a coordinated inhibitory network that can be partially reversed by PD-1/PD-L1 blockade [31].From a therapeutic perspective, PD-1/PD-L1 inhibitors not only restore T-cell activity but also reprogram TAMs toward an M1-like antitumor phenotype, thereby amplifying overall immune responses. However, the efficacy of this pathway is highly heterogeneous across lymphoma subtypes: while limited as monotherapy in DLBCL, PD-1 blockade shows remarkable clinical sensitivity in cHL, likely reflecting differences in TAM-derived PD-L1 expression.

Importantly, these findings indicate that macrophage-associated PD-L1 expression alone may be insufficient to predict therapeutic responsiveness. Instead, the spatial organization of immune cells, co-existing suppressive pathways, and overall TME composition are likely to collectively determine response to PD-1/PD-L1 blockade. Furthermore, accumulating evidence suggests that PD-1/PD-L1 inhibition primarily reactivates pre-existing antitumor immunity rather than generating de novo immune responses. Consequently, lymphomas characterized by profound macrophage-driven immune exclusion or low baseline T-cell infiltration may exhibit intrinsic resistance to checkpoint blockade despite PD-L1 expression. (Table 1).

Table 1. Clinical trails of antibodies in lymphoma.

Target	Drug Name	Type pf Antibody	Tumor Type	Phase	Trial Status	Outcomes	Sponsor/Recruter	Trial ID
CD47	AK117	mAb	Lymphoma	I/IB	Recruiting	Unavailable	Akeso Biopharma	NCT04349969
CD47	AK117	mAb	Lymphoma	I	Recruiting	Unavailable	Akeso Biopharma	NCT04728334
CD47	SRF231	mAb	Lymphoma or CLL	IA/IB	Completed	Unavailable	Surface Oncology	NCT03512340
CD47	SHR1603	mAb	Solid tumor or R/R lymphoma	I	Suspendend	the study was suspended because of a business decision before clinically significant antitumor activity could be established.	Jiangsu Hengrui Medicine Co	NCT03722186
CD47	IBI188	mAb	Lymphoma	I	Completed	Unavailable	Innovent Biologics	NCT03717103
CD47	TJC4	mAb	Lymphoma	I	Completed	Unavailable	I-Mab Biopharma	NCT03934814
CD47	ZL-1201	mAb	Lymphoma	I	Active, not recruiting	Unavailable	I-Mab Biopharma	NCT04257617
CD47	GenSci-059	mAb	Solid Malignancies and Non-Hodgkin Lymphoma	I	Recruiting	Unavailable	I-Mab Biopharma	NCT05221385
CD47	IMM01	SIRPα fusion protein	Lymphoma	I/II	Unknown	Unavailable	ImmuneOnco Biopharmaceuticals	NCT05833984
CD47	IMM01	SIRPα fusion protein	PD-(L)1-refractory Classical Hodgkin Lymphoma	III	Not yet recruiting	Unavailable	ImmuneOnco Biopharmaceuticals	NCT06465446
SIRPα	ALX148	SIRPα fusion protein	Lymphoma	I	Completed	Evorpacept plus rituximab was well tolerated with no dose-limiting toxicities or maximum tolerated dose identified; pharmacodynamics showed ≥85% CD47 target occupancy. In response-evaluable patients (N = 32), objective response rate was 50.0% (95% CI: 33.1–69.8%) in relapsed/refractory B-cell NHL, with a safety profile characterized mainly by mild-to-moderate rash and fatigue and low incidence of grade ≥3 treatment-related adverse events	ALX Oncology	NCT03013218
SIRPα	BYON4228	mAb	R/R CD20-positive B-NHL	I	Active, not recruiting	Unavailable	Byondis B.V.	NCT05737628
CD47/CD20	IMC-002	bispecific antibodies	Lymphoma	I	Recruiting	Unavailable	ImmuneOncia Therapeutics	NCT04306224
CD47/CD20	IMC-002	bispecific antibodies	R/R CD20-positive B-NHL	IB/IIA	Recruiting	Unavailable	ImmuneOnco Biopharmaceuticals	CTR20231000
CD47/CD20	IMC-002	bispecific antibodies	R/R CD20-positive B-NHL	IB/IIA	Unknown status	Unavailable	ImmuneOnco Biopharmaceuticals	NCT05771883
CD47/CD20	IMC-002	bispecific antibodies	R/R CD20-positive B-NHL	I	Suspended	Unavailable	ImmuneOnco Biopharmaceuticals	NCT04746131
CD47/CD19	TG-1801 (NI-1701)	bispecific antibodies	B-cell lymphoma/CLL	IB	Terminated	Unavailable	TG Therapeutics	NCT04806035

Table 1. *Cont.*

Target	Drug Name	Type pf Antibody	Tumor Type	Phase	Trial Status	Outcomes	Sponsor/Recruter	Trial ID
CD47/CD19	TG-1801 (NI-1701)	bispecific antibodies	B-cell lymphoma	I	Completed	Unavailable	TG Therapeutics	NCT03804996
CD47/SIRPα	IMM0306	bispecific antibodies	R/R CD20-positive B-NHL	I	Suspended	Unavailable	ImmuneOnco Biopharmaceuticals	NCT04746131
CD47/SIRPα	IMM0306	bispecific antibodies	R/R CD20-positive B-NHL	I/II	Not yet recruiting	Unavailable	ImmuneOnco Biopharmaceuticals	NCT05771883
CD47/SIRPα	IMM0306	bispecific antibodies	R/R CD20-positive B-NHL	I/II	Recruiting	Unavailable	ImmuneOnco Biopharmaceuticals	CTR20231000
CD47/PD-1	HX009	bispecific antibodies	R/R-lymphoma	I/II	Completed	13 patients who have had at least one post-baseline tumor assessments, partial responses (PR) have been achieved in 3 patients with the following lymphoma subtypes: PD-1 resistant DLBCL, PTCL, and a DLBCL transformed into PTCL. In addition, there are 4 patients with best overall response of stable disease (SD).	Hangzhou Hanx Biopharmaceuticals	NCT05189093
SIRPα/CD20	JMT601 (COP107)	bispecific antibodies	Advanced CD20-positive NHL	I/II	Terminated	Unavailable	Yiling Pharmaceutical	NCT04853329
CD47/CD20	Hu5F9-G4	bispecific antibodies	Non-Hodgkin lymphoma or Classic Hodgkin lymphoma or T cell lymphoma or DLBCL	II	Withdrawn	Unavailable	M.D. Anderson Cancer Center	NCT05929716
CD47/CD38	SG2501	bispecific antibodies	R/R hematological malignancies and lymphoma	IA/IB	Terminated	Unavailable	Hangzhou Sumgen Biotech Co., Ltd.	NCT05293912
CD19/CD22	GTB-1550	bispecific antibodies	B-lineage Leukemia/lymphoma	I/II	Completed	Unavailable	Masonic Cancer Center, University of Minnesota	NCT02370160
PD-1/PD-L1	Durvalumab (MEDI4736)	mAb	DLBCL	approved	Completed	20/37 (54.1%) patients receiving durvalumab + R-CHOP achieved complete response (CR), and seven (18.9%) partial response (PR); 25 (67.6% [95% CI 50.2–82.0]) continued to consolidation and were progression-free at 12 months.	Celgene	NCT03003520
PD-1/PD-L1	Camrelizumab	mAb	R/R Classic Hodgkin lymphoma	approved	Recruiting	Unavailable	Peking University	NCT04239170

Source: Clinical trial information was obtained from publicly available trial registries, including ClinicalTrials.gov and the corresponding clinical trial registries indicated by the registration numbers.

3.2. Strategies for the Activation of Macrophages

With the rapid advancement of lymphoma immunotherapy, TAMs have shifted from being viewed solely as tumor-promoting cells to highly plastic and actionable therapeutic targets. Accumulating evidence indicates that TAMs exhibit substantial reprogramming capacity within the lymphoma microenvironment, with their functional states dynamically regulated by immune checkpoints, cytokines, and metabolic signals, enabling transitions between pro-tumor and antitumor phenotypes [29]. Accordingly, strategies aimed at simple depletion of TAMs are increasingly being replaced by approaches focused on functional reprogramming or activation to restore their antitumor activity (Figure 3).

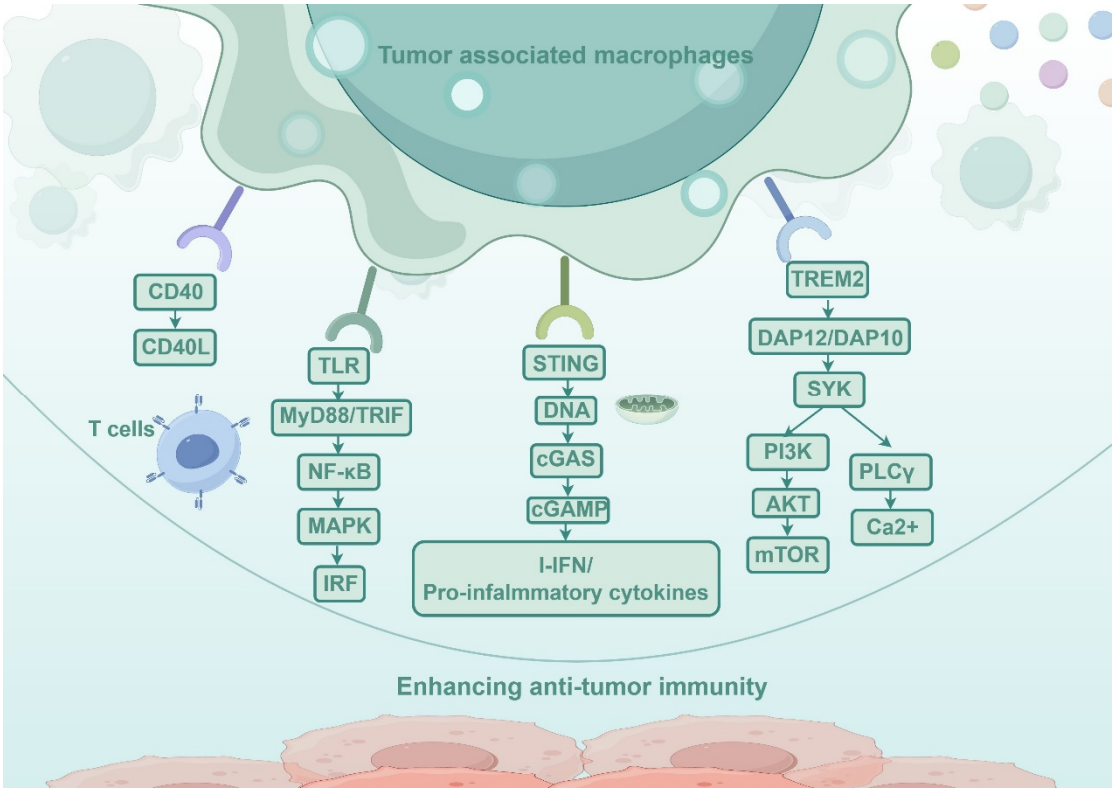

Figure 3. Macrophage reprogramming and activation of innate and adaptive immune responses. Cytokines, Toll-like receptors, interferon gene-stimulating factor (STING) agonists and monoclonal antibodies activate macrophage-mediated tumor cell killing. Macrophage reprogramming induces macrophage-mediated cancer cell killing, recruitment and activation of innate and adaptive lymphocytes, and remodeling of the tumor microenvironment.

3.2.1. CD40-CD40L Axis

CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, is expressed on antigen-presenting cells, including macrophages, while its ligand CD40L (CD154) is primarily expressed by activated T cells. Substantial experimental evidence demonstrates that CD40-CD40L interaction directly induces macrophage activation and enhances their antitumor effector functions [68–70]. Notably, in the presence of Th1 cytokines such as IFN-γ, CD40 stimulation markedly increases macrophage IL-12 production and direct tumoricidal activity, underscoring its therapeutic potential [71]. In DLBCL, CD40 signaling exerts dual roles. On one hand, tumor-intrinsic CD40 activation, such as via the MYC/miR-29/TRAF4 axis, can promote lymphoma progression and transformation from follicular lymphoma [72]. On the other hand, exogenous CD40 agonists can activate macrophages and dendritic cells, thereby enhancing antitumor immunity and counteracting tumor-promoting effects [73]. Similarly, in FL, the CD40-CD40L axis is critical for sustaining TME interactions, with aberrant activation promoting tumor cell proliferation and highlighting its central role in immune regulation [72]. More broadly, in hematologic malignancies including lymphoma, CD40 agonists have been shown to enhance antigen-presenting cell function, amplify T cell-mediated antitumor responses, and drive macrophage polarization toward a pro-inflammatory phenotype, thereby improving the efficacy of immunotherapy.

Importantly, despite encouraging immunostimulatory activity, clinical translation of CD40 agonists remains challenging because excessive systemic immune activation may induce cytokine-release toxicity and limit therapeutic tolerability. In addition, the context-dependent dual role of CD40 signaling in lymphoma suggests that therapeutic efficacy may vary according to tumor subtype and immune microenvironment composition. Therefore, current strategies increasingly focus on rational combination regimens and biomarker-guided patient selection to maximize antitumor efficacy while minimizing immune-related toxicity.

3.2.2. Toll-like Receptors

In lymphoma immunotherapy, Toll-like receptors (TLRs), as key innate pattern recognition receptors, have emerged as important targets for modulating TAMs function. TLR activation triggers MyD88- or TRIF-dependent signaling cascades, leading to activation of NF-κB, MAPK, and IRF pathways, induction of pro-inflammatory cytokines, and reprogramming of macrophages toward an M1-like antitumor phenotype, thereby enhancing antigen presentation and T-cell activation [74]. Notably, the effects of TLR signaling are highly context-dependent, capable of either promoting antitumor immunity or, under certain conditions, facilitating tumor progression [75].

In DLBCL, TLR signaling is closely associated with TAMs infiltration. TLR4 expression correlates positively with $CD68^+$ macrophage abundance, suggesting that TLR-driven inflammatory responses contribute to TAMs recruitment and microenvironmental regulation [76]. This highlights the dual role of TLRs as both therapeutic targets and potential mediators of tumor-supportive niches. In PCNSL, the TLR7/8 pathway is markedly upregulated in TAMs and microglia. Its activation promotes macrophage polarization toward an M1-like phenotype and enhances antitumor immunity, supporting TLR7/8 as a promising therapeutic target and underscoring the role of TLR agonists in converting "cold" tumors into "hot" tumors [77].

More broadly, in hematologic malignancies, including lymphoma models, TLR agonists such as those targeting TLR2 and TLR7/8 have been shown to induce M1-like polarization and potentiate antitumor immune responses, often synergizing with immune checkpoint inhibitors or vaccine-based strategies [78]. In addition, emerging delivery systems, such as nanocarriers for TLR7/8 agonists, enable selective targeting of TAMs and amplification of T-cell responses, offering new avenues for clinical translation [79].

Nevertheless, the clinical application of TLR agonists remains limited by excessive inflammatory toxicity and substantial context-dependent heterogeneity. Persistent or dysregulated TLR activation may paradoxically promote chronic inflammation and tumor-supportive immune remodeling. Accordingly, future translational strategies will likely require selective delivery systems, optimized dosing schedules, and combination approaches capable of enhancing macrophage activation while avoiding systemic immune dysregulation.

3.2.3. STING Signaling Pathways

The STING (stimulator of interferon genes) signaling pathway serves as a critical bridge between innate immune sensing and antitumor immunity, playing a central role in shaping the tumor immune microenvironment. STING activation is typically initiated by cytosolic DNA via the cGAS–cGAMP axis, leading to the production of type I interferons and pro-inflammatory cytokines, thereby triggering broad antitumor immune responses [80,81].

Within the TME, STING activation promotes dendritic cell maturation and antigen presentation, enhances $CD8^+$ T-cell and NK cell effector functions, and improves immune cell infiltration through modulation of tumor vasculature [82]. In parallel, STING signaling reprograms TAMs from an immunosuppressive M2-like phenotype toward a pro-inflammatory M1-like state, primarily through induction of type I interferon signaling and upregulation of costimulatory molecules such as CD86 [83]. In lymphoma, STING activation shows significant therapeutic potential. In DLBCL, enhanced STING signaling suppresses tumor growth and promotes antitumor immunity [84]. Moreover, combining STING agonists with immune checkpoint inhibitors (e.g., PD-1/PD-L1 blockade) augments antigen presentation and T-cell activation, thereby improving therapeutic efficacy [85]. Notably, in B-cell lymphoma models, STING agonists enhance the efficacy of anti-CD20 antibodies and reverse TAM-mediated immunosuppression, representing a key application of this strategy [86].

Additionally, the cGAS–STING pathway has been implicated in PTCL, where it is associated with tumor proliferation, indicating both therapeutic relevance and involvement in tumor biology [87]. However, STING signaling exhibits context-dependent duality: while acute activation promotes antitumor immunity, excessive or chronic activation may induce immunosuppression or inflammatory tolerance, thereby limiting therapeutic benefit [88]. Therefore, precise modulation of the intensity and duration of STING activation is likely critical for its successful clinical translation.

From a translational perspective, the therapeutic window of STING agonists remains incompletely defined, and systemic administration may induce excessive inflammatory responses. Moreover, heterogeneous baseline

STING pathway activity across lymphoma subtypes may substantially influence treatment responsiveness. These findings suggest that future clinical development should emphasize biomarker-guided stratification and rational combinations with immune checkpoint blockade or antibody-based therapies rather than STING agonist monotherapy.

3.2.4. TREM2

TREM2 (triggering receptor expressed on myeloid cells 2) is an immunoglobulin superfamily receptor expressed on myeloid cells and has recently been identified as a key marker of TAMs. Its signaling is mediated by adaptor proteins DAP12/DAP10, leading to activation of SYK and downstream PI3K–AKT–mTOR and PLCγ–Ca^{2+} pathways, thereby regulating macrophage metabolism, survival, and immune function [89]. Single-cell sequencing studies have shown that $TREM2^{+}$ macrophages are widely present across multiple tumor types and exhibit a characteristic immunosuppressive phenotype, including high expression of genes such as APOE, C1QA, and MRC1, contributing to immune evasion and tumor progression. In addition, TREM2 signaling suppresses NK cell recruitment and function, further impairing innate immune surveillance and highlighting its central role in the myeloid immunosuppressive axis [90].

Although studies in lymphoma remain limited, emerging evidence indicates that $TREM2^{+}$ macrophages are enriched in tumor-infiltrating regions and sites of lymph node involvement, where they are closely associated with an immunosuppressive microenvironment [91]. Insights from solid tumor models, such as colorectal cancer, breast cancer, and sarcoma, demonstrate that TREM2 deficiency suppresses tumor growth and enhances responses to anti-PD-1 therapy, suggesting potential translational relevance in B-cell lymphomas, including DLBCL and FL. Notably, in the context of anti-CD20 antibody therapy, $TREM2^{+}$ TAMs may contribute to treatment resistance by inhibiting phagocytosis and antibody-dependent effector functions. Thus, targeting TREM2 represents a promising strategy to restore macrophage-mediated antitumor activity.

However, the translational development of TREM2-targeted therapy in lymphoma remains at an early stage. Given the substantial heterogeneity of $TREM2^{+}$ macrophage populations across tumor types and disease stages, it remains unclear whether TREM2 uniformly represents an immunosuppressive TAMs subset in all lymphoma contexts. Therefore, future studies integrating single-cell transcriptomics and spatial profiling will be essential to determine whether TREM2 can serve as a predictive biomarker and actionable therapeutic target in lymphoma immunotherapy.

3.3. Deleting Macrophages or Inhibiting the Recruitment and Accumulation of Macrophages

In the lymphoma microenvironment, the accumulation of TAMs is governed by multilayered regulation involving monocyte recruitment, local expansion, survival, and phenotypic polarization. Accordingly, therapeutic strategies aimed at macrophage depletion or blockade of macrophage recruitment have emerged as important therapeutic approaches to disrupt tumor-promoting myeloid cell networks. Current studies have primarily focused on the CSF-1/CSF1R axis and chemokine networks, including CCL2/CCR2 and CCL3/CCR1, with the overarching goal of interrupting macrophage dependent tumor support and immunosuppression [92].

At the molecular level, CSF-1/CSF1R signaling represents a central pathway regulating macrophage survival, proliferation, and functional maintenance. Lymphoma cells secrete CSF-1 to induce CSF1R autophosphorylation and activate downstream PI3K-AKT-mTOR signaling, thereby promoting macrophage survival and reciprocally supporting tumor progression [93]. In PTCL, tumor-derived inflammatory mediators further induce in situ macrophage expansion, render TAMs a functionally “addicted” component of lymphoma progression. Consequently, dual inhibition of CSF1R and JAK signaling significantly depletes TAM populations and suppresses tumor growth [94]. Similar mechanisms have also observed in FL, where tumor-derived CCL2 and CSF-1 recruit monocytes and promote M2-like polarization. Pharmacological inhibition of CSF1R (e.g., pexidartinib) reduces immunosuppressive macrophage infiltration and enhances the efficacy of anti-CD20 immunotherapy [95].

Beyond macrophage depletion, blockade of macrophage recruitment represents another critical therapeutic strategy. The CCL2/CCR2 axis serves as a key pathway mediating monocyte trafficking into the tumor site. In DLBCL, this axis promotes M2-like macrophage accumulation and suppresses antitumor immunity, whereas targeting CCR2 significantly attenuates tumor progression [96]. In addition, in MCL and other B-cell lymphomas, CCL3/CCR1 signaling facilitates macrophage recruitment and M2-like polarization. Importantly, CCR1 blockade not only impairs macrophage recruitment but also induces phenotypic reprogramming toward an antitumor state, thereby exerting therapeutic effects [97]. Collectively, these chemokine axes constitute a “macrophage input system” that represents a critical therapeutic node.

Notably, increasing evidence indicates that macrophage depletion strategies exhibit both therapeutic potential and important biological limitations. Although CSF1R inhibition effectively reduces immunosuppressive TAM populations, indiscriminate macrophage depletion may simultaneously eliminate macrophage subsets with tissue-protective or antitumor functions, potentially impairing immune homeostasis and limiting long-term therapeutic efficacy. Recent single-cell transcriptomic and spatial profiling studies further reveal substantial context-dependent TAM heterogeneity in lymphoma and other malignancies. Rather than existing as a strict M1/M2-like binary population, TAMs comprise multiple dynamically regulated functional subsets characterized by distinct transcriptional programs, spatial localization patterns, and immunological functions [98]. Emerging immunosuppressive macrophage subsets, including $SPP1^+$, $APOE^+$, and $TREM2^+$ TAMs, may exhibit differential responsiveness to depletion strategies, thereby contributing to therapeutic variability across lymphoma subtypes and disease stages [91].

In addition to promoting tumor progression, TAMs also contribute to therapeutic resistance. In aggressive B-cell lymphomas, $CSF1R^+$ monocytic/macrophage populations suppress CAR-T cell activity through PGE_2–EP2/EP4 signaling, whereas CSF1R blockade restores CAR-T function and improves survival outcomes [99], highlighting that macrophage depletion may also enhance immunotherapeutic responses.

Overall, macrophage depletion and via CSF1R inhibition or reduced recruitment through blockade of chemokine axes such as CCL2/CCR2 and CCL3/CCR1 has demonstrated antitumor efficacy across multiple lymphoma subtypes, including PTCL, DLBCL, FL, and MCL. However, growing evidence suggests that macrophage depletion alone may be insufficient because TAMs display substantial functional heterogeneity and dynamic plasticity within the lymphoma microenvironment. Therefore, future therapeutic development should emphasize rational combination strategies integrating macrophage depletion with macrophage reprogramming approaches, CAR-T therapy, or immune checkpoint blockade, as well as biomarker-guided precision immunotherapy based on TAM spatial and functional heterogeneity.

3.4. Macrophage-Based Cell Therapy

In recent years, macrophage-based cell therapy has emerged as a promising next-generation immunotherapeutic strategy following CAR-T therapy, attracting increasing attention in lymphoma. The most representative approach is chimeric antigen receptor macrophage (CAR-M) therapy. This strategy harnesses the intrinsic phagocytic capacity, antigen-presenting function, and strong tumor infiltration ability of macrophages, and further engineers them to acquire tumor-specific recognition and cytotoxic activity, thereby actively reshaping the TME. Unlike CAR-T cells, CAR-M cells also exhibit enhanced infiltration into stromal-rich tumor regions and may overcome certain physical barriers within the immunosuppressive TME [49,100,101].

At the molecular level, CAR-M cells are engineered to express single-chain variable fragments (scFvs) targeting tumor-associated antigens such as CD19, CD20, or HER2. Upon antigen engagement, intracellular signaling domains (e.g., CD3ζ or FcRγ) activate immunoreceptor tyrosine-based activation motif (ITAM) signaling, thereby triggering the SYK–PI3K axis and driving ADCP and tumor cell clearance [92]. Concurrently, CAR-M cells are maintained in a pro-inflammatory M1-like state, characterized by the secretion of cytokines such as IL-12 and TNF-α and upregulation of MHC class I/II molecules, thereby enhancing antigen presentation and promoting $CD8^+$ T-cell activation. This establishes a macrophage–T cell amplification loop [102]. In addition, CAR-M cells can remodel the TME by reducing immunosuppressive signaling and enhancing immune cell infiltration, representing a key advantage over CAR-T cells. However, accumulating evidence suggests that macrophage phenotypes are highly dynamic and strongly influenced by the surrounding tumor microenvironment. Following infusion into tumors, CAR-M cells may undergo functional reprogramming toward immunosuppressive phenotypes under the influence of cytokines such as IL-10 and TGF-β, potentially limiting therapeutic durability and antitumor efficacy [103]. This context-dependent phenotypic instability represents a major challenge for sustained CAR-M activity in lymphoma.

Current applications of CAR-M in lymphoma remain largely at the translational and preclinical stages. CAR-M constructs targeting B-cell antigens such as CD19 have demonstrated potent antitumor activity in hematologic malignancy models by enhancing phagocytosis, antigen presentation, and TME reprogramming, thereby overcoming the intrinsic limitations of native macrophage phagocytic capacity [104]. Mechanistic studies further indicate that CAR-M cells not only directly engulf tumor cells but also promote cytokine release and T-cell recruitment, inducing epitope spreading and broadening antitumor immune responses [105]. Nevertheless, most current evidence remains limited to preclinical studies, and robust clinical efficacy data in lymphoma are still lacking. Compared with CAR-T cells, macrophages are considerably more difficult to genetically engineer and expand ex vivo due to their terminal differentiation status, intrinsic antiviral defense mechanisms, and limited

proliferative capacity. These biological characteristics substantially increase manufacturing complexity and create major challenges for large-scale GMP-compliant production and standardization of CAR-M products.

From a translational perspective, CAR-M therapy has entered early clinical evaluation. The first-in-human CAR-M trial (CT-0508), initiated in 2020, has demonstrated feasibility and safety. Although initially focused on solid tumors, its underlying mechanisms are equally applicable to lymphoma [106]. However, CAR-M therapy remains substantially less clinically mature than CAR-T therapy. Long-term safety, in vivo persistence, trafficking efficiency, and cytokine-related toxicities have not yet been fully characterized in patients. Furthermore, important regulatory challenges, including batch-to-batch consistency, quality control, release criteria standardization, and cost-effective manufacturing, remain unresolved barriers for broader clinical translation [107]. Therefore, although CAR-M therapy represents a promising macrophage-based immunotherapeutic strategy, significant optimization is still required before widespread clinical implementation becomes feasible.

4. Conclusions and Future Directions

TAMs represent a highly abundant and functionally plastic immune population within the TME. Their pronounced heterogeneity and phenotypic flexibility are closely linked to lymphoma initiation, angiogenesis, metastatic dissemination, and adverse clinical outcomes. Accordingly, TAMs have emerged as key therapeutic targets in lymphoma. Accumulating clinical and translational evidence supports macrophage-targeted therapeutic strategies as a promising component of precision oncology; however, their therapeutic responses remain highly context-dependent and are not yet fully predictable. Despite rapid progress, several fundamental aspects of TAM biology and therapeutic targeting in lymphoma remain incompletely defined, posing major barriers to clinical translation.

(1) TME interaction complexity and systems-level regulation

The TME is characterized by dynamic and bidirectional interactions among malignant cells, immune populations, and stromal components, necessitating a systems-level rather than reductionist analytical framework. In particular, macrophage–lymphoma crosstalk should be interpreted within spatially and temporally organized immune ecosystems rather than isolated signaling pathways. We hypothesize that therapeutic resistance and heterogeneous responses to TAM-targeted therapy arise from *spatially organized immune ecosystems*, in which TAMs function as adaptive hubs rather than linear effectors. This hypothesis can be tested using spatial transcriptomics and multiplex imaging approaches across lymphoma subtypes.

(2) Therapeutic efficacy, resistance mechanisms, and validation gaps

Extensive empirical validation is required to define the true clinical efficacy of current TAM-targeted strategies, particularly given the frequent discrepancy between preclinical efficacy and clinical outcomes. Emerging evidence suggests that therapeutic resistance is not a secondary event but an intrinsic property of the lymphoma ecosystem, driven by macrophage heterogeneity, compensatory immune checkpoint activation (e.g., PD-1/PD-L1), and cytokine redundancy (e.g., IL-10, TGF-β signaling). We propose that durable clinical responses will require simultaneous targeting of macrophage survival pathways (e.g., CSF-1R signaling) and adaptive immune checkpoints (e.g., PD-1/PD-L1 axis). This strategy warrants evaluation in rationally designed combination trials.

(3) Combination strategies and precision immunotherapy

Integration of TAM-directed therapies with chemotherapy, immune checkpoint blockade, or CAR-T cell therapy represents a promising strategy to overcome microenvironment-mediated resistance and may redefine therapeutic paradigms in lymphoma. Rather than single-pathway inhibition, future approaches should focus on coordinated reprogramming of the tumor microenvironment, integrating macrophage depletion, functional re-education, and reinforcement of adaptive antitumor immunity. Within this framework, TAM-targeted interventions are expected to function as modulators of immune ecosystem dynamics rather than standalone therapies. Importantly, biomarker-driven patient stratification will be critical for clinical success. Parameters such as TAM transcriptional states (e.g., $SPP1^+$ and $TREM2^+$ signatures), spatial distribution patterns, and CD47/CSF-1R pathway activity may serve as predictive determinants of therapeutic response and should be incorporated into future trial design.

In summary, TAMs play a central and non-redundant role in lymphoma progression and therapeutic resistance through coordinated regulation of immune suppression, angiogenesis, and tissue remodeling. TAM-targeted therapies have shown promising results in both preclinical stages and clinical trials. However, current clinical outcomes remain inconsistent, reflecting fundamental limitations related to macrophage plasticity, TME

redundancy, and insufficient patient stratification. Therefore, future success of TAM-targeted therapies will depend on the development of integrated strategies combining spatially resolved immune profiling, rational therapeutic combinations, and biomarker-guided patient selection. We propose that overcoming these challenges will enable a transition from empiric macrophage targeting to precision-directed remodeling of the lymphoma immune ecosystem, ultimately improving durable clinical responses in lymphoma patients.

Author Contributions

M.G. wrote the manuscript, M.G. and S.L. collected the related literature, and finished the figures. S.Z., W.L. and L.X. revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

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