ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

CANCER TREATMENT BY REGULATING MACROPHAGE PROLIFERATION

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Abstract: Tumor-associated macrophages (TAMs) are a major component of the leukocyte infiltrate in most solid tumors and play a critical, often pro-tumorigenic, role in cancer progression. They contribute to tumor growth, angiogenesis, immunosuppression, metastasis, and resistance to therapy. The accumulation of TAMs within the tumor microenvironment (TME) results from both the recruitment of monocytic precursors from the circulation and the local proliferation of resident macrophages. Recent evidence highlights that in situ proliferation significantly contributes to the TAM population in various cancers. This self-renewal capacity makes macrophage proliferation an attractive therapeutic target. This review discusses the significance of macrophage proliferation in the TME, the key molecular drivers, and the emerging therapeutic strategies aimed at inhibiting this process. We explore preclinical and clinical evidence for agents targeting pathways crucial for macrophage proliferation, such as the colony-stimulating factor 1 (CSF-1)/CSF-1 receptor (CSF-1R) axis, and discuss their impact on tumor growth and the immune landscape. Furthermore, we consider the potential of combining macrophage proliferation inhibitors with other anti-cancer treatments, including chemotherapy, radiotherapy, and immunotherapy, to enhance therapeutic efficacy. Challenges such as ensuring specificity for pro-tumor TAMs and overcoming compensatory mechanisms are also addressed, along with future perspectives for this promising therapeutic approach.

Keywords: Macrophage Proliferation, Tumor-Associated Macrophages (TAMs), Cancer Therapy, Targeted Therapy, Tumor Microenvironment (TME), CSF-1R, Immunotherapy, Cytokines.

INTRODUCTION

Cancer is a leading cause of morbidity and mortality globally, characterized by uncontrolled cell growth and the ability to invade and metastasize [6]. The TME, a complex ecosystem of cancer cells, stromal cells, immune cells, and extracellular matrix, plays a crucial role in modulating tumor development, progression, and response to therapy [7]. Among the immune cells infiltrating tumors, macrophages are often the most abundant, earning them the designation of tumor-associated macrophages (TAMs) [1].

Macrophages are highly plastic cells of the innate immune system with diverse functions, including host defense, tissue homeostasis, and wound repair [8]. In the context of cancer, their role is often described as a "double-edged sword." Classically activated (M1-like) macrophages can exert anti-tumor effects by producing pro-inflammatory cytokines, reactive oxygen/nitrogen species, and by presenting tumor antigens to T cells [9]. However, within the established TME, cancer cells often educate macrophages to adopt an alternatively activated (M2-like) phenotype. These M2-like TAMs promote tumor growth by secreting growth factors, enhancing angiogenesis, remodeling the extracellular matrix to facilitate invasion and metastasis, and suppressing anti-tumor immune responses [2, 10]. High TAM density is frequently associated with advanced tumor stage, increased metastasis, and poor patient outcomes across a wide range of malignancies [11].

The accumulation of TAMs in tumors was traditionally thought to primarily result from the continuous recruitment of blood monocytes that differentiate into macrophages upon entering the

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

tissue [12]. However, mounting evidence now indicates that local proliferation of resident or recruited macrophages is a significant contributor to the TAM pool in many cancer types, including gliomas, breast, lung, and pancreatic cancers [3, 4, 13]. This in situ expansion is driven by various tumor-derived and TME-derived factors, most notably colony-stimulating factor 1 (CSF-1) [14].

The realization that TAMs can self-renew within the TME opens up new therapeutic avenues. Specifically targeting the proliferation of these cells, rather than solely focusing on their recruitment or general depletion, could offer a more refined strategy to curtail their pro-tumorigenic activities. This approach might reduce the overall TAM burden, shift the balance towards an anti-tumor microenvironment, and potentially enhance the efficacy of other anti-cancer therapies.

This review aims to: Summarize the current understanding of macrophage proliferation within the TME and its contribution to cancer progression. Identify the key molecular drivers and signaling pathways that regulate TAM proliferation. Evaluate therapeutic strategies designed to inhibit macrophage proliferation, focusing on preclinical and emerging clinical data. Discuss the potential of combining macrophage proliferation inhibitors with existing cancer treatments. Highlight the challenges and future perspectives in targeting macrophage proliferation for cancer therapy.

MATERIALS AND METHODS

This review involved an extensive literature search of major biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search strategy utilized a combination of keywords and MeSH terms such as: "macrophage proliferation," "tumor-associated macrophages," "TAM proliferation," "CSF-1," "CSF-1R," "M-CSF," "cancer," "tumor microenvironment," "macrophage targeted therapy," "macrophage inhibitors," "GM-CSF cancer," "IL-4 macrophage," "MYC macrophage," and names of specific CSF-1R inhibitors (e.g., pexidartinib, PLX3397, emactuzumab).

The search included original research articles, review articles, meta-analyses, and relevant clinical trial information published in English, with a primary focus on literature from the last 15-20 years, while also including seminal older publications where appropriate. Articles were selected for inclusion if they provided information concerning: The mechanisms and extent of macrophage proliferation in various cancer models or human tumors. The molecular drivers (cytokines, growth factors, signaling pathways) of macrophage proliferation in the TME. The development and evaluation (preclinical or clinical) of therapeutic agents targeting macrophage proliferation. The impact of modulating macrophage proliferation on tumor growth, metastasis, angiogenesis, and anti-tumor immunity. Combination therapies involving inhibitors of macrophage proliferation.

Data extracted included the cancer type, experimental model (cell lines, animal models, human studies), specific factors or inhibitors studied, observed effects on macrophage numbers/proliferation, impact on tumor progression, and proposed mechanisms of action. This information was then critically analyzed, synthesized, and organized to provide a comprehensive overview of the current state of knowledge and future prospects for targeting macrophage proliferation in cancer therapy. Due to the breadth of the topic and the nature of a review, a formal meta-analysis was not performed.

RESULTS AND DISCUSSION

Macrophages in the Tumor Microenvironment - Origin and Heterogeneity of TAMs: TAMs originate from two main sources: circulating bone marrow-derived monocytes, primarily Ly6C$^+$ CCR2$^+$ monocytes in mice (classical monocytes in humans), which are recruited to the tumor site by chemokines like CCL2 (MCP-1), and tissue-resident macrophages that can self-renew through local proliferation [3, 12]. The relative contribution of these sources can vary depending on the tumor type, stage, and location [4]. Once in the TME, macrophages exhibit remarkable plasticity

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

and can differentiate into various functional phenotypes, broadly categorized as M1-like (pro-inflammatory, anti-tumor) and M2-like (anti-inflammatory, pro-tumor) [9]. However, this M1/M2 dichotomy is an oversimplification, as TAMs often display a spectrum of activation states with mixed phenotypes, influenced by the diverse signals they receive from cancer cells, stromal cells, and other immune cells [2, 15]. Generally, the TME skews TAMs towards an M2-like phenotype that supports tumor progression.

Pro-Tumorigenic Functions of TAMs: M2-like TAMs contribute to virtually all stages of cancer progression [10, 11]: Tumor Growth and Survival: TAMs secrete growth factors (e.g., EGF, FGF, HGF) that directly stimulate cancer cell proliferation and survival. Angiogenesis: They produce pro-angiogenic factors like VEGF, bFGF, and MMPs, promoting new blood vessel formation, which supplies tumors with nutrients and oxygen.

Immunosuppression: TAMs release anti-inflammatory cytokines (e.g., IL-10, TGF-β), express checkpoint ligands (e.g., PD-L1, PD-L2), and recruit regulatory T cells (Tregs), all of which dampen anti-tumor immune responses by inhibiting cytotoxic T cells and NK cells.

Invasion and Metastasis: They secrete enzymes like MMPs that degrade the extracellular matrix, facilitating cancer cell invasion and intravasation. TAMs can also escort cancer cells during migration and promote their survival in circulation and at metastatic sites.

Therapy Resistance: TAMs have been implicated in resistance to chemotherapy, radiotherapy, and targeted therapies through various mechanisms, including the secretion of protective factors and modulation of the TME.

The Significance of Macrophage Proliferation in Cancer - While monocyte recruitment is a well-established mechanism for TAM accumulation, the contribution of in situ proliferation of macrophages has gained significant attention in recent years [3, 4]. Studies using lineage tracing and proliferation markers (e.g., Ki67, BrdU incorporation) have demonstrated that a substantial fraction of TAMs in various solid tumors (e.g., glioma, breast, lung, pancreatic, ovarian cancer) arises from local division rather than solely from recruited monocytes [13, 16, 17]. For instance, in some brain tumor models, nearly all TAMs are derived from resident microglia that proliferate locally [16]. In other cancers, both recruitment and proliferation contribute significantly.

Key Drivers of Macrophage Proliferation in the TME: The proliferation of macrophages within the TME is orchestrated by a complex interplay of cytokines, growth factors, and signaling molecules, often produced by cancer cells or other stromal cells [14].

CSF-1 (M-CSF): Colony-Stimulating Factor 1 is a pivotal regulator of macrophage survival, differentiation, and proliferation. Cancer cells frequently overexpress CSF-1, which binds to its receptor CSF-1R (c-FMS) on macrophages, activating downstream signaling pathways (e.g., PI3K/Akt, MAPK/ERK) that promote cell cycle progression [14, 18].

IL-34: Another ligand for CSF-1R, IL-34, can also drive macrophage proliferation and exhibits tissue-specific expression patterns. Its role in cancer-associated macrophage proliferation is an active area of research [19].

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor can also support macrophage proliferation and differentiation, though its role in the TME can be context-dependent, sometimes promoting M1-like phenotypes [20].

IL-4 and IL-13: These Th2 cytokines, often abundant in the TME, promote M2 polarization and can also induce macrophage proliferation, contributing to the M2-like TAM pool [21].

Other Factors: Various other molecules, including chemokines (e.g., CCL2, which primarily acts as a chemoattractant but can also influence survival), growth factors, and components of the extracellular matrix, can directly or indirectly support macrophage proliferation and survival in the TME.

eISSN: 2349-5715 pISSN: 2349-5707

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Intracellular signaling molecules like MYC have also been shown to be crucial for sustained macrophage proliferation [22].

Table 1:

Key Factors Driving Macrophage Proliferation in the TME and Their Sources

Factor	Primary Source(s) in TME	Receptor on Macrophages	Key Effects on Macrophages/Cancer
CSF-1 (M-CSF)	Cancer cells, fibroblasts, endothelial cells	CSF-1R (c-FMS)	Promotes macrophage survival, differentiation, proliferation; supports M2-like TAM accumulation; pro-tumorigenic [14, 18]
IL-34	Cancer cells, stromal cells (tissue-specific)	CSF-1R (c-FMS)	Similar to CSF-1; promotes macrophage survival and proliferation; context-dependent roles [19]
GM-CSF	Cancer cells, T cells, endothelial cells	GM-CSFR	Supports macrophage proliferation and differentiation; can promote M1 or M2 depending on context [20]
IL-4	Cancer cells, Th2 cells, eosinophils, mast cells	IL-4Rα	Induces M2 polarization, promotes macrophage proliferation, immunosuppression; pro-tumorigenic [21]
IL-13	Cancer cells, Th2 cells	IL-4Rα/IL-13Rα1	Similar to IL-4; promotes M2 polarization and proliferation; pro-tumorigenic [21]
MYC (intracellular)	- (Transcription factor)	-	Essential for sustained macrophage proliferation programs; activated by various upstream signals [22]
CCL2 (MCP-1)	Cancer cells, stromal cells, macrophages	CCR2	Primarily chemoattractant for monocytes/macrophages; can also provide survival signals [12]

Contribution of Proliferating TAMs to Tumor Progression: Proliferating TAMs actively contribute to the maintenance and expansion of the pro-tumorigenic macrophage population. By sustaining their numbers locally, they continuously fuel the tumor with growth factors, angiogenic mediators, and immunosuppressive molecules, thereby exacerbating tumor growth, vascularization, and immune evasion [3, 17]. The ability of TAMs to proliferate within distinct tumor niches, such as hypoxic regions or perivascular areas, further highlights their adaptability and strategic role in supporting the tumor.

Therapeutic strategies targeting macrophage proliferation - Given the significant contribution of proliferation to TAM accumulation and function, inhibiting this process has emerged as a rational therapeutic strategy.

Inhibition of CSF-1/CSF-1R Signaling: The CSF-1/CSF-1R axis is the most extensively studied pathway in the context of TAM proliferation and survival. Blocking this pathway aims to reduce TAM numbers, partly by inhibiting their proliferation and survival, and potentially repolarize remaining TAMs towards a less pro-tumorigenic state [5, 18].

CSF-1R Inhibitors: Several approaches have been developed:

Monoclonal Antibodies: Target CSF-1 (e.g., RaGvac, an anti-CSF-1 vaccine) or CSF-1R (e.g., emactuzumab, cabiralizumab, AMG820). These antibodies can block ligand binding or induce receptor internalization and degradation.

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Small Molecule Kinase Inhibitors: These compounds (e.g., pexidartinib (PLX3397), BLZ945, JNJ-40346527, ARRY-382) enter cells and inhibit the tyrosine kinase activity of CSF-1R, thereby blocking downstream signaling. Many of these also inhibit other related kinases like KIT and FLT3.

Preclinical and Clinical Evidence: Numerous preclinical studies have shown that CSF-1/CSF-1R inhibitors can significantly reduce TAM density in various tumor models, leading to inhibited tumor growth, reduced angiogenesis, decreased metastasis, and enhanced anti-tumor immunity [23, 24]. These effects are often attributed to a combination of blocked monocyte recruitment, reduced macrophage proliferation, and induction of apoptosis in existing TAMs. Clinically, CSF-1R inhibitors have shown activity in certain cancers. Pexidartinib is approved for tenosynovial giant cell tumor, a neoplastic disorder driven by CSF-1 overexpression [25]. In other solid tumors, monotherapy efficacy has been modest, but promising results are emerging from combination therapies, particularly with immune checkpoint inhibitors [26]. The impact on TAM proliferation specifically has been confirmed in some clinical studies through biomarker analysis (e.g., reduced Ki67$^+$ TAMs).

Targeting Other Proliferative Pathways: Beyond CSF-1R, other pathways sustaining macrophage proliferation are being explored as potential targets.

GM-CSF/GM-CSFR Pathway: While GM-CSF can have complex roles, inhibiting its pro-proliferative effect on M2-like TAMs could be beneficial in specific contexts, though this is less explored than CSF-1R targeting for proliferation [20].

IL-4/IL-13 Signaling: Blocking IL-4Rα or downstream STAT6 signaling could inhibit the proliferation and M2 polarization of TAMs. Antibodies targeting IL-4 or IL-4Rα are in development, primarily for allergic diseases, but their potential in cancer is being considered [21].

Intracellular Signaling Nodes: MYC: The transcription factor MYC has been identified as a critical regulator of macrophage proliferation programs [22]. Pharmacological inhibition of MYC or its upstream activators (if specific to macrophages) could be a strategy, although targeting MYC directly has proven challenging. Cyclin-Dependent Kinases (CDKs): Like other proliferating cells, macrophages rely on CDKs for cell cycle progression. CDK4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib), approved for certain breast cancers, have also been shown to impact immune cell proliferation, including potentially TAMs [27]. However, their effects on TAMs specifically require more detailed investigation.

Table 2:
Therapeutic Agents Targeting Macrophage Proliferation: Mechanisms and Preclinical/Clinical Status

Agent/Target	Mechanism of Action regarding Proliferation	Cancer Models Studied (Preclinical)	Key Outcomes (Preclinical/Clinical)	Clinical Development Stage (Selected Examples)
Pexidartinib (PLX3397)	Small molecule CSF-1R, KIT, FLT3 inhibitor; inhibits CSF-1R signaling, reducing macrophage proliferation & survival	Glioma, breast, pancreatic, melanoma, TGCT	Reduced TAMs, tumor growth inhibition, improved anti-tumor immunity; Approved for TGCT	Approved (TGCT); Phase I/II (other solid tumors) [25]

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Emactuzumab (RG7155)	mAb targeting CSF-1R; blocks ligand binding, induces receptor degradation	Colorectal, melanoma, various solid tumors	Reduced TAMs, tumor stasis/regression, enhanced T cell activity	Phase I/II (solid tumors) [26]
Cabiralizumab (BMS-986227)	mAb targeting CSF-1R	Pancreatic cancer, various solid tumors	Reduced TAMs, synergy with immunotherapy	Phase I/II (solid tumors) [28]
BLZ945	Selective small molecule CSF-1R inhibitor	Glioblastoma, breast cancer	Reduced TAM proliferation, TAM depletion, anti-tumor effects, re-sensitizes to other therapies	Preclinical/Phase I [23]
Anti-IL-4Rα mAb	Blocks IL-4/IL-13 signaling	Lung, breast cancer	Reduced M2 TAM polarization and proliferation, enhanced anti-tumor immunity (preclinical)	Phase I/II (for allergic diseases, exploring cancer)
MYC inhibitors (e.g., OmoMYC)	Inhibit MYC transcriptional activity crucial for proliferation	Lung, pancreatic cancer (general MYC)	Reduced TAM proliferation (inferred), tumor growth inhibition (preclinical, requires specific macrophage targeting)	Preclinical/Phase I (general MYC inhibitors) [22]
CDK4/6 inhibitors (e.g., Palbociclib)	Inhibit cell cycle progression	Breast, melanoma, other solid tumors	Reduced cancer cell proliferation; potential to inhibit TAM proliferation (preclinical/emerging)	Approved (breast cancer); Investigational (other cancers/immune effects) [27]

Impact of Modulating Macrophage Proliferation on Anti-Tumor Immunity and Therapy Response. Inhibiting TAM proliferation is not only expected to reduce tumor burden directly but also to favorably reshape the TME, particularly by alleviating immunosuppression.

Enhancing Anti-Tumor Immunity: By decreasing the numbers of M2-like, immunosuppressive TAMs, proliferation inhibitors can lead to:

Increased infiltration and activation of cytotoxic T lymphocytes (CTLs) and NK cells.

Reduced levels of immunosuppressive cytokines (e.g., IL-10, TGF-β) and checkpoint ligands (e.g., PD-L1 on remaining TAMs).

A shift in the overall immune balance towards an M1-like, anti-tumor environment [23, 24].

Combination Therapies: The greatest potential for macrophage proliferation inhibitors likely lies in combination strategies:

With Chemotherapy/Radiotherapy: TAMs contribute to resistance to conventional cytotoxic therapies. Reducing their numbers by inhibiting proliferation could sensitize tumors to chemotherapy or radiotherapy [17].

eISSN: 2349-5715 pISSN: 2349-5707

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With Immunotherapy: This is a particularly promising area. TAMs are a major source of resistance to immune checkpoint inhibitors (ICIs) like anti-PD-1/PD-L1. Combining CSF-1R inhibitors (which reduce TAM proliferation and numbers) with ICIs has shown synergistic effects in preclinical models and early clinical trials, leading to enhanced anti-tumor responses [26, 28]. The rationale is that reducing immunosuppressive TAMs "releases the brakes" on T cell-mediated immunity, allowing ICIs to work more effectively.

Table 3:
Potential Combination Therapies Involving Modulation of Macrophage Proliferation

Strategy Targeting Macrophage Proliferation	Combination Partner(s)	Rationale	Expected Synergistic Effect	Key References/Hypothetical Basis
CSF-1R Inhibitors (e.g., Pexidartinib, Emactuzumab)	Immune Checkpoint Inhibitors (anti-PD-1/PD-L1, anti-CTLA-4)	Reduce immunosuppressive TAMs, alleviate T cell suppression, enhance antigen presentation.	Increased T cell infiltration and activation, improved ICI efficacy, durable responses.	[26, 28]
CSF-1R Inhibitors	Chemotherapy (e.g., gemcitabine, paclitaxel)	Reduce TAM-mediated chemoresistance, decrease TAM-derived survival factors for cancer cells.	Enhanced tumor cell killing, delayed relapse, reduced TAM-mediated repair.	[17, 23]
CSF-1R Inhibitors	Radiotherapy	Counteract radiation-induced TAM influx/proliferation and their pro-angiogenic/repair functions.	Improved local tumor control, reduced recurrence, potential abscopal effects when combined with immunotherapy.	[29]
CSF-1R Inhibitors	Anti-angiogenic therapy (e.g., anti-VEGF)	TAMs contribute to angiogenesis and resistance to anti-VEGF; dual targeting may be more effective.	More profound inhibition of angiogenesis, reduced tumor growth.	[30]
Inhibitors of IL-4Rα or MYC (future)	Immunotherapy / Chemotherapy	Similar rationale: reducing pro-tumor M2-like TAMs or their general expansion to	Enhanced anti-tumor immunity or chemosensitivity.	[21, 22] (Hypothetical)

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		enhance other therapies.		

Challenges and Future Perspectives - Despite the promise, targeting macrophage proliferation in cancer faces several challenges: Specificity: It is crucial to selectively target the proliferation of pro-tumorigenic TAMs while sparing beneficial anti-tumor macrophages (M1-like) or macrophages essential for normal tissue homeostasis. Current CSF-1R inhibitors tend to be broad, affecting most CSF-1R-dependent macrophages. Compensatory Mechanisms: Tumors might adapt to proliferation blockade by increasing the recruitment of monocytic precursors. Therefore, strategies that simultaneously target both proliferation and recruitment might be more effective. Biomarkers: Identifying predictive biomarkers to select patients whose tumors are highly dependent on TAM proliferation is essential for clinical success. This could involve assessing CSF-1 levels, TAM density/proliferation rates (Ki67$^+$ TAMs), or specific gene signatures. Resistance Mechanisms: Tumors may develop resistance to TAM proliferation inhibitors through various mechanisms, such as upregulation of alternative survival/proliferation pathways for macrophages or changes in the cancer cells themselves. Systemic Effects: Since target molecules like CSF-1R are also expressed on other cells or play roles in normal physiology, systemic administration of inhibitors can lead to side effects (e.g., hepatotoxicity, periorbital edema with CSF-1R inhibitors) [25]. Heterogeneity of TAMs: The diverse origins and phenotypes of TAMs, even within the same tumor, complicate targeting strategies. Proliferation rates and dependencies might vary between different TAM subsets.

Future Perspectives: Development of More Selective Inhibitors: Creating agents that preferentially inhibit the proliferation of M2-like TAMs or target proliferation drivers specific to the TME. Novel Delivery Systems: Using nanotechnology or tumor-targeted delivery approaches to concentrate inhibitors within the TME, enhancing efficacy and reducing systemic toxicity. Understanding Context Dependency: Further research into how the reliance on macrophage proliferation varies across different tumor types, stages, and treatment settings. Rational Combination Design: Optimizing combination therapies based on a deeper understanding of the interplay between TAM proliferation, the immune landscape, and other anti-cancer treatments. Exploiting Macrophage Reprogramming: Combining proliferation inhibitors with agents that can repolarize remaining TAMs from a pro-tumor (M2-like) to an anti-tumor (M1-like) phenotype.

CONCLUSION AND RECOMMENDATIONS

The proliferation of tumor-associated macrophages within the tumor microenvironment is a significant contributor to TAM accumulation and their pro-tumorigenic functions. This local expansion fuels cancer progression by promoting tumor cell growth, angiogenesis, immunosuppression, and therapy resistance. Targeting pathways crucial for macrophage proliferation, particularly the CSF-1/CSF-1R axis, has emerged as a promising therapeutic strategy. Preclinical studies and early clinical data with CSF-1R inhibitors have demonstrated their potential to reduce TAM numbers, reshape the TME, and inhibit tumor growth, especially when used in combination with other therapies like immunotherapy.

However, the successful clinical translation and broad application of macrophage proliferation inhibitors require addressing key challenges, including enhancing specificity, overcoming resistance, identifying predictive biomarkers, and managing potential side effects.

Recommendations for future research:

Deepen Mechanistic Understanding: Further investigate the molecular and cellular mechanisms regulating TAM proliferation in different cancer contexts, including the identification of novel proliferation drivers specific to pro-tumor TAMs.

eISSN: 2349-5715 pISSN: 2349-5707
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Develop Next-Generation Inhibitors: Design and evaluate novel therapeutic agents with improved selectivity for proliferating pro-tumor TAMs and better safety profiles.
Refine Biomarker Strategies: Identify and validate robust biomarkers to stratify patients who are most likely to benefit from therapies targeting macrophage proliferation.
Optimize Combination Therapies: Conduct well-designed preclinical and clinical studies to determine the most effective combination strategies, timings, and sequences of administration.
Investigate Resistance Mechanisms: Elucidate how tumors and TAMs develop resistance to proliferation inhibitors to devise strategies to overcome or prevent it.
Explore Tissue-Resident Macrophage Proliferation: Given the distinct origins and roles of tissue-resident versus monocyte-derived TAMs, explore whether proliferation mechanisms and therapeutic vulnerabilities differ between these populations.
In conclusion, regulating macrophage proliferation represents an innovative and viable approach to cancer therapy. Continued research and development in this area hold the potential to yield new treatments that can significantly improve outcomes for cancer patients by disrupting a key cellular component that supports tumor survival and immune evasion.

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eISSN: 2349-5715 pISSN: 2349-5707

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eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

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