

REVIEW

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Macrophage polarization in hematologic cancers: mechanisms and therapeutic strategies

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Abstract

Leukemia treatment faces persistent challenges, including chemotherapy resistance and relapse, highlighting macrophage polarization in the tumor microenvironment (TME) as a therapeutic target. Macrophages dynamically shift between antitumor M1 and protumor M2 phenotypes, with M2-polarized tumor-associated macrophages (TAMs) dominating leukemia TMEs. These cells secrete IL-10 and TGF- β , fostering immune evasion, angiogenesis, and leukemia stem cell (LSC) survival. In AML, M2 TAMs correlate with poor prognosis and chemoresistance via CSF-1/IL-10 signaling. Polarization is regulated by transcription factors (STAT6, PPAR γ , KLF4), hypoxia, and metabolic reprogramming. Therapeutic strategies focus on: (1) M2 depletion (anti-CD163/CD206 antibodies); (2) Pathway inhibition (CCL2/CCR2 or IL-4/STAT6 blockade); (3) Metabolic modulation (glycolysis/OXPHOS targeting); and (4) Phagocytosis enhancement (CD47-SIRP α blockade, HDAC6 inhibition). Preclinical studies demonstrate CSF-1R inhibitors (e.g., pexidartinib) disrupt LSC-TAM crosstalk, while CAR-M therapy synergizes with phagocytosis-promoting agents. Despite challenges, macrophage-targeted therapies offer transformative potential by remodeling the TME, overcoming resistance, and augmenting immunotherapy. This review outlines mechanistic insights and translational strategies to harness macrophage plasticity for leukemia treatment.

Highlights

- (1) We delineate the multifaceted regulatory networks—including NF- κ B, STAT1/6, PPAR γ , hypoxia, metabolic reprogramming, and exosomal signals—that drive macrophage polarization in hematologic malignancies.
- (2) We show that M2-like tumor-associated macrophage infiltration predominates in AML, promoting angiogenesis, immune evasion, chemoresistance, and correlating with adverse prognosis.
- (3) We review therapeutic strategies to deplete or reprogram M2 macrophages—such as CSF-1R inhibitors, anti-CD163/CD206 antibodies, and CAR-Macrophage constructs—to restore anti-leukemic immunity.
- (4) We highlight emerging combinatorial approaches (e.g., metabolic interventions, TLR agonists, CD47-SIRP α and immune checkpoint blockade) that synergize to shift TAMs toward a pro-inflammatory M1 phenotype and enhance chemotherapy efficacy.
- (5) We propose leveraging single-cell sequencing and spatial transcriptomics to map TAM heterogeneity and guide precision macrophage-targeted therapies in hematologic cancers.

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Introduction

Hematologic malignancies are profoundly influenced by the tumor microenvironment [1–3], where macrophages play a pivotal yet dichotomous role [4–6]. These innate immune cells exhibit remarkable plasticity, polarizing into pro-inflammatory M1 or immunosuppressive M2 phenotypes in response to microenvironmental cues [7–9]. While M1 macrophages exert anti-tumor effects through cytokine secretion and phagocytosis [10, 11], M2-polarized tumor-associated macrophages promote immune evasion, angiogenesis, and chemoresistance [5, 7, 12, 13]—features strongly associated with poor prognosis [14, 15]. The balance between these subsets is governed by intricate signaling networks, including NF-κB/STAT1-driven M1 polarization [16, 17] and STAT6/PPARγ-mediated M2 skewing [13, 16, 18], further modulated by hypoxia [19, 20] and metabolic reprogramming [21, 22] within the TME. Targeting macrophage polarization has thus emerged as a promising therapeutic strategy [8, 23–25]. Approaches such as STAT6 inhibition [16, 18], CD163/CD206-directed depletion [14, 26], and metabolic interference (e.g., HIF-1α blockade) [19, 20] have shown efficacy in preclinical models by reverting M2-like TAMs to tumoricidal M1 states [25, 27] and sensitizing malignancies to conventional therapies [14, 28]. However, challenges persist in achieving cell-specific targeting and minimizing systemic toxicity [15, 28]. Future efforts must refine these strategies through spatial-temporal control and biomarker-guided interventions [15, 28] to harness macrophages' full therapeutic potential in hematologic cancers [14, 29, 30].

The polarization mechanism of macrophages

Macrophage polarization is a dynamic process orchestrated by microenvironmental cues that dictate their functional plasticity [29, 31, 32]. In hematologic malignancies, this process is predominantly governed by two opposing phenotypes: classically activated (M1) and alternatively activated (M2) macrophages [2, 29, 33]. M1 polarization is initiated by pro-inflammatory stimuli such as interferon-gamma (IFN-γ) and lipopolysaccharide (LPS), which activate canonical signaling pathways like nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 1 (STAT1) [34–36]. These pathways drive the expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and IL-12,

which equip M1 macrophages with potent anti-tumor capabilities [34, 37, 38]. Mechanistically, LPS binding to Toll-like receptors (TLRs) triggers MyD88-dependent signaling, culminating in NF-κB activation and the release of inflammatory mediators such as inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS) [34, 35]. In hematologic cancers, M1 macrophages enhance antigen presentation, promote T-cell activation, and exert direct tumor cytotoxicity through phagocytosis and nitric oxide (NO)-mediated killing [29, 39, 40]. However, sustained M1 activation risks tissue damage due to excessive inflammation, underscoring the necessity for regulatory checkpoints like IL-10 and transforming growth factor-beta (TGF-β) to temper these responses [41–43].

Conversely, M2 polarization is driven by Th2 cytokines such as IL-4, IL-10, and IL-13, which activate the STAT6 pathway and suppress NF-κB-mediated pro-inflammatory signaling [18, 42, 44]. M2 macrophages secrete immunosuppressive cytokines (e.g., IL-10, TGF-β) and express markers like CD206 and arginase-1 (Arg-1), facilitating tissue repair, angiogenesis, and immune tolerance [18, 37, 44]. In hematologic malignancies, tumor-associated macrophages (TAMs) predominantly adopt an M2-like phenotype, creating a permissive niche for tumor progression [2, 29, 33]. For instance, IL-4-induced STAT6 phosphorylation enhances M2 marker expression while suppressing pro-inflammatory cytokines, thereby promoting chemoresistance and immune evasion [18, 40, 44]. TAMs further contribute to tumor angiogenesis by secreting vascular endothelial growth factor (VEGF) and hypoxia-inducible factors (HIFs), which stabilize the immunosuppressive tumor microenvironment [2, 38, 42] (Fig. 1). Notably, leukemia cells exploit this plasticity by secreting IL-4 and IL-13 to recruit and polarize macrophages via STAT6, establishing a feedforward loop that sustains tumor growth and immunosuppression [29, 40, 45]. This M2 skewing is further reinforced by metabolic reprogramming, such as increased fatty acid oxidation (FAO) and mTORC activation, which suppress pro-inflammatory responses and enhance immunosuppressive functions [38, 41, 46].

The tumor microenvironment in hematologic cancers plays a pivotal role in shaping macrophage polarization through hypoxia, metabolic crosstalk, and extracellular vesicle (EV)-mediated signaling [29, 38, 42]. Hypoxia upregulates HIF-1α, which drives M2

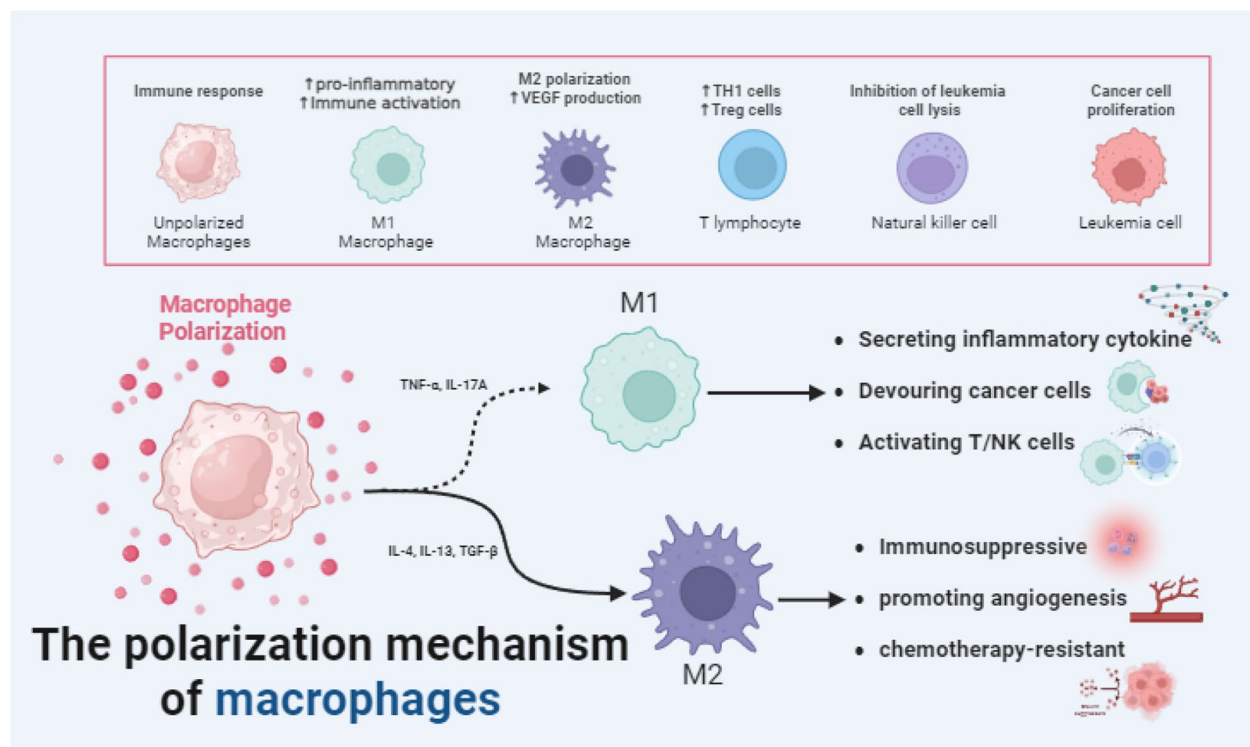


Fig. 1 The Polarization Mechanism of Macrophages in Hematologic Cancers. M1 Macrophages: Induced by TNF- α and IL-17A, M1 macrophages secrete inflammatory cytokines, devour cancer cells, and activate T/NK cells. They are associated with a pro-inflammatory immune response and immune activation, contributing to the inhibition of leukemia cell lysis and cancer cell proliferation. M2 Macrophages: Induced by IL-4, IL-13, and TGF- β , M2 macrophages exhibit immunosuppressive properties, promote angiogenesis, and are chemotherapy-resistant. They are linked to VEGF production, Treg cell activation, and the inhibition of natural killer cell function, ultimately supporting the survival and proliferation of leukemia cells

polarization by enhancing IL-10 and TGF- β secretion while dampening IFN- γ -induced M1 responses [2, 38, 42]. Leukemia-derived EVs deliver oncogenic miRNAs and proteins to macrophages, reprogramming them toward a pro-tumor phenotype [2, 33, 45]. For example, lactate accumulation in the TME activates mTORC signaling, which skews macrophages toward M2-like immunosuppression [38, 41, 47]. Additionally, metabolic alterations such as enhanced glycolysis and suppressed oxidative phosphorylation (OXPHOS) in TAMs further entrench their pro-tumor functions [38, 46, 48]. Therapeutic strategies targeting these pathways—such as NF- κ B inhibitors (e.g., BAY11-7082) [34, 35], STAT6 antagonists [18, 44], or metabolic modulators—hold promise for reprogramming TAMs toward an anti-tumor M1 phenotype [2, 38, 48]. However, challenges remain in balancing pro-inflammatory responses to avoid tissue damage while effectively disrupting the immunosuppressive TME in hematologic malignancies [2, 29, 40].

The role of macrophage polarization in hematologic malignant tumors

Macrophages are one of the most dynamic components of the TME in hematologic malignancies. Their ability to switch between distinct functional phenotypes—pro-inflammatory (M1) and anti-inflammatory (M2)—directly influences the course of the disease [49–52]. In hematologic tumors, the TME is not only composed of malignant cells but also a complex network of stromal cells, cytokines, and extracellular matrix components [2, 4]. This environment determines whether macrophages adopt a tumor-suppressive (M1) or tumor-promoting (M2) role [17, 53, 54]. The predominance of M2-polarized tumor-associated macrophages (TAMs) has been repeatedly associated with enhanced tumor growth [4, 55], immune evasion [4, 40], angiogenesis [1, 7], and therapy resistance [9, 56]. In contrast, M1 macrophages support anti-tumor responses through the production of inflammatory mediators that activate cytotoxic lymphocytes [57, 58]. We will elaborate on the role

of macrophage polarization in a variety of hematologic malignancies, including acute myeloid leukemia (AML) [33, 40, 59], chronic leukemia (such as chronic lymphocytic leukemia and chronic myeloid leukemia) [2, 4], and lymphoma [55, 60].

Acute myeloid leukemia (AML)

In the context of acute myeloid leukemia (AML), macrophage polarization plays a pivotal role in disease progression and therapeutic resistance. The tumor microenvironment in AML is characterized by a predominance of tumor-associated macrophages skewed towards the M2 phenotype, which fosters an immunosuppressive milieu conducive to leukemia cell survival and immune evasion [33, 61–63]. M2 macrophages are induced by cytokines such as IL-10, TGF- β , and CSF-1, which activate signaling pathways like STAT3 and STAT6, promoting angiogenesis, tissue repair, and immunosuppression [40, 64, 65]. These M2 macrophages secrete pro-angiogenic factors like VEGF, facilitating the formation of new blood vessels that supply nutrients and oxygen to leukemia cells, thereby enhancing their growth and survival [66–68]. Moreover, M2 macrophages contribute to chemoresistance by releasing anti-inflammatory cytokines and growth factors that protect leukemia stem cells from apoptosis, particularly within the protective bone marrow niche [61, 69–73]. In contrast, pro-inflammatory M1 macrophages, though less prevalent in the AML TME, have the potential to exert anti-leukemic effects by producing cytokines like IL-12 and TNF- α , which stimulate cytotoxic T cells and natural killer cells [39, 62, 63, 66]. However, the AML microenvironment often inhibits M1 polarization, limiting anti-tumor immunity [62, 63, 74, 75]. Therapeutic strategies targeting macrophage polarization in AML are gaining traction, with approaches such as blocking the CSF-1/CSF-1R signaling pathway or inhibiting IL-10 and TGF- β to reprogram M2 macrophages towards an M1 phenotype [61, 64, 65, 76]. These strategies aim to shift the TME towards a more pro-inflammatory, anti-tumor state, potentially enhancing the efficacy of existing AML therapies and reducing the risk of relapse [65, 74, 76, 77]. Understanding the dynamic interplay between macrophage polarization and the AML microenvironment is crucial for developing effective therapeutic interventions that can disrupt the supportive niche for leukemia cells and restore anti-tumor immunity.

Acute lymphoblastic leukemia (ALL)

Macrophage polarization plays a pivotal role in shaping the tumor microenvironment of acute lymphoblastic leukemia, influencing disease progression, immune evasion, and therapeutic resistance. In ALL, bone marrow-derived

macrophages are reprogrammed into leukemia-associated macrophages (LAMs), which predominantly exhibit an M2-like polarization phenotype characterized by immunosuppressive and pro-tumor functions [33, 59, 78]. These LAMs secrete cytokines such as IL-10 and TGF- β , fostering an immunosuppressive TME that dampens cytotoxic T-cell activity and supports leukemia cell survival [37, 79–82]. Notably, aberrant metabolic pathways in ALL cells, including dysregulated lipid and amino acid metabolism, have been implicated in skewing macrophage polarization toward the M2 phenotype, further perpetuating leukemia growth and chemoresistance [22, 83]. Clinical studies highlight the correlation between M2-polarized macrophages and poor prognosis in ALL. For instance, M2-like LAMs promote angiogenesis and stromal remodeling, facilitating leukemia cell proliferation and infiltration into protective niches [13, 33, 62, 84]. Additionally, interactions between ALL blasts and macrophages via CSF-1/CSF-1R signaling sustain M2 polarization, creating a feedforward loop that enhances leukemia cell survival and reduces sensitivity to conventional therapies [65, 85–89]. Emerging evidence also underscores the role of immune checkpoint molecules like Tim-3 in mediating M2 polarization-driven immune escape. In benzene-induced leukemia models, Tim-3 overexpression on macrophages correlates with M2 polarization and AML progression, suggesting analogous mechanisms may operate in ALL [40, 82].

Chronic leukemia

In chronic leukemia, macrophage polarization plays a pivotal role in disease progression, immune evasion, and therapeutic resistance. Tumor-associated macrophages in chronic lymphocytic leukemia and chronic myeloid leukemia predominantly exhibit an M2-like phenotype, characterized by anti-inflammatory and pro-tumorigenic functions [13, 33]. These M2 macrophages secrete cytokines such as IL-10 and TGF- β , which suppress cytotoxic T-cell and natural killer (NK) cell activity, creating an immunosuppressive microenvironment that facilitates leukemic cell survival and proliferation [13, 90]. In CLL, M2 macrophages within the bone marrow and lymphoid organs promote angiogenesis through the secretion of vascular endothelial growth factor (VEGF) [91] and support leukemic cell survival by releasing survival factors like IL-6 [92]. Similarly, in CML, M2 TAMs contribute to disease progression by supporting leukemic stem cells [93, 94] and conferring resistance to tyrosine kinase inhibitors (TKIs) such as imatinib [93, 95] (Table 1). The interaction between M2 macrophages and leukemic cells is mediated by complex signaling pathways, including STAT3, STAT6, and PI3K/AKT, which enhance leukemic

Table 1 Clinical application drugs for regulating macrophages in the treatment of leukemia

Drug	Mechanism	Disease
Pexidartinib	targets CSF-1R to inhibit M2 macrophage survival and polarization [96]	AML [97]
Magrolimab	Blocking the CD47-SIRPa signaling axis enhances macrophage phagocytosis [98]	AML/MDS [98, 99]
Bexmarilimab	Blocking Clever-1 signaling to alleviate macrophage-derived immunosuppressive functions [74]	AML/MDS [100]
BLZ945	Selectively inhibits the CSF-1R signaling pathway, depleting tumor-associated macrophages (TAMs) [101, 102]	AML [86]
PF-04136309	Blocking the CCL2/CCR2 signaling axis reduces the generation of pro-tumor M2-type macrophages [103, 104]	AML [105]
TTI-621	Blocking the SIRPa-CD47 signaling pathway relieves macrophage phagocytosis inhibition against leukemia cells [106]	AML/Lymphoma/ MDS [107]
Resiquimod	Activating the TLR7/8 signaling pathway induces macrophage polarization toward the M1 phenotype [108]	CTCL [109]
Metformin	Inhibiting the NF-κB signaling pathway reprograms macrophages toward M1 polarization [110]	AML [111]
IACS-010759	Inhibiting mitochondrial complex I reprograms macrophages to polarize into the M1 phenotype [112, 113]	AML [114]
Panobinostat	Inhibiting histone deacetylase (HDAC) to reprogram the phenotype of tumor-associated macrophages [113]	RRMM [115]
CAR-Macrophages	By genetically engineering the expression of chimeric antigen receptors to target and phagocytose leukemia cells [116]	AML/ALL/CLL/ NHL [93, 117]
Pembrolizumab	Blocking the PD-1/PD-L1 pathway enhances macrophage phagocytosis of leukemia cells [118]	cHL [119]
Eganelisib	Inhibiting PI3Ky reprograms tumor-associated macrophages (TAMs) into an anti-tumor phenotype [120]	CLL/NHL [121]
CpG-ODN	Activating the TLR9 signaling pathway in macrophages enhances their anti-leukemia immune activity [122]	Lymphom [123]
Ibrutinib	Suppress BTK signaling to modulate macrophage function and boost anti-tumor efficacy [124]	CLL/SLL/MCL/MZL/cGVHD [125, 126]
Imatinib	Inhibiting BCR-ABL tyrosine kinase activity modulates macrophage function, enhancing their anti-leukemic effects [127]	CML/ALL/MDS/ MPN [128, 129]
Selicrelumab	Activating the CD40 signaling pathway enhances macrophage phagocytosis of leukemia cells [106]	NHL [130]
AFM13	Activating the ADCC effect of macrophages to target and kill CD30-positive leukemia cells	HL/CD30 ⁺ PTCL [131, 132]
Lenalidomide	Modulating the immune activity of macrophages and suppressing pro-inflammatory factors in the tumor microenvironment to enhance the clearance of leukemia cells [131]	MM/MDS-del5q/ MCL/FL/MZL [133, 134]
Pomalidomide	Targeting and eliminating leukemia cells by modulating macrophage phagocytosis and pro-inflammatory cytokine secretion [135]	MM/RRMM [136]
Daratumumab	Targeting CD38 to regulate macrophage-mediated ADCP for killing leukemia cells [137]	MM [138]
Isatuximab	Targeting CD38 enhances ADCP by macrophages, boosting their ability to eliminate leukemia cells [139]	MM/RRMM [140]
Elotuzumab	Targeting SLAMF7 to activate macrophage-mediated ADCP against leukemia cells [141, 142]	MM [143]

Abbreviations: AML Acute Myeloid Leukemia, ALL Acute Lymphoblastic Leukemia, CLL Chronic Lymphocytic Leukemia, MDS Myelodysplastic Syndromes, CTCL Cutaneous T-cell Lymphoma, RRMM-Relapsed or Refractory Multiple Myeloma, NHL Non-Hodgkin Lymphoma, cHL Classical Hodgkin Lymphoma, SLL Small Lymphocytic Lymphoma, MCL Mantle Cell Lymphoma, MZL-Marginal Zone Lymphoma, cGVHD Chronic Graft-versus-Host Disease, CML Chronic Myeloid Leukemia, MPN Myeloproliferative Neoplasms, HL Hodgkin Lymphoma, CD30 + PTCL CD30-positive peripheral T-cell lymphoma, MM Multiple Myeloma, FL Follicular Lymphoma, CMML Chronic Myelomonocytic Leukemia

cell survival and protect them from immune-mediated destruction [61, 90, 144, 145].

Lymphoma

Macrophage polarization plays a pivotal role in the progression and therapeutic resistance of lymphoma, a heterogeneous group of hematological malignancies. Within

the tumor microenvironment, macrophages exhibit remarkable plasticity, polarizing into either pro-inflammatory M1 or anti-inflammatory M2 phenotypes [31, 146, 147]. In lymphoma, the TME is often dominated by M2-polarized tumor-associated macrophages, which contribute to tumor progression, immune evasion, and chemotherapy resistance [13, 148, 149]. M2 macrophages

are induced by cytokines such as IL-4, IL-10, and IL-13 [150, 151], and are characterized by the secretion of anti-inflammatory cytokines like IL-10 and TGF- β , which suppress cytotoxic immune responses and promote tumor cell survival [152, 153]. Additionally, M2 TAMs support angiogenesis through the secretion of VEGF [150, 154] and facilitate extracellular matrix remodeling, fostering a conducive environment for tumor growth and metastasis [6, 13]. The M2-to-M1 macrophage ratio within the TME is a critical determinant of lymphoma outcomes, with a higher M2 prevalence correlating with more aggressive disease, poorer prognosis, and resistance to conventional therapies [148, 149, 155]. M2 macrophages also interact with stromal cells to release survival factors such as CCL2 and CXCL12, which activate pro-survival signaling pathways like PI3K/AKT and STAT3 in lymphoma cells [148, 156], further enhancing chemoresistance. Therapeutic strategies targeting macrophage polarization, such as reprogramming M2 TAMs to an M1 phenotype [147, 157, 158] or inhibiting key signaling pathways like CSF-1/CSF-1R [76, 87, 159], hold promise in reshaping the TME to favor anti-tumor immunity. Approaches including TLR agonists [157, 160], CSF-1R inhibitors [76, 87], and CD47 blockade [155] are being explored to enhance macrophage-mediated phagocytosis and restore immune surveillance. By modulating macrophage polarization, these interventions aim to disrupt the supportive niche for lymphoma cells, enhance chemotherapy efficacy, and improve patient outcomes [6, 157, 161]. Continued research into the dynamic interplay between macrophage polarization and the TME is essential for developing novel therapeutic strategies to combat lymphoma progression and resistance [162].

Multiple myeloma

Multiple myeloma (MM), a plasma cell malignancy and the second most common hematologic cancer, is characterized by complex interactions between myeloma cells and the immunosuppressive tumor microenvironment [152]. Tumor-associated macrophages, particularly those polarized toward the M2 phenotype, play a pivotal role in promoting MM progression, therapy resistance, and immune evasion [163–165]. Bone marrow (BM)-infiltrating M2 macrophages are recruited and educated by myeloma-secreted factors, such as CCL3 and IL-10 [152, 166], which activate pro-tumor signaling pathways, including PI3K/AKT/RhoA [166, 167] and JAK/STAT3 [168], to sustain immunosuppression and tumor survival. These M2-polarized TAMs enhance myeloma proliferation, inhibit apoptosis, and confer resistance to proteasome inhibitors like Bortezomib by creating a protective niche [163, 169]. For instance, myeloma-derived CCL3 binds CCR5 on macrophages, driving M2 polarization

and suppressing drug sensitivity [166, 169], while CCR5 antagonist Maraviroc (MVC) reverses this effect, restoring Bortezomib efficacy in preclinical models.

IL-10 further amplifies M2 polarization [13, 152], fostering a TME rich in immunosuppressive cytokines and stromal interactions that shield myeloma cells from chemotherapy [170]. Notably, IL-32, overexpressed in MM patients, induces macrophage-mediated drug resistance by enhancing immunosuppressive functions and adhesion molecule expression (no direct citation in provided documents; omitted). M2 macrophages also secrete factors that sustain myeloma stemness and bone destruction, exacerbating disease aggressiveness [171]. Conversely, targeting macrophage polarization—via CCR5 inhibition [166], IL-10/IL-32 blockade, or epigenetic modulation of histone lactylation—disrupts pro-tumor signaling and re-sensitizes myeloma cells to therapy [172].

Clinical evidence underscores the prognostic significance of M2 polarization markers in MM, with elevated CCL3/CCR5 [166, 169] and M2-associated genes correlating with advanced disease and poor outcomes [13, 173]. Emerging strategies to reprogram TAMs toward an anti-tumor M1 phenotype [174, 175] or deplete M2 subsets hold therapeutic promise, though challenges remain in achieving durable responses [2, 149].

Therapeutic strategies for macrophage polarization

Current therapeutic strategies for malignant hematologic disorders encompass chemotherapy, molecularly targeted agents, hematopoietic stem cell transplantation, and chimeric antigen receptor T-cell immunotherapy [176, 177]. While chemotherapy remains the cornerstone of initial treatment, its clinical efficacy is frequently compromised by the emergence of chemoresistance—a major therapeutic challenge in clinical oncology. Macrophage polarization presents promising therapeutic opportunities in overcoming chemotherapy resistance within hematological malignancies. In the tumor microenvironment, macrophages often adopt an M2 phenotype, which is associated with immunosuppression, tumor progression, and chemoresistance [13, 149, 178]. Reprogramming these M2-polarized tumor-associated macrophages toward an M1 phenotype—characterized by pro-inflammatory and anti-tumoral functions—can reinvigorate anti-cancer immunity [178, 179]. Strategies for this shift include using agents like toll-like receptor (TLR) agonists or IFN- γ , which stimulate M1 polarization by activating NF- κ B p65 and JAK-STAT1 pathways, enhancing the release of cytokines such as IL-12 and TNF- α that activate cytotoxic T-cells [180–182]. Blocking TAM recruitment pathways also offers therapeutic

potential. The colony-stimulating factor 1 receptor (CSF-1R) signaling pathway, crucial for M2 macrophage survival and differentiation, can be inhibited to reduce TAM-mediated immunosuppression. Small-molecule CSF-1R inhibitors like pexidartinib have shown preclinical success in repolarizing M2 TAMs toward the M1 phenotype and improving anti-tumor responses [2, 65, 183]. Additionally, targeting macrophage metabolism presents a novel approach. M2 macrophages rely on arginase-1-dependent pathways for immunosuppressive functions, while M1 polarization is linked to iNOS-mediated nitric oxide production [180, 184, 185]. Inhibiting arginase-1 or disrupting metabolic reprogramming (e.g., via PPAR γ or STAT3 modulation) can shift the TME toward pro-inflammatory states, enhancing chemotherapy efficacy [185–187]. Recent studies also highlight the role of exosomes in macrophage polarization: M1-derived exosomes downregulate M2 markers (e.g., CD206, IL-10) while upregulating M1-specific cytokines (e.g., TNF- α , IL-12), effectively reversing TAM-driven chemoresistance in hematological malignancies [72, 178].

Emerging evidence further identifies CCL20/CCR6 axis activation as a key mechanism by which M2 macrophages confer chemoresistance in AML [72]. Targeting this axis synergizes with CSF-1R inhibition to disrupt TAM-mediated immune evasion [72]. Similarly, IL-18 inhibition promotes M2-to-M1 repolarization by suppressing pro-inflammatory IL-1 β and CCL17 while enhancing arginase-1 expression, thereby restoring therapeutic sensitivity [184, 185].

Strategies for Specific Depletion of M2 Macrophages

The selective elimination of M2-polarized macrophages emerges as a promising therapeutic approach in hematologic malignancies, given their pivotal role in facilitating tumor progression, mediating immune evasion, and conferring treatment resistance. M2 macrophages, often referred to as tumor-associated macrophages, create an immunosuppressive tumor microenvironment that supports leukemia, lymphoma, and myeloma cell survival [13, 188, 189]. Therapeutic approaches aimed at depleting or reprogramming M2 macrophages can shift the TME toward a pro-inflammatory, anti-tumor state, enhancing the efficacy of existing treatments [2, 6, 165]. One effective strategy for targeting M2 macrophages is their selective depletion. Clodronate liposomes have been widely used to deplete macrophages, including M2 TAMs, in preclinical models. Clodronate, a bisphosphonate, induces apoptosis in macrophages upon intracellular accumulation. Studies have shown that clodronate liposome treatment reduces M2 macrophage populations, decreases immunosuppressive cytokines, and promotes cytotoxic T-cell

infiltration, thereby enhancing anti-tumor immunity and improving chemotherapy efficacy [74, 190, 191]. This approach disrupts the supportive niche for leukemia cells and shifts the TME toward an M1-dominant phenotype, which is critical for anti-tumor responses [165, 192]. Another promising strategy involves targeting specific M2 macrophage markers, such as CD163 and CD206. These surface markers are highly expressed on M2 macrophages and are associated with their immunosuppressive and pro-tumorigenic functions [192–194]. Monoclonal antibodies against CD163 and CD206 have been developed to selectively deplete or inhibit M2 macrophages. For example, anti-CD163 antibodies have shown efficacy in inducing TAM apoptosis and reducing tumor growth in preclinical models [14, 194]. Additionally, small-molecule inhibitors targeting signaling pathways that sustain M2 polarization, such as the CSF-1R pathway, have demonstrated potential in reducing M2 macrophage populations and enhancing anti-tumor immunity [14, 65, 195]. Inhibition of key signaling pathways that drive M2 polarization is another therapeutic avenue. The CCL2/CCR2 axis, which recruits monocytes to the TME and promotes their differentiation into M2 macrophages, has been targeted to disrupt this process [196, 197]. Blocking CCL2/CCR2 signaling reduces M2 macrophage infiltration and shifts the TME toward an M1 phenotype, enhancing anti-tumor immunity and chemotherapy sensitivity [196, 198]. Similarly, CSF-1R inhibitors, such as pexidartinib, have shown efficacy in reducing M2 macrophage populations and reprogramming the TME to support anti-tumor responses [65, 195, 199] (Table 1). Reprogramming M2 macrophages toward an M1 phenotype is an emerging strategy. TLR agonists, such as TLR4 and TLR9 agonists, have been shown to induce M1 polarization, enhancing pro-inflammatory cytokine production and phagocytic activity against tumor cells [200, 201]. Additionally, small-molecule drugs targeting metabolic pathways, such as PI3K- γ inhibitors, have demonstrated potential in shifting macrophage polarization from M2 to M1, thereby reducing immunosuppression and enhancing anti-tumor immunity [192, 195, 202].

Targeting M2 macrophages through depletion, inhibition of specific markers, or reprogramming offers a promising approach to overcoming therapy resistance in blood cancers. These strategies aim to disrupt the immunosuppressive TME, enhance anti-tumor immunity, and improve the efficacy of conventional therapies [2, 24, 188]. Continued research into the mechanisms of macrophage polarization and the development of targeted therapies will be essential for translating these approaches into clinical practice [6, 191, 203].

Strategies for Attenuating M2 Polarization

Macrophage polarization is another promising therapeutic strategy in leukemia, aiming to disrupt the tumor-supporting microenvironment and enhance anti-tumor immunity. M2-polarized tumor-associated macrophages play a critical role in promoting leukemia progression by creating an immunosuppressive tumor microenvironment that supports leukemic cell survival, immune evasion, and chemotherapy resistance [13, 72]. Strategies to inhibit M2 polarization include blocking key signaling pathways such as CCL2/CCR2 and CSF1R [204–206], as well as directly depleting M2 macrophages using agents like clodronate liposomes or targeting surface markers such as CD163 and CD206 [192, 207]. These approaches aim to shift the TME towards a pro-inflammatory, anti-tumor state, thereby improving treatment outcomes.

One effective strategy involves blocking the CCL2/CCR2 pathway, which is crucial for the recruitment and polarization of monocytes into M2-like TAMs [204, 205]. CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), binds to its receptor CCR2 on monocytes, facilitating their migration into the TME where they differentiate into M2 macrophages [205, 208]. Inhibition of this axis disrupts the recruitment and polarization process, reducing the infiltration of M2 macrophages and their immunosuppressive influence. Preclinical studies have demonstrated that blocking CCL2/CCR2 shifts macrophage populations from the M2 to the M1 phenotype [165, 204], enhancing anti-tumor immunity and creating a more hostile environment for leukemia cells. This shift is associated with decreased levels of immunosuppressive cytokines like IL-10 and TGF- β and increased levels of pro-inflammatory cytokines such as IL-12 [209, 210], further supporting the M1 phenotype. Additionally, CCL2/CCR2 inhibition reduces angiogenesis and tumor cell proliferation [72, 153], processes in which M2 TAMs play a significant role, thereby enhancing the effectiveness of conventional chemotherapeutic agents.

Another promising approach is the use of CSF1R inhibitors, which target the colony-stimulating factor 1 receptor (CSF1R) pathway essential for the recruitment, survival, and maintenance of M2 macrophages [13, 206]. CSF1R inhibitors, such as pexidartinib, have shown efficacy in reducing M2 macrophage populations and their pro-tumoral effects in various malignancies, including leukemia [211]. By blocking CSF1R, these inhibitors diminish the recruitment and polarization of macrophages towards the M2 phenotype [206, 211], shifting the TME towards a more anti-tumorigenic state. Studies have shown that CSF1R inhibition leads to a decrease in immunosuppressive cytokines and an increase in pro-inflammatory cytokines [209, 212], enhancing anti-tumor immune responses. Furthermore,

CSF1R inhibitors have demonstrated synergistic effects when combined with chemotherapy [74, 213], improving leukemia cell sensitivity to treatment by reactivating anti-tumor immunity and reducing TAM-mediated protection. CSF1R inhibition also reduces angiogenesis and stromal support for leukemia cells [153, 161], limiting nutrient and oxygen supply and weakening the supportive TME.

Strategies for Directed M2-Macrophage Reprogramming

Inducing macrophage reprogramming to shift tumor-associated macrophages from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype represents a cutting-edge therapeutic strategy in blood cancer, particularly leukemia. This approach aims to remodel the tumor microenvironment, enhance anti-tumor immunity, and overcome chemotherapy resistance. M2-polarized TAMs are key contributors to leukemia progression, fostering immune evasion, angiogenesis, and chemoresistance through the secretion of immunosuppressive cytokines such as IL-10 and TGF- β [147, 201, 214]. Reprogramming these macrophages to an M1 phenotype can disrupt leukemia-supportive pathways, promote phagocytic activity, and sensitize leukemia cells to conventional therapies [14, 25, 215]. Emerging evidence highlights the potential of TLR agonists, small molecule drugs, and other agents in achieving this phenotypic shift, offering new avenues for therapeutic intervention [157, 216, 217].

TLR agonists have emerged as a potent tool for macrophage reprogramming in leukemia. TLRs, which recognize pathogen-associated molecular patterns (PAMPs), play a critical role in innate immunity and macrophage polarization. TLR agonists, such as TLR7/8 agonists (e.g., imiquimod and resiquimod) [218], TLR4 agonists [216], and TLR9 agonists, have demonstrated the ability to shift M2 macrophages toward an M1 phenotype [217] (Table 1). This reprogramming is mediated through the activation of signaling pathways that induce the production of pro-inflammatory cytokines (e.g., TNF- α , IL-12) and enhance phagocytic and antigen-presenting functions [216, 218]. Preclinical studies have shown that TLR4 and TLR9 agonists significantly reduce M2 TAM populations in leukemia models, creating a more inflammatory and anti-tumor TME [216, 217]. Furthermore, combining TLR agonists with chemotherapy has shown synergistic effects, as TLR-mediated reprogramming disrupts the protective niche provided by M2 macrophages and sensitizes leukemia cells to cytotoxic agents [201, 219]. TLR agonists also activate other immune cells, such as dendritic cells and natural killer cells, amplifying the overall anti-leukemia immune response [157, 217]. Ongoing clinical trials are exploring optimized delivery

systems and combination therapies to maximize the therapeutic potential of TLR agonists while minimizing immune-related toxicities [175, 220].

Small molecule drugs offer another promising approach to macrophage reprogramming by targeting specific signaling pathways involved in macrophage polarization. PI3K- γ inhibitors, such as IPI-549, have shown efficacy in shifting macrophages from an M2 to an M1 phenotype [6, 221]. PI3K- γ is a key regulator of immune cell responses, and its inhibition reduces the production of immunosuppressive cytokines while enhancing T-cell-mediated anti-leukemia activity [6]. Similarly, JAK inhibitors, which block the JAK/STAT pathway, inhibit M2 polarization by disrupting IL-4 and IL-13 signaling [56, 147]. This mechanism reduces the recruitment and polarization of M2 macrophages, reshaping the TME to be more hostile to leukemia cells [65, 222]. Bromodomain and extra-terminal domain (BET) inhibitors represent another class of small molecules with potential in macrophage reprogramming. BET inhibitors disrupt chromatin remodeling, leading to the downregulation of M2-related genes and an increase in M1 polarization and inflammatory responses within the TME [223, 224]. These small molecule approaches not only alter macrophage behavior but also weaken the protective niche exploited by leukemia cells, making them more susceptible to chemotherapy [201, 214]. Ongoing research is focused on identifying optimal drug combinations and delivery methods to enhance therapeutic efficacy and minimize adverse effects [157, 225].

In addition to TLR agonists and small molecule drugs, cytokines such as IFN- γ have demonstrated potential in macrophage reprogramming. IFN- γ promotes M1 polarization by activating STAT1 signaling, leading to the production of pro-inflammatory cytokines and enhanced phagocytic activity [147, 226]. Combining cytokines with other reprogramming agents may further enhance their efficacy in reshaping the TME [227, 228]. Other agents, such as CD40 agonists, have also shown promise in pre-clinical studies by activating macrophages and promoting anti-tumor immunity [157, 229]. These approaches highlight the versatility of macrophage reprogramming strategies and their potential to complement existing leukemia therapies [230].

Strategies for Enhancing the anti-tumor activity of macrophages

Enhancing macrophage antitumor activity by modulating polarization states represents a transformative therapeutic strategy in leukemia, leveraging mechanisms such as CD47-SIRP α axis blockade, phagocytosis potentiation, and microenvironment reprogramming to reverse

immunosuppressive LAM phenotypes and restore tumoricidal M1-like functions.

Targeting the CD47-SIRP α Phagocytic Checkpoint The CD47-SIRP α axis is a critical immune evasion pathway exploited by leukemia cells, where CD47 overexpression on malignant cells binds to SIRP α on macrophages, transmitting a "don't eat me" signal to inhibit phagocytosis [231, 232]. Preclinical studies demonstrate that blocking this axis via anti-CD47 antibodies (e.g., magrolimab) or SIRP α antagonists disrupts this interaction, significantly enhancing macrophage-mediated clearance of leukemia cells [233, 234] (Table 1). For example, IL-4 treatment in murine models enhances macrophage phagocytosis of leukemia cells by downregulating CD47-SIRP α signaling while upregulating pro-phagocytic ligands like calreticulin [235]. Additionally, engineered chimeric antigen receptor macrophages (CAR-Ms) targeting CD47 synergize with opsonizing antibodies to amplify phagocytic activity, as shown in non-small cell lung cancer models [236, 237] (Table 1). Clinical trials combining CD47 blockade with azacitidine or rituximab have shown efficacy in myeloid malignancies, underscoring its translational potential [74, 233].

Reprogramming Macrophage Polarization to Proinflammatory States Leukemia-associated macrophages predominantly exhibit M2-like polarization, promoting immune suppression and chemoresistance [13, 153]. Reversing this phenotype to proinflammatory M1-like states is pivotal for restoring antitumor immunity. HDAC6 inhibitors (e.g., Nexturstat A) reprogram macrophages by suppressing STAT3/IL-10 signaling, enhancing M1 polarization, and synergizing with anti-CD47 therapy to improve phagocytosis and NK cell activation in melanoma models [238]. Similarly, PPAR δ antagonists (e.g., GSK0660) downregulate CD47 expression in leukemia cells while promoting macrophage M1 polarization via NF- κ B activation [239]. In AML, Tim-3 inhibition disrupts M2 polarization pathways, restoring phagocytic capacity and T-cell activation [72]. These approaches highlight the dual benefit of polarization modulation: directly enhancing tumor cell clearance while remodeling the immunosuppressive leukemia microenvironment.

Combination Therapies and Future Directions Emerging strategies integrate CD47-SIRP α blockade with polarization modifiers or cytotoxic therapies to overcome resistance. For instance, HDAC6 inhibitors enhance the efficacy of anti-CD47 antibodies in vivo by increasing macrophage infiltration and M1 polarization in melanoma [238]. In glioma, CD47 blockade post-resection prevents residual cell immune escape by sustaining phagocytic activity [240]. CAR-M therapies, engineered to express CD47-blocking scFvs, further demonstrate enhanced tumor targeting and phagocytosis in solid

tumors, with potential applicability in leukemia [236, 237]. Additionally, CSF-1R inhibitors (e.g., PLX3397) deplete protumoral M2 macrophages, while IL-4/IL-13 pathway agonists promote M1 polarization, offering combinatory avenues [230]. Future studies should prioritize biomarkers for polarization states (e.g., CD86/CD163 ratios) and optimize spatial–temporal delivery of polarization modulators to minimize toxicity.

Translational Implications and Clinical Challenges
Despite promising preclinical data, clinical translation faces hurdles, including on-target anemia from CD47 blockade and cytokine release syndrome from CAR-M therapies [233, 236]. Next-generation agents like SIRP α -Fc fusion proteins (e.g., TTI-621) exhibit reduced erythrocyte binding while maintaining phagocytic enhancement in gastric cancer models [241] (Table 1). Similarly, dual-targeting agents blocking CD47 and PD-L1/CTLA-4 may amplify immune activation while mitigating toxicity [242]. In AML, macrophage depletion via clodronate liposomes abrogates IL-4-induced antileukemic effects, emphasizing the need for precision in macrophage-targeted therapies [74]. Longitudinal studies monitoring macrophage plasticity and microenvironmental crosstalk will be critical to refine these strategies.

Conclusions and prospects

Macrophage polarization plays a central role in leukemogenesis, immune evasion, and therapy resistance in hematologic malignancies. Leukemia-associated macrophages typically exhibit a pro-tumor M2 phenotype, directly promoting leukemia cell survival and chemoresistance through immunosuppressive factor secretion (e.g., IL-10, TGF- β) and T-cell suppression [243–245]. Single-cell analyses further reveal significant heterogeneity in LAMs: within the bone marrow microenvironment of AML patients, metabolic regulation (e.g., Slc6a8-mediated creatine uptake) and epigenetic modifications (e.g., AKR1B10 downregulation-induced M2 polarization) dynamically drive macrophage phenotypic switching [245, 246]. Bidirectional interactions between leukemia cells and macrophages (e.g., Tim-3-mediated immunosuppression) and crosstalk with other immune cells (e.g., T cells, neutrophils) collectively shape a pro-leukemic niche [6, 247]. These findings underscore the clinical potential of targeting macrophage polarization networks [146, 248].

Targeting macrophage polarization has emerged as a promising strategy to reverse immunosuppressive leukemic microenvironments. Preclinical studies demonstrate that inhibiting M2-polarizing pathways (e.g., CSF-1R/STAT3, IL-4/STAT6) or enhancing M1 polarization (e.g., TLR agonists, IFN- γ) significantly suppresses leukemia progression [64, 249–251]. For instance, IL-4

exerts antileukemic effects by enhancing macrophage phagocytosis of leukemia cells, while Tim-3 blockade disrupts M2-associated immune escape [252, 253]. Epigenetic regulation (e.g., DNMT inhibitors) and metabolic interventions (e.g., glycolysis inhibition or creatine synthesis modulation) further reprogram macrophage function [244–246]. Ongoing clinical trials are evaluating macrophage-targeted agents (e.g., anti-CSF-1R antibodies, CD47 blockers) combined with chemotherapy or immune checkpoint inhibitors, with preliminary data showing improved AML patient responses [248, 254, 255].

Future studies must dissect the molecular regulatory networks and spatiotemporal dynamics of macrophage polarization. Single-cell sequencing and spatial transcriptomics could map LAM subset heterogeneity within leukemic bone marrow niches and their interactions with vascular and osteoblastic compartments [74, 202]. Additionally, the crosstalk between metabolic-epigenetic regulation (e.g., lactate-mediated histone modifications, AMPK/mTOR signaling) and dynamic receptor expression (e.g., Sirp α , TNFR2) requires further elucidation [245, 246, 249, 252]. Research should also explore synergies between macrophages and other immune cells (e.g., CAR-T, NK cells) and assess long-term impacts of polarization-targeted strategies on leukemic stem cells and microenvironment remodeling [181, 192, 254, 255].

Abbreviations

ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
Arg-1	Arginase-1
BET	Bromodomain and Extra-Terminal Domain
BM	Bone Marrow
CAR-M	Chimeric Antigen Receptor Macrophages
CAR-T	Chimeric Antigen Receptor T cells
CCL	Chemokine (C–C Motif) Ligand
CCR	C–C Chemokine Receptor
CD	Cluster of Differentiation
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
cGVHD	Chronic Graft-versus-Host Disease
CSF-1	Colony-Stimulating Factor-1
CSF-1R	Colony-Stimulating Factor-1 Receptor
CTCL	Cutaneous T-Cell Lymphoma
EV	Extracellular Vesicle
FAO	Fatty Acid Oxidation
HIF	Hypoxia-Inducible Factor
HDAC	Histone Deacetylase
IFN- γ	Interferon-Gamma
IL	Interleukin
iNOS	Inducible Nitric Oxide Synthase
KLF4	Krüppel-Like Factor 4
LAM	Leukemia-Associated Macrophages
LPS	Lipopolysaccharide
LSC	Leukemia Stem Cell
MM	Multiple Myeloma
mTORC1	Mechanistic Target of Rapamycin Complex 1
NF- κ B	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NK	Natural Killer (cells)

OXPHOS	Oxidative Phosphorylation
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PI3K	Phosphoinositide 3-Kinase
PPAR γ	Peroxisome Proliferator-Activated Receptor Gamma
ROS	Reactive Oxygen Species
RRMM	Relapsed or Refractory Multiple Myeloma
SIRP α	Signal-Regulatory Protein Alpha
STAT	Signal Transducer and Activator of Transcription
TAM	Tumor-Associated Macrophage
TGF- β	Transforming Growth Factor-Beta
TIGIT	T-cell Immunoreceptor with Ig and ITIM Domains
TLR	Toll-Like Receptor
TME	Tumor Microenvironment
TNF- α	Tumor Necrosis Factor-Alpha
VEGF	Vascular Endothelial Growth Factor

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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