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REVIEW

Emerging Role of MDSCS as Novel Biomarkers and Therapeutic Targets for Cancer Immunotherapy

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Abstract: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate under pathological conditions such as cancer, where they contribute to immune evasion, tumor progression, and resistance to therapy. These cells exert potent immunosuppressive effects by inhibiting T cell activation, inducing regulatory T cells, modulating antigen-presenting cells, and shaping an immunosuppressive tumor microenvironment (TME). Their suppressive functions involve multiple mechanisms, including amino acid depletion, production of reactive oxygen and nitrogen species, expression of immune checkpoint ligands, and secretion of immunoregulatory cytokines such as IL-10 and TGF-β. Besides these immune-related roles, MDSCs also promote tumor growth through non-immunological mechanisms, including the stimulation of angiogenesis and undergoing metabolic reprogramming. These adaptations support their survival and function in the hostile TME. Given their multifaceted role in cancer, MDSCs represent a promising target for therapeutic intervention. Furthermore, their abundance and dynamic modulation during treatment confer them tremendous potential as biomarkers to monitor therapy efficacy and stratify patients. This review provides a comprehensive overview of MDSC biology, their mechanisms of action, and their emerging clinical relevance as biomarkers and therapeutic targets. We also explore current strategies aimed at targeting MDSCs, including their depletion, inhibition of recruitment, functional blockade, and promotion of their differentiation into mature myeloid cells. Integrating these approaches with existing cancer therapies holds great promise for enhancing antitumor immunity and overcoming resistance in both solid tumors and hematologic malignancies.

Keywords: myeloid-derived suppressor cells, tumor microenvironment, immunotherapy, immune biomarkers

Introduction

The interplay between the immune system and cancer cells is complex and remains a subject of thorough investigation. The immune system can recognize and eliminate malignant cells through a process designated immune surveillance.[1] However, established tumors often evade this defense mechanism by favoring an immunosuppressive tumor microenvironment (TME).[2] This intricate milieu contains various immune cell populations and signaling molecules that actively suppress anti-tumor immune responses, ultimately leading to tumor progression and therapy resistance.[3] Understanding the dynamic balance between immune control mechanisms and tumor-driven immunosuppression is key to advancing in the design of effective immunotherapeutic strategies against cancer.[1,3]

Among the cellular components of the immunosuppressive TME, myeloid-derived suppressor cells (MDSCs) have emerged as key mediators of immune evasion and major contributors to cancer progression.[4,5] This heterogeneous population of immature myeloid cells expands in both the TME and peripheral blood of cancer patients, where it suppresses T cells and natural killer (NK) cells activity and promotes tumor progression through immune and non-immune mechanisms. These include the induction of cancer-associated epithelial-mesenchymal transition (EMT), the

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expansion of cancer stem cells, the recruitment and activation of other inhibitory cells such as regulatory T cells (Tregs), and the enhancement of tumor cell migration and invasion.[1,4–6]

Elevated levels of MDSCs have been consistently associated with treatment resistance, encompassing immunotherapy, chemotherapy, and radiotherapy.[7] Numerous studies across various cancer types have demonstrated a significant correlation between increased levels of circulating or intratumoral MDSCs and poor clinical outcomes, including higher tumor burden, advanced disease stages, and reduced overall survival (OS).[7–11] Given their pivotal role in mediating immune escape, there has been growing interest in exploring these cells' potential both as therapeutic targets and as prognostic and predictive biomarkers in oncology.[7,12]

Various strategies are currently being explored to target MDSCs, including their depletion, inhibition of expansion and recruitment to the tumor sites, blockade of their immunosuppressive activity, and promotion of their differentiation into mature, non-suppressive myeloid cells.[3,12] Moreover, combining these approaches with other treatment modalities, such as immune checkpoint inhibitors,[13] has shown promising synergistic anti-tumor effects in pre-clinical and clinical trials (see below Combining Anti-MDSCs Therapies and Immunotherapy).

While MDSCs have been broadly reviewed in cancer biology, their clinical significance in immuno-oncology remains underexplored. This review seeks to fill this gap by integrating current insights into MDSCs' biology with translational and clinical perspectives, highlighting their dual role as biomarkers for patient stratification, response monitoring and therapeutic targets.

MDSCs: Definition, Origin, and Classification

Myeloid-derived suppressor cells are a heterogeneous population of immature cells that originate from bone marrow-derived hematopoietic precursor cells, from the myeloid lineage.[14] These cells are characterized by the expression of common myeloid markers, such as the cell surface proteins CD11b and CD33, but lack the expression of molecules typically associated with fully mature myeloid cells, most notably the major histocompatibility complex (MHC) class II molecule HLA-DR in humans.[14,15]

The development of MDSCs is closely linked to alterations in physiological myeloid differentiation. Under steady-state conditions, hematopoietic stem cells in the bone marrow differentiate into mature myeloid cells through well-defined pathways, involving common myeloid progenitors and granulocyte-macrophage progenitors.[14–16] However, under pathological stress, such as tumor-induced inflammation, this differentiation process is disrupted. As a consequence, immature myeloid cells accumulate, fail to undergo complete maturation, and instead acquire the immunosuppressive functions characteristic of MDSCs.[16] Tumor-derived factors such as granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and various pro-inflammatory cytokines (eg, interleukin 6 (IL-6)) are key drivers in skewing myelopoiesis towards the expansion of MDSCs.[14,17]

MDSCs are classified into three main subsets based on their stage of differentiation, morphology, surface markers, and functional properties: monocytic, granulocytic and early stage MDSCs.[15,17]

Monocytic MDSCs (M-MDSCs) exhibit a mononuclear morphology and are characterized in humans by the expression of CD33, CD11b and CD14, while lacking or having low expression of CD15 and HLA-DR.[15] M-MDSCs are highly immunosuppressive and exert their effects through the production of nitric oxide (NO) and arginase-1 (ARG1), which impair T cell receptor (TCR) signaling and proliferation.[18]

Granulocytic (G-MDSCs) or polymorphonuclear MDSCs (PMN-MDSCs) display a polymorphonuclear morphology resembling that of neutrophils, and are typically identified by $CD33^{+}$, CD11b+, $CD66b^{+}$ and CD15+ in humans, while being negative for CD14 and HLA-DR.[15,17] These cells mediate immunosuppression mainly through the release of reactive oxygen species (ROS) and ARG1, and often accumulate in large numbers within the TME.[18]

Early-stage MDSCs (e-MDSCs) comprise immature myeloid precursors that lack markers of mature monocytes and neutrophils (both $CD14^{-}$ and $CD15^{-}$), but retain expression of myeloid markers such as $CD33^{+}$ and $CD11b^{+}$.[15] This subset represents a transitional population capable of differentiating into either M-MDSCs or G-MDSCs, depending on environmental signals.[15,19]

MDSCS in Cancer

Beyond their phenotypic characteristics and ontogeny, MDSCs play a central role in immunoregulatory functions that ultimately shape the TME. The following section examines their mechanism of action, cellular interactions and impact on cancer development and progression.

Immunosuppressive Mechanisms

The mechanisms employed by MDSCs to suppress immune responses and shape the TME are summarized in Figure 1. The main molecular mediators regulating MDSC expansion, activation, and immunosuppressive functions are summarized in Table 1.

T Cell Suppression

MDSCs employ a wide range of mechanisms to inhibit T cell functions, contributing to immune evasion in cancer.[20] Among the most well-described mechanisms is the depletion of essential amino acids, such as L-arginine and cysteine. ARG1, commonly induced within MDSCs, catalyzes the hydrolysis of L-arginine into urea and L-ornithine. This depletion of extracellular L-arginine availability impairs the proliferation of activated T cells[26,27] as it leads to down-regulation of the CD3ζ chain of the TCR, arrest of the cell cycle in the G0–G1 phase, and overall suppression of metabolic paths required for clonal expansion.[28,29] Likewise, MDSCs consume cystine and do not return cysteine to the extracellular environment, which is crucial for T-cell activation. T cells lack the enzyme cystathionine γ-lyase, which converts methionine to cysteine, and do not express cystine transporters. Therefore, they cannot import cystine and reduce it intracellularly to cysteine. As a result, in the absence of cysteine-exporting cells such as macrophages or dendritic cells (DC), cysteine deprivation severely restricts T-cell activation.[30] Furthermore, tryptophan degradation into

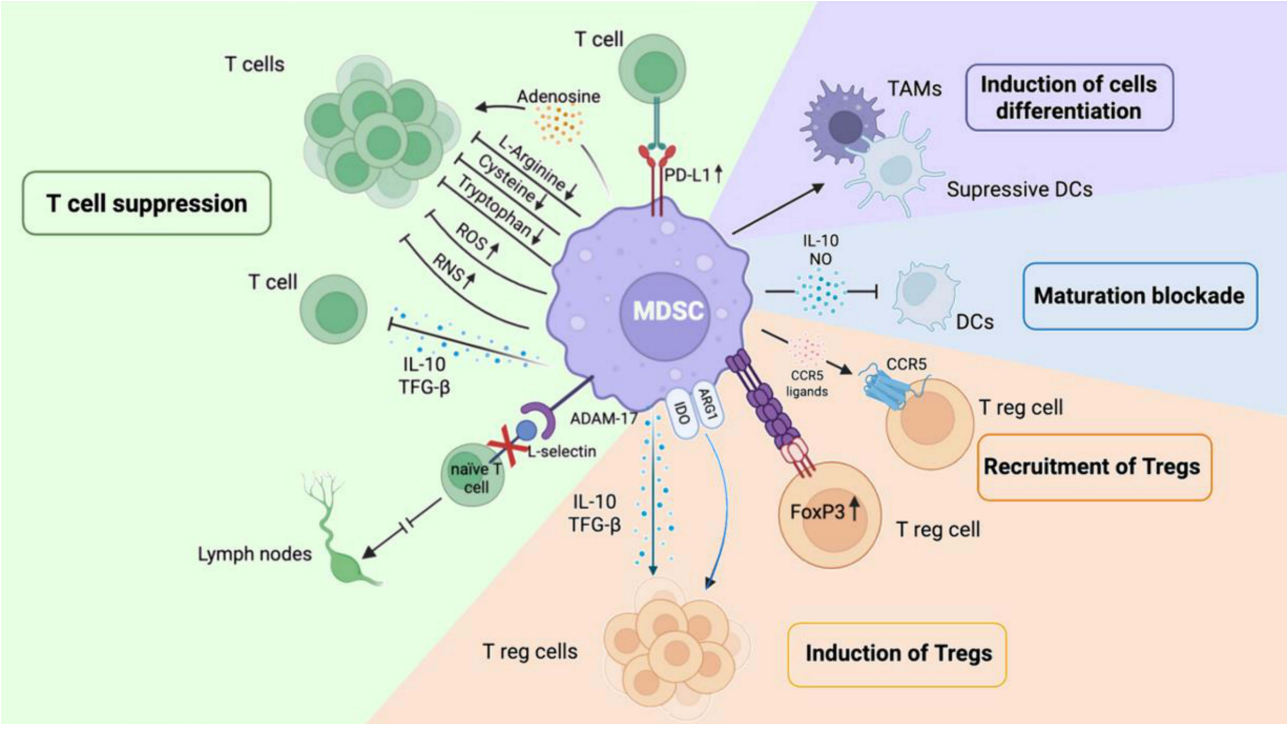

Figure 1 Mechanisms of immune escape mediated by Myeloid derived suppressor cells (MDSC). MDSCs employ diverse strategies to modulate the immune response, including:[20] (1) suppression of T cells; (2) promotion of recruitment and expansion of regulatory T cells (Tregs); (3) inhibition of dendritic cells (DCs) maturation; and (4) induction of differentiation of other suppressor cells. Collectively, these mechanisms shape an immunosuppressive tumor microenvironment that contributes to immune evasion. Upward arrows indicate an increase, whereas downward arrows denote a decrease.

Abbreviations: ADAM-17, A disintegrin and metalloproteinase 17; ARG1, arginase-1; CCR5, C-C chemokine receptor type 5; DCs, dendritic cells; FoxP3, forkhead box P3; IDO, indoleamine 2,3-dioxygenase; IL-10, interleukin 10; NO, nitric oxide; PD-L1, programmed death ligand 1; RNS, reactive nitrogen species; ROS, reactive oxygen species; TAMs, Tumor-associated macrophages; TGF-β, transforming growth factor beta.

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Table 1 Immunoregulatory Molecules Driving MDSC Expansion and Function

Molecular Category	Key Molecules	Function in MDSCs	Effects on Immune Cells	References
Cytokines & Growth Factors	IL-10, TGF-β, IFN-γ, G-CSF, M-CSF, GM-CSF, VEGF	Promote MDSCs expansion and activation; IL-10 and TGF-β suppress T cell responses; VEGF aids in angiogenesis.	Suppress T cell proliferation and activation; inhibit dendritic cell maturation; promote regulatory T cell induction.	[21,22]
Chemokines	CCL2, CCL3, CCL4, CCL5, CXCL1	Recruit MDSCs to tumor sites; facilitate their accumulation in the tumor microenvironment.	Enhance immunosuppressive milieu; impede effective T cell infiltration into tumors.	[14]
Enzymes & Mediators	ARG1, iNOS, ROS, NO	Deplete essential nutrients (eg, L-arginine); produce reactive species that impair T cell function.	Inhibit T cell proliferation and cytokine production; induce T cell apoptosis.	[22,23]
Surface Molecules	PD-L1, CTLA-4, CD40, CCR5	Engage inhibitory receptors on T cells; modulate immune checkpoint pathways.	Induce T cell exhaustion; reduce T cell activation and proliferation.	[22,24,25]
Transcription Factors	STAT3, HIF-1α	Regulate genes involved in MDSCs development, survival, and suppressive functions.	Indirectly suppress T cell responses by enhancing MDSC-mediated immunosuppression.	[22,24,25]

Abbreviations: ARG1, arginase-1; CCL2, C-C motif ligand 2; CCL3, C-C motif ligand 3; CCL4, C-C motif ligand 4; CCL5, C-C motif ligand 5; CCR5, C-C chemokine receptor 5; CD40, cluster of differentiation 40; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CXCL1, C-X-C motif ligand 1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIF-1α, hypoxia-inducible factor 1 alpha; IFN-γ, interferon-gamma; IL-10, interleukin 10; iNOS, inducible nitric oxide synthase; M-CSF, monocyte colony-stimulating factor; NO, nitric oxide; PD-L1, programmed death ligand 1; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

immunosuppressive kynurenine metabolites through indoleamine 2,3-dioxygenase[31] activity in MDSCs contributes to autophagy induction, cell cycle arrest, and T cell apoptosis.[26]

MDSCs express inhibitory immune checkpoint molecules as well, notably programmed death ligand 1 (PD-L1), which interacts with programmed cell death-1 (PD-1) receptor on T cells, inducing exhaustion and anergy. In addition, they may also express cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and other inhibitory ligands such as V-domain immunoglobulin suppressor of T-cell activation (VISTA), Galectin-9, and CD155, further dampening T cell responses.[32,33]

The production of ROS and reactive nitrogen species[34] represents another MDSC-mediated immunosuppressive mechanism.[34] PMN-MDSCs activity primarily depends on high levels of ROS and RNS, which inhibit antigen-specific T cell responses.[20] While ARG1-mediated suppression does not require cell-cell contact, ROS- and Inducible nitric oxide synthase (iNOS)- derived NO suppressive effects typically require close proximity to T cells.[26]

MDSCs further contribute to immune suppression through adenosine generation. Under hypoxic conditions, adenosine triphosphate (ATP) is released in tumor tissues, and subsequently degraded into adenosine, which activates signaling pathways through A2AR and A2BR adenosine receptors on T cells, inhibiting their effector functions.[35]

T cell trafficking impairment is an additional mechanism mediated by MDSCs. The expression of A disintegrin and metalloproteinase 17 (ADAM17) by MDSCs, a protease that cleaves L-selectin (CD62L) on naïve T cells, prevents their migration to lymph nodes and tumor sites.[36] L-selectin is a cell adhesion molecule present on $CD4^+$ and $CD8^+$ T cells, as well as on B cells in the spleen, and its downregulation correlates with increased MDSCs activity.

Moreover, NO produced by M-MDSCs hinders T cell extravasation and tissue infiltration by downregulating adhesion molecules such as CD44 (a receptor for hyaluronic acid) and CD162 (a P-selectin ligand). NO also reduces E-selectin expression on tumor endothelium, further inhibiting T cell trafficking to tumor tissues.[26,37]

In addition to these mechanisms, MDSCs may express Fas Ligand (FasL), triggering apoptosis in $CD4^+$ and $CD8^+$ T cells upon contact.[38] Finally, the secretion of transforming growth factor beta (TGF-β) and IL-10 by MDSCs further suppresses T and NK cells and promotes macrophage polarization toward an immunosuppressive phenotype.[3,14,32]

Altogether, these mechanisms enable MDSCs to exert significant control over T-cell immune responses, particularly within the TME, where their activity facilitates cancer progression.[20]

Interactions with Other Immune Cells

MDSCs engage complex interactions with other immune cells, most notably Tregs, macrophages, and DC, that together modulate immune responses, shaping an immunosuppressive TME.[39]

MDSCs can induce the de novo differentiation of forkhead box P3 positive ($FoxP3^+$) Tregs through mechanisms mediated by interferon-gamma (IFN-γ) and IL-10, independently of NO production.[40] FoxP3 is a transcription factor that defines the identity and suppressive function of Tregs, a key subset of T cells responsible for maintaining immune tolerance and limiting excessive immune responses.[40] In addition, they promote Tregs expansion through direct cell-cell interactions and the secretion of soluble factors such as IL-10 and TGF-β. The expression of enzymes and surface molecules including ARG1, IDO, and cluster of differentiation 40 (CD40) by MDSCs further supports Tregs induction.[40]

MDSCs contribute to Tregs recruitment to the TME by secreting chemokines such as C-C motif ligand (CCL) 2, CCL5, CCL3, and CCL4, which bind to C-C chemokine receptor 5 (CCR5) expressed on Tregs, facilitating their migration into tumor tissues.[41] In preclinical models of melanoma, M-MDSCs have shown to promote the recruitment of $CCR5^+$ Tregs through the production of these chemokines, reinforcing their contribution to the establishment of an immunosuppressive environment.[42]

Interestingly, Tregs can reciprocally contribute to MDSCs activity by inducing the expression of B7 family immunoregulatory ligands, including B7-H1 (PD-L1), B7-H3, and B7-H4, as well as promoting IL-10 production by MDSCs.[43] The B7 family of membrane proteins interacts with CD28 family receptors on T cells, delivering either co-stimulatory or co-inhibitory signals that enhance or attenuate immune responses, respectively.[44] This bidirectional relationship between Tregs and MDSCs promotes a vicious cycle of immunosuppression in the TME, fostering a tumor-favorable environment.

MDSCs not only influence T cells but also interact with other key immune players such as NK cells and macrophages. In early-stage gastrointestinal cancer, a subset of NK cells that recognize lipid antigens presented by the non-classical MHC molecule CD1d, can stimulate MDSCs to produce TGF-β via the IL-13/ IL-4 receptor (IL-4R)/ signal transducer and activator of transcription (STAT) 6 signaling pathway.[45] This contributes to the generation of inducible regulatory T cells (iTregs), characterized by the expression of CD4, CD25, and FoxP3, through MDSC-derived IL-10 and TGF-β secretion, thereby enhancing antigen-specific immune suppression.[40]

This same IL-10 and TGF-β production also contributes to macrophage polarization, promoting a shift towards the M2 phenotype, which supports tumor progression and angiogenesis.[8] Additionally, MDSC-derived S100A8/9 proteins promote the phenotypic transition from pro-inflammatory M1 to anti-inflammatory M2 tumor-associated macrophages (TAMs).[46] Direct MDSC-macrophage interactions can induce a type 2 immune response by increasing IL-10 and decreasing IL-12 levels, thus dampening macrophage-mediated antitumor activity and further suppressing T and NK cells.[47,48] Furthermore, M-MDSCs can differentiate into TAMs themselves (either M1 or M2), under hypoxic conditions, where hypoxia-inducible factor 1 (HIF-1) is downregulated and signal transducer and activator of transcription 3 (STAT3) activity is reduced, leading to the acquisition of TAM-like features.[21]

MDSCs also disrupt DCs maturation and activation, thereby limiting their ability to present antigens. IL-10 down-regulates co-stimulatory molecules and suppresses IL-12 production by DCs primarily via Janus kinase 1 (JAK1)/ STAT3 signaling pathway.[49] In addition, MDSCs derived NO can nitrate STAT1 in DC, disrupting antigen presentation, an effect shown to be reversible by iNOS inhibition.[50] Additionally, MDSCs interfere with DCs differentiation and maturation through the activation of Notch and STAT3 signaling, limiting their ability to initiate effective immune responses and contributing to the failure of DC-based immunotherapies.[50]

Altogether, these interactions illustrate the central coordinating role of MDSCs in creating an immunosuppressive milieu that hampers anti-tumor immune responses. Through diverse soluble mediators, receptor–ligand interactions, and transcriptional programs, MDSCs reinforce a tolerogenic environment that protects the tumor from immune attack.

Context-Dependent Specialization: Peripheral Blood vs Tissue

MDSCs exhibit remarkable phenotypic and functional plasticity, depending on their anatomical location, whether in peripheral blood, normal tissues or within the TME. Their suppressive activity is highly dependent on environmental molecular signals, which determine their function and impact on immune surveillance and tumor progression.[51]

In peripheral blood, MDSCs - mainly the polymorphonuclear subset - show a moderate immunosuppressive capacity. Their mechanisms are usually antigen-specific and rely on the production of ROS and peroxynitrite, which disrupt TCR

signaling. Expression of key immunosuppressive molecules such as PD-L1 or CD80 remains relatively low compared to their tumor-infiltrating counterparts.[52]

In contrast, in normal tissues, MDSCs are present at much lower frequencies and their role is less clearly defined. They are thought to contribute to immune regulation and tolerance under homeostatic conditions, exerting minimal suppressive effects.[39]

Within the TME, tumor-derived signals, such as cytokines (eg, G-CSF, M-CSF, IL-6) and exosomes, modulate the differentiation and function of MDSCs, reinforcing their suppressive phenotype and promoting their accumulation within tumor tissues.[53] High levels of inhibitory ligands such as PD-L1 and CD80 are expressed, which further reduces antitumor immunity.[54] Interestingly, evidence suggests that circulating MDSCs can undergo further activation and phenotypic adaptation upon infiltration into the TME, where they acquire stronger immunosuppressive properties, including elevated expression of ARG1, IDO, and immune checkpoints.[55] These functional differences have clinical relevance, as they imply that MDSCs levels and activity in peripheral blood may not always accurately reflect their suppressive potential within tumor tissues.[56]

Together, these findings underscore that MDSCs are not static immune regulators but highly adaptable cells whose suppressive potential and functional specialization are sculpted by the molecular and metabolic characteristics of their environment.

Non-Immunological Mechanisms for Tumor Progression

MDSCs not only exert pro-tumorigenic effects through immunosuppressive mechanisms, but also contribute to non-immunological processes,[6,14,16] among which angiogenesis and metabolic reprogramming represent two of the most important paths to sustain tumor growth, tissue remodeling and resistance to therapies.[14]

Angiogenesis Promotion

Beyond their immunosuppressive activity, MDSCs promote angiogenesis by releasing pro-angiogenic factors that stimulate neovascularization, thereby enhancing nutrient and oxygen supply to the tumor and supporting its growth and metastatic potential.[46]

In this context, the secretion of high levels of vascular endothelial growth factor (VEGF), a central pro-angiogenic cytokine that binds to its receptor on endothelial cells,[57] activating the JAK2/STAT3 signaling cascade and promoting their proliferation and migration. Notably, the expression of VEGF receptor 2 (VEGFR2) by MDSC, establishes an autocrine amplification loop that sustains its own angiogenic phenotype.[58]

Other potent angiogenic mediators include fibroblast growth factor 2 (FGF2), prokineticin 2 (also known as Bv8), TGF-β, and interleukin-1β (IL-1β), which contribute to the remodeling of the tumor vasculature.[59]

Furthermore, MDSCs secrete matrix metalloproteinase 9 (MMP9), responsible for the degradation of the extracellular matrix (ECM), not only facilitating the migration of endothelial cells but also liberating matrix-bound pro-angiogenic factors. This ECM remodeling is essential for capillary sprouting and vessel stabilization within the TME.[60]

MDSCs-derived exosomes are enriched in specific microRNAs, such as miR-126a and miR-9, which can be internalized by endothelial cells, reprogramming their phenotype to support angiogenic activity.[61,62]

Metabolic Reprogramming

Parallel to their angiogenic functions, MDSCs undergo significant metabolic reprogramming that enhances their immunosuppressive capacity.

While several of these pathways - such as ARG1-mediated arginine metabolism, cystine uptake, and ROS generation - are central to their immunosuppressive activity and have been detailed above, their broader metabolic profile contributes to tumor progression through additional, non-immunological effects.[63]

MDSCs upregulate fatty acid transporters and enzymes such as carnitine palmitoyltransferase 1A (CPT1A), promoting fatty acid oxidation and enhancing resistance to oxidative stress.[64,65] Increased glucose uptake via glucose transporter protein type 1 (GLUT1) and a shift toward aerobic glycolysis enable MDSCs to thrive in nutrient-poor tumor

environments, contributing to lactate accumulation and local acidosis, which can inhibit cytotoxic lymphocytes and promote tumor cell survival.[66,67]

Moreover, under hypoxic conditions within the TME, stabilization of HIF-1α in MDSCs, a transcription factor that drives upregulation of genes involved in glycolysis, fatty acid oxidation and immunoregulatory molecules such as PD-L1.[68,69]

These mechanisms underscore the pivotal role of MDSCs in facilitating tumor growth and immune evasion. Targeting MDSC-mediated angiogenesis and metabolic pathways presents a promising strategy for enhancing anti-tumor immunity and improving cancer therapies.[70]

Resistance to Cancer Therapies

MDSCs have emerged as key players in mediating resistance to multiple forms of cancer therapy, including immunotherapy, chemotherapy, and radiotherapy. Their capacity to suppress both innate and adaptive immune responses, remodel the TME, and promote tumor cell survival positions them as central modulators of therapeutic failure across cancer types.[8]

Impact on Immunotherapy Resistance

Immunotherapy has revolutionized cancer treatment by reactivating the immune system to recognize and eliminate tumor cells. However, a significant proportion of patients fail to benefit from these therapies due to either primary or secondary resistance.[71] MDSCs play a central role in both types of resistance, disrupting effective antitumor immunity. Their immunosuppressive activity hampers the efficacy of ICI such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, which rely on functional T cell responses to eliminate tumor cells.[71,72]

Through mechanisms previously described—such as ARG1-mediated arginine depletion, ROS/NO production, and checkpoint ligand expression—MDSCs undermine the antitumor activity of ICI through induction of T cell exhaustion via PD-L1 expression, and expansion of Tregs.[16,72] In addition, MDSCs can upregulate PD-1 expression on T cells and even on themselves, contributing to a suppressive loop that further reduces antitumor immunity.[26,72] Additionally, these cells impair the functionality of antigen-presenting cells, reduce the expression of co-stimulatory molecules, and contribute to a tolerogenic cytokine milieu via IL-10, TGF-β, and prostaglandin E2 (PGE2).[26] These mechanisms interfere with key steps required for immunotherapy success, including T cell priming, infiltration, and effector function.[15,26]

Elevated MDSCs levels in the TME and peripheral blood correlate with poor prognosis and reduced responses to ICI in various cancers, including non-small cell lung cancer (NSCLC), melanoma, breast cancer, hepatocellular carcinoma, and diffuse large B-cell lymphoma (DLBCL). In responders to ICI, MDSCs levels tend to decrease during treatment, while persistent MDSCs elevation is frequently observed in non-responders.[9,10,72,73] These observations are further supported by preclinical models in which the depletion or inhibition of MDSCs enhances the efficacy of checkpoint blockade (Table 2). Therefore, the combined use of MDSC-targeting strategies and ICI is currently under clinical investigation and may offer an alternative to overcome resistance in immune-refractory tumors (see below Combining Anti-MDSCs Therapies and Immunotherapy).

In B-cell lymphomas, patients with high baseline MDSCs levels showed poorer responses to immunomodulating agent lenalidomide-based regimens, while a decline in MDSCs levels during therapy is associated with improved OS.[10,11]

Indeed, MDSCs are involved in both primary and secondary resistance to immunotherapy. In the primary resistance setting, they help establish an immunologically suppressed TME by secreting IL-10, TGF-β, and engaging inhibitory checkpoints like PD-L1, VISTA, and Galectin-9.[71,94] In contrast, in patients who initially respond to immunotherapy, MDSCs can be recruited and activated in response to therapy-induced inflammation via cytokines such as G-CSF, M-CSF, IL-6, IL-1β, and VEGF, favoring secondary resistance and disease progression.[17,71,94] MDSCs may also impair DCs function and disrupt T cell trafficking to the tumor by modulating adhesion molecules, further limiting the effectiveness of immunotherapeutic strategies.[36]

Beyond checkpoint blockade, there is limited evidence on MDSCs direct contribution to resistance against other immunotherapies such as antibody-drug conjugates.

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Table 2 Therapeutic Strategies of Targeting MDSC in Preclinical Cancer Models

Therapeutic Targets	Preclinical Models	Type of Tumor	Treatment Combination	Mechanism	Reference
Promotion differentiation of MDSCs	Syngeneic models 4T1 and TS/A	Breast cancer	ATRA + DC101 (antibody targeting murine VEGFR2)	Blockade of the antiangiogenic therapy-induced expansion of MDSCs secreting high levels of vessel-destabilizing S100A8	[74]
	Metastatic TNBC models: 4T1 and E0771_ML_1	Breast cancer	DHODH inhibitor + PD-1 inhibitor	To facilitate MDSC maturation and differentiation	[75]
	Mice bearing two transplantable tumors (EL4, CT26) and two transgenic tumors (Ret melanoma and TRAMP prostate carcinoma)	Lymphoma, colon, melanoma and prostate carcinoma	JSI-124 (STAT3 inhibitor) +Sialidase	To control differentiation of MDSC into macrophage vía decreasing STAT3 activity	[21]
	Mice bearing MCA203 or the tumor-bearing mouse model using the G-CSF producing 4T1 cell line	Sarcoma and Breast cancer	VSSP + Anti-TLR4/anti-TLR2 mAb	To induce MDSCs differentiation to DC or macrophage	[76,77]
Inhibiting MDSC generation, recruitment and trafficking	NSG mice were transplanted subcutaneously of LLC tissue patient and HNM007 tissue patient	Lung and Esophageal squamous cell carcinoma	Entinostat+ 5´-azacytidine	Downregulation of CCR2 and CXCR2 and promoting MDSCs differentiation into a macrophage- like phenotype	[78]
	4T1 EGFRvIII tumor bearing mouse	Breast cancer	Olaparib + EGFRvIII-targeted CAR-T	To inhibit MDSCs migration via the SDF1α/CXCR4 axis	[22]
	LLC tumor-bearing mice	Lung	Icariside II+ α-PD1 mAb	To suppress the chemotactic migration of MDSCs by downregulating the expression of CXCL2 and CXCL3	[79]
	4T1 and PyMT breast tumor model or from patient with gastric cancer in vitro	Breast cancer and Gastric cancer	Maraviroc (CCR5 inhibitor) + anti-PD-1 mAb	To result in strong reductions of MDSCs via targeting autocrine CCL5-CCR5 axis	[80,81]
Preventing suppressive activity of MDSC	CLL cells from patients in vitro	Chronic Lymphocytic leukemia	Vitamin D	Down regulating MDSCs function as negative regulator of miR155	[82]
	Murine models lung and renal cell carcinoma	Lung and Renal cell carcinoma	Entinostat + anti-PD-1 mAb	Inhibition of immunosuppressive function of G-MDSC and M-MDSC populations by reducing ARG-1, iNOS and COX-2 levels	[83,84]
	Melanoma tumor-bering mice	Melanoma	UNC4241 (pan-TAM inhibitor) + α-PD-1 mAb	To diminish MDSCs suppression and differentiation through regulation of STAT3	[85]
	Neuroblastoma tumor-bering mice	Neuroblastoma	Ibrutinib (BTK inhibitor) + Anti-PD-L1	To alter NO production and decrease expression of IDO, ARG-1, TGFβ	[86]

Elimination of MDSC	NSCLC, PA, BIDC, CA, PDA cell lines in vitro	Lung, Prostate, Breast, Colon, Pancreas	Gemtuzumab ozogamicin + CAR-T	To deplete MDSCs for reactivating CAR-T cell responses against multiple cancers	[87]
	EL4-bearing mice and pancreatic cancer patients	Lymphoma and Pancreas	5-FU or Capecitabine + Gemcitabine	To elimination MDSCs via selectively induce MDSCs apoptosis	[88,89]
	4T1-HER2 murine breast cancer model	Breast	Cabozantinib + Anti-HER2 mAb	To delete MDSCs and improve the efficacy of anti-HER2	[90]
Decreasing immune checkpoint receptors expression on MDSC	MT-5 tumor-bearing mice and genetically engineered PDAC mouse model	Pancreas	Anti-CD200 mAb + Anti-PD-1	To limit $CD200R^+$ MDSCs expansion	[91]
	LLC tumor-bearing mice	Lung	Anti-gp49B (LILRB4) + Anti-PD-1	To decrease M-MDSC infiltration	[92]
	CT26, HCT15, A549, 4T1 tumor-bearing mice	Colon, Lung, Breast	HMBD-002 (anti-VISTA antibody)	To decrease the infiltration of MDSCs and increase T cell activity	[93]

Abbreviations: 5-FU, 5-fluoruracil; α-PD1, programmed cell death protein 1; ARG-1, arginase-1; ATRA, all-trans retinoic acid; BIDC, breast invasive ductal carcinoma; BTK, bruton tyrosine kinase; CA, colon adenocarcinoma; CAR-T, chimeric antigen receptor T cells; CLL, chronic lymphocytic leukemia; CCL5, (C-C motif) ligand 5; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; CD200, transmembrane protein related to the B7 family; COX-2, cyclooxigenase-2; CXCL2, chemokine ligand 2; CXCL3, chemokine ligand 3; CXCR2, interleukin 8 receptor beta; CXCR4, G-protein-coupled chemokine receptor; DC, dendritic cells; DHODH, dihydroorotate dehydrogenase; EGFRvIII, epidermal growth factor receptor variant III; G-CSF, granulocyte colony-stimulating factor; G-MDSC, granulocytic myeloid-derived suppressor cell; gp49B, leukocyte immunoglobulin-like receptor B4; HCT15, human colorectal adenocarcinoma cell line; HER2, human epidermal growth factor receptor 2; HNM007, murine esophageal squamous cell carcinoma cell line; IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; JSI-124, cucurbitacin I; LILRB4, leukocyte immunoglobulin-like receptor subfamily B member 4; M-MDSC, monocytic myeloid-derived suppressor cell; mAb, monoclonal antibody; MCA203, monoclonal antibody code number 203; miR155, microrna-155; MT-5, monoclonal antibody MT-5; NO, nitric oxide; NSCLC, non-small cell lung carcinoma; NSG, NOD scid gamma; PA, prostate adenocarcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PDA, pancreas duct adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; PyMT, polyoma middle T antigen; Ret, REarranged during transfection; S100A8, S100 calcium-binding protein A8; SDF1α, stromal cell-derived factor 1 alpha; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TGFβ, transforming growth factor beta; TLR4, toll-like receptor 4; TLR2, toll-like receptor 2; TNBC, triple negative breast cancer; TRAMP, transgenic adenocarcinoma of the mouse prostate; TS/A, mouse mammary adenocarcinoma cell line; VEGFR2, vascular endothelial growth factor receptor 2; VISTA, V-domain Ig suppressor of T cell activation; VSSP, very small size proteoliposomes.

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Interference with Chemotherapy and Radiotherapy

Beyond immunotherapy, MDSCs also impair the effectiveness of more conventional cytotoxic therapies, such as chemotherapy and radiotherapy.[72,95] These aim not only to induce direct DNA damage in tumor cells, but also to induce immunogenic cell death that can enhance antitumor immunity.[1,96] However, these effects are often blunted in the presence of MDSCs, due to compensatory mechanisms that promote MDSCs expansion.[72]

Following cytotoxic therapy, MDSCs can accumulate in response to tumor- and host-derived factors such as IL-6, G-CSF, M-CSF and PGE2, exerting potent immunosuppressive effects via ARG1, IDO, IL-10 and TGF-β.[72]

Ionizing radiation promotes the local production of pro-inflammatory cytokines such as IL-6, colony stimulating factor 2, and VEGF, which enhance MDSCs accumulation and expansion within the TME. MDSCs can promote radioresistance by facilitating tumor revascularization and by secreting TGF-β, a key factor in radiation-induced fibrosis and tumor cell repopulation.[97–99]

In breast cancer patients undergoing systemic therapy, increases in circulating MDSCs - particularly in patients who did not achieve clinical benefit - were associated with decreased expression of activation markers on T cells and increased expression of inhibitory receptors such as PD-1. In contrast, patients who responded to treatment exhibited a reduction in MDSCs levels, alongside improved T cell function.[9] Similar patterns have been observed in other malignancies. In patients with relapsed/refractory DLBCL, persistent elevation of monocytic and granulocytic MDSCs during chemotherapy was associated with shorter OS, whereas patients who showed a decline in MDSCs during treatment experienced better immune recovery and improved clinical outcomes. These findings reinforce the concept that MDSCs expansion during therapy not only reflects but may actively contribute to therapeutic resistance.[11]

Altogether, these results highlight the dual challenge posed by MDSCs in the context of cytotoxic therapies: not only do they impair immune surveillance, but they also support tumor cell adaptation, repair, and regrowth.[8,72] Monitoring MDSCs levels during treatment may provide valuable insight into therapeutic resistance and immune dynamics, and further supports the rationale for exploring their role as prognostic and predictive biomarkers (discussed in the following section).[8] Targeting MDSCs in combination with chemotherapy or radiotherapy may therefore enhance therapeutic efficacy by restoring antitumor immunity and limiting tumor relapse (discussed in Targeting MDSCS: Emerging Therapeutic Strategies).

MDSCS as Biomarkers in Cancer Therapy

Prognostic and Predictive Value of Circulating MDSCs

Circulating MDSCs have gained increasing attention as promising prognostic and predictive biomarkers in oncology. Their abundance in peripheral blood has been consistently associated with advanced tumor stage, increased metastatic potential, and reduced OS.[8,100]

From a prognostic viewpoint, several studies have demonstrated that higher baseline levels of M-MDSCs or G-MDSCs are associated with poor clinical outcomes, even in patients not receiving immunotherapy.[9,100,101]

In the context of immunotherapy, MDSCs have emerged as negative predictive biomarkers: higher pre-treatment levels of circulating MDSCs inversely correlate with T cell infiltration, and consequently lack of response to ICI. Conversely, lower levels of these cells during therapy have been associated with clinical response and improved survival outcomes.[8,100] These findings unveil the potential utility of MDSCs levels as predictive biomarkers of treatment efficacy through dynamic and real-time monitoring. In fact, this potential has been highlighted in multiple observational studies, in which changes in MDSCs levels correlated with response to treatment and survival, across both solid tumors and hematologic malignancies. For example, in breast, colorectal cancer, and DLBCL, elevated MDSCs counts have been linked to increased tumor burden, poor response to therapy, and shorter progression-free survival (PFS) and OS.[8,9,11,102]

Utility in Therapy Selection and Patient Stratification

Given their strong association with prognosis and treatment outcomes, MDSCs levels hold considerable potential as tools to guide therapeutic decision-making and patient stratification in cancer care. Their ability to reflect the immunosuppressive status of the host may help identify patients less likely to benefit from monotherapy.[8,103] However, current evidence remains insufficient to support clinical decisions based solely on MDSCs profiling, and a set of other factors

must be taken into consideration as well. The integration with other immune and tumor biomarkers may help refine precision oncology approaches and enable more personalized decision algorithms.[8] As such, their use in guiding treatment decisions should be considered exploratory.

Furthermore, dynamic monitoring of MDSCs during treatment may serve as an early indicator of response, enabling timely therapeutic adjustments, especially in patients showing persistent or rising MDSCs levels, which may indicate resistance.[8,71,104]

These insights underscore the relevance of incorporating MDSCs measurements into longitudinal immune monitoring frameworks.[105] Further research is warranted to translate these findings into real-world oncology practice.

Technical and Methodological Challenges in Standardizing Detection Methods

Despite their promising role as biomarkers, the clinical implementation of MDSCs profiling faces methodological and technical barriers, since there is a lack of standardized definitions and gating strategies to identify MDSCs subsets across studies and clinical settings.[15,103,105]

In humans, MDSCs are typically identified using flow cytometry based on a combination of surface markers, including CD11b+, CD33+, HLA-DR$^{low/-}$, with further classification into monocytic (CD14+ CD15$^-$), granulocytic (CD15+ CD14$^-$), and early-stage (CD14$^-$ CD15$^-$) subsets.[15,105] However, variations in marker panels, instrument settings, and gating protocols across institutions result in substantial inter-laboratory variability.[103] Moreover, differences in sample handling, such as anticoagulant type, processing delays, and storage conditions, can significantly alter MDSC phenotypes and function, further limiting reproducibility between studies.[105]

An additional limitation lies in the functional heterogeneity of MDSCs. Surface phenotype does not always correlate with suppressive activity, and relying solely on quantification based on immunophenotype may fail to accurately reflect their biological impact.[15,103] Functional assays, including metabolic characterization are emerging as more informative approaches, as they can capture the immunoregulatory status and activity of MDSCs. Nevertheless, such metabolomic analyses are technically demanding and less accessible, and not yet standardized for routine use.[106,107]

Moreover, the dynamic and context-dependent nature of MDSCs, shaped by inflammation, infection, autoimmune conditions, and tumor-related factors, further complicates capturing their biology at a single time point.[14,101]

Targeting MDSCS: Emerging Therapeutic Strategies

The TME plays an important role in supporting tumor growth and metastasis. Its composition is dual, integrating both anti-tumor immune cells, such as CD8$^+$ T cells and NK cells, and immunosuppressive populations, including TAMs (particularly M2 subtype), MDSCs and Tregs, among others.[8,108]

The rationale behind immunotherapy resides in the plasticity of the immune system and its capacity to generate powerful anti-tumor responses. As major orchestrators of immunosuppression within the TME, MDSCs have emerged as key targets to improve the efficacy of current immunotherapeutic approaches.[12] Accordingly, multiple therapeutic strategies aimed at targeting MDSCs are currently under active investigation.[108] In this section, we focus on MDSCs as therapeutic targets (Tables 2 and 3).

Strategies for Targeting MDSCs in Cancer

Multiple strategies have been developed to counteract the immunosuppressive functions of MDSCs, which can be broadly classified based on their mechanism of action. These include approaches aimed at depleting MDSCs circulating in peripheral blood, blocking their recruitment, inhibiting their suppressive activity, or promoting their differentiation into non-suppressive myeloid cells (Figure 2).

Depletion and Modulation of Circulating MDSCs

Several chemotherapeutic agents administered at low doses have demonstrated efficacy in depleting MDSCs while enhancing antitumor immune responses. Agents such as paclitaxel, 5-fluorouracil, cisplatin and gemcitabine have proven to reduce MDSCs and enhance antitumoral immune activity in both preclinical and clinical settings, across multiple tumor types, contributing to improved CD8$^+$ T cell activation and tumor control (Table 2).[12,88,109–111]

Table 3 Clinical Trials Targeting MDSC in Cancer

Settings	Target	Drug Combination	Clinical Trial Phase	Status	Clinical Trial Reference
Melanoma	Retinoic acid receptor	ATRA + Ipilimumab	II	Completed with results	NCT02403778
Melanoma	Nfr2	Omaveloxolone + Ipilimumab or nivolumab	I/II	Completed with results	NCT02259231
Melanoma	COX2	Aspirin + Ipilimumab, Pembrolizumab	II	Completed with results	NCT03396952
Advanced Melanoma	Retinoic acid receptor	ATRA + Pembrolizumab	I/Ib	Completed with results	NCT03200847
Metastatic Melanoma	CXCR1/2	SX-682 + Pembrolizumab	I	Active Recruiting	NCT03161431
Metastatic Melanoma	Tyrosine kinase	Dasatinib + DC vaccines	II	Completed with results	NCT01876212
HNSCC	PDE5	Tadalafil	Pilot Study	Completed	NCT00843635
NSCLC	Class I HDAC	Entinostat + Azatidine	II	Completed with results	NCT01207726
NSCLC	DNA/RNA synthesis	Gemcitabine + Nivolumab	II	Terminated with results	NCT03302247
Advanced lung and endometrial cancer	LXR	RGX-104 + Nivolumab, ipilimumab, docetaxel	I	Completed	NCT02922764
ND ALL/ABL; R/R ALL/ABL	Class I HDAC	Entinostat + Clofarabine	I	Completed	NCT01132573
ER+ Breast Cancer	Class I HDAC	Entinostat + Exemestane	III	Active not recruiting	NCT02115282
Metastatic TNBC	CXCR2	Reparixin + Paclitaxel	II	Completed with results	NCT02370238
Metastatic Prostate cancer	S100A9	Tasquinimod	III	Completed	NCT01234311
Renal cell carcinoma	VEGF and c-KIT	Sunitinib	II	Completed	NCT01499121
Metastatic colorectal cancer	CCR5	Maraviroc	Observational	Completed	NCT01736813
Glioblastoma	DNA/RNA synthesis	Capecitabine + Bevacizumab	0/I	Active not recruiting	NCT02669173
Advanced Solid Tumors	C/EBPα	MTL-CEBPA + Pembrolizumab	I	Completed with results	NCT04105335
Refractory Solid Tumors	ATRA	HF1K16	I	Active Recruiting	NCT05388487

Abbreviations: ATRA, all-trans retinoic acid; CCR5, C-C motif chemokine receptor type 5; c-Kit, proto-oncogene, receptor tyrosine kinase; C/EBPα, CCAAT/enhancer binding protein alpha; COX2, cyclooxygenase-2; CXCR2, CXC chemokine receptor 2; DC, dendritic cell; DNA, deoxyribonucleic acid; ER, estrogen receptor; HDAC, histone deacetylase; HF1K16, ATRA liposome formulation; HNSCC, head and neck squamous cell carcinoma; LXR, liver X receptor; MTL-CEBPA, microRNA targeting CCAAT/enhancer-binding protein alpha; ND ALL/ABL, newly diagnosed acute lymphoblastic leukemia/acute biphenotypic leukemia; Nfr2, erythroid 2-related factor 2; NSCLC, non-small cell lung carcinoma; PDE5, phosphodiesterase-5; R/R ALL/ABL, relapse/refractory acute lymphoblastic leukemia/acute biphenotypic leukemia; RGX-104, oral liver X receptor (LXR) agonist under investigation for immunotherapy; RNA, ribonucleic acid; S100A9, S100 calcium binding protein 9; SX-682, small molecule inhibitor of CXCR1/2 under investigation; TNBC, triple negative breast cancer; VEGF, vascular endothelial growth factor.

As mentioned above, VEGF is not only a powerful enhancer of neovascularization but also promotes the expansion of MDSCs, recruitment of Tregs, ultimately facilitating tumor progression. Consequently, targeting angiogenesis pathways has emerged as a promising dual strategy in various settings: impairing tumor vascularization while simultaneously immunomodulating the TME by reducing MDSCs expansion and activity.[112,113]

Bevacizumab, a monoclonal antibody targeting VEGF, was the first FDA-approved antiangiogenic therapy for advanced tumors and has shown potential to modulate the immune TME. By blocking VEGF, bevacizumab indirectly disrupts MDSCs recruitment and function, potentially enhancing the efficacy of concurrent immunotherapies.[114–116]

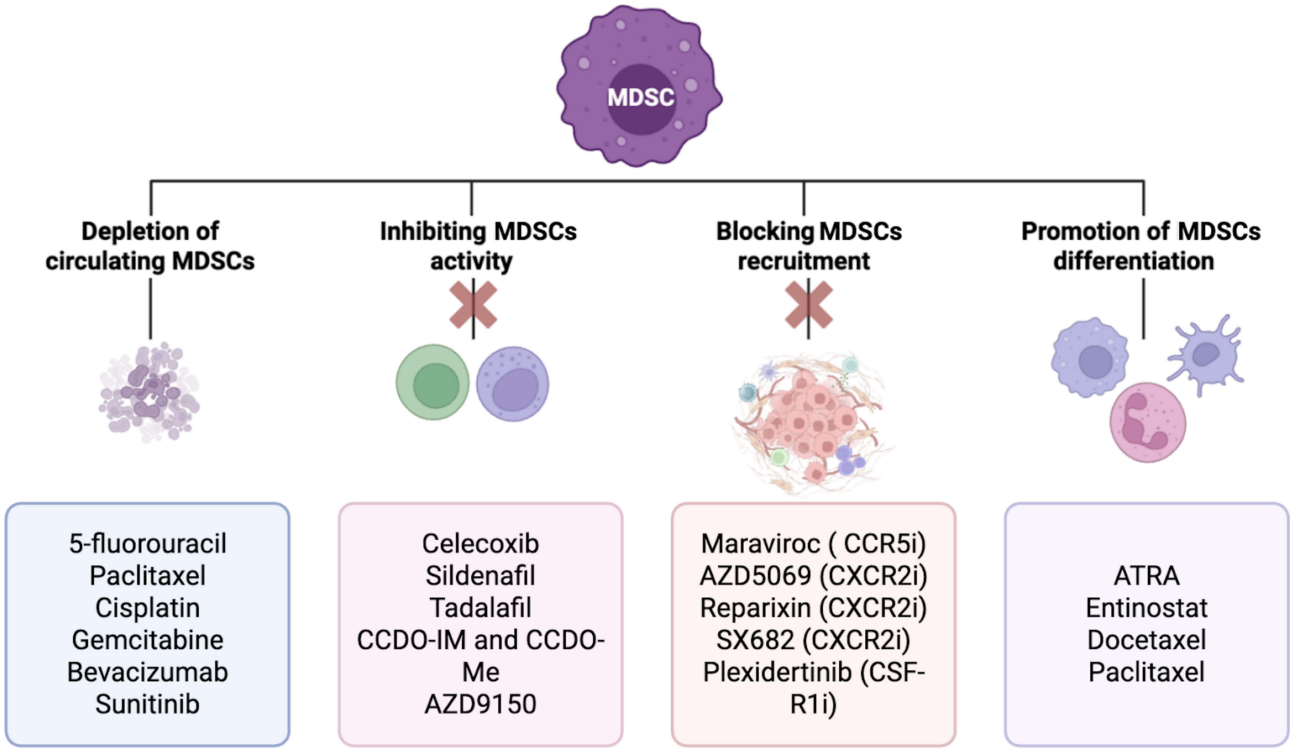

Figure 2 Therapeutic strategies targeting myeloid derived suppressor cells (MDSCs). Four major approaches have been developed to neutralize MDSC-mediated immunosuppression in cancer:[20] Depletion of circulating MDSCs using chemotherapeutic agents (such as 5-fluorouracil, paclitaxel, cisplatin, gemcitabine) or targeted therapies (including bevacizumab and sunitinib). (2) Inhibition of MDSCs activity by impairing their immunosuppressive mechanisms through inhibitors like celecoxib, sildenafil, tadalafil, triterpenoids (CCDO-IM and CCDO-Me), or STAT3-targeting drugs (eg, AZD9150). (3) Blocking MDSCs recruitment using chemokine receptor antagonists such as CCR5 or CXCR2 (eg, maraviroc, reparixin, SX682, AZD5069) or CSF-1R inhibitors like pexidartinib. (4) Promotion of MDSCs differentiation into mature non-suppressor cells, through agents such as ATRA, entinostat, docetaxel, or paclitaxel.
Abbreviations: ATRA, all-trans retinoic acid; CCR5, C-C chemokine receptor type 5; CCDO-IM/CCDO-Me, synthetic triterpenoid derivatives; CSF-1R, colony-stimulating factor 1 receptor; CXCR2, C-X-C chemokine receptor type 2; MDSC, myeloid-derived suppressor cell; STAT3, signal transducer and activator of transcription 3.

Likewise, antiangiogenic agents that target VEGF can transiently normalize tumor vasculature, restoring endothelial adhesion molecules, such as ICAM-1 and VCAM-1, thereby facilitating the infiltration of cytotoxic T lymphocytes and other effector cells. VEGF inhibition also decreases the recruitment and activity of Treg and MDSCs, and tumor-associated macrophages are reprogrammed toward a pro-inflammatory phenotype. However, these effects are context and dose dependent, and the sustained use of these drugs may have the opposite effect. Prolonged or high dose VEGF inhibition may exacerbate hypoxia, impair vascular access, and sustain immunosuppression by impairing delivery of immune cells. This dual action helps explain the limited clinical efficacy of anti-VEGF monotherapy and the shift towards using these agents in combination with immunotherapies.[116]

In renal cell carcinoma (RCC), sunitinib - a multi-target tyrosine kinase inhibitor (TKI) that blocks VEGFR and c-KIT signaling - has demonstrated significant immunomodulatory effects. It reduces both M-MDSCs and G-MDSCs populations, primarily through inhibition of VEGF- and STAT3-dependent pathways.[114,117,118] Clinical studies support that patients treated with sunitinib exhibit lower MDSCs levels and improved immune profiles.[117]

Notably, VEGF-A has also shown to upregulate the expression of multiple inhibitory immune checkpoints, including PD-1, CTLA-4, T-cell immunoglobulin and mucin domain-containing molecule 3 (Tim-3), and Lymphocyte Activation Gene 3 (Lag-3) on intratumoral $CD8^+$ T cells, which contributes to T cell exhaustion and immune evasion. Preclinical data has shown that anti-VEGF-A therapies can revert this exhausted phenotype and synergize with ICI, supporting the rationale for clinical combinations of these two targeted therapies.[116,119,120]

These findings support the integration of antiangiogenic agents and TKIs as part of combination strategies aimed at depleting MDSCs and overcoming immunosuppression in VEGF-driven tumors.[114,121] Notably, such combinations have

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already been translated into standard clinical practice: the atezolizumab (an anti-PD-L1 antibody) plus bevacizumab regimen has become the first-line treatment in advanced hepatocellular carcinoma (HCC), as demonstrated in the IMbrave150 trial, where the combination resulted in better OS and PFS compared to sorafenib.[20] Likewise, pembrolizumab combined with axitinib or lenvatinib is now routinely used in metastatic RCC.[122] Both combinations resulted in significant improvement in OS and PFS, as well as higher objective response rates compared with sunitinib.[123,124]

Although originally developed for their antiangiogenic activity, these agents also contribute to immune reprogramming of the TME, and part of their clinical benefit may derive from their capacity to deplete MDSC-mediated immunosuppression, thereby enhancing ICI efficacy.[119,120] Traditional regimens have typically relied on maximum tolerated doses to achieve direct cytotoxicity or anti-proliferative effects. However, such high-dose approaches can reduce vascularization excessively, increase hypoxia and paradoxically promote immunosuppression. By contrast, lower doses have demonstrated immunomodulatory benefits, including normalizing vascularization, enhancing immune cell trafficking and depleting MDSCs.[119–121,125]

Blocking MDSCs Recruitment

The role of chemokines as mediators of MDSCs recruitment to the TME is being extensively studied (Table 1). A variety of preclinical studies are underway, studying several chemokine axes as potential targets to block this process and thereby limit MDSCs mediated immunosuppression (Table 2).

The CCL2-CCR2 signaling pathway has been studied in preclinical mouse models in melanoma and HCC, where its inhibition reduced MDSCs recruitment and inhibited tumor growth.[126,127]

Another important target is the CCL5–CCR5 axis. Studies in tumor-bearing mouse models with melanoma show this axis' importance in MDSCs recruitment, as well as further activation of their suppressive functions in the TME, entailing potential therapeutic implications. In B16 melanoma-bearing mice, approaches such as anti-CCR5 antibodies, CCL5-neutralizing monoclonal antibodies and recombinant mCCR5-Ig fusion protein significantly decreased migration and suppressive capacity of MDSCs, reduced metastatic spread, increased survival and enhanced the efficacy of anti-PD-1 therapy.[128,129]

Chemokine (C-X-C motif) ligand 8, also known as IL-8, highly expressed in various tumor types, including colorectal, ovarian, breast, pancreatic, prostate and hematological malignancies, is a pro-inflammatory chemokine that promotes MDSCs recruitment to the TME via CXCR1/CXCR2 receptors.[130–133] IL-8 also enhances EMT and angiogenesis. Targeting the IL-8 axis with small-molecule inhibitors targeting CXCR1 and CXCR2, like reparixin or neutralizing antibodies, have shown promise in preclinical models. These agents can diminish MDSCs and neutrophil infiltration, reduce cancer stem cell populations, and sensitize tumors to chemotherapy and ICI.[131]

The colony-stimulating factor 1 receptor (CSF-1R), a tyrosine kinase receptor activated by ligand CSF-1, promotes the differentiation and expansion of MDSCs and TAM, facilitating their migration into tumors.[134] CSF-R1 is upregulated in pancreatic and breast cancer.[135,136] CSF-R1 is often upregulated in pancreatic and breast cancers. Inhibition of CSF-1/CSF-1R signaling has been shown to improve antitumor T cell responses. Therefore, combining CSF-R1 inhibitors with checkpoint blockade or adoptive T cell therapies have demonstrated enhanced T cell activation and tumor regression in preclinical studies.[134,137,138]

Finally, simultaneous targeting of multiple pathways may provide synergistic effects. For instance, co-administration of CSF-1R inhibitors with CXCR2 antagonists has been shown to reduce both TAMs and PMN-MDSCs populations, resulting in improved responses to anti-PD-1 therapy.[139]

Inhibiting MDSCs Activity

ROS, ARG1, NOS, cyclooxygenase-2 (COX2), peroxynitrite, among others, enhance immunosuppressive activity of MDSC. Hence, inhibition of these factors represents a potential therapeutic target to restore anti-tumor immunity.[14,140]

Disruption of the COX2/PGE2 signaling pathway reduces MDSCs recruitment and differentiation by downregulating ARG1 expression and ROS production. COX2 inhibitors, such as celecoxib, have demonstrated immunoregulatory potential since it suppresses MDSCs, enhancing anti-tumor T cell responses and improving the efficacy of immunotherapy.[141–145]

Phosphodiesterase 5 (PDE-5) inhibitors, including sildenafil and tadalafil, are also able to abolish MDSCs immunosuppressive mechanisms by downregulating ARG1 and iNOS expression. Both drugs have shown to reduce tumor-

associated inflammation, enhance T and NK cell responses and prolong survival in vivo.[146,147] Clinical trials incorporating these drugs displayed positive results in head and neck squamous cell carcinoma and metastatic melanoma patients,[148,149] associated with decreased MDSCs and Tregs populations, increased intra-tumor T cell activity and improved clinical outcomes (Table 3).[149,150]

Another promising target is the nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates activation and availability of antioxidant enzymes such as NADPH quinone oxidoreductase 1 (NQO1), hemoxigenase (HO), which reduce intracellular ROS levels. Selective activation of Nrf2 in MDSCs has been shown to impair their suppressive function, reduce metastasis and promote tumor regression.[151] Anti-inflammatory triterpenoids activate the Nrf2 gene in MDSC. Synthetic triterpenoids, such as CCDO-Im and CCDO-Me, reduce intracellular ROS production in MDSCs and have shown promising results in Phase 1 clinical trials (Table 3).[152–154]

Another relevant therapeutic target is the inhibition of the STAT3 pathway. AZD9150, an antisense oligonucleotide STAT3 inhibitor, has been used in combination with ICI in Phase 1b clinical trials for the treatment of DLBCL, decreasing G-MDSC population.[155]

Promotion of MDSCs Differentiation

An alternative strategy to neutralize MDSC-mediated immunosuppression is to promote their differentiation into mature, non-suppressive myeloid cells such as granulocytes, macrophages, and DCs. One of the most studied agents in this context is all-trans retinoic acid (ATRA), an agonist of the retinoid receptor that inhibits signaling and promotes the differentiation of MDSC. ATRA reduces ROS production and increases intracellular glutamine synthase expression.[156] Preclinical and clinical studies have demonstrated that ATRA treatment reduces circulating MDSC, improves T cell activation and enhances DCs function, particularly in patients with RCC and small-cell lung cancer.[157,158]

Epigenetic reprogramming is a novel promising approach to reprogram MDSCs. The class I histone deacetylase inhibitor entinostat has shown positive results in neutralizing MDSCs through epigenetic reprogramming in mouse models of pancreatic, breast, lung and RCC.[83,84] Combination of entinostat with ICI resulted in decreased immunosuppressive functions of both M-MDSCs and PMN-MDSCs, improved CD8+ T cell infiltration and prolonged survival. Clinical trials evaluating this strategy are currently ongoing.[83,84]

Additionally, some chemotherapeutic agents exhibit chemo-immunomodulatory properties. Docetaxel has shown to favor the polarization of MDSCs into M1-like macrophages,[159] while paclitaxel has been reported to promote their differentiation into DCs.[160] These effects may partially explain the immunomodulatory properties observed in certain chemotherapy regimens and their potential to synergize with immunotherapy.

Combining Anti-MDSCs Therapies and Immunotherapy

There is a growing interest in demonstrating the potential of MDSCs as a therapeutic target and in combination with different types of immunotherapies, as this strategy has shown promise in reducing tumor burden and metastasis, and ultimately improving survival outcomes in cancer patients (Figure 3).[12]

Anti-MDSCs Therapies Combined with Checkpoint Inhibitors

Immune checkpoint blockade (ICB) has significantly improved outcomes in various malignancies. However, a considerable proportion of patients fail to respond or eventually develop resistance, particularly in poorly immunogenic or "cold" tumors, where response rates remain below 10%, requiring additional strategies.[161–164]

High levels of circulating MDSCs have been associated with poor responses to these treatments, both anti-PD-L1 and anti-CTLA-4, and may serve as predictive biomarkers of treatment failure and the development of resistances.[165–168]

Preclinical studies have explored the combination of MDSC-targeted approaches with ICB. For instance, the addition of epigenetic modulators, such as entinostat and 5-azacytidine, to anti-PD-L1 and anti-CTLA-4 antibodies led to complete tumor regression and prevented metastatic progression in a murine triple-negative breast cancer model, achieving over 80% survival rate at 100 days after tumor implantation.[78,169]

Similarly, IL-6, a cytokine implicated in MDSCs expansion and activation, has been targeted in combination therapies, as its levels correlate positively with disease progression.[170] IL-6 blockade has restored ICB sensitivity in

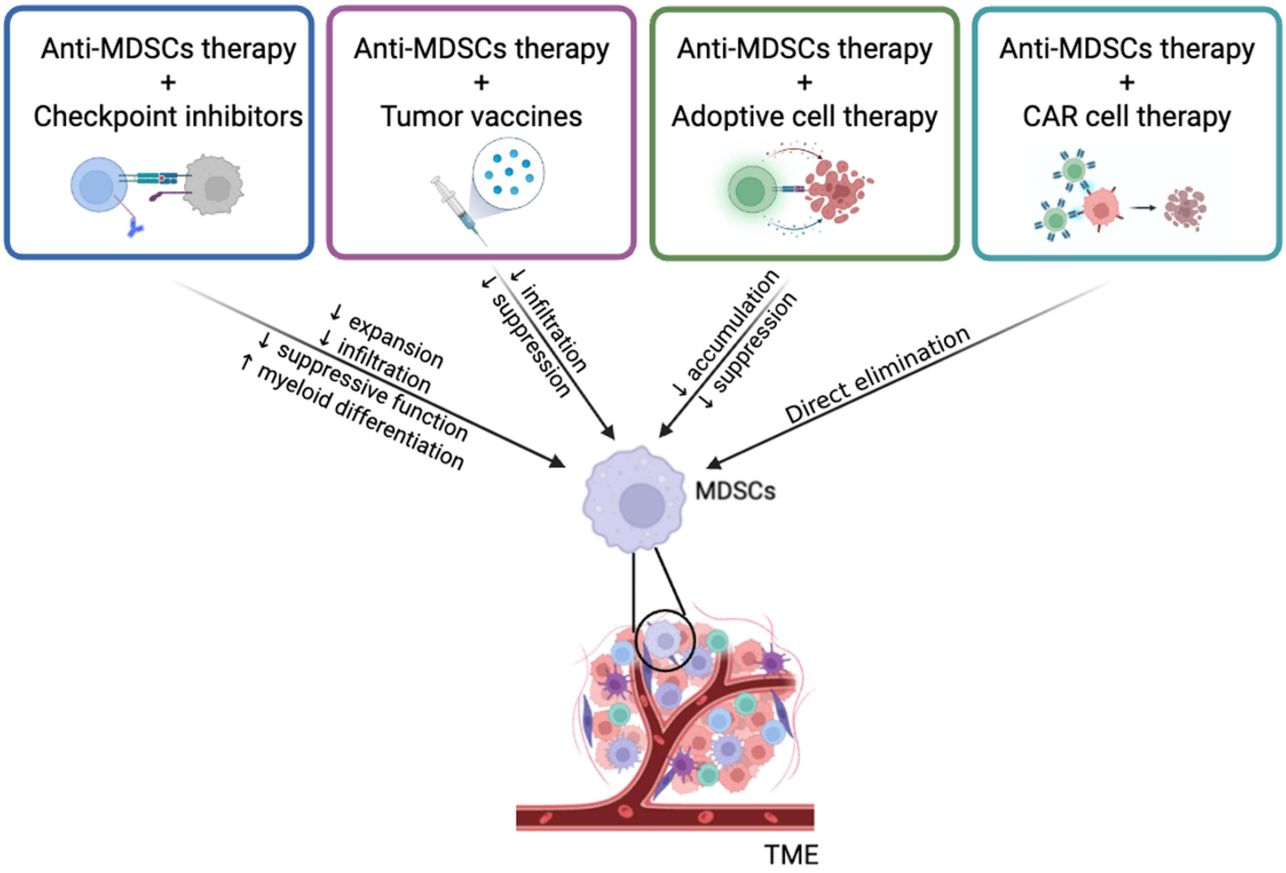

Figure 3 Combination of anti-MDSC therapies with immunotherapy. Approaches combining anti-MDSC agents with checkpoint inhibitors, vaccines, adoptive cell therapies, or CAR-T/CAR-NK enhance antitumor immunity by reducing the accumulation and suppressive activity of MDSCs within the TME. Upward arrows indicate an increase, whereas downward arrows denote a decrease.
Abbreviations: CAR, chimeric antigen receptor; MDSCs, myeloid-derived suppressor cells; TME, tumor microenvironment.

preclinical models of HCC, colorectal cancer, melanoma, triple negative breast cancer, and squamous cell carcinoma, by reducing MDSCs infiltration and increasing CD8+ T cell activity.[171]

ATRA has also shown synergistic effects with ICI in both preclinical and early-phase clinical studies. Clinical trials evaluating ATRA alone or in combination with ICI (NCT02403778, NCT03200847),[172] have demonstrated promising results in melanoma patients, with favorable tolerability and encouraging response rates, exceeding 70%.[172] Moreover, in preclinical models of breast cancer, ATRA enhanced the efficacy of anti-VEGFR2 antibodies, both in monotherapy and in combination with chemotherapy by reversing anti-VEGFR2-induced accumulation of MDSCs and mitigating tumor hypoxia.[74]

Aspirin, via COX inhibition and anti-inflammatory effects, has been proposed to modulate the tumor immune microenvironment and reduce MDSC-mediated immunosuppression. A Phase II clinical trial (NCT03396952) evaluated the combination of aspirin with ipilimumab (anti-CTLA-4) and pembrolizumab (anti-PD-1). Seventeen out of a total of twenty-seven patients achieved an objective response, resulting in an overall response rate (ORR) of 62.9% at 12 weeks. The 3-year PFS and the OS rates were 57.9% and 66.2%, respectively.[173] Clinical trials are underway to demonstrate the efficacy of these therapeutic combinations (Table 3).

Anti-MDSCs Therapies Combined with Tumor Vaccines

Tumor vaccines harness the tumor as a source of antigens to generate systemic and long-lasting antitumor immunity. Their mechanisms often include: isolating DCs from the patient, loading them ex vivo with tumor-associated antigens or neoantigens, and then re-infusing them into the patient; directly inject the antigens subcutaneously to activate patient's DCs in vivo.[174]

In preclinical studies, different formulations are being tested in a variety of solid tumors, and some have already demonstrated efficacy in reducing MDSC-mediated immunosuppression. For instance, in a syngeneic B16F0 melanoma model, a lentivector-based vaccine co-expressing IL-12 and a PD-L1 silencing small hairpin RNA, alongside tyrosinase-related protein 1 (TRP1) as the tumor antigen, counteracted the suppressive activity of MDSCs, contributing to the therapeutic benefit of the vaccine.[175] Similarly, in the B16F0 melanoma model, a DNA vaccine targeting DC, based on Macrophage Inflammatory Protein-3α (MIP-3α) fused to two common melanoma antigens - GP100 and TRP2 - was combined with IFN-ɣ and 5-Aza-2′-deoxycytidine, further promoting antigen presentation, reducing tumor-infiltrating MDSCs, and boosting cytotoxic T cell activity.[176]

Another approach used a prophylactic vaccine by employing exosomes derived from murine embryonic stem cells, engineered to produce GM-CSF (Granulocyte-macrophage colony-stimulating factor) (ES-exo/GM-CSF vaccine), effectively protecting mice from developing primary and metastatic lung cancer by decreasing tumor infiltration of Tregs and MDSCs.[177]

Despite these promising results, antitumor vaccines face major challenges, as they must maintain cytotoxic T cells activity, overcoming inhibitory signals from MDSCs and other regulatory components of the TME. Understanding the mechanisms of vaccine resistance and developing combination therapies that enhance antitumor immunity and long-lasting responses warrant future investigation.[12,178]

Anti-MDSCs Therapies Combined with Adoptive Cell Therapy

Adoptive cell therapies have emerged as powerful immunotherapeutic approaches for cancer treatment. Cytokine-induced killer (CIK) cell-based immunotherapy has shown effectiveness as adjuvant therapy in early-stage HCC, but its efficacy remains limited in advanced disease.[179] Preclinical studies using murine models are exploring the combination of CIK cells with a phosphodiesterase 5 (PDE5) inhibitor, reversing MDSCs suppressive function by blocking ARG1 and iNOS, thereby preventing their accumulation in the TME.[179] In vitro, PDE5 inhibition enhanced CIK cell-mediated cytotoxicity in human HCC cell lines, supporting the rationale for targeting MDSCs as an efficient strategy to restore antitumor immunity in these patients.[179]

Anti-MDSCs Therapies Combined with Chimeric Antigen Receptor (CAR) Cell Therapy

Given the immunosuppressive barriers posed by the TME in solid tumors, innovative strategies have been developed to directly target MDSCs using modified CAR-T cells, aiming to deliver targeted T cells to different tumor types.

In glioblastoma models, IL-15-modified CAR-T cells targeting IL-15 receptor alpha (IL-15Rα), expressed by MDSCs in human and murine tumor cells, generated a dual-targeting system that decreased both tumor and MDSCs burden, leading to prolonged survival.[180]

Another study engineered CAR-T cells to bind to an endogenous RNA - RN75L1 - which activates retinoic acid-inducible gene I (RIG-I) / Melanoma Differentiation-Associated protein 5 (MDA5) signaling. This modification enhanced memory phenotype CAR-T and promoted activation of DCs subpopulations, reducing MDSCs and TGF-β levels.[181]

Further strategies include the use of CAR-T cells incorporating the activating receptor NKG2D fused with intracellular signaling domains 4–1BB and CD3ζ. These NKG2D CAR-T cells selectively target MDSCs expressing NKG2D ligands within the TME, as demonstrated in a murine model of pancreatic ductal adenocarcinoma, resulting in enhanced antitumor activity.[182] Similar results were observed with genetically modified NK cells expressing NKG2D fused to the ζ-chain of the TCR (NKG2D.ζ). These NKG2D.ζ-engineered NK cells exhibited MDSC-depleting activity in neuroblastoma patients and are under evaluation in a clinical trial (NCT03373097).[183]

Other designs include CAR-T cells engineered to express anti-PD-L1 single-chain variable fragments (scFvs) or to express chimeric PD-L1-targeting receptors. These modifications aim to neutralize the immunosuppressive signals derived from both tumor cells and MDSCs, improving CAR-T persistence and antitumor potency.[184] A phase 1 clinical trial (NCT04684459) is currently assessing the efficacy of these approaches in patients with advanced solid tumors, displaying pleural and peritoneal metastasis.

Additionally, preclinical studies in breast cancer models have explored the combination of olaparib with Epidermal Growth Factor Receptor variant III (EGFRvIII) - targeting CAR-T cells (806–28ZCAR). Olaparib was found to inhibit MDSCs recruitment to the TME, thereby improving CAR-T infiltration and survival. These findings support the rationale for combining CAR-T therapy with agents that modulate the TME to overcome MDSC-mediated resistance.[22]

Conclusion and Future Perspectives

MDSCs are key players in cancer immunology, acting as potent regulators of tumor-induced immune suppression, both within the TME and in peripheral blood. Their dual role in mediating immune evasion and directly supporting tumor progression underscores their relevance as potential biomarkers of prognosis and therapy response, as well as attractive therapeutic targets for combined immunotherapy strategies.

Increasing evidence has highlighted their utility as biomarkers, allowing for a minimally invasive monitoring of tumor evolution, and possibly contributing for patient stratification. Nonetheless, challenges remain in standardizing detection methods, quantification, phenotypic definitions and functional assays limitations that currently limit the full clinical translation of MDSC-targeting strategies. In addition, the phenotypical and functional heterogeneity of MDSCs, across cancer types and between circulating and intratumoral compartments, adds complexity to this translational effort.

Numerous preclinical studies have identified promising mechanisms to target MDSCs with the aim of enhancing the efficacy of conventional therapies, among the most encouraging approaches are depleting MDSCs, blocking their recruitment, or reprogramming their suppressive phenotype. Several of these strategies are currently being evaluated in clinical trials, either as monotherapy or in combination with ICI, chemotherapy, or radiotherapy.

Combining conventional therapies with agents that modulate MDSCs may help overcome resistance mechanisms and restore antitumor immunity in cancer patients, potentially leading to more effective and durable responses across diverse cancer types in the foreseen future. Incorporating longitudinal immune monitoring into clinical trials will also be critical to better understand the dynamic behavior of MDSCs and their association with treatment outcomes.

Abbreviations

ADAM17, A disintegrin and metalloproteinase 17; ARG1, Arginase-1; ATP, Adenosine triphosphate; ATRA, All-trans retinoic acid; CAR, Chimeric antigen receptor; CCL, C-C motif ligand; CCR5, C-C chemokine receptor 5; CD40, Cluster of differentiation 40; CIK, Cytokine-induced killer; COX2, Cyclooxygenase-2; CPT1A, Carnitine palmitoyltransferase 1A; CSF-1R, Colony-stimulating factor 1 receptor; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; DC, Dendritic cells; DLBCL, Diffuse large B-cell lymphoma; e-MDSCs, Early-stage myeloid-derived suppressor cells; ECM, Extracellular matrix; EGFRvIII, Epidermal Growth Factor Receptor variant III; EMT, Epithelial-mesenchymal transition; FasL, Fas ligand; FGF2, Fibroblast growth factor 2; FoxP3 +, Forkhead box P3 positive; G-CSF, Granulocyte colony-stimulating factor; G-MDSCs, Granulocytic myeloid-derived suppressor cells; GLUT1, Glucose transporter protein type 1; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HIF-1, Hypoxia-inducible factor 1; HLA-DR, Human Leukocyte Antigen – DR isotype; HO, Hemoxigenase; ICB, Immune checkpoint blockade; ICI, Immune checkpoint inhibitors; IFN-γ, Interferon-gamma; IL-15Rα, Interleukin 15 receptor alpha; IL-1β, Interleukin 1 beta; IL-4R, Interleukin 4 receptor; IL-6, Interleukin 6; iNOS, Inducible nitric oxide synthase; iTregs, Inducible regulatory T cells; JAK1, Janus kinase 1; M-CSF, Macrophage colony-stimulating factor; M-MDSCs, Monocytic myeloid-derived suppressor cells; MDA5, Melanoma Differentiation-Associated protein 5; MDSCs, Myeloid-derived suppressor cells; MHC, Major histocompatibility complex; MIP-3α, Macrophage Inflammatory Protein-3 alfa; MMP9, Matrix metalloproteinase 9; NK, Natural killer; NKG2D.ζ, Natural Killer Group 2, Member D fused to the ζ-chain of the T Cell Receptor; NO, Nitric oxide; NQO1, Nicotinamide Adenine Dinucleotide Phosphate quinone oxidoreductase 1; Nrf2, Nuclear factor erythroid 2-related factor 2; NSCLC, Non-small cell lung cancer; OS, Overall survival; PD-1, Programmed cell death protein 1; PD-L1, Programmed death ligand 1; PDE-5, Phosphodiesterase 5; PFS, Progression-free survival; PGE2-, Prostaglandin E2; PMN-MDSCs, Polymorphonuclear myeloid-derived suppressor cells; RCC, Renal cell carcinoma; RIG-I, Retinoic acid-inducible gene I; ROS, Reactive oxygen species; scFvs, Single-chain variable fragments; STAT, Signal transducer and activator of transcription; STAT3, Signal transducer and activator of transcription 3; TAMs, Tumor-associated macrophages; TCR, T cell receptor; TGF-β, Transforming growth factor beta; Tim-3, T-cell

immunoglobulin and mucin domain-containing molecule 3; TME, Tumor microenvironment; Tregs, Regulatory T cells; TRP1, Tyrosinase-related protein 1; VEGF, Vascular endothelial growth factor; VEGFR2, Vascular endothelial growth factor receptor 2; VISTA, V-domain immunoglobulin suppressor of T-cell activation.

Disclosure

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