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Myeloid-Driven Mechanisms as Barriers to Antitumor CD8⁺ T Cell Activity

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Abstract

The adaptive immune system is essential for host defense against pathogenic challenges, and a major constituent is the CD8⁺ cytotoxic T cell. Ordinarily, CD8⁺ T cells are endowed with a unique ability to specifically recognize and destroy their targets. However, in cases where disease emerges, especially in cancer, the efficacy of the CD8⁺ T cell response is frequently counterbalanced in a ‘tug-of-war’ by networks of tumor-driven mechanisms of immune suppression. As a result, antitumor CD8⁺ T cell activity is hampered, which contributes to clinical manifestations of disease. It is now well-recognized that prominent elements of that network include myeloid-derived suppressor cells (MDSC) and macrophages which assume tumor-supportive phenotypes. Both myeloid populations are thought to arise as consequences of chronic inflammatory cues produced during the neoplastic process. Numerous preclinical studies have now shown that inhibiting the production, trafficking and/or function of these immune suppressive myeloid populations restore antitumor CD8⁺ T cell responses during both immune surveillance or in response to immune-targeted interventions. Correlative studies in cancer patients support these preclinical findings and, thus, have laid the foundation for ongoing clinical trials in patients receiving novel agents that target such myeloid elements alone or in combination with immunotherapy to potentially improve cancer patient outcomes. Accordingly, this review focuses on how and why it is important to study the myeloid-T cell interplay as an innovative strategy to boost or reinvigorate the CD8⁺ T cell response as a critical weapon in the battle against malignancy.

Keywords

Myeloid-derived Suppressor Cells; Macrophages; CD8⁺ T cells; Immune Suppression; Immunotherapy

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Introduction

Understanding fundamental mechanisms by which the immune system mediates anti-neoplastic activity has been a longstanding interest in the field of cancer biology. Indeed, investigations in the immune system-tumor interaction has led to the discovery of novel therapeutic strategies, known as immunotherapy, that exploit the capacity of the immune system to recognize and kill cancer cells. Of note is the ability of the cytotoxic CD8⁺ T cell, a major subpopulation of the adaptive immune system, to mediate tumor cell destruction following engagement of the T-cell receptor (TCR) with tumor-derived antigens (Ag) expressed in the context of major histocompatibility complex (MHC) class I proteins on the surface of the cancer cell. Based on this fundamental knowledge, diverse types of T cell-based therapies have been developed and now are effectively implemented as clinically relevant strategies in the field of oncology. These reflect both *passive* strategies, such as adoptive T cell transfer of *ex vivo*-expanded Ag-primed populations or genetic engineering of autologous T cells to express chimeric antigen receptors (i.e., CAR) for immune recognition, or *active* strategies, such as immune checkpoint blockade (ICB) to reinvigorate *in vivo* exhausted endogenous T cells.¹⁻⁴ Such strategies share a common goal of bolstering the ability of CD8⁺ T cells to infiltrate, persist, and eradicate Ag-bearing tumor cells within the tumor microenvironment (TME).

While each of these therapies has shown promise in several cancer types, the ability to achieve objective clinical responses in greater proportions of those patient populations continue to remain challenging. One potential major reason for the limitation of such therapeutic interventions is the ability of tumor cells to reshape their environment in favor of their growth by suppressing the infiltration and/or function of mobilized CD8⁺ T cells. Through the recruitment of suppressive innate immune populations, tumors create a hostile environment, which acts as a significant barrier to immune attack and immunotherapy efficacy.⁵ Specifically, two prominent components of this suppressive innate immune cellular compartment are myeloid-derived suppressor cells (MDSC) and macrophages, both of which are highly recruited to the TME and impede the ability of CD8⁺ T cells to kill tumor cells effectively.⁶ In this review, we will discuss not only the mechanisms by which MDSC and macrophages impede the effectiveness of T cell-based therapies, but will also highlight the latest approaches developed to eliminate or reprogram such myeloid populations within the TME to potentially bolster the therapeutic potency of the antitumor CD8⁺ T cell response.

MDSC in Cancer

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of largely immature myeloid cells, which arise from hematopoietic progenitors within the bone marrow as a consequence of disruption of normal myelopoiesis during states of chronic inflammation, including neoplasia.⁷ Under these conditions, MDSC are generated through a highly complex process wherein the secretion of persistently high levels of myeloid-dependent cytokines and inflammatory mediators, including G-CSF, GM-CSF, IL-6, and PGE₂ by the malignancy or stromal constituents of the TME circulate to the bone marrow to redirect hematopoiesis toward the production of MDSC at the expense of normal monocytes,

macrophages and dendritic cells (DCs).^{8–10} MDSC travel and accumulate in the peripheral blood, the spleen, and the TME upon exiting the bone marrow. The accumulation of MDSC in many cancer settings is significantly correlated with disease stage and patient survival, which validate their biologic relevance.^{11–14}

The total or bulk population of MDSC can be further dichotomized into at least two major subsets observed in both mice and in humans. Polymorphonuclear MDSC (PMN-MDSC) arise from the granulocytic lineage and resemble neutrophils, while monocytic MDSC (MMDSC) arise from the monocytic lineage and resemble monocytes. Our laboratory has demonstrated that PMN-MDSC arise from early granulopoietic progenitors in the bone marrow exposed to high levels of granulocyte colony-stimulating factor (G-CSF) and other myelopoietic growth factors secreted by tumors.^{7, 8} Recently, a novel progenitor population, termed monocyte-like precursors of granulocytes (MLPG), has been found to elicit a portion of the PMN-MDSC output.¹⁵ Furthermore, in humans, a third subset known as the early MDSC (E-MDSC) has been observed, and lacks both conventional neutrophilic and monocytic markers; however, further studies on this subset are warranted to fully appreciate their relevance in disease.^{16, 17} The specific markers used to identify MDSC populations have been extensively reviewed elsewhere.¹⁷

Despite the challenges in distinguishing MDSC from mature myeloid populations based on phenotype alone, functional assays are used in combination with phenotypic assessment to define MDSC. These assays measure the ability of such myeloid cell types to suppress adaptive immune responses, such as activation or effector function. Within the context of cancer, immune suppression by MDSC leads to decreased antitumor immunity and a poorer prognosis across a wide range of cancers, including head-and-neck squamous cell carcinoma (HNSCC), ovarian, cervical, colon, breast, melanoma, and multiple myeloma.^{18–23} Recent evidence suggests that in at least several cancer types, MDSC can accumulate in the periphery of patients under “pre-malignant” conditions, and can be utilized as a predictive indicator of therapeutic outcomes.^{24–26}

Mechanisms of MDSC-Mediated T Cell Suppression

CD8⁺ T cells are a main target of MDSC-mediated immune suppression, and suppression is achieved through a variety of mechanisms (Figure 1). These mechanisms can be broadly categorized by the ability of MDSC to deplete essential CD8⁺ T cell nutrients from the TME, the production of immunosuppressive cytokines, and the expression of effector molecules which can directly inhibit CD8⁺ T cell proliferation and activity. MDSC express high levels of arginase 1 (Arg1), and can deplete the TME of L-arginine, an amino acid that is critical for T cell metabolism and ultimately their activation.^{27, 28} In the absence of sufficient L-arginine, CD8⁺ T cells lack the expression of the TCR zeta-chain (TCR- ζ) and, thus, cannot form a complete TCR complex, thereby preventing Ag recognition and immune activation.^{29, 30} This mechanism has been implicated as a key driver of CD8⁺ T cell inhibition in both mouse tumor models and cancer patients.³¹ MDSC also express the cystine/glutamate transporter protein Xc, and have been demonstrated to consume cystine from the TME. However, unlike functionally mature antigen presenting cells (APC), MDSC do not subsequently secrete cysteine. As a result, the TME becomes depleted of cysteine, a

critical amino acid for CD8⁺ T cells due to their inability to convert cystine to cysteine themselves.³² MDSC are also able to deplete the TME of the essential amino acid tryptophan via the enzyme indoleamine 2,3-dioxygenase (IDO).³³ IDO production by MDSC was recently highlighted as being negatively correlated with clinical outcome and patient responsiveness to immunotherapy in breast cancer.³⁴

Another classical mechanism of MDSC-mediated immune suppression is the expression of inducible nitrous oxide synthase (iNOS), and the subsequent production of nitric oxide (NO).^{35, 36} NO inhibits the phosphorylation of the JAK/STAT signaling proteins, which directly inhibits their ability to signal through the IL-2 receptor, a critical element for clonal expansion in response to IL-2 exposure. NO has also been implicated in lowering IL-2 mRNA stability, preventing IL-2 synthesis.^{37, 38} MDSC also produce reactive oxygen species (ROS), such as hydrogen peroxide, which inhibits CD3 surface expression by, and IFN- γ secretion from, CD8⁺ T cells, and peroxynitrite, which can nitrate tyrosine residues on the TCR to disrupt its ability to efficiently bind to MHC molecules on the Ag-bearing target cell.^{39, 40} Interestingly, a recent study suggested a novel mechanism by which MDSC can inhibit naïve T cell trafficking to tumor-draining lymph nodes. Ku *et al.* demonstrated that MDSC are capable of cleaving L-selectin on naïve T cells, preventing their accumulation in the draining lymph nodes for subsequent Ag exposure and activation.⁴¹ Although checkpoint ligands, such as programmed death-ligand 1 (PD-L1) can be expressed by tumor cells, evidence has accumulated to demonstrate that MDSC can express PD-L1, providing a mechanism of CD8⁺ T cell-specific immune suppression by MDSC.⁴²

Interleukin-10 (IL-10) is one of many classically immune suppressive cytokines that can be produced by MDSC. In addition to its role in recruiting regulatory T cells to the TME, a recent study suggested a previously unrecognized mechanism by which this cytokine directly suppresses CD8⁺ T cell responses. IL-10 was shown to promote the branching of glycoproteins on the surface of the CD8⁺ T cell, directly decreasing their sensitivity to Ag binding.⁴³ Collectively, through these and other mechanisms, MDSC are potentially capable of inhibiting CD8⁺ T cell antitumor activity.

Therapeutic Strategies to Target MDSC in Cancer

Targeting MDSC therapeutically has been an attractive strategy for restoring CD8⁺ T cell antitumor activity, with a growing body-of- work demonstrating that depleting MDSC, dampening their suppressive function or impeding their trafficking to the TME improves the efficacy of T cell-based therapies.⁴⁴ Strategies to target MDSC are diverse, but for the most part fall into a distinct set of categories based on therapeutic mechanism.^{45, 46}

One therapeutic strategy is preventing the accumulation of MDSC within the TME, either through direct killing (depletion) or inhibiting their trafficking. MDSC have been demonstrated to be susceptible to killing by low doses of chemotherapy, such as gemcitabine, decitabine, or 5-fluorouracil.^{47–50} These strategies, however, are often hampered by off-target effects of such chemotherapeutic agents, and poor *in vivo* delivery. In this light, recent work has focused on delivering such agents to target MDSC in a more efficient manner. For example, it was recently demonstrated that treatment of tumor-bearing

mice with gemcitabine-loaded dendrimers complexed to an antibody directed against vascular endothelial growth factor receptor-1 (VEGFR1), a surface receptor highly expressed by MDSC, resulted in specific depletion of tumor-induced MDSC, and subsequent reactivation of antitumor T cell responses.⁵¹ In a similar manner, the delivery of gemcitabine as an anti-MDSC agent has been shown to be significantly improved by delivering gemcitabine in the context of lipid-coated calcium phosphate nanoparticles.⁵²

MDSC in cancer are known to constitutively undergo high levels of endoplasmic reticulum (ER) stress, which predisposes them to TRAIL-R2 mediated apoptosis, but has also been demonstrated to be necessary for the production of suppressive mediators like Arg1.⁵³ In view of this knowledge, it was recently demonstrated in patients with late-stage HNSCC that the exploitation of this pathway through the use of an agonistic TRAIL-R2-targeting antibody resulted in significant killing of MDSC, and correlated with an increase in progression-free survival (PFS).⁵⁴ Depletion of MDSC through antibody-based methods such as anti-Gr-1 has also been an attractive area of research, although the efficacy of these therapies has been limited due to non-specific depletion of functionally mature monocytes and neutrophils which also express Gr-1.^{55, 56} More recently, however, the development of peptide-Fc fusion proteins with specificity for S100A8/A9 proteins highly expressed by MDSC, has been shown to be more specific and efficacious in the depletion of MDSC.⁵⁷ In humans, studies in myelodysplastic syndrome (MDS) patients has shown that an Fc-engineered anti-CD33 antibody, one of several canonical markers of human MDSC, results in the killing of MDSC by antibody-dependent cellular cytotoxicity (ADCC).⁵⁸ While CD33 expression is not exclusive to MDSC, anti-CD33 may be efficacious for targeting MDSC in diseases or disorders associated with high MDSC burden.

Inhibiting MDSC trafficking to the TME is another approach to interfere with their ability to interact with and suppress CD8⁺ T cell function. However, as with the other strategies, chemokine targeting is not specific for MDSC and can impact other immune populations.^{59, 60} Nonetheless in MDSC-driven cancers, significant progress has been made in producing combination chemokine-blockade therapies to efficiently inhibit the homing of MDSC to the TME.^{60, 61} A novel small-molecule inhibitor of both CXCR1 and CXCR2, for example, significantly reduced the number of tumor-infiltrating PMN-MDSC and enhanced the accumulation of both endogenous and adoptively transferred T cells in mouse tumor models.⁶²

Another broad strategy to target MDSC is blocking their suppressive mechanisms. As described earlier, MDSC mediate their activities through a multitude of suppressive mechanisms, offering a range of potential therapeutic targets. Inhibition of Arg1 activity is known to restore L-arginine availability to T cells, allowing them to become more efficiently activated.³¹ Recently, a novel Arg1/2 inhibitor was demonstrated to significantly increase L-arginine levels in the TME in clinically relevant orthotopic mouse tumor models of non-small cell lung cancer (NSCLC), which led to a restoration in CD8⁺ T cell function and increased tumor control.⁶³ VEGFR inhibition combined with ICB directed against cytotoxic T lymphocyte-associated protein-4 (anti-CTLA-4) has also been shown to reduce MDSC-mediated T cell suppression in mouse models of metastatic melanoma.⁶⁴ Inhibition of IDO

in anti-PD-1-resistant lung tumor mouse models has been shown to reduce MDSC-mediated immune suppression as well, resulting in the reactivation of antitumor CD8⁺ T responses.⁶⁵

Inhibiting MDSC generation or enforcing their maturation into functional immune cell types represents another pathway to target MDSC therapeutically. Certain transcription factors or signaling molecules are known to either stimulate or inhibit the development of MDSC, including interferon regulatory factor-8 (IRF8), signal transducer and activator of transcription 3 (STAT3) or PGE₂; thus, appropriate regulation of their expression has been shown to hinder MDSC production or accumulation.⁶⁶ In this regard, our laboratory has demonstrated that STAT3-dependent downregulation of IRF8 in myeloid progenitors is critical to the production and expansion of PMN-MDSC, and that the overexpression of IRF8 (using transgenic models) in tumor-bearing mice can mitigate their accumulation and improve responses to immunotherapy.^{7, 8, 14, 44} In models of both prostate cancer and HNSCC, novel small-molecule inhibitors of STAT3 were shown to inhibit the generation and accumulation of MDSC.^{67, 68} Similarly, it was reported that a novel inhibitor of STAT3 phosphorylation induced apoptosis of MDSC and subsequent attenuation of CD8⁺ T cell suppression.⁶⁹ Inhibition of PGE₂ through various methods including targeting by oncolytic virus has been shown in both mouse models and human patient-derived MDSC to prevent their production.^{70, 71} In addition to preventing their generation, strategies to enforce MDSC maturation into functional non-suppressive immune cells have been investigated. All-*trans* retinoic acid (ATRA), for example, has been demonstrated in both mice and humans to enforce differentiation of MDSC into macrophages and DC.⁷² Recently, in patients with metastatic advanced-stage melanoma, ATRA was demonstrated to significantly reduce circulating MDSC compared to patients treated with anti-CTLA-4 therapy alone.⁷³ Thus, through the use of multiple approaches to disrupt the contribution of MDSC to immune suppression, it is possible to restore or enhance antitumor CD8⁺ T cell activity.

Targeting MDSC to Improve Outcomes of T Cell-Based Therapies

Regardless of the methods used to alter the contribution of MDSC to immune suppression, the outcome of such strategies improves the efficacy of T cell-based therapies in both mice and humans. Treatment with Ipilimumab to block the immune checkpoint protein CTLA-4 in patients with advanced malignant melanoma has been demonstrated to significantly decrease MDSC, as well as increase the detection of CD8⁺ effector-memory T cells.⁷⁴ Similarly, treatment of patients with melanoma with a combination of ATRA and Ipilimumab significantly decreased the detection of MDSC and improved responses to therapy when compared to Ipilimumab alone.⁷³ In multiple mouse cancer models including HNSCC and rhabdomyosarcoma, a reduction in MDSC through blockade of phosphoinositide 3-kinase (PI3K), a signaling molecule implicated in cytokine production by MDSC, or blockade of CXCR2 has been demonstrated to improve the efficacy of additional ICB therapies including anti-PD-1 or anti-PD-L1.^{75, 76}

In the case of adoptively transferred T cells as a therapeutic strategy, in mouse models of melanoma and breast cancer, targeting MDSC using chemotherapy or dual CXCR1/CXCR2 blockade was shown to significantly improve the efficacy of adoptively transferred CD8⁺ T cells to enter the TME and effectively kill tumor cells.^{62, 77} Recently, a novel mechanism of

MDSC targeting through the activation of LXR/ApoE, a protein implicated in lipoprotein metabolism, was demonstrated to deplete MDSC from the TME, leading to increased activation of CD8⁺ T cells and increased effectiveness of adoptively transferred Ag-specific CD8⁺ T cells in melanoma.⁷⁸

Responses to engineered CAR-T cell therapies have also shown marked improvement in pediatric sarcoma, colon cancer, breast cancer, mesothelioma, and neuroblastoma when administered in combination with MDSC-targeting strategies, such as ATRA (to enforce their differentiation), polyinosinic-polycytidylic acid (poly I:C; a toll-like receptor 3 (TLR3) agonist known to reduce MDSC numbers in tumor-bearing mice) or gemcitabine (to deplete MDSC).^{79–81} In a clinical trial with late-stage small cell lung cancer patients, ATRA combined with a DC vaccine targeting p53 showed a significant decrease in MDSC, increased CD8⁺ T cell activation and improved responses to the vaccine.⁸² Together, these results indicate that efficient targeting of MDSC can be accomplished through a myriad of mechanisms, and that when accomplished, can have a significant and positive impact on CD8⁺ T cell activity, particularly in response to CD8⁺ T cell-based therapies in both pre-clinical and clinical settings.

Macrophage Heterogeneity in Cancer

Macrophages are abundant in just about every organ or tissue. Macrophages that are important for maintaining tissue homeostasis are known as tissue-resident macrophages. While MDSC originate from bone marrow, tissue-resident macrophages may originate from either embryonic or bone marrow precursors.^{7, 83, 84} The composition of tissue-resident macrophages is determined by the given organ/tissue. For example, embryonic precursors seed the fetal brain and differentiate into microglia, which are maintained in the brain throughout adulthood with minimal contribution from bone marrow sources. Other organs, such as the lung and liver, are also seeded by embryonic precursors during development to produce alveolar macrophages and Kupffer cells, respectively, but may also be replenished by bone marrow-derived monocytes during adulthood. Intestine and dermis are examples of organs with tissue-resident macrophages that are frequently replenished by bone marrow-derived monocytes.⁸⁴ On the other hand, during acute or chronic inflammation within a particular tissue or organ, bone marrow-derived monocytes are commonly recruited via the circulation, which may differentiate into macrophages within the inflamed site. Such macrophages that inhabit these inflammatory microenvironments may be functionally distinct from the naturally dwelling tissue-resident macrophages.⁸⁴ Delineating the specific functional roles of tissue-resident macrophages versus bone marrow-derived macrophages during disease processes, especially in cancer, remain active areas of investigation.

While tissue-resident or bone marrow-derived macrophages may contribute to tumor regression or progression via shared as well as unique mechanisms, recent studies are beginning to recognize the importance of macrophage developmental origin on functional response.^{85–88} However, in most studies, macrophages remain broadly classified as CD45⁺F4/80⁺ in mice and CD45⁺CD68⁺ in humans.⁸⁹ Such broad macrophage classification is employed in both preclinical and clinical studies to determine correlations of macrophage abundance with cancer prognosis.⁶ Since F4/80 and CD68 are glycoproteins,

such markers, however, cannot effectively differentiate macrophage functional state nor their developmental origin. Although clinically utilized, CD68 also has limitations as a marker since it is not entirely macrophage-specific.⁶ Identifying specific markers to distinguish tissue-resident or bone marrow-derived macrophages is of ongoing importance, which will aid to better understand how the different macrophage populations and their developmental origins contribute to the regression or progression of a disease state, such as cancer.

In addition to multiple developmental origins, such macrophage populations may exhibit diverse functional states. They may acquire either immune activating or immune suppressive functions within the TME. It is thought that such functional dichotomy or ‘plasticity’ emerges in response to the inflammatory *milieu* that macrophages sense within the organ/tissue or the TME.⁸⁴ Thus, specific environmental cues ultimately dictate the type of macrophage response. The resultant macrophage functional states, in turn, act to either promote or inhibit the antitumor CD8⁺ T cell response.

Mechanisms of Macrophage-Mediated T Cell Stimulation or Suppression

In contrast to MDSC, which serve an immune suppressive role, macrophages can serve both activating and suppressive roles. Macrophages are an important component of immune stimulation due to their ability to sense a variety of stimuli, including microbial products and inflammatory cytokines. Macrophage recognition of pathogen-associated molecular patterns (PAMP) on bacterial, fungal, or viral pathogens is mediated by surface or endosomal expression of pattern recognition receptors (PRR). Downstream signaling of PRR activates macrophages for phagocytic potential, inflammatory cytokine production, and secretion of antimicrobial molecules.⁸³ Phagocytosis of microbes or tumor cells promotes pathogen or tumor destruction via lysosomal degradation, yielding a rich source of microbial or tumor Ag for Ag presentation. Macrophages have a potent ability to present Ag as macrophages abundantly express surface MHC class II molecules and costimulatory receptors, such as CD80 or CD86.^{83, 90} Macrophage display of microbial or tumor Ag bound to MHC class II proteins promote CD4⁺ T cell recognition, while macrophage expression of costimulatory molecules enhances subsequent immune activation. Furthermore, interleukin-12 (IL-12) production by macrophages potentiates CD4⁺ T-helper 1 (T_H1) differentiation, CD8⁺ T cell expansion, and cytotoxic CD8⁺ T cell activity.^{90, 91} Therefore, macrophages have a robust ability to promote adaptive immunity, particularly CD8⁺ T cell responses during infection or cancer.

In response to chronic inflammation, however, immune stimulatory properties of macrophages are downregulated.⁹² Anti-inflammatory cytokines and immune suppressive factors are secreted (Figure 1), resembling a wound-healing response. IL-10 production by macrophages reduces CD8⁺ T cell activation and expansion, antagonizing the biologic effects of IL-12.⁹³ Similarly to MDSC, Arg1 activity in macrophages reduces L-arginine availability, a key T cell metabolite for inducing the expression of the CD3 zeta-chain of the TCR. Lack of L-arginine thus contributes to inhibition of TCR signaling in response to Ag, as previously discussed for MDSC.⁹⁴ Although ROS or reactive-nitrogen species (RNS) may exert beneficial antimicrobial or antitumor activity, the effects of ROS or RNS may be deleterious for CD8⁺ T cells by dissociating the CD3 zeta-chain or inducing T cell death.⁸⁹

Furthermore, macrophages impact immune checkpoint regulation of activated T cells (Figure 1). Macrophage expression of CD80 or CD86 strongly binds to the immune checkpoint molecule CTLA-4 on activated CD8⁺ T cells, inducing cell cycle arrest of CD8⁺ T cells and decreasing cytotoxic activity.⁹⁰ As with MDSC, the expression of PD-L1 or PD-L2 by macrophages binds to PD-1 expressed by activated CD8⁺ T cells, contributing to CD8⁺ T cell exhaustion and apoptosis.⁹⁵ Through these various mechanisms, macrophages may limit CD8⁺ T cell expansion and cytotoxic effector function.

Therapeutic Strategies to Target Macrophages in Cancer

While macrophages may aid tumor cell killing or CD8⁺ T cell stimulation, such antitumor activity is often subverted in cancer.⁹⁰ Similarly to MDSC, macrophage-targeted therapies may be broadly characterized into three main categories: 1) blockade of macrophage recruitment to the TME; 2) macrophage depletion; and 3) reprogramming macrophages to yield antitumor immunity. Inhibiting macrophage recruitment and inducing subsequent depletion has been commonly achieved through blockade of the CC-chemokine CCL2, CCL2-receptor (CCR2), or colony-stimulating factor 1 receptor (CSF1R).^{85, 90, 93, 96} Such depletion strategies prolong overall survival and reduce metastasis in mouse tumor models, such as mammary cancer. Additional strategies for macrophage depletion include various pharmacologic agents. Trabectedin specifically deletes macrophages in a number of cancers including fibrosarcoma and ovarian carcinoma.⁹⁷ Recent usage of trabectedin in pancreatic cancer and melanoma significantly decreased the number of macrophages within the TME, increased CD8⁺ T cell infiltration, and subsequent tumor control.^{98, 99} Another macrophage-depleting agent is clodronate, a first generation bisphosphonate drug originally utilized as an anti-osteoporosis medication.¹⁰⁰ Clodronate-induced depletion of macrophages in mouse models of teratocarcinoma and rhabdomyosarcoma decreased tumor growth.¹⁰¹ Additionally, clodronate-induced depletion of macrophages within metastatic sites reduced metastatic tumor growth.⁸⁶

Rather than depleting macrophages entirely, macrophage reprogramming may serve as an alternative therapeutic strategy for improving antitumor CD8⁺ T cell responses. Such reprogramming mechanisms involve inhibition of immunosuppressive-skewing transcription factors or enzymes. In particular, STAT3 is a prominent target as it is upregulated in multiple cancers and limits macrophage immune stimulatory properties.^{83, 102} Recently, pharmacologic inhibition of STAT3 reduced macrophage proliferation within neurofibroma tumors and significantly reduced *in vivo* tumor growth.¹⁰³ A macrophage receptor CD163-targeting liposome was constructed to contain an anti-STAT3 drug, corosolic acid, and demonstrated specific inhibition of STAT3 in human monocytes and macrophages.¹⁰⁴ Such anti-STAT3 treatment decreased IL-10 expression, while increasing tumor necrosis factor- α (TNF- α) and IL-12, indicating that an immune stimulatory phenotype may be achieved in a macrophage-specific manner within the TME.

Similar to STAT3, STAT6 is another potential transcriptional target of macrophages as it negatively regulates macrophage immune stimulatory properties.^{83, 90} STAT6 may upregulate PD-L2 expression on macrophages and STAT6 inhibition reduced macrophage expression of Arg1 and mannose receptor C-type 1 (Mrc-1), contributing to decreased tumor

growth in a mouse mammary cancer model.^{105, 106} In regard to enzymatic activities that facilitate macrophage-mediated immune suppression, Arg1 and cyclooxygenase-2 (COX-2) are of particular therapeutic interest. Downregulation of Arg1 via dual inhibition of PI3K and bromodomain-containing protein 4 (BRD4) contributes to increased CD8⁺ T cell infiltration and potent antitumor activity in mouse models of lung and colon cancer.¹⁰⁷ COX-2 enzymatic activity has been associated with PD-L1 expression on both macrophages and MDSC, and such PD-L1 expression may be reduced upon pharmacologic inhibition of COX-2.¹⁰⁸ Therefore, therapeutic targeting of macrophages may yield beneficial consequences for tumor control.

Targeting Macrophages to Improve Outcomes of T Cell-Based Therapies

As with MDSC, a growing body-of-work suggests that removal or reprogramming of suppressive macrophages is an important strategy for improving outcomes of CD8⁺ T cell-based therapies. In cases of ICB therapy, targeting macrophages improves response in a number of cancer models.¹⁰⁹ Combining PD-1 blockade with vascular endothelial receptor-2 (VEGFR-2) inhibition in models of hepatocellular carcinoma shifts macrophages toward immune stimulatory phenotypes, increasing CD8⁺ T cell activation and antitumor activity.¹¹⁰ In an anti-PD-1-resistant model of lung adenocarcinoma, the combination of anti-PD-1 with toll-like receptor 7/8 (TLR7/8)-loaded nanoparticles, a type of PRR, promotes macrophage stimulation and potent antitumor activity in a CD8⁺ T cell-dependent manner.¹¹¹ CSF1R blockade also improves responses to ICB therapy in a melanoma model.¹¹² Furthermore, CSF1R blockade in combination with anti-PD-1 promotes CD8⁺ T cell infiltration within tumor islets, reducing *in vivo* tumor growth of a mouse mammary carcinoma.¹¹³ Interestingly, the production of “Armored” CAR T cells may serve as another form of T cell-based therapy, which have been engineered to not only express a chimeric Ag receptor, but also to constitutively secrete IL-12 to modify the TME. In a syngeneic model of ovarian peritoneal carcinomatosis, “Armored” CAR T cells significantly depleted macrophages within the TME, resisted inhibition by tumor-mediated PD-L1 expression, and improved overall survival of tumor-bearing mice.¹¹⁴ Altogether, these results provide substantial evidence that targeting suppressive macrophages in cancer provides a potentially impactful strategy for the improving CD8⁺ T cell-based therapies.

Ongoing Clinical Trials of T Cell-based Therapies in Combination with MDSC or Macrophage Targeting Agents

Studies demonstrating that inhibiting MDSC or macrophage accumulation or function improves responses to anticancer therapies in preclinical settings have led to various ongoing clinical trials (Table 1). For example, in patients with HNSCC, tadalafil is being tested to inhibit MDSC function to improve the efficacy of a MUC1-based tumor Ag vaccine. Direct killing of MDSC by gemcitabine in combination with DC-based vaccination is being tested in both adults and children with multiple subtypes of sarcoma. Differentiation of MDSCs using ATRA is being tested in advanced melanoma to improve responses to ipilimumab (anti-CTLA-4 therapy).

As discussed earlier, strategies that target CSF1R can inhibit macrophage recruitment to the TME and/or deplete them by blocking the binding to its ligand CSF1, which is critical for macrophage survival and expansion. This was revealed in preclinical studies utilizing CSF1R blockade, which increased overall survival and reduced metastases.^{90, 96, 109} CSF1R blockade in combination with ICB (anti-PD-1) also greatly improved response rates and decreased tumor growth in preclinical models.^{112, 113} Currently, CSF1R blockade is being tested in the clinical trials through the administration of tyrosine kinase inhibitors of CSF1R, such as Pexidartinib or ARRY-382, or Cabiralizumab, a monoclonal antibody that blocks CSF1 binding to CSF1R (Table 1). In ongoing clinical trials, CSF1R blockade is combined with ICB, such as anti-PD-L1 or anti-PD-1, but the results are yet to be determined (Table 1). Alternatively, blocking chemokine receptors may inhibit macrophage recruitment to the TME. For example, CCR2 blockade may serve as a mechanism to inhibit signaling mediated by the monocyte chemoattractant, CCL2. In preclinical studies, CCR2 blockade increased survival rates and reduced metastases in tumor-bearing mice.^{90, 96, 109} Currently, a dual antagonist of CCR2 and CCR5, referred to as BMS-813160, is being tested in clinic trials in combination with anti-PD-1 therapy (Table 1).

Future Prospects

Numerous preclinical studies enabled the identification and functional contribution of immune suppressive myeloid populations, namely MDSC and macrophages, as major barriers to the efficacy of antitumor CD8⁺ T cell responses. Such fundamental discoveries paved the way for rationale translational and clinical investigations to mono- or combination strategies that target such myeloid elements alone or in combination with immune-based therapies, respectively, to potentially improve cancer patient outcomes (Table 1). Clinical trials aimed at impacting MDSC populations are ongoing in numerous cancer types including HNSCC, soft tissue sarcoma, and melanoma (, ,). Macrophage-targeting therapies are also being tested in the clinic for colorectal cancer, pancreatic cancer, and other advanced solid tumors (, ,). Table 1 features a list of active and recently completed clinical trials focused on therapeutic agents that target MDSC or macrophages. While the results of these trials are still being analyzed, the future remains promising that such novel therapeutic modalities will expand the armamentarium of immune oncology weapons that can potentially augment human anticancer CD8⁺ T cell responses.

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Highlights

- CD8+ T cells are crucial for antitumor immunity
- Tumors drive the production of immune suppressive MDSC and macrophages
- Such MDSC and macrophages may act to impede antitumor CD8+ T cell activity
- Therapies that target MDSC and macrophages boost antitumor CD8+ T cell responses

Figure 1: Suppression of CD8⁺ T cell activity by myeloid-derived suppressor cells (MDSC) and macrophages.

MDSC and macrophages may inhibit CD8⁺ T cell responses by secreting immunosuppressive cytokines such as IL-10 or TGF-β. Release of reactive oxygen or nitrogen species may be deleterious to CD8⁺ T cells within MDSC or macrophage proximity. Enzymatic activity within MDSC and macrophages influences nutrient availability for T cells. In particular, Arg1 and IDO reduce the abundance of L-arginine and tryptophan metabolites. Furthermore, direct contact of MDSC or macrophages with CD8⁺ T cells via the PD-L1-PD-1 axis promotes CD8⁺ T cell exhaustion and apoptosis. Macrophages may further downregulate CD8⁺ T cell lytic activity through the CD80/86-CTLA-4 axis. Lastly, MDSC may limit CD8⁺ T cell activation by cleaving a T cell trafficking molecule, L-selectin, reducing naïve CD8⁺ T cell recruitment to lymph nodes for subsequent antigen exposure.

Table 1.**Therapeutic Strategies in Clinical Trials for Targeting MDSC or Macrophages**

No.	Target	Trial Title	Disease(s)	Intervention(s)	Trial No.
1	MDSC	PDE5 Inhibition Via Tadalafil to Enhance Anti-Tumor MUC1 Vaccine Efficacy in Patients With HNSCC	Head and Neck Cancer	Tadalafil, Anti-MUC1 Vaccine, Anti-Influenza Vaccine	
2	MDSC	Dendritic Cell Vaccine With or Without Gemcitabine Pre-Treatment for Adults and Children with Sarcoma	Sarcoma, Soft Tissue Sarcoma, Bone Sarcoma	Dendritic Cell Vaccine, Lysate of tumor, Gemcitabine, Imiquimod	
3	MDSC	Ipilimumab and All-Trans Retinoic Acid Combination Treatment of Advanced Melanoma	Melanoma	VESANOID (ATRA), Ipilimumab	
4	MDSC	Ibrutinib and Nivolumab in Treating Participants with Metastatic Solid Tumors	Metastatic Malignant Solid Neoplasm	Ibrutinib, Nivolumab	
5	MDSC	A Study of RGX-104 in Patients With Advanced Solid Malignancies and Lymphoma	Malignant Neoplasms	RGX-104, Nivolumab, Ipilimumab, Docetaxel, Pembrolizumab, Carboplatin, Pemetrexed	
6	Macrophage	Evaluation of Safety and Activity of an Anti-PDL1 Antibody (DURVALUMAB) Combined With CSF-1R TKI (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers (MEDIPLEX)	Colorectal Cancer, Pancreatic Cancer, Metastatic Cancer, Advanced Cancer	Pexidartinib, Durvalumab	
7	Macrophage	A Study of ARRY-382 in Combination With Pembrolizumab for the Treatment of Patients With Advanced Solid Tumors	Advanced Solid Tumors	ARRY-382, Pembrolizumab	
8	Macrophage	A Study of Cabiralizumab Given by Itself or With Nivolumab in Advanced Cancer or Cancer That Has Spread	Advanced Malignancies	Cabiralizumab, Nivolumab	
9	Macrophage	A Study of BMS-813160 in Combination With Chemotherapy or Nivolumab in Patients With Advanced Solid Tumors	Colorectal Cancer, Pancreatic Cancer	BMS-813160, Nivolumab, Nab-paclitaxel, Gemcitabine, 5-fluorouracil, Leucovorin, Irinotecan	
10	Macrophage	A Study of Cabiralizumab Given With Nivolumab With and Without Chemotherapy in Patients With Advanced Pancreatic Cancer	Advanced Pancreatic Cancer	Cabiralizumab, Nab-paclitaxel, Onivyde, Nivolumab, Fluorouracil, Gemcitabine, Oxaliplatin, Leucovorin, Irinotecan	