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Review

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Role of myeloid cells in the tumor microenvironment

Arpita Balakrishnan, Mohini Vig, Shweta Dubey

Amity Institute of Virology and Immunology, Amity University Uttar Pradesh (AUUP), Noida 201303, India.

Correspondence to: Dr. Shweta Dubey, Amity Institute of Virology & Immunology, Amity University Uttar Pradesh (AUUP), Noida 201303, India. E-mail: sdubey@amity.edu

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Abstract

The dynamic interplay between tumor cells and immune cells in the microenvironment plays a crucial role in determining disease severity and therapeutic outcome in cancer. Myeloid cells are the most abundantly available cell population in the tumor microenvironment. Myeloid cells have been shown to exist in diverse phenotypes and play both antitumoral and protumoral roles in cancer. Understanding the biology of myeloid cells can lay the foundation for the development of therapeutic strategies aimed at enhancing the antitumoral role of myeloid cells. This article presents an overview of the role of myeloid cells in tumor development and various mechanisms by which myeloid cells aid tumor progression. Existing drugs against cancer that utilize myeloid cells and the role of myeloid cells in drug resistance are also discussed.

Keywords: Myeloid cells, tumor, cancer, tumor microenvironment, tumor-associated macrophages, dendritic cells, tumor-associated neutrophils, myeloid-derived suppressor cells

INTRODUCTION

Tumor progression is modulated by genetic and epigenetic changes in tumor cells. The mutual and dynamic crosstalk with the components of the tumor microenvironment (TME) also play a substantial role in tumor progression[1]. As defined by the National Cancer Institute, "TME is a group of normal cells, molecules, and blood vessels that surround and aid in the growth of the tumor cell. Tumor development tends to shape the microenvironment, which in turn affects the way a tumor grows and spreads"[2]. TME is comprised of proliferating tumor cells, tumor stroma, blood vessels, recruited immune cells, a variety of associated tissue

cells (non-cellular components of extracellular matrix), and soluble mediators[3,4]. Interaction of the tumor with the components of TME may contribute to the expansion of tumorigenesis stages and may lead to the induction of chemotherapeutic drug resistance[1,5-7]. Due to the crucial role of TME in malignancy, understanding how TME affects cancer progression may help uncover the underlying mechanisms of tumor growth and metastasis.

Myeloid cells constitute the predominant cellular population in TME. They are the most abundant hematopoietic cells in the human body with various functions, comprise a heterogeneous group of immune cells such as monocytes, macrophages, and dendritic cells (DCs), and have an important role in regulating T cell responses[8]. Myeloid cells are the predominant population which establishes an immunosuppressive milieu and leads to tumor immune evasion[8]. In the presence of activation signals such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), Fms-like tyrosine kinase 3-ligand (Flt3-L), chemokine (C-C motif) ligand 2 (CCL2), vascular endothelial growth factor (VEGF), and S100 calcium-binding protein A8/A9 (S100A8/9) proteins[8], monocytes and granulocyte progenitors undergo terminal differentiation to form mature macrophages, DCs, or granulocytes. Pathological signals or the presence of immunosuppressive cytokines may trigger an alternative activation and formation of tumor-associated macrophages (TAMs), tumor-associated DCs, myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils (TANs), as shown in Figure 1. Expansion of myeloid cells in the tumor is associated with tumor burden according to various patient studies[9]. There is also substantial evidence to suggest that myeloid cells within TME are responsible for the suboptimal therapeutic responses in various cancers.

Role of myeloid cells in shaping tumor progression

Immunoediting, also referred to as the 3Es, as proposed by Dunn and Schreiber, refers to the ability of the immune system to regulate and shape cancer progression[9,10]. It is a dynamic process involving both immune cells and cancer cells[8]. Recognition and elimination of tumor cells by various cells of the innate and adaptive immune system is the main function of immunoediting. This is carried out in three phases: elimination, equilibrium, and escape[11,12]. The elimination phase, as the name suggests, denotes the elimination of tumor cells. The key players in this phase are natural killer cells (NK) and T cells, which through interferon-γ (IFN-γ) and interleukin-12 (IL-12) production, eliminate the tumor cells. The next and the longest phase is known as the equilibrium phase, where the immune selection of tumor variants occurs. Tumors, in turn, continue to incorporate multiple mutations to survive this selection. The last phase, the escape phase, follows when the tumor variants start to overwhelm the immune response and expand in an uncontrolled manner, which eventually leads to malignancy. The role of myeloid cells is primarily important in equilibrium and escape phases. Particularly, TAMs serve as modulators against tumor immunogenicity; they can be activated by NK cells or T cells[8]. The activity of tumor-infiltrating myeloid cells (TIMs) is also enhanced by inhibition of the glycolysis pathway in TAN, TAM, and mature DCs[8,13,14].

The persistence of cancer along with the immune cells (that have pro- or antitumor properties) in the escape phase leads to inflammation. The escape phase is the third and final stage, where the tumor becomes clinically apparent and establishes an immunosuppressive TME[15]. This persistence is supported and further sustained by TAMs, TANs, and MDSCs, which are recruited through factors secreted by the tumors (these factors and their functions are listed in Table 1)[8]. These three subsets are the key myeloid populations that are well established in cancers. TAMs and MDSCs are known to exert immunosuppressive functions and thereby suppress T cell-mediated tumor killing; suppression occurs through a variety of processes, as detailed in Figure 2B. They recruit Tregs through CCL22 secretion, which also supports the suppression of immune functions[16]. TANs, on the other hand, do not exhibit suppressive activities, but it has been demonstrated that the elimination of TANs leads to the increased cytotoxic activity of T cells[17]. Conditions

Table 1. Function of factors that are produced by tumor cells

Factors	Function
GM-CSF	• Myelopoiesis and DC differentiation[102]
G-CSF	• Differentiation, proliferation and survival of granulocytes[102] • Downregulates Interferon regulatory factor - 8 (IRF8) in DC progenitors, and thus results in reduced DC development[8] • More recruitment of MDSCs[8] • Mobilize granulocytic myeloid cells from the bone marrow to promote angiogenesis[8]
M-CSF	• Differentiation, proliferation and survival of macrophages[102] • Suppresses the differentiation of DCs while enhancing TAM2 polarization[103]
VEGF	• Promoting angiogenesis

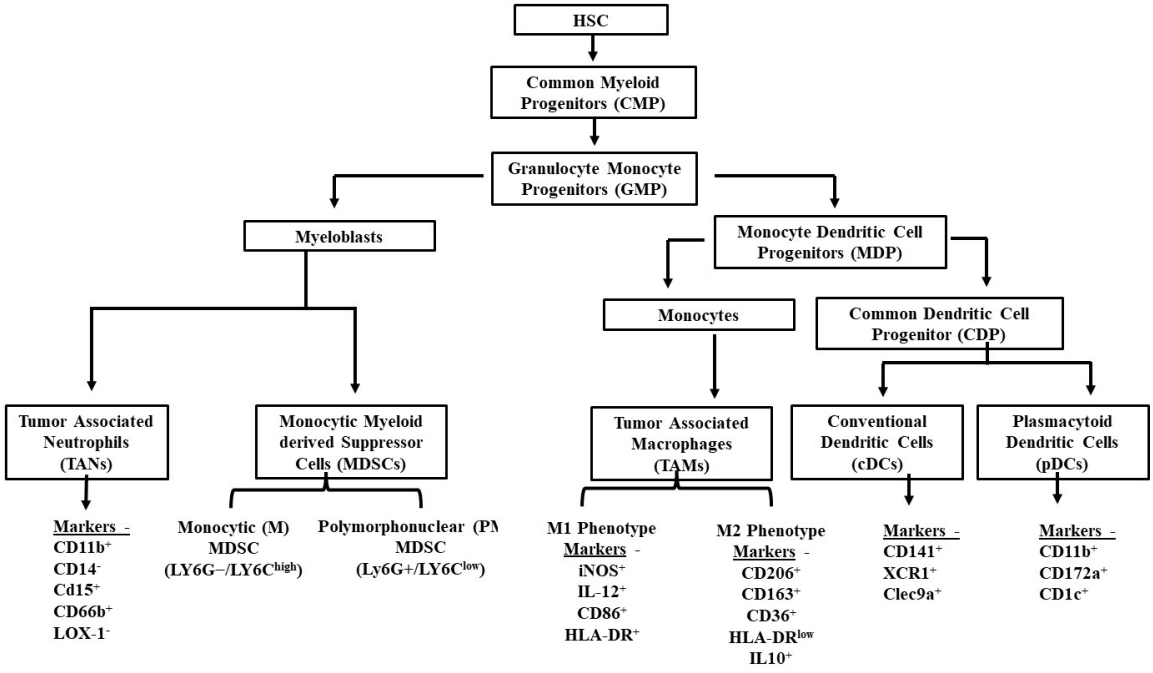

Figure 1. Myeloid cells in the tumor microenvironment. Myeloid cell differentiation induced by persistent stimulation with tumor-derived factors from hematopoietic stem cells (HSCs)[8]. In the presence of normal activation signals (such as G-CSF, GM-CSF, Flt3-L, CCL2, VEGF, and S100A8/9[8]), the monocytes and granulocyte progenitors undergo terminal differentiation to form mature macrophages, DCs, or granulocytes. Induction of an alternative activation pathway induces the formation of tumor-associated macrophages (TAMs), DCs, myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils (TANs). The markers of these myeloid cells are also indicated in the figure.

such as the presence of lactate, extracellular adenosine, and hypoxia in TME affect the ability of DCs to present antigens, which eventually hampers adaptive immunity[17]. Thus, it can be seen that factors secreted by the tumor shape TME and skew the function of myeloid cells strategically to facilitate immune evasion. Further sections in this article discuss the myeloid cells present in TME and how they impact tumor therapy.

Dendritic cells

Dendritic cells (DCs) are versatile antigen-presenting cells and serve to prime naïve T cell response. A decline in DC functions contributes to tumor immune evasion and compromised cell-mediated immune response in tumors[18]. DCs present tumor antigens to T cells in an immunogenic context by the production of cytokine interleukin 12 (IL-12p70), which induces T-helper (Th1) lineage commitment and subsequent

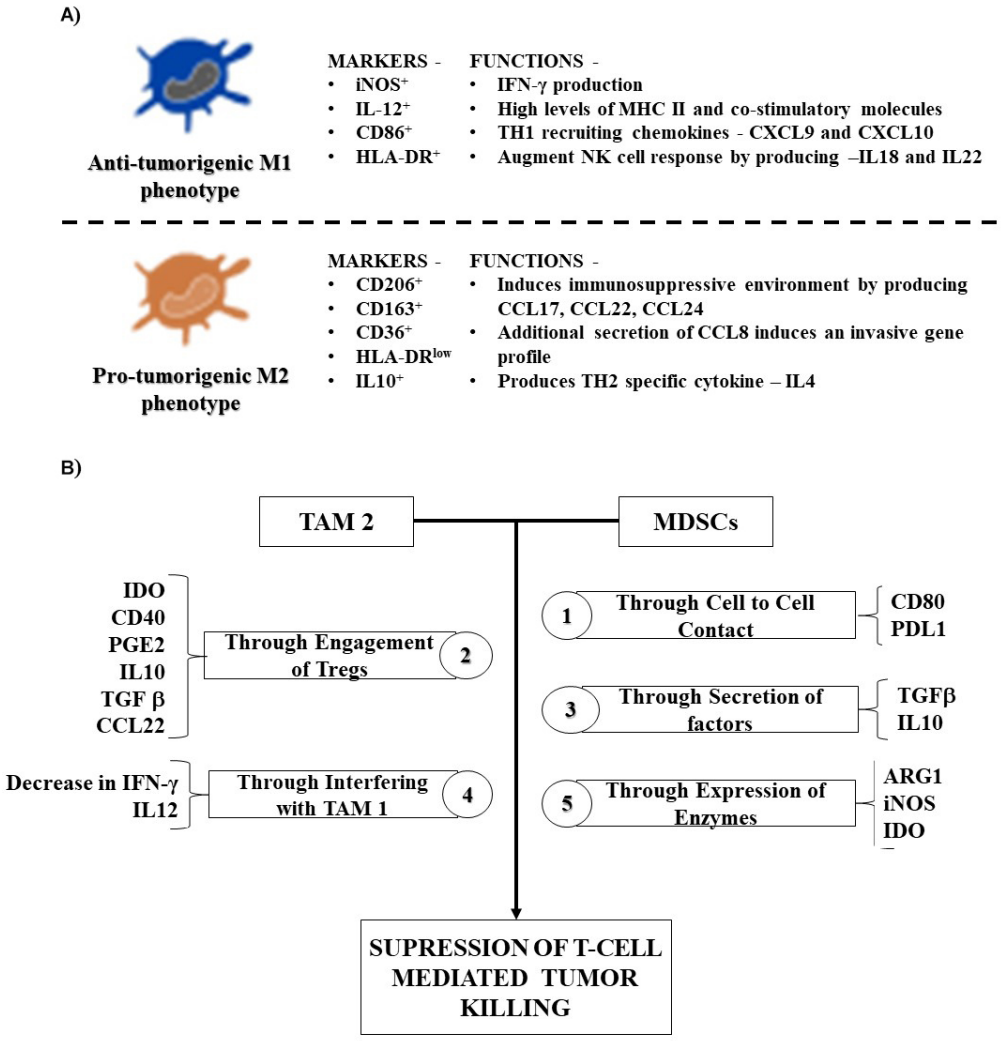

Figure 2. The immunosuppressive role of macrophages and myeloid-derived suppressor cells (MDSCs) in tumors. (A) The two phenotypes of TAMs and their respective markers and functions. (B) TAM2 and MDSCs suppress tumor killing through five immunosuppressive mechanisms: (i) via cell-to-cell contact, e.g., programmed cell death ligand-1(PD-L1) and cluster of differentiation 80 (CD80); (ii) secreted factors interleukin-10 (IL-10) and transforming growth factor-β (TGFβ); (iii) expression of enzymes arginase-1 (ARG1), inducible nitric oxide synthase (iNOS), and indoleamine 2,3 deoxygenase (IDO); (iv) engaging Tregs to aid in suppression by expression of factors that stimulate differentiation (e.g., IDO, prostaglandin E2 (PGE2), IL-10, and TGFβ) or recruitment (e.g., CCL22); and (v) interfering with TAM activity by suppressing the expression of IFN-γ and IL-12 which impact direct tumor killing and activation of killer T cells[8,15,20-23].

tumor elimination by IFN-γ, IL-12, and IL-21 production[19,20].

There are two types of DCs, known as conventional dendritic cells (cDCs) and plasmacytoid DCs (pDCs), as shown in Figure 1. The cDCs are the dominant subset and are made up of two precursors, cDC1 and cDC2; their respective markers are given in Table 2.

Notch signaling plays a role in DC differentiation, maturation, and activity as well[21-23]. Notch signaling produces cDCs at higher yields from the HSCs[24]. Out of the two precursors, cDC1 was shown to be an important provider of chemokine (C-X-C motif) ligand 9 (CXCL9) and CXCL10 in tumor populations,

Table 2. Conventional dendritic cell precursors with their markers and the factors expressed by them

Precursor	Markers	Instructed by	Factors expressed
cDC1	$CD141^+$ $XCR1^+$ $Clec9a^+$	FLT3L	IRF8, BATF3, ID2
cDC2	$CD11b^+$ $CD172a^+$ $CD1c^+$	GM-CSF	IRF4, Notch 2, RelB

which correlates with the level of T cell infiltration in patients with breast, lung, and head and neck cancer[25-27].

The cDC1 deficient mice experiments by Liu *et al.* helped establish the importance of this precursor in immunotherapy[28]. Further, prevention of B-16 ovalbumin (OVA) melanoma progression in mice was seen when vaccinated with cDC1 syngeneic spleen[29]. Combination therapy with program cell death protein-1 (PD-1) treatment has shown to be significantly more effective in immunotherapy[20]. For example, clinical trials of anti-PD-1 with DC vaccine combination therapy, in the case of melanoma, colorectal cancer, and many others, are underway[30,31]. The cDC2 subset is known to be more capable of activating CD4 T cells than CD8 T cells, and it may even collaborate with cDC1 to promote Th1 lineage[32]. The role of cDC2 is less explored and needs further investigation, as a combination of both might lead to the discovery of a potent therapeutic option. pDCs are known for producing type 1 IFN which drives the stimulation of cDCs[33]; however, the presence of pDCs in a tumor is often linked with poor prognosis of cancer and expression of immunosuppressive factors such as Indolamine-2,3-dioxygenase 1(IDO), interleukin-10 (IL10), or OX40. Thus, the role of pDCs in tumor suppression is quite elusive and needs more research for its use as a therapy[32,34,35]. In the case of radiotherapy (RT), ionization kills malignant cells by induced immunogenic cell death (ICD), which leads DCs to acquire tumor-associated antigen (TAA) to activate $CD8^+$ T cells[36,37]. ICD can also be induced by anthracyclines chemotherapy regimens, leading to a similar result[38]. Immune checkpoint therapy using PD-L1 binding to DCs was shown to hinder tumor growth; these DCs recruit T cells against the tumor, thus aiding in the success of the therapy[39,40].

Tumor-associated neutrophils

Tumor-associated neutrophils (TANs) are different from circulating neutrophils in surface markers and chemokine activities. The surface markers carried by TANs are given in Figure 1.

TANs are known to be inhibitors of tumor progression, but many studies have shown that the presence of TANs is associated with the promotion of metastatic potential of tumor and poor prognosis of tumor in cases of melanoma, renal carcinoma, *etc.*[41-44]. This is characterized by the presence of a high neutrophil-to-lymphocyte ratio in the peripheral blood[45]. In the early stages of cancer, they are shown to be T cell response stimulators and secrete pro-inflammatory mediators with anti-tumorigenic functions[46], such as direct tumor killing and coordination with adaptive lymphocytes. Some studies also indicate their anti-metastatic function[47,48]. All observations indicate that TANs have both anti-tumorigenic and pro-tumorigenic properties.

This has led to their bifurcation into N1 and N2 subsets. N1 subsets are anti-tumorigenic, with characteristic high levels of tumor necrosis factor α (TNFα), CCL3, ICAM-1 (intercellular adhesion molecule 1) and low levels of arginase. N2 subsets stimulate immunosuppression, characterized by upregulation of chemokines such as CCL2, CCL3, CCL4, CCL8, CXCL8, and CXCL16[49]. IL-17 produces γδ T cells (γδT17) when induced by a tumor, which has been shown to influence the expansion and

polarization of neutrophils toward pro-metastatic neutrophils or N2 subsets. γδT17 promotes N2 TANs in an IL-8-, TNF-, and GM-CSF-dependent manner[50]. In a murine model, it was found that migration of melanoma cells was promoted by UV-induced inflammation, which stimulates angiogenesis by neutrophil activity. This migration is directed toward the endothelial cells. This phenomenon is referred to as "angiotrophism"[51].

The studies on TANs have been done mainly on murine models due to difficulty in accessing them in humans, but, as murine neutrophils differ greatly from the human ones, an accurate depiction of their activity is not possible. Using a humanized mouse model may serve as a great tool for this purpose. In the case of hepatocellular carcinoma (HCC), Zhou *et al*. experimented with a humanized mouse model and suggested that TANs which were $CCL17^+$ and $CCL2^+$ support tumor progression by promoting macrophage ($F4/80^+$) infiltration Tregs ($FoxP3^+$) from TME[52]. HCC cells educated the neutrophils to skew toward an N2 phenotype via mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. Tumor progression was accompanied by greater tumor size, level of differentiation, and advanced vascularization[52].

Tumor-associated macrophages

The origin of TAMs is described in Figure 1 for what are called monocyte-derived macrophages; alternatively, they can arise from tissue-resident macrophages as well. This process is referred to as "emergency myelopoiesis". During carcinogenesis and proliferation, these tissue-resident TAMs undergo phenotypic changes which sustain them in the tumor environment[53]. They are the most abundant populations of myeloid cells in tumors. There are conflicting observations in the case of TAMs, as their high density in tumors can be associated with poor prognosis (in the case of lung, neck, and breast cancer) as well as with improved tumor-fighting efficiency (in the case of colon and gastric cancer)[54,55]. In a study by Badawi and colleagues on colon cancer, it was demonstrated that macrophage infiltration was significantly higher in malignant cases than in benign polyps. Lymph node metastasis influenced high macrophage infiltration and hypervascularity[56].

TAMs in tumors take on two lineages, the "M1" classical phenotype or the "M2" alternate phenotype. M1 (anti-tumorigenic) is a promoting phenotype where it promotes cancer treatment. M2 (pro-tumorigenic) is referred to as the phenotype which interferes with cancer treatments. The markers of both phenotypes are shown in Figure 2A. Some studies indicate that tissue-resident macrophages are sometimes more inclined toward the M2 phenotype[53]. M1 macrophages arise due to stimulus from IFN and TLR ligands (specifically TLR4[57]); M2 expands in response to IL4, IL13, TGFβ, and glucocorticoids. The mechanism of action of M1 macrophages in an anti-tumorigenic fashion is depicted in Figure 2A. In contrast, M2 macrophages are more phagocytic, express higher levels of mannose and galactose receptors, and have a highly active arginase (ARG1) pathway, which is detrimental to T cells[58]. In addition, M2 macrophages produce CCL17, CCL22, and CCL24, which leads to the formation of T helper 2 (Th2) or Tregs, eosinophils, and basophils recruitment. This recruitment induces an immunosuppressive environment[59]. It has also been shown that additional secretion of CCL8 and IL-4 induces an invasive gene expression profile[60].

It is worth noting here that the M1/M2 phenotyping is an oversimplified version of the macrophage lineage. The lineage of macrophages is a broad spectrum and is not limited to these two extremities. It has also been seen that notch signaling is responsible for the M1/M2 polarization. M2 has decreased notch activity, meaning that the notch signals support an M1 phenotype[61,62]. Notch signals help in the expression of IL-1β and CCL2 to recruit TAMs, as shown by Shen *et al*.[63]. Furthermore, cytokines, which are produced by macrophages, aid in the stimulation of notch signals in tumor cells. Additionally, paracrine loops between

macrophages and cancer cells can also promote tumor survival[23].

Experiments have shed light on therapies directed toward TAMs. For example, RT has been shown to influence the M1 phenotype in TAMs[64]. Conversely, chemotherapies are hindered by TAMs; for example, in the case of treatment with paclitaxel, an accumulation of TAMs was observed, which led to the failure of the therapy due to acquired resistance[65].

Treatment strategies usually focus on CCL2 and CSF-1 as they are the key players in TAM recruitment; inhibition of CSF-1R impacts the level of TAMs in tumors and reduces their immunosuppressive functions. Humanized CSF-1R antibody emactuzumab has shown positive results[66,67]. CCL2 blockade combination trials are underway as well[67]. Furthermore, program death ligand-1 (PD-L1) expression on TAMs promoted tumor growth, and TAM-specific PD-L1 inhibition has been demonstrated to induce a reduction in tumor growth[68].

New therapeutics using the RNAi (RNA interference) delivery system have been shown to be quite beneficial. The systems for targeting TAMs are grouped into liposomes, polymers, and inorganic nanoparticles in Table 3.

Myeloid-derived suppressor cells

MDSCs are heterogeneous cells of myeloid lineage which exhibit immunosuppressive activity. These cells have been shown to play a pathological role in cancers and other infectious diseases[26]. An important role for MDSCs has also been shown in conditions such as aging, pregnancy, and neonates[69]. Overall, MDSCs have been shown to induce immunosuppression in diverse inflammatory conditions[70]. The characteristic role in disease pathology orchestrated by MDSCs is incompletely understood. In a tumor setting, myeloblasts receive instructions from tumors to form MDSCs, as shown in Figure 1.

MDSCs have been broadly divided into two major subsets based on cellular, molecular, biochemical, and functional characteristics. The monocytic MDSC (M-MDSC) is morphologically similar to monocytes, while the polymorphonuclear MDSC (PMN-MDSC) is morphologically similar to neutrophils[68,71]. Recruitment of MDSCs to tumor site occurs via G-CSF, GM-CSF, or hypoxia. MDSCs induce immunosuppressive effects via IL-6, TNF-α, and PGE2[26]. PMN-MDSCs produce reactive oxygen species (ROS), nitric oxide synthase (NOS), and peroxynitrite[72], which inhibit the T cell functions by inducing T cell apoptosis and anergy. PMN-MDSCs inhibit T cell function in an antigen-specific manner. M-MDSCs inhibit in both antigen-specific and non-specific manners, via production of arginase enzyme, interleukin-10 (IL-10), cyclooxygenase 2 (COX2), and transforming growth factor beta (TGFβ)[21,72-74]. It has been shown that tumor progression is also promoted by MDSCs through enhanced production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metallopeptidase 9 (MMP9)[75].

The presence of circulating MDSCs has a negative influence on patient outcomes and hampers immunotherapy, as seen in lung, breast, and colorectal cancer[76-78]. All-trans retinoic acid (ATRA) has been shown to decrease the number of circulating MDSCs and reduce ROS production[43,44]. Notch signaling exhibits a controversial role in MDSC biology. In some studies, the accumulation of MDSCs is correlated to notch signaling[41,42,47], while others show that inhibition of notch signaling leads to abnormal differentiation of myeloid cells[42]. PMN-MDSCs show less immunosuppressive effects when notch signaling is blocked[48]. It has also been proposed that notch signaling induces metastasis of cancer by inducing the migration of MDSCs[23]. Notch receptors function by binding to Jagged or DLL membrane ligands and trigger canonical or non-canonical notch signaling pathways[79]. Inhibition of the notch pathway by anti-Jagged antibodies

Table 3. Gene silencing strategies for inhibition of TAM recruitment, survival, and reprogramming

Therapy strategy	siRNA target	Nanomaterial	Function
Inhibition of TAM recruitment	• CCR2 siRNA	• Liposome	It blocks the expression of the C-C chemokine receptor type 2 (CCR2) chemokine receptor, which is essential for recruitment[104]
	• VEGF siRNA	• Inorganic nanoparticle	In a lung cancer model, M2 peptide (M2pep)-functionalized Au nanoparticles loaded with VEGF siRNA were designed for cancer immunotherapy by targeting TAMs[105]
Inhibition of survival	• CSF1R siRNA	• Polymer	An anti-CSF1R siRNA, with α-peptide (a scavenger receptor B type 1-binding peptide) linked with M2 macrophage-binding peptide (M2pep) on the particle surface, is known to block the survival signal of TAMs and deplete them from melanoma tumors[106]
Reprogramming	• STAT siRNA	• Liposome	Protumor TAMs are generated by signal transducer and activator of transcription 3 (STAT3) signaling cascade, suggesting that inhibition of STAT3 can convert them to antitumor M1 type macrophages[107]

has been shown to block immunosuppression by MDSCs in tumors and promote tumor-specific T cell response[80]

MDSCs are heterogeneous and lack specific cell markers, which makes it challenging to study and utilize them effectively[26]. MDSCs have been shown to modulate therapeutic efficacy in immunotherapy, RT, or chemotherapeutic approaches. Efficacy of adoptive T cell immunotherapy (ACT) is shown to be affected by the presence of MDSCs in the TME, as MDSCs inhibit T cell proliferation and induce expression of cytotoxic mediators, which are major requirements for the success of ACT[23,49]. MDSC depletion has also been seen to improve the efficacy of RT[50]. Chemotherapy by gemcitabine and 5-fluorouracil has been shown to reduce MDSC numbers, which in turn reduces their immunosuppressive effects and helps enable CD8+ T cell-dependent anticancer immune response[81]. MDSC depletion and prevention of their trafficking to the tumor site have been shown to improve antitumor immune responses, as shown by Highfill *et al*. in a mouse model[82]. IL-8 neutralization by HuMax-IL8 mAb in triple-negative breast cancer has been shown to decrease the recruitment of PMN-MDSCs to the tumor site and facilitate tumor killing[83].

CANCER THERAPY USING MYELOID CELLS

Given the crucial role of immunosuppressive myeloid cells in tumor immune evasion, various therapeutic strategies aimed at reprogramming myeloid cells from an immunosuppressive to immunostimulatory mode have been explored. Table 4 highlights the therapeutic strategies of the myeloid cells cumulatively.

Myeloid cells in resistance to cancer therapy

Myeloid cells, especially TAMs, have been shown to play a pivotal role in tumor drug resistance. Drug resistance in cancer has several causes, including genetic mutations and/or epigenetic modifications, conserved but elevated drug efflux, and a variety of additional cellular and molecular pathways[84-87]. Paclitaxel is an anti-microtubule drug from the taxane family that is used to treat ovary, breast, and non-small cell lung cancers. The infiltration of macrophages in mammary tumors, as well as cathepsin levels, increases after paclitaxel treatment. Macrophages conferred protection on cancer cells from paclitaxel treatment in co-culture experiments by inducing cathepsins B and S expression, suggesting that combined inhibition of TAMs with chemotherapy may be a strategy to overcome resistance[88]. B-Raf is a serine/threonine-protein kinase that functions in the MAPK/extracellular signal-regulated kinase (ERK) signaling pathway and works downstream of RAS. In melanoma, the BRAF gene is frequently altered, resulting in the B-Raf protein's constitutive action[89]. Concurrent therapy with the CSF-1R inhibitor PLX3397 and the BRAF inhibitor vemurafenib resulted in increased antitumor responses in a murine model of melanoma, owing to a considerable decrease in tumor-infiltrating myeloid cells and an increase in tumor-infiltrating lymphocytes[90]. In mice with pancreatic ductal adenocarcinoma (PDAC) tumors,

Table 4. Therapeutic strategies using myeloid cells

Drug targets		Target role	Drug name
Dendritic cells			
Dual CCR2/CCR5		Receptor for chemokine CCL2 and CCL5, respectively, for attracting monocytes to tissues[108,109]	BMS-813160 (NCT03184870)
CSF1R		Differentiation, recruitment, proliferation, and survival of monocytes[110]	PLX-3397 (Pexidartinib) (NCT02371369)
SIRP		Myeloid-specific immune checkpoint blockade that inhibits phagocytosis of tumor cells; it is the ligand for the CD47 "do not eat me" signal present on DCs' surface[111-113]	ALX-148 (NCT03013218)
A2AR		Adenosine accumulation and downstream processing of the adenosine A2a receptor (A2AR) pathway show immunosuppressive effects[114,115]	CPI-444 (NCT02655822)
Toll-like receptors	TLR7	They can selectively activate a subset of DCs to take on stimulatory and pro-inflammatory phenotypes[116]	Imiquimod (NCT03558503)
	TLR4		G100 (NCT02501473)
	TLR9		Lefitolimod (NCT02099868)
CD40		Tumor necrosis factor receptors (TNFRs) family member CD40 is expressed on DCs and results in the upregulation of immunostimulatory cytokines, major histocompatibility complex (MHC) molecules, and the costimulatory ligands CD80 and CD86[117]	APX-005M (NCT03719430)
Tumor-associated neutrophils			
CXCL8		In the N2 subset, CXCL8 is upregulated and serves as a target for drugs and an ongoing trial that targets this particular chemokine	BMS-986253 (NCT03689699)
Arginase		Arginase, when reduced, helps to stimulate systemic immunity TANs and inhibit T cell proliferation by inducing high levels of ARG1	ARG1-18 (NCT03689192)
			CB-1158 (NCT03314935)
Tumor-associated macrophages			
CSF-1R		CSF-1R is known to impact the level of TAMs in tumors as well as reduce their immunosuppressive functions	PLX-3397 (NCT01596751)
ARG1		Arginase is an immunosuppressive effector molecule	ARG1-18 (NCT03689192)
Myeloid-derived suppressor cells			
MDSC levels		Reduction of MDSC levels and inhibition of suppressive activity[118,119]	Paclitaxel
MDSC differentiation		Promotes MDSC differentiation[120]	Docetaxel
M-MDSC development		Reduction of MDSC levels and inhibition of M-MDSC development[121]	Vemurafenib
STAT3		Reduction of MDSC levels through STAT3 inhibition[122]	Axitinib
ARG-1		Inhibition of ARG-1 expression and reduction of M-MDSC and G-MDSC numbers[123]	Ipilimumab

depletion of myeloid-lineage cells improved anticancer immunity associated with gemcitabine (GEM) treatment[91].

The efficacy of RT may also be influenced by the presence of myeloid cells. Irradiation with a local daily dosage of 3 Gy for five days in a prostate cancer animal model resulted in a systemic rise in MDSCs in lymph nodes, lung, spleen, and peripheral blood, as well as a two-fold increase in CSF-1 in tumors. Following RT of mammary tumor-bearing mice with localized gamma irradiation (5 Gy), blocking CSF-1 with a neutralizing monoclonal antibody (mAb) or a small molecule inhibitor against the CSF-1 receptor kinase (PLX3397) caused macrophage depletion and significantly inhibited tumor growth in a similar study. This was linked to an increase in CD8+ T cells in tumors and a decrease in CD4+ T cells, the main source of the Th2 cytokine IL4, which can provide malignancies with an advantage[92]. The M1 or M2 polarization of macrophages has significant therapeutic implications in human malignancies. It is speculated that the M2

subtype promotes tumor development. TAMs had an M1-like phenotype and function at baseline in a spontaneous mouse model of gastrointestinal stromal tumor (GIST) as well as in freshly obtained human GISTs; however, treatment with imatinib, a KIT oncoprotein inhibitor, caused TAMs to become M2-like in both mice and humans[93]. In patients receiving platinum-based chemotherapy, the relevance of TAM polarization is obvious. Chemoresistance is linked to increased levels of PGE2 (prostaglandin E2) and IL-6, two inflammatory mediators mediated by COX. These inflammatory mediators induce monocyte differentiation to the tumor-promoting M2 phenotype. Increased levels of activated STAT3 and lower levels of activated STAT1 and STAT6, respectively, were associated with tumor-produced IL-6 and PGE2. In breast and lung cancer xenograft models, myeloid bone marrow-derived cells (BMDCs), particularly macrophages, rapidly accumulated in tumors after local irradiation with 21 Gy. SDF-1α/CXCL12, a chemokine that supports the retention of BMDCs in the tissue, was found to be higher in the tumor two days after local irradiation. Radiation combined with an inhibitor of the stromal cell-derived factor 1α (SDF-1α) receptor (AMD3100) significantly slowed tumor regrowth. These findings show that increased SDF-1α expression by macrophages promotes tumor recurrence after radiation[94].

Role of myeloid cells in therapeutic response to immunotherapy

Most cancer cells have a large number of genetic and epigenetic alterations, which offer a large number of TAAs that the host immune system can recognize, necessitating tumors to evolve particular immune resistance mechanisms. Immunological-inhibitory pathways known as immune checkpoints, which ordinarily control immune tolerance and minimize collateral tissue damage, are an essential immune resistance mechanism. The immune-checkpoint receptor cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which reduces the amplitude of T cell activation, is particularly significant. Antibody inhibition of CTLA-4 induced antitumor immunity in cancer mice models has been well studied. Melanoma activity was proven in clinical investigations utilizing antagonistic CTLA-4 antibodies. In two randomized Phase III trials, this treatment improved survival despite a high rate of immune-related harm. Anti-CTLA4 medication was the first to show a survival benefit in advanced melanoma patients[95]. T cell effector capabilities are limited within tissues by another immune-checkpoint receptor known as programmed death 1 (PD-1). Tumor cells suppress antitumor immune responses in the TME by upregulating PD-1 ligands. Blocking the PD-1 pathway, according to early-stage clinical trials, causes long-term tumor regression in a variety of tumor types. The expression of PD-1 ligands by tumor cells may correlate with therapeutic response to PD-1 blocking[95].

In tumor immunotherapy, the current goal is to predict responders and evaluate the potential cause of immunotherapy resistance in non-responders. The circulating and tumor resident myeloid cell population may be used as a predictive biomarker for anti-CTLA-4 and anti-PD-1 therapy as myeloid cells are the primary determinants of T cell response in antitumor immunity[96]. Many studies have analyzed the impact of tumor-infiltrating myeloid cells on cancer patient prognosis and the mechanisms of negative and positive antitumor immune response modulation. Although the majority of the findings come from murine malignancies, clinical evidence is beginning to emerge that links the presence of myeloid cells in TME to the effectiveness of approved immune checkpoint therapies[96].

Among all myeloid cells, MDSCs have been shown to play a substantial role in determining the efficacy of immunotherapy in human cancers[97]. MDSCs play an important part in the formation of powerful immunosuppression on both systemic and tumor levels, and some research has begun to shed light on their potential as biomarkers of immune checkpoint inhibitor (ICI) response[96]. Besides MDSCs, studies have also shown roles for monocytes, tumor-derived neutrophils, or immature myeloid cells as predictors for response to ICIs[97].

Ipilimumab is a fully human IgG1 antibody targeted against CTLA-4 and has shown clinical efficacy in metastatic melanoma in phase III clinical trials. The mechanism of action of ipilimumab is believed to be linked to the enhancement of T cell-mediated killing of tumor cells. The exact mechanism by which anti-CTLA-4 antibodies promote this immune-mediated tumor-killing is still not completely understood. Some studies indicate induction of tumor-specific CD8+ T cells, while others have speculated that the effect might be conveyed through the inhibition of regulatory T cells. In addition, treatment with ipilimumab has been reported to reduce the frequency of MDSCs[98,99]. The long-term monitoring of Tregs, MDSCs, and tumor antigen responses at three, six, and nine months following treatment with ipilimumab resulted in several important findings. First, the significant increase in Treg (CD4+CD25hi+Foxp3+ and CD4+CD25hi+CD39+) at six weeks reversed at three months. Second, CD4+CD25hiCD39+ Treg and HLA-DR+lowCD14+ MDSCs may be baseline markers of immunotherapeutic benefit and warrant further study. Finally, antigen-specific T cell immunity against shared TAAs (gp-100, MART-1, and NY-ESO-1) was boosted with CTLA4 blockade[100]. In another study focused on analyzing alterations in the myeloid cell compartment and possible correlations of clinical outcomes with ICIs on MDSCs, it was reported that MDSC frequency correlated with the outcome of anti-CTLA-4 treatment[76] as indicated in Figure 3 although anti-CTLA-4 treatment is supposed to have a direct inhibitory role on T-effector cells and T-regulatory cells, monocytes and MDSCs also express low levels of CTLA-4 and may be amenable to CTLA-4 blockade. Anti-CTLA-4 treatment may have both T cell-specific and MDSC-specific roles; the balance of inhibition of both T cell-specific and MDSC-specific pathways may be responsible for determining the therapeutic response to CTLA-4 blockade.

In patients with Metastatic Urothelial Carcinoma (mUC), ICI treatment correlated with distinct changes in PD1 and PDL1 expression by specific peripheral immune cell subsets such as cytotoxic T lymphocytes (CTLs) and MDSCs. Higher PD1 expression by CTL following ICI therapy correlated with a higher objective response rate. Further studies are required to validate immune biomarker expression in mUC and explore its utility in guiding therapeutic decision-making and clinical trial eligibility/stratification[101]. Elevated PDL-1 expression has also been reported in tumor extracellular vesicles (TEVs) and correlates with disease pathology in many human cancers. TEVs have also been shown to overexpress IL-3 Ra receptor. Blockade of IL-3 R alpha signaling has been shown to enhance antitumor immune response by interfering with epigenetic modifications that alter the transport of PDL-1 expression in TEVs[99].

CONCLUSION

The TME comprises diverse myeloid cells, particularly TAMs, TANs, DCs, and MDSCs, which contribute to tumor progression, enhanced angiogenesis, metastasis, and immunotherapy resistance. Substantial evidence indicates that tumor elimination may require multiple targets for achieving a satisfactory therapeutic response. Myeloid cells have all the critical attributes of playing a regulatory role in tumor biology. Therefore, deciphering the role of the individual myeloid cell population in TME is essential for developing combinatorial therapeutic strategies in cancer. Immune cell-based therapies are gaining substantial success, making them innovative approaches to cancer treatment. Understanding the crosstalks that occur among the tumor-infiltrating myeloid cells and immune cells may be the first step in the development of therapeutic strategies. Clinical trials of various immunotherapies, alone or in combination, to enhance TME cells to repolarize their function to support cancer prevention are underway, but much more research is required for optimum and successful implementation of myeloid cell-specific therapies. Despite the advances in cancer treatment over the last few decades, resistance to traditional chemotherapeutic agents and/or revolutionary targeted medications remains a major issue in cancer therapy, accounting for the majority of relapses and one of the leading causes of cancer death. The promising results of clinical trials combining ICIs with myeloid-targeting therapies reinforce the notion that

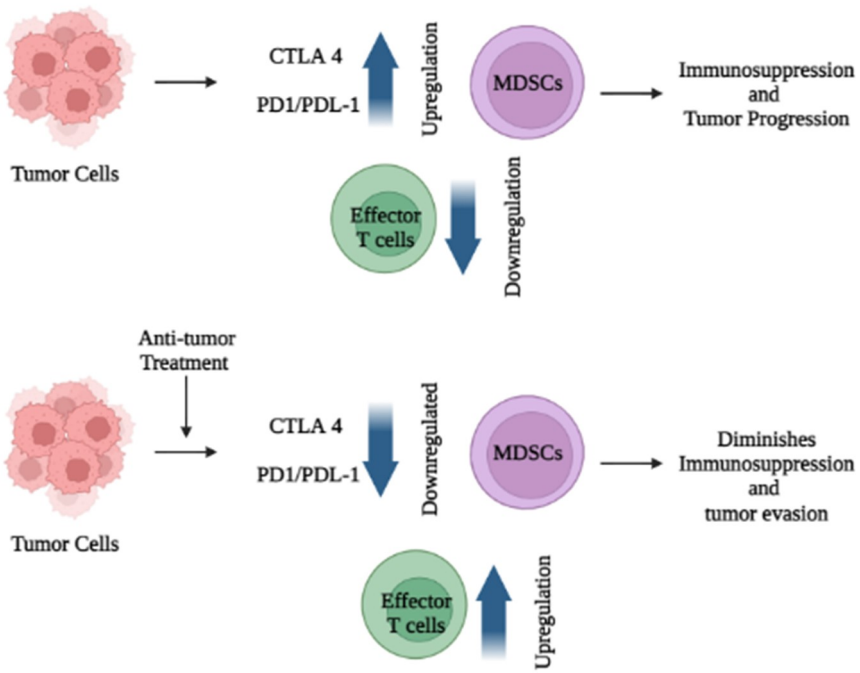

Figure 3. Immune checkpoint inhibitors and myeloid-derived suppressor cells (MDSCs). Suppressive factors from the tumor microenvironment upregulate immune checkpoint receptors and enhance immunosuppression by myeloid cells while downregulating effector T cells. Blocking immune checkpoint molecules with monoclonal antibodies such as ipilimumab may enhance T cell immune response and reduce the frequency of immunosuppressive myeloid cells in cancer. It is also suggested that immune checkpoint inhibitors may also inhibit Tregs (not shown in the figure) and contribute to an overall augmentation in antitumor immune response.

limiting the expansion, recruitment, and activity of myeloid cells in malignancies is critical for extending the benefit of immunotherapies to non-responding patients.

DECLARATIONS

Authors' contributions

Conceived the idea: Dubey S
Performed literature analysis and preparation of initial and final draft and figures: Balakrishnan A
Performed literature analysis and compilation: Vig M

Availability of data and materials

The data utilized in the article is available in public domain.

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All authors declared that there are no conflicts of interest.

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Consent for publication

Not applicable.

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