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SYMPOSIUM-IN-WRITING PAPER

Interactions among myeloid regulatory cells in cancer

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Abstract

Mounting evidence has accumulated on the critical role of the different myeloid cells in the regulation of the cancerous process, and in particular in the modulation of the immune reaction to cancer. Myeloid cells are a major component of host cells infiltrating tumors, interacting with each other, with tumor cells and other stromal cells, and demonstrating a prominent plasticity. We describe here various myeloid regulatory cells (MRCs) in mice and human as well as their relevant therapeutic targets. We first address the role of the monocytes and macrophages that can contribute to angiogenesis, immunosuppression and metastatic dissemination. Next, we discuss the differential role of neutrophil subsets in tumor development, enhancing the dual and sometimes contradicting role of these cells. A heterogeneous population of immature myeloid cells, MDSCs, was shown to be generated and accumulated during tumor progression as well as to be an important player in cancer-related immune suppression. Lastly, we discuss the role of myeloid DCs, which can either contribute to effective anti-tumor responses or play a more regulatory role. We believe that MRCs play a critical role in cancer-related immune regulation and suggest that future anti-cancer therapies will focus on these abundant cells.

Keywords Myeloid regulatory cells · Mye-EUNITER · Macrophages · Neutrophils · Myeloid-derived suppressor cells · Dendritic cells

Abbreviations

Arg	Arginase
CCL	C–C motif ligand
cDC	Classical dendritic cell
CXCL	C–X–C motif ligand
DCs	Dendritic cells
EBV	Epstein–Barr virus
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
HDNs	High-density neutrophils
HGF	Hepatocyte growth factor
iNOS	Inducible NO synthase
LDNs	Low-density neutrophils
LFA	Lymphocyte function-associated antigen
Mac	Macrophage antigen
M-CSF	Macrophage colony-stimulating factor
M-MDSCs	Monocytic MDSCs
MMPs	Matrix metalloproteinases
MRCs	Myeloid regulatory cells
NLR	Neutrophil to lymphocyte ratio
PDGF	Platelet-derived growth factor
PLGF	Placenta growth factor
PMN-MDSCs	Polymorphonuclear MDSCs
TAMs	Tumor-associated macrophages
TANs	Tumor-associated neutrophils
TGF	Transforming growth factor

Introduction

Various investigations have presented strong data that different tumors were able to display immunogenic properties, stimulating robust anti-tumor immune responses, in which T cells were demonstrated to play a major role [1]. An increased infiltration of tumor lesions with T lymphocytes has been demonstrated in patients with a large spectrum of

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tumors to correlate markedly with better clinical outcome [2]. However, multiple studies in the last decade have indicated a critical role of myeloid cell subsets in the development of an immunosuppressive tumor microenvironment, resulting in cancer progression. On the other side, some myeloid cell subsets could be indispensable for the induction of efficient anti-tumor immune responses. Myeloid cells represent a major component of host cells infiltrating tumors and are characterized by an extraordinary plasticity [3]. They may not only interact with each other, with other host cells (especially T lymphocytes) and tumor cells but they can also undergo a conversion from one subset to another. Importantly, the recruitment and enrichment of myeloid cells with immunosuppressive/regulatory properties designated in this series of reviews as myeloid regulatory cells (MRCs), at the tumor site was found to be stimulated by chronic inflammatory conditions developing in the tumor microenvironment [4].

The phenotypic characterization of circulating and tumor-infiltrating MRCs is difficult due to the fact that MRC subsets could express overlapping set of markers. Last years were characterized by an ongoing discussion regarding the relationship between neutrophils and polymorphonuclear MDSCs (PMN-MDSCs) or tumor-associated macrophages (TAMs) and monocytic MDSCs (M-MDSCs). For example, classical neutrophils and PMN-MDSCs share markers [5]. Despite numerous efforts to determine the similarities and differences between these two cell populations, further studies are still needed to better identify their molecular identity and functional characteristics. A comprehensive analysis of the phenotypic markers, molecular signaling pathways and functional capacities of various MRC subsets is presented by Cassetta et al. and Bruger et al. [6] in companion reviews in this symposium-in-writing. In the current review, we will focus on the characterization of various MRC subpopulations, including monocytes/macrophages, neutrophils, MDSCs and DCs, their interactions and therapeutic targeting both in mouse tumor models and in cancer patients (Figs. 1, 2).

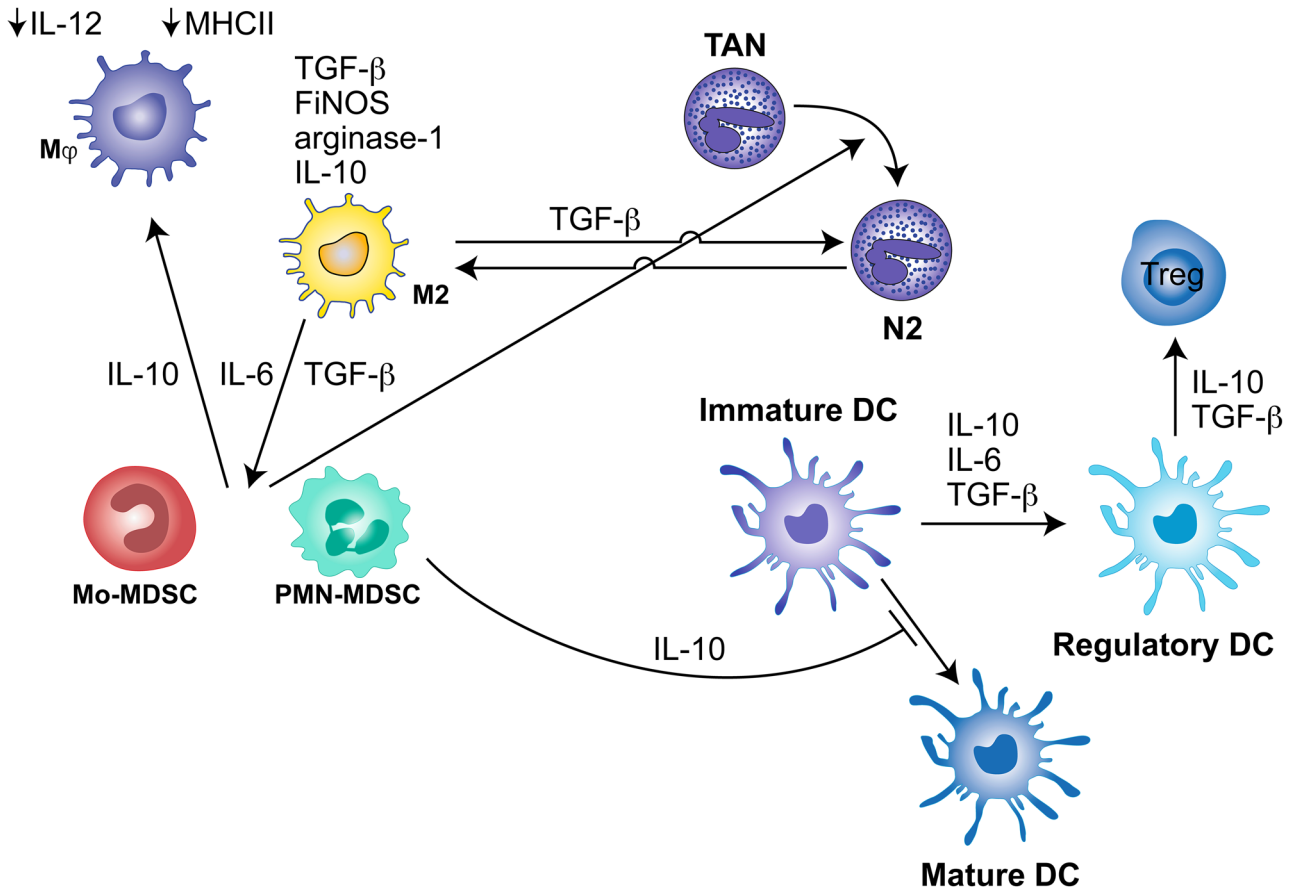

Fig. 1 Multiple effects and interactions among the different types of MRCs in cancer. *Mϕ* Macrophages, *M2* M2 macrophages, *TAN* tumor-associated neutrophils, *N2* N2 TAN, *Mo-MDSC* monocytic myeloid-derived suppressor cells, *PMN-MDSC* polymorphonuclear MDSC, *DC* dendritic cells, *Treg* regulatory T cells

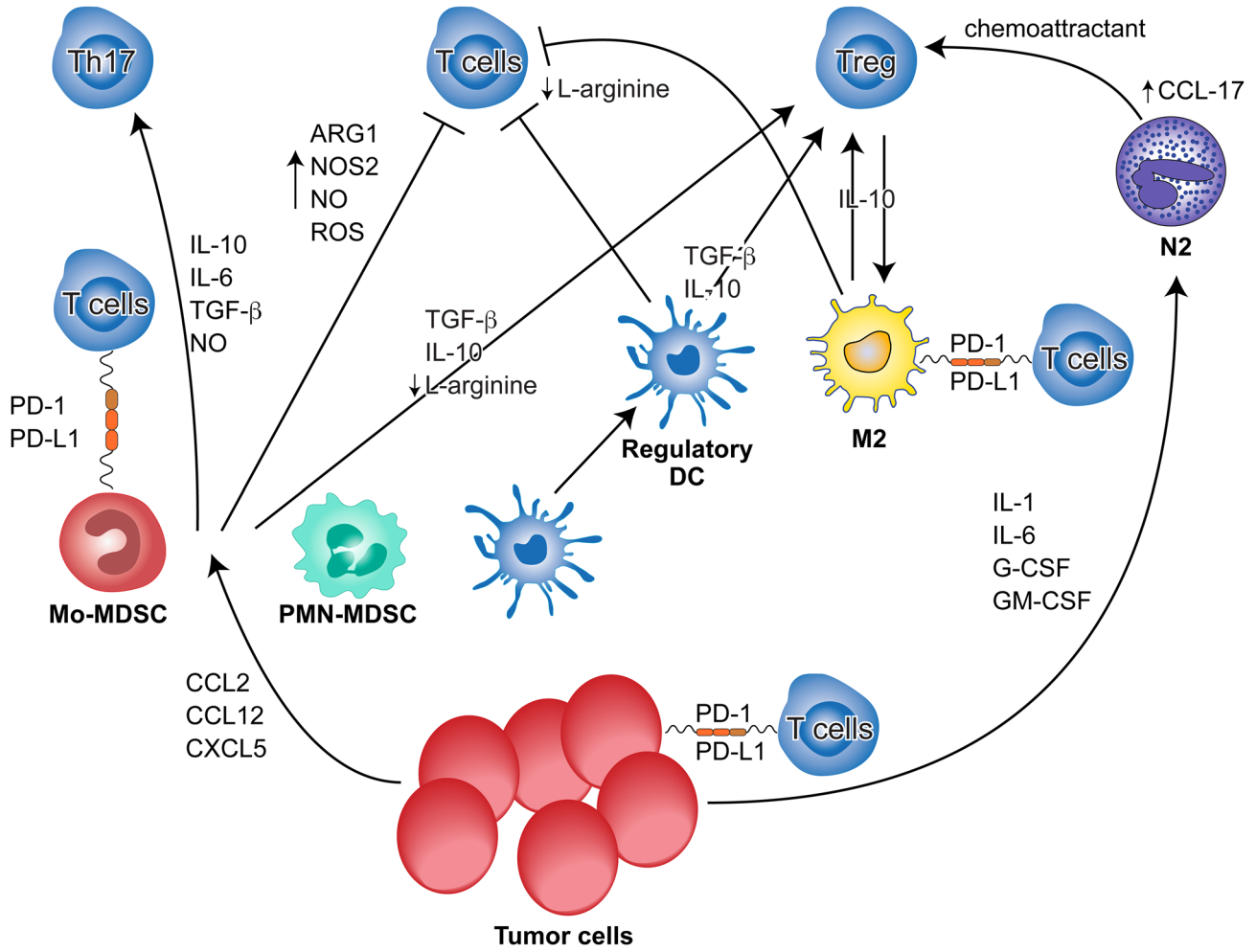

Fig. 2 Effects of tumor cells on MRC subsets and that of MRCs on T cell subpopulations in cancer. *M2* M2 macrophages, *N2* N2 tumor-associated neutrophils, *Mo-MDSC* monocytic myeloid-derived suppressor cells, *PMN-MDSC* polymorphonuclear MDSC, *DC* dendritic cells, *Treg* regulatory T cells

Monocytes and macrophages

Macrophages reside in every tissue and perform, under homeostatic conditions, crucial housekeeping functions. Tissue-resident macrophages seed the organs pre-birth from embryonal precursors and are maintained throughout life with a variable contribution of monocytes depending on the organ [7]. Although monocytes were traditionally considered to comprise the main source of tissue macrophages [8] it is now known that many of the tissue-resident macrophages are of embryonic origin, derived either directly from progenitors of the yolk-sac or the fetal liver [7, 9, 10]. Monocytes appear to adopt the phenotype of tissue-resident macrophages if the correct niche is available [11]. In tumors, macrophages can be abundant and contribute to angiogenesis, immunosuppression and metastasis; therefore, their enrichment is correlated with a worse clinical prognosis [12].

In multiple mouse tumor models, the majority of TAMs were shown to derive from classical Ly6C^{hi} monocytes and is continuously replaced via monocyte recruitment [13]. Although the spleen may be a source of monocyte precursors, the largest fraction of TAM originates from the bone marrow [14]. However, in the spontaneous MMTV-PyMT and MMTV-Neu breast cancer models, the TAM pools are maintained through in situ proliferation of tissue-resident cells [15]. Moreover, tissue-resident microglia can contribute to the environment of brain tumors, and embryonic pancreatic macrophages are crucial tumor-promoting cells in pancreatic ductal adenocarcinoma, besides monocyte-derived cells [16–18]. It has been demonstrated that monocytes entering the hypoxic tumor microenvironment turn into potent MDSCs followed by the differentiation into TAMs under the influence of hypoxia [19]. Importantly, hypoxia could determine the protumoral activity of TAMs [20], and preventing TAM from migrating into hypoxic areas resulted

in a reduced tumor growth [21]. This monocyte/MDSC-macrophage differentiation in tumors and their acquisition of tumor-promoting functions was reported to be supported by macrophage colony stimulating factor (M-CSF) [22].

Many papers proposed to test the MHC class-II expression to define distinct TAM subsets (MHC-II^{lo} versus MHC-II^{hi}) [13, 23]. In this respect, MHC-II^{lo} TAM resemble M2 macrophages and are superior in suppressing T-cell activity and angiogenic activity, whereas MHC-II^{hi} TAM are more M1-like and more permissive to anti-tumor immunity [13, 18]. On the other side, monocytes were shown to differentiate in tumors into MHC-II^{hi}CD11c^{hi} (Tip)-DC that produced TNF and NO, captured antigens but suppress T cell functions [24]. Furthermore, TAM may hamper the stimulatory capacity of conventional DC and T cells through IL-10 production [23, 25].

Besides influencing primary tumor growth, macrophages are known to influence the dissemination of cancer cells to distant organs. Perivascular Tie2^{hi} macrophages cause transient vascular permeability and cancer cell intravasation through the VEGF secretion [26]. Macrophages were shown in preclinical tumor models to contribute to metastasis establishment. For example, lung metastasis of breast cancer cells critically depends on the recruitment of Ly6C^{hi} monocytes via the chemokine (C–C motif) ligand (CCL) 2; upon CCL2 triggering, monocytes produced CCL3, entrapping them at the metastatic site through interaction with C–C chemokine receptor (CCR) 1 [27]. Once retained in the lung, these metastasis-associated macrophages self-maintain via the autocrine production of M-CSF under the influence of Flt1 (VEGFR1) signaling [28]. Importantly, macrophages contribute to the preparation of the metastatic niche even before cancer cells reach the target organ. Thus, macrophage-secreted granulin was reported to induce liver fibrosis, supporting pancreatic cancer metastasis to this organ [29]. In addition, liver-tropic metastatic cells could secrete exosomes that induce the acquisition of pro-metastatic properties by liver macrophages [30].

Numerous clinical studies indicated that the expansion of circulating monocytes and increased macrophage numbers in the tumor microenvironment was adversely correlated with the clinical outcomes in many human cancers [31–35]. It was shown that the survival of cancer stem cells could be supported by TAMs [36]. Furthermore, TAMs were shown to be involved in the reduced responsiveness of different cancers to standard chemotherapy [37, 38]. Moreover, different soluble factors secreted by TAMs in the tumor microenvironment such as epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)-β, could affect the proliferation of cancer cells [39]. TAMs were also described to promote tumor growth by supporting neoangiogenesis due to their ability to secrete a number of angiogenic factors such as VEGF, platelet-derived growth factor (PDGF), placenta growth factor (PLGF), C–X–C motif chemokine ligand (CXCL) 8, FGF, and matrix metalloproteinases (MMPs) [40]. The subpopulation of TAMs contributing to angiogenesis was reported to be derived from Tie-2 expressing monocytes that could exert tumor-supporting effects in various human cancers [41, 42].

On the other side, monocytes and TAMs could promote metastasis independently of the induction of neovascularization. It has been shown that TAMs enhance the motility of breast cancer [43] and hepatocellular carcinoma cells [44]. The release of EGF as well as MMPs, which degrade extracellular matrix and augment the invasiveness of tumor cells, were reported among the underlying mechanisms of the pro-metastatic effect of TAMs [27, 45]. Moreover, TAMs have been reported to be involved in the formation of the pre-metastatic niches at the site of metastases [46].

Immunosuppressive properties of TAMs and their contribution to the immune escape of malignant cells are well documented. These cells have been reported to inhibit T cell activity both directly via PD-1/PD-L1 signaling [47] and indirectly by the upregulation of Treg functions [48]. Furthermore, TAMs infiltrating Hodgkin's lymphoma promoted the induction of Th17 responses or immunosuppression via the expression of TGF-β and IL-10 [49]. In addition, in EBV-associated nasopharyngeal carcinoma, TAMs were described to express the enzyme IDO, resulting in T cell inhibition via tryptophan depletion [50]. In addition, TAMs could attract other myeloid cell populations with immunosuppressive properties such as MDSCs that led to further inhibition of anti-tumor immune responses [51, 52].

Since TAMs were considered to support tumor progression, strategies aimed to target macrophage recruitment and monocyte–macrophage differentiation as well as to reprogram TAM into anti-tumoral M1-like cells were developed to normalize the tumor vasculature, to increase an anti-tumor reactivity of T cells and to exert direct anti-tumor cytotoxic effects [53] (Table 1).

Neutrophils

Neutrophils, the most abundant myeloid blood cells, play a crucial role in inflammation-driven tumorigenesis. Only recently, it has been recognized that neutrophils are not a homogeneous cell population and that their differentiation and phenotype could be modulated by the tumor milieu, resulting in diverse phenotypic and functional states [54–56]. Neutrophils in tumor-bearing hosts have been shown to exert contradictory functional activities, leading to potentiation or inhibition of cancer progression. Anti-tumor N1 neutrophils have a hypersegmented nucleus typical for mature neutrophils, while pro-tumor N2 population consist

Table 1 Targeting of monocytes/macrophages

Target	Drug	Mechanism of action	Therapeutic indication
Anti-CCL2 antibody	Carlumab	Inhibition of recruitment and differentiation of macrophages	Metastatic castration-resistant prostate cancer (CNTO 888) Advanced solid tumor (NCT01204996)
CCR2 antagonist	PF-04136309	Inhibition of recruitment of macrophages	Pancreatic ductal adenocarcinoma (NCT01413022)
CCR5 antagonist	Maraviroc	Inhibition of recruitment of macrophages	Advanced stage CRC
Anti-CSF-1R antibody	Emactuzumab (RG7155)	Inhibition of differentiation and recruitment macrophages	Diffuse-type tenosynovial giant-cell tumor
CSF-1R inhibitor	BLZ945	Inhibition of macrophage differentiation and recruitment	Glioblastoma multiforme
Anti-CSF-1R antibody	AFS98	Inhibition of macrophage differentiation and recruitment	Breast carcinoma
CSF-1R inhibitor	GW2580	Inhibition of macrophage differentiation and recruitment	Ovarian cancer
Macrophages	Clodronate in liposomes	Induction of apoptosis in macrophages	Breast and prostate cancer with bone metastasis
Anti-CD47 antibody	Hu5F9-G4	Induction of apoptosis in macrophages	Solid tumors
Macrophages	Trabectedin	Inhibition of survival and killing of macrophages	Ovarian cancer
TAM	IFN-γ	Reprogramming of TAM towards an anti-tumor phenotype	Ovarian cancer
Anti-CD40 agonist antibody	CP-870,893	Reprogramming of TAM towards an anti-tumor phenotype	Advanced stage pancreatic cancer

of cells with immature-banded nuclei [57]. It is not clear yet if diverse tumor-associated neutrophils (TANs) are different neutrophil subpopulations or rather flexible and dynamic cells that change their activity due to environmental cues. Furthermore, the differentiation between N2 TANs and PMN-MDSCs in the tumor is difficult due to overlapping phenotypic and functional properties of these closely related granulocytic subpopulations.

In a tumor situation, the number of circulating neutrophils continuously increases with tumor progression, possibly due to elevated emergency myelopoiesis [58]. It has been recently proposed that upon cancer pressure, extramedullary granulopoiesis occurred in the spleen that became a site of production and a reservoir of TANs [59]. Neutrophil migration into tissues and tumors is induced by specific chemokines (e.g., CXCL1, CXCL2 or CXCL4), cytokines (e.g., TNF-α and IFN-γ) and cell adhesion molecules [e.g., lymphocyte function associated antigen (LFA)-1 and macrophage (Mac)-1 antigen] [60–62]. The primary tumor milieu influences migratory capacities of neutrophils that accumulate in certain organs and form a pre-metastatic niche [63–65]. Neutrophils can accumulate in large numbers in pre-metastatic organs and release factors attracting tumor cells and facilitating their proliferation such as BV8, S100A8 and S100A9 [64]. Moreover, neutrophils support the seeding of tumor cells in secondary target organs by the release of neutrophil extracellular traps [66] or by the establishment of an immunosuppressive environment in target organs [67]. Conversely, neutrophils may acquire a cytotoxic phenotype-limiting metastatic seeding [64, 68].

Neutrophils represent a significant portion of tumor-infiltrating myeloid cells. TANs differ significantly from their blood counterparts as their activation and tissue association seem to be strongly dependent on the tumor milieu. TANs were reported to exert pro- or anti-tumor effects, depending on cytokines available in the tumor microenvironment (e.g., TGF-β or IFNs) [64, 65, 69, 70]. TANs were shown to produce pro-angiogenic and proteolytic factors that support tumor angiogenesis such as VEGF or MMP9 [61]. They were also implicated in promoting tumor growth via matrix degradation, and by the stimulation of tumor cell proliferation, survival and metastasis [64, 65]. Furthermore, neutrophils were shown to recruit other cells to the tumor, suppressing adaptive immune responses [71, 72].

On the other hand, neutrophils were described to have anti-tumor properties, including the capacity to kill tumor cells via direct or antibody-dependent cell cytotoxicity [73, 74] or by boosting T cell-mediated anti-tumor responses [57, 75]. Furthermore, neutrophils could enhance the efficiency of some immunotherapies. They favored photodynamic therapy-induced CD8 T cell activation [76], promoted T cell recruitment and improved the efficacy of BCG immunotherapy of bladder cancer [77], and exerted cytotoxicity under

immunotherapy with tumor-specific monoclonal antibodies in melanoma and breast cancer [78].

Data regarding neutrophils in cancer patients are very scarce, and their nature and function in the tumor microenvironment are largely unknown. The lack of sizeable biopsy samples together with the poor characterization of appropriate functional and phenotypic markers for the myeloid subsets in patients are major issues to be resolved. Gene signatures from over 10,000 cancer biopsies demonstrated the presence of neutrophils in over 30 solid malignancies [79]. Strikingly, neutrophil signatures emerged as the most significant adverse cancer-wide prognostic population [79]. This is consistent with the growing number of studies that link high levels of intra-tumoral neutrophils to poor clinical outcome [80].

The main mechanisms of pro-tumoral functions of human circulating neutrophils are associated with their immunosuppressive and angiogenic properties [81]. The immunosuppressive mechanisms include production of arginase-1 (Arg-1), reactive oxygen and nitrogen species to impair T cell activation and proliferation [82, 83]. Neutrophils have also been shown to be important sources of VEGF and MMP9 [84].

As in mouse models, the protective effect of neutrophils was shown in patients undergoing therapy. For example, higher TAN density in colorectal cancer was associated with better response to 5-FU-based chemotherapy [85]. Moreover, the administration of IFN-α in chronic myeloid leukemia and melanoma patients stimulated the release of TRAIL by neutrophils, inducing apoptosis of TRAIL-sensitive cancer cells [86].

Circulating blood neutrophils may be separated using a density gradient into normal neutrophils (called high density, HDNs or normal density, NDNs) and low-density LDNs, co-separated in the mononuclear fraction. Of note, there is no clear immunotype that fits LDNs or HDNs since they often share the same surface markers and functions. Nevertheless, LDNs are enriched for immature cells and activated neutrophils compared with HDN [87, 88]. Neutrophils were found to be accumulated in the peripheral blood of patients with various types of cancer, especially in advanced stages [89, 90]. Furthermore, neutrophilia was reported to be associated with poor prognosis in many tumors such as bronchoalveolar carcinoma [91] and metastatic melanoma [89]. A high neutrophil to lymphocyte ratio (NLR) caused by tumor-induced neutrophilia and lymphocyte apoptosis is a robust marker of poor clinical outcome in cancer patients. The NLR has been validated as an independent prognostic factor in a variety of tumor types [92].

There is still little information on tumor-infiltrating neutrophils and their clinical relevance is only beginning to emerge. Nevertheless, TANs were demonstrated to be associated with poor clinical outcome in patients with renal cancer [93], non-small-cell lung carcinoma [94] and melanoma [95]. It has been reported that the enrichment of TANs was associated with metastases in various tumor entities and they were suggested to be involved in metastatic process [96]. Neutrophils infiltrating bronchoalveolar and cholangiocellular carcinoma have been shown to produce hepatocyte growth factor (HGF), enhancing the invasive capacity of cancer cells [97]. The recruitment of neutrophils within the tumor microenvironment relies on several chemokines, including but not limited to, CXCL8/IL-8, CXCL5 and macrophage migration inhibitory factor [54–56, 88]. Therefore, most of therapeutic strategies to target neutrophils in tumor-bearing hosts are dealing with the blocking of their migration into the tumor site (Table 2).

Myeloid-derived suppressor cells

One of the important consequences of chronic inflammatory conditions typical for the tumor microenvironment is the generation and accumulation of immunosuppressive myeloid cells designated as MDSCs [98–103]. These cells were shown to exert a strong capacity to inhibit anti-tumor functions of T and NK cells [99, 102–107]. Numerous studies indicated that a variety of inflammatory factors produced by tumor and host cells, including IFN-γ, IL-1β, prostaglandin E2, IL-6, IL-10, IL-13, COX-2, TGF-β,

Table 2 Targeting of neutrophils

Target	Drug	Mechanism of action	Therapeutic indication
CXCR1 and CXCR2 inhibitor	Reparixin	Inhibition of neutrophil migration into the tumor	Triple-negative breast cancer (NCT02370238) HER2-negative metastatic breast cancer (NCT02001974)
G-CSF	Anti-G-CSF antibodies	Inhibition of neutrophil mobilization and angiogenesis	Pancreatic adenocarcinoma
TGF-β receptor inhibitor	Galunisertib (LY2157299 monohydrate)	N2–N1 shift	Glioma

complement component C5a, VEGF, G-CSF, M-CSF, GM-CSF, MMP-9, CCL2, CCL3, CCL4, CCL5, S100A8, S100A9, etc. were involved in MDSC enrichment and activation [99–102, 108]. Most of these factors use STAT3 and janus kinase signaling pathways that trigger signals for cell survival, proliferation, differentiation and apoptosis [99, 103, 108].

MDSCs represent a heterogeneous population of myeloid cells with a strong immunosuppressive capacity [99, 102, 105, 106]. In humans, PMN-MDSCs can be recognized as $CD11b^+$ or $CD33^+$, $CD15^+$ or $CD66b^+$, and $CD14^-$ while M-MDSCs are $CD11b^+$ or $CD33^+$, $CD14^+$, and HLA-DR^{low} cells; Lin^- (including CD3, CD14, CD15, CD19, and CD56) HLA-DR^-CD33^+ cells are considered as early stage (e) MDSC [103]. Mouse MDSCs are characterized by Gr1 and CD11b expression and contain three subsets: PMN-MDSC characterized as $CD11b^+Ly6G^+Ly6C^{low}$, M-MDSCs as $CD11b^+Ly6G^-Ly6C^{high}$, as well as non-PMN-MDSCs and non-M-MDSCs defined as $CD11b^+Ly6G^{med}Ly6C^{med}$ cells [103].

MDSC subpopulations effectively inhibit T lymphocyte activity through various mechanisms, including the upregulation of Arg-1 expression that is responsible for arginine depletion; stimulation of inducible NO synthase (iNOS), leading to the production of NO; secretion of reactive nitrogen and oxygen species; activation of IDO, resulting in tryptophan depletion; upregulation of PD-L1 expression. Furthermore, MDSCs produce high levels of immunosuppressive cytokines such as IL-10 and TGF-β [99, 102, 103, 108, 109]. Interestingly, M-MDSCs mediate immunosuppression mainly via NO, whereas PMN-MDSCs produce large amounts of ROS and express high levels of Arg-1. However, both subsets could use common immunosuppressive molecules such as PD-L1, IL-10 and TGF-β [87, 102, 103, 108, 109]. In addition, murine non-PMN- and non-M-MDSCs could also possess immunosuppressive functions mainly via IL-10 [110]. A recent study directly compared the immunosuppressive capacity and clinical relevance of the three human circulating MDSC subsets and identified mature PMN-MDSCs as dominant inhibitors of T cell functions mediated by Arg-1 [111].

For a detailed critical review of MDSC-T cell functional interactions, we refer the reader to the companion review by Bruger et al. [6] in this symposium-in-writing series.

In addition to the direct T cell inhibition, MDSCs are able to induce and recruit Treg via TGF-β and IL-10 production and CD40-CD40L signaling [112, 113]. Moreover, MDSCs may induce Th17 cell polarization from naive $CD4^+$ T cells through the production of IL-1β, IL-6, IL-23 and NO [114]. On the other hand, IL-17 produced by Th17 cells was shown to upregulate the expression of Arg-1, IDO and COX-2 in a mouse breast cancer model, boosting thereby the immunosuppressive activity of MDSCs [115].

In tumors, MDSC suppress effector T cells not only directly but also by the generation of M2 TAMs and N2 TANs. As a result of this cross talk, IL-10 produced by MDSC not only inhibits IL-12 and TNF-α but also stimulates IL-10 production in macrophages that in turn enhances the release of IL-10 by MDSCs [51, 52]. Tumor-infiltrating MDSCs could also directly differentiate into potent immunosuppressive TAMs [116]. Furthermore, TGF-β secreted by tumor stroma cells, including MDSCs [99, 102], was reported to convert neutrophils into N2 TANs producing CCL17, a well-known chemoattractant for Treg [57]. Similar to M2 TAMs, MDSCs were shown to inhibit IL-12 and induce IL-10 production by DC [117]. Moreover, MDSC-derived VEGF and IL-10 could downregulate the expression of MHC class II and co-stimulatory molecules on DC via activation of STAT3 [118]. In addition, the antigen uptake by DC was found to be diminished in the presence of MDSCs [119]. This results in the inhibition of the DC capacity to stimulate T cell-mediated anti-tumor immune responses.

Numerous studies reported on the accumulation of highly immunosuppressive MDSCs in patients with various tumors, including hepatocellular carcinoma, melanoma, prostate cancer, bladder cancer, non-small cell lung cancer, head and neck squamous cell carcinoma as well as breast, gastric and colorectal cancer, which indicates the clinical significance of these cells [105, 118, 120–125]. Interestingly, HLA-$DR^-CD33^+CD11b^+CD14^+$ M-MDSCs were also detected in patients with EBV-associated lymphoid tumor, the extranodal natural killer NK/T cell lymphoma, which can develop after chronic active Epstein–Barr virus (EBV) infection [126]. In another EBV-associated tumor, nasopharyngeal carcinoma, an expansion of $CD33^+$ MDSCs was found to be due to a latent membrane protein-1 in tumor cells that could induce the production of IL-1β, IL-6 and GM-CSF critical for MDSC generation [127]. An increased MDSC frequency in the peripheral blood was found to correlate with tumor progression and worse clinical outcome in patients with different tumors [105, 118, 120, 122, 123, 128, 129]. Moreover, several publications described that the decreased frequency and immunosuppressive function of both M- and PMN-MDSCs correlated with beneficial therapeutic effects in cancer patients treated with the negative immune checkpoint inhibitors [122, 130, 131].

Besides immunosuppressive functions, MDSCs may contribute to the remodeling of the tumor microenvironment by producing VEGF, FGF and MMPs. These factors stimulate tumor neoangiogenesis as well as cancer cell motility and invasion [106, 107]. Interestingly, MDSCs were reported to transdifferentiate towards endothelial cells contributing to tumor angiogenesis [132]. Moreover, TGF-β, HGF, and EGF produced by tumor-infiltrating MDSCs were found to contribute to cancer-associated epithelial to mesenchymal transition [133].

Given a critical role of MDSC in tumor progression, several strategies to neutralize these cells were developed, including (1) prevention of MDSC generation; (2) MDSC depletion or blocking their expansion and activation; (3) inhibition of MDSC recruitment; and (4) blocking MDSC immunosuppressive function [102, 106, 109, 134–136] (Table 3).

Dendritic cells

DCs can be divided into myeloid and plasmacytoid DCs. In mice, myeloid DCs could be further subdivided in classical type I DCs (cDC1) ($CD11c^+/CD8\alpha^+$) and type 2 DCs (cDC2) ($CD11c^+/CD11b^+$) cells [137]. The cDC1, which in tissues express CD103, can efficiently cross-present antigens to $CD8^+$ T cells, while $CD11b^+$ DCs mainly present antigens on MHC class II to $CD4^+$ T cells [138]. Besides these classical DC subsets, monocytes and M-MDSCs can also contribute to the pool of tumor-infiltrating DCs by differentiating into inflammatory DCs [139]. In mice, these cells can be identified as $MHC\text{-}II^+/CD11b^+/CD11c^+/F4/80^+/Ly6C^+$ and also express CD64 and FcεRI, which can be used to distinguish inflammatory DCs from classical DCs and macrophages [139]. Studying the composition of myeloid DCs in different tumor models, Laoui et al. [24] demonstrated that $CD103^+$ DCs were generally the smallest subset, whereas $CD11b^+$ cDC2 were always well represented. Interestingly, the number of monocyte-derived/inflammatory DCs varies widely in different tumor models [24].

Depending on the factors in the tumor microenvironment, myeloid DC subsets can either contribute to effective antitumor responses or show a more immature and/or regulatory phenotype. The presence of IL-10, IL-6 and VEGF in the tumor microenvironment induces prolonged STAT3 activation in DCs [140]. This limits DC maturation and IL-12 production and induces the production of the immunosuppressive cytokine IL-10. Furthermore, tumor-derived TLR2 ligands were found to stimulate an autocrine secretion of IL-10 and IL-6 by DCs and to enhance expression of the

Table 3 Targeting of MDSCs

Target	Drug	Mechanism of action	Therapeutic indication
iNOS inhibitors	Phosphodiesterase-5 (PDE-5) inhibitors: tadalafil, sildenafil, nitro-aspirin	Inhibition of MDSC function	Multiple myeloma (NCT01374217) Head and neck cancer (NCT00843635) Non-small cell lung carcinoma (NCT00752115) Pancreatic cancer (NCT01342224) Colorectal cancer (NCT00331786)
Arginase inhibitors	Celecoxib, *N*-hydroxy-L-Arginine (NOHA), N(G)-Nitro-L-Arginine, Methyl Ester (L-NAME)	Inhibition of MDSC function	Colon cancer
ROS inhibitors	Bardoxolone methyl (CDDO-Me)	Inhibition of MDSC function	Pancreatic cancer (RTA 402-C-0702)
Anti-glycan antibodies	Receptor for Advanced glycation end products (RAGE)	Inhibition of MDSC migration	Colon cancer
CSF-1R inhibitor	GW2580	Inhibition of MDSC migration	Prostate cancer
Retinoid-activated transcriptional regulators	All-trans retinoic acid	Promotion of MDSC maturation	Renal cell carcinoma Lung adenocarcinoma Small cell lung cancer
Triterpenoids	RTA 408	Promotion of MDSC maturation	Melanoma
Vitamins	25-hydroxy-vitamin D	Promotion of MDSC maturation	Head and neck cancer
MMP9	Biphosphonates	Inhibition of MDSC generation	Pancreatic cancer
STAT3	Cucurbitacin B (CuB) STAT3 DECOY AZD9150 Sunitinib	Inhibition of MDSC generation	Advanced lung cancer Head and neck cancer Advanced hepatocellular carcinoma
Unknown	Cisplatin 5-Fluorouracil Paclitaxel	MDSC depletion	Bronchoalveolar carcinoma Lewis lung carcinoma
IL-6R	Gemcitabine	MDSC depletion	Lung cancer
CCR5	Soluble fusion protein mCCR5-Ig	MDSC depletion	Melanoma
BRAF inhibitors	Vemurafenib	MDSC depletion	Melanoma
Fas ligand	IL-2 and anti-CD40 agonistic antibody	MDSC depletion	Renal adenocarcinoma
CTLA-4	Ipilimumab	MDSC depletion	Melanoma

corresponding cytokine receptors, thus boosting STAT3 activation and DC dysfunction [141]. In addition to these cytokines, TGF-β and other immunoregulatory agents such as prostaglandins, lactic acid, adenosine, galectins and mucins were reported to play a role in the induction of immunosuppressive DCs [140, 142].

The accumulation of lipids in DCs could further contribute to their dysfunction in the tumor microenvironment [143, 144]. Lipid-loaded DCs did not differ in the expression of MHC or co-stimulatory molecules but had a reduced capacity to process antigens. Tumor-infiltrating DCs displayed the highest levels of lipids. In the spleen of tumor-bearing mice, increased lipid levels could be detected in both cDC1 and cDC2. The presence of oxidized lipids was also shown to inhibit cross-presentation [144].

Although immunosuppressive DCs displayed no unique markers, they often showed a reduced expression of maturation markers (CD80, CD86) and/or increased expression of inhibitory receptors such as PD-L1 and immunoglobulin-like transcripts (ILTs), limiting T cell activation. It has been reported that monocyte-derived DCs exhibited regulatory properties with increased iNOS expression and IL-10 to IL-12 ratio, resulting in the inhibition of $CD4^+$ and $CD8^+$ T cell proliferation in a lung carcinoma model [24].

Tumor-infiltrating DCs were reported to activate anti-tumor functions of other myeloid cells by producing IFN-β that induced anti-tumor polarization of TANs [145]. This type I IFN response was largely dependent on tumor-infiltrating myeloid DCs in multiple tumor models, and was induced via the STING pathway, through the recognition of tumor DNA [146, 147]. Moreover, IFN-β reduced the accumulation of proangiogenic TANs by influencing the expression of CXCR2 and its ligands CXCL1, CXCL2 and CXCL5 [60, 61]. In addition, Type I IFNs have been shown to induce MDSC maturation and reduce their immunosuppressive activity [148]. Importantly, IFNs were also demonstrated to inhibit the recruitment of TAMs [149].

IL-12 production by mature DCs can also broadly affect MRCs, reversing the suppressive function of MDSCs [150] and TAMs [151]. Furthermore, IL-12 is known as a potent inducer of IFN-γ production by T cells and NK cells. However, tumor-infiltrating DCs often show a regulatory/dysfunctional phenotype with low levels of IL-12 and increased IL-10 and TGFβ production, leading to an enhanced suppressive function of MRCs rather than enforcing their immune stimulatory activity. These immunosuppressive cytokines can support the development of pro-tumoral macrophages and neutrophils [57, 152, 153]. Tumor-infiltrating regulatory DCs also produced significantly higher levels of the chemokines CCL2, CCL4 and CXCL1, attracting monocytes and neutrophils as compared to other DC populations [24]. In this way, regulatory DCs could sustain the immunosuppressive tumor microenvironment created together with the other MRCs. Therefore, it is crucial to interrupt this vicious cycle of immunosuppression for effective anti-tumor immunotherapy.

Intratumoral DCs mainly affect the tumor progression or regression via an activation or inhibition of T cells and NK cells or induction of Treg. It has been recently demonstrated that tumor-infiltrating $CD103^+$ cDC1 could not only induce an antigen cross-presentation to $CD8^+$ T cells, but also support the T cell recruitment into the tumor [154]. However, when intratumoral DCs gain regulatory functions they are not able to efficiently activate T cells but can rather counteract T cell functions, protecting tumor cells from immune-mediated killing [155].

Similar to mouse-circulating myeloid DCs, their human counterparts could be divided into two main subsets: $CD141^+$ ($BDCA3^+$) cDC1 (so-called cross-presenting subset) and $CD1c^+$ ($BDCA1^+$) cDC2 [137, 138]. In addition to these classical DC subsets, monocyte-derived "inflammatory DCs" could also be found under inflammatory conditions in humans. They express HLA-DR, CD11c, BDCA1, CD1a, FcεRI, CD206, CD172a, CD14 and CD11b markers [138]. The presence of these DC subsets has been described in different human tumors, including lung and colorectal cancer [138]. As suggested from mouse studies, the accumulation of cDC1 was found to correlate with better clinical outcome in patients with various tumors [156, 157].

Most factors known to trigger regulatory DCs in mice have also been shown to induce a regulatory phenotype in human DCs in vitro. Indeed, tumor cell-conditioned medium could stimulate STAT3 activation, limit DC maturation, decrease IL-12 to IL-10 ratio and increase lipid levels in human monocyte-derived DCs [140, 143, 158, 159]. Therefore, one of the critical questions to address is how to prevent the detrimental effects of the tumor microenvironment on DC function in cancer patients. To this end, both small-molecule inhibitors and antibodies targeting DCs are currently under investigation to block their tolerogenic capacities and activate their immunostimulatory functions to increase the efficiency of tumor immunotherapy [160, 161] (Table 4). An additional novel strategy to target all abovementioned subsets of MRCs in cancer involves vaccination against immunosuppressive proteins expressed by these cells, e.g., IDO or Arg-1 [162].

Conclusion

In the current review that is a part of a symposium-in-writing on MRCs generated following the MYE-EUNITER COST action, we combined the knowledge of many researchers in the field, and described the effects and importance of MRCs in the development and progression of cancer. The myeloid immune system, affected by powerful influences from the

Table 4 Targeting of DCs

Target	Drug	Mechanism of action	Therapeutic indication
Anti-PD-1 antibody	Nivolumab, pembrolizumab	Enhancement of T cell activation	Advanced melanoma Non-small cell lung cancer castration-resistant prostate cancer Renal cell carcinoma Colorectal cancer
Anti-Tim-3 antibody	Anti-Tim-3 antibodies	Enhancement of T cell proliferation	Hepatocellular Carcinoma

tumor and stroma, becomes a crucial player in determining the fate of cancer cells and metastases. As we have shown, all the different types of myeloid cells, i.e., monocytes and macrophages, neutrophils, MDSCs and DCs can have both supportive and detrimental roles in cancer, and their regulation is a potential key target in future anti-cancer therapeutics. The understanding of the regulatory effects of these cells has grown tremendously during the last decade, and it is now clear that these cells are important players that should be explored and targeted in the battle to conquer cancer.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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