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Tumor Microenvironment and Myeloid-Derived Suppressor Cells

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Abstract Tumor progression has been demonstrated to be supported by chronic inflammatory conditions developed in the tumor microenvironment and characterized by the long-term secretion of various inflammatory soluble factors (including cytokines, chemokines, growth factors, reactive oxygen and nitrogen species, prostaglandins etc.) and strong leukocyte infiltration. Among leukocytes infiltrating tumors, myeloid-derived suppressor cells (MDSCs) represent one of the most important players mediating immunosuppression. These cells may not only strongly inhibit an anti-tumor immune reactions mediated by T cells but also directly stimulate tumorigenesis, tumor growth and metastasis by enhancing neoangiogenesis and creating a suitable environment for the metastatic formation. This review provides an overview of interactions between MDSCs and tumor cells leading to MDSC generation, activation and migration to the tumor site, where they can strongly enhance tumor progression. Better understanding of the MDSC-tumor interplay is critical for the development of new strategies of tumor immunotherapy.

Keywords Myeloid-derived suppressor cells · Cancer · Immunosuppression · Tumor microenvironment · Chronic inflammatory factors · Tumorigenesis

Abbreviations

MDSCs	myeloid-derived suppressor cells
VEGF	vascular endothelial growth factor
TGF	transforming growth factor
IL	interleukin
Tregs	regulatory T cells
TAMs	tumor-associated macrophages
DCs	dendritic cells
STAT	signal transducer and activator of transcription
iNOS	inducible nitric oxide synthase
ARG	arginase
NO	nitric oxide
ROS	reactive oxygen species
TCR	T cell receptor
TNF	tumor necrosis factor
IFN	interferon
GM-CSF	granulocyte-macrophage colony-stimulating factor
G-CSF	granulocyte colony-stimulating factor
M-CSF	macrophage colony-stimulating factor
CCL	chemokine C-C motif ligand
COX	cyclooxygenase
PGE2	prostaglandin E2
SCF	stem cell factor
ATRA	all-trans-retinoic acid

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Introduction

It has been well-documented in the recent decade that various tumors were able to exert immunogenic properties inducing strong anti-tumor immune reactions, in which T cells were shown to play a key role [1–3]. Numerous publications revealed a strong correlation between an infiltration of tumor lesions in cancer patients with T lymphocytes and better clinical outcome [3–5]. Moreover, an identification of large numbers of cancer-associated antigens stimulated numerous clinical trials in patients with different tumor types using i) vaccination with tumor-specific peptides, proteins, DNA encoding these proteins or dendritic cells

loaded with tumor-derived peptides [6, 7] as well as ii) adoptive transfer of tumor-specific activated T cells [8]. However, despite great expectations and some promising results, the overall results of these trials are largely disappointing.

Such situation seems to be due to the immune escape of tumors mediated by different mechanisms dealing with structural and functional changes both in tumor and stroma cells, leading finally to the inability of even activated effector immune cells to reject the tumor. These mechanisms were reported to include on the side of tumor cells i) the down-regulation or complete loss of MHC class I molecules [9, 10], ii) structural alterations of the antigen processing machinery components related to the changes in the expression of oncogenes, tumor suppressor genes and members of signal transduction pathways [11], iii) down-regulation in the expression of tumor-associated antigens and the lack of danger signals needed for the activation of antigen-presenting cells [12], and iv) an intensive secretion of immunosuppressive factors such as vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β, interleukin (IL)-10, reactive oxygen and nitrogen species or prostaglandins [13, 14].

The contribution of stroma cells in the immune escape, which has been intensively studied in the last decade is represented by a rapid recruitment, expansion and activation of various immunosuppressive cells of lymphoid and myeloid origin in the tumor microenvironment including regulatory T cells (Tregs) [15, 16], tumor-associated M2 macrophages (TAMs) [17], Tie2-expressing monocytes [18], N2 neutrophiles [19], regulatory/tolerogenic dendritic cells (DCs) [20] and myeloid-derived suppressor cells (MDSCs) [21–23]. The latter extremely heterogeneous population of immature myeloid cells representing precursors of granulocytes, macrophages, and DCs has recently attracted much attention as one of the key cells promoting tumor progression and creating immunosuppressive tumor microenvironment. In this review, we will focus on the interaction between MDSCs and tumor cells as well as on the checkpoints of such interaction, which could be applied as potential therapeutic targets.

General Characteristic of MDSCs

MDSCs are immature myeloid cells that fail to complete their differentiation under chronic inflammatory conditions that are typical for the tumor microenvironment [24, 25]. Importantly, these cells acquire strong immunosuppressive functions that allow them to inhibit efficiently T-cell mediated anti-tumor reactivity by various mechanisms [22, 26, 27]. Whereas in mice, MDSCs express Gr1 and CD11b surface markers, the situation with the human counterpart is much more complicated due to the absence of human analog of Gr1. Mouse MDSCs consist of two major subsets: granulocytic $CD11b^{+}Ly6G^{+}Ly6C^{low}$ and monocytic $CD11b^{+}Ly6G^{+/-}Ly6C^{high}$ cells which may differ in their immunosuppressive mechanisms [26, 28, 29]. Among human MDSCs, the same two subsets can be distinguished as $Lin^{-}HLA\text{-}DR^{-}CD33^{+}$ or $CD11b^{+}CD14^{-}CD15^{+}$ for granulocytic and $CD14^{+}HLA\text{-}DR^{neg/lo}$ or $CD11b^{+}CD14^{+}HLA\text{-}DR^{neg/lo}$ for monocytic cells [21, 30, 31]. MDSCs derive from the bone marrow hematopoietic precursors due to the altering of myelopoiesis by chronic inflammatory mediators [24, 25, 32]. Among them are the signal transducer and activator of transcription (STAT) family of factors (STAT3, STAT6 and STAT1), NF-κB as well as S100 calcium-binding proteins A8 (S100A8) and S100A9 that induce a strong activation of inducible nitric oxide synthase (iNOS) and arginase (ARG)-1, the up-regulated production of TGF-β, and the expression of cyclin D1, MYC and survivin [22, 26, 33].

Main mechanisms of MDSC-mediated immunosuppression in tumor-bearing hosts were reported to deal with the inhibition of anti-tumor T-cell reactivity including i) the production of nitric oxide (NO) and reactive oxygen species (ROS) leading to T cell apoptosis, the nitration of chemokines and T cell receptors (TCR) blocking T cell migration and tumor cell killing, and finally resulting in the inhibition of cytokine production that are crucial for T cell anti-tumor functions [21, 22, 34, 35], ii) the induction of the expression of TGF-β1 on cell membrane stimulating anergy of immune effector cells [21, 36], iii) a deprivation of arginine and cysteine which are critically needed for multiple T cell functions [22, 37–39], iv) the reduction of T cell migration to lymph nodes via the down-regulation of L-selectin, a T cell homing marker, leading to the alteration of T cell priming [40], and v) the down-regulation of the expression of TCR ζ-chain disabling T cells to transmit activation signals from the cell membrane [25, 41, 42]. Interestingly, NO produced by MDSC and accumulated in the tumor microenvironment was found to stimulate the development of chemoresistance in tumor cells thorough an inactivation of the caspase cascade [43]. Moreover, it has been demonstrated that MDSCs were able to i) secrete angiogenic factors promoting neoangiogenesis [44], and ii) produce growth factors, matrix metalloproteinases and cytokines directly stimulating tumor growth as well skewing immune responses towards protumoral Th2 type and activation of Tregs [28, 45, 46]. Thus, MDSCs could be considered as playing a critical role in the development of immunosuppressive tumor microenvironment.

How Tumor Induce MDSC Expansion, Recruitment and Activation

It has been reported that chronic inflammatory mediators accumulated in the process of tumor progression could

strongly stimulate the MDSC expansion, migration into tumor lesions and MDSCs and stimulation of their immunosuppressive capacity [21, 22, 24, 25]. Interestingly, chronic inflammation has been shown to provide conditions for MDSC accumulation and stimulation also in the absence of tumor impact [25, 47]. Moreover, neutralization of chronic inflammation has been reported to cause a significant reduction of frequencies and immunosuppressive functions of tumor-infiltrating MDSCs [48–50]. In contrast, if the production of chronic inflammatory factors was stimulated by low-dose cyclophosphamide, MDSC systemic expansion, activation and accumulation in tumor lesions were observed [47, 51].

The above-mentioned chronic inflammatory factors include cytokines like interleukin IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ; growth factors such as VEGF, TGF-β, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and macrophage colony-stimulating factor (M-CSF); chemokines C-C motif ligand (CCL) 2, CCL4, CCL5, C-X-C motif ligand (CXCL) 1, CXCL8, and CXCL12; cyclooxygenase-2 (COX-2) as well as prostaglandin E2 (PGE2) [21, 22, 25, 52]. All these factors exert their effects in combination and in dose-dependent manner. They can affect myeloid cells both directly in tumor lesions and upon transportation to hematopoietic organs by tumor-derived exosomes or in soluble form by skewing the normal myeloid cell differentiation in the favor of MDSCs [22, 26, 53, 54].

Under physiological conditions, GM-CSF drives myelopoiesis, whereas G-CSF and M-CSF induce further differentiation of myeloid cells to granulocytes or macrophages respectively [55]. However, in tumor lesions, all three growth factors have been shown to be overproduced [56, 57]. Tumor-derived GM-CSF has been reported recently to be one of the key factors involved in the generation of MDSC in the dose-dependent manner [58, 59]. Thus, low GM-CSF concentrations without IL-4 caused a robust generation of MDSCs and immature DCs from bone marrow hematopoietic precursor cells in vitro, high concentrations induced the development of neutrophiles and mature DCs. Furthermore, GM-CSF being combined with IL-6, IL-1β, PGE2, TNF-α or VEGF has been shown to mediate the generation of highly suppressive MDSCs in vitro from $CD33^+$ mononuclear cells isolated from the peripheral blood of healthy donors [60].

Interestingly, VEGF and TGF-β have been also demonstrated to regulate the hematopoiesis [61, 62], and being produced at high levels in various tumors could exert a strong impact on the MDSC generation and accumulation [24, 25]. Thus, tumor-derived VEGF has been shown to interfere with the proliferation, differentiation and maturation of immature granulocyte-macrophage progenitors, blocking DC maturation and activation as well as inducing the development of immunosuppressive M2 TAMs and their recruitment to the tumor site [63, 64]. Acting together with VEGF, accumulated in tumor lesions TGF-β was also able to prevent the DC maturation and to polarize myeloid cells differentiation towards immunosuppressive MDSCs and TAMs in the tumor microenvironment [65].

Among various cytokines and chemokines accumulated in the tumor microenvironment, IL-1β has been reported to play a central role in the altering of normal myelopoiesis and generation of immunosuppressive myeloid cells [66, 67]. This cytokine has been demonstrated to stimulate the MDSC generation in the bone marrow and in their migration towards tumor lesions [67, 68]. Moreover, by inducing the COX-2 expression at the tumor site, IL-1β together with PGE2 was shown to inhibit the maturation and immune functions of antigen-presenting cells by mediating an accumulation of MDSCs and TAMs and promoting tumor thereby progression [69, 70]. Furthermore, IL-1β has been found to up-regulate TNF-α concentrations in the tumor microenvironment through induction of the production of latter cytokine by myeloid and/or tumor cells [71, 72]. In addition, IL-1β has been shown to stimulate the production of IL-10, IL-5 and IL-13, which induced type 2 immune reactions and attracted MDSCs to the tumor site [73, 74]. Finally, it has been recently reported that IL-1β could induce and maintain tumor angiogenesis by stimulating the VEGF production [66, 75].

Like IL-1β and TNF-α IFN-γ has been also detected at high levels in various tumors, leading to a continuous activation of myeloid cells and an enhancement of chronic inflammation in situ [25, 40]. All these cytokine were demonstrated to stimulate the production of NO that mediates an MDSC immunosuppressive activity [76].

IL-6 has been reported to be strongly associated with chronic inflammation and cancer [77]. Elevated IL-6 levels have been found to correlate with increased MDSC frequencies and suppressive functions in tumor-bearing hosts [48, 78]. It has been shown that IL-6 mediated the generation, migration and activation of MDSCs via transcription factor STAT3 [26, 33, 79]. In mouse tumor models, inhibition of IL-6 and/or IL-6R resulted in the drastic reduction of tumor infiltrating MDSCs and in the inhibition of tumor progression [80].

The pattern of chemokines involved in the MDSC recruitment to the tumor seems to be dependent on the tumor model and to be specific for the particular MDSC subset. It has been documented that the recruitment of monocytic MDSCs into melanoma and prostate cancer lesions occurred via an interaction between CCL2 and its receptors CCR2, CCR4 and CCR5 [81, 82]. Moreover, melanoma-infiltrating monocytic MDSCs exhibited CCR2-dependent immunosuppressive activities under the conditions of the long-term

production of GM-CSF [81]. The PGE2-driven production of CCL2, CXCL8 (also known as IL-8), and CXCL12 has been reported to induce the MDSC accumulation in ovarian and gastric cancer microenvironment [83, 84]. Other groups underlined a critical role of CXCL-1, CCL5 and CCL7 in the MDSC accumulation in colon and liver tumor lesions [85, 86]. Investigating numerous transplantable tumor mouse models, Sawanobori et al. [87] were able to state that the migration of distinct MDSC subsets into the tumor microenvironment was mediated by different chemokines. The accumulation of monocytic MDSCs has been shown to be driven by CCR2/CCL2 axis, whereas the migration of the granulocytic subset was important regulated by an enhanced production of CXCR2 ligands in the tumor milieu. It is therefore conceivable that the migration of particular MDSC subsets into the tumor site can be strongly determined by the tumor histology and the spectrum of chemokines produced by these tumors.

Using *ret* transgenic mouse model of spontaneous melanoma that mimics human melanoma with respect to tumor growth, metastatic profile, histopathology and expression of melanoma associated antigens [88–90], we have studied the frequencies and activities of $Gr1^+CD11b^+$ MDSCs in melanoma lesions [48]. It has been found a remarkable accumulation of MDSCs in skin tumors and metastatic lymph nodes that significantly correlated with the tumor progression. Importantly, an investigation of inflammatory cytokines, chemokines and growth factors revealed a strong accumulation of VEGF, IL-1β, IL-6, GM-CSF, TNF-α, IFN-γ in tumor lesions [48]. These data indicate that an observed enhanced production of these factors during melanoma progression in *ret* transgenic mice may attract MDSCs into tumor lesions. Furthermore, MDSC enrichment at the site of chronic inflammation has been previously described in the mouse model of chronic inflammation [25]. One of the important consequences of the enhanced MDSC proportion in tumor-bearing hosts could be diminished numbers of mature myeloid cells like DCs [21, 22]. Indeed, we have recently observed a significant decrease in numbers of mature conventional DCs in melanoma lesions and lymphoid organs from *ret* transgenic mice [91].

Accumulated MDSCs were highly activated as reflected by an intensive NO production, and ARG-1 expression associated with a strong capacity to suppress T cell reactivity [22, 28, 37, 38]. One of the major mechanisms of MDSC-mediated T cell inhibition is associated with a remarkable decrease in the expression of TCR ζ-chain, which plays a central role in coupling the TCR-mediated antigen recognition to various signaling pathways [25, 41, 42]. In *ret* transgenic spontaneous melanoma model, a profound down-regulation of TCR ζ-chain expression has been detected in T lymphocytes infiltrating melanoma lesions in *ret* transgenic mice [48], in T cells from cancer patients [92, 93], and in chronically inflamed mice [41, 94], suggesting an amazing resemblance of both pathological processes. Moreover, a direct inhibition of TCR ζ-chain expression has been observed upon an in vitro coculture of MDSCs isolated from tumor-bearing mice or animals under chronic inflammatory conditions with normal T lymphocytes [41, 48, 94].

Modulation of Tumorigenesis and Tumor Progression by MDSCs

In addition to the reported role tumor-derived factors in the generation, migration and stimulation of MDSCs, there are growing evidences that expanded MDSCs can directly support tumorigenesis. Applying transgenic mouse lung cancer model, Qu et al. [46, 95] found that the long-term induction of apoptosis inhibitor 6 (Api6/AIM/Sp alpha) or matrix metalloproteinase-12 in myeloid cells resulted in a significant increase in frequencies of MDSCs, DCs, neutrophiles and macrophages linked to a severe inflammation and a massive tissue remodeling in lungs; leading to the development of lung adenocarcinoma in 35 % of animals. Furthermore, it has been demonstrated that abruptions of the LAL/hormonal ligand/PPAR pathway in myeloid cells induced a skewing of hematopoietic progenitors toward the myeloid-lineage expansion and MDSC formation followed by the development of chronic inflammation [32] The latter created conditions for the down-regulation of T-cell functions and for the spontaneous development of carcinomas and sarcomas [32].

MDSC-mediated stimulation of tumor growth and progression has been also documented by their strong capability to secrete VEGF, basic fibroblast growth factor, hypoxia-induced factor-1, TGF-β, and MMP9, which can promote neoangiogenesis and create an environment for the metastatic formation [44, 96]. Moreover, inflammatory proteins S100A8 and S100A9 produced by MDSCs have been reported to induce the activation of MAPK and NF-κB signaling pathways in tumor cells, enhancing thereby their growth and metastatic potential [86, 97]. Together with discussed above MDSC-mediated suppression of anti-tumor T-cell reactivity, the ability of these myeloid cells to stimulate directly tumor growth underlines an important role of the neutralization of MDSC functions for the development of more efficient tumor immunotherapies.

Inhibiting Immunosuppressive Functions of MDSCs

Reduction of MDSC frequencies and/or blocking their activities has been reported to delay the tumor development and to prolong the survival both in pre-clinical models and cancer patients [21, 30, 31, 98]. The latter may be achieved

by three major strategies that include i) regulation of myelopoiesis; ii) reduction of MDSC accumulation in tumor lesions by blocking their trafficking towards tumors; and iii) inhibition of MDSC immunosuppressive properties.

The first approach is linked to the prevention of MDSC generation from bone marrow precursor cells and the stimulation of further MDSC differentiation towards mature DCs and/or macrophages. One of main targets in the circumvention of MDSC formation is stem cell factor (SCF). The knockdown of SCF with siRNA and the prevention of SCF signaling by anti-c-kit antibodies or tyrosine kinase inhibitors such as sunitinib, pazopanib and sorafenib have been reported to reduce frequencies of MDSCs developed from human bone marrow precursors in vitro and in murine models of colon and Lewis lung carcinoma [99, 100]. In mice, a decrease of MDSC levels was associated with enhanced tumor-specific immune responses, tumor regression and significantly prolonged survival. In addition, sunitinib has been demonstrated to reverse the MDSC accumulation in patients with renal cell carcinoma (RCC), resulting in the accumulation of Th1 cells and the reduction of Tregs [101]. Such beneficial sunitinib effect was also found in the murine RCC model correlated with the neutralization of immunosuppressive functions of tumor-infiltrating MDSCs [100].

MDSCs have been shown to differentiate into mature macrophages, DCs or granulocytes upon the administration of all-trans-retinoic acid (ATRA) [28, 102] or ultra-low non-cytotoxic doses of paclitaxel [103]. Although retinoic acid receptors (RARs and RXRs) are known to be expressed on various cell types, receptors RARα and RXRα were detected predominantly on myeloid cells [104]. The combination of RA with G-CSF is a driving force for granulocyte differentiation, whereas RA together with vitamin D can induce monocytic development [104]. The first data on ATRA effects on MDSCs in patients with metastatic renal cell carcinoma were published in 2006 [102]. The authors demonstrated that upon the administration of ATRA with IL-2, the frequency of MDSC in the peripheral blood was significantly reduced, leading to the improvement of DC functions and enhancement of the tumor-specific T-cell reactivity. Using mouse HPV-tumor model, another group has reported that ATRA injections into tumor-bearing mice together with HPV therapeutic vaccination could cause a decrease in MDSC frequencies and immunosuppressive functions of the $CD80^{dim}$ MDSC subset [105]. Moreover, these impairments in MDSCs were associated with the restoration of functionally active tumor-specific T cells and strong anti-tumor effects [105].

In our recent studies, we have shown that the administration of chemotherapeutic drug paclitaxel at ultra-low non-cytotoxic doses, previously described as chemoimmunomodulation [106], in healthy C57BL/6 mice significantly reduced the amount of $CD11b^{+}Gr1^{+}$ immature myeloid cells [107] that are known as an MDSC counterpart in normal mice [28]. Such MDSC down-regulation was associated with increased natural killer cell frequencies in the bone marrow and their ability to produce IFN-γ. Moreover, paclitaxel chemoimmunomodulation enhanced the efficiency of vaccination with the peptide derived from melanoma-associated antigen tyrosinase related protein-2 [107]. Upon ultra-low paclitaxel administration in tumor-bearing *ret* transgenic animals, we revealed a drastic reduction in MDSC frequencies as well as their ability to produce NO and to suppress T cell proliferation in vitro. Moreover, the concentration of numerous chronic inflammatory factors (such as IL-β, IL-6, TNF-α, IFN-γ, GM-CSF, and IL-10) in melanoma lesions was significantly diminished. These changes were associated with a partial recovery of tumor-specific T cell responses that were resulted in profound anti-melanoma effects indicated by a delayed tumor growth and prolonged animal survival (V.U.,A.S., unpublished results). To decipher the molecular mechanisms of MDSC inhibition under ultra-low paclitaxel treatment, MDSCs were generated in vitro from the bone marrow precursors and treated paclitaxel at ultra-low, nanomolar concentrations [103]. Under these conditions, paclitaxel failed to impair the MDSC generation from bone marrow precursors or to stimulate MDSC apoptosis, whereas the differentiation of these cells towards DCs was found to be significantly stimulated in the toll-like receptor 4-independent way.

Direct selective elimination of MDSCs has been reported to be achieved by the administration of gemcitabine [108] or 5-fluorouracil [109]. It has been found that these agents were to deplete MDSCs without any toxic effect on other leukocyte subpopulations, which led to a markedly enhanced anti-tumor effect in several mouse transplantable tumor models. The targeting of tumor-derived chemokines was also applied to inhibit MDSC migration towards tumor lesions. Thus, prostate, breast and Lewis lung carcinomas, melanomas, and colorectal cancer have been demonstrated to produce various ligands for CCR2 (including CCL2), which were reported to attract MDSC and to maintain their suppressive activity [82, 110]. Direct CCL2 binding by bindarit [82] or the blocking of production of these chemokine in tumors [110] has been shown to diminish MDSC frequencies in tumor microenvironment, to inhibit metastasis and neoangiogenesis and suppress the development of transplantable tumors [82, 110].

Finally, MDSCs could be neutralized through an inhibition of their immunosuppressive activity. Once attracted to the tumor microenvironment, MDSCs have been shown to affect anti-tumor immune responses by numerous mechanisms including a strong activation of iNOS and ARG-1, leading to an intensive NO production and a deprivation of the amino acid L-arginine, essential for T lymphocytes [21, 22, 37, 38]. It has been recently reported that phosphodiesterase

(PDE)-5 inhibitors (like Sildenafil or Tadalafil), which are widely used for the treatment of erectile dysfunction, pulmonary hypertension and cardiac hypertrophy [111], displayed strong anti-tumor effects in various transplantation mouse models by blocking MDSC immunosuppressive functions that resulted in the TIL accumulation and stimulation [45, 112, 113]. Such MDSC inhibition was found to be due to an elevated intracellular concentrations of cyclic guanosine monophosphate leading to the down-regulation of iNOS and ARG-1 activities and decreased NO synthesis in MDSCs. In *ret* transgenic melanoma model, the chronic Sildenafil administration with the drinking water caused a significant reduction in the production of NO and in the expression of ARG-1 associated with the partial restoration of anti-tumor CD8 T cell responses [48]. Moreover, sildenafil could significantly diminish chronic inflammation in the melanoma lesions indicated by a reduction of IL-1β, IL-6, VEGF, GM-CSF, CCL2, CCL3 and S100A9 production. All these changes induced by sildenafil resulted in the significantly prolonged survival of tumor-bearing animals. In addition to PDE-5 inhibitors, the activity of iNOS and ARG-1 has been reported to be directly blocked by corresponding inhibitors [112, 114] or by nitro-aspirin [115], leading to a significant T cell stimulation and strong anti-tumor effects. Moreover, it has been recently reported that the iNOS inhibition in melanoma cells with the small molecule inhibitor L-NIL was able to block the expression of STAT3 and production of reactive oxygen species in MDSCs and to abolish their suppressive function [116]. Experiments with VEGF-depleting antibody and recombinant VEGF identified a key role for VEGF in the iNOS-dependent induction of MDSC. Thus, L-NIL normalized elevated serum VEGF levels, downregulated activated STAT3 and ROS production in MDSC, and reversed tumor-mediated immunosuppression [116].

Interestingly, some agents that prevented MDSC migration towards tumor lesions have been also demonstrated to inhibit MDSC immunosuppressive functions. In particular, the inhibition of COX-2 activity and PGE2 production reported to reduce the MDSC trafficking mediated by chemokines CXCR4/CXCL12 and CXCR1-CXCR2/CXCL8 [83] has been also shown to impair the MDSC-mediated immunosuppression through the down-regulation of ROS and NO production [117, 118] or ARG-1 expression in these cells [119].

Conclusion

During the last several years, the role of heterogeneous population of highly immunosuppressive MDSCs in the tumorigenesis and tumor progression was clearly elucidated both in pre-clinical animal tumor models and cancer patients. Developing tumors were documented to produce multiple soluble factors that could impair the myelopoiesis favoring the formation, migration into the tumor lesions and activation of MDSCs. On the other side, MDSCs were found to support further tumor progression by promoting neoangiogenesis and creating an environment for the metastatic formation. Therefore, both MDSCs and tumor cells may depend on and support each other in all aspects. There are no doubts that the efficiency of different immunotherapeutic strategies could be strongly enhanced after the neutralization of MDSC-induced immunosuppression. Even adoptively transferred functionally active tumor-specific CD8 T cells can develop anergy or undergo apoptosis upon the successful migration into in the tumor microenvironment, where they met powerful immunosuppressive myeloid and lymphoid cells including MDSCs. Therefore, understanding the mechanisms and checkpoint regulators of the interplay between MDSCs and tumor cells is critically important for overcoming immunosuppression in the tumor microenvironment to achieve better efficiency of cancer immunotherapy.

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Conflict of Interest The authors declare that they have no conflict of interest.

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