Functional diversity of MDSCs: the multitasking Hydra of cancer

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Abstract

Myeloid derived suppressor cells (MDSCs) are immature suppressive cells found in tumors and immunological niches. Here, we highlight the ability of MDSCs to promote IL-17 producing T cells (Th17) and regulatory T cells (Tregs) in addition to suppressing cytotoxic T cells in different tumor models. These interactions between MDSCs and T cells support tumor growth because IL-17 is tumorigenic in many cancer types and Tregs suppress antitumor T cells. Besides T cells, MDSCs promote regulatory B cells (Bregs) and suppress overall B cell function; however, tumor evoked Bregs also regulate MDSC function suggesting cross-regulation between MDSCs and B cells. These multiple functions shed light on how MDSCs dysregulate several arms of host immune response. Moreover, MDSCs promote tumor cell survival and angiogenesis to support tumors. Therefore, the multifunctional feature of MDSCs make them attractive immunotherapeutic targets.

Introduction

MDSCs are gaining importance due to their key role in promoting resistance to current therapies in different types of cancer (1–3). In cancer, tumor derived growth factors and inflammatory cytokines increase proliferation but prevent terminal differentiation of myeloid cells, resulting in increased frequencies of MDSCs (4). This is consistent with their initial characterization as immature cells of monocytic or granulocytic origin. They are distinct from monocytes and neutrophils due to their ability to suppress antigen-specific and non-antigen specific T cells in many tumor models. Historically, MDSCs were considered inhibitory macrophages (5). However, MDSCs are phenotypically distinct from macrophages and dendritic cells (DCs) due to reduced expression of F4/80 (macrophage marker), MHC class II (antigen presenting molecule) and CD11c (DC marker) (6). During their lifespan, some MDSCs differentiate to tumor associated macrophages (TAMs) and DCs and others remain undifferentiated (7, 8) (Fig. 1). Although TAMs suppress T cells, they mainly promote an IL-4 dependent type 2 response, produce epidermal growth factor (EGF), and produce proteases to promote tumors (9). Therefore, MDSCs have a robust immunosuppressive activity among myeloid cells in cancer.

MDSCs were originally identified by the Gr-1 antibody (clone RB6–8C5), which recognizes both Ly6C (monocyte marker) and Ly6G (granulocyte marker) antigens (6). However, Gr-1 antibody binds with more affinity to Ly6G than to Ly6C. As a result, CD11b+Gr-1^{lo} cells

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are identified as monocytic MDSCs (M-MDSCs) and CD11b+Gr-1^{hi} cells as polymorphonuclear MDSCs (PMN-MDSCs) (10). Antibodies specific to Ly6C or Ly6G showed that M-MDSCs are CD11b+Ly6C+Ly6G- and PMN-MDSCs are CD11b+Ly6G+Ly6C^{lo} (11). Recently, a consensus was reached about the criteria for classifying myeloid cells as MDSCs (11). Myeloid cells expressing Ly6C or Ly6G and capable of suppressing T cell proliferation or function are identified as MDSCs. Some studies report the function of total MDSCs (CD11b+Gr-1+) but others delineate subset specific mechanisms of MDSCs (Table I). Evaluating the importance of MDSC subsets in dysregulating antitumor immunity is useful for defining effective treatment strategies. For example, in colon cancer, several reports show that M-MDSCs promote tumor growth by suppressing T cells (12–14) but recent studies show that PMN-MDSCs are also critical for tumor progression (15–17). In addition to M-MDSCs, an intermediate MDSC (I-MDSC) subset was found in spleens of tumor bearing Apc$^{Min/+}$ mice (18), which have high circulating level of GM-CSF (19). Compared to M-MDSCs, I-MDSCs express intermediate levels of Ly6C and Ly6G suggesting a heterogeneous composition of cells within this subset (20). Consistently, an I-MDSC like subset accumulated in mice with CT26 colon carcinoma overexpressing GM-CSF and in mice with breast tumor cells expressing high GM-CSF (6, 10). In lung cancer, patients with more M-MDSCs experienced disease relapse after treatment (21). However, in murine lung cancer, there is higher accumulation of PMN-MDSCs compared to M-MDSCs and most studies report the suppressive potential of total MDSCs (22–24). Therefore, additional evidence will provide a complete picture of MDSC function in different tumor models.

MDSCs also express Tie2 and CD31 that are markers of endothelial cells (5, 6). Consistently in a CRC tumor model (MC26), they acquire VEGF receptor and VE-cadherin expression and incorporate into tumor endothelium (25). However, it is unknown if these MDSCs perform the function of endothelial cells. MDSCs from bone marrow (BM) of mice with 4T1 tumors induced bone metastases, suppressed T cells and differentiated to osteoclasts to cause bone degradation (26). Absence of F4/80 showed that these osteoclasts are not macrophages. The ability of MDSCs to differentiate to other cell types is an indication of their plasticity but also suggests a stem cell like feature providing clues about how MDSCs multitask. Stem cells have the ability to differentiate into other cell types. As cells progress to a terminally differentiated state, some genes are silenced to acquire a specific function. In MDSCs, it is likely that the transcriptional program determining whether MDSCs eventually differentiate into DCs or macrophages or neutrophils are all functional, allowing them to perform multiple functions in response to growth factors or cytokines. Apart from immunosuppression, other mechanisms also contribute to the pro-tumor capabilities of MDSCs as previously reviewed (27) (Table I). MDSCs thrive in a tumor environment rich in growth factors, cytokines, and chemokines (28). GM-CSF is a growth factor promoting MDSC accumulation, and it activates the transcription factor CEBP/β to control expansion of MDSC subsets and its ability to suppress antigen specific T cells (10). IL-6 activated Stat3 also contributes to the suppressive potential of MDSCs (29). A combination of growth factors and cytokines can lead to waves of gene expression changes in MDSCs locally in tumors or systemically to, focus their cumulative immunosuppressive strength in preventing cytotoxic T cell expansion and simultaneously perform other tumorigenic functions. The

tumor environment could shift the functional direction of each MDSC subset. However, the component of the tumor environment determining this dynamic balance in MDSC function is unclear at present and understanding the underlying mechanisms is valuable. This concept suggests why MDSCs occupy an important niche in promoting tumor development in a variety of cancers and why it is a hurdle for effective immunotherapy.

To consider new strategies for targeting MDSCs in cancer, we aimed to gain better understanding of the functional diversity of MDSCs by evaluating all mechanisms by which MDSCs support tumors. Here we offer our perspective about the diverse roles of MDSC subsets in modulating T and B cell immunity, and other tumorigenic functions.

Regulation of T cell immunity

MDSCs suppress CD4 and CD8 T cells

The immunosuppressive function of MDSCs is critical for their classification and distinction from mature myeloid cells. IL-4 receptor α (IL-4Rα) on MDSCs is linked to their immunosuppressive potential due to IL-4R dependent activation of arginase and inducible nitric oxide synthase (iNOS) (12). Arginase prevents non-antigen specific T cell proliferation by depleting essential nutrients such as arginine (12, 30). iNOS in M-MDSCs produces nitric oxide (NO) to suppress T cells by nitrating the T cell receptor (TCR), which blocks downstream signaling events required for activating T cells (22, 31). IL-4Rα on MDSCs mediates suppression of both antigen specific and non-antigen specific T cells in breast tumor (4T1) and colon cancer (CT26) models (32). In murine melanoma (B16 tumors overexpressing IDO), M-MDSCs rather than PMN-MDSCs from tumors suppress non-antigen specific T cells, express IL-4Rα and arginase, and correlate with tumor growth (30). Loss of autophagy related genes in M-MDSCs increases MHC class ll expression to promote CD8 T cell cytotoxicity and CD4 T cell proliferation in murine melanoma (33). In general, M-MDSCs are more suppressive than PMN-MDSCs (4). PMN-MDSCs primarily suppress antigen specific T cells by producing reactive oxygen species (ROS) (22). NADPH oxidase (NOX2) produces reactive oxygen species (ROS) in MDSCs from colon cancer (CT26 and MC38), lung cancer (LLC), mammary cancer (DA3), and fibrosarcomas (MethA and C3 sarcomas) (23). These findings demonstrate that M-MDSCs and PMN-MDSCs use different mechanisms for suppressing T cells (4). However, in EL-4 tumor bearing mice both MDSC subsets from spleen suppressed antigen specific CD8 T cells similarly and their suppressive function was independent of IL-4Rα (22). Similarly, peripheral blood MDSCs from different tumor models such as 4T1, CT26, and TSA were not dependent on IL-4Rα for suppressing antigen specific T cells (34).

Programmed death ligand 1 (PD-L1) belongs to the B7 family of ligands that regulate T cells. Although blockade of PD-L1 reversed T cell suppression by MDSCs under hypoxic condition (35), PD-L1 on in vitro generated MDSCs or MDSCs from EL-4 tumor bearing mice did not suppress T cells (22, 36). When co-inhibited with other mediators of suppression such as transforming growth factor β (TGFβ) or NO, PD-L1 appears to mediate T cell suppression (30). This suggests that other co-inhibitory ligands in the B7 family such as B7-H3, B7-H4, and V-domain Ig suppressor of T cell activation (VISTA), which are known to inhibit T cell proliferation could mediate the suppressive function of MDSCs (37).

Moreover, cyclooxygenase 2 (COX-2) induced prostaglandin 2 (PGE2) in MDSCs promotes immunosuppressive function by upregulating indoleamine 2,3- dioxygenase (IDO) among other mediators of T cell suppression (38). IDO is an important mechanism of immunosuppression preventing antitumor immunity (39). Therefore, more than one mechanism contributes to the suppressive function of MDSCs. A better understanding of mechanisms contributing to MDSC mediated suppression of antitumor cells is vital for improving anticancer therapy and for the design and development of new therapeutics that can have lasting effect on the survival and overall quality of life of cancer patients.

MDSCs support Th17 cell function

In murine colon cancer, MDSCs (Gr-1+ myeloid cells) but not macrophages increase IL-17 production by CD4+ T cells to promote tumor progression (40). Similarly in a carcinoma model, MDSCs differentiated lL-17 producing CD4 T cells whereas TAMs promoted TGFβ producing T cells, which are likely Tregs (41). We showed that I-MDSCs promote the development of IL-17 producing CD4 T cells, which is essential for intestinal tumor progression (20). CD4 T cells differentiate into T helper 1 cells (Th1), T helper 2 cells (Th2), T helper 17 cells (Th17), or T regulatory cells (Tregs) depending on the cytokines they are exposed to. The cytokines IL-1β, IL-23, and IL-6 differentiate CD4 T cells to disease causing (pathogenic) Th17 cells in experimental autoimmune encephalitis (EAE) compared to Th17 cells generated with IL-6 and TGFβ (42). Total MDSCs from ovarian cancer produced IL-1β, IL-23, IL-6, and TGFβ, which upregulate endogenous nitric oxide synthase 2 (NOS2) in T cells to promote IL-17 production (43). Addition of TGFβ to the cytokine cocktail (IL-1β, IL-23, and IL-6) inducing Th17 cells dramatically decreased IL-17 production by CD4 T cells; however, these Th17 cells produced IL-17 than unstimulated T cells. Therefore, MDSCs producing TGFβ promoted some IL-17 production, and the absence of TGFβ possibly increased IL-17 production (43). TGFβ also reduced expression of IL-23 receptor (IL-23R), which suggests that it dampens the responsiveness of Th17 cells to IL-23 (42) and likely reduces the survival of Th17 cells in vivo. This is consistent with the necessity of IL-23 for maintaining pathogenic Th17 cells (44) and with the ability of IL-23 in increasing IL-17 producing CD4 T cells in the brain and spinal cord to promote disease severity in EAE (45). Therefore, MDSCs producing less TGFβ could promote Th17 cells with more disease causing potential. These studies shed light on the ability of MDSCs to generate Th17 cells and suppress antitumor T cells to accomplish the overall aim of promoting tumor growth (Fig.1). Moreover, MDSC like cells regulate Th17 cells by recruiting them to tumors. In murine skin cancer, immature Gr-1+ myeloid cells (IMCs) lacking suppressive function recruited CD4 T cells via CCL4 to promote carcinogen induced skin tumors by IL-17 (46). In castration resistant prostate cancer (CRPC), PMN-MDSCs produced abundant IL-23, which activated the Stat3-RORγ pathway in tumor cells to promote survival (47). IL-23 produced by these PMN-MDSCs could also promote Th17 differentiation, however it is unknown if this mechanism occurs concurrently in CRPC. Together, these studies illustrate the potential of MDSCs to alter the dynamic balance of the tumor immune system to create a self-promoting cycle.

Regulation between MDSCs and Tregs

In mismatch repair proficient (MMR) CRC patients, Tregs were associated with reduced cytotoxic response (48). Tregs were increased in CRC patients before surgery, suppressed antigen specific CD4 T cells, and were associated with tumor recurrence (49). In a colon tumor model, M-MDSCs induced Tregs in vitro and tumor growth was dependent on MDSC induced Tregs (50). This study showed that MDSCs induce Tregs and suppress antigen specific CD4 T cells simultaneously to promote tumors. In a B cell lymphoma model, induction of Tregs was dependent on the arginase activity of MDSCs (51). These tumor-derived MDSCs inhibited antigen specific CD4 T cell proliferation but promoted the expansion of Tregs from naturally occurring Tregs and not from naïve T cells. In this case, inhibition of T cell suppression allowed Treg expansion suggesting that a shift in MDSC function could favor Treg expansion versus suppression of CD4 T cells. In murine melanoma, IDO induced Tregs were critical for recruitment of MDSCs and their suppressive function (30). Together, these studies show that MDSCs promote Tregs and Tregs in turn support MDSC function to promote an immunosuppresive environment conducive for tumor progression.

Interaction between MDSCs and B cells

The functional relationship between MDSCs and B cells is inter-dependent where MDSCs regulate different B cell functions and vice versa. Bregs are a type of regulatory B cells that primarily produce IL-10, accumulate in various cancers and is one of the immunosuppressive mechanisms supporting tumor progression (52). In MCA205 fibrosarcoma, MDSCs promote Breg like cells (B220+CD138+) that are dependent on IL-10 and TGFβ for producing IgA antibodies (53). These Bregs are similar to regulatory plasma B cells that also produce antibodies and suppress antitumor T cells (54). In a 4T1 breast cancer model, MDSCs appear to expand Bregs with high PD-L1 that produce IL-10 and IgA, and also suppressed T cells by inducing apoptosis (55). MDSCs also non-selectively suppress B cells to disable another arm of antitumor immunity (54). In an orthotopic lung cancer model (LLC), MDSCs suppressed IL-4 and lipopolysaccharide (LPS) activated B cell proliferation in a T cell dependent and independent manner (56). Moreover, MDSCs restrict B cell trafficking to lymph nodes by downregulating L-selectin on B and T cells in 4T1 breast cancer (57). Together, these studies show that MDSCs regulate B cells in tumor systems.

CD19+CD20^{lo} Bregs expanded in mice with 4T1 tumors, in which B cells were depleted with CD20 antibody (58). In this study, Bregs promoted the generation of Tregs to support tumor growth and metastasis. On B cells, CD19 is expressed in early development stages and CD20 is expressed in more differentiated B cells (44). This explains why depleting B cells with CD20 antibody deleted differentiated B cells while allowing less differentiated CD19+ B cells to develop into Bregs (CD19+CD20^{lo}). In B cell deficient mice with breast cancer or melanoma, MDSCs were poorly suppressive (59). In this model, tumor evoked Bregs contributed to the suppressive potential of MDSCs resulting in increased metastasis. These Bregs regulated the immunosuppressive function of MDSC partly through TGFβ signaling (60). Secretory IgM from B cells in mice with chronic lymphocytic leukemia (CLL) and LLC tumors promoted the suppressive function of MDSCs (61). These studies

show that in breast cancer and melanoma, Bregs contribute to MDSC function and in fibrosarcoma, lung cancer, and breast cancer, MDSCs promote Bregs, suppress total B cell function, and reduce B cell trafficking. This illustrates the complex role of B cells in dysregulating immunity in cancer.

MDSCs promote tumor cell proliferation

MDSCs produce IL-6, IL-1β, vascular endothelial growth factor (VEGF), and cyclooxygenase 2 (COX-2), all of which promote tumor cell proliferation (4, 62, 63). MDSCs cultured with murine 4T1, CT26, TS/A, or MC38 tumor cells produced more IL-6 compared to tumor cells themselves, showing that MDSCs are a source of IL-6 that supports tumor growth (62). This is consistent with the role of IL-6 induced Stat3 in inhibiting apoptosis to promote tumor cell survival (64). IL-1β promotes tumor cell proliferation by increasing angiogenesis in B16 melanoma and DA/3 mammary adenocarcinoma (65). This is accomplished by inducing chemokines to recruit inflammatory immune cells and promoting VEGF synthesis (66). In this manner, IL-1β activates endothelial cells by VEGF to vascularize tumors resulting in tumor growth. In several cancers, VEGF is critical for developing tumor vasculature to supply additional growth factors to tumors and for migration of inflammatory and suppressor cells to tumors (67). Similarly, COX-2 induced prostaglandin 2 (PGE-2) increases angiogenesis and promotes proliferation of tumor cells (68). From these reports, it appears that besides regulating T cell function, MDSCs also produce cytokines, growth factors, and inflammatory mediators to promote tumor growth by preventing apoptosis, supporting angiogenesis, and expanding MDSCs.

MDSC subsets manipulate tumor immunity

Among the various functions of MDSCs, their immunosuppressive ability stands out as their definitive singular feature. M-MDSCs are most immunosuppressive per cell due to their ability to suppress antigen specific or non-antigen specific T cells. This was demonstrated in B16-IDO, C26-GM, CT26, and MCA26 tumor models and was associated with their ability to express both arginase and iNOS. In 4T1, C26-GM or MCA203 fibrosarcoma tumors, CD11b+Gr-1^{lo} cells (M-MDSCs) are relatively more suppressive than CD11b+Gr-1^{hi} or CD11b+Gr-1^{int} subsets (6). PMN-MDSCs supplement this process by suppressing T cells by producing ROS but their immunosuppressive strength is weaker than M-MDSCs (4, 6, 10). They suppress antigen specific T cells and are more abundant than M-MDSCs in many tumor models (22). In murine colon cancer, total MDSCs promote Th17 cells but in another colon tumor model, M-MDSCs expressing CSF-1R promote Tregs that are critical for tumor progression. It is unknown if PMN-MDSCs promote Tregs. PMN-MDSCs produce tumor-promoting factors such as IL-23 to support resistance by increasing tumor growth after surgical removal of prostate tumors (47). Due to IL-23 production, these PMN-MDSCs could promote Th17 cells. This suggests that MDSC subsets could differ in their ability to promote Tregs and Th17 cells. This also raises the question as to how these two process co-exist in the same cancer type. In cancer, Tregs promote tumors by suppressing T cells, and Th17 cells support tumor progression by promoting cell survival and angiogenesis. Occurrence of these processes in colon cancer demonstrates the multitasking capacity of MDSCs in regulating different arms of T cell immunity. These studies also suggest that different MDSC subsets promote Tregs versus Th17 cells in addition to their overall ability

to suppress T cells. Although inhibition of suppressive function may not reduce their ability to promote Tregs or Th17 cells, more evidence is required to substantiate these assumptions conclusively.

By inducing EMT in 4T1 breast tumor cells, M-MDSCs promote the release and migration of tumor cells to metastatic niches (69). In this model, lung infiltrating PMN-MDSCs upregulate genes associated with metastasis. MDSCs also suppressed cytotoxic CD8 T cells to promote lung metastases in 4T1 breast cancer (70). Consistently, lung metastases were reduced after resection of primary 4T1 breast tumors in Stat6 deficient mice, which was dependent on cytotoxic CD8 activity. A recent study showed that MDSCs suppress T cells by arginase activity to promote lung metastases independent of VEGF activity in a 4T1 breast cancer model (71). These reports suggest that MDSCs promote tumor metastasis by suppressing T cells and by promoting metastatic tumor cell transformation.

Taken together, M-MDSCs are highly immunosuppressive, induce the generation of Tregs, and promote metastasis. In a cancer setting, this is a potent resistance mechanism for preventing cytotoxic activity of antitumor cells both directly and through Tregs. PMN-MDSCs also suppress T cells, promote tumor growth, and metastasis. Therefore, M-MDSCs and PMN-MDSCs possess multiple mechanisms to promote tumorigenesis supporting the idea that they are versatile and can adapt to suppress the host immune response in a demanding tumor environment (Fig.1).

Impact on cancer immunotherapy

Immunotherapy is an effective strategy for treating most cancers. The success of checkpoint inhibition in increasing survival of patients with aggressive lung cancer and melanoma has provided significant relief from high mortality (72). A subset of CRC patients with high mutation burden are also responsive to checkpoint inhibitor treatment (73). However, efficacy of this treatment is reduced due to the emergence of immunosuppressive mechanisms including MDSCs and Tregs (3, 74).

Existing literature demonstrate the value of targeting MDSCs and possibilities to block MDSC function in cancer to improve treatment are reviewed previously (28, 74). Efforts to inhibit MDSCs are focused on depleting MDSCs, inhibiting their function, or diverting their differentiation to activating DCs or tumoricidal macrophages (4, 28). M-MDSCs retain the potential to differentiate to macrophages or DCs and therefore are amenable to re-education to immunostimulatory myeloid cells that could prime T cells to generate antitumor T cells (22, 75). The close link between CSF-1R+ MDSCs that are similar to M-MDSCs and melanoma and colon cancer progression suggests that blocking CSF-1R could target M-MDSCs by inhibiting their proliferation (1, 50). In a tumor free condition, PMN-MDSCs convert to neutrophils that have a short life span and might not result in long-lasting antitumor immunity unlike antigen presenting cells such as DCs or macrophages. Studies assessing if MDSC depletion reduce tumor growth use the Gr-1 antibody that primarily depletes PMN-MDSCs. Using antibodies that recognize alarmins S100A8 and S100A9, both M-MDSCs and PMN-MDSCs were depleted resulting in greater decease of EL4 tumor growth indicating the importance of M-MDSCs in tumor progression (76). However, these alarmins do not distinguish between PMN-MDSCs and neutrophils. Neutrophils are required

for maintaining host immunity, which highlights the importance of finding PMN-MDSC specific targets. A different approach to targeting PMN-MDSCs is by identifying subsets within PMN-MDSCs that are directly related to tumor development. In NSCLC patients, PMN-MDSCs expressing lectin-type oxidized LDL receptor-1 (LOX-1) were more immunosuppressive than total PMN-MDSCs suggesting that LOX-1 could differentiate between PMN-MDSCs and neutrophils (77). This finding suggests that PMN-MDSCs could be specifically depleted using LOX-1 without affecting neutrophils. In CRC, both M-MDSCs and PMN-MDSCs promote tumors. However, the specific mechanisms by which MDSC subsets alter T cells to promote tumor progression in CRC requires further study. Although immunosuppression and induction of Tregs by these subsets could be contributing to disease progression, the association of IL-17 and MDSCs with reduced overall survival and the role of MDSCs in promoting Th17 cells in colon cancer pinpoint the importance of the mechanism by which MDSCs regulate Th17 cells (15). By inhibiting the ability of MDSCs in suppressing T cells, promoting Tregs, and Th17 cells, there is a better likelihood of promoting antitumor immunity. This has significant potential for defining novel therapies for colon cancer by identifying targets in MDSC subsets.

Several clinical trials of commonly used chemotherapeutic and immunotherapeutic agents for targeting MDSC function in various cancers are currently ongoing (74). Despite these intense efforts to divert MDSC function to antitumor activity, their adaptability to support tumor progression is a hurdle that researchers are fighting to overcome. With recent success of immunotherapy in bringing unprecedented improvement in survival, there is widespread interest in finding more translatable therapies to boost efficacy and reduce toxicity. This exemplifies the vital need to target MDSC mechanisms to improve the efficacy of checkpoint inhibitors and surgical removal of tumors. By studying various facets of MDSC function and functional relationship with other immune cell populations, it will be possible to optimally block tumor-promoting function of MDSCs.

Conclusions

We illustrate the multifarious roles of MDSCs in a tumor-promoting environment. Considering that host immune response is protective, MDSCs are a singular example of how tumors dysregulate antitumor immunity using different mechanisms. The immunosuppressive function of MDSCs has the ability to overpower antitumor immunity and is a signature feature of MDSCs. When other mechanisms of MDSCs are taken into account, we get an overall picture of how MDSCs multitask to accomplish the goal of promoting tumor development. The feedback between MDSCs and tumor cells creates a tumor promoting cycle, which can be interrupted to identify immunotherapeutic targets. Several questions arise from this analysis of studies about MDSCs. First, M-MDSCs play a critical role in regulating differentiation of T cells into Tregs in colon cancer model. The relative contribution of M-MDSCs versus PMN-MDSCs in regulating tumor-promoting Tregs is unclear. Second, the critical component or process in MDSCs that promotes regulatory cells such as Tregs and Bregs versus proinflammatory T cells such as Th17 cells is unknown. Third, the interaction between MDSCs and Bregs in breast cancer and melanoma are studied but their role in CRC is unknown. Depending on the type of cancer and related treatment regimens, targeting MDSCs could improve existing treatments and can

serve as indicators of disease progression. Knowledge about MDSC mechanisms in each cancer type could provide critical input for devising targeted therapies to improve existing treatments and reduce the intensity of refractory mechanisms.

Acknowledgments

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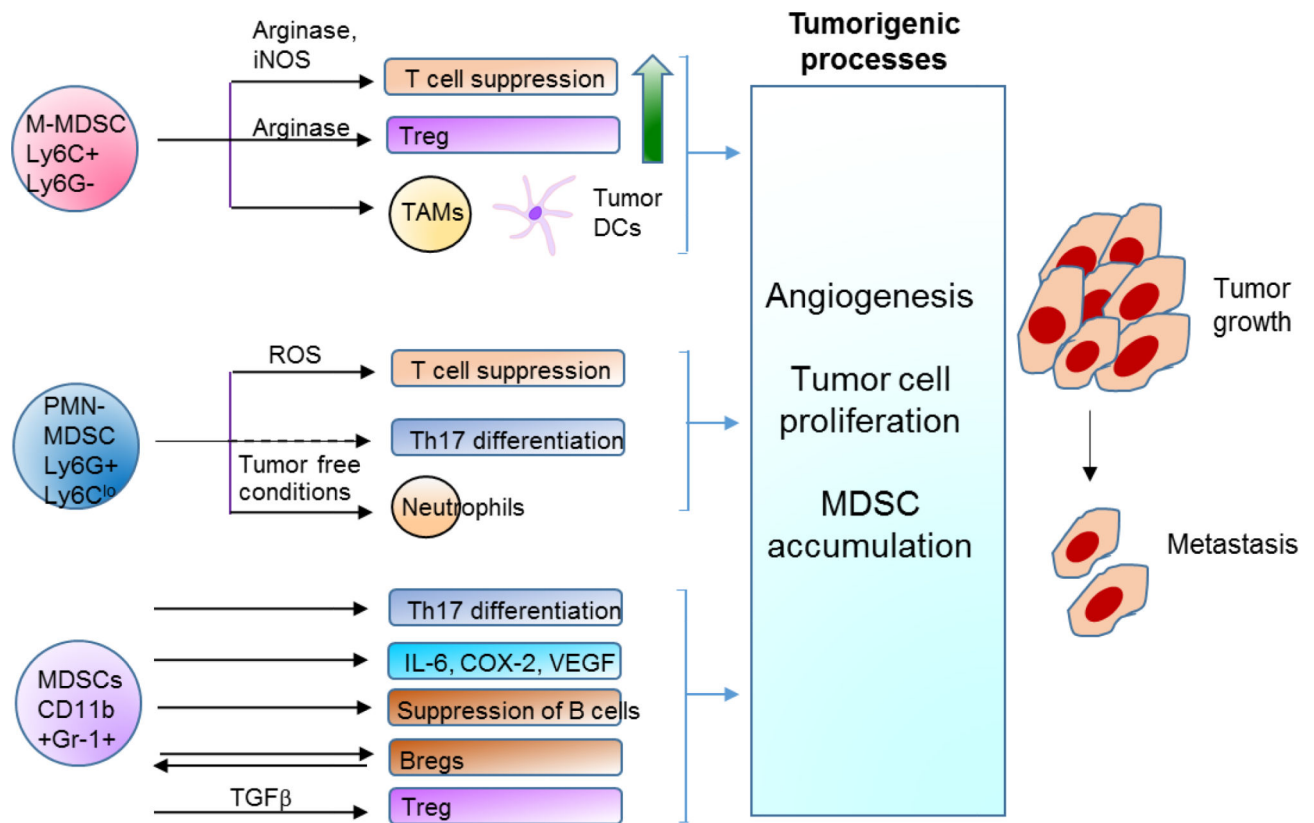
Figure. 1. Diverse functions of MDSCs in cancer.

MDSCs are generated from hematopoietic stem cells from the bone marrow under the influence of growth factors including GM-CSF and G-CSF, and COX-2. They acquire immunosuppressive potential on activation by cytokines including IL-6 and IL-4. COX-2 by itself can expand MDSCs and confer suppressive function. With Ly6C and Ly6G, MDSCs can be separated into M-MDSCs, I-MDSCs, and PMN-MDSCs. They suppress T cell function, promote expansion of Tregs and Th17 cells, modulate B cells by both suppressing B cells and promoting Bregs, and also produce inflammatory cytokines. Overall, MDSCs use these different mechanisms to promote tumor growth, angiogenesis, and metastasis.

Table I.

MDSCs are identified by CD11b+Gr-1+ as total MDSCs or with Ly6C as M-MDSCs or Ly6G as PMN-MDSCs or G-MDSCs. Sources of MDSCs are tumor or bone marrow or spleen or peripheral blood of tumor bearing animals. Most studies were performed in transplanted tumor models and some studies included tumor models with endogenous mutation such as the Apc$^{Min/+}$ model which carries a common CRC mutation, adenomatous polyposis coli (APC) and in APC-CPC colon tumor model. Recent studies have begun showing that MDSCs also promote tumors through mechanisms regulating B cells, Th17 cells, Tregs, or by direct effects on tumors in addition to suppressing T cells. CT26 colon carcinoma overexpressing GM-CSF; MC38, colon carcinoma; 4T1, breast cancer; DA3, mammary carcinoma; MCA-26 intrahepatic metastatic colon cancer; LLC, lewis lung carcinoma, LLC-OVA, LLC expressing ovalbumin; EL-4 thymoma, DA3 mammary carcinoma, MethA and C3 sarcoma; MCA203, fibrosarcoma; MBL-2, lymphoma; MN-MCA sarcoma; Renca, kidney tumor; pancreatic cancer, KPC; B16, melanoma; B16-IDO, B16 expressing IDO; APC-CPC, colon tumor model; Apc$^{Min/+}$, intestinal tumor model with adenomatous polyposis coli (APC) mutation; TRAMP-C1, prostate cancer

MDSC nomenclature and phenotype	Cancer	Source	Function	Mechanism	Tumor-related role	Reference
Immature Gr-1+ myeloid cells CD11b+Gr-1+	MCA-26	Spleen, BM	MDSCs from BM and spleen suppress proliferation of naïve splenocytes stimulated with anti-CD3 and anti-CD28. BM MDSCs also suppressed mixed lymphocyte reaction	Inducible nitric oxide synthase (iNOS) induced nitric oxide (NO) and superoxide dismutase (SOD) mediated superoxides together suppressed non-antigen specific T cell proliferation	Tumor related MDSCs suppressed T cells.	Kusmartsev et al., 2000
Myeloid suppressor cells (MSC) CD11b+Gr-1+	CT26 and C26-GM, MSC-2 cell line	Spleen	Splenic MSCs from mice with C26-GM tumors express arginase and suppress cytolytic activity of allogeneic splenocytes	IL-4 upregulates arginase 1 in MSC-2 to suppress T cells. Arginase 1 activated superoxide radicals induce T cell apoptosis through the iNOS reductase domain.	MSCs were expanded and CD4 and CD8 T cells were reduced. Tumor GM-CSF increased MSCs.	Bronte et al., 2003
MSC Fr.2 Gr-1+CD115+ (M-MDSCs (monocytic MDSCs)), Fr.2 Gr-1+CD11b+	MCA26	Spleen, BM	M-MDSCs suppress antigen specific CD4 T cells more than total MDSCs	MSCs suppressed antigen specific CD4 T cells by iNOS and promoted Tregs.	Tregs generated by MSCs promote tumor growth	Huang et al., 2006
MDSC CD11b+Gr-1+	CT26, MC38, LLC, EL-4, DA3, MethA and C3 sarcoma	Spleen	MDSCs from mice with EL-4 tumors produces reactive oxygen species (ROS) via nicotinamide adenosine dinucleotide phosphate dehydrogenase (NADPH) oxidase to inhibit IFNγ by antigen specific OT-1 T cells	Stat3 dependent NADPH oxidase regulates ROS in MDSCs. NADPH oxidase deficient MDSCs differentiate into macrophages and DCs	Tumor related MDSCs produced ROS to suppress T cells	Corzo et al., 2009
MDSCs CD11b+Gr-1+, CD11b+Ly6C+Ly6G-, CD11b+Ly6G+Ly6C^{lo}	CT26, C26-GM, MBL-2, EL-4, EG7-OVA, MN-MCA, MCA203	Spleen, BM	BM CD11b+Gr-1+ cells suppress cytotoxicity of antigen specific CD8 T cells. CD11b+Gr-1^{lo} cells are most immunosuppressive followed by CD11b +Gr-1^{int} and CD11b+Gr-1^{hi}. Splenic	GM-CSF dependent C/EBPβ is required for the suppressive function of in vitro generated MDSCs and MDSCs from mice with EG-7 tumors. It regulates arginase and	Depletion of MDSCs reduced lung metastases but not the growth of primary fibrosarcoma	Marigo et al., 2010

MDSC nomenclature and phenotype	Cancer	Source	Function	Mechanism	Tumor-related role	Reference
			MDSCs also suppress antigen specific CD8 T cells.	nitric oxide synthase 2 (NOS2) expression		
MDSCs CD11b+Gr-1+	APC-CPC	Tumors	MDSCs and not tumor associated macrophage (TAMs) promoted IL-17 production by CD4 T cells	MDSCs defective in TLR2 failed to promote IL-17 production	Colons tumors were dependent on IL-23 and IL-17	Grivennikov et al., 2012
M-MDSCs CD11b+Ly6C+Ly6G- polymorphonuclear MDSCs (**PMN-MDSCs**) CD11b+LyG+Ly6C^lo **MDSCs** CD11b+Gr-1+	EL4, LLC-OVA, KPC, 4T1, CT26	Blood, spleen, BM	MDSCs express more death receptor 5 (DR5) and undergo cell death; but this results in MDSC expansion	Activating DR5 by agonistic antibody reduces both M-MDSCs and PMN-MDSCs	Tumor reduction after blocking DR5 is dependent on CD8 T cells and increased antigen specific T cell IFNγ.	Condamine et al., 2014
MDSCs CD11b+Gr-1+	B16, B16-indoleamine 2, 3 dioxygenase (IDO), 4T1	Tumor	CD11b+Gr-1^int MDSCs and not CD11b +Gr-1^hi MDSCs from B16-IDO tumors suppress polyclonally activated CD8 T cells. CD11b+Gr-1^int MDSCs from spleen in this tumor model are not suppressive	CD11b+Gr-1^int MDSCs from tumors suppress CD8 T cells by arginase. iNOS, TGFβ, and PD-L1 are also important for suppression in different combinations but not by themselves	Tregs attract MDSCs to the tumor to acquire suppressive function. Treg depletion or IDO inhibition reduces tumor growth.	Holmgaard et al., 2015
M-MDSCs CD11b+Ly6C+Ly6G- **PMN-MDSCs** CD11b+LyG+Ly6C^lo	B16, 4T1	Spleen, PB	Tumor evoked Bregs (tBregs) promote the suppressive function and metastatic potential of M-MDSCs and PMN-MDSCs	tBregs upregulated arginase, ROS and NOX2, and iNOS genes. However, TGFβ signaling in MDSCs suppresses T cells.	tBreg educated MDSCs increased lung metastases	Bodogai et al., 2015
M-MDSCs CD11b+Ly6C+Ly6G- granulocytic MDSCs (**G-MDSCs**) CD11b+LyG+Ly6C^lo **MDSCs** CD11b+Gr-1+	4T1	BM, tumor	Compared to WT MDSCs, CCL5 negative tumor MDSCs poorly suppressed anti CD3/CD28 activated T cells	MDSCs suppressed T cells by NOS2. Absence of CCL5 alters phagocytic capacity of MDSCs, increases MHC II and CD86, and reduces TAMs. CCL5 deletion inhibits differentiation of BM M-MDSCs to Ly6G^hi cells	Autocrine CCL5 by myeloid cells appears to regulate CD8 cytotoxic activity and Treg accumulation to promote tumor growth	Ban et al., 2017
M-MDSCs CD11b+Ly6C+Ly6G- **I-MDSCs** CD11b+Ly6C^int Ly6G^int **PMN-MDSCs** CD11b+LyG+Ly6C^lo	Apc^Min/+	Spleen and LP	Stat6 deletion reduces M-MDSCs, I-MDSCs, and PMN-MDSCs in the spleen and lamina propria (LP) of small intestine	Reduction of MDSCs correlated with increased splenic CD8 cytotoxic cells	Absence of Stat6 reduced tumor growth and MDSCs to enhance antitumor CD8 response.	Jayakumar and Bothwell., 2017
MDSCs CD11b+Gr-1+	4T1	Spleen	CD19+ B cells and MDSCs accumulate in mice with 4T1 tumors.	MDSCs upregulated PD-L1 on B cells and induced IL-10 and IgA. MDSC educated Bregs suppressed T cells by inducing IL-10		Shen et al., 2017
MDSCs CD11b+Gr-1+	LLC	Tumor	Tumor MDSCs reduce frequency and proliferation of B cells	MDSCs suppress B cells in a T cell dependent and independent manner		Wang et al., 2018

MDSC nomenclature and phenotype	Cancer	Source	Function	Mechanism	Tumor-related role	Reference
PMN-MDSCs CD11b+Gr-1+	TRAMP-C1	Tumor	Tumor PMN-MDSCs were increased in mice with castration resistant prostate cancer and produce IL-23.	IL-23 promotes RORγ dependent tumor cell proliferation and Stat3 activation in tumor cells	IL-23 resists survival after surgical removal of prostate tumors	Calcinotto et al., 2018
M-MDSCs CD11b+Ly6C+Ly6G- **G-MDSCs** CD11b+LyG+Ly6C^{lo}	B16-F10	Tumors, spleen	Autophagy genes in M-MDSCs promote suppressive function	Atg5 deficient MDSCs promote CD4 T cell proliferation and increased CD8 cytotoxicity. Loss of Atg5 also increased MHC II in these MDSCs.	Deletion of Atg5 in myeloid cells reduced melanoma and lung tumors	Alisaafi et al., 2018