HHS Public Access

Author manuscript

Cancer Immunol Res. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Cancer Immunol Res. 2017 January ; 5(1): 3–8. doi:10.1158/2326-6066.CIR-16-0297.

Myeloid-derived suppressor cells

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Abstract

Myeloid cells evolutionary developed as a major mechanism to protect the host. They evolved as a critical barrier against infections and are important contributors to tissue remodeling. However, in cancer, myeloid cells are largely converted to serve a new master – tumor cells. This process is epitomized by myeloid-derived suppressor cells (MDSC). These cells are closely related to neutrophils and monocytes. MDSC are not present at steady state in healthy individuals and appear in cancer and pathological conditions associated with chronic inflammation or stress. These cells have emerged as an important contributor to tumor progression. In recent years, ample evidence supports a key role of MDSC in immune suppression in cancer, as well as their prominent role in tumor angiogenesis, drug resistance, and promotion of tumor metastases. MDSC have a fascinating biology and are implicated in limiting the effects of cancer immunotherapy. Therefore, targeting these cells may represent an attractive therapeutic opportunity.

Introduction

Myeloid cells are a highly diverse population. Mononuclear myeloid cells include terminally differentiated macrophages and dendritic cells (DC), as well as monocytes, which under inflammatory conditions differentiate in tissues to macrophages and DCs. Granulocytic myeloid cells include populations of terminally differentiated polymorphonuclear neutrophils, eosinophils, basophils, and mast cells. Myelopoiesis in response to pathogenic stimuli is a fundamental mechanism protecting the host. It largely manifests in expansion of activated neutrophils and monocytes. Classical activation of these cells takes place in a response to strong signals that usually come in form of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) molecules. This activation is relatively short-lived and manifests in robust phagocytosis, respiratory burst, and release of pro-inflammatory cytokines. It terminates upon cessation of the stimuli. In contrast, persistent stimulation associated with chronic infection, inflammation, or cancer involves relatively low-strength signals. This induces modest but persistent myelopoiesis. Myeloid cells generated under these conditions, although similar to neutrophils and monocytes in morphology and phenotype, have different genomic and biochemical profiles and functional activity. The main functional characteristic of these cells is their potent ability to suppress various types of immune responses. It is possible that this mechanism evolved as

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Financial Interests

Author declare no financial interests relevant to the subject of this paper

a form of protection from extensive tissue damage caused by an uncontrolled immune response associated with unresolved inflammation.

Reports on the accumulation of immune suppressive myeloid cells associated with tumor progression were published sporadically beginning in the early 1970s (1). During the 1980s and early 1990s, work from the laboratories of Diana Lopez, Jim Talmadge, M. Rita Young, and Hans Schreiber, demonstrated that various types of myeloid cells could inhibit immune function in cancer. However, the specific nature and biological significance of these cells remained largely unclear. The field started changing in the late 1990s when the $Gr1^{+}CD11b^{+}$ cellular phenotype was suggested as defining the immune suppressive myeloid cells in spleens of mice and when these cells were shown to be phenotypically similar but functionally distinct from monocytes and neutrophils (2, 3). The observations of accumulation of large numbers of these cells in spleens and tumors with potent immune suppressive activity were readily reproducible in most murine tumor models. However, it quickly became apparent that $CD11b^{+}Gr\text{-}1^{+}$ cells were heterogeneous. Different phenotypic criteria and multiple mechanisms of action were used to define these cells. In 2007, in an attempt to unify different descriptions of these cells, the name myeloid-derived suppressor cells (MDSC) was proposed (4). This name was based on the myeloid origin of the cells and their main functional trait – potent immune suppressive activity. In the following years, interest in these cells skyrocketed with almost 2,500 papers published in less than 10 years. MDSC were implicated in various aspects of immune regulation, not only cancer, but also in diseases that involve chronic inflammation, infection, autoimmune diseases, trauma, graft versus host disease, etc. Evidence of the clinical significance of MDSC in cancer has emerged, and MDSC have become an important part of the tumor immunology field. However, as often happens with most teenagers, MDSC periodically have an identity crisis and a difficult relationship with the more established cells in the field. Only recently have MDSC entered a more mature age where their identity and place among other myeloid cells has become clear.

Main phenotypic and functional characteristics of MDSC

MDSC consist of two large groups of cells termed granulocytic or polymorphonuclear (PMN-MDSC), which are phenotypically and morphologically similar to neutrophils; and monocytic (M-MDSC) – phenotypically and morphologically similar to monocytes. Therefore phenotypic criteria alone are not sufficient to identify cells as MDSC. In most types of cancer, PMN-MDSC represent more than 80% of all MDSC. In addition to these two main populations, MDSC include a small group (less than 3%) of cells with myeloid colony forming activity representing a mixture of myeloid progenitors and precursors. In mice, MDSC were mostly described in bone marrow, peripheral blood, spleen, liver, lung, or tumors of various organs. PMN-MDSC can be defined as $CD11b^{+}Ly6G^{+}Ly6C^{lo}$ and M-MDSC as $CD11b^{+}Ly6G^{-}Ly6C^{hi}$, with other markers under investigation. In humans, MDSC were mostly described in blood and tumors of various organs with number of studies describing these cells in bone marrow. Criteria for the phenotypic characterization of these cells by flow cytometry are now relatively well defined (5, 6). Among peripheral blood mononuclear cells (PBMC), PMN-MDSC are defined as $CD11b^{+}CD14^{-}CD15^{+}$ or $CD11b^{+}CD14^{-}CD66b^{+}$, and M-MDSC as $CD11b^{+}CD14^{+}HLA\text{-}DR^{-/lo}CD15^{-}$. Lin^{-}

(including CD3, CD14, CD15, CD19, CD56) HLA-DR^{-}CD33^{+} cells contain mixed groups of MDSC comprising more immature progenitors. The term “early-stage MDSC” (e-MDSC) was recently proposed for this latter population (7).

In humans, M-MDSC could be separated from monocytes based on the expression of MHC class II molecule - HLA-DR. Until recently, the only method allowing for separation of neutrophils from PMN-MDSC in humans was gradient centrifugation using a standard Ficoll gradient. PMN-MDSC are enriched in the low-density fraction (PBMC), whereas neutrophils are high density cells (8). Recently, we identified lectin-type oxidized LDL receptor 1 (LOX-1) as a marker of PMN-MDSC in humans (9). If confirmed in further studies, LOX-1 expression on neutrophils can be used for direct identification of PMN-MDSC in blood and tissues. In mice, the phenotypic distinction between neutrophils and PMN-MDSC in the same mouse is difficult. Several different markers were suggested but thus far, none of them allow for definitive identification of PMN-MDSC.

Immune suppression is a main feature of MDSC. Although MDSC were implicated in suppression of different cells of the immune system, the main targets of MDSC are T cells. The main factors implicated in MDSC-mediated immune suppression include arginase (ARG1), iNOS, TGFβ, IL-10, COX2, indoleamine 2,3-dioxygenase (IDO) sequestration of cysteine, decrease of L-selectin expression by T-cells and many others. In recent years, it became clear that M-MDSC and PMN-MDSC utilize different mechanisms of immune suppression. M-MDSC suppress T-cell responses both in antigen-specific and non-specific manners utilizing mechanisms associated with production of NO and cytokines (reviewed in (10)). PMN-MDSC, on the other hand, are capable of suppressing immune responses primarily in an antigen-specific manner. Induction of antigen-specific T-cell tolerance is one of the major characteristics of these cells (11, 12). Reactive oxygen species (ROS) production is essential for this ability. Reaction of NO with superoxide generates peroxynitrite (PNT), which directly inhibits T-cells by nitrating T-cell receptors and reducing their responsiveness to cognate antigen-MHC complexes (13). PNT also reduces the binding of antigenic peptides to MHC molecules on tumor cells (14) and blocks T-cell migration by nitrating T-cell specific chemokines (15). (Fig. 1)

The large number of different immune suppressive mechanisms described for MDSC does not mean that these mechanisms are simultaneously operational. The prevalence of a particular immune suppressive mechanism depends on the type of MDSC expanded, as well as on the stage of the disease and the site where the suppression is occurring. It is likely that at any given time there is a dominant suppressive mechanism used by MDSC and that this mechanism could change throughout the progression of the disease.

Besides immune suppressive mechanisms, MDSC promote tumor progression by affecting the remodeling of the tumor microenvironment and tumor angiogenesis via production of VEGF, bFGF, Bv8, and MMP9 (16–18). MDSC were implicated in the formation of pre-metastatic niches (19–22), and the promotion of metastases by infiltrating primary tumors (23, 24). CD11b^{+}Gr1^{+} cells were shown to oppose cellular senescence in a model of spontaneous prostate cancer by antagonizing IL-1α mediated senescence (25). In contrast, a

recent report indicated that $CCR2^+$ myeloid cells, represented largely by monocytic cells, supported senescence in a model of liver cancer (26).

Major mechanisms regulating MDSC accumulation and differentiation

Accumulation of MDSC is a complex phenomenon. We have previously proposed a two-signal model describing this process (27). This model asserts that accumulation of MDSC requires two distinct although partially overlapping types of signals: the first is responsible for the expansion of immature myeloid cells associated with inhibition of their terminal differentiation, and the second is responsible for the pathological activation of these cells, converting immature myeloid cells to MDSC.

The first group of signals is mostly driven by tumor-derived growth factors and involves such factors as STAT3, IRF8, C/EBPβ, Notch, adenosine receptors A2b signaling, NLRP3 (reviewed in (27)). Recently, the retinoblastoma protein 1 (Rb1) was implicated in the ability of some M-MDSC to differentiate to PMN-MDSC. While $Rb1^{hi}$ M-MDSC mainly gave rise to macrophages and DC, the vast majority of $Rb1^{lo}$ M-MDSC differentiated towards PMN-MDSC (28). Recently, the accumulation of $Rb1^{lo}$ $Ly6G^+$ PMN-MDSC was confirmed in the PyMT transgenic model of breast cancer (29).

The second group of signals are mediated by factors produced mostly by the tumor stroma (pro-inflammatory cytokines, HMGB1) and include the NF-κB pathway, STAT1, STAT6, prostaglandin E2 (PGE2) and cyclooxygenase 2 (COX2) (reviewed in (27)). Recently, the endoplasmic reticulum (ER) stress response pathway was implicated in the suppressive activity of MDSC. The ER stress response is an evolutionary conserved mechanism developed to protect cells from various stress conditions including hypoxia, nutrient deprivation, low pH, etc. MDSC isolated from tumor-bearing mice and cancer patients overexpressed several markers of ER stress including sXBP1 and CHOP, and displayed an enlarged endoplasmic reticulum, one of the hallmarks of ER stress (30). Administration of an ER stress inducer to tumor-bearing mice was shown to increase the accumulation of MDSC and their suppressive activity (31). Induction of ER stress with thapsigargin converted human neutrophils to immune suppressive PMN-MDSC (9). The transcription factor CHOP was implicated in the suppressive activity of MDSC in the tumor site. CHOP-deficient MDSC lost the ability to suppress T-cells stimulated in an antigen non-specific manner and were even able to stimulate T-cells (32). However, CHOP-deficient MDSC retained the ability to suppress the T-cell response in an antigen-specific stimulation (33). More studies will be necessary to clarify the role of the specific mechanisms of ER stress responses in MDSC function.

In tumor tissues, M-MDSC rapidly differentiate to TAM (34, 35). A recent study implicates down-regulation of STAT3 activity in tumor associated M-MDSC in this phenomenon. This effect was controlled by hypoxia-inducible activation of CD45 phosphatase in these cells.

MDSC place among other myeloid cells

MDSC are pathologically activated myeloid cells. This raises the question of whether MDSC are really different from neutrophils and monocytes. In many studies, cells with

typical MDSC features were called monocytes and neutrophils, and cells were called MDSC even in the absence of those features. Accumulated data in recent years allow us to make a conclusion about the specific nature of MDSC. This conclusion is based on several lines of evidence.

- Immune suppressive activity is intrinsic feature of MDSC. Mature neutrophils or monocytes cannot be converted to potent immune suppressive cells *in vitro* (at a level similar to MDSC) by simply activating them with PAMPs and DAMPs or pro-inflammatory cytokines. Moreover, in some cases neutrophils can promote antitumor response (36).
- Human PMN-MDSC have a unique genomic profile distinguishing them from neutrophils in the same patient, whereas neutrophils from healthy donors and cancer patients have very similar gene expression (9). Mouse MDSC were also characterized by specific proteome (37–39) and transcriptome (40, 41) profiles.
- Phenotypically, M-MDSC can be distinguished from TAMs by increased relative expression of F4/80, low to intermediate expression of Ly6C and low or undetectable expression of S100A9 protein, low expression of IRF8, and increased M-CSF receptor, CD115 (42). Most of the published data indicate that cells with the phenotype of inflammatory monocytes ($CD11b^{+}Ly6C^{hi}Ly6G^{-}$) in tumors have potent immune suppressive activity and thus can be attributed to M-MDSC (43).
- There are number of biochemical features that clearly differentiate MDSC from their control counterparts. These features include high arginase and iNOS expression and activity, high and persistent level of ROS including superoxide, myeloperoxidase, hydroxyl peroxide, and peroxynitrite. PMN-MDSC and M-MDSC also can be distinguished from neutrophils and monocytes by their elevated ER stress response. More details are provided in a recent review (7).

Thus, MDSC represent a relatively stable, distinct state of functional activity of neutrophils and monocytes. Although PMN-MDSC concept is widely accepted, there are number of studies that use different approach to nomenclature of tumor associated neutrophils (TAN) based on concept of phenotypic plasticity of TAN, which is modulated through distinct micro-environmental signals, at different stages of tumor progression (36, 44). In these reports neutrophils with immunosuppressive and tumor promoting functions are called N2, as opposed to antitumor N1, neutrophils (8, 9). Although this point of view is definitely has some rationale, it is difficult to envision that short-lived, terminally differentiated PMN could be effectively polarized in tumor tissues. It is more likely that N1 cells represent activated bona fide PMN cells, whereas N2 cells are in fact PMN-MDSCs. Indeed, number of reports demonstrated potent immune suppressive activity by TAN, which defines these cells as PMN-MDSC (45–47).

Better characterization of MDSC in recent years shed new light on MDSC biology. Recent evidence has linked the accumulation of immature myeloid cells with an MDSC-like phenotype during chronic inflammation to the early stages of tumor development. Exposure of mice to cigarette smoke caused accumulation of these cells in lungs and spleens (48).

However, only after the development of lung cancer did these cells become immune suppressive MDSC. Nevertheless, their depletion increased survival (48). In a model of skin carcinogenesis, accumulation of immature myeloid cells without suppressive function in the skin of mice promoted tumor development (49). This suggests that cells with an MDSC-like phenotype may play a significant role in tumor development and progression via mechanisms not necessarily related to their ability to suppress tumor-specific immune responses. It is possible that accumulation of MDSC is a gradual process. Myeloid progenitors and precursors affected by low-strength pathological signals coming from the developing tumor gradually acquire changes leading to their pathological activation. Bona fide MDSC is the latest stage of this process. Cells at intermediate stages (MDSC-like cells), though they do not possess potent immune suppressive activity, may actively contribute to tumor progression and metastases. Future study will determine whether this concept is correct.

Basic strategies to therapeutically target MDSC

Ample evidence supports a close association between MDSC accumulation and clinical outcome in cancer patients (50, 51). Recent meta-analysis of the studies of 442 patients with various solid tumors demonstrated that MDSC were highly significantly associated with poor overall and progression-free survival (52). MDSC have been implicated in resistance to anti-cancer therapies including sunitinib (53), cisplatin and other chemotherapeutics in lung cancer (54–56), and doxorubicin and melphalan in multiple myeloma (57). Recent studies show an association of MDSC level with patient response to CTLA4/ipilimumab (58, 59) and PD-1 (60, 61).

The fact that MDSC play an important role in the regulation of tumor growth has stimulated the search for a way to therapeutically target these cells.

MDSC can be eliminated with relatively low doses of chemotherapy with gemcitabine and 5-fluorouracil (62–64). It was recently shown that targeting the TRAIL receptor could be a potent and selective method of MDSC depletion (30). Peptibodies consisting of S100A9-derived peptides conjugated to antibody Fc fragments have shown potential in eliminating MDSC in mouse models (65).

MDSC can be functionally inactivated by targeting their suppressive machinery. Recent clinical reports indicated that head and neck and multiple myeloma cancer patients treated with the PDE-5 inhibitor tadalafil had fewer circulating MDSC, lower iNOS and arginase expression in these cells, and a greater number of spontaneously generated tumor specific T-cells (66–68). Nrf2 is a transcription factor that plays an important role in the cellular protection against free radical damage. Synthetic triterpenoid reduced the production of ROS by MDSC and their suppressive activity by upregulating Nrf2 (69). Inhibition of COX-2 downregulated the production of immune suppressive prostaglandin E2, and nitroaspirin has been shown to downregulate NO production (70, 71). Class I HDAC inhibitor entinostat was shown to have an inhibitory effect on MDSC (72), although the mechanism behind effect remains unclear.

MDSC expansion and differentiation can be targeted by all-trans-retinoic acid (ATRA) (73). In lung cancer patients, immune responses to a p53 vaccine were improved if the patients received a short course of ATRA (74). STAT3 inhibition can induce MDSC differentiation into immunogenic DC (75, 76). Phospholipid phosphatidylserine (PS) targeting antibody was shown to decrease frequency of MDSC in tumor-bearing mice although mechanism by which this occurs is unclear (77).

Conclusions

MDSC are a critical factor regulating immune responses under many pathological conditions and have recently became a prominent fixture of tumor immunology. However, their biological role can be established only if methods to selectively target these cells are developed. This requires specific markers of these cells to be identified, which would be possible if the molecular mechanisms governing the development of these cells were better characterized. Hopefully, the next couple of years will bring new and exciting data addressing those challenges.

Acknowledgments

This work was supported by NIH grants CA 141438 and CA 084488 to DIG.

References

1. Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. Nat Rev Cancer. 2013; 13:739–52. [PubMed: 24060865]
2. Bronte V, Chappell DB, Apolloni E, Cabrelle A, Wang M, Hwu P, et al. Unopposed Production of Granulocyte-Macrophage Colony-Stimulating Factor by Tumors Inhibits CD8+ T Cell Responses by Dysregulating Antigen-Presenting Cell Maturation. J Immunol. 1999; 162:5728–37. [PubMed: 10229805]
3. Gabrilovich D, Ishida T, Oyama T, Ran S, Kravtsov V, Nadaf S, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. Blood. 1998; 92:4150–66. [PubMed: 9834220]
4. Gabrilovich DI, Bronte V, Chen SH, Colombo MP, Ochoa A, Ostrand-Rosenberg S, et al. The terminology issue for myeloid-derived suppressor cells. Cancer Res. 2007; 67:425. author reply 6. [PubMed: 17210725]
5. Mandruzzato S, Brandau S, Britten CM, Bronte V, Damuzzo V, Gouttefangeas C, et al. Toward harmonized phenotyping of human myeloid-derived suppressor cells by flow cytometry: results from an interim study. Cancer Immunology, Immunotherapy. 2016; 65:161–9. [PubMed: 26728481]
6. Liu T, Daniels CK, Cao S. Comprehensive review on the HSC70 functions, interactions with related molecules and involvement in clinical diseases and therapeutic potential. Pharmacol Ther. 2012; 136:354–74. [PubMed: 22960394]
7. Bronte V, Brandau S, Chen S-H, Colombo M, Frey A, Greten T, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 2016; 7:12150. [PubMed: 27381735]
8. Dumitru CA, Moses K, Trellakis S, Lang S, Brandau S. Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. Cancer Immunol Immunother. 2012; 61:1155–67. [PubMed: 22692756]
9. Condamine T, Dominguez G, Youn J, Kossenkov A, Mony S, Alicea-Torres K, et al. Lectin-type oxidized LDL receptor 1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. Science Immunol. 2016:1.

10. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012; 12:253–68. [PubMed: 22437938]
11. Koehn BH, Apostolova P, Haverkamp JM, Miller JS, McCullar V, Tolar J, et al. GVHD-associated, inflammasome-mediated loss of function in adoptively transferred myeloid-derived suppressor cells. Blood. 2015; 126:1621–8. [PubMed: 26265697]
12. Marigo I, Bosio E, Solito S, Mesa C, Fernandez A, Dolcetti L, et al. Tumor-induced tolerance and immune suppression depend on the C/EBPbeta transcription factor. Immunity. 2010; 32:790–802. [PubMed: 20605485]
13. Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, et al. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. Nat Med. 2007; 13:828–35. [PubMed: 17603493]
14. Lu T, Ramakrishnan R, Altiok S, Youn J-I, Cheng P, Celis E, et al. Tumor-infiltrating myeloid cells induce tumor cell resistance to cytotoxic T cells in mice. The Journal of Clinical Investigation. 2011; 121:4015–29. [PubMed: 21911941]
15. Molon B, Ugel S, Del Pozzo F, Soldani C, Zilio S, Avella D, et al. Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. J Exp Med. 2011; 208:1949–62. [PubMed: 21930770]
16. Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. Cancer Metastasis Rev. 2011; 30:83–95. [PubMed: 21249423]
17. Casella I, Feccia T, Chelucci C, Samoggia P, Castelli G, Guerriero R, et al. Autocrine-paracrine VEGF loops potentiate the maturation of megakaryocytic precursors through Flt1 receptor. Blood. 2003; 101:1316–23. [PubMed: 12406876]
18. Shojaei F, Wu X, Qu X, Kowanetz M, Yu L, Tan M, et al. G-CSF-initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. Proc Natl Acad Sci U S A. 2009; 106:6742–7. [PubMed: 19346489]
19. Yan HH, Pickup M, Pang Y, Gorska AE, Li Z, Chytil A, et al. Gr-1+CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. Cancer Res. 2010; 70:6139–49. [PubMed: 20631080]
20. Hiratsuka S, Watanabe A, Aburatani H, Maru Y. Tumour-mediated upregulation of chemoattractants and recruitment of myeloid cells predetermines lung metastasis. Nat Cell Biol. 2006; 8:1369–75. [PubMed: 17128264]
21. Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell. 2009; 15:35–44. [PubMed: 19111879]
22. Deng J, Liu Y, Lee H, Herrmann A, Zhang W, Zhang C, et al. S1PR1-STAT3 signaling is crucial for myeloid cell colonization at future metastatic sites. Cancer Cell. 2012; 21:642–54. [PubMed: 22624714]
23. Cui TX, Kryczek I, Zhao L, Zhao E, Kuick R, Roh MH, et al. Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. Immunity. 2013; 39:611–21. [PubMed: 24012420]
24. Toh B, Wang X, Keeble J, Sim WJ, Khoo K, Wong W-C, et al. Mesenchymal Transition and Dissemination of Cancer Cells Is Driven by Myeloid-Derived Suppressor Cells Infiltrating the Primary Tumor. PLoS biology. 2011; 9:e1001162. [PubMed: 21980263]
25. Di Mitri D, Toso A, Chen JJ, Sarti M, Pinton S, Jost TR, et al. Tumour-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. Nature. 2014; 515:134–7. [PubMed: 25156255]
26. Eggert T, Wolter K, Ji J, Ma C, Yevsa T, Klotz S, et al. Distinct Functions of Senescence-Associated Immune Responses in Liver Tumor Surveillance and Tumor Progression. Cancer Cell. 2016; 30:533–47. [PubMed: 27728804]
27. Condamine T, Mastio J, Gabrilovich DI. Transcriptional regulation of myeloid-derived suppressor cells. J Leukoc Biol. 2015

28. Youn JI, Kumar V, Collazo M, Nefedova Y, Condamine T, Cheng P, et al. Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. Nat Immunol. 2013; 14:211–20. [PubMed: 23354483]
29. Casbon AJ, Reynaud D, Park C, Khuc E, Gan DD, Schepers K, et al. Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. Proc Natl Acad Sci U S A. 2015; 112:E566–75. [PubMed: 25624500]
30. Condamine T, Kumar V, Ramachandran IR, Youn JI, Celis E, Finnberg N, et al. ER stress regulates myeloid-derived suppressor cell fate through TRAIL-R-mediated apoptosis. J Clin Invest. 2014; 124:2626–39. [PubMed: 24789911]
31. Lee BR, Chang SY, Hong EH, Kwon BE, Kim HM, Kim YJ, et al. Elevated endoplasmic reticulum stress reinforced immunosuppression in the tumor microenvironment via myeloid-derived suppressor cells. Oncotarget. 2014; 5:12331–45. [PubMed: 25514597]
32. Thevenot PT, Sierra RA, Raber PL, Al-Khami AA, Trillo-Tinoco J, Zarreii P, et al. The stress-response sensor chop regulates the function and accumulation of myeloid-derived suppressor cells in tumors. Immunity. 2014; 41:389–401. [PubMed: 25238096]
33. Condamine T, Gabrilovich DI. Can the Suppressive Activity of Myeloid-Derived Suppressor Cells Be “Chop”ped? Immunity. 2014; 41:341–2. [PubMed: 25238087]
34. Corzo CA, Condamine T, Lu L, Cotter MJ, Youn JI, Cheng P, et al. HIF-1alpha regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. J Exp Med. 2010; 207:2439–53. [PubMed: 20876310]
35. Kumar V, Cheng P, Condamine T, Mony S, Languino L, McCaffrey J, et al. CD45 phosphatase regulates the fate of myeloid cells in tumor microenvironment by inhibiting STAT3 activity. Immunity. 2016; 44:303–15. [PubMed: 26885857]
36. Eruslanov EB, Bhojnagarwala PS, Quatromoni JG, Stephen TL, Ranganathan A, Deshpande C, et al. Tumor-associated neutrophils stimulate T cell responses in early-stage human lung cancer. J Clin Invest. 2014; 124:5466–80. [PubMed: 25384214]
37. Choksawangkarn W, Graham LM, Burke M, Lee SB, Ostrand-Rosenberg S, Fenselau C, et al. Peptide-based systems analysis of inflammation induced myeloid-derived suppressor cells reveals diverse signaling pathways. Proteomics. 2016; 16:1881–8. [PubMed: 27193397]
38. Gato M, Blanco-Luquin I, Zudaire M, de Morentin XM, Perez-Valderrama E, Zabaleta A, et al. Drafting the proteome landscape of myeloid-derived suppressor cells. Proteomics. 2016; 16:367–78. [PubMed: 26403437]
39. Gato-Canas M, Martinez de Morentin X, Blanco-Luquin I, Fernandez-Irigoyen J, Zudaire I, Liechtenstein T, et al. A core of kinase-regulated interactomes defines the neoplastic MDSC lineage. Oncotarget. 2015; 6:27160–75. [PubMed: 26320174]
40. Fridlender ZG, Sun J, Mishalian I, Singhal S, Cheng G, Kapoor V, et al. Transcriptomic analysis comparing tumor-associated neutrophils with granulocytic myeloid-derived suppressor cells and normal neutrophils. PloS one. 2012; 7:e31524. [PubMed: 22348096]
41. Chornoguz O, Grmai L, Sinha P, Artemenko KA, Zubarev RA, Ostrand-Rosenberg S. Proteomic pathway analysis reveals inflammation increases myeloid-derived suppressor cell resistance to apoptosis. Mol Cell Proteomics. 2011; 10:M110 002980.
42. Strauss L, Sangaletti S, Consonni FM, Szebeni G, Morlacchi S, Totaro MG, et al. RORC1 Regulates Tumor-Promoting “Emergency” Granulo-Monocytopoiesis. Cancer Cell. 2015; 28:253–69. [PubMed: 26267538]
43. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol. 2016
44. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: “N1” versus “N2” TAN. Cancer Cell. 2009; 16:183–94. [PubMed: 19732719]
45. Cimen Bozkus C, Elzey BD, Crist SA, Ellies LG, Ratliff TL. Expression of Cationic Amino Acid Transporter 2 Is Required for Myeloid-Derived Suppressor Cell-Mediated Control of T Cell Immunity. J Immunol. 2015; 195:5237–50. [PubMed: 26491198]
46. Mairhofer DG, Ortner D, Tripp CH, Schaffenrath S, Fleming V, Heger L, et al. Impaired gp100-Specific CD8(+) T-Cell Responses in the Presence of Myeloid-Derived Suppressor Cells in a

Spontaneous Mouse Melanoma Model. J Invest Dermatol. 2015; 135:2785–93. [PubMed: 26121214]

47. Raber PL, Thevenot P, Sierra R, Wyczechowska D, Halle D, Ramirez ME, et al. Subpopulations of myeloid-derived suppressor cells impair T cell responses through independent nitric oxide-related pathways. Int J Cancer. 2014; 134:2853–64. [PubMed: 24259296]
48. Ortiz M, Lu L, Ramachandran I, Gabrilovich D. Myeloid-Derived Suppressor Cells in the Development of Lung Cancer. Cancer Immunol Res. 2014; 2:50–8. [PubMed: 24778162]
49. Ortiz M, Kumar V, Martner A, Mony S, Donthireddy L, Condamine T, et al. Immature myeloid cells directly contribute to skin tumor development by recruiting IL-17 producing CD4+ T cells. J Exp Med. 2015 in press.
50. Messmer MN, Netherby CS, Banik D, Abrams SI. Tumor-induced myeloid dysfunction and its implications for cancer immunotherapy. Cancer Immunol Immunother. 2015; 64:1–13. [PubMed: 25432147]
51. Solito S, Marigo I, Pinton L, Damuzzo V, Mandruzzato S, Bronte V. Myeloid-derived suppressor cell heterogeneity in human cancers. Ann NY Acad Sci. 2014; 1319:47–65. [PubMed: 24965257]
52. Zhang S, Ma X, Zhu C, Liu L, Wang G, Yuan X. The Role of Myeloid-Derived Suppressor Cells in Patients with Solid Tumors: A Meta-Analysis. PloS one. 2016; 11:e0164514. [PubMed: 27780254]
53. Finke J, Ko J, Rini B, Rayman P, Ireland J, Cohen P. MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. Int Immunopharmacol. 2011; 11:856–61. [PubMed: 21315783]
54. Feng PH, Lee KY, Chang YL, Chan YF, Kuo LW, Lin TY, et al. CD14(+)S100A9(+) monocytic myeloid-derived suppressor cells and their clinical relevance in non-small cell lung cancer. American journal of respiratory and critical care medicine. 2012; 186:1025–36. [PubMed: 22955317]
55. Vetsika E-K, Koinis F, Gioulbasani M, Aggouraki D, Koutoulaki A, Skalidaki E, et al. A Circulating Subpopulation of Monocytic Myeloid-Derived Suppressor Cells as an Independent Prognostic/Predictive Factor in Untreated Non-Small Lung Cancer Patients. Journal of Immunology Research. 2014; 2014:12.
56. Liu CY, Wang YM, Wang CL, Feng PH, Ko HW, Liu YH, et al. Population alterations of L-arginase- and inducible nitric oxide synthase-expressed CD11b+/CD14(−)/CD15+/CD33+ myeloid-derived suppressor cells and CD8+ T lymphocytes in patients with advanced-stage non-small cell lung cancer. J Cancer Res Clin Oncol. 2010; 136:35–45. [PubMed: 19572148]
57. Ramachandran IR, Condamine T, Lin C, Herlihy SE, Garfall A, Vogl DT, et al. Bone marrow PMN-MDSCs and neutrophils are functionally similar in protection of multiple myeloma from chemotherapy. Cancer Letters. 2016; 371:117–24. [PubMed: 26639197]
58. Meyer C, Cagnon L, Costa-Nunes CM, Baumgaertner P, Montandon N, Leyvraz L, et al. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. Cancer Immunol Immunother. 2014; 63:247–57. [PubMed: 24357148]
59. Tarhini AA, Edington H, Butterfield LH, Lin Y, Shuai Y, Tawbi H, et al. Immune Monitoring of the Circulation and the Tumor Microenvironment in Patients with Regionally Advanced Melanoma Receiving Neoadjuvant Ipilimumab. PloS one. 2014; 9:e87705. [PubMed: 24498358]
60. Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Science translational medicine. 2014; 6:237ra67.
61. Weber J, Gibney G, Kudchadkar R, Yu B, Cheng P, Martinez AJ, et al. Phase I/II Study of Metastatic Melanoma Patients Treated with Nivolumab Who Had Progressed after Ipilimumab. Cancer Immunol Res. 2016; 4:345–53. [PubMed: 26873574]
62. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. Clin Cancer Res. 2005; 11:6713–21. [PubMed: 16166452]
63. Le HK, Graham L, Cha E, Morales JK, Manjili MH, Bear HD. Gemcitabine directly inhibits myeloid derived suppressor cells in BALB/c mice bearing 4T1 mammary carcinoma and augments expansion of T cells from tumor-bearing mice. Int Immunopharmacol. 2009; 9:900–9. [PubMed: 19336265]

64. Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res. 2010; 70:3052–61. [PubMed: 20388795]

65. Qin H, Lerman B, Sakamaki I, Wei G, Cha SC, Rao SS, et al. Generation of a new therapeutic peptide that depletes myeloid-derived suppressor cells in tumor-bearing mice. Nat Med. 2014; 20:676–81. [PubMed: 24859530]

66. Califano JA, Khan Z, Noonan KA, Rudraraju L, Zhang Z, Wang H, et al. Tadalafil Augments Tumor Specific Immunity in Patients with Head and Neck Squamous Cell Carcinoma. Clinical Cancer Research. 2015; 21:30–8. [PubMed: 25564570]

67. Weed DT, Vella JL, Reis IM, De la Fuente AC, Gomez C, Sargi Z, et al. Tadalafil reduces myeloid-derived suppressor cells and regulatory T cells and promotes tumor immunity in patients with head and neck squamous cell carcinoma. Clin Cancer Res. 2015; 21:39–48. [PubMed: 25320361]

68. Noonan KA, Ghosh N, Rudraraju L, Bui M, Borrello I. Targeting immune suppression with PDE5 inhibition in end-stage multiple myeloma. Cancer Immunol Res. 2014; 2:725–31. [PubMed: 24878583]

69. Nagaraj S, Youn J-I, Weber H, Iclozan C, Lu L, Cotter MJ, et al. Anti-inflammatory Triterpenoid Blocks Immune Suppressive Function of MDSCs and Improves Immune Response in Cancer. Clinical Cancer Research. 2010; 16:1812–23. [PubMed: 20215551]

70. Rodriguez PC, Hernandez CP, Quiceno D, Dubinett SM, Zabaleta J, Ochoa JB, et al. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. The Journal of Experimental Medicine. 2005; 202:931–9. [PubMed: 16186186]

71. De Santo C, Serafini P, Marigo I, Dolcetti L, Bolla M, Del Soldato P, et al. Nitroaspirin corrects immune dysfunction in tumor-bearing hosts and promotes tumor eradication by cancer vaccination. Proc Natl Acad Sci U S A. 2005; 102:4185–90. [PubMed: 15753302]

72. Kim K, Skora AD, Li Z, Liu Q, Tam AJ, Blosser RL, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. Proc Natl Acad Sci U S A. 2014; 111:11774–9. [PubMed: 25071169]

73. Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res. 2006; 66:9299–307. [PubMed: 16982775]

74. Iclozan C, Antonia S, Chiappori A, Chen DT, Gabrilovich D. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer Immunol Immunother. 2013; 62:909–18. [PubMed: 23589106]

75. Nefedova Y, Nagaraj S, Rosenbauer A, Muro-Cacho C, Sebti SM, Gabrilovich DI. Regulation of dendritic cell differentiation and antitumor immune response in cancer by pharmacologic-selective inhibition of the janus-activated kinase 2/signal transducers and activators of transcription 3 pathway. Cancer Res. 2005; 65:9525–35. [PubMed: 16230418]

76. Sansone P, Bromberg J. Targeting the interleukin-6/Jak/stat pathway in human malignancies. J Clin Oncol. 2012; 30:1005–14. [PubMed: 22355058]

77. Freimark BD, Gong J, Ye D, Gray MJ, Nguyen V, Yin S, et al. Antibody-Mediated Phosphatidylserine Blockade Enhances the Antitumor Responses to CTLA-4 and PD-1 Antibodies in Melanoma. Cancer Immunol Res. 2016; 4:531–40. [PubMed: 27045021]

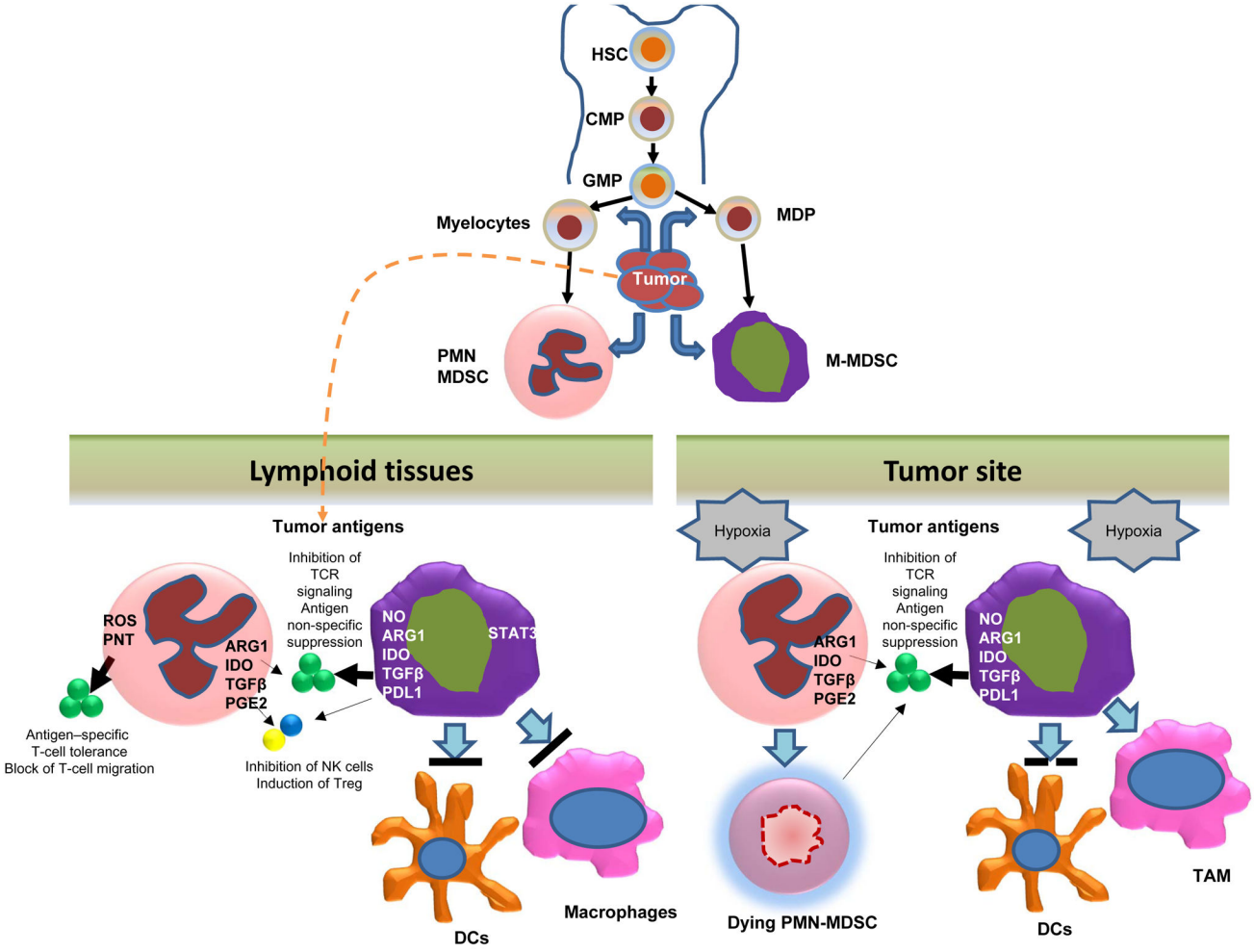

Figure. Development and function of MDSC

Tumor derived factors affect different stages of myeloid cell differentiation resulting in generation of pathologically activated M-MDSC and PMN-MDSC. HSC-hematopoietic stem cells; CMP – common myeloid progenitor; GMP-granulocyte-macrophage progenitor; MDP – macrophage/dendritic cell progenitors. PMN-MDSC and M-MDSC migrate to lymphoid organs and to tumor site. The function and fate of these cells is different in different sites. In peripheral lymphoid organs PMN-MDSC retain high level of various ROS and cause antigen-specific T-cell suppression/tolerance. M-MDSC produce large array of different factors that enable these cells suppress not only antigen-specific but also non-specific T cell responses. M-MDSC maintain high activity of STAT3 that prevent their quick differentiation to DCs or macrophages. In tumor site, largely due to the effect of hypoxia STATA3 activity in MDSC is dramatically reduced. This result in rapid differentiation of M-MDSC to tumor associated macrophages (TAM). ROS level in PMN-MDSC is substantially reduced, but up-regulation of arginase 1(ARG1) and other factors responsible for nonspecific T-cell suppression is increased. The same happens with M-MDSC. PMN-MDSC are dying rapidly. Factors released by dying cells can contribute to immune suppressive mechanisms.