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History of myeloid derived suppressor cells (MDSCs) in the macro- and micro-environment of tumour-bearing hosts

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Abstract

Tumour-induced granulocytic hyperplasia is associated with tumour vasculogenesis and escape from immunity via T-cell suppression. Initially, these myeloid cells were identified as granulocytes or monocytes; however, recent studies revealed that this hyperplasia was associated with populations of multi-potent progenitor cells identified as myeloid-derived suppressor cells (MDSCs). The discovery and study of MDSCs have provided a wealth of information regarding tumour pathobiology, extended our understanding of neoplastic progression, and modified our approaches to immune adjuvant therapy. In this perspective, we discuss the history of MDSCs, their influence on tumour progression and metastasis, and the crosstalk between tumour cells, MDSCs, and the host macroenvironment.

INTRODUCTION

One characteristic of tumour progression, originally described in the early 1900s¹, is an increase in extramedullary haematopoiesis (EMH) and neutrophilia that was later shown to result in immune evasion and tumour vascularization. Classically, this occurs within the host macroenvironment and is associated with increased serum haematopoietic, colony-stimulating activity² and abnormal myeloid cell differentiation resulting in a bidirectional molecular crosstalk between tumour cells and myeloid progenitor cells. Originally, these abnormal myeloid cells were described as veto cells, null cells, or natural-suppressor (NS) cells and were later shown to inhibit lymphocyte numbers, cytotoxic T-lymphocyte (CTL) induction, and activity³. These cells lacked membrane markers for mature T-cells, B-cells, and natural killer (NK) cells, as well as, macrophages^{4, 5}, resulting in the nomenclature of null cells. Initially, their phenotypic characterization was contentious, and it continues to be partially unresolved due to investigator-dependent phenotypic marker profiles and cellular heterogeneity⁶. Consistent with tumor heterogeneity⁷, there is a tumour-dependent variability in myeloid-cell expansion that may be associated with the secretion of differing

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cytokines and chemokines. In recent years, the concept of myeloid-derived suppressor cells (MDSCs) was introduced to reflect the abnormal nature of myelopoiesis in cancer, which is the focus of this review. These studies have revealed that circulating MDSC numbers correlate with a poor prognosis, tumour vasculogenesis, osteoporosis, and tumour evasion of host immunity^{8–10}.

A direct relationship between tumour burden and MDSC frequency has been demonstrated in several mouse tumour models^{11, 12} and clinical studies^{8–10}, as well as, an inverse correlation between MDSC and T-cell frequency in the peripheral blood (PB)¹². While this may be model and, potentially, tumour dependent, a direct relationship between tumour burden and MDSC frequency and numbers is generally accepted. In support of this observation, the resection of solid tumours has been shown to decrease MDSC frequency in the PB and to reverse T-cell suppression^{13, 14}. The increase in MDSCs depends both on tumour burden^{12, 15, 16} and the tumor-secreted factors^{17–19} regulating myeloid progenitor cell survival and expansion. Antibody-mediated depletion of MDSCs also restores T-cell frequency and function^{20, 21}. Confirmation of these observations using transplantable tumours has been provided with a mouse mammary tumour virus (MMTV) c-erbB-2 transgenic mouse model of breast cancer²². In this model, there was a direct association between the spontaneous development of metastatic mammary tumours and MDSC expansion. Similar observations have been observed clinically with solid tumours, including a direct relationship with tumour state and indirectly with T-cell dysfunction¹⁰.

HISTORY OF SUPPRESSIVE MYELOID CELLS; PHENOTYPES AND SUBSETS

In the mid-1960s, NS cells within tumour-bearing mice were reported to induce a leukemoid reaction that was related to the duration of tumour growth and myeloid-cell infiltration^{23, 24}. These cells were not only associated with tumour growth, but were also a major component of inflammatory and haematopoietic processes³, including a presence in neonatal/newborn spleens, adult bone marrow (BM)³, and adult spleens following total body irradiation (TBI)⁴. Subsequent studies revealed an increase in NS cells in lymphoid and some parenchymal organs during tumour growth^{24, 25} and following Bacillus Calmette-Guerin (BCG)^{26, 27} injection. The tumour-induced granulocytosis, associated lymphopenia²⁴, and loss of T-cell function²⁵ suggested a potential impact on cancer outcome, as well as, therapeutic potential if NS cells were down-regulated. This potential has been supported by studies demonstrating that decreasing myeloid cells in tumour-bearing mice is therapeutic^{13, 28}. In the late 1970s, it was documented that leukemoid reaction(s) included cellular population(s), which could inhibit CTL induction²⁹ and activity³. These cells, due to a lack of conventional membrane markers for T-cells, B-cells, NK cells, and macrophages, were also described as NS or “null” cells^{5, 30}. Functionally, they inhibited T-cell proliferative responses, antibody production, and CTL induction. They also suppressed antitumour immune responses and promoted immune evasion.

Mouse myeloid suppressor cells

Initially, the phenotypic characterization of null or NS cells in mice was contentious due to a lack of phenotypic markers, and they were defined based on a suppressive function³. Subsequently, mouse studies identified their phenotype (BOX 1) using the expression of single membrane markers, including CD34³¹, Gr1^{32, 33}, or CD11b³⁴. NS cells in tumour-bearing mice were also characterized as committed myeloid progenitor cells and quantified as cycling progenitor cells, or immature cells of monocyte-macrophage lineage using soft agar colony-forming assay³⁵. NS activity was also reported to be mediated by multiple cell populations^{6, 36} including cells from the spleen or BM³⁷. Early studies suggested that the most potent cyclophosphamide (CTX)-induced suppressor-cell population was derived from cells with a granulocyte-monocyte lineage that expressed CD11b⁶. This was supported by an observed 600-fold increase in granulocyte-macrophage colony-forming cells in the blood of mice following CTX injection as compared to untreated controls³⁵. Cells with an NS phenotype and function were also identified at sites of intense haematopoiesis³⁸ and found to be increased by tumour secretion^{38–40}, or exogenous administration of haematopoietic growth factors including granulocyte-macrophage colony-stimulating factor (GM-CSF)⁴¹ and granulocyte-CSF (G-CSF)⁴². Thus, not only does tumour growth increase myeloid suppressor cells, but their numbers are also expanded by haematopoietic growth factor administration with potential impact on therapeutic intervention. It should be noted that cells with this phenotype are observed in the BM of naïve mice, but in the absence of T-cell suppressive activity. It has been suggested that in addition to their expansion, these immature cells need to be activated in order to be immunosuppressive⁴³, such that in naïve mice these cells are not MDSCs.

Phenotypic heterogeneity^{44, 45} without consensus regarding the cellular phenotype(s) that induces T-cell dysfunction broadened the already diverse nomenclature to include immature myeloid cells (iMCs), myeloid suppressor cells (MSCs), and Gr1⁺ myeloid cells^{46, 47}. Not until the Gr1⁺CD11b⁺ cellular phenotype was suggested in the late 1990s, was there general agreement that a cell population existed, classified as NS cells, that was distinct from monocytes and granulocytes^{48, 49}. In 2007, the nomenclature controversy was largely resolved when a letter was published⁵⁰ and a consensus⁵¹ reached identifying MDSC as the term for this cellular phenotype and function. However, MDSC does not testify to the immaturity of these cells, and some investigators continue to describe them as iMCs. Because, iMC does not speak to T-cell suppression, MDSC has become the preferred terminology⁵², however, although the nomenclature differs, the cellular phenotypes for MDSCs and iMCs remain consistent.

Cytology (macrophage and granulocytic) and gene expression (differential expression of inducible nitric oxide synthase (iNOS) and arginase) studies support MDSC heterogeneity, and recently, markers that subdivide mouse MDSCs have been identified based on expression of Ly-6C and Ly-6G⁵³. CD11b⁺Ly-6G^{low}Ly-6C^{high} cells have a monocytic-like morphology, preferentially express nitric oxide synthase 2 (NOS2), have increased T-cell suppressive activity, and are identified as monocytic-MDSCs (Mo-MDSCs)⁵³. This contrasts with CD11b⁺Ly-6G⁺Ly-6C^{low} cells that have a granulocyte-like morphology, express high levels of arginase type 1 (ARG1), and are identified as granulocytic-MDSCs

(G-MDSCs). These cells have a polymorphonuclear morphology and, therefore, the term polymorphonuclear (PMN)-MDSC is used interchangeably with G-MDSC. In the majority of tumour-bearing mice, the G-MDSC population consistently increases, whereas the Mo-MDSC frequency is significantly increased in a limited number of tumour models⁵³. Further, even in mice whose tumours have substantial increases in Mo-MDSCs, the G-MDSC population is also increased. Thus, the G-MDSC subset is the predominant MDSC population in tumour-bearing mice⁵³. This subset distinction can also be clarified by CD11b and Gr-1 staining⁵⁴. Two cellular fractions are generally recognized, a Gr-1^{Br} subset, mainly composed of G-MDSCs, and a Gr-1^{int} subset encompassing Mo-MDSCs¹⁷.

Additional MDSC subsets have been based on the intensity of Gr1 expression (Gr1^{lo}, Gr1^{int}, Gr1^{Br})¹⁷ or the use of alternative phenotypic markers including F4/80 or MHCII expression markers, which are also used to identify tumour-associated macrophages (TAMs). TAMs are a cellular population that histologically can be confused with MDSCs, but are defined as mature, differentiated macrophages⁵⁵. Distinguishing MDSCs from macrophages and, to a lesser extent, granulocytes can be technically challenging. Mouse Mo-MDSCs have been classified as CD11b⁺Ly6G^{lo/int}Ly6C^{hi} cells that express low levels of F4/80 (a marker for macrophages) and higher levels of Gr1 than TAMs⁵⁶. Further, both MDSCs and TAMs express interleukin 4 receptor α (IL4R α ; also known as CD124) and M-CSF receptor (also known as CD115)⁵⁶. Mo-MDSCs are a mixture of myeloid progenitor cells in varying stages of differentiation^{55, 57}, which can differentiate into macrophages, dendritic cells (DCs), or granulocytes. Studies to distinguish TAMs from Mo-MDSCs have linked inducible NOS2 expression to the overall differentiation and maturation stage. NOS2⁺ cells do not generally express granulocyte markers, including chemokine (C-X-C motif) receptor 2 (CXCR2) and lymphocyte antigen 6G (Ly6G), which are expressed by NOS2⁻ MDSCs⁵⁸. However, intracellular NOS2 staining of tumour-infiltrating MDSCs has also identified a NOS2⁺ cellular subset with a ring-shaped nuclei⁵⁸. This subset has T-suppressive activity, and the ring-shaped nuclei are characteristic of immature neutrophils. Thus, tumours affect haematopoietic progenitor cell differentiation, resulting in the accumulation of cells with neutrophil-like ring nuclei, but no macrophage differentiation markers, such as F4/80. This is consistent with prior studies that demonstrated cellular phenotypes in the BM with the potential to differentiate into macrophages in response to M-CSF⁵⁹. Further, this cellular subset, as well as, Mo-MDSCs can differentiate into F4/80⁺ TAMs in the tumour microenvironment⁶⁰. In one study, MDSCs were subset based on CD49d expression with CD49d⁺ MDSCs demonstrating a monocytic phenotype and immunosuppressive activity. In this study CD49d⁻ MDSCs were granulocytic with little T-cell inhibitory activity⁶¹. However, subsequent studies were unable to distinguish between the granulocytic and iNOS⁺ MDSCs based on CD49d expression⁵⁸. Studies using rodent MDSC subsets have been paralleled by human studies that, in general, revealed similar phenotypes including differences in enzyme expression by MDSC subsets and differentiation into granulocytic and monocytic subsets⁶².

Human MDSCs

In the mid-1990s, G-CSF or GM-CSF stem-cell mobilization for autologous PB stem-cell transplantation, predominantly for the treatment of patients with breast cancer or lymphoma,

was found to result in myeloid cells with T-cell suppressive activity that were defined as suppressive CD14⁺ monocytes^{63–65}. Indeed, studies of monocyte associated suppressive activity revealed a direct relationship between the number of CD14⁺ cells and suppressor cell function in mobilized stem cell products⁶⁴, as well as, characteristics of cells with a monocyte lineage⁶⁶. Subsequent studies of breast cancer patients following stem cell transplantation revealed that T-cell number and function inversely correlated with T-cell suppressor activity and CD14 cell frequency in the PB post transplantation^{38, 64} and from patients with advanced disease⁶⁷. This inhibitory cell was isolated from PB stem cell (PBSC) products and shown to be a CD14⁺ myeloid cell⁶⁸ comprising up to 40% of the cells in the apheresis product. Further, 10% or more of PB leukocytes following peripheral stem cell transplant (PSCT)⁶⁹ were shown to be CD14⁺ with T-cell suppressive activity⁶⁵.

In the late 1990s, human MDSCs were also described in patients with head and neck cancer based on CD34 expression and T-cell suppression in patients with GM-CSF-secreting cancers^{38, 64, 70}. However, these MDSCs were lineage-negative (Lin[−]) CD34⁺ cells, a phenotype that also defines haematopoietic progenitor cells. Thereafter, the MDSC phenotype was extended to include a phenotype that included negativity for human leukocyte antigen D-related (HLA-DR) expression and a myeloid marker⁷¹. In cancer patients, MDSCs express either or both of the common myeloid markers CD33 or CD11b, are Lin[−], and or are HLA-DR[−]⁷¹. Thus, human MDSCs were initially defined as HLA-DR[−]CD33⁺⁷¹ or CD14[−]CD11b⁺ cells⁷² with both phenotypes identifying cell populations with T-cell suppressive activity. Recently, more rigorous marker subsets have defined MDSCs, including Mo-MDSC expression of CD14^{+/dull}^{73, 74} and G-MDSC expression of CD15⁺, as observed primarily in patients with advanced renal-cell cancer (RCC)^{67, 75}. The expression of CD14 on MDSCs as a Mo-MDSC, initially controversial, has become accepted. Nonetheless, CD14 expression is difficult to use as a lineage marker as PMNs also express lower levels of this marker. Thus, differentiation between CD14 bright versus dim in the assessment of MDSCs is critical. Human MDSCs have been further subdivided based on maturity⁷⁶, although, definition of these subsets has not yet reached consensus. The identification of a precursor subset supports MDSC plasticity and their potential to differentiate into not only granulocytes, monocytes, and DCs, but also osteoclasts (OCs) and endothelial cells (ECs). Now, there are additional phenotypic parameters under investigation including, but not limited to, high CD66b levels, low levels of CD62L, low CD16 expression⁷⁶, vascular endothelial growth-factor receptor 1 (VEGFR1) expression⁷⁵, and S100A9⁷⁷, although the latter phenotype is not membrane expressed and cannot be used to isolate cells.

Myeloid cell populations are the predominant population in the PB, both in number and function, tumour infiltration, and supporting tumour growth and progression⁷⁸. Although granulocytes are the first line of defense against tumour challenge, they also have a pro-tumourigenic role providing an immune paradox. The basis for this functional MDSC “plasticity,” observed in both mice and humans, is based on their capability to express different functional profiles in response to varying environmental signals including cytokines, growth factors and acidosis, hypoxia, interstitial pressure, and glucose levels. Hypoxia and hypoxia-inducible factor-1 alpha (HIF-1α) in the tumor microenvironment are partially responsible for the regulation of ARG-1 and NOS expression by murine MDSC and

their differentiation. Similarly, the tumor-dependent profile of secreted cytokines also regulates MDSC differentiation supporting the conversion between MDSC phenotypes, differentiation, and activation. However, the exact combination and sequence of tumour-derived and microenvironmental factors that regulate MDSC mobilization, proliferation, abnormal differentiation, and activation remain poorly understood. Consequently, the current focus is directed towards mechanisms and molecules driving the protumoural skewing and the phenotypic heterogeneity of circulating and tumour infiltrating MDSCs. Similar to mouse MDSCs, human MDSCs are haematopoietic progenitors that can differentiate into not only granulocytes and monocytes, but also ECs and OCs. While specific growth factors drive MDSCs to differentiate, whether differing MDSC profiles between tumours are due to tumour heterogeneity, or if a profile consistency exists based on tumour histiotype, is unstudied.

Mechanisms of myeloid cell and tumour cross-regulation

Haematopoietic abnormalities in tumour-bearing hosts, originally described as neutrophilia characterized by abundant less mature cells⁷⁹, have long been observed¹. Mechanistically, this is associated with tumour secretion of cytokines and chemokines that induce myeloid cell proliferation, accumulation, and tumour infiltration^{18, 22, 80}. Recently, it was reported that many of these accumulating cells were not mature cells as originally described, but rather progenitor cells with immunosuppressive activity and the ability to differentiate not only into granulocytes, histiocytes, and DCs, but also EC precursors and OCs. Myeloid cells respond to a wide range of stimuli most notably their molecular microenvironment and the heterogeneous milieu of tumor-secreted cytokines. The plasma cytokines and chemokines differ between tumour-bearing hosts (both in humans and mice), resulting in tumour-dependent proliferation, site(s) of accumulation, and infiltration, which have made it difficult to determine the crucial factors that result in MDSC activity in the tumour microenvironment. Further, not only do tumours secrete growth factors that induce myelopoiesis and chemokines that mobilize and marginate MDSCs, they may also limit their maturation and differentiation thereby contributing to their accumulation⁸¹. Thus, tumour necrosis factor-alpha (TNF- α) impairs MDSC maturation⁸² by regulating the receptor for advanced glycation end products (RAGE) and its ligands (S100A8 and S100A9 proteins)⁸³. Additional, proinflammatory mediators, such as IL-1 beta (IL-1 β), IL-6, leukotriene D4 (LTD4), and prostaglandin E2 (PGE2) that regulate MDSC accumulation and activation, may also affect MDSC differentiation, but remain to be assessed for these functions. The heterogeneity in the processes (BOX 2) that regulate MDSC proliferation, accumulation, and trafficking have been documented in both rodent models⁵³ and clinically⁸⁴. These processes include mobilization and proliferation (most notably as EMH), maturation, arrest, trafficking, and margination all of which contribute to organ and tumour accumulation. Indeed, MDSCs within tumours have been shown in the 4T1 tumour model to be derived from splenic and hepatic EMH prior to tumour infiltration¹¹. Therefore, macroenvironmental changes, such as types and extent of circulating cytokines and chemokines, have a critical role in regulating infiltrating cells in the tumour microenvironment such that MDSC pathobiology is regulated by the macroenvironment via altered myelopoiesis and differentiation^{56, 85, 86} in association with tumour-derived haematopoietic growth factors and chemokines.

MACROENVIRONMENTAL REGULATION OF MDSCS

Regulation of MDSC proliferation

Building on our understanding of tumour progression and metastasis, tumour-secreted chemokines, growth factors, and enzymes that contribute to myeloid-cell expansion, differentiation, and recruitment also have been suggested to regulate tumour progression and metastasis. The effect of MDSCs on tumour progression and metastasis is observed *in vivo* by down-regulation of neutrophilia following tumour resection^{13, 14, 28, 87}, intervention using antibodies to myeloid cells^{18, 88}, or molecular growth-factor inhibitors²⁰. The increase in circulating myeloid cells in tumor-bearing hosts, originally termed reactive neutrophilia or emergency granulopoiesis, was associated with an increased frequency of iMCs. Improvements in biomarkers identified neutrophilia with an increase in circulating colony forming unit in culture (CFU-c) and, recently, MDSCs. Mechanistic studies using tumour-conditioned media (TCM) to cultures of spleen¹⁵, BM⁵⁶, or isolated myeloid/progenitor cell subsets^{53, 89} have identified mediators and effected MDSC survival, proliferation, differentiation, and function, as well as, T-cell proliferation and DC function⁹⁰ and differentiation³³. Tumours that stimulate MDSC proliferation have been shown to secrete VEGF^{32, 33, 81, 91}, GM-CSF⁴⁰, stem cell factor (SCF)⁹², FMS-like tyrosine kinase 3 ligand (FLT3-L)⁹³, G-CSF^{17, 18, 41}, and/or macrophage-colony stimulating factor (M-CSF)⁵⁷. Indeed, studies using transplantable tumours linked tumour GM-CSF secretion to MDSC expansion^{17, 40, 41, 94} by the knock down of GM-CSF in tumor cell lines resulting in an altered MDSC number and subset distribution following tumour growth¹⁷. Consistent with such studies, and depending on the tumour studied, antibody or molecular inhibitor neutralization of GM-CSF, or its receptor^{15, 94, 95}, M-CSF^{96, 97}, VEGF^{91, 98}, S100A8/A9⁸¹, G-CSF¹⁸, or SCF⁹², have also been shown to inhibit MDSC accumulation, MDSC recruitment to the tumour microenvironment, and delay tumour development (Table 1). In a mouse model of mammary cancer (BALB-neuT mice, which develop c-erb-2-driven mammary tumours), investigators reported a direct correlation between tumour progression and numbers of immature Gr1⁺CD11b⁺CD131⁺ cells with immunosuppressive activity⁹¹. G-CSF, similar to GM-CSF, can also facilitate G-MDSC accumulation, as well as, regulate granulopoiesis and neutrophil mobilization⁹⁹. Increased G-CSF levels have been shown to inhibit innate and adaptive immunity¹⁰⁰ and are aberrantly expressed by diverse human tumours¹⁰¹. G-CSF production also correlates with atypical MDSC-like responses in mouse tumour models^{22, 80}; however, the correlation between G-CSF and MDSC accumulation has focused largely on systemic MDSC responses¹⁰² with limited studies assessing the impact of G-CSF on Mo- versus G-MDSC subsets¹¹. While it remains unclear whether a specific growth factor is unique to a defined tumour histotype, tumour secretion of growth factors regulates MDSC proliferation.

In vitro mechanistic studies to assess MDSC regulation have used TCM and demonstrated that TCM, but not control media, can induce the proliferation of c-kit⁺ MDSC precursors¹⁵; resulting in a cell population that is predominantly Gr-1⁺CD11b⁺¹⁰³. In one study, proliferation and differentiation of c-kit⁺ MDSC splenocytes was only observed with GM-CSF and not with recombinant VEGF or SCF, and only minimally with IL-6¹⁵. However, an intermediate level of proliferation was observed with high concentrations of M-CSF. More

critically, addition of a neutralizing GM-CSF antibody to the TCM culture abrogated MDSC generation from c-kit⁺ precursors. Neutralizing antibodies to other cytokines, such as SCF, IL-6, or IL-1 β , had no effect suggesting that GM-CSF is both necessary and sufficient to generate functional, immunosuppressive MDSCs *in vitro*. Thus, GM-CSF was suggested to be the tumour-associated proliferative factor for MDSC differentiation and proliferation (i.e., secreted by tumours, not by normal epithelial cells, resulting in suppressive MDSCs from c-kit⁺ splenocytes)¹⁵.

Recently, organ-¹⁶ and tumour-dependent¹⁰⁴ MDSC proliferation was shown to rely, in part, on tumour-derived microenvironmental and macroenvironmental growth factor levels, which vary in a tumour and anatomical manner^{3, 12, 16, 95}. In one study, MDSC numbers in the spleen directly correlated with tumour G-CSF transcript levels, whereas MDSC numbers in the tumour directly correlated with splenic GM-CSF transcript levels, tumour volume, and tumour cell numbers¹⁴. The observation of EMH in reticuloendothelial⁶ and parenchymal tissues^{3, 24} is well established; however, its role in MDSC accumulation has been little studied^{32, 105}. Indeed, adult, non-tumour-bearing mice have few splenic progenitor cells³³; however, when stressed, haematopoietic progenitor cells mobilize from the marrow, arrest, and accumulate in lymphoid and parenchymal organs¹⁰⁶. Studies using 4T1 tumour-bearing mice revealed a splenic myeloid-cell reservoir that consists primarily of CD11b⁺Ly6G^{Br} cells¹¹. Circulating MDSCs arrest and accumulate in the splenic marginal zones and periaerterolar lymphatic sheaths, migrate to the red pulp, and proliferate within the subcapsular red pulp. The Gr1^{dull} subset of MDSCs was reported to have a higher proliferation rate in the BM¹⁰⁷; although, both MDSC subsets proliferate in the spleen^{11, 108}. Similarly, clinical and rodent therapeutic strategies (Table 1) to induce MDSC differentiation, such as the administration of all trans-retinoic acid (ATRA)^{109, 110} or vitamin D^{70, 111}, have also been shown to reduce MDSC number and/or function.

The proinflammatory proteins, S100A8 and S100A9, can also support MDSC expansion and block myeloid precursor differentiation. S100A8 and S100A9 are highly expressed in the tumour microenvironment, potentially supporting MDSC recruitment¹¹². Tumour secretion of VEGF, G-CSF, and GM-CSF, as discussed above, is also at least partially responsible for MDSC expansion⁹¹. However, other mechanisms are involved including matrix metalloproteinase-9 (MMP9) secretion and the associated remodeling of the ECM, promotion of angiogenesis, and stimulation of VEGF production¹¹³.

Regulation of MDSC mobilization

The haematopoietic system cycles continually from a small population of pluripotent haematopoietic stem cells (HSCs) as part of a delicate balance between quiescence and proliferation in addition to self-renewal and differentiation. Quiescence and self-renewal are tightly regulated by both cell-intrinsic signals and environmental factors¹¹⁴. However, tumours subvert this niche-signal-mediated maintenance of HSC dormancy leading to rapid HSC proliferation and differentiation resulting in a selective loss of lymphocytes with maintenance of myeloid lineage cells. In adults under steady-state conditions, HSCs and progenitor cells are primarily found in the BM, although low numbers circulate in the blood and traffic to haematopoietic and non-haematopoietic organs¹¹⁵ where they proliferate and

differentiate as EMH¹¹⁶. Mobilization is the first step in myeloid progenitor trafficking to inflammatory sites. However, there has been little study into the mechanisms governing MDSC mobilization, their subsequent trafficking to sites of EMH and tumours, and the suppression of these processes (Table 1). These processes include, but are not limited to, alterations in the adhesive interactions between myeloid progenitors and stromal cells during transmigration through the subendothelial basal lamina and the EC layer¹¹⁷. During steady-state haematopoiesis, GM-CSF and G-CSF not only regulate proliferation, but also (directly or indirectly) mobilization from the BM and spleen¹¹⁸. In addition, growth factor administration or secretion from tumours results in myeloid hyperplasia thereby increasing prosteroid and neutral protease secretion that also regulates mobilization, myeloid progenitor survival, and their distribution between marginal and circulating pools¹¹⁹. Because MDSCs include myeloid-committed haematopoietic progenitors and are likely fixed at an immature differentiation stage¹²⁰, the mechanisms associated with their mobilization may be similar to those of haematopoietic progenitor cells.

Treatment of humans or mice with selective antagonists of CXCR4, CXCR4-blocking antibodies, or CXCL12 expression¹²¹, results in a rapid (1–4 hours) mobilization of neutrophils, myeloid progenitors, and MDSCs^{57, 121} into the blood. This suggests that disrupting CXCR4 signaling can contribute to G-CSF-induced mobilization and granulopoiesis^{89, 121}. G-CSF administration also induces protease secretion in the BM microenvironment contributing to cellular mobilization¹²². The rapid mobilization by chemokines (minutes to hours) compared with G-CSF (days) supports multiple mechanisms. Accumulating evidence suggests that CXCL12 has a key role in controlling myeloid cell mobilization and homeostasis¹²³. Thus, mice deficient in CXCL12 or CXCR4 die perinatally with neutrophilia and fail to establish BM myelopoiesis¹²⁴. CXCL12 also acts as a retention signal, constraining CXCR4-expressing haematopoietic progenitor cells to the BM. However, CXCL12 is subject to NH₂- and COOH-terminal proteolytic modification, reducing its chemotactic activity¹²⁵.

Regulation of MDSC trafficking and arrest

Chemokines have a role in leukocyte recruitment and arrest in the tumour microenvironment as do members of the integrin and selectin adhesion molecule families¹²⁶. A number of chemokines^{89, 112} attract myeloid cells to the tumour microenvironment¹²⁷, as well as, stimulate the secretion of matrix-degrading enzymes¹²⁷. However, myeloid cells also express integrins^{128, 129} providing another mechanisms to regulate cellular trafficking within vascular microenvironments¹³⁰. One of these integrins is $\alpha 4\beta 1$, a receptor for vascular cell adhesion molecule (VCAM) and fibronectin, that selectively promotes the arrest of endothelial progenitor cells¹³¹ and monocytes^{130, 132}, to neovascular tissue. Human CD34⁺ and mouse Lin⁻Sca1⁺ progenitor cells, as well as, BM-derived myeloid cells (CD14⁺CD11b⁺) adhere to tumour endothelium *in vivo* via integrin $\alpha 4\beta 1$ (VLA-4). The blockade of $\alpha 4\beta 1$ in tumour-bearing mice suppresses myeloid progenitor tumour infiltration and reduces blood vessel density. Integrins also mediate progenitor cell arrest at sites of ischemia¹³³ such that circulating endothelial progenitor cell (EPC) adhesion to endothelial monolayers requires $\beta 2$ integrin expression.

Adoptive transfer studies^{16, 57} with carboxyfluorescein succinimidyl ester (CFSE)-labeled MDSCs from tumour-bearing mice demonstrated that MDSCs rapidly transverse the pulmonary capillary networks and accumulate in the spleens¹⁶. In contrast, injection into naïve mice results in MDSC arrest primarily in the lungs. Consistent with these findings, an analysis of MDSC proliferation by BrdU labeling revealed proliferation predominantly within the spleens of both naïve and tumour-bearing mice¹⁶. MDSC accumulation is also a result of prolonged MDSC survival, decreased apoptosis, and significantly increased proliferation and accumulation within the spleens, but not the BM, of tumour-bearing mice. Support for this observation was provided by Ki-67 staining, which revealed that MDSCs proliferated in the cords of the sub-capsular red pulp, with Gr1⁺ cells infiltrating throughout the red pulp and marginal zones³⁸. In these studies using 4T1 tumour-bearing mice, the spleen, but not the BM, was shown to be the primary site of MDSC proliferation, as well as, providing a reservoir of Ly6G⁺ MDSCs that can rapidly demarginate and recirculate¹⁶. Further, this organ-specific proliferation is tumour unique¹³⁴, and the frequency of Mo-versus G-MDSCs subsets differs between tumours and organs¹⁶ such that in 4T1 tumour-bearing mice, G-MDSCs have a significantly higher cellular frequency than Mo-MDSCs in the PB and spleen^{53, 60, 95}. This higher frequency is also present in the liver, but not the lungs. Most MDSC studies have focused on MDSCs within the PB, spleen, or tumours; however, MDSCs also accumulate in the liver^{12, 135}, including following adoptive transfer of splenic MDSCs¹¹. Further, MDSC tumour infiltration is tumour dependent and associated with a high frequency and absolute number of MDSCs infiltrating the spleen, liver, lungs, and PB¹⁶.

MDSC REGULATION OF TUMOUR PROGRESSION AND METASTASIS

The tumour regulation of MDSCs is bidirectional, and activated MDSCs secrete chemokines, cytokines, and enzymes¹³⁶ that contribute to tumour cell invasion, proliferation, survival, adhesion, and chemoattraction resulting in a crosstalk that can impact tumour progression, invasion, and metastasis¹³⁷. Tumour progression and metastasis are multistage processes that are facilitated by MDSCs as documented by inverse correlations between outcome parameters and myeloid cell infiltration of tumours and circulating MDSC frequency^{10, 138}. The stages of tumour progression and metastasis and their regulation by MDSCs are shown in Figure 2. Studies in the late 1970s, stimulated research into the pathobiology of metastasis building on the studies by Paget who developed the “seed and soil” hypothesis¹³⁹. Since then, our understanding has exploded as to the tumour-promoting role of chronic inflammation. We have identified many of the key soluble and cellular mediators involved in this process, and promising studies in mice focused on the control of MDSC number and function have emerged. The adoptive transfer of MDSCs has been shown to significantly promote tumour growth in animal models^{113, 140}, and Gr1⁺ cell depletion in tumour-bearing mice inhibits tumour growth, reduces metastasis, and prolongs survival^{20, 21, 141}. Some chemotherapeutic agents preferentially suppress MDSCs including gemcitabine¹⁴¹, 5-fluorouracil¹⁴², and docetaxel¹⁴³. Numerous studies of tumour-bearing mice, and a few clinical studies using therapeutics that target MDSCs or their function, have shown that in mice MDSC reduction delays tumour initiation, progression, and prolongs survival (Table 1)^{110, 144, 145}.

Definitive proof that a clinical reversal in MDSC number or function can significantly delay tumour progression or growth remains to be established. However, what has been demonstrated recently is that immune evasion limits cancer immunotherapies; and MDSC suppressive activity appears to be one of the more prevalent mechanisms present in cancer patients providing an obstacle to immune based intervention. It should be stressed that the mechanism of T-cell suppression and the responsible MDSC subset critical to immune subversion remains controversial. Thus, in contrast to results to date, adding interventional strategies that reverse MDSC immune suppressive activity supports adjuvant immunotherapy^{110, 146} and slowing of tumor growth¹⁴⁷. MDSC diversity results in multiple roles during tumour progression, and future studies must define the mechanisms underlying their different functions with respect to tumour progression. Clearly, investigators should pursue other therapeutic mechanisms to regulate MDSCs based on their multiple pro-tumourigenic activities (Figure 2).

MDSC regulation of tumour invasion

Tumour and myeloid cell secretion of enzymes facilitate invasion, and positive correlations have been reported between proteases, such as MMP9, and tumour malignancy¹⁴⁸. MicroRNA-494⁸⁹ and HIF-1 α ^{149, 150} also have a role in regulating the non-immunological activity of MDSCs by enhancing their ability to infiltrate tumor tissue and, in the case of MicroRNA-494, to facilitate tumor invasion via the upregulation of MMPs⁸⁹. Therefore, MDSCs, which secrete high levels of proteolytic enzymes, may facilitate invasion into the host stroma, but also intravasation through capillary basement membranes resulting in increased numbers of circulating tumour cells. MDSCs promote tumour invasion by the secretion of MMPs¹⁵⁰, which have an essential role in extracellular matrix degradation^{113, 151}. Support for an MDSC role in tumour invasion was provided by studies that used a mammary carcinoma lacking the type II transforming growth factor beta (TGF β) receptor¹⁵¹ that resulted in an enhanced incidence of metastasis and an increased MDSC infiltrate¹⁵². The enhanced invasion was MMP-dependent; however, it was not clear if the MMPs were secreted by MDSCs or by the carcinoma cells in response to MDSC stimulation¹⁵¹. Both cell populations are likely involved as MDSCs derived from tumour-bearing hosts have increased MMP levels compared to “MDSCs” from non-tumour-bearing hosts¹⁵¹ suggesting that some of the increased invasive ability may be from MDSC-derived MMP secretion.

MDSC regulation of tumor cell arrest and niche formation

While metastasis is an inefficient process¹⁵³, such that few tumour cells survive trafficking through the circulation, arrest, and interactions with host immunity, survival is facilitated by the formation of heterotypic emboli secondary to tumour cell interactions with myeloid cells and platelets¹⁵⁴. These emboli physically protect tumour cells from the host immunity, as well as, larger emboli that more frequently arrest within the organ parenchyma. However, once tumour cells have extravasated, their growth is regulated by the cellular and growth factor milieu in the microenvironment¹⁵⁵, which has been termed a metastatic niche¹⁵⁶. These niches are controlled, in part, by macroenvironmental changes including the number of circulating MDSCs and EPCs. Such niches have been suggested to act as chemoattractants¹⁵⁷; however, this may be irrelevant as tumour cells circulate and arrest

based on physical constraints and adhesion factor expression. Further, increases in MDSC and EPC numbers, at least in tumour-bearing mice, occur in numerous solid organs, including the spleen, lung, and liver. Indeed, in rodent models MDSC frequency is highest in the spleen; however, in mice this site is abnormal for metastatic formation by carcinomas. In contrast, MDSCs also occur at a high frequency in lungs and livers, which are frequent metastatic sites. However, as reported by Hart, *et al.*, even when organ fragments are implanted ectopically, specific organ milieu regulate tumour cell arrest and growth suggesting that mechanisms, in addition to myeloid cell expansion and angiogenesis, are critical, notably hormonal and organ-specific growth factors¹⁵⁵. Thus, metastasis is both selective and inefficient¹⁵⁸, and only a few cells survive to form a micrometastasis, a process partially regulated by MDSCs and other myeloid cells.

MDSC regulation of vasculogenesis and angiogenesis

Infiltrating and circulating MDSCs also have been suggested to have a role in tumour angiogenesis and vasculogenesis. Tumor growth can create an imbalance between inhibitory and stimulatory angiogenic molecules resulting in EC proliferation and recruitment. Haematopoietic and EPC proliferation results in an increase in their circulating number, which, in response to tumour-derived chemokine secretion, recruits leukocytes to nascent primary and secondary tumor foci contributing to the neovasculature. This increased vascularity facilitates tumour growth and access to the circulation and is associated with a positive correlation between vascular density and tumour grade¹⁵⁹.

Angiogenesis, the formation of new vessels from preexisting ECs, is not the only mechanism of tumour neovascularization. Tumour vasculature can also arise by vasculogenesis, *i.e.*, *de novo* vessel formation by the recruitment, migration, proliferation, and differentiation of BM-derived EPCs¹⁶⁰. Mobilized from the BM by growth factors or chemotherapy¹⁶¹, EPCs become involved in tumour vasculogenesis¹⁶². Further, inhibiting EPC mobilization can slow or prevent tumour growth¹⁶³, and several studies have shown that circulating EPC numbers correlate with clinical outcomes¹⁶⁴. A major regulator, which can affect EPC proliferation and differentiation, is VEGFA, which can attract EPCs and is blocked by neutralizing VEGFA antibody^{91, 165}. Taken together, these studies indicate that tumour-secreted factors can induce the proliferation, differentiation, and support the survival of EPCs and ECs¹⁶⁶.

The extent of MDSC-derived tumour vasculature may depend on the tumour such that EPCs are found at high levels in mice bearing Lewis lung carcinomas, but are absent in mice bearing B16 melanomas, despite relatively similar levels of microvasculature¹⁶⁷. In addition to directly contributing to the vasculature, myeloid progenitor cells also promote tumour growth. Admixing myeloid cells with tumour cells, under conditions that promote vascular leukocyte generation, results in larger and more highly vascularized tumours¹⁶⁸. Both G-CSF and VEGFA mobilize EPCs into the peripheral circulation and promote angiogenesis¹⁶⁹. Indeed, splenic MDSCs contribute to tumour vasculogenesis by directly differentiating into EPCs¹¹³; however, a subset of circulating progenitor cells is CD11b⁻¹⁷⁰, and as such, Gr1⁺CD11b⁺ cells may be precursors that differentiate and participate in tumour vasculogenesis (BOX 1). Since EPCs can become part of the tumour vasculature¹⁷⁰,

their mobilization in response to tumour secretion of VEGF, G-CSF, or GM-CSF, contributes to tumour vascular formation. In contrast to tumour-bearing mice, non-tumour-bearing mice injected with G-CSF do not increase circulating EPCs, suggesting that additional tumour-associated cytokines are required, such as VEGFA, which can also mobilize EPCs from the BM¹⁶⁹.

MDSC regulation of host defense

The tumour microenvironment, once established, can inhibit host immunity. Tumours are not passive targets for host immunity; rather, they can down regulate anti-tumour immune responses through multiple mechanisms including tumour-secreted factors, as well as, mechanisms that result from changes in tissue homeostasis. During tumour progression and immunotherapy, tumor cell populations may be selected with increased resistance to immunosurveillance and immunotherapy. In addition, variants arise that can interfere with multiple stages of immune cell development, differentiation, migration, and cytotoxicity¹⁵⁸. Thus, multiple aspects of antitumour immunity are subject to regulation by the tumour microenvironment¹⁷¹.

Although there are multiple mechanisms supporting tumour escape from host immunity¹⁷², in recent years, MDSCs have been a focus primarily because they are ubiquitous and associated with disease progression and poor prognosis^{173, 174}. Many studies that examined hosts with advanced tumour burden also reported reduced T-cell frequency and function. The relationship between tumour burden and immunosuppression raises the question of whether tumour-induced immunosuppression is reversible by surgical removal of the primary tumour. Several studies have assessed immunosuppression after primary tumour resection in mice^{13, 14, 28}, and varying effects on immunosuppression have been reported including partial recovery of T-cell function^{13, 28}. VEGFA is an immunosuppressive cytokine that blocks normal myeloid-cell differentiation, resulting in increased MDSC-mediated inhibition of T-cell activity^{46, 71, 175}. Thus, surgery may reverse immunosuppression in some cases, and this is associated with a reduction in immunosuppressive factors, thereby supporting immune recovery. However, immunosuppression may reoccur as metastatic lesions grow and inhibitory cytokine levels increase. Numerous reviews of the mechanisms associated with MDSC suppression of T-cell function have been written in recent years which focus is on NOS2¹⁷⁶, reactive oxygen species (ROS), ARG1¹⁷⁷, cyclooxygenase 2 (COX2), and potentially upregulation of IL-10 as primary mechanisms. The reader is directed to any of the recent reviews on this subject for additional information^{43, 73, 178}.

MDSCS AS THERAPEUTIC TARGETS AND POTENTIAL REGULATORS OF CANCER THERAPY

Numerous enzymes, growth factors, and cytokines regulate the MDSC lifecycle, including their expansion, trafficking, differentiation, and function (BOX 2). Inhibitors of most of these regulatory mediators are identified in Table 1. These molecular inhibitors include a variety of drugs that target tyrosine kinases⁶⁷, such as PDE5¹⁴⁴, peroxisome proliferator-activated receptor gamma (PPAR γ)¹⁷⁹, amino-bisphosphonates¹⁸⁰, and COX2¹⁸¹, in

addition to the antibodies and molecular inhibitors of cytokines and chemokines discussed above. Indeed, several recent reviews have focused on this aspect of MDSC pathobiology¹⁷³; therefore, we will briefly discuss the ability of MDSCs to inhibit responses to standard-of-care therapeutics. For example, VEGFR2 tyrosine kinase inhibitors (TKIs) that target angiogenesis also partially inhibit the tumour growth stimulatory effects of G-CSF via MDSC proliferation, an observation supporting a role for VEGFA in tumor progression and evasion of host immunity. Clinically, administration of the TKI inhibitor, sunitinib, to metastatic RCC patients significantly reduces MDSC numbers in the PB^{67, 182}. MDSCs may also contribute to resistance to sunitinib therapy via secretion of the *Bombina variagata* peptide 8 homologue (BV8)¹⁸³, potentially secondary to its upregulation by tumour-secreted G-CSF¹⁹. IL-8 also contributes to sunitinib resistance as shown in a RCC xenograft model in which sunitinib-induced resistance was reversed by co-treatment with anti-IL-8¹⁸⁴. Since IL-8 has potent proangiogenic activity, its up-regulation may induce proangiogenic pathways that allow tumours to escape the anti-angiogenic activity of sunitinib. Additional growth factors may also block therapeutic responses VEGFA signaling inhibitors by recruiting myeloid cells that promote angiogenesis and immune tolerance^{185, 186}. In addition to factors that directly drive angiogenesis¹⁸⁷, mediators may also function by recruiting myeloid cells to release angiogenic factors¹⁸⁸. The BM-derived myeloid cells that produce angiogenic factors and the accompanying escape from VEGFA inhibitors have also been observed in preclinical tumour models^{95, 186}. Tumours resistant to inhibitors of VEGFA signaling can secrete cytokines that recruit myeloid cells that promote angiogenesis and immune tolerance¹⁸⁵. In support of a role for chemokines in tumour progression, plasma levels of CXCL12 have been shown to correlate with metastasis in bevacizumab (monoclonal antibody to VEGF)-treated patients with advanced rectal cancer¹⁸⁹.

CONCLUDING REMARKS

In recent years, there has been a heightened interest in MDSCs and their biological function in tumor pathobiology. As this timeline emphasizes, their contribution to tumor pathologic processes goes far beyond immune suppression. MDSCs are a heterogeneous population of immature haematopoietic cells that have a role in immune tolerance, tumour progression, and metastasis. Tumour progression is associated with increased numbers of these iMCs in the primary tumour microenvironment and circulation, which in turn is associated with a poor prognosis, supporting a role in metastasis. Recently, the controversy regarding the phenotype of human MDSCs has resolved with agreement concerning which subset(s) should be monitored, *i.e.*, Lin⁻HLA-DR⁻ and CD11b⁺ or CD33⁺ cells, with additional subsetting based on CD14^{dim} or CD15⁺ expression. This consensus will greatly facilitate studies into the clinical relevance of tumour-infiltrating myeloid cells and their role in tumour progression and metastasis. The mechanisms responsible for the abnormal differentiation of hematopoietic progenitor cells into MDSCs remain to be clearly elucidated and provide a goal for near term studies.

Biographies

Dr. Talmadge has over 45 years' experience in cancer research and tumour immunology and is currently head of the Transplantation Immunology Lab at the University of Nebraska Medical Center. His laboratory is focused on stem cell transplantation, immune response to transplantation and immunotherapy, and gene and cellular therapeutics.

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Glossary

Extramedullary hematopoiesis	(EMH) is the proliferation of hematopoietic cells outside of the bone marrow in response to pathologic processes, such as tumor growth, and can occur at different locations, such as the liver and spleen.
Host macroenvironment	Includes the systemic factors (growth factors, cells, tissues, and organs) that can regulate tumor growth, progression, and metastasis including factors, such as age, menopausal status, body mass index, as well as, overall immune status.
Tumor microenvironment	The milieu surrounding tumors including normal cells, blood vessels, soluble factors, and molecules that can influence and be influenced by the tumour's growth.
Leukemoid reactions	A peripheral blood phenotype resembling that of leukemia, or indistinguishable from it, based on cellular morphologic appearance; observed in some infectious diseases, inflammatory conditions, and neoplasia.
Margination	A process that occurs during the early phases of inflammation; as a result of capillary dilation and slowing of the bloodstream, leukocytes occupy the periphery of the cross-sectional lumen and adhere to the ECs that line the vessels.
Mobilization	The release of hematopoietic progenitor cells from the bone marrow into the peripheral blood.
Plasticity	The capacity of cells with the same genotype to vary in differentiation, in phenotype, or in function in response to varying environmental conditions.
Neutrophilia	An absolute or relative increase in the normal number of neutrophils and their precursors in the circulating blood that may be associated with acute infections, malignancy, or following severe hemorrhage, or neutropenia (compensatory neutrophilia).

Tumor angiogenesis	The growth of blood vessels and capillary beds from existing vessels into a solid tumor.
Tumor vasculogenesis	The formation of new capillaries and blood vessels by EC progenitors.

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Online Summary

- EMH and neutrophilia have been recognized as a cornerstone of neoplasia since the early 1900s. However, the specific role, phenotypes, and nomenclature for these myelopoietic cells have only been studied since the late 1970s.
- Currently, mouse MDSCs are defined as Gr1⁺CD11b⁺ cells, and human MDSCs are defined as Lin-HLA-DR-CD11b⁺. These cells are further subdivided into granulocytic and monocytic committed variants, as well as, being defined using additional and alternative phenotypic markers.
- MDSCs have a role in all steps of tumour progression and metastasis. However, important questions remain, as well as, the need for focused studies to fully understand the mechanisms regulating these processes.
- The crosstalk between tumour cells and myeloid cells is critical to these processes, although, the majority of studies have focused on the effect of tumours on myeloid cell proliferation, trafficking, biodistribution, and survival. Future studies need to assess the effect of myeloid cells on tumour cell signaling and molecular expression.

Phenotypic markers on murine and human MDSCs

The table below identifies phenotypic markers of murine and human MDSCs. Their phenotypes have been controversial and numerous marker subsets have been used to define MDSCs and their subsets. In some instances, the expression levels are identified as low (lo) or bright (Br) a difference that may be relevant to other markers as well. In this table, the cellular phenotypes have been subset into monocyte (Mo), granulocyte (G) and endothelial-committed MDSCs. These circulating endothelial progenitors (EPCs) have not been as well studied, and numerous markers have not been assessed (ND). Indeed, the relationship between EPCs and MDSCs remains obscure and are presented here to suggest a potential relationship. Review papers that discuss MDSC phenotypic markers are referenced for murine^{60, 81} and human^{76, 84, 174, 190, 191} studies.

Murine	Mo-MDSC	G-MDSC	EPC
CCR2	+++	+++	+++
CXCR4	+++	+++	+++
CXCR2	+++	+++	+++
CD11b	+++	+++	+++
CD11c	subset	subset	ND
CD16low	+++	+++	ND
CD31	---	---	+++
CD45	+++	+++	+++
CD62L	lo	lo	ND
CD80	+++	+++	ND
CD115 (M-CSF R)	++	subset	ND
CD117 (cKIT)	---	---	ND
CD124 (IL-4Ralpha)	+++	+++	ND
F4/80	+++	---	+++
Gr1	lo	Br	+++
Ly6C	+++	lo	+++
Ly6G	---	+++	ND
MHC I	+++	+++	ND
MHC II	some models	Some models	---
Sca-1	subset	subset	+++
TIE-2	---	---	+++
VEGFR1 (Flt-1)	+++	+++	
VEGFR2 (KDR/Flk-1)	+++	+++	+++
VLA-4 (CD49d)	subset	---	ND
Human			
CCR2	++	---	===
CXCR4	+++	+++	+++
CD11b+	+++	+++	+++
CD11c+	subset	subset	ND

Murine	Mo-MDSC	G-MDSC	EPC
CD13	subset	subset	ND
CD14	+++	lo	+++
CD15	---	+++	ND
CD16low	subset	subset	ND
CD31	---	---	+++
CD33	subset	subset	subset
CD34	subset	subset	+++
CD38	subset	subset	+++
CD39	+++	+++	ND
CD45	+++	+++	+++
CD62L	lo	lo	ND
CD66b (CEACAM8)	---	+++	ND
CD115 (M-CSF R)	++	---	ND
CD117 (cKIT)	lo	++	+++
CD124 (IL-4Ralpha)	+++	+++	ND
HLA-DR negative	+++	+++	+++
Lin negative	+++	+++	+++
Tie-2	+++	---	+++
VEGFR1 (Flt-1)	+++	+++	+++
VEGFR2 (KDR/Flk-1)	+++	+++	+++
VLA-4 (CD49d)	subset	subset	ND

Since the first characterization of MDSCs, previously known as NS or null cells, they have been controversial. They are similar to monocytes and granulocytes with common morphologic and phenotypic features. However, MDSCs result from the expansion of myeloid precursor cells and are defined as iMCs with potent immune suppressive activity. They have an impaired ability to differentiate into mature myeloid cells, and accumulate in peripheral lymphoid and parenchymal organs. Despite, phenotypic homogeneity, MDSCs do not exist in healthy hosts, at least in the absence of activation, and are only observed during chronic pathological conditions, such as infections, inflammation, or cancer. Further, the mechanisms responsible for MDSC expansion, trafficking, abnormal differentiation, and function remain to be clarified. The table below identifies the mechanisms and some of the mediators that regulate MDSCs and is patterned on the mobilization of hematopoietic progenitors, which are the "normal" cellular population most similar to MDSCs.

Factors and mechanisms regulating MDSCs	
Process mechanism	Examples of mediators
MDSC proliferation in the BM and EMH ^{12, 20–23, 48, 91, 95}	G-CSF, GM-CSF, SCF
MDSCs have an impaired differentiation ^{45, 69, 78–80}	TNF, VEGFA
Mobilization of MDSCs can occur from the marrow and sites of EMH ^{23, 175, 182}	CXCL8, G-CSF, GM-CSF
Chemotaxis of MDSCs to an inflammatory or tumor site ^{80, 87, 192}	CCL2, CXCL12
Organ or tumor arrest of circulating MDSCs ^{12, 126, 129}	VLA4, C5a
Activation of MDSCs resulting in increased enzyme secretion and T-cell suppression ^{183, 184}	PGE2, LTD4, TLR agonists
MDSCs can differentiate into OCs, monocytes, granulocytes, OCs, ECs or DCs ^{68, 103, 111}	ATRA, Vitamin D

Historical Progression of MDSCs in the Literature

Historical Progression of MDSCs in the Literature

Figure 1. Timeline: Historical Progression of MDSCs in the Literature
 Antibody (Ab); a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10); all-trans retinoic acid (ATRA); bombina variagata peptide 8 (BV8); colony

stimulating factor (CSF); FMS-like tyrosine kinase 3 (FLT3); granulocyte colony stimulating factor (G-CSF); granulocyte-macrophage colony stimulating factor (GM-CSF); graft versus host disease (GVHD); hypoxia inducible factor 1 alpha (HIF-1 α); head and neck squamous cell carcinoma (HNSCC); knock out (KO); macrophage colony stimulating factor (M-CSF); myeloid-derived suppressor cell (MDSC); micro RNA 494 (miRNA-494); mixed lymphocyte reaction (MLR); myeloid differentiation primary response 88 (MYD88); nuclear factor kappa beta (NF- κ B); nitric oxide (NO); nitric oxide synthase 2 (NOS2); natural suppressor (NS); phosphodiesterase type 5 (PDE5); renal cell carcinoma (RCC); signal transducer and activator of transcription 3 (STAT3); tumour bearing (TB); and, vascular endothelial growth factor (VEGF).

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Figure 2. The role of MDSCs in the process of cancer progression and metastasis

The process of cancer metastasis consists of sequential, interlinked, and selective steps with some stochastic elements. The outcome of each step is influenced by the interaction of metastatic cellular subpopulations with homeostatic factors and cells. Each step of the metastatic cascade is potentially rate limiting such that failure of a tumour cell to complete any step effectively impedes that portion of the process. Therefore, the formation of clinically relevant metastases represents the survival and growth of selected subpopulations of cells that preexist in primary tumours. The interactions between MDSCs and tumour cells

during tumour progression and metastasis are highlighted. The role of tumour cells is indicated by green text, and those of MDSCs and other myeloid cells are indicated in red.

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Table 1

Therapeutic Agent	Target	Type of Cancer Tested	Effect on MDSCs
Neutralizing Ab to receptor tyrosine kinase (cKit) ⁹²	Growth factor	Colon carcinoma (mice)	Inhibition of proliferation
Prokineticin 2 (PROK2)-specific Ab ¹⁸³	Growth factor	Tumours of human & mouse origin in nude mice	Inhibition of PMN/MDSC expansion & tumour recruitment
Neutralizing Ab to granulocyte-macrophage colony-stimulating factor (GM-CSF) ¹⁵	Growth factor	Pancreatic Cancer (mice)	Inhibition of proliferation
Neutralizing Ab to granulocyte colony-stimulating factor (G-CSF) ⁴²	Growth factor	Colon carcinoma (mice)	Inhibition of proliferation
Colony stimulating factor 1 receptor (CSF1R) & protein kinase (KIT) tyrosine kinase inhibitor (TKI) (PLX3397) ⁹⁷	Growth factor	Breast cancer (human)	Inhibition of TAM recruitment
CSF1R antagonist (GW2580) ⁹⁶	Growth factor	Lung carcinoma & prostate cancer (mice)	Inhibition of MDSC & macrophage proliferation
Vascular endothelial growth factor (VEGF)-trap ⁹⁸	Growth factor	Solid tumours (human)	No activity
Ab to VEGF (Avastin) ¹⁸⁵	Growth factor	Metastatic renal cell carcinoma (RCC) (human)	Weak inhibition of proliferation
Ab to interleukin 6 receptor (IL-6R) & gemcitabine ¹⁴¹	Interleukin & Cytotoxic	Carcinoma (mice)	Inhibits accumulation of Mo- & G-MDSCs
CXC chemokine receptor 2 (CXCR2) (S-265610) & CXCR4 (AMD3100) antagonists ¹⁵¹	Chemokine	mammary cancer (mice)	Altered recruitment of iMCs to the tumour
Neutralizing Ab to chemokine (C-C motif) ligand 2 (CCL2) ¹⁹²	Chemokine	Mammary carcinoma (mouse & human xenografts)	Targeting inflammatory monocytes & macrophages
Gemcitabine ¹⁴⁵	Cytotoxic	Lung & mammary cancer (mice)	Inhibition of proliferation
Doxorubicin-cyclophosphamide ¹⁰	Cytotoxic	Breast cancer (human)	Weak inhibition of proliferation
5-fluorouracil ¹⁴²	Cytotoxic	Thymoma (mice)	Inhibition of MDSC expansion
Docetaxel ¹⁴³	Cytotoxic	Mammary carcinoma (mice)	Inhibition of MDSC expansion & macrophage polarization to M1 phenotype
Cyclooxygenase 2 (COX2) inhibitor (Celebrex) ¹⁸¹	Enzyme inhibitor (Inhib.)	Mammary carcinoma (mice)	Inhibition of proliferation/activation
Amino-biphosphonate ^{180, 193}	Enzyme inhib.	Mammary tumours (mice)	Inhibition of proliferation
Phosphodiesterase-5 (PDE5) inhibitors ¹⁴⁴	Enzyme inhib.	Mammary and colon carcinoma and fibrosarcoma (mice)	Inhibition of proliferation & T-cell suppression
TKI (sunitinib) ^{67, 95, 182, 184}	Signal inhib.	RCC (human)	Inhibition of proliferation
Peroxisome proliferator-activated receptor-g (PPARg) inhibitor ¹⁷⁹	Signal inhib.	Carcinoma & myeloid sarcoma (mice)	Induces proliferation of MDSCs