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Myeloid-derived suppressor cells: Therapeutic modulation in cancer

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1. ABSTRACT

Improved understanding of the cellular and molecular basis of adaptive immunity has been realized over the past few decades, leading to the development of novel immunotherapeutic strategies capable of promoting host anti-tumor immunity. In order to achieve clinically meaningful results, further understanding of the mechanisms by which tumors suppress host immunity, and the development of therapeutic strategies which overcome tumor-associated immune suppression, will be necessary. Myeloid-derived cells with potent immunosuppressive properties are ubiquitous in human cancers. Improved mechanistic understanding of factors promoting their development, activation and mechanisms of immune suppression are being translated into novel therapeutic approaches, and will be summarized herein.

2. INTRODUCTION

Since Rudolf Virchow first implicated chronic inflammation in carcinogenesis almost 150 years ago (1), a wealth of data ranging from epidemiologic observations to studies performed in murine tumor models support this association (2). Both the innate and adaptive arms of the host immune response may directly promote tumor growth and development. For example, host anti-tumor immunity may contribute to the emergence of poorly immunogenic tumors via a process of immunologic selection and immune evasion (3). On the other hand, malignant cells may promote the development of an aberrant immune response, either locally within the tumor microenvironment or systemically, resulting in the suppression of effective host anti-tumor immunity (4-6). Furthermore, oncogenesis and immune suppression may be linked. Activation of traditional growth factor receptors and oncogenes may

culminate in the activation of pathways leading to the production of important mediators of immune suppression (7-12). A variety of nonhematopoietic [e.g. mesenchymal stem cells (13, 14), fibroblasts (15) and tumor endothelium (16)] and hematopoietic cells, including myeloid- and lymphoid-derived cells, may negatively regulate host anti-tumor immunity (6). While mast cells (17), immature conventional dendritic cells (DC) (18), plasmacytoid DC (19), tumor-associated macrophages (2, 20), NK T cells (21, 22), gamma-delta T cells (23) and regulatory T cells (24) contribute to immune suppression, in the current review we will discuss the suppressive role of myeloid-derived suppressor cells (MDSC), as they are ubiquitous in cancer and the emergence of novel therapeutic strategies targeting these cells highlights the clinical relevance of understanding their development, recruitment and effector functions.

Work performed over the past few decades has implicated myeloid-derived cells in the suppression of host anti-tumor immunity. In the 1980's, Lewis lung carcinoma cells with colony stimulating factor activity were shown to stimulate hematopoiesis, producing a relative monocytosis in tumor-bearing mice (25). Bone marrow derived cells, possibly monocytes (26), from these mice were shown to inhibit T-cell activation. Similarly, work performed by Hans Schreiber's group demonstrated that a tumor variant (i.e. "progressor" tumor) capable of escaping host immunity in immunocompetent mice spontaneously regressed following granulocyte depletion (27). In the years since these seminal observations, MDSC (28) have been more clearly defined and their immunologic and non-immunologic contributions to a vast array of pathologic processes, including tumorigenesis, described (29).

MDSC are not a discrete subset of myeloid-derived cells, but are a heterogenous population of immature myeloid cells functionally defined by their shared suppressive activity. In mice, MDSC are $GR1^+CD11b^+$ cells and may be further subdivided into at least two discrete subsets based on the differential surface expression of the GR1 epitopes LY6G and LY6C (30), including granulocytic $CD11b^+LY6G^+LY6C^{low}$ MDSC and monocytic $CD11b^+LY6G^-LY6C^{high}$ MDSC. While various other markers, like CD124 (IL-4Rα) (31), CD115 (M-CSF receptor) (32), and CD80 (B7-1) (33) may be inducibly expressed on MDSC subsets in various tumor models; currently, murine MDSC are best defined by the coexpression of GR1 and CD11b. More recent work supports the contention that additional MDSC subsets may be characterized, each of which may be differentially regulated and possess unique suppressive functions (34-36). In humans, MDSC express the common myeloid marker CD33, are $CD11b^+HLA\text{-}DR^{-/low}$ and generally lineage negative (Lin^-) (37-39). Human MDSC, like their murine counterparts, are heterogenous and may variously express the granulocytic marker CD15(40) or the monocytic marker CD14 (41, 42), suggesting the presence of both granulocytic and monocytic MDSC (43, 44). MDSC (or at least cells with an identical immunophenotype) comprise only a small percentage of splenocytes (<5%) in normal mice and approximately 0.5% of peripheral blood mononuclear cells in normal humans (38, 44). During a systemic inflammatory state, as may be observed in tumor-bearing animals, MDSC greatly expand in response to both tumor- and stromal-derived factors and accumulate within the bone marrow, peripheral blood, spleen, lymph nodes, liver and tumors (39, 41, 44-54).

3. MDSC DEVELOPMENT AND ACTIVATION

The expansion of MDSC in the tumor-bearing host is mediated by tumor- or stromal-derived factors, many of which are characteristic of a chronic inflammatory response, that are abundant within the tumor microenvironment, if not systemically (55-60). For example, many tumors highly express cyclooxygenase (COX)-2, resulting in the production of the arachidonic acid metabolite prostaglandin E_2 (PGE_2) (61, 62). Mouse MDSC express PGE_2 receptors and may be generated from bone marrow precursors in response to PGE_2 agonists. Experiments performed with a COX-2 inhibitor and in tumor-bearing mice deficient for a PGE_2 receptor further support the role of PGE_2 in the development of MDSC (63-65).

Hematopoietic cytokines, including stem cell factor (SCF) (66), macrophage-colony stimulating factor (M-CSF) (67) and granulocyte/macrophage-colony stimulating factor (GM-CSF), drive myelopoiesis and promote the generation of MDSC. GM-CSF is particularly interesting given its use as a vaccine adjuvant. Work performed in murine models demonstrating the superiority of GM-CSF producing tumor vaccines has led to its widespread incorporation into clinical trials using a variety of tumor vaccine strategies (68, 69). However, its affect on tumor immunity is variable, likely due to dose dependent affects (69). While lower doses which fail to achieve appreciable systemic levels of GM-CSF are associated with immune augmentation, higher doses leading to high systemic concentrations of GM-CSF may be associated with immune suppression via the generation of MDSC (50, 69, 70). This may be explained, at least in part, to concentration dependent differences in phosphorylation of the GM-CSF receptor and downstream signaling events. Low concentrations of GM-CSF promote cell survival, whereas higher concentrations promote survival and proliferation (71, 72). For example, a direct correlation has been demonstrated between tumor-derived GM-CSF in head and neck cancer patients and the frequency of circulating MDSC (73). This is highlighted by recent work demonstrating that the incorporation of GM-CSF into an autologous heat shock protein gp96 tumor vaccine impaired the generation of vaccine-specific immunity (69, 74, 75). These same investigators went on to demonstrate that GM-CSF promoted the expansion of $CD14^+HLA\text{-}DR^-$ MDSC in these patients (41). While this affect may be dose dependent, interpretation of the available data is confounded by the observation that the endogenous production of GM-CSF may lead to systemic elevations of this cytokine (76, 77). Furthermore, patient- and tumor-specific factors may contribute to wide variability in endogenous GM-CSF production, rendering the affects of its administration, whether at "low" or "high" doses,

difficult to predict. Whether granulocyte-colony stimulating factor (G-CSF), widely used to prevent chemotherapy-associated neutropenia, may promote the development of MDSC in a fashion similar to GM-CSF is unknown. However, a direct association between splenic MDSC and G-CSF transcript levels has been observed in a mouse model (78) and G-CSF was shown to promote the development of low-density granulocytes capable of suppressing T cells and preventing acute graft versus host disease (aGVHD) (79). G-CSF is also used to promote stem cell mobilization prior to peripheral blood stem cell (PBSC) transplantation. Compared with stem cells obtained directly from the bone marrow, PBSC contain approximately ten times as many T cells. Despite this, allogeneic PBSC transplantation is not associated with a marked increase in the frequency or severity of acute GVHD (80-82). This may be explained by G-CSF-induced mobilization of $CD14^+$ monocytes capable of suppressing T-cell proliferation (83, 84). The extent to which G-CSF mobilized monocytes (or MDSC) contribute to the suppression of GVHD in allogeneic PBSC transplant recipients may warrant further investigation. Collectively, these observations suggest that G-CSF, like other hematopoietic cytokines, may contribute to the expansion of MDSC. Given its widespread use in cancer patients, this hypothesis may warrant consideration.

Other tumor-derived factors may be required in order for hematopoietic cytokines, like GM-CSF, to promote the generation of MDSC. Vascular endothelial growth factor (VEGF), better known for its role in angiogenesis, provides one example. VEGF, produced by many tumors and systemically elevated in many cancer patients, has pleiotropic immunologic affects, including the inhibition of dendritic cell (DC) differentiation and maturation (85, 86). Murine experiments were conducted in which infusion pumps were used to continuously deliver VEGF, achieving plasma concentrations felt by investigators to closely approximate levels present in patients (87). MDSC were found to accumulate in these mice in a VEGFR2-dependent (and VEGFR1 independent) manner. In subsequent work, bone marrow cells were transduced with green fluorescent protein (GFP) and VEGFR2 and adoptively transferred into lethally irradiated recipients (88). Following activation of VEGFR2 expression in these mice, GFP^+ (but not GFP^-) MDSC were observed. In contrast, myeloid progenitor cells in these mice were GFP^+ or GFP^-, suggesting that VEGFR2 expression was required for the expansion of MDSC, but increased myelopoiesis was independent of VEGF signaling. In this model, VEGFR2 signaling resulted in the upregulation of GM-CSF, which in turn drives myelopoiesis in a paracrine fashion. Collectively, this data suggests that hematopoietic cytokines, like GM-CSF, may drive myelopoiesis, while other factors, like VEGF, may impair myeloid differentiation and promote the generation of MDSC from progenitor cells (88).

In addition to tumor-derived factors, factors released by phagocytes and non-hematopoeitic cells (e.g. epithelial cells) in response to cell stress, so-called damage-associated molecular pattern proteins (DAMPs), may promote the generation and recruitment of MDSC. For example, S100A8 and S100A9, members of a large family of calcium-binding proteins that are expressed by granulocytes and monocytes, regulate the cytoskeleton, promote endothelial cell activation and leukocyte recruitment (89). Recent work performed in vitro demonstrated that the ability of tumor-conditioned media to skew myelopoiesis in favor of MDSC and impair DC and macrophage differentiation was dependent upon progenitor cell expression of S100A9 (90). Similarly, stem cells which overexpressed S100A9 remained immature and were unable to differentiate into DC when cultured in the appropriate conditions (90). Myeloid progenitor cells accumulated in S100A9 transgenic mice, but were apparently impaired in their ability to differentiate into macrophages and DC, as the relative percentage of splenic macrophages and DC was reduced among GFP-reporter positive cells in these mice. In contrast, S100A9 deficient mice were impaired in their ability to generate MDSC in response to tumor growth (90). In fact, the majority of these mice rejected an implantable tumor cell line that progressed in the wild-type controls. However, S100A9 knockouts became susceptible to tumor growth upon the adoptive transfer of MDSC derived from wild-type mice. S100A8 and S100A9 also influence MDSC trafficking, as these proteins bind carboxylated-N-glycan receptors on MDSC in an autocrine fashion and promote MDSC chemotaxis in an NFκB dependent manner (48).

Pro-inflammatory cytokines, like IL-1 beta and IL-6, are frequently elevated in cancer patients with advanced stage disease and promote the generation of MDSC, as demonstrated in murine models utilizing either cytokine-transfected transplantable tumors or transgenic expression of the cytokine in a particular organ (91-93). For example, transgenic mice expressing IL-1 beta under the control of a stomach-specific promoter not only develop gastric cancer, but were found to have increased levels of long-lived MDSC that were more potent suppressors of T-cell immunity than similar cells generated from wild-type controls (94). Comparable results have been observed in mice deficient for IL-1 receptor antagonist (IL-1Ra), the endogenous IL-1 beta antagonist (92, 93). Many MDSC fail to express IL-1 receptor, suggesting that many of the affects of IL-1 beta on MDSC observed in these models are indirect. Cytokines, like IL-6, which contribute to the generation of MDSC and are downstream of IL-1 beta, may be responsible, at least in part, for the observed affects of IL-1 beta in these models (91, 92). More recently, the administration of IL-1Ra to patients with smoldering multiple myeloma slowed the rate of progression to overt myeloma (95). IL-1Ra, via the inhibition of IL-6, directly inhibits the growth and survival of malignant plasma cells and may explain this finding. However, the demonstration of $CD14^+$ MDSC in myeloma raises the possibility that IL-Ra may also inhibit the expansion of MDSC in this disease (96).

Many of the cytokines required for the generation of MDSC activate Janus kinases (JAK), thus leading to the downstream phosphorylation of signal transducer and activator of transcription 3 (STAT3) (97, 98). STAT3,

constitutively activated by cytokines, growth factor receptors and oncoproteins in many cancers, is not only anti-apoptotic and mitogenic(99), but also inhibits the production of proinflammatory mediators while stimulating the release of factors which promote tumor angiogenesis and immune suppression(100), including VEGF (101-104), IL-6 (104) and IL-10 (104, 105). In turn, these tumor-derived factors activate STAT3 in both myeloid- and lymphoid-derived cells, including MDSC. Compared with myeloid progenitor cells from non-tumor-bearing mice, MDSC from tumor-bearing mice highly express phosphorylated STAT3, which promotes the proliferation and survival of these cells (106). Not surprisingly then, STAT3 inhibition impairs the generation of MDSC from myeloid progenitors (99, 100, 106-108) and promotes the generation of mature DC (109). Cytokine-mediated activation of STAT3 may further augment the generation of MDSC via the upregulation of additional factors, like S100A8/S100A9, VEGF or IL-10, which contribute to the generation and recruitment of MDSC within the tumor microenvironment (48, 90).

While tumor-derived factors contribute to the expansion of MDSC, a growing body of evidence demonstrates that additional factors, many of which may be produced by "stromal" and inflammatory cells within the tumor microenvironment, are required for their functional activation. For example, MDSC from tumor-bearing mice were adoptively transferred into congenic tumor-bearing recipients. Many of the adoptively transferred MDSC differentiated into macrophages, DC and granulocytes in the spleens of the tumor-bearing hosts and lacked suppressive activity. In contrast, the adoptively transferred MDSC upon isolation from the tumor were able to promote the induction of T-cell apoptosis and phenotypically resembled immature tumor-associated macrophages (TAM) that highly expressed both arginase I and inducible nitric oxide synthase. While these TAM failed to express activated STAT3, phosphorylated STAT1 was observed and TAM isolated from STAT1 deficient mice lacked arginase I and iNOS and were unable to suppress the T-cell response (110). Similarly, suppression by monocytic MDSC was both IFN-gamma and STAT-1 dependent, whereas suppression mediated by granulocytic MDSC, while IFN-gamma dependent, did not require STAT-1 expression (34). STAT-6, activated downstream of IL-4Ralpha upon IL-4 or IL-13 binding, regulates arginase 1 and TGF-beta production by MDSC, thus contributing to MDSC activation and suppression (111, 112). Therefore, factors which activate STAT3 may contribute to the expansion of MDSC while factors present within the tumor microenvironment promote MDSC activation via the activation of STAT1 and STAT6.

B7-H1 (PD-L1, CD274), a B7 homologue which inhibits T-cell activation and effector function and is widely expressed by both tumor cells and myeloid-derived cells within the tumor microenvironment, has been observed on MDSC in both mice (34, 113, 114) and humans (44). In a murine ovarian cancer model, B7-H1 expressing MDSC isolated from ascites suppressed T-cell cytokine production in mixed splenocyte cultures in a B7-H1 dependent manner. In the model used, both regulatory T cells and MDSC were required to suppress T-cell production of IFN-gamma, as neither regulatory cell alone was suppressive. More importantly, MDSC-mediated suppression was, in part, dependent upon B7-H1 expression by MDSC. Blocking B7-H1, or its receptor PD-1, in coculture experiments partially inhibited MDSC-mediated suppression (114). In related work by the same authors, B7-H1 and its counter-receptors PD-1 and B7-1 (CD80) were shown to be important in the induction of arginase 1 expression by MDSC (113). Collectively, this data clearly implicates B7-H1 and its receptors in MDSC activation. However, the interpretation of this data is confounded by the observation that B7-H1 and its receptors are expressed by both MDSC and Treg. In addition, reverse signaling via B7-H1 has been demonstrated (115). Therefore, it is possible that the affects observed may be mediated by signaling downstream of either B7-H1 or one of its receptors. In addition, B7-H1 contributes to the induction of Treg in both murine and human models, but the extent to which B7-H1$^+$ MDSC contributed to the induction and/or maintenance of Treg in this model was not addressed (44, 116). Both IFN-gamma and Toll-like receptor (TLR) ligands, via STAT-1 and MyD88-dependent pathways (117-119), post-transcriptionally regulate B7-H1 expression and both STAT-1 and MyD88 have been implicated in the expansion or activation of MDSC (52). Whether STAT-1 and/or MyD88-mediated MDSC expansion and activation is partially B7-H1 dependent is an interesting, but untested, hypothesis.

4. MECHANISMS OF MDSC-MEDIATED SUPPRESSION

T-cell suppression mediated by MDSC occurs in both a tissue-specific, MDSC subset-specific, and at least in the periphery, in an antigen-independent manner. In secondary lymphoid organs, MDSC suppression of T-cell immunity likely requires cell contact and may occur in an antigen-dependent manner. This may be supported by *in vitro* studies demonstrating that MDSC derived from tumor-bearing mice inhibit antigen-specific CD8$^+$ T cells in a cell-contact and MHC-dependent fashion (120). In a landmark paper, Nagaraj et. al. demonstrated that lymph nodes from tumor-bearing mice contained many MDSC that were in direct contact with CD8$^+$ T cells (121). Both antigen-specific transgenic T cells and purified MDSC were adoptively transferred into non-tumor bearing mice prior to immunization with the relevant peptide. MDSC obtained from both wild-type and iNOS-deficient mice were able to induce tolerance in antigen-specific T cells. In contrast, MDSC obtained from gp91^{phox}-deficient mice, which lack a functional NADPH complex and are unable to generate reactive oxygen species (ROS), failed to induce tolerance. Nitric oxide (NO) and ROS (i.e. superoxide anion) chemically react to form peroxynitrite (ONOO$^-$), which is a stong oxidant associated with tumor progression in many tumors (122-125), and may inhibit the activation of naïve T cells (126). Generation of peroxynitrite results in the nitration and nitrosylation of proteins, including those that are rich in the amino acid tyrosine. Uric acid, which neutralizes peroxynitrite, was found to abolish the

tolerogenic affect of MDSC in this model. MDSC-mediated nitration of CD8 and the T-cell receptor in these mice was demonstrated and disrupted binding to the MHC-bound peptide, likely explaining T-cell tolerance observed in this model. Consistent with their previous work, these investigators demonstrated that MDSC may process and present tumor-associated antigens (47), resulting in the induction of T-cell tolerance. It is notable that T-cell tolerance induced in this model could be overcome by *in vitro* restimulation with mature DC, suggesting that appropriate costimulation, provided by mature DC, may overcome MDSC-mediated suppression. Downregulation of L-selectin (CD62L) on naïve T cells and impaired trafficking into secondary lymphoid organs provides another, albeit indirect, mechanism by which MDSC inhibit the activation of naïve antigen-specific T cells (127).

Within the tumor microenvironment, MDSC-mediated suppression is linked to the metabolism of L-arginine (128). L-arginine is metabolized by the enzymes arginase (ARG) and nitric oxide synthase (NOS), generating urea and L-ornithine, and NO and L-citrulline, respectively. Arginase 1 (ARG1) is inducibly expressed in myeloid cells, including MDSC, in response to IL-4, IL-13 (129-131), TGF-beta (132) and GM-CSF (133). Upregulation of ARG1 is frequently associated with the upregulation of amino-acid transporters, resulting in shuttling of extracellular L-arginine into the intracellular compartment, thus compensating for its degradation (128). STAT6, phosphorylated in response to the Th2 cytokines IL-4 and IL-13, plays an important role in the induction of ARG1 expression in MDSC, as previously noted. Depletion of L-arginine ultimately results in the disruption of protein translation, the downregulation of CD3-zeta (134, 135), and disruption of cell-cycle regulators (136), culminating in the inhibition of T-cell proliferation.

Like ARG1, an inducible isoform of NOS (iNOS or NOS2), is inducibly expressed in myeloid cells in response to IFN-gamma, TLR agonists, inflammatory cytokines and CD40 activation (128, 137-141). The generation of NO results in protein nitrosylation and the production of cGMP, both of which interfere with JAK/STAT phosphorylation downstream of the IL-2 receptor, thus impairing T-cell expansion following activation (142-145). In addition, NO may also inhibit IL-2 production (142, 146), inhibit the expression of MHC class II (147), and promote T-cell apoptosis (148, 149).

The differential regulation of ARG1 and iNOS raises the possibility of their differential expression. For example, NO was shown to be an important mediator of monocytic MDSC mediated suppression and was regulated, at least partially, by both IFN-gamma and STAT1 (34). In contrast, suppression mediated by granulocytic MDSC was strictly dependent upon IFN-gamma, but did not require either STAT1 activation or NO production. Similarly, granulocytic MDSC were shown to produce high levels of ROS and undetectable NO, whereas the converse was true for monocytic MDSC (30). Despite these differences, the suppressive capacity of both subsets was comparable.

In addition to their independent actions, ARG1, iNOS and NADPH oxidase may cooperate, leading to the production of superoxide (O_2^-), culminating in the generation of reactive nitrogen-oxide species (RNOS), including peroxynitrite. Peroxynitrites are membrane permeable and following post-translational protein modification prime T cells for apoptosis (128, 150, 151). In a human prostate adenocarcinoma model, tumor tissue expressed both ARG1 and iNOS and tumor-infiltrating lymphocytes contained high levels of nitrotyrosine residues and were unresponsive to antigenic stimulation. However, T-cell responsiveness was restored following the inhibition of both ARG1 and iNOS and was associated with a decrease in intracellular nitrotyrosine (152).

While ARG1 and iNOS contribute to the suppression mediated by MDSC, inhibition of ARG1 and iNOS does not abolish MDSC-mediated suppression in all models (34), thus raising the possibility that additional factors may contribute to MDSC-mediated suppression. The repetitive administration of LPS in mice was recently shown to expand a population of MDSC capable of suppressing T-cell proliferation and cytokine production independently of both ARG1 and iNOS (153). Instead, these cells expressed heme oxygenase-1 (HO-1) and the inhibition mediated by LPS-expanded MDSC was dependent upon both HO-1 and IL-10. IL-10 expression is regulated by HO-1 (154-156), suggesting that HO-1 may contribute to MDSC-mediated suppression via IL-10 upregulation, as IL-10 itself has been previously identified as a mediator of MDSC-mediated suppression (84, 157-159). In addition to L-arginine, T cells require the amino acid cysteine, which can be acquired by two mechanisms in mammalian cells. The first involves the transport of extracellular cystine into the intracellular compartment whereupon it's reduced to cysteine (160, 161). Alternatively, cysteine may be enzymatically generated from intracellular methionine (162, 163). As T cells lack both mechanisms (164, 165), they are dependent upon antigen-presenting cells for cysteine delivery, which T cells import via the plasma membrane ASC neutral amino acid transporter. Antigen-presenting cells export cysteine by the same ASC transporter; alternatively, the secretion of thioredoxin by these cells leads to the generation of extracellular cysteine from cystine (166-169). In this fashion, cysteine is made available for uptake by T cells. Srivastava et. al. made the novel observation that MDSC, while able to import extracellular cystine, lack the ASC transporter (160). In this way, MDSC sequester cysteine, thus depriving T cells of an essential amino acid required for T-cell activation.

In addition to the direct inhibition of T-cell activation and effector function, MDSC may also indirectly impair T-cell immunity by the induction of $FoxP3^+$ regulatory T cells (Treg) (32). Coculture experiments with sorted MDSC demonstrated that MDSC were able to induce FoxP3 expression and regulatory activity in cultured T cells. These results were further confirmed *in vivo* using an adoptive transfer approach. Notably, the suppression of tumor-specific T cells observed following the adoptive transfer of MDSC in this model could largely be attributed

to the induction of Treg. Experiments performed with both blocking antibodies and knockout mice revealed the MDSC-mediated induction of Treg was dependent upon IFN-gamma/STAT1 and IL-10/IL-10R. In addition, the ability of MDSC to induce Treg was independent of their iNOS-dependent suppressive function, demonstrating that direct MDSC-mediated suppression and the induction of Treg may not be closely linked. Dendritic cells were recently demonstrated to promote the induction of Treg in both murine and human models in a B7-H1 dependent fashion (44, 116). As B7-H1 is expressed by MDSC and IFN-gamma is a potent inducer of its expression (44, 170), it seems reasonable to speculate that B7-H1 may also contribute to the MDSC-mediated induction of Treg. This possibility is strengthened by the observation that $CD14^{+}HLA\text{-}DR^{-/low}$ MDSC isolated from patients with hepatocellular carcinoma were shown to induce $FoxP3^{+}$ Treg in a cell-contact dependent manner (42).

While much of the current literature emphasizes the association between MDSC and the suppression of T-cell immunity, emerging evidence also highlights their ability to suppress components of the innate immune response, including NK cells. MDSC were shown to directly suppress NK cell cytotoxicity and cytokine production in a cell-contact and TGF-beta dependent manner (171). In contrast, NK cell inhibition mediated by $CD14^{+}HLA\text{-}DR^{-/low}$ MDSC isolated from hepatocellular carcinoma patients was shown to be dependent upon the engagement of the NK-activating receptor NKp30, although the NKp30 ligand expressed by MDSC is unknown (172). MDSC-mediated NK cell suppression was partially reversed upon NKp30 blockade, suggesting that additional ligands may be involved in NK cell inhibition. In contrast to these findings, MDSC were shown to stimulate NK-cell production of IFN-gamma upon stimulation of the NK-activating receptor NKG2D by MDSC (173). Whether NK-cell derived IFN-gamma may contribute to MDSC activation was not examined.

5. MDSC AS A THERAPEUTIC TARGET

Myeloid-derived suppressor cells impair both innate and adaptive immunity in the tumor-bearing host directly and indirectly, via cross-talk with other immunoregulatory cells. Therefore, strategies capable of preventing MDSC expansion (or promoting their differentiation, if not outright depletion), interfering with their migration into the tumor microenvironment or inhibiting their function are attractive therapeutic strategies.

A diverse array of cytokines and other tumor cell or stromal-derived factors promote the expansion of MDSC in the tumor-bearing host. While neutralization of these factors is both feasible and promising, the number of factors involved, many of which may be at least partially tumor or site-specific, if not functionally redundant, makes this a daunting task. Stem cell factor (SCF), upon binding its receptor c-kit, has been shown to promote MDSC accumulation and the induction of T-cell anergy in a mouse model (66). In this model SCF knockdown or c-kit antibody blockade partially inhibited MDSC accumulation, prevented the induction of T-cell anergy, decreased tumor angiogenesis and improved the anti-tumor response of anti-CD137 based immunotherapy. This approach is certainly clinically relevant, as tyrosine kinase inhibitors which inhibit c-kit (among other tyrosine kinases, including the receptors for VEGF), are readily available and in clinical use (e.g. imatinib, sunitinib, sorafenib). For example, the frequency of MDSC in metastatic renal cell carcinoma was shown to decline following treatment with sunitinib, with MDSC levels almost returning to normal following 2 cycles of treatment (174). Reduction of MDSC levels in these patients was associated with increased IFN-gamma production by patient T cells and the *in vitro* depletion of MDSC from patient PBMC as well as MDSC inhibition by sunitinib enhanced T-cell activity. Whether or not the diminished MDSC accumulation observed in these patients is due to inhibition of c-kit, VEGF or CSF-1 receptors is unknown (175). It is also noteworthy that sunitinib was shown to inhibit MDSC-mediated suppression *in vitro*, suggesting that sunitinib may also directly impair the suppressive capacity of these cells, independently of its ability to prevent their accumulation. In addition, sunitinib decreased the frequency of both neutrophils and monocytes in renal cell carcinoma patients given sunitinib for 4 weeks, followed by 2 weeks off treatment. At week 6, following the 2 weeks off treatment, a substantial increase in the frequency of dendritic cells was observed, particularly among those patients who responded to treatment (176). At the very least, this observation suggests that sunitinib may restore normal myeloid differentiation.

Bevacizumab is a VEGF-targeting monoclonal antibody in clinical use in a wide variety of malignancies. As VEGF contributes to the development of MDSC, multiple investigators have examined the ability of its neutralization to prevent MDSC accumulation with mixed results. In a small series of patients with solid tumors treated with VEGF-trap, no significant reduction in MDSC accumulation was observed (177). In contrast, bevacizumab administration in mice implanted with renal cell carcinoma xenografts was shown to diminish the population of MDSC in these animals (178). Whether or not VEGF neutralization is associated with a concurrent increase in T-cell immunity is unknown.

Matrix metalloproteinase-9 (MMP-9) plays a multifactorial role in tumor progression, including the promotion of tumor angiogenesis by promoting the release of extracellular matrix-bound VEGF. While MMP-9 represents a rational therapeutic target, MMP-9 inhibitors have had little success clinically (179, 180). In contrast, amino-bisphosphonates (e.g. pamidronate and zoledronate) are widely used in cancer patients with bone involvement and generally well tolerated. Amino-bisphosphonates, in addition to their well described effects on osteoclasts, inhibit MMP-9 and decrease the availability of VEGF, thus impairing tumor angiogenesis (181). Predictably, amino-bisphosphonates were subsequently shown to decrease serum pro-MMP-9 and VEGF levels in a mouse model, leading to a reduction in the frequency of MDSC which normally expand in these mice and a significant improvement in the response to a tumor vaccine (182).

Many of the factors involved in driving the expansion and activation of MDSC converge on common intracellular signaling pathways, each of which represents an attractive therapeutic target. STAT3 has emerged as a central regulator of MDSC expansion, recruitment and function (100). Both peptides and peptidomimetic drugs, upon binding the SH2 domain of STAT3, may inhibit STAT3 (183). Two selective small molecule inhibitors of STAT3 have been identified following the virtual screening of large databases (184). Alternatively, a cell line expressing a reporter gene under the control of a STAT3 promoter was used to screen over 1000 compounds. This approach identified the STAT3 inhibitor nifuroxazide, which was shown to inhibit the survival of myeloma cells through the inhibition of the JAK kinases JAK2 and TYK2 (185). The therapeutic potential these approaches represent was further supported by the observation that the pharmacologic inhibition of STAT3 phosphorylation promotes NK-cell antitumor immunity, deplete MDSC within the tumor microenvironment and promote MDSC differentiation (106, 108). In a similar fashion, the IFN-gamma/STAT1 and IL-13/IL-4/STAT6 pathways represent other therapeutic targets.

MDSC accumulation is explained not only by enhanced myelopeoisis, but by impaired myeloid differentiation. The role of retinoids, including vitamin A metabolites, in MDSC biology is supported by the observation that vitamin A deficiency is associated with MDSC accumulation (186) and administration of retinoic acid receptor (RAR) antagonists in mice leads to MDSC accumulation in these animals (187). The vitamin A derivative, all-trans-retinoic acid (ATRA), promotes myeloid differentiation in acute promyelocytic leukemia. Similarly, ATRA promotes the *in vitro* differentiation of MDSC obtained from tumor-bearing mice into myeloid DC when combined with GM-CSF (120, 188). Furthermore, ATRA administration promoted the *in vivo* differentiation of MDSC in adoptive transfer experiments. More recently, a decrease in the frequency of MDSC and improved T-cell immunity was observed in metastatic renal cell carcinoma patients who achieved adequate plasma concentrations of ATRA following its administration (189). Limited evidence suggests that the administration of 25-hydroxyvitamin D_3 may also promote MDSC differentiation (190).

Just as multiple factors promote the expansion of MDSC, a variety of chemokines promote the recruitment of these cells to the tumor microenvironment, each of which represents a potential therapeutic target. Mediators of the complement system, in addition to their contribution to the innate immune response, are potent chemoattractants and localize to the tumor endothelium (191). Markiewski et. al. made the interesting observation that a transplanted tumor grew more slowly in mice that were deficient in the complement component C3 when compared to wild-type mice (192).They went on to demonstrate that C5a, deposited in the tumor vasculature, promoted the recruitment of MDSC, which express the receptor for C5a. Impressively, a peptide antagonist of the C5a receptor was as effective as systemic chemotherapy in slowing tumor growth. Whether the C5-blocking monoclonal antibody eculizumab may have a similar effect is unknown (193). In a murine breast cancer model, MDSC were recruited directly to the tumor microenvironment in mice deficient in the type II TGF-beta receptor. MDSC recruitment was regulated by the chemokines SDF-1 and CXCL5, both of which could be targeted with antagonists of their respective receptors, CXCR4 and CXCR2 (194). Chemokines implicated in the recruitment of monocytes and tumor-associated macrophages, including CCL2 and CCL5, have likewise been implicated in the recruitment of MDSC and represent attractive therapeutic targets (195, 196).

The functional inhibition of MDSC also represents an attractive therapeutic strategy, as has been repeatedly demonstrated by the *in vitro* use of both ARG1 and iNOS inhibitors, like nor-NOHA and l-NMMA, respectively. While these compounds are not useful clinically, alternative strategies may be imagined. For example, COX-2 inhibitors suppress PGE_2 production, which contributes to MDSC accumulation and activation (64, 65). Not surprisingly then, COX-2 inhibitors were shown to inhibit MDSC and enhance the anti-tumor immune response (39, 63). The phosphodiesterase 5 inhibitor sildenafil has been shown to downregulate ARG1 and iNOS expression by MDSC, increase T-cell activation and tumor infiltration and slow tumor growth in a murine model (96). The clinical relevance of this observation was supported by the additional finding that sildenafil promoted the *in vitro* expansion of T cells in PBMC of cancer patients. Finally, coupling of a NO moiety to classical nonsteroidal antiinflammatory drugs was performed to reduce the gastrointestinal side effects of these drugs. These drugs not only suppress ROS generation (197), but also inhibit iNOS (198, 199). Nitroaspirin was administered to tumor-bearing mice and was shown to inhibit both ARG1 and iNOS activity, increase tumor-antigen specific T cells, and improve the efficacy of a cancer vaccine (200).

While targeting those factors which promote MDSC expansion, migration and suppression are rational therapeutic approaches, an alternative approach simply seeks to deplete these cells altogether. In addition to their tumoricidal effects, conventional chemotherapeutic agents are increasingly appreciated for their immunomodulatory properties (201), including the ability to deplete MDSC in tumor-bearing animals. Perhaps the best example is gemcitabine, which was shown to dramatically reduce the frequency of MDSC in multiple murine tumor models without inducing concomitant lymphopenia. This was accompanied by improved T-cell and NK-cell immunity (202, 203). Taxane-based chemotherapy may also partially deplete MDSC in patients with metastatic melanoma (204).

6. CONCLUSION

Mounting evidence continues to highlight the association between cancer and aberrant myelopoiesis, most notably the emergence of MDSC, and its role in the suppression of host anti-tumor immunity. Additional interactions between MDSC and other cellular elements,

whether hematopoietic cells, tumor cells or other constituents of the tumor microenvironment, will continue to be discovered and their respective contributions to the subversion of host immunity dissected. On the other hand, it would be naïve to think that the role of MDSC is limited to their immunologic impact, as recent work so elegantly demonstrates (205-210), or even to cancer (211). Consequently, the restoration of normal myelopoiesis and the depletion or suppression of MDSC in cancer patients is an important therapeutic goal which has implications extending beyond tumor immunotherapy or even cancer biology.

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