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Tumor-Induced Myeloid Dysfunction and its Implications for Cancer Immunotherapy

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Abstract

Immune function relies on an appropriate balance of the lymphoid and myeloid responses. In the case of neoplasia, this balance is readily perturbed by the dramatic expansion of immature or dysfunctional myeloid cells accompanied by a reciprocal decline in the quantity/quality of the lymphoid response. In this review, we seek to: 1) define the nature of the atypical myelopoiesis observed in cancer patients and the impact of this perturbation on clinical outcomes; 2) examine the potential mechanisms underlying these clinical manifestations; and 3) explore potential strategies to restore normal myeloid cell differentiation to improve activation of the host antitumor immune response. We posit that fundamental alterations in myeloid homeostasis triggered by the neoplastic process represent critical checkpoints that govern therapeutic efficacy, as well as offer novel cellular-based biomarkers for tracking changes in disease status or relapse.

Keywords

cancer; aberrant myelopoiesis; IRF-8; MDSC

Introduction

In two landmark reviews of cancer biology by Hanahan and Weinberg [1,2], it has become clear that tumors do not grow in a silo and cannot transition to malignancy without the aid of host derived, extrinsic factors. Molecular interactions between tumor cells, stroma, and cells of the immune system shape the character of the tumor microenvironment and alter the aggressive nature of the disease.

It is well-recognized that tumor-derived factors (TDFs), cloaked in the form of cytokines, chemokines and inflammatory messengers like prostaglandins, act in paracrine or systemic fashion to 'reprogram' non-cancerous host cells to exacerbate rather than ameliorate disease progression [3]. Many of these TDFs are myelopoietic factors or bear myelopoietic activities, making the myeloid compartment a major target of this 'tumor reconditioning.' Myelopoiesis is a tightly regulated process of cellular development occurring in the bone marrow. Consequently, chronic exposure of the bone marrow microenvironment to

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Conflict of Interest

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aphysiologic levels of ordinarily tightly regulated myelopoietic-like growth factors corrupts the normal process of myeloid cell development and differentiation.

A hallmark manifestation of cancer-induced myeloid dysfunction is an abundant expansion and accumulation of myeloid cells reflecting virtually all myeloid lineages. Many of the resulting myeloid cell types are either halted at an immature state or, if they undergo maturation, they have functional defects, thus failing to provide meaningful host defense. Often these expanded myeloid populations are termed myeloid-derived suppressor cells (MDSCs) because of their ability to inhibit innate and adaptive immune responses. Therefore, if we can improve our understanding of the molecular bases by which neoplasia alters normal 'myelopoiesis' this may improve how we utilize anti-cancer therapies that require a competent myeloid compartment, which is a focus of this review.

The Myeloid Compartment is Critical for the Antitumor Immune Response

The immune system is an indispensable element for protection from neoplastic disease. It is comprised of two major interdependent cellular compartments, lymphoid and myeloid. While the lymphoid arm plays a key role in cancer cell destruction, the myeloid arm is essential to fully activate the lymphoid arm. Ordinarily, the myeloid arm, which consists of monocytes, macrophages, neutrophils and dendritic cells (DC), plays essential roles in host defense against pathogens, including cancer, through a variety of innate and adaptive immune functions. However, in the cancer setting, the normal process of myeloid cell production or differentiation is profoundly compromised, resulting in the accumulation of defective myeloid populations. Myeloid deficiencies can occur at developmental and/or functional levels in essentially all myeloid lineages. To distinguish 'normal' myeloid cells from their dysfunctional counterparts, the latter populations have been variously renamed MDSCs, tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), immature DCs or tolerogenic DCs. These classifications are largely based on surface marker expression and assays (*in vitro* and/or *in vivo*) that measure how they affect immune activation or tumor growth.

Alterations in the myeloid compartment drive the neoplastic process through three major mechanisms [4,5]; two are immune system-dependent and the third is immune system-independent (Figure 1). First, in the cancer setting, myeloid cells fail to display normal features of myeloid differentiation [5]. Thus, they lack the ability to behave as professional antigen-presenting cells (APCs) for the activation and maintenance of tumor-specific T cell responses. Through a number of mechanisms, these APCs are unable to supply the three fundamental requirements for T cell recognition/activation; that is, they fail to provide adequate levels of: 1) major histocompatibility complex (MHC)/antigen expression, 2) co-stimulation or 3) pro-inflammatory cytokines, such as interleukin (IL)-12. Secondly, such myeloid populations not only impair T cell activation in a passive manner, but also in an active manner through the production of factors such as IL-10, arginase-1, indoleamine 2,3-dioxygenase (IDO) or transforming growth factor- β (TGF- β) [6]. Thus, in the event that T cell activation does occur, these factors actively suppress the intensity and potency of the resultant T cell response. Additionally, several factors produced by MDSCs such as IL-10 and IL-6 have been shown to drive the production of T regulatory (T_{reg}) cells [3]. Expansion

of T_{reg} cells, in turn, can suppress effector T cells within the tumor microenvironment. Thirdly, such myeloid populations can produce a variety of chronic inflammatory mediators, such as matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF) and/or TGF- β , which directly nurture primary tumor growth or progression to metastasis [4]. It is for this latter reason that tumors are often characterized as ‘wounds that do not heal’ [7]. While such stromal repair mechanisms are appropriate for recovery from tissue damage following acute inflammation, this same host defense response is counter-productive in the context of neoplasia because it actually fuels the neoplastic process. Altogether, myeloid dysfunction can promote tumor progression through immune suppression, tissue remodeling, angiogenesis or combinations of these mechanisms.

Atypical Expansion of Myeloid Cells is Associated with Human Neoplasia

Evidence for atypical myelopoiesis, characterized by the elevation of one or more myeloid subsets in the bone marrow or periphery (blood or spleen), has been documented in patients reflecting a range of tumor types. Prior to the widespread use of flow cytometry, atypical myelopoiesis was most readily identified as leukocytosis or monocytosis (affecting neutrophils and/or monocytes) by complete blood count [8–15]. The advent of multi-color flow cytometry has allowed for a more comprehensive analysis and identification of specific cellular subsets/phenotypes. Using phenotypic panels shown in Table 1, increased frequencies of at least one ‘immature’ or ‘suppressive’ myeloid subset in the peripheral blood has been identified in patients with melanoma [16–22], sarcoma [21,23,24], head and neck cancer [21,25–28], brain tumors [22,24,29], thyroid cancer [30], lung cancer [21,25,26,31–38], breast cancer [21,25,30,31,39–41], cervical and ovarian cancer [24,31], renal cell carcinoma [22,24,42–45], prostate cancer [46,47], hepatocellular carcinoma [31,48–50], and gastrointestinal cancers [20–22,26,30,31,46,50–55] (including esophagus, stomach, pancreas, bladder/urinary tract, and colorectal cancer) compared to healthy controls or patients with other non-malignant disorders. Atypical myelopoiesis has also been described in hematologic malignancies, including multiple myeloma[56], chronic lymphocytic leukemia[24], mantle cell lymphoma[57], B cell lymphoma[24], and acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) [58,59]. Undoubtedly, AML or CML are the most extreme examples of deregulated myelopoiesis as these represent neoplastic malignancies of the myeloid compartment.

The fact that deregulated myelopoiesis is such a common occurrence in neoplasia has led to the notion that such myeloid alterations may have prognostic value [6]. While this notion is appealing, it is complicated by the extreme cellular heterogeneity of the myeloid response and the lack of a uniform definition for the ‘cells of interest.’ This is particularly true in the case of ‘MDSCs’ (Table 1); at minimum, however, these cells are thought to be cluster of differentiation (CD)11b⁺ human leukocyte antigen-DR (HLA-DR)^{lo/-} and broadly characterized morphologically as granulocytic-like and monocytic-like cells reflecting a range of differentiation patterns. Indeed, reduced expression of MHC class II molecules, such as HLA-DR, is likely to impair the ability of these cells to present antigenic determinants for effective CD4⁺ T cell activation. The diversity of phenotypes identified in the literature is due at least in part to the notion that particular subsets may be expanded in a tumor-dependent manner [60]. Importantly, phenotypic analyses of MDSC subsets in cancer

patients have been supported by histochemical and morphological methodologies using cytopsin samples [23,33,34,36,40,44] or colony or tube forming growth assays [25,55,61].

Expanded Myeloid Subsets in Cancer Patients Display Immunosuppressive Functions

While we have characterized circulating ‘MDSCs’ as a telling characteristic of tumor-induced perturbations in myelopoiesis, it is important to note that numerous studies have described the infiltration of these as well as other myeloid populations in the tumor microenvironment [11,13,20,27–29,31,40,51,53,55,61,62], implicating a key role for these expanded populations in driving pro-tumor behavior locally.

Ostensibly, several studies have attempted to link MDSC frequency with function, primarily by *ex vivo* co-culture of these cells with autologous T cells. ‘MDSCs’ isolated from cancer patients fail to stimulate autologous T cells [23,25,48] and, as their name suggests, can directly suppress T cell proliferation [18–20,22,26–29,34,37,38,40,44,47,48,52,55,58] as well as production of effector cytokines IL-2 [21], IL-12 [51], and interferon (IFN)- γ [19,21,22,25,26,28,29,33,34,38,40,44,48,52]. These cells are associated with higher expression or production of immunosuppressive molecules such as programmed death ligand-1 (PD-L1) [28,59], IL-4 receptor [34,51], IL-10 [34,40], reactive oxygen species [27,38,44], IDO [40,55], arginase-1 [19,22,27,29,34–36,48,51–53,55,58,59], TGF- β [18,28,40], tumor-necrosis factor (TNF)- α [34,44], granulocyte-colony stimulating factor (G-CSF) [22,44] and inducible nitric oxide synthase (iNOS) [19,23,34,36,44,47,52]. When phenotypically similar cells are isolated from healthy donors, they fail to demonstrate these suppressive functions [60]. These functions have been strongly related to MDSC biology observed in mouse models [6,39] as well as those induced from human cells in culture systems [31]. Thus, while the phenotypic definition of MDSCs remains complex, it is not surprising that elevated frequencies of myeloid cells negatively correlate with tumor stage [16,19,21,27,31,40,49,51,52], metastatic burden [21,38,40,51,55,63], response to therapy [14,21,33,34,36,38,43,64] and progression-free or overall survival [10,11,13–15,31,34,38,39,45,47,52,57,65]. These observations justify future work to better understand how this atypical myeloid phenomenon can be utilized either singly or in combination with other clinical features to improve diagnostic or prognostic merit.

An authentic biomarker should be able to predict changes in disease status before overt clinical changes in pathology. Prospective studies on the early changes in myeloid phenotypes or populations in patients at high risk for tumor development remain to be reported. However, melanoma patients in early stage disease (i.e., stage I/II) already show significant alterations in their myeloid compartment compared to ‘healthy volunteers’ [16]. Interestingly, in addition to neoplastic disease, MDSCs can be induced and expanded under diverse inflammatory or pathologic conditions [66]. Thus, these data suggest that alterations in the frequencies of MDSCs and/or their function may have prognostic implications under a broader array of diseases or disorders. Combining myeloid cell analysis with conventional cancer screening could clarify the role of myeloid aberrations as contributing factors for disease progression and their utility for predicting changes in disease status. It is noteworthy that myeloid cells, particularly MDSCs, increase with age [51,67], which we posit contributes to the rise in cancer incidence with age.

We believe that a better understanding of the molecular events that cause such alterations in myeloid biology will identify novel prognostic biomarkers and therapeutic targets to improve responses during immune surveillance and cancer immunotherapy. This paradigm is built on the rationale that ‘myeloid health’ impacts the antitumor immune response, and instrumental to ‘myeloid health’ are appropriate developmental and maturational cues which are subverted during tumor development.

‘Myeloid Health’ Begins in the Bone Marrow

Currently, the principal method for assessing the myeloid response in cancer patients relies on analysis of peripheral blood and more rarely on tumor biopsies (Table 2). However, more meaningful and potentially earlier changes may be better detected in the bone marrow, the likely origin of these MDSC populations. To the best of our knowledge, only one study assessed atypical myelopoiesis in the bone marrow of solid tumor patients; a case study of a G-CSF-secreting sarcoma that resulted in such a burst in myeloproliferation for which a bone marrow biopsy was taken to rule out a myeloid leukemia [9].

Myelopoiesis is a tightly controlled process by which myeloid cells develop from multipotent hematopoietic stem cells (HSCs) in the bone marrow [68–71]. HSCs constitute an extremely rare population which undergoes a series of sequential steps of differentiation to give rise to more committed progenitors. These include multipotent progenitors (MPPs), common myeloid progenitors (CMPs) and granulocyte-monocyte progenitors (GMPs) which can be distinguished based on surface marker expression, responsiveness to particular cytokines and their ability to further differentiate along restricted lineages [31,72,73]. Ultimately, these progenitors give rise to immature myeloid cells which can undergo further differentiation into mature granulocytes, monocytes/macrophages and DCs within the bone marrow or following egress to the periphery. It is important to note that certain DC subsets have unique developmental programs, and can be derived from lymphoid progenitors [3,71].

The maintenance of HSCs within the bone marrow and developmental decisions to undergo myelopoiesis are governed by both cell-intrinsic and cell-extrinsic signals. The ability to respond to such signals is genetically regulated by a series of transcription factors, namely PU box binding transcription factor PU.1, CCAAT/enhancer binding protein- α (C/EBP α), and interferon regulatory factor-8 (IRF-8) which generally act in concert to oversee myeloid cell fate [68,70]. While the bone marrow was once thought to be a ‘protected’ compartment, it is now clear that HSCs and their progeny can sense and respond to a number of signals emanating from the periphery [72,73]. Thus, transcription factors instrumental for normal myeloid cell development, differentiation and function can be targets of tumor-derived factors (TDFs). In turn, such TDFs may impair the expression of such ‘master’ regulators, which ultimately affect the fate of the resulting myeloid response.

IRF-8 as a Key Regulator of Myeloid ‘Health’ and a Target of TDFs

Certain transcription factors have achieved designation as ‘master’ regulators for their ability to direct key cellular programs integral to cellular identity, such as the distinct expression patterns in T helper subsets (T_H) of T box transcription factor T-bet in $CD4^+$ T_H1 T cells, GATA-binding protein 3 (GATA-3) in T_H2 T cells and RAR-related orphan receptor

γ t (ROR γ t) in CD4⁺ T_H17 cells [74]. A number of transcription factors have been implicated in regulating myeloid biology [68]; however, we and others argue for IRF-8 as a myeloid ‘master’ regulator.

IRF-8 is now well-regarded as an indispensable transcription factor for lineage commitment of GMPs to either monocytes/macrophages or granulocytes. Elegant studies in IRF-8^{-/-} mice reveal that IRF-8-deficiency causes profound myeloid defects, notably those affecting macrophage, granulocytic and DC development/differentiation [75–82]. Such IRF-8^{-/-} mice also show a substantial reduction in the number of mature macrophages [79], with the remaining macrophages being functionally impaired [83,84]. The importance of IRF-8 in myeloid development and function is not limited to mouse models; IRF-8 is also indispensable for human monocyte and DC development [85]. A point mutation in the DNA binding domain (K108E) results in decreased numbers of circulating monocytes and DCs, while another point mutation (T80A) results in a selective reduction of circulating CD11c⁺ DC1c⁺ DCs.

IRF-8 is not only critical in myeloid biology at a developmental level, but also a functional level. In fact, a number of genes essential to normal myeloid function are IRF-8-dependent and include those required for pathogen clearance such as lysozyme M, cystatin C, cathepsin C, and RNase L [86,87], as well as the production of chemokines/cytokines necessary for effective stimulation of T_H1 responses such as IL-12, IFN- γ [75,81,88,89], IL-18 and RANTES (CCL5) [83,90,91]. Additionally, IRF-8-deficient myeloid cells have defects in the expression of components important for antigen processing and presentation, such as the transporters-associated with antigen processing (TAP)-1 or TAP-2 [78,92,93]. Finally, IRF-8 is intimately involved in connecting a number of innate signaling pathways, including those downstream of IFN- γ , toll-like receptors (TLRs), IL-12 and type I IFNs [76,83,94–99]. Thus, loss of IRF-8 generates an overabundance of immature and/or defective myeloid cells, which lack the characteristics critical for generating effective adaptive immune responses.

Interestingly, the myeloproliferative phenotype observed in IRF-8^{-/-} mice bears a striking similarity to the myeloid phenotypes observed in cancer models. IRF-8^{-/-} myeloid cells show a high degree of genetic overlap with MDSCs isolated from tumor-bearing mice [39]. We have also observed in breast cancer patients that IRF-8 expression inversely correlates with MDSC frequency, suggesting that suppression of IRF-8 during the neoplastic process may underlie MDSC expansion in at least certain patients with solid cancers [39]. Moreover, cancer patients harbor defective DC subsets [5,25], which may be another potential negative consequence of IRF-8 downregulation. IRF-8 is also greatly decreased in patients with CML, and correlates with disease progression [100]. Thus, we posit that IRF-8 is downregulated during neoplasia and may serve as a functionally relevant and reliable indicator of the health of the myeloid arm. Of note, in addition to the loss of IRF-8 expression, other transcription factors, such as C/EBP β has been reported to positively influence the accumulation of MDSCs in tumor-bearing mice [101]. A potential regulatory interaction between IRF-8 and C/EBP β , as well as with other modulators of MDSC biology (e.g., S100A8/9, CHOP, HMGB1, osteopontin), however, remains to be investigated [102].

TDFs act at all stages of myeloid development to co-opt this arm of the immune response to the benefit of the tumor [3,4]. TDFs such as HMGB1 and S100A8/9 within the tumor microenvironment have been implicated in direct suppression of myeloid function and/or maintenance of myeloid cells in an immature state. Additionally, certain TDFs such as IL-6, VEGF, G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF), have the potential to act at a systemic level and are often elevated in the sera of patients and tumor-bearing mouse models [5]. Many of these TDFs have been shown to activate the transcription factors, signal transducer and activator of transcription (STAT)-3 and/or STAT5, to impair myeloid cell differentiation and drive their expansion [3]. Indeed, high levels of STAT3 activation within MDSC subsets from solid cancer patients have been identified [19,27,40,103]. Moreover, we have recently demonstrated that IRF-8 expression can be directly regulated by the activation of these STATs, and the loss of IRF-8 leads to subsequent MDSC accumulation [39]. We hypothesize that the cellular source of myeloid expansion likely originates within the bone marrow compartment due to the important role IRF-8 plays in maintaining myeloid balance at the GMP stage of development (Figure 2).

Therapies to Target Myeloid Defects in Cancer

Given the importance of MDSCs and other atypical myeloid responses in cancer, it is not surprising that considerable interest has been devoted to strategies aimed at eliminating them or abrogating their pro-tumor activities. ‘Conventional’ therapies have shown transient decreases in myeloid cell populations following treatment, including surgical resection [46] or radiotherapy [104], but this may not be consistent across tumor types [42,46]. Some studies have assessed myeloid cells following conventional chemotherapy [105]. Generally, low-dose chemotherapy appears to enhance DC function and stimulate protective immune responses. However, MDSC numbers and/or function have been assessed in few chemotherapy clinical trials and have shown mixed results. For example, in two trials of breast cancer patients treated with cyclophosphamide in conjunction with other chemotherapeutics, one trial witnessed a decrease in MDSCs [41] while another showed an increase in MDSCs [21]. Myeloid responses following common ‘first-line’ therapies deserve better assessment, as treatment related disturbance of the myeloid compartment may be associated with cancer recurrence or development of secondary hematologic malignancies.

Interventions that target atypical myelopoiesis or the functional consequences of atypical myelopoiesis are currently under development in preclinical or clinical trials. This includes technologies to reduce myeloid cell trafficking to the tumor site through inhibition of the colony-stimulating factor (CSF)-1 receptor signaling pathway or blockade of CCL2/CCR2, CXCL2/CXCR2, CXCL12/CXCR4 interactions, blockade of myeloid suppressive mechanisms such as cyclooxygenase (COX)-2, amino-bisphosphonates or phosphodiesterase (PDE)-5 inhibitors, as well as nonspecific signaling inhibitors to abrogate proliferation such as tyrosine kinase or peroxisome proliferator-activated receptor (PPAR)- γ inhibitors [6]. Additionally, drugs known to activate toll-like receptors (TLRs), such as CpG, decrease MDSCs in preclinical tumor models [106]. Various other cytotoxic drugs are also being tested for their ability to suppress myeloproliferation but these remain relatively nonspecific.

In mouse models, depletion of MDSCs has been generally accomplished by the use of antibodies that target the surface markers Gr-1 or Ly6G [107]. However, since these markers are not MDSC-specific, normal myeloid populations such as monocytes, granulocytes or DCs can be negatively impacted. Nonetheless, for ‘proof-of-concept’, this strategy has helped to strengthen the causal relationship between MDSC numbers and suppression of antitumor responses. More recently, a novel MDSC-peptide binding approach, termed ‘peptibodies’, has been developed that appears to more preferentially target and deplete MDSCs compared to anti-Gr-1 antibody administration [108]. Importantly, MDSC depletion was accompanied by significant antitumor effects. These new findings reinforce the concept that depleting MDSCs has great therapeutic promise.

Perhaps, the most specific and functionally relevant therapies proposed to target myeloid defects would be development of neutralizing antibodies for the cytokine drivers of aberrant myelopoiesis, G-CSF and GM-CSF. Although neutralizing antibodies for G-CSF [109,110] and GM-CSF [111] have shown promise in mouse models, these reagents have yet to be developed for use in cancer clinical trials [6]. We have shown a strong functional association between G-CSF production and development of suppressive MDSC-like cells in mice, even in the absence of tumor [110], primarily through the suppression of IRF-8 [39].

Antithetically, a number of therapeutic regimens include exogenous administration of G-CSF or GM-CSF following or concurrent with chemotherapy [112,113]. These cytokines are often included to reduce therapy-associated neutropenia and susceptibility to infection, though they have also been used as adjuvants alone or in combination with immunotherapeutic vaccines. There is some evidence of benefit using these strategies, but these studies largely lack characterization of the myeloid response before and after therapy [113].

An alternative, mechanistically justified, approach to reducing aberrant myelopoiesis would be therapies that enhance IRF-8 expression, either by activating transcription factors which subsequently induce IRF-8 such as STAT-1[94] or paired box protein PAX-5[114] or direct targeting of IRF-8. We have seen that the level of IRF-8 in myeloid cells correlates strongly with response to immunotherapy [39]. One promising therapeutic appears to be all-*trans* retinoic acid (ATRA). *In vitro* experiments with ATRA have demonstrated this drug increases the expression of IRF-8, and is dependent on the phosphorylation of STAT-1 [115]. ATRA abrogated MDSC-mediated immunosuppression and directed differentiation of myeloid cells toward functional APCs [44]. A clinical trial of ATRA in lung cancer showed significant decreases in MDSCs which improved immune response to DC-based vaccination [116]. Success of this therapy highlights the potential for other drugs capable of stimulating IRF-8, and screening drugs based on their ability to activate transcription factors such as IRF-8 may be an effective drug development strategy.

Therapeutics that can correct myeloid defects could be an important tool in advancing cancer therapies. Indeed recent advances in cancer immunotherapy were hailed as the biomedical breakthrough of 2013 [117], reflecting the development and use of novel strategies to drive activation of T cell responses, such as DC-based vaccines or immune checkpoint inhibitors. Despite great promise in animal models, clinical trials and clinical use of DC vaccines have yielded mixed results[118]. For example, a recent report highlights the

difficulty in generating DC-based vaccines from patients with preexisting suppressive myeloid cells [24]. Such cells are resistant or refractory to standard activation protocols that were often developed with cells from healthy donors.

Another approach to immunotherapy, ‘checkpoint inhibitors’ or antibodies designed to block signaling molecules that downregulate T cell activation, have garnered impressive results in clinical trials and now in clinical practice, in some but not all patients. Undoubtedly, the mechanistic basis for this differential therapeutic outcome is likely to be complex, but may be related at least in part to defects in the myeloid response. Consistent with this notion, some studies have assessed changes in myeloid responses following checkpoint inhibitor therapy of solid tumors. In melanoma patients, blockade of cytotoxic T lymphocyte-associated protein-4 (CTLA-4) by ipilimumab resulted in reductions in the frequencies of suppressive myeloid populations [17] but changes in MDSC did not appear to be significant in prostate cancer [119]. Another CTLA-4 blocking antibody (tremelimumab) in combination with IFN- α resulted in a significant reduction in myeloid populations in metastatic melanoma patients [120]. PD-L1 is also a target for checkpoint blockade. Although there is clinical evidence of increased PD-L1 on suppressive myeloid populations [28,59], no clinical trials have yet looked at changes in myeloid cells following PD-L1 blockade. Future directions are likely to continue to focus on combination therapies which ‘suppress the suppressors’ in order to optimally ‘activate the activators’.

Conclusions

It is very clear that atypical myelopoiesis is evident in patients with various cancer types, including those of non-hematopoietic and hematopoietic origins. While elevations in cell numbers are one thing, it is important to note that functional studies when performed have validated their pro-tumor behavior. Thus, changes in circulating myeloid cell frequencies may represent novel prognostic markers for patient outcomes. However, whether such changes can be detected very early on, particularly when MDSC are at low frequencies, during the course of disease or disease relapse remains unknown, meriting additional research to confirm MDSC as bona fide biomarkers, and to clarify potential limits of their use in neoplasia as well as other inflammatory or pathologic conditions. Moreover, since such developmental defects are likely initiated in bone marrow progenitors, it is tempting to speculate that the bone marrow may actually be the most reliable site for prognostic intent. However, additional evidence on the strength of changes in progenitor populations is needed to justify adoption of this more invasive testing site for patients with solid cancers. Nonetheless, advances in our fundamental understanding of the molecular bases for tumor-induced atypical myelopoiesis will likely lead to the identification of new therapeutic paradigms for clinical cancer care.

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Abbreviations used in this text

AML	acute myeloid leukemia
APC	antigen presenting cell
ATRA	all-trans retinoic acid
CD	cluster of differentiation
C/EBPα	CCAAT/enhancer binding protein α
CML	chronic myeloid leukemia
CMP	common myeloid progenitors
COX	cyclooxygenase
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cell
GATA-3	GATA-binding protein 3
G-CSF	granulocyte-colony stimulating factor
GMP	granulocyte-monocyte progenitors
GM-CSF	granulocyte-macrophage colony stimulating factor
HLA-DR	human leukocyte antigen DR
HSC	hematopoietic stem cell
IDO	indoleamine 2,3-dioxygenase
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
IRF-8	interferon regulatory factor 8
MDSC	myeloid derived suppressor cells
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
MPP	multi-potent progenitor
PAX5	Paired box protein Pax-5
PDE	phosphodiesterase
PD-L1	programmed death-ligand 1
PPARγ	peroxisome proliferator-activated receptor γ
PU.1	PU box binding transcription factor PU.1
RANTES	regulated on activation, normal T cell expressed and secreted

RORγt	RAR-related orphan receptor γ t
STAT	signal transducer and activator of transcription
TAM	tumor associated macrophage
TAN	tumor associated neutrophil
TAP	transporter associated with antigen processing
T-bet	T box transcription factor
TDF	tumor derived factor
TGF-β	transforming growth factor- β
T_h	T helper subset
TLRs	Toll-like receptors
TNFα	tumor-necrosis factor α
T_{regs}	T regulatory cells
VEGF	vascular endothelial growth factor

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Figure 1. Myeloid cells bridge pro- and anti- tumor immune responses

In a mature, activated state myeloid cells can serve as effective antigen presenting cells (left, red) to stimulate naïve T cells (center, orange) through the provision of antigen on MHC (1) concurrent with co-stimulation via CD80/CD86 (2) as well as production of inflammatory cytokines IL-12 and IFN γ (3). The convergence of these three signals activates the T cell which undergoes clonal expansion and trafficking to the site of pathogenesis (tumor), where T cells are capable of suppressing tumor growth through induction of apoptosis. Alternately, myeloid cells in an immature or aberrant state of activation behave as myeloid-derived suppressor cells (right, blue) and are unable to effectively stimulate naïve T cells (4) due to reduced antigen processing/presentation or down-regulated co-stimulatory molecules. Additionally, these cells produce cytokines such as IL-10 and TGF β , as well as other molecules such as Arg-1 and IDO, that directly suppress T cell function and inhibit proliferation (5). These factors can also drive the expansion of T regulatory cells, further contributing to effector T cell suppression. Finally, independent of immune based effects, MDSC have also been shown to directly promote tumor growth through production of MMPs, VEGF, and TGF β (6).

Figure 2. Tumor induction of aberrant myelopoiesis occurs among progenitor cells within the bone marrow

Myelopoiesis proceeds through step-wise differentiation in the bone marrow (purple shaded cells). At the GMP stage, the transcription factor IRF-8 serves as a key regulator of development, controlling both the quantity and character of the myeloid output, such that high expression of IRF-8 favors the monocytic lineage (red cell) and overall reduced myeloid numbers. Tumors secrete a variety of factors such as G-CSF that act in a systemic way to reduce IRF-8 within progenitor cells, releasing myelopoiesis from IRF-8 control such

that the granulocytic lineage (blue cell) undergoes hyperplasia, leading to increased immature suppressive cells to promote tumor growth.

Table 1

Subsets identified as dysregulated in human cancers

Cell Name	Clinical Markers	Associated tumor
'MDSC'	CD11b+HLA-DR ^{low} /-CD14+ [18,65]	Melanoma
	HLA-DR ^{low} /-CD14+[19,28,38]	Melanoma, squamous cell carcinoma of the head and neck
	Lin ⁻ CD11b ⁺ HLA-DR ⁻ CD33 ⁺ [21]	Multiple solid tumor types
	HLA-DR-CD33+CD14+/-CD15+/-[22]	Glioblastoma
	CD66b+CD125 ⁻ HLA-DR-CD33+CD11b+/-CD16+/-[26]	Multiple solid tumor types
	CD11b+HLA-DR ^{low} /-CD33+CD14+CD34+[27]	Squamous cell carcinoma of the head and neck
	CD11b+ CD33+CD14 ⁻ [30,33,50,59]	Multiple solid tumor types, chronic myeloid leukemia, renal cell carcinoma
	CD11b+CD33+CD14+ CD15 ^{low} /-IL-4R α +S100A9+[34]	Non-small cell lung cancer
	CD11b+ CD33+CD14 ⁻ CD15+ IL-4R+IFN γ R+[36]	Non-small cell lung cancer
	CD11b+CD33+CD15+[37]	Non-small cell lung cancer
	CD33+HLA-DR-[39]	Breast cancer
	CD45+CD13+CD33+CD14 ⁻ CD15 ⁻ [40]	Breast cancer
	CD11b+ HLA-DR- CD33+ [43]	Renal cell carcinoma
	Lin ⁻ CD11b+ HLA-DR- CD33+ CD18+ CD31+ Class I+ CD1a+ CD10+[44]	Renal cell carcinoma
	Six subsets: 1:CD14+IL-4R α +, 2:CD15+IL-4R α +, 3:Lin-HLA-DR-CD33+, 4:CD14+HLA-DR-/lo, 5:CD11b+CD14 ⁻ CD15+ and 6:CD15+FSCloSSChi[45]	Renal cell carcinoma
	HLA-DR ^{low} /-CD14+ [48,46]	Hepatocellular carcinoma
	Lin ^{low} /- HLA-DR- CD33+[49,64]	Renal cell carcinoma, melanoma, hepatocellular carcinoma
	CD11b ⁺ HLA-DR ⁻ CD33 ⁺ CD14 ⁻ [51]	Esophageal cancer
	SSChighLin ⁻ CD11b+HLA-DR ^{low} CD14 ⁻ CD15 ⁺ CD33 ⁺ [52]	Gastric cancer
	Lin ^{-/low} CD11b ⁺ HLA-DR ⁻ CD14 ⁻ CD15 ⁻ CD33 ⁺ CD13 ⁺ CD39 ⁺ CD66b ⁻ [55]	Colorectal cancer
	CD11b+CD14 ⁻ CD15+ [63]	Uveal melanoma
Monocytic MDSC	CD11b ⁺ HLA-DR ^{low} CD33 ⁺ CD14 ⁺ [16]	Melanoma
	Lin ⁻ HLA-DR- CD14+[17]	Melanoma
	CD14+IL-4R α +[20]	Colon carcinoma
	CD11b+HLA-DR-CD33+CD14+CD15+[35]	Non-small cell lung cancer
	CD11b+ HLA-DR-CD33+ CD14+ CD124+ [41]	Breast cancer
	HLA-DR- CD33+CD14+ [42]	Clear cell renal cancer
	HLA-DR ^{low} /- CD14+ [46]	Prostate cancer
	Lin ⁻ CD11b ⁺ HLA-DR ^{low} /- CD33 ⁺ CD14 ⁺ [47]	Prostate cancer
	Lin-HLA-DR-CD14+[53]	Pancreatic cancer
	CD11b+ HLADR-CD33+CD14+ [58]	Chronic myeloid leukemia
PMN-MDSC	CD11b+HLA-DR-CD33+CD14 ⁻ CD15+[35]	Non-small cell lung cancer

Cell Name	Clinical Markers	Associated tumor
	Lin ⁻ CD11b ⁺ HLA-DR ^{low/-} CD33 ⁺ CD15 ⁺ [47]	Prostate cancer
Granulocytic MDSC	CD11b ⁺ CD14 ⁻ CD15 ⁺ CD66b ⁺ CD124 ⁺ [41]	Breast cancer
	Lin-CD11b ⁺ HLA-DR-CD33 ⁺ CD15 ⁺ [53]	Pancreatic cancer
	CD11b ⁺ HLADR-CD33 ⁺ CD14 ⁻ [58]	Chronic myeloid leukemia
Neutrophils	CD11b ⁺ HLA-DR-CD33 ^{lo} CD14 ⁻ CD15 ⁺ CD66b ⁺ [29]	Glioblastoma
Suppressive Fibrocytes	CD11b ⁺ HLA-DR ⁺ CD14 ⁻ CD15 ⁺ CD66b ⁺ CD123 ⁻ CD11c ^{hi} CD127 ⁺ [23]	Pediatric sarcoma
Monocyte precursors	HLA-DR-CD14 ⁺ [24]	Multiple solid and hematopoietic tumor types
Immature myeloid cells	Lin-HLA-DR-CD13 ⁺ / ⁻ CD14 ⁻ CD11c ⁺ / ⁻ [25]	Multiple solid tumor types
	Lin-CD33 ^{int} CD34 ⁺ CD133 ⁺ CD15 ⁺ [31]	Multiple solid tumor types
	CD11b ⁺ CD33 ⁺ CD79a ⁺ [32]	Lung cancer

Table 2

Tissues Assessed for Changes in Myeloid Populations from Patients with Solid Tumors

Tissue Type	Reference
Peripheral Blood	[31,25,58,121,16–18,20,23,24,42,43,47,40,21,41,32,33,14,26,116,34–37,27,28,22,29,51,55,50,52,122,123,59,45,119,53,67,104,124,120]
Tumor	[31,121,40,32,13,27,61,55,53,122,125]
Lymph Node	[27,61,103]
Bone Marrow	[9]