OncoImmunology 2:4, e24117; April 2013; © 2013 Landes Bioscience

Myeloid derived suppressor cells
Targets for therapy

Todd J. Waldron,[1,2,†] Jon G. Quatromoni,[3,†] Tatiana A. Karakasheva,[1,2] Sunil Singhal[3,4] and Anil K. Rustgi[1,2,5]

[1]Gastroenterology Division; Department of Medicine; University of Pennsylvania; Philadelphia, PA USA; [2]Abramson Cancer Center; University of Pennsylvania; Philadelphia, PA USA; [3]Division of Thoracic Surgery; Department of Surgery; Hospital of the University of Pennsylvania School of Medicine; Philadelphia, PA USA; [4]Surgery Service; Philadelphia Veterans Affairs Medical Center; Philadelphia, PA USA; [5]Department of Genetics; University of Pennsylvania; Philadelphia, Pennsylvania

[†]These authors contributed equally to this work.

Keywords: myeloid derived suppressor cells, docetaxol, RNA aptamer, CpG oligodeoxynucleotides (ODN), cyclophosphamide, gemcitabine, curcumin

The goal of achieving measurable response with cancer immunotherapy requires counteracting the immunosuppressive characteristics of tumors. One of the mechanisms that tumors utilize to escape immunosurveillance is the activation of myeloid derived suppressor cells (MDSCs). Upon activation by tumor-derived signals, MDSCs inhibit the ability of the host to mount an anti-tumor immune response via their capacity to suppress both the innate and adaptive immune systems. Despite their relatively recent discovery and characterization, anti-MDSC agents have been identified, which may improve immunotherapy efficacy.

Introduction

Over the past two decades, it has become increasingly clear that tumor-associated immunosuppression contributes significantly to tumor progression and resistance to immunotherapeutic approaches.[1] MDSCs represent one of many potential avenues through which tumors implement their suppressive agendas. While the specific phenotypes of MDSCs and their associated subpopulations have yet to be clearly defined, MDSC-dependent mechanisms of immune suppression have been well-described.[2] Accumulation of MDSCs occurs in most mouse models of cancer, including transplant and spontaneous tumors,[3] and their presence in peripheral blood of cancer patients is well established[4] and correlates with stage of disease in cancer patients.[5] Traditionally, the literature has organized the framework for mechanisms by which MDSCs suppress the immune response around the dependence or independence on L-arginine metabolism.[6] Through these mechanisms, MDSCs possess the capacity for suppression of both the innate and adaptive immune responses.[7] However, MDSCs have been more recently implicated in playing a broader role in tumor progression, as other non immune-suppressive mechanisms continue to be uncovered.[8] Many classes of drugs and biologic inhibitors have demonstrated the capacity to inhibit MDSCs by promoting their differentiation, maturation, accumulation or function. Here we review and provide updates on the status of MDSC-targeted therapeutics, including several novel strategies discovered in the last few years, and report on their potential use in the clinic.

*Correspondence to: Anil K. Rustgi; Email: anil2@mail.med.upenn.edu
Submitted: 01/29/13; Revised: 02/22/13; Accepted: 02/26/13
Citation: Waldron TJ, Quatromoni JG, Karakasheva TA, Singhal S, Rustgi AK. Myeloid-derived suppressor cells: Targets for therapy. OncoImmunology 2013; 2:e24117; http://dx.doi.org/10.4161/onci.24117

MDSCs in Cancer

The rationale behind targeting immunosuppressive populations, such as MDSCs, as part of a comprehensive therapeutic strategy is derived from the wealth of data demonstrating the capacity of a functional immune system to suppress tumor growth and progression.[9] The interaction of the human immune system and tumors has been referred to as immunoediting and can be broken down into three basic processes in which the immune system influences tumor growth to varying degrees: (1) elimination, a process in which the immune system recognizes and eliminates nascent tumor cells, (2) equilibrium, as the name suggests, where the immune system prevents further tumor growth and invasion, and (3) escape, a process in which tumor growth is no longer inhibited by the immune system, leading to tumor growth and progression.[10]

Elimination of tumor cells involves both the innate and adaptive immune systems,[11] while equilibrium, where tumor growth is kept in check, is maintained by the adaptive immune system[12] and may endure for extended periods.[13] Immune evasion may occur very early or late in the disease process, and arises primarily for one of two reasons: the selective process of immunoediting results in a non-immunogenic cancer cell population, or the tumor induces immunosuppressive cell populations, effectively hijacking the natural process of immune suppression for the purpose of preventing immune effector cells from recognizing and clearing cancer cells.[14] Myeloid-derived suppressor cells are a population, which is often commandeered during the course of tumorigenesis that induce immune suppression and contribute to immune escape. Made up of heterogeneous populations of immature myeloid cells including myeloid progenitor cells, and immature macrophages, immature granulocytes and immature

dendritic cells, MDSCs span a range of phenotypes, which share common functional attributes[15] and will be discussed below.

L-arginine-dependent mechanisms of immunosuppression require the activity of two enzymes for which L-arginine serves as a substrate: arginase-1 (ARG1) and inducible nitric oxide synthase-2 (iNOS2) (the two main immune-related isoforms).[16-18] ARG1 converts L-arginine into urea and L-ornithine, while iNOS-2 metabolizes it into nitric oxide (NO) and L-citrulline.[16] MDSCs are induced to express these two enzymes at very high levels as a result of exposure to specific cytokines, including the Th2 cytokines TGFβ and IL-10 for ARG1, and the Th1 cytokines IFNγ, IL-1, IFNα, and TNFα for iNOS2.[19-22] Increased activity of these enzymes has been repeatedly shown to inhibit T-cell function and proliferation, albeit through different mechanisms. High MDSC arginase activity depletes the microenvironment of arginine. The absence of this amino acid decreases T cell-CD3ζ expression, whose absence renders T cells unable to transmit signals required for activation.[23,24] Furthermore, it may inhibit the cell cycle regulatory proteins cyclin D3 and cyclin-dependent kinase 4, which blocks T-cell proliferation.[25] By contrast, high levels of NO, produced by MDSC iNOS2, are thought to interfere with T-cell JAK/STAT signaling proteins required for numerous T-cell functions, inhibit MHC Class II expression, and induce T-cell apoptosis.[26-29]

ARG1 and iNOS2 expression were once thought to be mutually exclusive, but recent evidence indicates that both enzymes can act simultaneously within the same MDSCs.[22] When L-arginase depletes arginine, iNOS2 then generates superoxide and NO which combine rapidly to form peroxynitrites, a powerful oxidant.[30] High levels of peroxynitrites produced by MDSCs during direct contact with T cells result in nitration of the T-cell receptor (TCR) and CD8 molecules on T cells. This modification has been shown to directly alter the specific peptide binding of the T cells in mice, which renders them unresponsive to antigen-specific stimulation.[26,31,32]

The other mechanisms of MDSC-mediated immunosuppression are L-arginine independent. These include reactive oxygen species (ROS) production, TGFβ production, cysteine depletion, CD62L downregulation, and other non-T cell-specific effects.[3] ROS production likely occurs via the NADPH oxidase machinery present in all phagocytic cells.[33] The importance of ROS production to MDSC-mediated immunosuppression has been demonstrated by in vitro studies that show complete abrogation of suppressive effect when ROS production is inhibited.[34-36] ROS, akin to peroxynitrites, are also thought to catalyze the nitration of TCR, thus preventing T cell-peptide MHC interactions.[31] TGFβ, among other soluble mediators, has been implicated in inducing increased ROS production in MDSCs.[37] MDSCs themselves can produce TGFβ, but it appears to be somewhat subtype-specific: a $CD11b^{+}GR1^{intermediate}$ murine MDSC subset, but not a $CD11b^{+}GR1^{high}$ MDSC subset, selectively produces TGFβ.[38,39] Similarly, not all tumors can produce TGFβ: tumor cells deficient in TGFβ RII lead to higher intratumoral TGFβ secondary to the chemoattraction of specific MDSC subtypes capable of producing TGFβ.[40]

Like L-arginine, MDSCs deplete the environment of cysteine, an amino acid essential for T-cell activation.[41] T cells depend upon extracellular sources because they lack both the enzyme to convert methionine to cysteine and the membrane transporter to import cystine for intracellular reduction to cysteine. Similarly, MDSCs are unable to generate cysteine from methionine, necessitating import of cystine for intracellular conversion to cysteine. Normally, antigen-presenting cells (APCs), namely, dendritic cells (DCs) and macrophages, serve as the reservoir of cysteine for T cells. They synthesize cysteine from methionine, import extracellular cystine for conversion to cysteine, and, most importantly, export surplus cysteine during antigen presentation to T cells for T-cell sustenance. However, when MDSCs are present in high concentrations, they import most of the available cystine, depriving DCs and macrophages of cystine. As a result, APCs do not export cysteine, thus depriving T cells of this amino acid which they need to synthesize proteins for activation.[7,41]

T-cell activation is impaired further by MDSC-mediated downregulation of L-selectin (CD62L).[42] CD62L is a plasma membrane molecule required for the homing of naïve T cells to lymph nodes. Without CD62L, both naïve CD4 and CD8 T cells will not encounter tumor antigen in the lymph nodes where it is presented by APCs. T-cell activation is then reduced because they cannot properly migrate to lymph nodes.[42]

Other MDSC-mediated immunosuppression that impacts adaptive tumor immunity includes the polarization of T cells toward a tumor-promoting type 2 phenotype. MDSCs accomplish this feat by producing IL-10 and downregulating macrophage-production of the Type I cytokine IL-12.[43] In a positive feedback cycle, these skewed macrophages can then induce further IL-10 production by MDSCs.

MDSC-directed immunosuppression often extends to other cells as well. Perhaps the most thoroughly described mechanism is the induction of de novo $FOXP3^{+}$ T-regulatory cells (Tregs).[44] The induction of Tregs by MDSCs occurs through a direct cell-cell interaction or via production of specific soluble factors, including IL-10 in the presence of TGFβ, or arginase (which is TGFβ independent).[45,46] Animal studies have implicated cytotoxic lymphocyte antigen-4 (CTLA4) expression by MDSCs as a prerequisite for Treg induction.[44] Once formed, Tregs downregulate the activation and expansion of antitumor-reactive T cells[7] among other cells.

While the mechanisms discussed thus far center around the inhibition of anti-tumor lymphoid responses, MDSCs also suppress important members of the innate immune system. For example, they have been shown to inhibit the activation, cytotoxicity, and expansion of anti-tumor natural killer (NK) cells by preventing NK cell-production of IFNγ through a cell-contact dependent mechanism.[47-49] This suppression is mediated by inhibition of the NK cell activation-receptor, NKG2D, and requires the presence of membrane-bound TGFβ.[47] Furthermore, it has been shown that the interaction between innate immunity and MDSCs are bidirectional. Type II NKT cells, a tumor-promoting population similar to M2 macrophages, produce IL-13, which induces the accumulation of MDSC.[50] By contrast,

Type I NKT cells, an anti-tumoral population, inhibits MDSC accumulation.[51]

The MDSC repertoire also involves non-immune suppressive mechanisms. These mechanisms directly promote various hallmarks ultimately required for tumor development; prominent among these are angiogenesis and vasculogenesis. MDSCs are actively recruited to the tumor microenvironment, where they not only release factors that promote blood vessel formation, but they differentiate into CD31$^+$ cells that incorporate into the newly forming endothelium.[8] These infiltrating cells produce matrix-metalloproteinase-9 (MMP-9),[21] which functions as an angiogenic switch by releasing matrix-bound VEGF and recruiting pericytes required for further blood vessel formation.[52] Further evidence for the importance of MMP-9 stems from studies investigating the reason for the failure of VEGF-inhibitors to suppress tumor growth, which found that anti-VEGF refractoriness was completely dependent on the tumor's capacity for CD11b+Gr1+ MDSC recruitment.[53] Furthermore, when MDSCs and tumor cells are co-injected, tumors grow faster and have increased blood vessel density; conversely, when MDSC-recruitment to tumors is inhibited, tumor angiogenesis is reduced.[8,40]

MDSC-Targeted Therapeutics

Translating our improved understanding of the development of cancer to improved therapeutics, specifically immunotherapy, has proceeded more slowly than expected.[54] In part, the failure is attributable to the lack of recognition that immunosuppression, with MDSCs as major contributors, has a critical role in promoting tumor progression. As a result, several therapeutic strategies that target the block in differentiation, accumulation at the tumor site, expansion, and function of these cells have been developed (see **Table 1**).

Differentiation. All trans-retinoic acid (ATRA) has been used successfully to induce differentiation of MDSCs in both mice and humans[4,55] through activation of ERK1/2, leading to the upregulation of the ROS scavenger GSH to induce differentiation.[33] Similarly, scavenging ROS with catalase led to differentiation of MDSCs obtained from tumor bearing mice,[56] suggesting that targeting ROS to disrupt the differentiation halt in MDSCs holds promise; however, use of ATRA to target myeloid suppressor populations in the clinic has not been reported widely.

Icariin and its derivative 3, 5, 7-Trihydroxy-4'-emthoxy-8-(3-hydroxy-3-methylbutyl)-flavone (ICT) showed anti-MDSC activity in the 4T1-Neu tumor-bearing mice, where treatment with Icariin or ICT led to reduction in MDSC percentages, likely due to induced differentiation toward dendritic cell or macrophage phenotype.[57] Differentiation was induced by inhibition of S100A8/9 expression, as well as inhibition of the STAT3 and AKT signaling pathways. The end result of ICT treatment was reduced production of NO and ROS by MDSCs, and increased IFNγ production by CD8$^+$ T cells.

In a cell-based approach activated NKT cells were used to induce differentiation of MDSCs into APCs.[58] The strategy of loading dendritic cells with α-galactosylceramide (αGalCer), an invariant NKT ligand, on their CD1d produced sustained NKT immune responses in patients.[59] Taking this approach one step further, MDSCs loaded with αGalCer and induced to present tumor-specific antigenic peptides on MHC Class I molecules elicited a robust anti-tumor response, via activation of CD8$^+$

Table 1. Myeloid-derived suppressor cells as target for therapy

Target	Agent	Summary of anti-MDSC activity
Differentiation	ATRA	Activation of ERK1/2, leading to the upregulation of the ROS scavenger GSH
	Catalase	ROS scavenger
	Icariin and ICT	Inhibition of S100A8/9 expression, inhibition of STAT3 and AKT signaling pathways, resulting in differentiation to DC or MΦ
	NKT cells	Differentiation into APCs and activation of antitumor responses
	MPSSS	Differentiation into M1-like macrophages
Function	COX2 inhibitors	Prevents ARG1 upregulation
	PDE-5 inhibitors	Reduces ARG1 and iNOS expression
	ROS inhibitors	Reduces immunosuppression by limiting ROS production
	Nitroaspirin	Inhibits ROS production, limits ARG1 and iNOS expression
	NAC	Reduces ROS production, increases the extracellular pool of cysteine
	CpG ODNs	Limit iNOS and ARG1 expression; favor differentiation to M1 macrophages
	MMP9 inhibitors	Reduce MDSC abundance through unknown mechanism
Ablation	L-NIL	Reduces the accumulation of MDSCs by limiting circulating VEGF levels; inhibits MDSC activation by downregulating STAT3 and by limiting ROS production
	RNA aptamer	Induces MDSC apoptosis
	Curcumin	Inhibits expansion; promotes apoptosis; induces differentiation
	Gemcitabine	Induces MDSC apoptosis and necrosis
	5-FU	Cytotoxic for MDSCs
	Docetaxel	Reduces pSTAT3 levels, resulting in lower amount of MDSCs

CTLs and NK cells.[58] This approach conferred prolonged survival and reduced metastasis frequency in tumor bearing mice. Converting MDSCs from an immunosuppressive population into a functional population of antigen-presenting cells is appealing from a therapeutic standpoint; however, a similar strategy in cancer patients would require identification and production of tumor-specific, antigenic peptides.

The polysaccharide MPSSS derived from Lentinus edodes possesses the capacity to induce MDSC differentiation, thereby reducing MDSC numbers.[60] MPSSS treatment inhibited tumor growth owing to reduction in MDSC levels and immunosuppressive capacity, which resulted from induction of MDSC differentiation to a M1-like macrophage population.

Immunosuppressive function. The four main therapeutic approaches for inhibiting the function of MDSCs include inhibition of ARG, inhibition of iNOS, inhibition of ROS production, and elevation of cysteine levels. Representative drugs that address these approaches include cyclooxygenase-2 (COX2) inhibitors, phosphodiesterase-5 (PDE-5) inhibitors, ROS inhibitors, and N-acetyl cysteine (NAC). Many tumors, such as lung breast colon, pancreatic, and prostate, express high levels of COX2.[61] COX2 is required for prostaglandin E2 (PGE2) synthesis, which has been shown to upregulate ARG1 expression in MDSCs.[62] Thus, COX2 inhibitors reduce a major mechanism of MDSC-mediated immunosuppression. In line with this hypothesis, the inhibition of PGE2 synthesis in tumor-bearing mice and cancer patients have been shown to improve anti-tumor T cell-responses.[63] Furthermore, use of celecoxib, a COX2 inhibitor, in a murine model of mesothelioima resulted in reduced levels of tumor-infiltrating MDSCs, and potentiated a dendritic cell-based immunotherapy.[64]

Along the same lines, PDE-5 inhibitors have been shown to not only reduce the MDSC expression of ARG, but iNOS as well. In animal models, these inhibitors have proven to delay tumor progression.[65] Specifically, treatment with the PDE-5 inhibitor sildenafil resulted in an increase in $CD8^+$ T-cell tumor infiltration, as well as in improved activation of T cells. PDE-5 blockade inhibits immunosuppressive capacity of MDSCs by lowering the concentrations of the IL-4α receptor and effector molecules ARG1 and iNOS, although the exact mechanism remains to be elucidated. Serafini et al.[65] demonstrated that sildenafil treatment restored T-cell proliferation in PBMCs from patients with head and neck squamous cell carcinoma (HNSCC) and multiple myeloma, suggesting that the therapeutic effect observed in mice can be translated into treatment of human cancer. Since PDE-5 inhibitors (sildenafil and tadalafil) are used widely for treatment of nonmalignant conditions such as erectile dysfunction, their pharmacokinetics and toxicity are already well studied. This implies that these compounds may be safely used to target MDSCs in cancer patients. However, it is important to note that even though treatment with PDE-5 inhibitors induces a CTL response, such treatment alone is unlikely to cause complete tumor elimination. Thus, combination with conventional therapeutics may prove to be more efficient.

A Phase II clinical trial (clinicaltrials.gov ID NCT01697800) that aims to deplete MDSCs with the PDE-5 inhibitor tadalafil is currently recruiting HNSCC patients. Tadalafil will be used in combination with conventional therapy for HNSCC, and the number and function of MDSCs and Tregs in patients' peripheral blood will be assessed upon treatment with the PDE-5 inhibitor or placebo.

The importance of ROS to MDSC mediated immunosuppression has been repeatedly confirmed. Efforts to inhibit this arm of the MDSC repertoire have proven beneficial. Nitroaspirin, a non-steroidal anti-inflammatory drug coupled to a NO-releasing moiety, has been shown to effectively inhibit the production of ROS, limit the activity of ARG1, and limit iNOS in MDSCs.[26,66] Similarly, NAC has been suggested as a potentially useful anti-tumor agent based on its ability to reduce ROS. It too has demonstrated efficacy in animal tumor models. However, NAC differs from other agents that reduce oxidative stress in its ability to increase the extracellular pools of cysteine in the presence of high levels of MDSCs.[67]

Several studies have described the ability of CpG oligodeoxynucleotides (ODN) to elicit a robust tumor-specific immune response when injected intra-tumorally.[68,69] Recently, it was discovered that CpG ODN therapy acts, at least in part, through effects on MDSCs.[70] CpG ODN treatment inhibited production of iNOS and ARG1 activity, thereby leading to recovery of T-cell proliferation. Strikingly, exposure of MDSCs, even briefly in vitro, led to differentiation to type M1 macrophages exhibiting anti-tumoral activity resulting in tumor progression followed by significantly delayed growth.

While it is known that non-immune MDSC mechanisms of suppression exist, no current treatments have been able to effectively address these methods. VEGF, a tumor-derived factor, is known to be involved in promoting MDSC expansion, not function.[26] However, patients with solid tumors in clinical trials have shown limited benefit with this approach. In patients with aggressive metastatic renal cancer, responses were short-lived and without cure.[71] Furthermore, in a clinical trial of patients with refractory solid tumors, treatment with a fusion protein that traps VEGF showed no effect on MDSC numbers or T-cell responses.[72] MMP-9 inhibitors have shown promise in animal models, but the mechanism remains unclear. In any case, MMP-9 inhibitors have decreased the number of MDSCs in splenic and tumor tissues, resulting in a delay of NeuT tumor growth.[73] At the present time, it is thought that anti-angiogenesis medications only transiently affect tumor growth, with most patients progressing over the course of months as tumors adapt and bypass VEGF-dependence via alternative proangiogenic signaling pathways.[21,74,75]

Accumulation/Ablation. Expression of iNOS has been demonstrated in solid tumors and correlates with poor prognosis.[76,77] Production of NO by tumors induces a range of tumor-promoting functions including cell motility and invasion[77] and the genesis of the inflammatory tumor microenvironment.[78] Pharmacologic inhibition of iNOS with the small molecule inhibitor L-NIL reduced accumulation of MDSC through reduction in serum VEGF and inhibited activation of MDSCs via downregulation of activated STAT3 and ROS production, resulting in enhanced immune-mediated control over growth of transplanted melanoma tumors.[79]

In order to target MDSCs in a highly precise manner, Roth et al.[80] engineered a RNA aptamer, specific for mouse and human IL4Rα, a cell surface receptor known to be upregulated in the MDSCs of tumor-bearing mice,[81] as well as cancer patients.[82] Use of the aptamer induced MDSC apoptosis leading to lower intratumoral MDSC levels, greater T-cell infiltration, and slower tumor growth.[80] The effects of the aptamer were due to inhibition of STAT6 signaling, suggesting that engagement of IL4Rα by the aptamer may abrogate survival signals generated by IL-13 binding to IL4Rα on the MDSC cell surface.[80] Though use of the aptamer alone did not induce tumor regression, the specific manner in which MDSC ablation was induced, coupled with the prevalence of IL4Rα on the surface of some MDSC populations in cancer patients makes this aptamer worthy of further examination as a potential therapeutic agent.

Curcumin, a naturally occurring antitumor agent, has a multitude of effects on MDSC biology, which could prove useful in a therapeutic setting.[83] Whether delivered via IP injection or as a dietary supplement, curcumin inhibits MDSC expansion and promotes apoptosis. Furthermore, secretion of IL-6 by MDSCs is inhibited by curcumin. Curcumin promotes adoption of a M1 phenotype, while inhibiting NFκB and STAT3 signaling in MDSCs.

Some conventional therapeutics, such as gemcitabine[84] and 5-FU,[85] possess MDSC-specific cytoxicity. Gemcitabine induces MDSC death through apoptosis and necrosis, and has the capacity to potentiate immunotherapy as demonstrated when gemcitabine is combined with intratumoral injection of IFNβ-expressing adenovirus.[84] 5-FU treatment exhibited MDSC cytotoxicity and was sufficient to increase survival of tumor-bearing mice, likely as a result of improved $CD8^+$ T-cell activation; however, 5-FU treatment was not curative.[85] It was recently discovered that the efficacy of 5-FU therapy is limited by induction of Nlrp3 inflammasome, leading to MDSC-derived IL-1beta secretion and induction of angiogenesis, suggesting that combination of 5-FU with anti-IL1beta or Nlrp3 inflammasome inhibitors to increase therapeutic potential.[86] Another combination of therapeutics, namely cyclophosphamide and gemcitabine, used to target Treg and MDSCs, respectively, demonstrated the potential to effect T cell-mediated tumor immunity by inhibiting immune suppressor populations.[87]

Like gemcitabine and 5-FU, docetaxel is another commonly used chemotherapeutic with anti-MDSC activity. The capacity of Docetaxel to inhibit the immunosuppressive capacity of MDSCs was demonstrated in mice bearing 4T1-Neu mammary tumors.[88] Owing to its inhibition of the STAT3 pathway, Docetaxel treatment inhibited MDSC levels in tumor-bearing mice and induced the remaining MDSCs to adopt an M1-like phenotype. Docetaxel-treated naïve and tumor-bearing mice exhibited increased numbers of activated ($IFN\gamma^+$) and total T cells. In fact, T cells from Docetaxel-treated mice exhibited greater tumoricidal activity than controls. Docetaxel may also potentiate total body irradiation (TBI) as a means of eliminating MDSCs. As demonstrated in mice, TBI has the potential of depleting MDSCs; however, reconstitution occurs with MDSCs exhibiting increased immunosuppressive capacity suggesting that such an approach may yield undesirable results. Docetaxel administration was able to abrogate MDSC reconstitution and a therapeutic benefit was observed when TBI, adoptive T-cell transfer, dendritic cell vaccination and docetaxel were combined in a model of melanoma.[89]

Conclusion

The capacity of the human immune system to inhibit tumor formation and progression provides the promise that its power may be utilized in therapeutic approaches. Immunoediting shapes tumor growth, often resulting in tumors that can suppress the capacity of the immune system to effect elimination or equilibrium and allowing tumor escape and progression into a clinically defined cancer. One mechanism of immunosuppression commonly found in advanced stage tumors is the activation and accumulation of MDSCs upon stimulation with tumor-derived factors. MDSCs affect a number of immunosuppressive pathways to promote cancer growth and progression, and have been recently targeted for inhibition using a variety of strategies. Some groups have demonstrated that MDSCs can be induced to differentiate, others have shown that accumulation can be effectively inhibited. Inhibition of suppressive mechanisms has also proven successful, while selective ablation was demonstrated to be a viable goal as well. No matter what the strategy, limiting or eliminating the capacity of MDSCs to suppress the ability of patients' immune systems to fight tumor growth represents a worthy objective. With the onset of the first clinical trial aimed at pharmacologically targeting MDSCs in cancer patients, the promise of targeting these immunosuppressive populations in the fight against cancer will be evaluated. If anti-MDSC therapy proves effective, clinicians may eventually choose to test their efficacy in combination therapy, especially in patients in advanced disease, when MDSCs are typically abundant, and potent inhibitors of anti-tumor immunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported by the National Institutes of Health/NCI grant P01-CA098101 (AKR, TW), National Institutes of Health/NCI grant U01-CA14305603 (AKR), National Institutes of Health/NIDDK (T32-DK007066) (TW), National Institutes of Health (F32-CA162719) (TW), National Institutes of Health/NIDDK Center for Molecular Studies in Digestive and Liver Diseases (P30-DK050306), and American Cancer Society (RP-10–033–01-CCE). We are grateful for members of the Rustgi and Singhal labs for discussions.

References

1. Quatromoni JG, Eruslanov E. Tumor-associated macrophages: function, phenotype, and link to prognosis in human lung cancer. American journal of translational research 2012; 4:376-89
2. Bronte V, Zanovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol 2005; 5:641-54; PMID:16056256; http://dx.doi.org/10.1038/nri1668
3. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol 2009; 182:4499-506; PMID:19342621; http://dx.doi.org/10.4049/jimmunol.0802740

4. Almand B, Clark JI, Nikitina E, van Beynen J, English NR, Knight SC, et al. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol 2001; 166:678-89; PMID:11123353
5. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009; 58:49-59; PMID:18446337; http://dx.doi.org/10.1007/s00262-008-0523-4
6. Nagaraj S, Gabrilovich DI. Myeloid-derived suppressor cells in human cancer. Cancer J 2010; 16:348-53; PMID:20693846; http://dx.doi.org/10.1097/PPO.0b013e3181eb3358
7. Srivastava MK, Andersson A, Zhu L, Harris-White M, Lee JM, Dubinett S, et al. Myeloid suppressor cells and immune modulation in lung cancer. Immunotherapy 2012; 4:291-304; PMID:22401635; http://dx.doi.org/10.2217/imt.11.178
8. Yang L, DeBusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Shyr Y, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 2004; 6:409-21; PMID:15488763; http://dx.doi.org/10.1016/j.ccr.2004.08.031
9. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011; 331:1565-70; PMID:21436444; http://dx.doi.org/10.1126/science.1203486
10. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002; 3:991-8; PMID:12407406; http://dx.doi.org/10.1038/ni1102-991
11. Smyth MJ, Godfrey DI, Trapani JA. A fresh look at tumor immunosurveillance and immunotherapy. Nat Immunol 2001; 2:293-9; PMID:11276199; http://dx.doi.org/10.1038/86297
12. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, et al. Adaptive immunity maintains occult cancer in an equilibrium state. Nature 2007; 450:903-7; PMID:18026089; http://dx.doi.org/10.1038/nature06309
13. Teng MW, Vesely MD, Duret H, McLaughlin N, Towne JE, Schreiber RD, et al. Opposing roles for IL-23 and IL-12 in maintaining occult cancer in an equilibrium state. Cancer Res 2012; 72:3987-96; PMID:22869585; http://dx.doi.org/10.1158/0008-5472.CAN-12-1337
14. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004; 21:137-48; PMID:15308095; http://dx.doi.org/10.1016/j.immuni.2004.07.017
15. Youn JI, Gabrilovich DI. The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. Eur J Immunol 2010; 40:2969-75; PMID:21061430; http://dx.doi.org/10.1002/eji.201040895
16. Bogdan C. Nitric oxide and the immune response. Nat Immunol 2001; 2:907-16; PMID:11577346; http://dx.doi.org/10.1038/ni1001-907
17. Corzo CA, Cotter MJ, Cheng P, Cheng F, Kusmartsev S, Sotomayor E, et al. Mechanism regulating reactive oxygen species in tumor-induced myeloid-derived suppressor cells. J Immunol 2009; 182:5693-701; PMID:19380816; http://dx.doi.org/10.4049/jimmunol.0900092
18. Rodríguez PC, Ochoa AC. Arginine regulation by myeloid derived suppressor cells and tolerance in cancer: mechanisms and therapeutic perspectives. Immunol Rev 2008; 222:180-91; PMID:18364002; http://dx.doi.org/10.1111/j.1600-065X.2008.00608.x
19. Mazzoni A, Bronte V, Visintin A, Spitzer JH, Apolloni E, Serafini P, et al. Myeloid suppressor lines inhibit T cell responses by an NO-dependent mechanism. J Immunol 2002; 168:689-95; PMID:11777962
20. Ochoa AC, Zea AH, Hernandez C, Rodriguez PC. Arginase, prostaglandins, and myeloid-derived suppressor cells in renal cell carcinoma. Clin Cancer Res 2007; 13:721s-6s; PMID:17255300; http://dx.doi.org/10.1158/1078-0432.CCR-06-2197
21. Ko JS, Bukowski RM, Fincke JH. Myeloid-derived suppressor cells: a novel therapeutic target. Curr Oncol Rep 2009; 11:87-93; PMID:19216839; http://dx.doi.org/10.1007/s11912-009-0014-6
22. Marigo I, Dolcetti L, Serafini P, Zanovello P, Bronte V. Tumor-induced tolerance and immune suppression by myeloid derived suppressor cells. Immunol Rev 2008; 222:162-79; PMID:18364001; http://dx.doi.org/10.1111/j.1600-065X.2008.00602.x
23. Rodriguez PC, Quiceno DG, Zabaleta J, Ortiz B, Zea AH, Piazuelo MB, et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. Cancer Res 2004; 64:5839-49; PMID:15313928; http://dx.doi.org/10.1158/0008-5472.CAN-04-0465
24. Rodriguez PC, Zea AH, DeSalvo J, Culotta KS, Zabaleta J, Quiceno DG, et al. L-arginine consumption by macrophages modulates the expression of CD3 zeta chain in T lymphocytes. J Immunol 2003; 171:1232-9; PMID:12874210
25. Rodriguez PC, Quiceno DG, Ochoa AC. L-arginine availability regulates T-lymphocyte cell-cycle progression. Blood 2007; 109:1568-73; PMID:17023580; http://dx.doi.org/10.1182/blood-2006-06-031856
26. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009; 9:162-74; PMID:19197294; http://dx.doi.org/10.1038/nri2506
27. Bingisser RM, Tilbrook PA, Holt PG, Kees UR. Macrophage-derived nitric oxide regulates T cell activation via reversible disruption of the Jak3/STAT5 signaling pathway. J Immunol 1998; 160:5729-34; PMID:9637481
28. Harari O, Liao JK. Inhibition of MHC II gene transcription by nitric oxide and antioxidants. Curr Pharm Des 2004; 10:893-8; PMID:15032692; http://dx.doi.org/10.2174/1381612043452893
29. Rivoltini L, Carrabba M, Huber V, Castelli C, Novellino L, Dalerba P, et al. Immunity to cancer: attack and escape in T lymphocyte-tumor cell interaction. Immunol Rev 2002; 188:97-113; PMID:12445284; http://dx.doi.org/10.1034/j.1600-065X.2002.18809.x
30. Talmadge JE. Pathways mediating the expansion and immunosuppressive activity of myeloid-derived suppressor cells and their relevance to cancer therapy. Clin Cancer Res 2007; 13:5243-8; PMID:17875751; http://dx.doi.org/10.1158/1078-0432.CCR-07-0182
31. Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, et al. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. Nat Med 2007; 13:828-35; PMID:17603493; http://dx.doi.org/10.1038/nm1609
32. Kusmartsev S, Nagaraj S, Gabrilovich DI. Tumor-associated CD8+ T cell tolerance induced by bone marrow-derived immature myeloid cells. J Immunol 2005; 175:4583-92; PMID:16177103
33. Nefedova Y, Fishman M, Sherman S, Wang X, Beg AA, Gabrilovich DI. Mechanism of all-trans retinoic acid effect on tumor-associated myeloid-derived suppressor cells. Cancer Res 2007; 67:11021-8; PMID:18006848; http://dx.doi.org/10.1158/0008-5472.CAN-07-2593
34. Szuster-Ciesielska A, Hryciuk-Umer E, Stepulak A, Kupisz K, Kandefer-Szersze M. Reactive oxygen species production by blood neutrophils of patients with laryngeal carcinoma and antioxidative enzyme activity in their blood. Acta Oncol 2004; 43:252-8; PMID:15244248; http://dx.doi.org/10.1080/02841860410029708
35. Schmielau J, Finn OJ. Activated granulocytes and granulocyte-derived hydrogen peroxide are the underlying mechanism of suppression of t-cell function in advanced cancer patients. Cancer Res 2001; 61:4756-60; PMID:11406548
36. Kusmartsev S, Nefedova Y, Yoder D, Gabrilovich DI. Antigen-specific inhibition of CD8+ T cell response by immature myeloid cells in cancer is mediated by reactive oxygen species. J Immunol 2004; 172:989-99; PMID:14707072
37. Sauer H, Wartenberg M, Hescheler J. Reactive oxygen species as intracellular messengers during cell growth and differentiation. Cellular physiology and biochemistry: international journal of experimental cellular physiology, biochemistry, and pharmacology 2001; 11:173-86
38. Fichtner-Feigl S, Terabe M, Kitani A, Young CA, Fuss I, Geissler EK, et al. Restoration of tumor immunosurveillance via targeting of interleukin-13 receptor-alpha 2. Cancer Res 2008; 68:3467-75; PMID:18451175; http://dx.doi.org/10.1158/0008-5472.CAN-07-5301
39. Terabe M, Matsui S, Park JM, Mamura M, Noben-Trauth N, Donaldson DD, et al. Transforming growth factor-beta production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block cytotoxic T lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. J Exp Med 2003; 198:1741-52; PMID:14657224; http://dx.doi.org/10.1084/jem.20022227
40. Yang L, Huang J, Ren X, Gorska AE, Chytil A, Aakre M, et al. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. Cancer Cell 2008; 13:23-35; PMID:18167337; http://dx.doi.org/10.1016/j.ccr.2007.12.004
41. Srivastava MK, Sinha P, Clements VK, Rodriguez P, Ostrand-Rosenberg S. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res 2010; 70:68-77; PMID:20028852; http://dx.doi.org/10.1158/0008-5472.CAN-09-2587
42. Hanson EM, Clements VK, Sinha P, Ilkovitch D, Ostrand-Rosenberg S. Myeloid-derived suppressor cells down-regulate L-selectin expression on CD4+ and CD8+ T cells. J Immunol 2009; 183:937-44; PMID:19553533; http://dx.doi.org/10.4049/jimmunol.0804253
43. Sinha P, Clements VK, Bunt SK, Albelda SM, Ostrand-Rosenberg S. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol 2007; 179:977-83; PMID:17617589
44. Yang R, Cai Z, Zhang Y, Yutzy WH 4th, Roby KF, Roden RB. CD80 in immune suppression by mouse ovarian carcinoma-associated Gr-1+CD11b+ myeloid cells. Cancer Res 2006; 66:6807-15; PMID:16818658; http://dx.doi.org/10.1158/0008-5472.CAN-05-3755
45. Serafini P, Mgebroff S, Noonan K, Borrello I. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. Cancer Res 2008; 68:5439-49; PMID:18593947; http://dx.doi.org/10.1158/0008-5472.CAN-07-6621
46. Huang B, Pan PY, Li Q, Sato AI, Levy DE, Bromberg J, et al. Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. Cancer Res 2006; 66:1123-31; PMID:16424049; http://dx.doi.org/10.1158/0008-5472.CAN-05-1299
47. Li H, Han Y, Guo Q, Zhang M, Cao X. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-beta 1. J Immunol 2009; 182:240-9; PMID:19109155
48. Liu C, Yu S, Kappes J, Wang J, Grizzle WE, Zinn KR, et al. Expansion of spleen myeloid suppressor cells represses NK cell cytotoxicity in tumor-bearing host. Blood 2007; 109:4336-42; PMID:17244679; http://dx.doi.org/10.1182/blood-2006-09-046201

49. Elkabets M, Ribeiro VS, Dinarello CA, Ostrand-Rosenberg S, Di Santo JP, Apte RN, et al. IL-1β regulates a novel myeloid-derived suppressor cell subset that impairs NK cell development and function. Eur J Immunol 2010; 40:3347-57; PMID:21110318; http://dx.doi.org/10.1002/eji.201041037
50. Terabe M, Swann J, Ambrosino E, Sinha P, Takaku S, Hayakawa Y, et al. A nonclassical non-Valpha14Jalpha18 CD1d-restricted (Type II) NKT cell is sufficient for down-regulation of tumor immunosurveillance. J Exp Med 2005; 202:1627-33; PMID:16365146; http://dx.doi.org/10.1084/jem.20051381
51. Stewart TJ, Smyth MJ, Fernando GJ, Frazer IH, Leggatt GR. Inhibition of early tumor growth requires J alpha 18-positive (natural killer T) cells. Cancer Res 2003; 63:3058-60; PMID:12810627
52. Chantrain CF, Shimada H, Jodele S, Groshen S, Ye W, Shalinsky DR, et al. Stromal matrix metalloproteinase-9 regulates the vascular architecture in neuroblastoma by promoting pericyte recruitment. Cancer Res 2004; 64:1675-86; PMID:14996727; http://dx.doi.org/10.1158/0008-5472.CAN-03-0160
53. Shojaei F, Wu X, Malik AK, Zhong C, Baldwin ME, Schanz S, et al. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+Gr1+ myeloid cells. Nat Biotechnol 2007; 25:911-20; PMID:17664940; http://dx.doi.org/10.1038/nbt1323
54. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med 2004; 10:909-15; PMID:15340416; http://dx.doi.org/10.1038/nm1100
55. Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res 2006; 66:9299-307; PMID:16982775; http://dx.doi.org/10.1158/0008-5472.CAN-06-1690
56. Kusmartsev S, Cheng F, Yu B, Nefedova Y, Sotomayor E, Lush R, et al. All-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination. Cancer Res 2003; 63:4441-9; PMID:12907617
57. Zhou J, Wu J, Chen X, Fortenbery N, Eksioglu E, Kodumudi KN, et al. Icariin and its derivative, ICT, exert anti-inflammatory, anti-tumor effects, and modulate myeloid derived suppressive cells (MDSCs) functions. Int Immunopharmacol 2011; 11:890-8; PMID:21244860; http://dx.doi.org/10.1016/j.intimp.2011.01.007
58. Ko HJ, Lee JM, Kim YJ, Kim YS, Lee KA, Kang CY. Immunosuppressive myeloid-derived suppressor cells can be converted into immunogenic APCs with the help of activated NKT cells: an alternative cell-based antitumor vaccine. J Immunol 2009; 182:1818-28; PMID:19201833; http://dx.doi.org/10.4049/jimmunol.0802430
59. Chang DH, Osman K, Connolly J, Kukreja A, Krasovsky J, Pack M, et al. Sustained expansion of NKT cells and antigen-specific T cells after injection of alpha-galactosyl-ceramide loaded mature dendritic cells in cancer patients. J Exp Med 2005; 201:1503-17; PMID:15867097; http://dx.doi.org/10.1084/jem.20042592
60. Wu H, Tao N, Liu X, Li X, Tang J, Ma C, et al. Polysaccharide from Lentinus edodes inhibits the immunosuppressive function of myeloid-derived suppressor cells. PLoS One 2012; 7:e51751; PMID:23272159; http://dx.doi.org/10.1371/journal.pone.0051751
61. Harris RE. Cyclooxygenase-2 (cox-2) and the inflammogenesis of cancer. Subcell Biochem 2007; 42:93-126; PMID:17612047; http://dx.doi.org/10.1007/1-4020-5688-5_4
62. Sinha P, Clements VK, Fulton AM, Ostrand-Rosenberg S. Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. Cancer Res 2007; 67:4507-13; PMID:17483367; http://dx.doi.org/10.1158/0008-5472.CAN-06-4174
63. Talmadge JE, Hood KC, Zobel LC, Shafer LR, Coles M, Toth B. Chemoprevention by cyclooxygenase-2 inhibition reduces immature myeloid suppressor cell expansion. Int Immunopharmacol 2007; 7:140-51; PMID:17178380; http://dx.doi.org/10.1016/j.intimp.2006.09.021
64. Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Aerts JG, et al. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. BMC Cancer 2010; 10:464; PMID:20804550; http://dx.doi.org/10.1186/1471-2407-10-464
65. Serafini P, Meckel K, Kelso M, Noonan K, Califano J, Koch W, et al. Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. J Exp Med 2006; 203:2691-702; PMID:17101732; http://dx.doi.org/10.1084/jem.20061104
66. De Santo C, Serafini P, Marigo I, Dolcetti L, Bolla M, Del Soldato P, et al. Nitroaspirin corrects immune dysfunction in tumor-bearing hosts and promotes tumor eradication by cancer vaccination. Proc Natl Acad Sci U S A 2005; 102:4185-90; PMID:15753302; http://dx.doi.org/10.1073/pnas.0409783102
67. Gao P, Zhang H, Dinavahi R, Li F, Xiang Y, Raman V, et al. HIF-dependent antitumorigenic effect of antioxidants in vivo. Cancer Cell 2007; 12:230-8; PMID:17785204; http://dx.doi.org/10.1016/j.ccr.2007.08.004
68. Heckelsmiller K, Rall K, Beck S, Schlamp A, Seiderer J, Jahrsdörfer B, et al. Peritumoral CpG DNA elicits a coordinated response of CD8 T cells and innate effectors to cure established tumors in a murine colon carcinoma model. J Immunol 2002; 169:3892-9; PMID:12244187
69. Kawarada Y, Ganss R, Garbi N, Sacher T, Arnold B, Hämmerling GJ. NK- and CD8(+) T cell-mediated eradication of established tumors by peritumoral injection of CpG-containing oligodeoxynucleotides. J Immunol 2001; 167:5247-53; PMID:11673539
70. Shirota Y, Shirota H, Klinman DM. Intratumoral injection of CpG oligonucleotides induces the differentiation and reduces the immunosuppressive activity of myeloid-derived suppressor cells. J Immunol 2012; 188:1592-9; PMID:22231700; http://dx.doi.org/10.4049/jimmunol.1101304
71. Shojaei F, Ferrara N. Antiangiogenic therapy for cancer: an update. Cancer J 2007; 13:345-8; PMID:18032969; http://dx.doi.org/10.1097/PPO.0b013e31815a7b69
72. Fricke I, Mirza N, Dupont J, Lockhart C, Jackson A, Lee JH, et al. Vascular endothelial growth factor-trap overcomes defects in dendritic cell differentiation but does not improve antigen-specific immune responses. Clin Cancer Res 2007; 13:4840-8; PMID:17699863; http://dx.doi.org/10.1158/1078-0432.CCR-07-0409
73. Melani C, Sangaletti S, Barazzetta FM, Werb Z, Colombo MP. Amino-biphosphonate-mediated MMP-9 inhibition breaks the tumor-bone marrow axis responsible for myeloid-derived suppressor cell expansion and macrophage infiltration in tumor stroma. Cancer Res 2007; 67:11438-46; PMID:18056472; http://dx.doi.org/10.1158/0008-5472.CAN-07-1882
74. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer 2008; 8:592-603; PMID:18650835; http://dx.doi.org/10.1038/nrc2442
75. Miller KD, Sweeney CJ, Sledge GW Jr. Can tumor angiogenesis be inhibited without resistance? EXS 2005; 94:95-112; PMID:15617473; http://dx.doi.org/10.1007/3-7643-7311-3_7
76. Ekmekcioglu S, Ellerhorst J, Smid CM, Prieto VG, Munsell M, Buzaid AC, et al. Inducible nitric oxide synthase and nitrotyrosine in human metastatic melanoma tumors correlate with poor survival. Clin Cancer Res 2000; 6:4768-75; PMID:11156233
77. Glynn SA, Boersma BJ, Dorsey TH, Yi M, Yfantis HG, Ridnour LA, et al. Increased NOS2 predicts poor survival in estrogen receptor-negative breast cancer patients. J Clin Invest 2010; 120:3843-54; PMID:20978357; http://dx.doi.org/10.1172/JCI42059
78. Tanese K, Grimm EA, Ekmekcioglu S. The role of melanoma tumor-derived nitric oxide in the tumor inflammatory microenvironment: its impact on the chemokine expression profile, including suppression of CXCL10. Int J Cancer 2012; 131:891-901; PMID:21953496; http://dx.doi.org/10.1002/ijc.26451
79. Jayaraman P, Parikh F, Lopez-Rivera E, Hailemichael Y, Clark A, Ma G, et al. Tumor-expressed inducible nitric oxide synthase controls induction of functional myeloid-derived suppressor cells through modulation of vascular endothelial growth factor release. J Immunol 2012; 188:5365-76; PMID:22529296; http://dx.doi.org/10.4049/jimmunol.1103553
80. Roth F, De La Fuente AC, Vella JL, Zoso A, Inverardi L, Serafini P. Aptamer-mediated blockade of IL4Rα triggers apoptosis of MDSCs and limits tumor progression. Cancer Res 2012; 72:1373-83; PMID:22282665; http://dx.doi.org/10.1158/0008-5472.CAN-11-2772
81. Gallina G, Dolcetti L, Serafini P, De Santo C, Marigo I, Colombo MP, et al. Tumors induce a subset of inflammatory monocytes with immunosuppressive activity on CD8+ T cells. J Clin Invest 2006; 116:2777-90; PMID:17016559; http://dx.doi.org/10.1172/JCI28828
82. Mandruzzato S, Solito S, Falisi E, Francescato S, Chiarion-Sileni V, Mocellin S, et al. IL4Ralpha+ myeloid-derived suppressor cell expansion in cancer patients. J Immunol 2009; 182:6562-8; PMID:19414811; http://dx.doi.org/10.4049/jimmunol.0803831
83. Tu SP, Jin H, Shi JD, Zhu LM, Suo Y, Lu G, et al. Curcumin induces the differentiation of myeloid-derived suppressor cells and inhibits their interaction with cancer cells and related tumor growth. Cancer Prev Res (Phila) 2012; 5:205-15; PMID:22030090; http://dx.doi.org/10.1158/1940-6207.CAPR-11-0247
84. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. Clin Cancer Res 2005; 11:6713-21; PMID:16166452; http://dx.doi.org/10.1158/1078-0432.CCR-05-0883
85. Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res 2010; 70:3052-61; PMID:20388795; http://dx.doi.org/10.1158/0008-5472.CAN-09-3690
86. Bruchard M, Mignot G, Derangère V, Chalmin F, Chevriaux A, Végran F, et al. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. Nat Med 2013; 19:57-64; PMID:23202296; http://dx.doi.org/10.1038/nm.2999
87. Tongu M, Harashima N, Monma H, Inao T, Yamada T, Kawauchi H, et al. Metronomic chemotherapy with low-dose cyclophosphamide plus gemcitabine can induce anti-tumor T cell immunity in vivo. Cancer Immunol Immunother 2013; 62:383-91; http://dx.doi.org/10.1007/s00262-012-1343-0; PMID:22926062
88. Kodumudi KN, Woan K, Gilvary DL, Sahakian E, Wei S, Djeu JY. A novel chemoimmunomodulating property of docetaxel: suppression of myeloid-derived suppressor cells in tumor bearers. Clin Cancer Res 2010; 16:4583-94; PMID:20702612; http://dx.doi.org/10.1158/1078-0432.CCR-10-0733
89. Kodumudi KN, Weber A, Sarnaik AA, Pilon-Thomas S. Blockade of myeloid-derived suppressor cells after induction of lymphopenia improves adoptive T cell therapy in a murine model of melanoma. J Immunol 2012; 189:5147-54; PMID:23100512; http://dx.doi.org/10.4049/jimmunol.1200274