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Myeloid-derived Suppressor Cells: The Green Light for Myeloma Immune Escape

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Abstract

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous, immature myeloid cell population with the ability to suppress innate and adaptive immune responses that promote tumor growth. MDSCs are increased in patients with multiple myeloma (MM) and have bidirectional interaction with tumors within the MM microenvironment. MM-MDSCs promote MM tumor growth and induce immune suppression, while conversely, MM cells induce MDSC development and survival. Although the role of MDSCs in infections, inflammatory diseases and solid tumors has been extensively characterized, their tumor-promoting and immune-suppressive role in MM and the MM microenvironment is only beginning to emerge. The presence and activation of MDSCs in MM patients has been well documented, however direct actions and functional consequences of MDSCs on cancer cells is poorly defined. Immunosuppressive MDSCs play an important role in tumor-progression primarily because of their capability to promote immune-escape, angiogenesis, drug resistance and metastasis. However, their role in the bone marrow

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Conflict of interest

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(BM), the primary MM site, is poorly understood. MM remains an incurable malignancy, and it is likely that the BM microenvironment protects MM against chemotherapy agents and the host immune system. A growing body of evidence suggests that host immune cells with a suppressive phenotype contribute to a myeloma immunosuppressive network. Among the known suppressor cells, MDSCs and T regulatory cells (Tregs) have been found to be significantly increased in myeloma patients and their levels correlate with disease stage and clinical outcome. Furthermore, it has been shown that MDSC can mediate suppression of myeloma-specific T-cell responses through the induction of T-cell anergy and Treg development in the MM microenvironment. Here, we review clinical correlations and the preclinical proof-of-principle data on the role of MDSCs in myeloma immunotolerance and highlight the mechanistically relevant MDSC-targeted compounds and their potential utility in a new approach for anti-myeloma therapy.

Keywords

Multiple myeloma; Myeloid-derived suppressor cells; Immunotherapy; Pre-clinical models

1. Introduction

Despite the advent of novel agents and doubling of survival rates, multiple myeloma (MM) is still considered an incurable malignancy [1–3]. MM is characterized by generalized immune suppression that contributes to susceptibility to infection as well as tumor progression [4–6] and the discovery that anti-MM novel agents (i.e., bortezomib and lenalidomide) retain immunomodulatory properties underlies the role of the deregulated immune effector cells in this disease [7–10]. T-lymphocyte and natural killer mediated immunotherapy have been evaluated or are currently under investigation as potential new avenues to overcome the myeloma immunosuppressive network and boost a specific anti-MM immune response [11–13].

A well-recognized feature of MM is the bidirectional interaction between malignant plasma cells and the bone marrow microenvironment, which provides a protective niche from the patient's immune system and chemotherapy agents. Importantly, inadequate prediction of myeloma progression based on gene-expression profiling of isolated malignant plasma cells underscores the likely essential role for non-plasma cells components in MM disease progression and survival [14]. While MM is a more widespread disease compared to smoldering multiple myeloma (SMM) and monogammopathy of unknown significance (MGUS), it harbors the same genetic defects as the other two subtypes of plasma cell dyscrasias [15,16] suggesting that genetic mutations are necessary but not enough for developing symptomatic myeloma. Transformation of MGUS to MM seems to be caused by a developing permissive myeloma microenvironment which leads to "immune escape" and advancement toward full-blown myeloma [12,17]. Also, the myeloma microenvironment has a substantial role in chemotherapy resistance and thereby the persistence of residual disease, which is the source of frequent relapses leading to poor clinical outcomes [18–21].

The MM microenvironment includes osteoclast, osteoblasts, endothelial and immune cells with the structural support of an extracellular matrix, adhesion molecules and cytokines [21].

Increased immune suppressor cells have been reported in the bone marrow of myeloma patients, which correlates with clinical outcomes, emphasizing the important role of these cells in providing the “immune escape” that favors myeloma progression. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in different cancer types, including MM. Besides immune regulation, MDSCs promote tumor angiogenesis and tumor growth through the secretion of cytokines and growth factors. Recently, the role of MDSCs in tumor-induced immunosuppression has been established in a variety of malignancies. MDSCs are a heterogeneous mixture of myeloid cells in different maturation stages with the antigen-presenting ability that contributes to immune evasion of cancer cells [22–25]. They are comprised of immature granulocytes and precursors of macrophages and dendritic cells that promote tumor growth by suppressive adaptive immunity, leading to suppression of CD4 and CD8 cell-mediated immunity [22,26,27]. These cells secrete arginase, which is able to deplete the microenvironment of arginine, an essential amino acid for T-cell activity. Moreover, MDSCs inhibit T-cell receptors by nitrosylation and reactive oxygen species (ROS) release [28]. MDSCs are activated by a key transcription factor, signal transducer and activator of transcription 3 (STAT3) [29]. This review presents a summary of preclinical data and clinical correlations and highlights the MDSCs as an important target for therapeutics development for patients with MM.

2. MDSC evolution and phenotype

In mice, MDSCs are classified according to presence of Ly-6C or Ly-6G on their membrane, respectively. In humans, they are characterized as $CD33^+$ cells, common myeloid marker, and $CD11b^+$ with no marker for mature lymphoid or myeloid on their membrane including HLA-DR. They can be divided in two main groups based on CD14 positivity; granulocyte MDSCs (G-MDSCs) are $CD11b^+$ $CD14^-$ $CD33^+$ $CD15^+$ $HLA\text{-}DR^{low/-}$ and monocytic-MDSC (M-MDSCs) that are $CD11b^+$ $CD14^+$ $CD33^+$ $HLA\text{-}DR^{low/-}$ [30,31]. Detailed information about the different subsets of MDSCs can be found elsewhere [32].

MDSC evolution from hematopoietic progenitor cells (HPC) includes a primarily MDSC expansion phase and a second phase of MDSC activation. The first phase is mediated by a variety of cytokines, including GM-CSF, M-CSF, G-CSF, IL-6 and vascular endothelial growth factor (VEGF), produced by tumors or bone marrow stromal cells, and activation of STAT3 and STAT5. These signals promote proliferation of immature myeloid cells from hematopoietic progenitor cells and prevent their differentiation to more mature myeloid cells. The second phase involves MDSC activation through STAT1 and NF-kB pathway activation which involves a different set of cytokines such as IL-13, toll-like receptor (TLR) ligands and leads to upregulation of arginase and nitric oxide (NO). Importantly, to mount a full MDSC effect during tumorigenesis or chronic inflammation the simultaneous activation of two phases is required. In myeloma the G-MDSC forms the predominant MDSC population in bone marrow as well as peripheral blood samples as opposed to M-MDSC [33]. MDSCs are phenotypically different in humans and mice.

3. Clinical correlations

Higher Peripheral blood MDSC levels correlates with higher tumor stage and volume at diagnosis in a variety of solid tumors as well as malignant hematology neoplasms and confers chemoresistance[34,35]. On multiple reports, MDSCs were functionally and phenotypically different in MM patients compared to patients with MGUS and normal individuals [33,36,37]. Also, $CD14^{+}HLA\text{-}DR^{-/low}$ M-MDSCs increase in newly diagnosed and relapsed MM compared to a myeloma patient who is in remission. More importantly the MDSC burden correlates with MM stages and poor clinical outcome with proteasome inhibitors[38]. A balanced amalgam of different immune system compartments including NK cells, Tregs, MDSCs, Th17 and T helper cells correlates with long-term remission after initial anti-myeloma therapy [39,40]. Details regarding the potential role of MDSCs as a population influencing the GVHD as well as Donor Lymphocyte Infusion (DLI) outcome after stem cell transplant is also emerging (section 5.2).

4. Role of MDSCs in the tumor-induced immunosuppressive network

While MDSCs are rare or absent in healthy individuals, they play a prominent role in some physiologic process like fetal allotolerance during pregnancy as well as in pathologic conditions such as limiting the inflammatory response due to infections [41], and the development of immunotolerance to different types of malignancies[42,43]. During the process of metastasis, the shift of myeloid-progenitor cells to MDSCs is a transition observed in the microenvironment of organs such as lung or liver now viewed to be a critical step in enabling establishment of new metastases [44].

The myelomagenesis process, from MGUS to symptomatic myeloma, creates a suppressed immunome through a complicated cross-talk of the immune effecter cells and cytokines. The main deregulated elements of MM immunome are: Tregs, dendritic cells (DC), MDSCs and T-helper 17 (TH17) [45,46]. However, MDSCs are emerging as the main regulatory population, playing an essential role in disease progression through the orchestration of immune suppression (Figure 1) [47].

4.1. Suppressive effect of MDSC on T cell function

MDSCs suppress T-cell function through three main mechanisms: 1) arginine depletion 2) production of high levels of nitric oxide (NO) and 3) production of reactive oxygen species (ROS). MDSCs contain high levels of argeninase which depletes the microenvironment of L-arginine, leading to impaired production of the CD3ζ chain, an integral part of T-cell receptors (TCR). Also, L-arginine depletion causes T-cell proliferation arrest by affecting cell cycle regulators [48,49]. NO can increase T-cell apoptosis [50,51], and can also inhibit the IL-2 induced inflammatory cascade by inhibiting phosphorylation of downstream IL-2 pathways such as Stat5 or Jak3 [52]. Also, accumulation of ROS can suppress T-cell functions as peroxynitrite is known to lead to receptor modification including TCR/MHC modification. Lastly, MDSCs upregulate the immunoregulatory molecules, Cox-2 and prostaglandin E2 (PGE2) [53].

4.2. Stimulatory effect of MDSC on regulatory T cells

MDSCs can promote regulatory T-cells (Tregs) and interfere with lymph node homing of naïve T-cells [54,55]. MDSCs also promote the expansion of induced Treg (iTreg) cells from naïve Tregs through TGF-β-dependent and -independent mechanisms which involve surface receptor interaction of CD40-CD40L or IL-10 and IFN-gamma secretion, respectively [56]. The latter may be important in the MDSC suppression of NK cell as well as natural killer T-cell (NKT cell) mediated tumor responses in the myeloma microenvironment [57].

4.2.1. The MDSC role in NK cell anergy—Cancer-induced MDSCs can induce anergy of NK cells via membrane-bound TGF-β1 [58]. Also, prostaglandins are involved in MDSC-mediated NK cell suppression [59]. There is also an essential role for transforming growth factor β (TGF-β) in the biology of MDSCs and NK cell suppression. TGF-β1 is a cytokine with potent immunosuppressive effects which is overexpressed in many tumors. Inhibitors of TGF-β1 suppress development and function of MDSCs and enhance the efficacy of anti-tumor vaccination [60]. More importantly, MDSCs have been shown to induce NK anergy through membrane-bound TGF-β1, while TGF-β1 inhibition leads to more tumor-toxic NK cells [58]. Gr-1^{+}CD11b^{+} cells contribute to TGFβ-mediated metastasis through enhancing tumor cell invasion and metastasis [61]. Tumor exosomal TGF-β1 leads to MDSCs accumulation and tumor growth promotion [62]. NK surveillance and cytotoxicity against MM decreases as disease progresses [63–65].

4.3. MDSCs enhance the tumor-promoting effect of T helper 17

CD4^{+} T cells, upon activation and expansion, develop into different T helper cell subsets with different cytokine profiles. A subset of IL-17-producing effector T helper cells, called Th17 cells, has now been characterized which favors angiogenesis and tumor growth in a variety of malignancies including MM [66,67]. MDSCs recruit Th17 cells and increases IL-17 production [68,69]. NLRP3 inflammasome activation has been suggested as the mechanism of MDSC-mediated Th17 activation [70,71].

4.4. MDSC expansion as a counter-regulatory mechanism after anti-myeloma therapy

The alkylating agents melphalan and cyclophosphamide induce a robust initial antitumor immune response, which however is also associated with M-MDSC expansion, and an attenuated antitumor CD4^{+} T cell response through activation of PD1-PD-L1 axis [72]. This may provide a conceptual platform to test the potential synergistic effect of alkylating agents and MDSC-directed therapies to enhance the anti-myeloma immune response.

IMiDs modify the myeloma immunome in a specific way. Busch et al. provided a comprehensive analysis of the immune system in 68 myeloma patients who were treated with these agents[73]. These investigators showed increased numbers of Tregs and MDSCs, consistent with observations reported by others [74,75]. The observations include a demonstrated increase in both the number and activity of effector T and NK cells along with elevated HLA-DR expression, consistent with other studies [76–78]. These findings suggest that MDSC expansion exists as a counter-regulatory mechanism elicited by certain anti-myeloma agents, and suggests concomitant MDSC suppression could be an important strategy to prevent relapse after autologous stem cell transplant and chemoimmunotherapy

[79]. Interestingly, dexamethasone potentiates MDSC immunosuppressive effects [80,81] which is considered a mechanism of action for glucocorticoids in the allograft setting [82].

5. Role of MDSC in Myeloma Immunotherapy

5.1. MDSC impairs the efficacy of Myeloma vaccine and check point inhibitors

The premise of implementing different modalities of immunotherapy in MM is based upon the observation that myeloma evolution that correspond by progressive loss of T cell repertoire surveillance, suppression of antigen-presenting function and increased number and function of inhibitory accessory cells. A variety of strategies to reverse the myeloma-induced immunosuppression has been developed and are in clinical trials.

Dendritic cell (DC) has a critical role in the antigen presenting and developing anti-myeloma immune response. DC vaccination using different tumor antigens can render an active and potentially long lasting immunization against the tumor. In this method DCs are loaded with tumor antigen exhibit a potent T-cell stimulatory activity currently is under study. However, the vaccine trials have had mixed result. Studies suggest MDSC impair the immune response from DC vaccines [83]. This is important because the current method of DC ex vivo growth may collect MDSC. The most common approach to generate DC vaccine is DC ex vivo expansion before load them with tumor antigen. In this method most protocols uses $CD14^+$ cells to generate their DC produce from primary patient samples. Although this method can generate active DCs from normal individuals but has limitation to generate matures DC population from cancer patients that correlate with abundance of monocytes with altered surface marker expression (CD14+HLA-$DR^{lo/neg}$) which shows similarity with increased MDSC population in patient with cancer[84]. This underlines the importance of MDSC-suppressive strategies to augment the DC vaccination effect.

MDSCs from peripheral blood and bone marrow of myeloma patient contains more PD-L1 in compare to normal individuals [85]. Indeed, PD-L1 expression on MDSC is higher than antigen-presenting cells including dendritic cells and PD-1/PD-L1 blockade limits myeloma-promoting effect of MDSC [86]. In another study, Disruption of MDSC trafficking abrogate the response to PD1 inhibition [87], providing the framework for evaluation of check point inhibitor combination with MDSC-targeted agents.

5.2. MDSC role in GVHD and stem cell transplant outcomes

Allogeneic hematopoietic stem cell transplant and donor lymphocyte infusion (DLI) confers a prolonged remission in a subgroup of myeloma patients. This is due to “graft versus myeloma” effect as an effective immunologic therapy. However, the application of this modality of therapy is limited by high transplant-related mortality and GVHD. Interestingly, MDSCs are collected with G-CSF-mobilized stem cell collection from healthy donors [88], and the fraction of MDSC in the collected peripheral blood $CD34^+$ cells inversely correlates with occurrence of acute Graft vs. Host Disease (GVHD) [89 89]. Messmann et al. demonstrated in-vitro-generated MDSCs prevent murine GVHD by tipping the TH2/TH1 balance in favor of TH2 cells without disabling antitumor cytotoxicity of the graft. This effect is independent of MHC class I and may be exploited to treat GVHD without affecting

graft-versus-tumor (GVT) effect by expansion and infusion of autologous MDSCs from an individual patient [90]. In another study the number of circulating peripheral blood MDSCs negatively correlates with donor lymphocyte infusion (DLI) efficacy in the post allogeneic stem cell transplant setting [91]. The intensity of the conditioning regimen affects the expansion rate of MDSC populations post-transplant inversely, which may contribute to the higher GVHD incidence by myeloablative compared to a non-myeloablative conditioning regimens [92]. Moreover, MDSCs populate the bone marrow and increase Treg activity, leading to delayed T-cell immunity [93].

5.3. MDSCs role in future anti-myeloma CAR-T cells therapies

Genetically engineered T-cells with chimeric antigen receptors (CAR-T) endow T cell populations with high antigen specificity and remarkable anti-tumor activity in acute leukemia[94,95]. Currently, there are two ongoing clinical trials using CAR-T targeting the kappa light chain and CD138 testing the effectiveness of this modality in MM. There are more anti-myeloma CARs in pre-clinical development using the B cell maturation antigen (BCMA) and cell surface glycoprotein CS1 antigens [96]. This modality of therapy is emerging as an effective therapy with a curative potential of allogeneic stem cell transplant without morbidities related to graft versus host disease (GVHD). However, there have been challenges to implement this modality. Although, CAR-T cells are designed based on a restrictive antigen on tumor cells and are invariably able to lyse tumor cells in-vitro, they most often fail to expand and mount an anti-tumor effect in-vivo [97]. Mounting evidence suggests the suppressive role of MDSCs against in-vivo expansion of these engineered T-cells [98]. It has been observed that MDSCs are able to inhibit CAR-T cell expansion in vitro and the extent of T-cell proliferation correlates inversely with circulating MDSC counts in a pivotal trial of CAR-T therapy in acute leukemia [95]. Importantly, suppression of MDSCs by all-trans retinoic acid (ATRA) followed by infusion of antigen specific CART enhanced the anti-tumor effect of CAR-T therapy [87].

6. Myeloma preclinical models and therapeutic targeting of MDSCs

6.1. Immunocompetent myeloma mouse models

Most preclinical studies of the development and function of immune suppressor cells in MM have been done using an immunocompetent mouse model, C57BL/KaLwRij, and two murine myeloma cell lines originated from the mice, 5T2MM and 5T33MM. These models resemble the human myeloma disease as they exhibit widespread systemic disease with bony lesions. 5T33MM cells develop a more aggressive myeloma that grows in 3 weeks, while 5T2MM cells grow in 12 weeks with a slower paced disease.

Valckenborgh and colleagues, using the immunocompetent mouse and murine myeloma cells, demonstrated that immunosuppressive MDSCs subsets ($CD11b^{high}Ly6G^{low}$) are present in MM and their immunosuppressive capacity is induced by myeloma cells [99]. In another study, the Dana-Farber group demonstrated a bidirectional interaction between myeloma cells and MDSCs, influencing the cell mediated immune response. They demonstrated that myeloma cells promote development of MDSCs from healthy donor peripheral blood mononuclear cells and conversely, that MDSCs favor myeloma growth by

suppressing T-cell mediated immune responses [30]. MDSC-mediated T-cell suppression is partially dependent on arginine and NO synthase. Interestingly, they showed that bortezomib and melphalan abrogate the effect of MDSC suppressor factors (IL-6, IL-10, ARG1, iNOS and ROS).

5.2. MDSC cellular interactions in the myeloma microenvironment

The S100A9 knock-out (KO) murine model lacks S100A9, a STAT3-inducible myeloid-related protein crucial in MDSC production and accumulation in a tumor-bearing mouse, and thus provides a good model to study the effect of MDSC depletion in MM progression [33]. Ramachandran and colleagues showed that MDSCs play an essential role at early stages of MM as well as disease progression using this murine myeloma model [33]. These experiments were done in mice on a mixed FVB/N × C57BL/6 background, which develop spontaneous MM and subsequent widespread myeloma measurable by serum electrophoresis. Th1 $CD4^+$ cell activation and antigen-mediated T-cell expansion in the BM is accelerated in the S100A9KO model leading to slower myeloma progression in this model. These data highlight the important role of MDSC to create a quiescent immunological microenvironment for myeloma cells. Apart from immunosuppressive effects, MDSCs also exert a direct tumor-promoting effect on myeloma cells. AMP-activated protein kinase (AMPK), a key regulator of energy homeostasis in MM, increases after co-culture of MDSCs with myeloma cells with increased protection against apoptosis induced by bortezomib and melphalan [100]. Furthermore, the intrinsic plasticity of MDSCs to differentiate to osteoclasts, an essential element of the myeloma niche, may contribute to the dynamics of the myeloma microenvironment, favoring disease progression[101,102]. It appears that the osteoclast differentiation of MDSCs is mediated through a variety of osteoclastogenic growth factors, including RANTES and MCP-1 secreted by tumor cells. Zoledronic acid, a potent bisphophonate, is able to reduce accumulation of MDSCs within the bone marrow and a concomitant decrease in osteoclastogenesis [101].

5.3. MDSC distribution through myeloma progression

Veirman et al. studied MDSC distribution throughout the myeloma progression course. They showed that BM MDSCs increase early in MM progression in the 5TMM mouse model, and that they appear in the peripheral blood at later stages. Also, the immunosuppressive capacity of MDSC subsets is increased early in the myelomagenesis process. Furthermore, co-culture with MDSCs promotes MM cell survival by upregulation of AMPK, the anti-apoptotic factors MCL-1 and BCL2, and contributes to resistance to bortezomib and melphalan [100]. Also, they demonstrated that MDSC-suppressive therapies by anti-GR1 and 5-fluorouracil can augment the anti-myeloma effects of bortezomib.

MDSCs have been shown to exert T-cell suppression and to prolong survival of MM cells in vitro [103]. Also, MDSC targeting by anti-GR1 antibody resulted in a significant anti-tumor effect in vivo. MCL-1 up-regulation showed a major survival mechanism for MM-induced MDSC. STAT3 inhibition abolishes the suppressive effect of MDSCs on T cells [104] and inhibition of MDSC STAT3 mediated by sunitinib, a multitargeted tyrosine kinase inhibitor, blocks MDSCs proliferation and restores T-cell function [105,106].

5.4. MDSC-targeted strategies

The increased understanding of the underlying mechanisms responsible for MDSC development, trafficking and function has contributed to the exploration of a variety of strategies that may effectively target the cancer immunosuppression network. For example, ATRA has been used to promote MDSC differentiation into more mature cells [107]. STAT3 inhibitors lead to S100A9 protein depletion, which affects MDSC accumulation and their activation in cancer sites [29]. There are several promising STAT3 inhibitor compounds which are in phase II and III clinical trials, mainly for malignancies other than MM, and some of their anti-tumor efficacy may be attributed to MDSC-suppressive effects [108]. The combination of these compounds with standard anti-myeloma agents should be explored in early phase clinical trials. The downregulatory effect of phosphodiesterase inhibitors on arginase 1, nitric oxide synthase-2 expression and subsequent MDSC inaction and depletion [28] was translated into MDSC-directed clinical trials for myeloma patients; Gosh and colleges reported a combination therapy study using tadalafil, a phosphodiesterase 5 inhibitor, and lenalidomide [109]. Thirteen lenalidomide-refractory patients were recruited; one patient achieved minimal response and 4 patients, stable disease. Although tolerable, this approach lacked efficacy. MDSCs were measured by flow cytometry using $CD14^+$, $CD33^+$, $HLADR^{low}$, $IL4R\alpha^+$ or $CD15^+$, $CD33^+$, $HLADR^{low}$ on pre and post-treatment samples. Importantly, MDSCs were not detected in the pre-treatment blood or bone marrow samples of these heavily treated patients. Therefore, it was speculated that the poor response from MDSC-suppressive therapy was due to the lack of sufficient target cells (MDSCs) in these patient populations.

Immunosuppressive effects of MDSCs can also be inhibited by the class of small molecules known as triterpenoids [110]. In mouse models, RTA 408 depletes tumor nitrotyrosine burden and inhibits MDSC activity with subsequent enhancement of T-cell antitumor activity. This finding was utilized to augment the effect of checkpoint inhibitors in melanoma. Currently, the next generation of synthetic triterpenoids RTA 408 I are in a phase 1b/2 clinical trial in melanoma patients to test their ability to augment checkpoint inhibitors such as ipilimumab and PD1 inhibitors. A summary of the different MDSC-targeting agents based on the mechanism of action is presented in Table 1.

7. Summary and future directions

During the last decade, a growing effort has been devoted to understanding the role of immune regulatory cells in tumor progression. MDSCs appear to play a critical role in the generation of an immune dysfunctional microenvironment in patients with multiple myeloma. Identification of molecular pathways involved in MDSC evolution, circulation and function could potentially lead to new targets for therapeutics development. Novel agents targeting intermediates in these pathways will have the capacity to disrupt the myeloma immunosuppressive network, and will be incorporated in unique strategies that could improve the efficacy of current therapies as well as form the basis for cancer chemoprevention throughout the myelomagenesis process. Inhibition of the tumor-promoting and immune-suppressive functions of MDSCs in MM represents a needed and promising novel immune-based therapeutic approach in this disease.

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Practice Points

- Myeloma-induced immunosuppression is result of a complex cross-talk between immunoeffector and immunosuppressive cells.
- MDSCs are increased in myeloma patients in compare to normal individuals and their presence correlate to response to therapy.
- There is bidirectional talk between myeloma cells and MDSC; Myeloma cells promote MDSC differentiation and function and MDSC contributes to chemotherapy resistance.
- MDSCs play a central role to orchestrate the myeloma immunosuppression network by affecting NK, effector T cells, Tregs and dendritic cells.
- Therapeutics to overcome MDSCs can augment the effect of upcoming immunotherapy for MM.

Research Agenda

- Investigate MDSC trafficking further to elucidate the underlying mechanisms of cell-cell interactions between MDSC and other component of immune system.
- Study MDSC-targeting agents in conjunction with current and future anti-myeloma agents, specifically immunotherapy modalities.

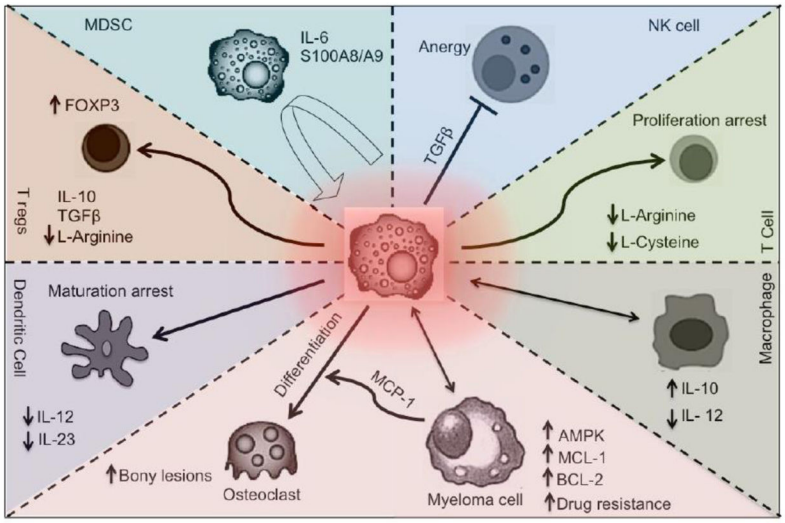

Figure 1.

Myeloid derived suppressor cells (MDSCs) interaction with myeloma cells and multiple mechanisms used by these cells to dampen anti-myeloma immunity. AMPK: AMP-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; MCL-1: Myeloid Cell Leukemia 1; TGF: Transforming growth factor.

Table 1

Potential therapeutic agents targeting MDSC classified according to mechanism.

Mechanism of Action	Compounds
Differentiation Promotion	Triterponoids[111]
	HDAC inhibitor[112]
	All-trans-retinoic-acid (ATRA)[113,114]
	Vit D3[115]
Maturation blockage	Sunitinib[116]
	STAT3 inhibitors (anti-apoptotic genes suppression and reduced ROC)[29]
	MMP9 inhibitors[117]
	Bevacizumab[118]
	Anti-BV8 mAb[119]
	Axitinib[120]
	Amino-Bisphoonates (Zoldronate) [117]
MDSC Trafficking	Gemcitabine[121]
	5-FU[122]
	Doxorubicin[123]
	CXCR2 and CXCR6 antagonist[124]
Function	Phosphodiestrase-5 inhibitor[125]
	Triterponoids[111]
	TGF-β inhibitors[60]
	ROS inhibitor (Nitraspirin and N-Acetyl Cysteine)[126]
	COX2 inhibitors (decrease in ARG and NOS expression)[127]