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REVIEW

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Improving cancer immunotherapy by targeting the STATe of MDSCs

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ABSTRACT

Cancer immunotherapy is a promising therapeutic avenue; however, in practice its efficacy is hampered by an immunosuppressive tumor microenvironment that consists of suppressive cell types like myeloid-derived suppressor cells (MDSCs). Eradication or reprogramming of MDSCs could therefore enhance clinical responses to immunotherapy. Here, we review clinically available drugs that target MDSCs, often through inhibition of STAT signaling, which is essential for MDSC accumulation and suppressive functions. Interestingly, several drugs used for non-cancerous indications and natural compounds similarly inhibit MDSCs by STAT inhibition, but have fewer side effects than anticancer drugs. Therefore, they show great potential for combination strategies with immunotherapy.

Abbreviations: APC, Antigen-presenting cell; ATRA, All-trans-retinoic acid; DC, Dendritic cell; GM-CSF, Granulocyte macrophage colony-stimulating factor; G-MDSC, Granulocytic myeloid-derived suppressor cell; HNSCC, Head and neck squamous cell carcinoma; IFN, Interferon; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; MDSC, Myeloid-derived suppressor cell; M-MDSC, Monocytic myeloid-derived suppressor cell; NOX, NADPH oxidase; PDE, Phosphodiesterase; PGE2, Prostaglandin E2; PPAR, Peroxisome proliferator-activated receptor; RCC, Renal cell carcinoma; ROS, Reactive oxygen species; STAT, Signal transducer and activator of transcription; TCR, T cell receptor; TGF, Transforming growth factor; TME, Tumor microenvironment; Treg, Regulatory T cell; VEGF, Vascular endothelial growth factor

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The immunosuppressive tumor microenvironment

In the past decade, cancer research has focused on the development of novel strategies, such as targeted therapies and immunotherapy, many of which have been approved for clinical use. These novel modalities are based on targeting specific pathways exploited by cancers using small molecule inhibitors or on empowering the immune system to eradicate cancer cells. Targeting immune checkpoints like cytotoxic T lymphocyte-associated protein 4 and programmed cell death protein 1 shows impressive results.[1] Other promising immunotherapies include adoptive cell transfer with tumor-infiltrating lymphocytes, vaccination with tumor-associated antigens and dendritic cell (DC)-based vaccines. Although these therapies show survival benefits and have lower incidences of lethal drug resistance than traditional chemotherapy, still not every cancer patient benefits from them.[2] One of the challenges that remains is generated by the tumors themselves, as they can evade immune responses by modulating the immune system in their local microenvironment.[3] This tumor-engineered local environment has been termed the immunosuppressive tumor microenvironment (TME), as it very effectively suppresses anti-tumor immune responses. Myeloid-derived suppressor cells (MDSCs) are key players in the TME and studies showing the importance of MDSCs in pathological conditions have accumulated in the past years. Many of these studies report an increased frequency of MDSCs in the blood of patients suffering from different types of cancer.[4,5] In addition, the presence of MDSCs in the TME is correlated with decreased efficacy of immunotherapies, including adoptive cell therapy, DC vaccination and ipilimumab treatment,[6-8] making MDSCs an important target for enhancing the efficacy of these therapies. This is substantiated by experiments in mice where eradication of MDSCs increased the efficacy of anticancer vaccines, adoptive cell therapy and anti-vascular endothelial growth factor (VEGF) antibody therapy.[9-11]

Here, we discuss the role of MDSCs in the immunosuppressive TME and detail the role of Signal Transducers and Activators of Transcription (STAT) proteins in MDSC accumulation and suppressive mechanisms. We elaborate on the potential of several clinically available drugs and natural compounds to inhibit MDSCs as an unintended effect, often mediated by STAT inhibition. Ultimately, we present some interesting strategies for combination regimens of these drugs and natural compounds with immunotherapy. The insights we discuss in this review relieve immunosuppression by targeting MDSCs

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and likely result in enhancement of antitumor immune responses by immunotherapy.

Myeloid-derived suppressor cells

In healthy individuals, myeloid progenitor cells and immature myeloid cells arise in the bone marrow and mature into granulocytes, macrophages or DCs. However, during cancer progression, tumor-derived factors, like granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate myelopoiesis, but disturb maturation.[12] This leads to the appearance of a heterogeneous population of immature myeloid cells in the blood that have the morphology of granulocytes or monocytes, but lack some of the markers expressed by these cells.[13] Based on their ability to efficiently inhibit T cell function, these cells are referred to as MDSCs. In mice, MDSCs can be identified by the expression of Gr-1 and CD11b and can be subdivided into granulocytic or monocytic MDSCs (G-MDSCs or M-MDSCs) based on the expression of Ly6G or Ly6C, respectively.[14] In humans, adequate characterization is challenging due to the lack of specific markers. As a consequence, MDSCs have been defined by different marker combinations in different studies.[15] Generally, MDSCs can be defined as $CD33^{+}CD11b^{+}HLA\text{-}DR^{-/low}$ cells that can be further subdivided into G-MDSCs or M-MDSCs by the co-expression of either CD15 or CD14, respectively.[16] The importance for clinical outcome of the frequency of either MDSC subtype differs across cancer types. For example, high numbers of M-MDSCs, but not G-MDSCs, are associated with negative response of non-small-cell lung cancer patients to platinum-based chemotherapy and the combination treatment of platinum with bevacizumab.[17] Furthermore, elevated frequencies of M-MDSCs are also associated with decreased survival of melanoma patients, regardless of previous therapy.[18]

MDSC suppressive mechanisms inhibit T cell development and function

After activation, MDSCs can inhibit both innate and adaptive arms of the immune system. They affect the innate immune system mostly indirect by secretion of immune inhibitory cytokines like IL-10 and transforming growth factor (TGF)-β, driving macrophages to a suppressive M2 phenotype,[19] and negatively affecting natural killer cell maturation, respectively (Fig.1A).[20] The effect of MDSCs on adaptive immunity is more direct, involving the suppression of T cells, using several mechanisms. First, MDSCs inhibit T cell function and proliferation by depleting the essential amino acids L-arginine and L-cysteine from the TME (Fig.1B). L-arginine is a substrate for arginase-I and inducible nitric oxide synthase (iNOS), which are both highly expressed by MDSCs.[13] Depletion of L-arginine leads to loss of the T cell receptor (TCR)ζ chain, resulting in decreased growth and differentiation.[21] Similarly, MDSCs can deplete L-cysteine from the TME, resulting in decreased proliferation and activation of T cells.[22] Second, MDSCs produce reactive oxygen (ROS) and nitrogen species, like hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^{-}$) (Fig. 1C). iNOS produces NO after T-cell-derived interferon (IFN)γ stimulation, which subsequently forms peroxynitrite after reacting with a superoxide anion ($O_2^{\cdot -}$).[23] Superoxide anions are produced by NADPH oxidase (NOX) and can react with water to form H_2O_2. $ONOO^{-}$ causes nitration and nitrosylation of components of the TCR signaling complex and H_2O_2 causes loss of the TCRζ-chain, both thus decreasing T cell activation.[24,25] $ONOO^{-}$ release also leads to nitrosylation of chemokines like CCL2, resulting in decreased recruitment of tumor-infiltrating T cells and high infiltration of immunosuppressive myeloid cells, including tumor-associated macrophages and MDSCs.[26] Lastly, MDSCs can induce the development of regulatory T cells (Tregs), and expand the existing Treg population, both of these mechanisms requiring direct cell–cell contact (Fig. 1D).[27,28] The secretion of several factors by MDSCs, including, TGF-β and IL-10 might be involved in this process, although the mechanism is still unclear.[29] Finally, L-arginine depletion by MDSCs also contributes to Treg expansion.[28]

STAT protein signaling is important in regulation of MDSCs

MDSC expansion and suppressive mechanisms are mainly regulated by the STAT signaling pathway. This protein family consists of seven proteins that regulate many vital cellular functions, such as proliferation and cell survival. They are activated through binding of cytokines or growth factors to their receptors, leading to activation of Janus kinase (JAK) tyrosine kinases, which phosphorylate STAT proteins. The phosphorylated STATs then translocate to the nucleus and regulate the expression of STAT target genes.[30]

Many tumors exploit STAT signaling through the secretion of tumor-derived factors (Fig. 2). This hijacking of STAT signaling plays an important role during cancer initiation and progression and in maintaining an immunosuppressive TME, for instance by inducing accumulation of MDSCs or stimulation of their suppressive capacity.[12] Tumor-derived factors, like G-CSF, GM-CSF and VEGF, induce STAT3 signaling, resulting in increased expression of proliferation-inducing and anti-apoptotic proteins, including c-Myc, Bcl-XL, cyclin D1 and survivin. These proteins promote proliferation of immature myeloid cells, while preventing apoptosis and differentiation into mature cells, resulting in increased MDSC frequencies.[31] Additionally, STAT3 directly regulates MDSC suppressive mechanisms by inducing NOX2 expression,[32] and arginase production.[33] STAT3 also induces the gene expression and protein level of the pro-inflammatory protein S100A9 in myeloid progenitors. Overexpression of S100A9 prevents differentiation into mature myeloid cell types by directly facilitating ROS production, resulting in expansion of MDSCs.[34] Furthermore, S100A9 binds to CD33 on MDSCs and induces production of IL-10, TGF-β, arginase and ROS.[34,35] The presence of constitutively active STAT1 correlates with increased frequency of MDSCs in tumors of breast cancer patients [36] and induces proliferation and suppressive capacity by regulating iNOS and arginase-I activity.[31,37] A third STAT protein, STAT5 induces MDSC expansion by reducing differentiation into mature myeloid cells through inhibition of interferon regulatory factor (IRF)-8.[38] STAT6 induces MDSC proliferation and survival and enhances arginase-I activity in MDSCs.[39-41]

The immunosuppressive capacity of MDSCs and their negative correlation with disease stage, treatment response and survival clearly suggest their importance in cancer progression and suboptimal outcomes of cancer immunotherapy. Eradication or reprogramming of MDSCs is a logical strategy to re-engineer

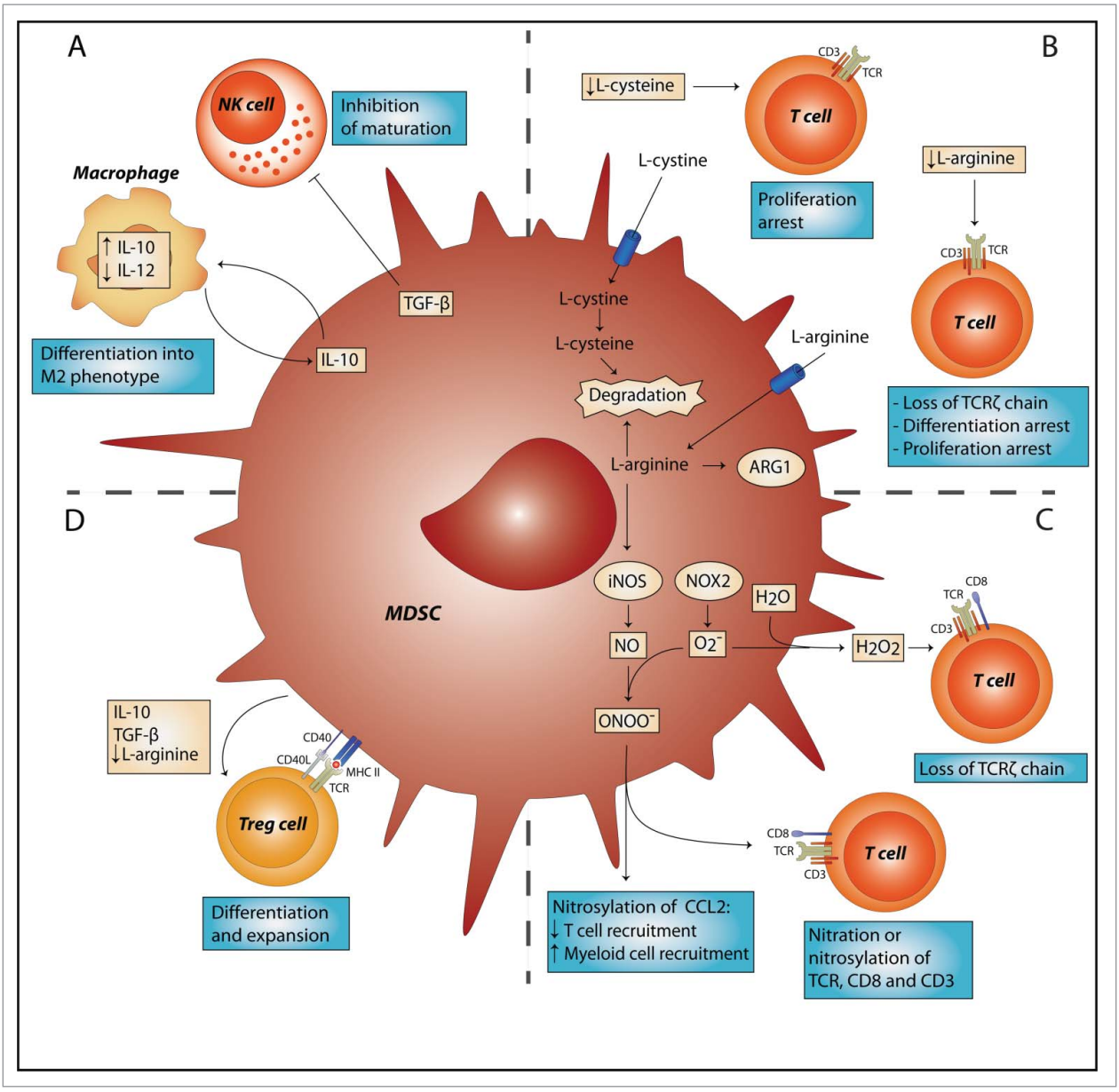

Figure 1. MDSC-suppressive mechanisms target innate and adaptive arms of the immune system. (A) Myeloid-derived suppressor cells (MDSCs) can inhibit the innate immune system by TGF-β-induced inhibition of NK cell function and induction of a M2 macrophage phenotype by secretion of IL-10. (B) MDSCs deprive T cells of amino acids L-cysteine and L-arginine, which are essential for proliferation and differentiation. (C) MDSCs release reactive oxygen species, such as hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$). H_2O_2 causes loss of the T cell receptor (TCR)ζ-chain and peroxynitrite causes nitration and nitrosylation of chemokines like CCL2 and components of the TCR signaling complex, thereby both inhibiting T cell activation and recruitment. (D) MDSCs induce the development of regulatory T cells (Tregs) or expand existing Treg cell populations; these effects are mediated by interaction of the TCR with MHC-II and CD40 with CD40L. Furthermore, secretion of factors like IL-10 and TGF-β, and deprivation of L-arginine by MDSCs induce Treg polarization. ARG1, arginase 1; CCL2, chemokine (C–C motif) ligand 2; iNOS, inducible nitric oxide synthase; NOX2, NADPH oxidase 2; NO, nitric oxide; NK, natural killer; TGF-β, transforming growth factor-β; IL, interleukin.

the TME and improve immunotherapy efficacy. The important role of STATs in accumulation and function of MDSCs, make the STAT proteins interesting targets to achieve this goal.

MDSCs as a target for enhancing immunotherapy efficacy

Drugs are known to have off-target effects, which are the main source of unwanted drug-related side effects. However, increasing evidence shows that chemotherapeutics and other drugs also have unintended effects that are beneficial, such as stimulation of immune responses by reduction of inhibitory molecules on DCs [42] and inhibitory effects on MDSCs. Several chemotherapeutics, drugs that are currently not used in cancer treatment and natural compounds have unintended effects on MDSCs (Table 1). Generally, these effects can result in inhibition of expansion and recruitment of MDSCs, inhibition of suppressive functions, or induction of MDSC differentiation into mature myeloid cells (Fig. 3). Several of these drugs modulate STAT signaling pathways, further emphasizing the potential of this pathway as a MDSC-inhibitory target.

Inhibition of MDSC expansion and recruitment

Targeted cancer therapies, like vemurafenib, affect MDSC expansion. Vemurafenib is a small molecule serine-threonine

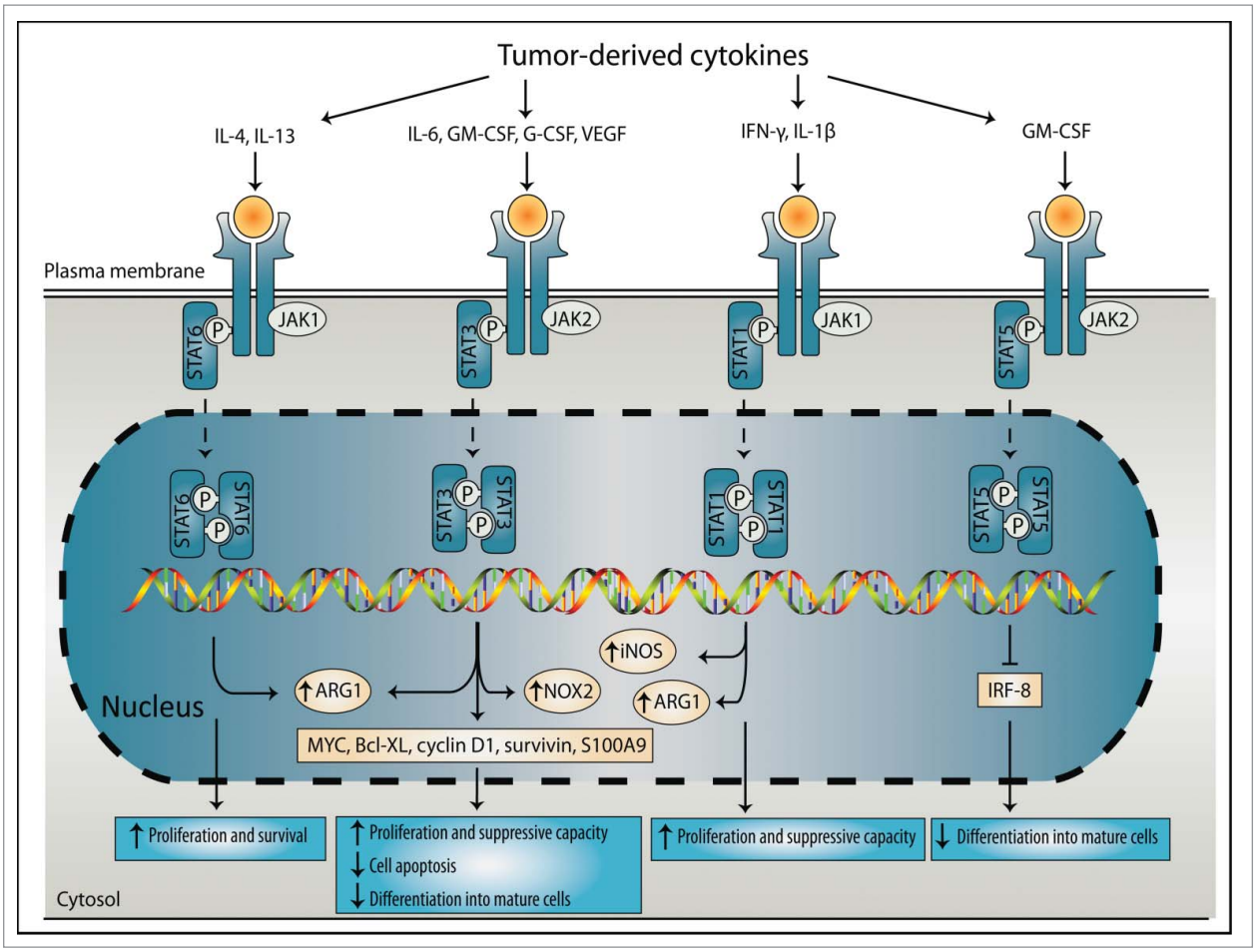

Figure 2. Induction of MDSC expansion and suppressive functions by the STAT signaling proteins. Tumor-derived factors induce signal transducers of activators of transcription (STAT) signaling, which stimulated MDSC expansion and suppressive functions. IL-4 and IL-13 induce STAT6 that regulates ARG1, leading to enhanced MDSC proliferation and survival. IL-6, GM-CSF, G-CSF and VEGF induce STAT3 signaling, which regulates ARG1, NOX2 and the expression of factors like MYC, Bcl-XL, cyclin D1, survivin and S100A9. This leads to enhanced MDSC proliferation and suppressive capacity, reduced apoptosis and inhibition of differentiation into mature cells. IFNγ and IL-1β regulate STAT1 activation, which induces iNOS and ARG1 expression by MDSCs, leading to induced proliferation and suppressive capacity. STAT5 signaling is induced by GM-CSF and inhibits the differentiation of MDSCs into mature cells through inhibition of IRF-8. IL, interleukin; IRF, interferon regulatory factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte-colony stimulating factor; VEGF, vascular endothelial growth factor; IFNγ, interferon-γ; JAK, Janus kinase; ARG1, arginase 1; NOX2, NADPH oxidase 2; iNOS, inducible nitric oxide synthase; Bcl-XL, B-cell lymphoma-extra-large.

kinase inhibitor that is specific for V600 mutated, constitutively active, B-RAF and is used to treat melanoma patients. In a recent clinical trial, decreased M-MDSCs and G-MDSCs frequencies were observed in patients that achieved a clinical response. In addition, vemurafenib inhibited the production of cytokines, like IL-6, by melanoma cells, thereby inhibiting M-MDSC development.[43,44] Other kinase inhibitors also showed the potential to inhibit MSDC expansion, although this was mainly shown in preclinical models. Tyrosine kinase inhibitors axitinib, sorafenib and sunitinib inhibited tumor growth by inhibiting several growth factor receptors, including VEGF and platelet-derived growth factor receptor.[45] Axitinib treatment of mice significantly decreased the number of MDSCs in the spleen and tumor, by downregulating STAT3 expression.[46] Furthermore, the combination of axitinib with DC vaccination enhanced elimination of MDSCs compared to axitinib or vaccination alone.[47] Sorafenib similarly decreased MDSC frequency and their analogous mechanisms of action suggest that, like axitinib, sorafenib targets STAT3.[48] Sunitinib is used to treat metastatic renal cell carcinoma (RCC) patients, in whom it decreased the frequency of both G-MDSCs and M-MDSCs in peripheral blood, and partially restored IFNγ production by T cells.[49,50] However, intratumoral MDSCs are often less affected and can develop resistance to sunitinib. This was observed in RCC patients, where the majority of patients treated with sunitinib prior to primary tumor resection showed high intratumoral MDSC frequencies compared to non-treated primary tumors.[50] GM-CSF-induced STAT5 signaling is crucial in the development of sunitinib resistance, as MDSCs cultured in the presence of GM-CSF, developed sunitinib resistance via increased STAT5 signaling.[51] Additionally, sunitinib enhanced stromal cell-derived factor-1-dependent induction of MDSC frequency in mice bearing human RCC xenografts. Taken together, the overall effect of sunitinib on MDSCs remains unclear.[52]

Other drugs that, similar to axitinib, sorafenib and sunitinib, inhibit VEGF can also induce MDSC eradication. The anti-VEGF antibody bevacizumab, reduced the frequency of immature myeloid cells in colorectal cancer patients.[53]

Besides targeted cancer therapies, MDSC expansion can also be inhibited by drugs that are currently not used in cancer therapy. In a preclinical model, a significant reduction in early MDSC accumulation in the blood was obtained with the peroxisome proliferator-

Table 1. Overview of drugs that target MDSCs.

Drug name	Cancer type	Effect on MDSCs	References
Drugs for cancer therapy			
Chemotherapeutic drugs			
Decitabine	Colon carcinoma[a]	Stimulation of differentiation into mature APCs	68
All-trans-retinoic acid (ATRA)	Colon carcinoma[a], metastatic renal cell carcinoma[b], small cell lung carcinoma[b]	Stimulation of differentiation into mature APCs, reduction of ROS production	69-72
Paclitaxel	Mammary tumor[a], melanoma[a]	Stimulation of differentiation into DCs, reduction of MDSC levels and inhibition of suppressive capacity	73-75
Docetaxel	Mammary tumor[a]	Promotion of MDSC differentiation into M1-macrophages	76
Kinase inhibitors			
Vemurafenib	Melanoma[b]	Reduction of MDSC levels and inhibition of M-MDSC development	43,44
Axitinib	Metastatic renal cell carcinoma[a], melanoma[a]	Reduction of MDSC levels through STAT3 inhibition	46,47
Sorafenib	Hepatocellular carcinoma[a]	Reduction of MDSC levels	48
Sunitinib	Metastatic renal cell carcinoma	Reduction of MDSC levels	49
Monoclonal antibodies			
Bevacizumab	Colorectal cancer[b]	Reduction of immature myeloid cell levels	53
Ipilimumab	Melanoma[b]	Inhibition of ARG-1 expression and reduction of M-MDSC and G-MDSC numbers	56,57
Drugs for other indication			
PPAR-γ activators			
Rosiglitazone	Pancreatic carcinoma[a]	Reduction of early MDSC accumulation	54
Histamine blockers			
Cimetidine	Lung carcinoma[a]	Reduction of MDSC expansion by induction of apoptosis and inhibition of NOS and ARG-I expression	55
Phosphodiesterase-5 inhibitors			
Sildenafil	Colon carcinoma[a], melanoma[a], head and neck squamous cell carcinoma[b], multiple myeloma[b]	Inhibition of iNOS and ARG-I activity by downregulation of IL-4Rα	59,60
Tadalafil	Head and neck squamous cell carcinoma[b], multiple myeloma[b]	Reduction of MDSC levels, reduction of arginase and iNOS production	61-63
Diuretics			
Amiloride	Colorectal carcinoma[b]	Inhibition MDSC suppressive capacity via reduced exosome secretion	66
Natural compounds			
Icariin	Mammary carcinoma[a]	Inhibition of NO and ROS production via STAT3 inhibition and induction of differentiation into macrophages and DCs	67
Cucurbitacin I, cucurbitacin B	MethA sarcoma[a], lung cancer[b]	Stimulation of differentiation into DCs through inhibition of JAK2/STAT3	77,78
Curcumin	Gastric cancer[a], colon carcinoma[a]	Stimulation of differentiation into M1 macrophages through inhibition of JAK2/STAT3	80
1α,25-hydroxyvitamin D3	Lung carcinoma[a], head and neck squamous cell carcinoma[b]	Stimulation of immature myeloid cells differentiation into DCs	81,82

[a]Murine cancer model
[b]human cancer

activated receptor (PPAR)-γ activator rosiglitazone, which is used in diabetes treatment.[54] Similarly, the histamine blocker cimetidine blocked the expansion of MDSCs in tumor-bearing mice by induction of apoptosis and by inhibition of NO and arginase production.[55]

Inhibition of MDSC-suppressive activity

Investigating changes in MDSC-suppressive capacity in clinical settings is challenging and studies addressing this issue are limited. The most notable study reports that ipilimumab decreased the expression of arginase in melanoma patients, indicative for loss of MDSC suppressive capacity. Furthermore, treatment with ipilimumab for more than 3 weeks decreased the frequencies of G-MDSCs and M-MDSCs.[56,57] Phosphodiesterase-5 (PDE-5) inhibitors, like sildenafil, are generally used in erectile dysfunction and pulmonary hypertension and inhibit IL-4Rα signaling, which regulates suppressive pathways in MDSCs via STAT6.[58] Indeed, administration of sildenafil downregulated the activity of iNOS and arginase-I in MDSCs through a STAT6-mediated pathway, resulting in prolonged survival of melanoma-bearing mice.[59,60] Not much is known about the effects of sildenafil on human MDSCs, but intriguingly, sildenafil increased T cell proliferation of *in-vitro*-treated PBMCs obtained from patients with multiple myeloma and head and neck squamous cell carcinoma (HNSCC).[59] Recent clinical trials showed that tadalafil, another PDE-5 inhibitor, reduced the number of MDSCs as well as their production of arginase and iNOS in HNSCC and multiple myeloma patients, resulting in increased numbers of tumor-specific T cells.[61-63] Additionally, it was shown that NO release can activate cyclooxygenase enzymes.[64] Cyclooxygenase 2 is a key regulator of prostaglandin (PG)E2 synthesis, which can induce the expression of immunosuppressive factors, like IL-10 and IL-4Rα and

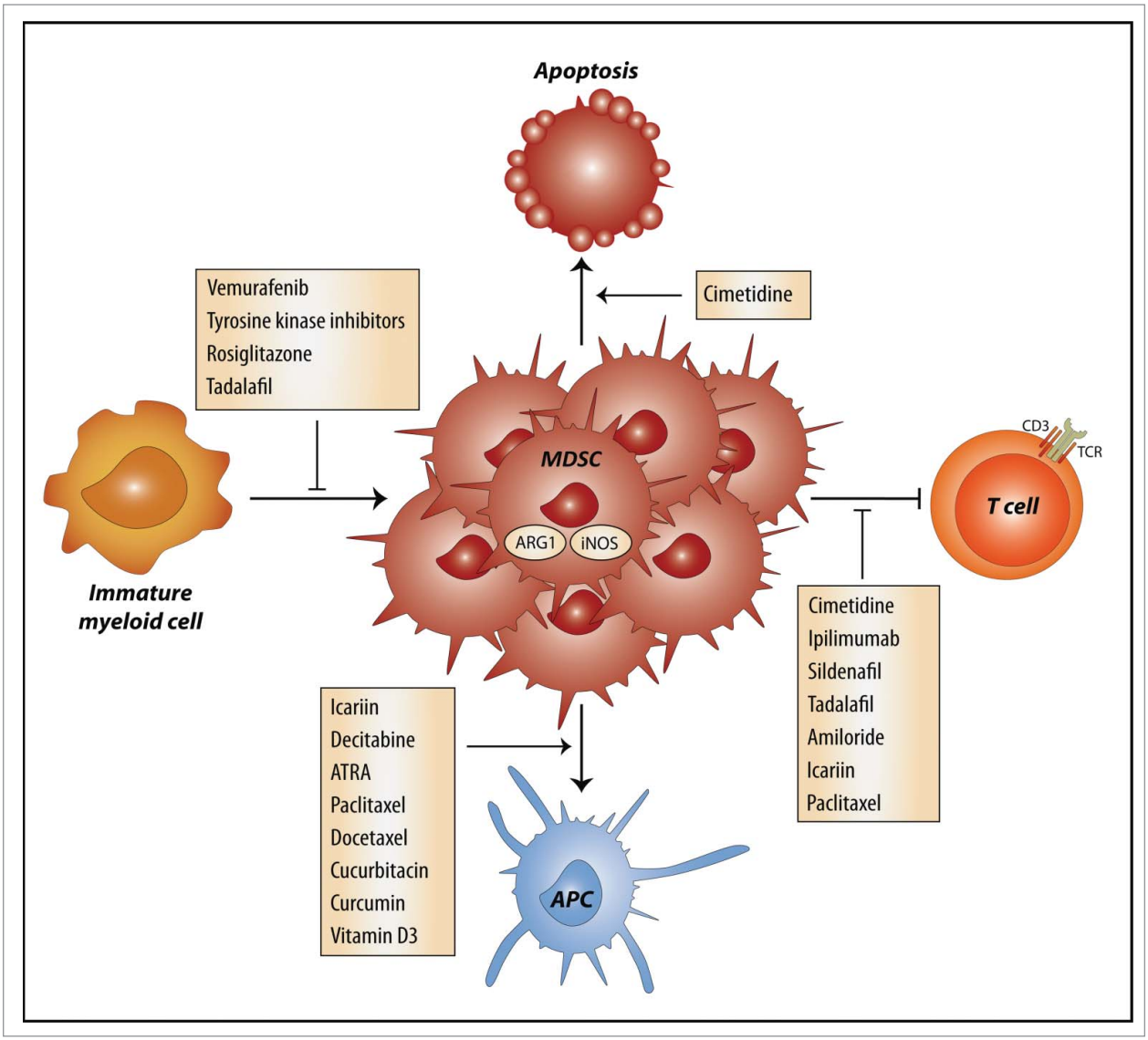

Figure 3. Mechanisms by which drugs and natural compounds inhibit MDSCs. Several drugs and natural compounds used in cancer treatment or for other indications have off-target effects that result in inhibition of myeloid-derived suppressive cells (MDSCs) through four distinct mechanisms. The off-target effects can inhibit expansion of MDSCs, inhibit their T cells suppressive capacity or induce the differentiation of MDSCs into mature APCs. Cimetidine induces the apoptosis of MDSCs. ARG1, arginase 1; iNOS, inducible nitric oxide synthase; APC, antigen-presenting cell; TCR, T cell receptor; ATRA, all-trans retinoid acid.

inhibitory molecules, like programmed death-ligand (PD-L)1, by MDSCs.[65] Indirect inhibition of PGE2 release through inhibition of NO release by PDE-5 inhibitors could also contribute to the inhibitory effects of these drugs on MDSCs. These findings clearly illustrate the potential of PDE-5 inhibition as a way to inhibit MDSCs via STAT signaling regulation. Another interesting drug is amiloride, which is a diuretic drug used to treat high blood pressure. Amiloride inhibited MDSCs suppressive capacity by inhibiting the secretion of CSF-containing exosomes by the tumor and consequently inhibiting IL-6/STAT3 signaling. Patients with colorectal cancer receiving amiloride treatment indeed had decreased STAT3 activation and reduced MDSC suppressive capacity.[66]

In addition to drugs, natural compounds can also have unintended effects on MDSC suppressive capacity. The natural compound icariin, the active ingredient of a herb used in Chinese medicine, inhibited ROS and NO production by MDSCs, through inhibition of STAT3 and AKT phosphorylation. Furthermore, it reduced MDSC frequency and promoted differentiation into macrophages and DCs.[67]

In summary, the checkpoint inhibitor ipilimumab and several drugs that are currently not used as direct anticancer agents, like PDE-5 inhibitors, can inhibit MDSC suppressive mechanisms. Similar to the PDE-5 inhibitors, amiloride and icariin induce their effect by regulating STAT signaling pathways. The known mechanism of action and the fact that these drugs induce mild side effects compared to anticancer drugs make them the most promising candidates to use in combination strategies with immunotherapy.

Induction of MDSC differentiation into mature cells

Chemotherapeutic drugs, like the DNA methyltransferase inhibitor decitabine, can inhibit MDSCs by inducing their differentiation into mature antigen-presenting cells (APCs).[68] Furthermore,

the metabolite of vitamin A, all-trans retinoic acid (ATRA), which is also used in the treatment of cancer, promoted the differentiation of MDSCs into mature myeloid cells in both tumor-bearing mice and metastatic RCC patients.[69,70] A clinical trial in patients with small cell lung cancer showed that combining ATRA with DC vaccination significantly reduced MDSC frequencies and enhanced IFNγ production by $CD8^+$ cells compared to vaccination alone.[71] Additionally, by acting through ERK-dependent induction of glutathione, ATRA also reduced ROS production by MDSCs.[72] Paclitaxel, a chemotherapeutic of the taxane group, induced differentiation of MDSCs into DCs, via a Toll-like receptor 4-dependent mechanism.[73,74] Treatment of tumor-bearing mice with paclitaxel inhibited the number of tumor-infiltrating MDSCs and abrogated their T cell suppressive capacity.[75] Another taxane family member, docetaxel, decreased the frequency of MDSCs by promoting differentiation into M1-like macrophages.[76]

Several natural compounds induce MDSC differentiation by direct inhibition of STAT signaling. *In vitro*, cucurbitacin I and B enhanced differentiation of spleen-derived immature myeloid cells into mature DCs by inhibition of the JAK2/STAT3 pathway. This coincided with a decrease of immature myeloid cells in spleens of treated tumor-bearing mice and in patients with advanced lung cancer.[77,78] However, tumor MDSCs were not sensitive to cucurbitacin I. Tumors have the ability to inhibit STAT3 activity in MDSCs by creating a state of hypoxia. These MDSCs then become functionally independent of STAT3, which diminishes the inhibitory effect of cucurbitacin. Interestingly, STAT3 expression in these tumor MDSCs could be restored by treatment with the CD45PTP-inhibitor sialidase, which blocked hypoxia-induced STAT3 downregulation. Combination treatment consisting of cucurbitacin I together with sialidase significantly decreased the frequencies of tumor MDSCs compared to cucurbitacin I alone.[79] Similarly, curcumin induced differentiation of MDSCs into M1-type macrophages through interaction with JAK2/STAT3.[80] Although an involvement of STAT signaling has not been reported, 1α,25-hydroxyvitamin D3 induced differentiation of $CD34^+$ immature cells into mature DCs in both tumor-bearing mice and HNSCC patients.[81,82] Treatment of HNSCC patients with vitamin D3 before tumor resection resulted in higher levels of intratumoral $CD8^+$ T cells and prolonged recurrence-free survival, which could be due to its effect on MDSCs.[83] Taken together, both chemotherapeutics and natural compounds are capable of inducing MDSC differentiation into mature cells, thereby preventing immune suppressive activity. However, due to possible severe side effects of chemotherapeutics like ATRA, and the known involvement of STAT3 in the mechanisms of action of cucurbitacin or curcumin, these compounds would be most promising to synergize with immunotherapy.

Discussion and future perspectives

Inhibition of the immunosuppressive TME and the presence of MDSCs in the TME is correlated with increased efficacy of immunotherapy. Targeting MDSCs by using clinically available drugs and natural compounds could improve antitumor immune responses induced by immunotherapy. The importance of STAT signaling pathways in the expansion and suppressive capacity provides a promising target to inhibit MDSCs. We discussed a number of drugs that can, as an unintended effect, inhibit the expansion of MDSCs, inhibit their suppressive functions, or promote their differentiation into mature APCs, often mediated by inhibition of STAT signaling pathways. Targeted cancer therapies, like tyrosine kinase inhibitors, and several chemotherapeutics reduce MDSC expansion or induce their differentiation into non-suppressive mature myeloid cells, but also have the potential for severe side effects.[84,85] Patients treated with immunotherapy can already experience severe side effects, which might be exacerbated when combined with these drugs.[86] We therefore propose to combine immunotherapy with drugs that have similar effects on MDSC expansion and function, but induce less severe side effects compared to conventional chemotherapy and some targeted therapies used in cancer treatment. We have highlighted several drugs and natural compounds used for diverse indications, which modulate MDSC function and differentiation. On a molecular level, most of these drugs exert their effect on MDSCs by interfering with the STAT signaling pathway. For instance, sildenafil and amiloride inhibit the suppressive mechanisms of MDSCs by interfering with STAT6 and STAT3 signaling, respectively. Natural compounds, like icariin, cucurbitacin and curcumin, inhibit the suppressive capacity of MDSCs or induce their maturation, by inhibiting STAT3. There is still a group of MDSC-inhibiting drugs, including rosiglitazone and cimetidine, for which the mechanism of action is unknown. However, the importance of STAT signaling in MDSC inhibition indicates that this pathway could be a potential mechanism for their effect. Furthermore, two specific JAK-inhibitors, tofacitinib and ruxolitinib, were FDA approved for the treatment of several auto-inflammatory diseases, including rheumatoid arthritis. Their specific targeting of JAK/STAT signaling makes them interesting candidates to target STAT signaling in MDSCs and to be used in combination with immunotherapy in anticancer regimes. However, the only study available on these drugs is in the context of rheumatoid arthritis and in that setting tofacitinib surprisingly resulted in the expansion of MDSCs.[87] On the other hand, in a melanoma mouse model, specific JAK inhibition with the experimental compound AZD1480 reduced MDSC frequencies, but it also enhanced their suppressive capacity.[88] These results could indicate that blocking of JAK signaling might not result in inhibition of STAT signaling and show that the effect of JAK signaling on MDSC expansion and suppressive capacity is still unclear and requires more research.

We propose that the drugs sildenafil and amiloride together with the natural compounds icariin, cucurbitacin I, cucurbitacin B and curcumin would be the prime candidates to test in combination with immunotherapy, as they were shown in experimental settings to inhibit the suppressive mechanisms of MDSCs or induce their maturation by targeting STAT6 or STAT3, with only mild side effects compared to chemotherapy and targeted cancer therapies. Clinical trials combining these possible candidate drugs with immunotherapy will have to prove their potential in the clinic.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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