World Journal of Gastrointestinal Oncology

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*World J Gastrointest Oncol* 2024 May 15; 16(5): 1690-1704

DOI: 10.4251/wjgo.v16.i5.1690

ISSN 1948-5204 (online)

*REVIEW*

# Mechanisms of myeloid-derived suppressor cell-mediated immunosuppression in colorectal cancer and related therapies

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**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Moldovan CA, Romania

**Received:** December 27, 2023
**Peer-review started:** December 27, 2023
**First decision:** January 16, 2024
**Revised:** January 30, 2024
**Accepted:** March 11, 2024
**Article in press:** March 11, 2024
**Published online:** May 15, 2024

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## Abstract

Severe immunosuppression is a hallmark of colorectal cancer (CRC). Myeloid-derived suppressor cells (MDSCs), one of the most abundant components of the tumor stroma, play an important role in the invasion, metastasis, and immune escape of CRC. MDSCs create an immunosuppressive microenvironment by inhibiting the proliferation and activation of immunoreactive cells, including T and natural killer cells, as well as by inducing the proliferation of immunosuppressive cells, such as regulatory T cells and tumor-associated macrophages, which, in turn, promote the growth of cancer cells. Thus, MDSCs are key contributors to the emergence of an immunosuppressive microenvironment in CRC and play an important role in the breakdown of antitumor immunity. In this narrative review, we explore the mechanisms through which MDSCs contribute to the immunosuppressive microenvironment, the current therapeutic approaches and technologies targeting MDSCs, and the therapeutic potential of modulating MDSCs in CRC treatment. This study provides ideas and methods to enhance survival rates in patients with CRC.

**Key Words:** Myeloid-derived suppressor cells; Tumor microenvironment; Colorectal cancer; Therapy; Immunosuppression

**Core Tip:** Severe immunosuppression is a hallmark of colorectal cancer (CRC). Myeloid-derived suppressor cells (MDSCs), one of the most abundant components of the tumor stroma, play an important role in the invasion, metastasis, and immune escape of CRC. In this study, we focused on the mechanisms through which MDSCs contribute to the immunosuppressive microenvironment, current therapeutic approaches and technologies targeting MDSCs, and the therapeutic potential of modulating MDSCs in CRC treatment. This study provides ideas and methods to enhance survival rates in patients with CRC.

**Citation:** Nie SC, Jing YH, Lu L, Ren SS, Ji G, Xu HC. Mechanisms of myeloid-derived suppressor cell-mediated immunosuppression in colorectal cancer and related therapies. *World J Gastrointest Oncol* 2024; 16(5): 1690-1704
**URL:** https://www.wjgnet.com/1948-5204/full/v16/i5/1690.htm
**DOI:** https://dx.doi.org/10.4251/wjgo.v16.i5.1690

## INTRODUCTION

Colorectal cancer (CRC) ranks as the third most common malignancy and the second leading cause of cancer-related deaths worldwide[1,2]. Standard treatments for CRC include surgery, chemotherapy, radiotherapy, and combinations thereof[3]. In recent years, significant advancements have been made in the diagnosis and treatment of CRC, particularly with the introduction of immunotherapy[4-6]. Pembrolizumab, for instance, has improved the median survival time for patients with metastatic CRC from 8.2 to 16.5 months, becoming established as the standard first-line treatment option for metastatic microsatellite instability-high (MSI-H) and mismatch repair-deficient (dMMR) CRC[7,8]. However, immune checkpoint inhibitors (ICIs) are only effective in CRC patients with MSI-H/dMMR, who account for approximately 15% of cases[9-12]. Furthermore, even among these patients, the response rate to ICI is only about 40%[13,14], contributing to a high mortality rate, especially in patients with stage IV CRC, who have a 5-year survival rate of only 14%[15]. Therefore, improving the efficacy of immunotherapy remains a critical challenge in improving the prognosis for CRC patients[16].

CRC is a highly malignant disease with a complex tumor microenvironment (TME), marked by interactions between the tumor, stromal, and immune cells. The major cellular components of the TME in CRC include tumor cells, myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), cancer-associated fibroblasts, tumor-associated macrophages (TAMs), natural killer (NK) cells, and regulatory T cells (Tregs), among other immune cells[17,18]. Crosstalk between cancer cells and the TME is an important factor that contributes to tumor immune escape, metastasis, recurrence, and poor immunotherapy efficacy[19,20]. MDSCs, which originate from hematopoietic stem cells, are one of the most abundant and dominant components of the TME. Several studies have demonstrated that MDSCs can cause immunosuppression, which in turn is involved in CRC progression, recurrence, and metastasis[15,17,21,22]. Increased levels of circulating and tumor-infiltrating MDSCs have been observed in CRC patients[23,24]. Thus, targeted inhibition of MDSCs attenuates immunosuppression and activates antitumor immune responses, such as T and NK cells, which in turn enhances antitumor immunotherapy[25,26]. Inhibiting MDSC trafficking to the TME has been proposed as a novel strategy in microsatellite-stable CRC, with the potential to reprogram the immune system[27]. A previous study reported that a high-salt diet inhibited tumor growth in mice by reducing MDSC activity and enhancing antitumor immune surveillance[28]. Furthermore, targeting TAMs and granulocytic MDSCs (G-MDSCs) augments the effects of ICIs and programmed cell death protein 1 (PD-1) blockade in cholangiocarcinoma[29]. Therefore, this review focuses on MDSCs, exploring and discussing their roles and mechanisms in tumor progression, and examining the current application of pharmacological and non-pharmacological therapies aimed at inhibiting MDSCs, including combination therapies with ICIs. This discussion aims to provide therapeutic ideas and targets for improving the immunosuppressive microenvironment in CRC, thereby enhancing the efficacy of immunotherapy and improving patient prognosis.

## MDSC: ORIGIN, PHENOTYPE, AND FUNCTION

Under physiological conditions, hematopoietic progenitor cells in the bone marrow differentiate into common myeloid progenitors (Figure 1), and then undergo granulocyte-macrophage progenitor, myeloblast, and monocyte-DC progenitor processes that culminate in their differentiation into monocytes or neutrophils[30]. When a healthy human is subjected to acute infection or trauma, the bone marrow quickly releases large numbers of immature myeloid cells that differentiate into mature myeloid cells, such as polymorphonuclear neutrophils and monocytes, to help eliminate the acute pathological conditions[31,32]. However, in patients with tumors, continuous stimulation often leads to defective differentiation of immature myeloid cells, which eventually differentiate into MDSCs with immunosuppressive properties[33,34]. MDSCs are classified into two subsets: Monocytic MDSCs (M-MDSCs) and granulocytic polymorphonuclear MDSCs (PMN-MDSCs), with the latter comprising approximately 80% of the total MDSC population[35,36]. In mice, PMN-MDSCs are identified by the markers $CD11b^{+}Ly6G^{+}Ly6C^{low}$, whereas M-MDSCs are characterized as $CD11b^{+}Ly6G^{-}Ly6C^{high}$[37-40]. In humans, PMN-MDSCs and M-MDSCs can be distinguished by their respective markers: CD14-CD11b+CD15+CD66b+CD33+ HLA-DR- for PMN-MDSCs and CD14+CD11b+CD15-CD66b-CD33+HLA-DR- for M-MDSCs[41-43].

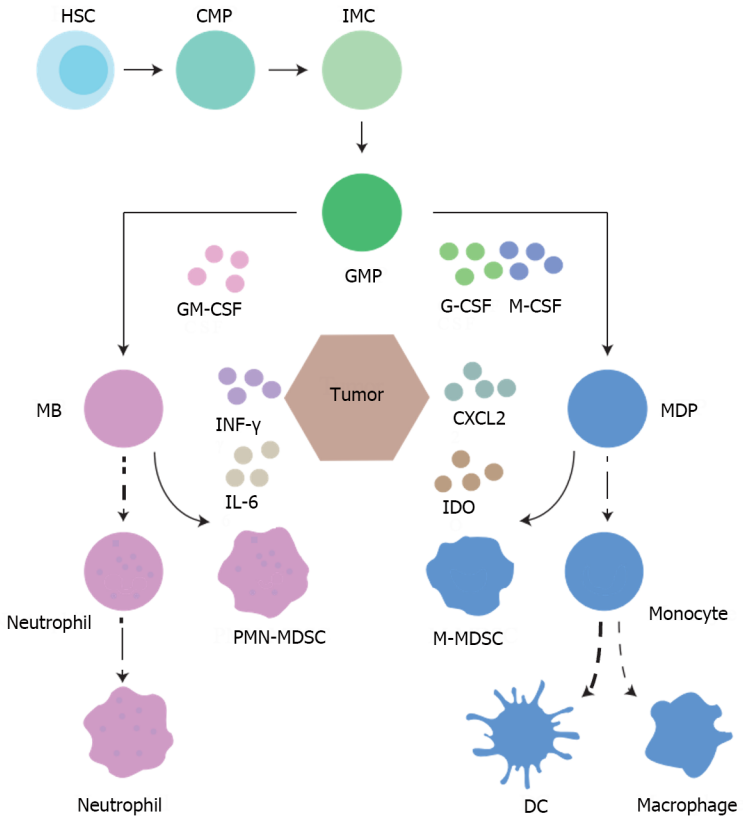


**Figure 1 Schematic diagram of myeloid-derived suppressor cell development and differentiation.** Hematopoietic stem cells in the bone marrow differentiate into common myeloid progenitors (CMP) and then undergo CMP, myeloblast, and monocyte-dendritic cell progenitor processes that culminate in differentiation into monocytes or neutrophils. However, in patients with tumors, continuous stimulation often leads to defective differentiation of immature myeloid cells, which eventually differentiate into myeloid-derived suppressor cells (MDSCs) with immunosuppressive properties. MDSCs are classified into two subsets: Monocytic MDSC and granulocytic polymorphonuclear MDSC. HSC: Hematopoietic stem cells; CMP: Common myeloid progenitors; GMP: Granulocyte-macrophage progenitor; MB: Myeloblast; MDP: Monocyte-dendritic cell progenitor; IMC: Immature myeloid cell.

The hallmark of MDSCs is immunosuppression, primarily targeting immunoreactive cells such as T and NK cells, with a particular focus on T cells. They utilize multiple pathways that promote tumor immune evasion, leading to antitumor immune resistance[44,45]. However, PMN-MDSCs and M-MDSCs exert their immunosuppressive effects *via* different mechanisms. PMN-MDSCs mediate immunosuppression *via* the production of reactive oxygen species (ROS), peroxynitrite, and arginase 1 (ARG1), while M-MDSCs produce nitric oxide (NO) and immunoregulatory cytokines, including interleukin (IL)-10 and transforming growth factor beta (TGF-β). M-MDSCs also contribute to immunosuppression by upregulating the expression of immunoregulatory molecules such as programmed cell death 1 ligand 1 (PD-L1)[46]. Due to the induction of these tumor-derived growth factors and pro-inflammatory cytokines, the MDSC population is greatly expanded in the TME[47].

In addition to their immunosuppressive functions, MDSCs can also promote tumor progression by influencing remodeling and tumor angiogenesis through the production of vascular endothelial growth factor (VEGF), bFGF, Bv8, and MMP9[48-51]. MDSCs promote epithelial-mesenchymal transition (EMT) by activating the PI3K-AKT-mTOR pathway in cancer cells, thereby increasing the invasiveness and metastatic potential of breast cancer cells[52,53]. MDSCs also directly promote tumor growth and metastasis. A previous study confirmed that human MDSCs promote CRC development by enhancing CRC cell stemness and growth *via* exosomal S100A9[54]. Furthermore, MDSCs drive tumor progression by producing IL-6 (which activates STAT3 in cancer cells) and NO (which activates the Notch pathway and maintains STAT3 activation), thereby inducing stem cell-like features in breast cancer cells[55].

## MECHANISMS OF MDSC-MEDIATED IMMUNOSUPPRESSION IN CRC

### *Inhibition of T-cell function*

MDSC can recruit and induce other suppressive or regulatory cells (Figure 2), such as Tregs, and inhibit the immune function of various T cell types, including NK cells and $CD8^+$ T cells, through multiple pathways, thereby affecting the immune function of patients with tumors[56,57]. Activated MDSCs within the TME express ARG1 and cystine–glutamate transporters (Xc-), thus depriving T cells of L-arginine and L-cysteine, which are essential for proliferation and activation [47,58]. T cells, which require cysteine for activation and function, can only acquire cysteine from antigen-presenting cells, such as macrophages and DCs, due to their inability to transport cysteine. However, MDSCs compete with these antigen-

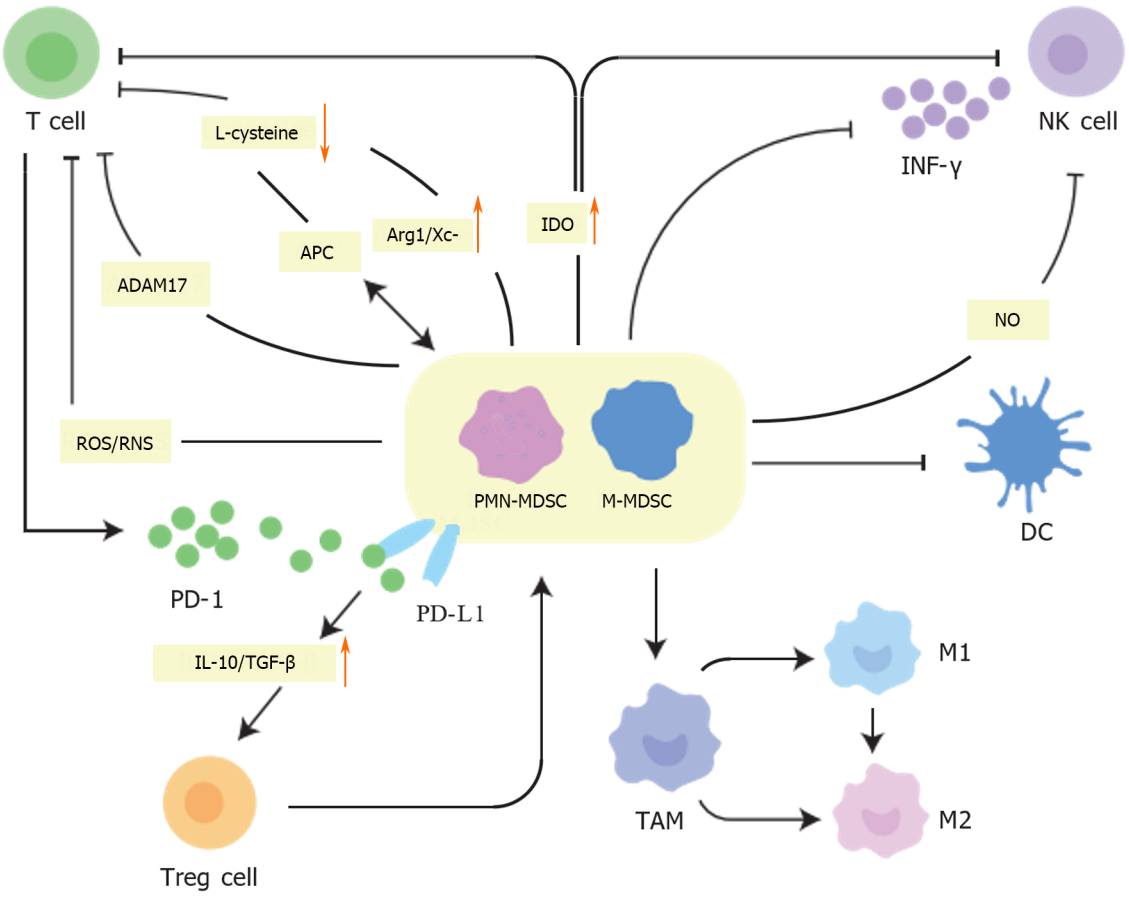


**Figure 2 Mechanisms of myeloid-derived suppressor cells-mediated immunosuppression.** The activated myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment express arginase 1 and cystine-glutamate transporters, thus depriving T cells of L-arginine and L-cysteine, which are essential for proliferation and activation. MDSCs compete with antigen-presenting cells for extracellular cysteine and are unable to export cysteine to prevent T cell proliferation and activation. MDSCs also express indoleamine 2,3-dioxygenase 1 to inhibits the activity of T and natural killer (NK) cells under inflammatory conditions. Furthermore, MDSCs express ADAM17 to prevent naïve T cells from migrating to tumors or lymph nodes and subsequently forming effector T cells. MDSCs release reactive oxygen species and reactive nitrogen species to dysregulate the function of T cell. Activated MDSCs express programmed cell death 1 ligand 1, which bind programmed cell death protein 1 on T cells and secrete interleukin-10 and transforming growth factor beta to stimulate Treg activation and expansion. Activated Tregs release immunosuppressive cytokines and suppress other immune cells to inhibit anti-tumor immune responses. MDSC can impair Fc receptor-mediated function of NK cells by producing nitric oxide. MDSCs could impair NK cell function and cytotoxicity by suppressing the production of interferon-γ from NK cells. Since MDSC and dendritic cells (DC) share a common progenitor cell, the reduction in mature DC observed in cancer patients may be due to skewing of the common MDSC/DC progenitor towards preferential differentiation of MDSC at the expense of DC. MDSCs can continue to differentiate into tumor-associated macrophage, which can be divided into the M1 subset that inhibits tumor growth and the M2 subset that promotes tumor growth. In the presence of MDSCs, macrophages are converted to an M2 or alternatively activated phenotype to enhances tumor progression. ROS: Reactive oxygen species; ARG1: Arginase 1; NO: Nitric oxide; IL-10: Interleukin-10; TGF-β: Transforming growth factor beta; VEGF: Vascular endothelial growth factor; Xc-: Cystine-glutamate transporters; DC: Dendritic cells; TAM: Tumor-associated macrophage.

presenting cells for extracellular cysteine and are unable to export it, thus inhibiting T cell proliferation and activation [59]. MDSCs also express indoleamine 2,3-dioxygenase 1, a tryptophan-catabolizing enzyme with immunological functions capable of inhibiting the activity of T and NK cells under inflammatory conditions[60]. MDSCs also express ADAM17, which cleaves CD62L, thereby preventing naïve T cells from migrating to tumors or lymph nodes and hindering their development into effector T cells[61]. In addition, MDSCs release ROS and reactive nitrogen species, which downregulate the ζ chain expression on T cell receptors, dysregulating T cell function[36,62]. Conversely, activated MDSCs express PD-L1, which binds PD-1 on T cells, and secrete IL-10 and TGF-β to stimulate Treg activation and expansion[63]. Tregs, known for their immunosuppressive capabilities, release cytokines that suppress other immune cells, thereby inhibiting antitumor immune responses[64,65]. In a mouse model of colon carcinoma, interferon-γ (IFN-γ)-activated MDSCs were shown to promote the expansion and recruitment of Treg cells, possibly through the upregulation of major histocompatibility class 2 (MHC-II), IL-10, and TGF-β[66]. Further, a previous clinical trial showed that patients with advanced CRC have elevated levels of circulating MDSCs in their blood and that M-MDSCs are positively correlated with Tregs. These results suggest that MDSCs, and particularly M-MDSCs, are potential targets for CRC immunotherapy [67].

### *Inhibition of NK cell function*

NK cells are cytolytic and cytokine-producing effector innate lymphoid cells with a critical role in immune activation

against abnormal cells[68]. MDSCs produce TGF-β, which is a master regulator of NK cell functions in tumors[69]. Co-culture of MDSC with NK cells results in impaired tumor cytotoxic activity of NK cells and induces immune tolerance [70]. Further, MDSC can have either direct or indirect effects on angiogenesis through their interactions with NK and immunosuppressive activities[69]. MDSC-mediated NK cell incompetence is associated with the ability of MDSCs to downregulate CD247 expression on the surface of NK cells[71]. MDSCs also inhibit NK cells in hepatocellular carcinoma patients *via* the NKp30 receptor[72]. In addition, inhibition of MDSC trafficking has been shown to potentially enhance NK cell immunotherapy in head and neck cancer models[73]. MDSCs can also impair Fc receptor-mediated functions of NK cells by producing NO[74]. In addition, MDSCs can impair NK cell function and cytotoxicity by suppressing the production of IFN-γ from NK cells and decreasing the expression of NK group 2 member D[17,75].

### *Inhibition of the function of other immune cells*

DCs are specialized antigen-presenting cells that play a crucial role in activating T cells to drive antitumor responses[76]. However, multiple conditions and factors within the TME, including hypoxia, lactic acid build-up, and accumulation of adenosine, can cause DC abnormalities. Since MDSCs and DCs originate from a common progenitor cell, the observed reduction in mature DCs in cancer patients may result from this progenitor being skewed towards MDSC differentiation at the expense of DC maturation[77].

MDSCs can continue to differentiate into TAMs within the TME. TAMs can be categorized into two subsets: an M1 subset that inhibits tumor growth and an M2 subset that promotes tumor growth. The TME's vascular distortion and rapid tumor cell growth cause hypoxia. This hypoxia then contributes to TME immunosuppression through the secretion of immunosuppressive factors, such as VEGF and TGF-β. VEGF, in particular, could enhance the infiltration of TAMs into tumor sites[78]. In the presence of MDSCs, macrophages tend to adopt an M2 or alternatively activated phenotype, which furthers tumor progression by decreasing the macrophage's production of IL-12[79].

### *MDSC-mediated low response to immunotherapy*

Elevated numbers of MDSCs are linked to poor prognosis and diminished response to treatment in several solid tumors [80,81]. MDSCs function as immunosuppressors by promoting immune evasion and resistance to cancer progression[82]. Presently, most treatments for tumors, especially CRC, rely on immunotherapy. The failure of immunotherapy is mainly related to the development of resistance to ICIs[83], which are designed to modulate and alter the response of T lymphocytes to tumors[84]. Anti-PD-1 and anti-PD-L1 antibodies represent the main types of ICIs. As discussed above, MDSCs can promote tumor immunosuppression, leading to ICI resistance by inhibiting T cell function[85]. Additionally, MDSCs increased PD-L1 expression on their surface, contributing to immunosuppression[84,86]. The immunosuppressive TME fosters resistance to anti-PD-1/PD-L1 therapies, and inhibiting MDSCs can synergize with PD-1/PD-L1 inhibitors to exert antitumor effects. HDAC expression in MDSCs promotes their differentiation into less inhibitory cells. HDAC inhibitors upregulate PD-1 or PD-L1 expression in tumors or immune cells and sensitize hormonal mice to anti-PD-1/PD-L1 therapy[87]. Kim *et al*[88] demonstrated that the removal of MDSCs results in the disappearance of tumor cells resistant to PD-1 antibody treatment. SLC25A22 knockout inhibits MDSC infiltration and function. The reduction of MDSCs through SLC25A22 knockout, particularly when combined with anti-PD1 therapy, synergistically induces CD8+ T-cell infiltration and IFN-γ expression, identifying SLC25A22 as a promising target for sensitizing KRAS-mutant CRC to immune checkpoint blockade therapy[89]. A growing body of research suggests that MDSCs are a potential therapeutic target for reducing tumor-promoting and immunosuppressive activities, as well as for boosting the efficacy of checkpoint inhibitors[90].

## STRATEGIES FOR TARGETING MDSC INHIBITION

### *Inhibition of MDSC recruitment*

By inhibiting the recruitment and transport of MDSCs to tumor tissues and the spleen, immunosuppression can be reversed, and the antitumor activity of T and NK cells can be activated to inhibit tumor proliferation and enhance the efficacy of antitumor therapy. Previous studies have shown that VEGF, hypoxia, S100A8/A9, chemokine receptors, and CSF1-R inhibitors can inhibit the recruitment and transit of MDSCs. For instance, bevacizumab has been shown to significantly reduce G-MDSC levels in the peripheral blood of patients with non-small cell lung cancer[91]. In addition, chemotherapeutic agents also exhibit MDSC-inhibitory effects. For example, the combination of sulforaphane and doxorubicin has been shown to effectively inhibit breast cancer proliferation and MDSC aggregation while increasing CD8+ T cell levels[92]. Chemotherapy (cisplatin + pemetrexed) combined with a PD-1 checkpoint inhibitor inhibits the proliferation of malignant mesothelioma cells by reducing MDSC accumulation and angiogenesis[93]. Further, polypeptide nanoformulations containing doxorubicin and the immune regulator 1-methyl-DL-tryptophan have been shown to inhibit the recruitment of Tregs and MDSCs while increasing the frequency of tumor-infiltrating CD8+ T cells, thus exerting synergistic antitumor effects[94]. Blocking STAT3 signaling, for example, with the use of Embelin and Flubendazole, can reduce the levels of MDSCs and inhibit their activity. Embelin can directly reduce MDSC production, as well as their immunosuppressive activity, by inhibiting the C/EBPβ and STAT3 signaling pathways[95]. Meanwhile, Flubendazole reduces MDSC levels in tumor tissues *via* the inhibition of the transducer and activator signaling activity of STAT3[96]. IL-6 silences the TNFα-RIP1 necrotic pathway to maintain MDSC survival and accumulation by mediating activation of the STAT3-DNMT axis[97]. Thus, the inhibition of STAT3 activation suppresses MDSC levels. IL-17, on the other hand, can induce MDSC differentiation, inhibit MDSC proliferation, and promote apoptosis by activating STAT3 [98]. A deficiency in CXCR2 hampers MDSC migration to tumor sites, significantly boosting the antitumor effects of PD-1

[99]. Small molecules of traditional Chinese medicine also exhibit MDSC inhibitory effects. Nanoparticles containing curcumin can exert antitumor effects by inhibiting the recruitment and accumulation of MDSCs[100]. Carnosic acid reduces the proportion of MDSCs, enhances the function of CD8+ T cells by decreasing the levels of iNOS2, Arg-1, and MMP9, and enhances the cytotoxic effects of cisplatin on lung cancer cells[101]. Some anti-inflammatory and antifungal drugs also have the ability to inhibit MDSC aggregation. Terbinafine inhibits CRC proliferation by reversing intestinal fungal dysbiosis, inhibiting MDSC infiltration, and restoring antitumor immune responses[102]. The anti-inflammatory drug dimethyl itaconate protects against colitis-associated CRC by decreasing the number of macrophages and MDSCs [103]. OSU-53 (a PPAR-inactive derivative that stimulates AMPK kinase) has been shown to significantly reduce MDSCs in the spleens and tumors of EMT-6 mice[104]. LDK378 (an anaplastic lymphoma kinase inhibitor) partially blocks lipopolysaccharide-induced p38 phosphorylation, reduces cell surface CCR2 expression, and inhibits the migration of MDSCs to the spleen[105]. In addition, the targeted inhibition of SLC25A22, YTHDF2, and G-CSF inhibits MDSC migration and aggregation[89,106,107].

### *MDSC depletion*

Previous studies have shown that chemotherapeutic agents, such as 5-Fluorouracil, docetaxel, and gemcitabine, can effectively deplete MDSCs. 5-Fluorouracil promotes MDSC apoptosis by upregulating the expression of Fas and p53 on these cells and increasing the infiltration of toxic T lymphocytes into tumor tissues[108]. Docetaxel promotes the polarization of MDSCs from an M1 (CCR7) to an M2 (CD206) type and increases the differentiation of macrophages towards an M1 phenotype[109]. Metformin, a drug commonly used to treat diabetes, inhibits MDSCs and M2-type macrophages in the CRC microenvironment by activating AMPK and inhibiting mTOR signaling[110]. Lenalidomide reduces the number of MDSCs and Tregs in lymphoma-loaded mice[111]. Sunitinib also reduces MDSC levels and restores the normal function of splenic T cells in mice[112]. Furthermore, the combination of OX40 (agonist anti-OX40 antibody) with belapectin (galectin-3 inhibitor) significantly reduces M-MDSCs levels and MHC-II hi macrophages thereby attenuating M-MDSC-induced immunosuppression[113]. Histamine dihydrochloride (a NOX2 inhibitor) in combination with low-dose IL-2, reduces M-MDSC levels in peripheral blood and enhances the antitumor efficacy of PD-1/PD-L1[114]. Apt/PDGs$^{s@pMOF}$ (a tumor-targeting and light-responsive penetrable nanoplatform) can deplete MDSCs and reverse immunosuppression[115]. The application of DS-8273a (TRAIL-R2 agonistic antibody) results in the depletion of MDSCs in approximately 50% of patients, without affecting mature bone marrow cells or lymphocytes[116]. Aminobiophosphonates (MMP-9 inhibitors) inhibit tumor and bone marrow cell proliferation and attenuate immunosuppression[117]. The herbal molecule Baicalein decreases MDSC levels by regulating the Nrf2/HO-1 signaling pathway and NLRP3 expression in MDSCs[118]. The Shugan Jianpi Formula enhances immune surveillance by reducing CD8+ T cell apoptosis and tumor cell activity, inhibiting MDSC proliferation, and improving the survival of mice with breast cancer tumors[119]. In addition, the depletion of MDSCs and attenuation of immunosuppression can be achieved by targeting and inhibiting molecules closely related to MDSC function. NLRP3, for instance, promotes melanoma progression by inducing MDSC expansion and immune escape, yet its targeted inhibition can enhance the efficacy of PD-1[120]. IL4Rα is a key signaling molecule for MDSC survival; hence, blocking IL4Rα can directly deplete MDSCs and TAMs[121].

### *Inducing MDSC differentiation*

The effectiveness of immunotherapy can be enhanced by reducing the number of MDSCs and promoting the differentiation of immature myeloid cells. Angiotensin-converting enzymes or angiotensin receptor blockers can induce the maturation of myeloid cells towards non-suppressive neutrophils/monocytes, thus preventing them from becoming immature MDSCs[122]. The DHODH inhibitor, brequinar, prevents early myeloid progenitor cells from generating MDSCs and promotes their maturation, which, in turn, enhances the antitumor and anti-metastatic activity of PD-1 in ICI-resistant breast cancer models[123]. Vitamins A, D3, and E have been shown to reduce immature MDSCs and enhance the antitumor activity of T cells in both a mouse model and in patients with head and neck cancer[124,125]. Casein kinase 2 substantially reduces the number of PMN-MDSCs and TAMs, thereby enhancing the effectiveness of CTLA4 checkpoint inhibitors[126].

### *Inhibiting MDSC activity*

Another category involves the direct inhibition of the immunosuppressive activity of MDSCs. Celecoxib, (COX-2 inhibitor) inhibits MDSC amplification[127]. Entinostat inhibits the immunosuppressive activity of HER2+ breast cancer G-MDSCs and promotes a macrophage shift to the M1 type[128]. Sildenafil, (PDE-5 inhibitor) can downregulate the expression of ARG1, IL4Ra, and ROS, restore the antitumor activity of NK cells, and reduce the postoperative recurrence of abdominal malignancies[70]. Ibrutinib (a BTK inhibitor) can reverse MDSC-induced immunosuppression, increase CD8+ T cell infiltration, and enhance PD-L1 efficacy[129]. Compared with sorafenib, tivozanib (a c-Kit/SCF antagonist) significantly reduces the levels of Foxp3+ Tregs, MDSCs, and exhausted T cells, thereby reversing immunosuppression [130]. Cimetidine promotes MDSC apoptosis and inhibits lung cancer cell proliferation by inducing Fas/FasL expression on the surface of MDSCs[131]. IFN-α/β upregulates TRAIL expression on T cells and enhances the inhibitory effect of TNF-α on MDSC through the TRAIL-DR5 pathway[132]. The herbal molecule Curcuma kwangsiensis also induces MDSC apoptosis in the G0/G1 phase by upregulating caspase 3/9, PARP, and Bax and downregulating Bcl-xl[133,134]. Asparagus polysaccharide could induce MDSC apoptosis and attenuate immunosuppression through the toll-like receptor4 pathway[135]. In addition, application of Cimetidine[131], TJ-M2010-5 (MyD88 inhibitor)[136], MF-766 (EP4 antagonist)[137], low-dose IPI-145 (PI3Kδ/γ inhibitor)[138], mitochondria-targeted complex I inhibitors[139], and compound39 (potent GCN2 inhibitor)[140], or targeted inhibition of jagged[141], SCARB1 (scavenger receptor type B-1) [142], and ROS levels, inhibits MDSC activity[143] (Table 1).

**Table 1 Pharmacologic strategies for targeting myeloid-derived suppressor cells inhibition**

| Function | Drug | Target pathway | Synergistic | Diseases | Ref. |
|---|---|---|---|---|---|
| Inhibition of MDSC recruitment | Bevacizumab | | | Non-small cell lung cancer | Koinis *et al*[91] |
| | IL-17 | | | Breast cancer | Ma *et al*[98] |
| | flubendazole | STAT3 | | Melanoma | Li *et al*[96] |
| | CXCR2 | | | Rhabdomyosarcoma | Highfill *et al*[99] |
| | IL-6 | STAT3-DNMT | | Colorectal cancer | Smith *et al*[97] |
| | G-CSF | | | Colorectal cancer | Li *et al*[107] |
| | Carnosic acid | | Cisplatin | Lung cancer | Liu *et al*[101] |
| | CDDP and PEM | | | Mesothelioma | Otsuka *et al*[93] |
| | Dimethyl itaconate | | | Colorectal cancer | Wang *et al*[103] |
| | Embelin | C/EBPβ and STAT3 | | Colitis-associated cancer | Wu *et al*[95] |
| | LDK378 | p38-GRK2-CCR2 | | Sepsis | Hu *et al*[105] |
| | Inhibition of YTHDF2 | | | Autoimmune hepatitis | Lyu *et al*[106] |
| | Terbinafine | | | Colorectal cancer | Hu *et al*[102] |
| | Targeting of SLC25A22 | | Immunotherapeutic | KRAS-mutant colorectal cancer | Zhou *et al*[89] |
| | Sulforaphane and doxorubicin | | | Breast cancer | Rong *et al*[92] |
| | Polypeptide nanoformulation | | Immunotherapeutic | Breast cancer and colon cancer | Feng *et al*[94] |
| | OSU-53 | AMPK | | Melanoma | Trikha *et al*[104] |
| | Curcumin | | | Lung cancer | Wang *et al*[100] |
| MDSC depletion | 5-Fluorouracil | p53-Fas | | Colorectal cancer | Yang *et al*[108] |
| | Docetaxel | | | Breast cancer | Kodumudi *et al*[109] |
| | Metformin | | | Colorectal cancer | Kang *et al*[110] |
| | Amino-biphosphonate | MMP-9 | | Breast cancer | Melani *et al*[117] |
| | Apt/PDGs$^{s@pMOF}$ | | | Triple-negative breast cancer | Chen *et al*[115] |
| | Baicalein | Nrf2/HO-1 | | Lupus nephritis | Li *et al*[118] |
| | DS-8273a | TRAIL-R2 | | Pan-cancer | Dominguez *et al*[116] |
| | Histamine | | Anti-PD-1/PD-L1 | Pan-cancer | Grauers *et al*[114] |
| | Shugan Jianpi Formula | | | Breast cancer | Lu *et al*[119] |
| | OLT1177 | NLRP3 | Anti–PD-1 | Melanoma | Tengesdal *et al*[120] |
| | Aptamer | IL4Rα | | Breast cancer | Roth *et al*[121] |
| | Sunitinib | STAT5 | | Renal cell carcinoma | Ko *et al*[112] |
| | Lenalidomide | | Cancer vaccine | Lymphomas | Sakamaki *et al*[111] |
| Inducting MDSC differentiation | ACEI | | | Colorectal Cancer | Bueno *et al*[112] |
| | Brequinar | DHODH | Anti–PD-1 | Breast cancer | Colligan *et al*[123] |
| | Vitamins A, D3, and E | | | Head and neck cancer | Lathers *et al*[124]; Lee *et al*[125] |
| | Casein kinase 2 | | Anti-CTLA4 | Pan-cancer | Hashimoto *et al*[126] |
| Inhibiting MDSC activity | Celecoxib | COX-2 | | Mesothelioma | Veltman *et al*[127] |
| | Entinostat | HDAC | | HER2+ Breast Tumor | Sidiropoulos *et al*[128] |
| | Cimetidine | | | Lung tumor | Zheng *et al*[131] |

| | | | | |
|---|---|---|---|---|
| Compound39 | potent GCN2 inhibitor | | Renal carcinoma | Jackson *et al*[140] |
| CTX014 | Jagged1/2 | | Pan-cancer | Sierra *et al*[141] |
| Asparagus polysaccharide | | | Colorectal Cancer | Zhang *et al*[135] |
| Curcuma | TLR4-NF-κB | | Pan-cancer | Jiang *et al*[134] |
| Ibrutinib | | Anti-PD-L1 | Neuroblastoma | Ishfaq *et al*[129] |
| IFN-α/β | | Anti-PD-1 | Colorectal cancer | Chen *et al*[132] |
| TJ-M2010-5 | Myd88 | | Colorectal cancer | Wang *et al*[136] |
| Tivozanib | c-Kit/SCF | | HCC | Kalathil *et al*[130] |
| Sildenafil | Phosphodiesterase-5 | | Abdominal malignancies | Tai *et al*[70] |
| IPI-145 | PI3Kδ/γ | Anti-PD-L1 | Head and neck cancers | Davis *et al*[138] |
| Mitochondrial complex I inhibitors | | | Melanoma | AbuEid *et al*[139] |
| MF-766 | | Anti-PD-1 | Pan-cancer | Wang *et al*[137] |
| Lipoprotein Nanoparticle | | | Lung carcinoma | Plebanek *et al*[142] |

MDSC: Myeloid-derived suppressor cells; HCC: Hepatocellular carcinoma; PD-L1: Programmed cell death 1 ligand 1; PD-1: Programmed cell death protein 1.

## NON-PHARMACOLOGICAL STRATEGIES FOR MDSC INHIBITION

Treatments for CRC, such as chemotherapy, immunotherapy, and targeted therapy, are continuously evolving, yet surgery remains the preferred treatment option for patients with CRC[144]. In mouse models with CRC, MDSCs are known to be enriched in the peritoneal cavity, and are associated with poor prognosis after tumor resection[145]. On the other hand, chemotherapy and radiotherapy typically lead to tumor cell death by mechanisms such as inducing significant DNA damage[146]. Radiotherapy, specifically, can alter the abundance and immunosuppressive activity of MDSCs, ultimately negatively impacting treatment outcomes[147]. Notably, the expansion of MDSCs following radiotherapy is associated with an incomplete treatment response in preclinical tumor models[148]. Therefore, to improve the overall survival of CRC patients and reduce the probability of tumor metastasis, it is essential to develop therapeutic approaches that specifically target MDSCs. Certain non-pharmacological approaches, such as chimeric antigen receptor (CAR-T) and fecal microbiota transplantation (FMT), can improve the TME by targeting MDSCs, thereby helping inhibit tumor progression.

CAR-T cells are genetically modified to express engineered receptors and chimeric constructs that recognize and react specifically to cancerous antigens in an MHC-independent manner and react specifically against them[149]. In recent years, many basic and clinical studies on the treatment of CRC with CAR-T cells have been published, with encouraging progress[150,151]. One study investigated CAR-T cell therapy in ten patients with metastatic carcinoembryonic antigen-positive CRC, seven of whom had stable disease after treatment. Two patients had stable disease for more than 30 wk, and positron emission tomography/computed tomography and magnetic resonance imaging analyses showed tumor shrinkage in two patients and a significant decrease in carcinoembryonic antigen levels in the majority of patients, which confirms the efficacy of CAR-T in the treatment of CRC[152]. Moreover, PD-1-TREM2-targeting scFv inhibited the activation of the PD-1/PD-L1 pathway. In addition, the secreted scFvs blocked the binding of ligands to TREM2 receptors present on MDSCs and TAMs, reduced the proportion of MDSCs and TAMs, and enhanced T-cell effector function, thereby mitigating immune resistance in the TME[153]. This demonstrates that CAR-T therapy can affect the TME *via* MDSC.

Many studies have suggested that disorders of intestinal microbiota play key roles in the pathogenesis of CRC[18,154,155]. The regulation of the intestinal flora also plays a role in improving the immunosuppressive microenvironment of tumors[156]. Recently, FMT has become a popular topic. In a mouse model of CRC, the application of terbinafine decreased fungus-induced MDSC infiltration and tumor load, whereas FMT in untreated with-terbinafine donor mice increased MDSC infiltration and promoted tumor proliferation[102]. Transplantation of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated donor mouse feces into antibiotic-treated mice induces MDSCs and increases Tregs[157]. This suggests that intestinal microbiota can influence tumor growth through MDSC. Another study showed that a fecal suspension from the astragalus polysaccharide group inhibited tumor growth in melanoma mice, decreased MDSC, and increased CD8+ T cells in tumor tissues, confirming that FMT could reverse the tumor immunosuppressive microenvironment[158]. Therefore, we believe that FMT is a promising therapeutic approach for improving the tumor immunosuppressive microenvironment by inhibiting MDSC, thus exerting antitumor effects.

## CONCLUSION

Tumors exploit various immunosuppressive pathways to actively evade immune recognition. MDSCs can create an immunosuppressive microenvironment in CRC by suppressing the immune function of T cells, NK cells, DCs, and macrophages, resulting in immune escape and resistance to immunotherapy. Therefore, therapeutic targeting of MDSCs presents a promising strategy to halt CRC progression and enhance the efficacy of immunotherapy. This involves preventing the expansion and accumulation of MDSCs, regulating their differentiation, and inhibiting their immunosuppressive activities. In this review, we focused on the role of MDSCs in CRC and the mechanisms through which they contribute to immunosuppression. We have also extensively discussed the currently available pharmacological and non-pharmacological treatments and strategies for targeting MDSC. This comprehensive analysis offers an objective understanding of the role of MDSCs in CRC and the methods to target MDSC-mediated suppression, ultimately aiming to improve the effectiveness of immunotherapy.

## FOOTNOTES

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**Author contributions:** Nie SC and Jing YH contributed to original draft preparation and image drawing; Nie SC was mainly responsible for writing the manuscript on the background knowledge of MDSC and the mechanism involved in immune regulation; Jing YH was mainly responsible for writing the manuscript on the therapeutic strategy of targeting MDSC; Ren SS participated in literature collection; Lu L, Ji G and Xu HC revised the manuscript; all authors wrote, read, and approved the final manuscript. Nie SC and Jing YH contributed equally to this work. The research was performed as a collaborative effort, and the designation of co-first authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. The reasons for designating Ji G and Xu HC as co-corresponding authors are twofold. Ji G and Xu HC were the co-corresponding authors of this manuscript because they discussed and selected topics together and developed the framework of the entire manuscript; And after the first draft was completed, they revised and improved the manuscript together, they jointly guided the completion of this manuscript and made the same contribution to this manuscript.

**Supported by** National Natural Science Foundation of China, No. 82320108022, No. 82322076 and No. 82104466.

**Conflict-of-interest statement:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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**S-Editor:** Qu XL
**L-Editor:** A
**P-Editor:** Cai YX

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