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Myeloid-derived suppressor cells: Key immunosuppressive regulators and therapeutic targets in colorectal cancer (Review)

WENJUAN ZENG[1,2*], HAOHAN LIU[1*], YUANHAO MAO[3*], SHIHAO JIANG[1], HAO YI[1], ZITONG ZHANG[1,2], MENGHUI WANG[1,2] and ZHEN ZONG[1]

[1]Department of Gastrointestinal Surgery, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [2]HuanKui Academy, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [3]Fuzhou Medical College, Nanchang University, Fuzhou, Jiangxi 330006, P.R. China

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Abstract. Globally, colorectal cancer (CRC) is the third most common type of cancer. CRC has no apparent symptoms in the early stages of disease, and most patients receive a confirmed diagnosis in the middle or late disease stages. The incidence of CRC continues to increase, and the affected population tends to be younger. Therefore, determining how to achieve an early CRC diagnosis and treatment has become a top priority for prolonging patient survival. Myeloid-derived suppressor cells (MDSCs) are a group of bone marrow-derived immuno-negative regulatory cells that are divided into two subpopulations, polymorphonuclear-MDSCs and monocytic-MDSCs, based on their phenotypic similarities to neutrophils and monocytes, respectively. These cells can inhibit the immune response and promote cancer cell metastasis in the tumour microenvironment (TME). A large aggregation of MDSCs in the TME is often a marker of cancer and a poor prognosis in inflammatory diseases of the intestine (such as colonic adenoma and ulcerative colitis). In the present review, the phenotypic classification of MDSCs in the CRC microenvironment are first discussed. Then, the amplification, role and metastatic mechanism of MDSCs in the CRC TME are described, focusing on genes, gene modifications, proteins and the intestinal microenvironment. Finally, the progress in CRC-targeted therapies that aim to modulate the quantity, function and structure of MDSCs are summarized in the hope of identifying potential screening markers for CRC and improving CRC prognosis and therapeutic options.

Correspondence to: Dr Zhen Zong, Department of Gastrointestinal Surgery, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, 1 MinDe Road, Nanchang, Jiangxi 330006, P.R. China
E-mail: ndefy16133@ncu.edu.cn

*Contributed equally

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Contents

1. Introduction

Colorectal cancer (CRC), which includes cancers of the colon and rectum, ranks as the third most prevalent cancer worldwide, constituting 10% of all new cancer cases, and is the second leading cause of cancer-related mortality, resulting in >930,000 deaths annually (1,2). Currently, surgical intervention, chemotherapy and targeted therapy constitute the cornerstone of CRC treatment. However, at the time of diagnosis, approximately one-quarter of patients with CRC are diagnosed with advanced disease, and an additional 20% develop distant metastases, frequently rendering surgical methods insufficient for improving prognosis and ineffective for identifying cancer that has propagated to adjacent organs (3). Thus, improving the prognosis of patients with locally advanced rectal cancer and metastatic CRC (mCRC) remains a pivotal and formidable challenge. Survival rates have demonstrated that 70-75% of patients with mCRC survive beyond 1 year, 30-35% survive >3 years and <20% survive >5 years (4,5). Furthermore, after neoadjuvant chemoradiation therapy and total mesorectal excision surgery, 54% of patients with rectal cancer relapse. Adjuvant chemotherapy or radiotherapy is required for ~66% of patients with stage II-III colon cancer and 50% of patients with stage II-III rectal cancer (6). The challenge of treating advanced CRC is compounded by resistance to chemotherapy, radiotherapy, targeted therapy and immunotherapy. Encouragingly, clinical evidence has demonstrated the effectiveness of neoantigens (cancer-specific abnormal peptides) in generating immune responses (7). Therefore, identifying novel components of the host immune system as relevant

biomarkers and therapeutic targets is crucial. A previous study has emphasized the role of the tumour microenvironment (TME) in treatment resistance (8). Components of the TME, such as tumour-associated macrophages (TAMs), regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), have been shown to dampen the immune response and influence CRC progression (9-11). As such, the potential roles of these cells in cancer metastasis and therapy have garnered significant interest.

MDSCs constitute diverse immature cell populations originating from the bone marrow, all of which exhibit immunosuppressive activity (12). As outlined by the dual signalling mode (13), three key processes occur within MDSCs, namely, migration, expansion and activation, each of which partially overlap and are facilitated by factors boosting myelopoiesis and hindering differentiation of mature myeloid cells and factors promoting the activation of MDSCs. Before these cells can become functional within the TME, these steps are imperative (14). Additionally, MDSCs display several biochemical characteristics crucial for suppressing immune responses, including enhanced signal transducer and activator of transcription 3 (STAT3) expression, the induction of endoplasmic reticulum (ER) stress (which can independently induce apoptosis and regulate ER chaperones, protecting cells by ensuring proper protein folding and preventing the accumulation of misfolded proteins) and the expression of arginase 1 (ARG-1) and S100 calcium binding protein A8/A9 (S100A8/A9) (15,16).

In healthy individuals, immature myeloid cells (IMCs) differentiate into granulocytes, macrophages or dendritic cells (DCs), eventually migrating to specific organs and tissues to perform regular immune functions (17). However, under pathological conditions or chronic inflammation, IMCs deviate from their typical differentiation pathway (18), evolving into granulocyte-monocyte progenitor cells under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF) and interleukin (IL)-6 (19). These cells then gradually migrate from the bone marrow into the peripheral blood and spleen where they are activated by proinflammatory cytokines such as interferon-γ (IFN-γ), IL-1β and IL-4, consequently forming relatively immature cells termed MDSCs, which exhibit the morphology of neutrophils and monocytes and possess immunosuppressive functions (20-22).

MDSCs are typically divided into two subsets: Granulocytic or polymorphonuclear-MDSCs (PMN-MDSCs) and monocytic-MDSCs (M-MDSCs) (12,23,24), with considerably more PMN-MDSCs than M-MDSCs noted in most tumours (18,25). MDSCs have an important role in the malignant progression of tumours (26,27), and the presence of MDSCs has been shown to obstruct the infiltration of $CD8^+$ T cells into tumours, promote Tregs and modulate natural killer (NK) cell activity, among other functions (28,29). As such, the suppressive actions of MDSCs contribute to tumour growth. Furthermore, the concentration of MDSCs in the peripheral blood is positively associated with the cancer stage; specifically, elevated levels indicate a more advanced cancer stage (30). MDSCs also promote tumour angiogenesis and create premetastatic niches by suppressing immune cells (26,27). This dual activity encourages the spread of cancer cells while concurrently diminishing the efficacy of antitumour drugs and fostering drug resistance, consequently influencing the inception, progression and prognosis of tumours (31-33). Research has demonstrated that distinct MDSC populations, which are involved in CRC (34) metastasis and progression through multiple mechanisms, are detected in tumour tissues and peripheral blood of patients with CRC (35).

The present review describes the mechanisms underlying MDSC aggregation and migration and illustrates the role of MDSCs in the CRC TME. The present review also surveys current therapeutic strategies, providing insights that may benefit the diagnosis, prognosis and treatment of CRC.

2. Phenotypes of MDSCs

The phenomenon of extramedullary haematopoiesis and neutrophilia frequently accompanies malignancy (such as CRC), and these manifestations include cells with suppressive activity that were initially termed IMCs (17). With advances in research clarifying their origin and function, these cells were ultimately designated MDSCs (36) (Fig. 1).

Initially, to distinguish immature MDSCs from normal cells, researchers detected MDSCs in mice using surface biomarkers, with the goal of gaining insight into human MDSCs. It was found that MDSCs in mice are characterized by the markers, CD11b and Gr-1, and that the Gr-1 antigen complex comprises the components Ly-6G and Ly-6C. Specifically, mouse PMN-MDSCs are $CD11b^+Gr\text{-}1^+Ly6G^+Ly6C^{low}$ and are phenotypically and morphologically similar to neutrophils. M-MDSCs are $CD11b^+Gr\text{-}1^+Ly6G^-Ly6C^{high}$ and are phenotypically and morphologically similar to monocytes (37-39). However, a subsequent study has shown that the two characteristic markers of mouse MDSCs, CD11b and Gr-1, are not optimal markers for distinguishing different species of MDSCs in humans (40).

Researchers have identified key surface markers, such as human leukocyte antigen DR (HLA-DR), CD11b and CD14, which are intrinsic to monocytes, as pivotal in distinguishing human MDSCs (41). Another signature of M-MDSCs is the positive expression of C-C motif chemokine receptor 2 (CCR2) and C-X3-C motif chemokine receptor 1 (CX3CR1) (42,43). A subset of cells bearing the phenotype of $HLA\text{-}DR^{low/-}CD11b^+CD14^-CD15^+$ has been categorized as granulocytic-MDSCs (12,23). Given their morphological and phenotypic resemblance to neutrophils, they are also aptly referred to as PMN-MDSCs. Conversely, cells characterized as $HLA\text{-}DR^{low/-}CD11b^+CD14^+CD15^-$ are termed M-MDSCs, given their resemblance to monocytes (12).

The aforementioned subtypes also exhibit distinct T-cell suppressive activities and mechanisms. Additionally, human M-MDSCs express more CD33 than PMN-MDSCs (44). The distinction among human monocytes, neutrophils and MDSCs is achieved through the expression of surface molecules such as HLA-DR and lectin-type oxidized LDL receptor 1 or CD14, which serve as differentiating markers (45-48). Previous investigations have identified early-stage MDSCs (12,49) and fibrocytic MDSCs (50-52), with the former capable of colony formation and distinguished by a $lineage^-$ (Lin^-) (including CD3, CD14, CD15, CD19 and CD56) HLA-DR $CD33^+$ phenotype. The latter, a subpopulation with fibrocytic characteristics and immunosuppressive functions, differs

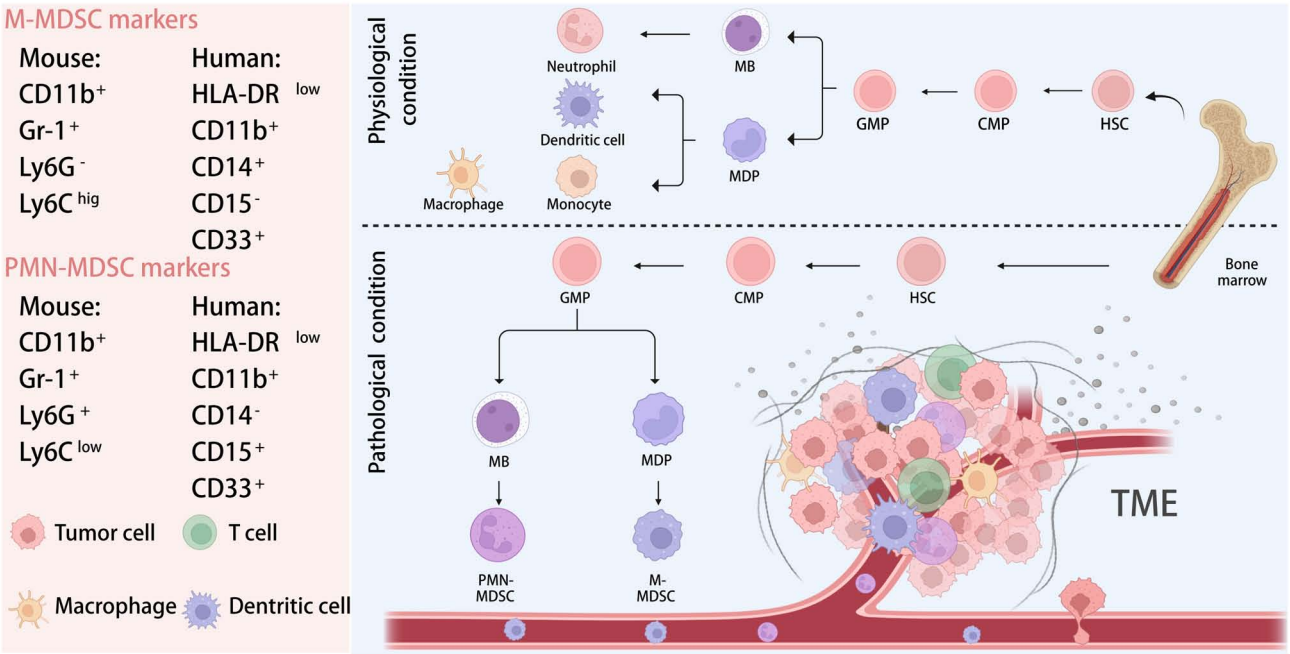

Figure 1. The origin of MDSCs. MDSCs originate from the bone marrow, where they are derived from HSCs and GMPs. GMPs differentiate into MBs and MDPs. In cancer, MB and MDP deviate from the normal differentiation pathway and transform into PMN-MDSCs and M-MDSCs. Created with BioRender.com (https://app.biorender.com/). TME, tumour microenvironment; HSC, haematopoietic stem cell; CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; MDP, monocyte-dendritic cell progenitor; MB, myeloblast; PMN-MDSC, polymorphonuclear-MDSC; M-MDSC, monocytic-MDSC; MDSC, myeloid-derived suppressor cell; HLA-DR, human leukocyte antigen DR.

from umbilical cord blood precursors and can be identified by a $CD11b^{low}CD11c^{low}CD33$ IL-4Ra^{+} phenotype. Furthermore, CD49d is a potential marker that complements CD11b for MDSC categorization (53). A study by Alshetaiwi *et al* (54) revealed that high concentrations of MDSCs in the spleen and primary tumour sites correspond to significant expression of both CD84 and junction adhesion molecule-like, suggesting that CD84, which is typically a lymphoid marker, may represent a novel and specific marker for MDSCs in CRC.

3. Chemotaxis and amplification of MDSCs in CRC

Chemotaxis and the accumulation of MDSCs in the colorectum are critical for colorectal tumorigenesis. Furthermore, gene sequence and epigenetic variations are significant risk factors for MDSC accumulation (33). In CRC, mutations in the oncogene, Kirsten rat sarcoma viral oncogene homologue gene (KRAS), are observed in up to 40% of cases and are associated with increased tumour aggressiveness and metastasis (55-57). Previous studies have highlighted the essential role of the SLC25A22 gene in enhancing KRAS mutation-induced CRC immunosuppression by facilitating asparagine binding and SRC phosphorylation activation (58,59). This process promotes ERK/ETS proto-oncogene 2 signalling and drives C-X-C motif chemokine ligand 1 (CXCL1) transcription. The secreted CXCL1 then acts as a chemoattractant for MDSCs through the chemokine C-X-C motif receptor 2 (CXCR2), creating an immunosuppressive microenvironment (60). Furthermore, MDSCs suppress interferon regulatory factor 2 expression, resulting in increased CXCL3 binding to CXCR2 on MDSCs and promoting MDSC migration into the TME, leading to MDSC overaccumulation (58,61). YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) regulates CXCL1 expression via promoting p65 protein expression to activate NF-κB signal transduction, impacting MDSC migration through the CXCL1/CXCR2 axis; furthermore, a reduction in MDSC number is observed upon YTHDF1 gene knockdown (62).

N6-methyladenosine (m6A) RNA methylation, a posttranscriptional RNA modification, involves m6A methylase complexes (writers), demethylases (erasers) and binding proteins (readers) that regulate their respective axes, promoting normal biological processes. However, aberrant m6A RNA methylation promotes MDSC recruitment at the gene expression level, thereby increasing CRC risk. For instance, the methyltransferase 3 methylase N6-adenosine-methyltransferase complex catalytic subunit promotes m6A methylation of the transcription factor, basic helix-loop-helix family member e41, which stimulates CXCL1 expression and mediates MDSC migration and aggregation in the TME of CRC, forming an immunosuppressive environment and weakening the immune system, promoting CRC development (63,64). Furthermore, the demethylase, Alk B homologue 5 (Alkbh5), recruits MDSCs and diminishes NK and CD8^{+} T cell populations by decreasing the mRNA stability and demethylation of axis inhibition protein 2 mRNA, leading to its dissociation from the m6A reader, insulin like growth factor 2 mRNA binding protein 1 (65), thereby resulting in Wnt/β-catenin pathway overactivation. Human Alkbh5 also contributes to gene splicing by placing m6A modifications near splice sites, influencing MDSC migration and aggregation in the TME (66-68). In addition, Alkbh5 affects changes in metabolite content. Alkbh5 modulates monocarboxylate transporter 4 expression (a key enzyme that rapidly transports lactic acid to plasma membranes) and lactate concentration in

the TME (69). Additionally, lactate can increase the frequency of MDSCs and upregulate expression of FoxP3, an important transcription factor in Treg development and function (68-70).

The pathogenesis, progression and metastasis of CRC are intricately linked to genetic factors within the host as well as the specific tissue milieu in which the cancer resides. This local milieu, consisting of immune cells, malignant cells, fibroblasts, various non-immune cells and connective tissues, constitutes the TME (71). In contrast to being a static entity, the TME is dynamic and complex. Within this setting, common myeloid progenitor cells (CMPs) located in the bone marrow can differentiate into MDSCs during tumour progression. In response to inflammatory signals or tumour-released factors, including growth factors, chemokines and inflammatory cytokines, CMPs proliferate, promoting the recruitment and expansion of MDSCs to the tumour locus (72). This process not only facilitates the influx of IMCs but also inhibits the innate antitumour response of the host.

Since their initial discovery in 1986 (73), over 50 human chemokines, small secreted proteins that direct immune cell movement, have been identified (74). These chemokines are divided into four subfamilies, including CXC, CC, C and CX3C, based on variations in the sequence of the first two conserved cysteines at the N-terminus (75). Chemokines expressed by tumour cells play a pivotal role in recruiting MDSCs into the TME by binding to specific receptors on the MDSC surface. In CRC, MDSC recruitment is predominantly associated with two chemokines, one from the CC subfamily (CCL2, CCL5 and CSF1) and the other from the CXC subfamily (CXCL1/2/3/5/6/8/12).

CCL2, also known as monocyte chemotactic protein-1, is a vital component of the CC chemokine family. This protein significantly impacts the growth, progression and metastasis of various tumours, including CRC (76-78). CCL2-mediated recruitment of the CCR2 receptor, which has a high affinity for MDSCs, supports CRC cell proliferation (79). Evidence suggests that MDSC accumulation induced by CCL2 enhances their immunosuppressive capabilities during colorectal carcinogenesis, with a corresponding increase in CCL2 levels as the cancer progresses (76,80). Moreover, reactive nitrogen species produced by MDSCs can modify chemokines such as CCL2 to nitro-CCL2, which preferentially recruits myeloid cells, in contrast to unmodified CCL2, which attracts $CD8^+$ T cells (81).

Conversely, MDSCs positive for CXCR2 can engage with CXCL1/2/3, facilitating the recruitment of MDSC clusters in the colon and rectum (61,82). The migration and recruitment orchestrated by members of the CC family, including CCL2, CCL5 and CSF1, predominantly involve M-MDSCs and monocytes. By contrast, CXC family members, such as CXCL1, CXCL5, CXCL6, CXCL8 and CXCL12, are more closely involved with the recruitment of PMN-MDSCs and granulocytes in CRC. MDSCs express various chemokine receptors, including CCR2, CCR5 and CXCR2 (21,47). Additionally, CXCL1 and CXCL2 are crucial in the context of colitis-associated tumours and chronic colonic inflammation (83).

The regulation of MDSCs extends beyond that of chemokines to include other inflammatory mediators, such as prostaglandins and histamine. For instance, histamine enhances the proliferation of M-MDSCs and increases the expression of enzymes such as inducible nitric oxide synthase (iNOS) and ARG-1 in the CRC (84). Conversely, histamine suppresses the expression of these enzymes in PMN-MDSCs while promoting the production of the interleukins, IL-13 and IL-4 (85). Hence, histamine differentially modulates M-MDSC and PMN-MDSC activities (86).

Additionally, cyclooxygenase-2 (COX-2)-synthesized prostaglandin E2 (PGE2), an inflammatory mediator, is upregulated in CRC (87). PGE2 not only induces myeloid cells to secrete procarcinogenic factors, such as IL-6, CXCL1 and G-CSF, that create a tumour-friendly microenvironment, but also promotes tumour proliferation and MDSC activation via STAT3 phosphorylation (87-91). The PGE2 receptor EP1-4, a set of related G protein-coupled receptors, influences MDSC differentiation in CRC (92). In particular, interactions with EP4 promote the differentiation of immunosuppressive M2 macrophages and MDSCs while diminishing the proliferation of immunostimulatory M1 macrophages (93).

Leukotriene B4, a 5-lipoxygenase (5LO) derivative of arachidonic acid, has a chemotactic impact on MDSCs, affecting their aggregation. Reduced 5LO expression is associated with decreased MDSC levels in circulation and diminished ARG-1 and iNOS activity (94,95).

Hypoxia is a common condition within the CRC TME and plays a crucial role in promoting MDSC proliferation. Hypoxia-inducible factor 1α (HIF-1α) stimulates the production of ectonucleoside triphosphate diphosphohydrolase 2 (ENTPD2), and ENTPD2 functions as an exonuclease on MDSCs, significantly contributing to their expansion within the CRC TME (17). Furthermore, hypoxia elevates the levels of vascular endothelial growth factor (VEGF) and its associated molecules. In addition to their known role in angiogenesis, these factors also promote MDSC migration from the bone marrow to the tumour bed (the original tumour site prior to any treatment) thereby enhancing MDSC proliferation in the CRC TME (96,97). Additionally, extracellular vesicles such as exosomes, which are secreted by tumour cells, directly stimulate the formation of MDSCs while modulating their activity, a phenomenon observed in various tumour types, including CRC (98,99).

The presence of gut microorganisms is important for MDSC amplification and normal metabolism in the gastrointestinal tract. A recent study has shown that the accumulation of anaerobic *Pseudomonas aeruginosa* (*Peptostreptococcus anaerobius*) in tumour lesions can mediate MDSC recruitment into the CRC microenvironment and promote IL-23 secretion by MDSCs, which leads to epithelial-mesenchymal transition (EMT) and CRC cell resistance to chemotherapy (100). *Fusobacterium nucleatum* plays a role in the early development of inflammatory bowel disease and colorectal adenomas (101). Patients with CRC with higher levels of *F. nucleatum* in the TME have elevated numbers of both M-MDSCs and PMN-MDSCs and suppressed NK cell numbers, conditions that promote CRC development (102-104).

4. Mechanistic role of MDSCs in CRC

The immunosuppressive functions of activated MDSCs are mediated by intercellular contacts and paracrine or exosomal mechanisms. These functions inhibit immune cell activity,

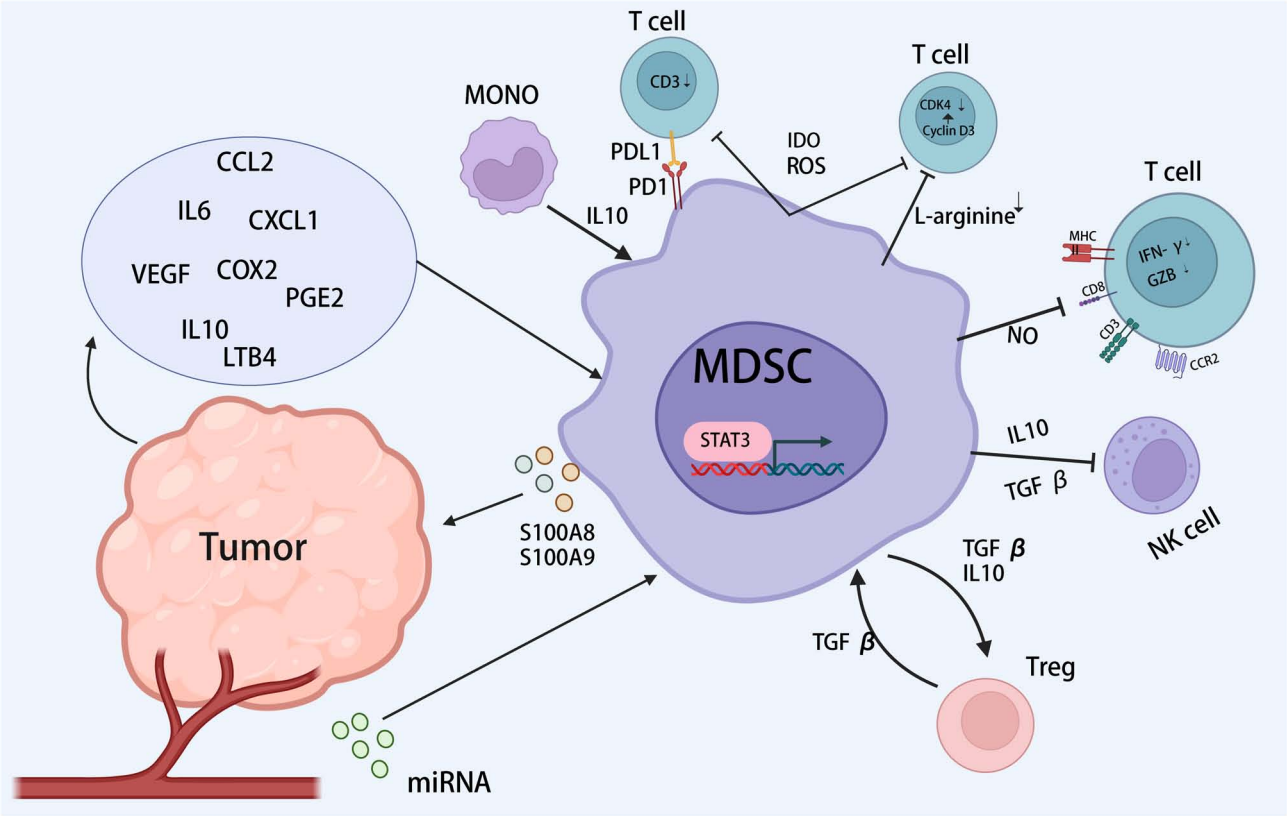

Figure 2. Crosstalk between MDSCs and other cells in the tumour microenvironment. Created with BioRender.com (https://app.biorender.com/). MDSC, myeloid-derived suppressor cell; STAT3, signal transducer and activator of transcription 3; MONO, monocytes; IL-10, interleukin-10; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death protein 1; IDO, indoleamine 2,3-dioxygenase; ROS, reactive oxygen species; MHC, major histocompatibility complex; NO, nitric oxide; TGF-β, transforming growth factor β; S100A8, S100 calcium binding protein A8; CCL2, chemokine (C-C motif) ligand 2; IL-6, interleukin-6; CXCL1, C-X-C motif chemokine ligand 1; VEGF, vascular endothelial growth factor; COX2, cyclooxygenase 2; PGE2, prostaglandin E2; LTB4, leukotriene B4; NK cell, natural killer cell; Treg, regulatory T cell; miRNA, micro RNA.

including the degradation of L-arginine, the production of reactive oxygen and nitrogen species (RONS), engagement of the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, the production of immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β), the suppression of T cells and the induction of other immunosuppressive cells (105-107) (Fig. 2). Among the subtypes of MDSCs, M-MDSCs are characterized by elevated secretion of TGF-β and the inhibitory cytokines, IL-10, ARG-1 and iNOS, which collectively suppress non-specific immune responses. By contrast, PMN-MDSCs predominantly produce high levels of reactive oxygen species (ROS) and PGE2, and influence antigen-specific immune responses through direct cell-to-cell interactions (47).

L-arginine metabolism. The metabolism of L-arginine within the TME is fundamentally associated with the immunosuppressive effects exerted by MDSCs. These cells can metabolize L-arginine through elevated expression of ARG-1 and iNOS, both of which notably suppress T-cell function (20,108,109). The depletion of L-arginine by MDSCs leads to reduced expression of the T cell receptor (TCR)-ζ chain, diminished production of IFN-γ and decreased proliferation of activated T cells (110,111). ARG-1, in particular, transforms environmental arginine into urea and L-ornithine, disrupting T-cell activation by increasing cell cycle protein D3 and cyclin-dependent kinase 4 levels and consequently halting the T-cell cycle at the G0-G1 phase (112). Studies in colon cancer models have shown that ARG-1 impairs the expansion and functionality of $CD8^+$ T cells and NK cells within tumours and hinders the production of inflammatory cytokines and interferon-inducible genes (113,114). iNOS generates nitric oxide (NO), which mediates the suppressive impact of MDSCs on immune cell proliferation and activity (115). Moreover, iNOS-modulated NO participates in the nitration of the chemokine, CCL2, thereby reducing $CD8^+$ T-cell infiltration (81). For instance, G-CSF enhances iNOS levels in MDSCs associated with colitis-linked CRC, thus facilitating tumour immune evasion. Conversely, inhibiting G-CSF reduces iNOS expression in MDSCs, which has been identified as a potential therapeutic target for combating MDSC-induced immunosuppression in CRC (83,116).

ROS production. ROS serve as a principal immunosuppressive mechanism employed by MDSCs. Elevated ROS levels within the CRC microenvironment not only induce oxidative stress that irreversibly destroys DNA, proteins and lipids but also results in cell death (117). ROS also impede antigen-specific T-cell responses by reducing CD3ζ chain expression (106). In addition to NADPH oxidase 2, tumour-derived factors, such as IL-3, IL-6, IL-10, TGF-β, platelet-derived growth factor and GM-CSF enhance ROS production in MDSCs through the

STAT3 pathway (12,107,118). In an MC38 xenograft model, ROS and peroxynitrite synthesized by MDSCs facilitated tumour cell proliferation by causing the nitration of TCRs on $CD8^+$ T cells and suppressing their proliferation (117,119).

Association with the PD-1/PD-L1 axis. A notable study revealed that MDSCs sourced from tumour locations exhibited a distinctive upregulation of PD-L1 compared with splenic MDSCs (120). This differential expression was associated with the selective enhancement of PD-L1 on MDSCs by HIF-1α under hypoxic conditions and was concurrent with a decrease in IL-6 and IL-10 levels in MDSCs, correlated with heightened T-cell activation. Furthermore, the expression of PD-L1 and Fas ligand (FasL) on the surface of MDSCs is associated with induced T-cell apoptosis (120-123). Studies utilizing *in vitro* culture systems and clinical data have revealed that tumour cell-secreted factors such as macrophage CSF and VEGF are responsible for inducing PD-L1 expression in MDSCs (124,125). Notably, the proportion of PD-L1-expressing MDSCs in patients with CRC has been shown to be significantly greater than that in healthy donors and posttreatment patients (126). Additionally, HIF-1α-driven ENTPD2 expression leads to the conversion of extracellular ATP into 5'-AMP, which subsequently hinders MDSC differentiation and perpetuates their immunosuppressive function (127).

Effects on T cells. T cells are a primary target for MDSCs within the TME. MDSCs employ various mechanisms to inhibit T-cell proliferation and counteract T cell-mediated immune responses, including direct contact killing, depletion of essential amino acids crucial for T-cell viability, NO production and reduction of TCR chain expression (128).

The intercellular contact route of MDSCs functions as a key link between inflammation and cancer and is largely facilitated by STAT3 activation. The expression of STAT3 leads to enhanced expression of proapoptotic agents, such as FasL, perforin and granzyme A, in MDSCs and macrophages. This arrangement facilitates the elimination of $CD4^+$ and $CD8^+$ T cells upon direct contact, shifting the balance from tumour immune surveillance to tumour-promoting inflammation (128).

In addition to affecting L-arginine metabolism, the impact of MDSCs on T cells involves cysteine and tryptophan, two additional amino acids vital for T-cell function (111,129). MDSCs express indoleamine 2,3-dioxygenase (IDO), which suppresses T-cell proliferation through cytotoxic metabolite production and depletion of L-tryptophan (130). MDSC proliferation within the TME leads to the exhaustion of cysteine and tryptophan reserves, which are essential for T-cell activity. Concurrently, NO emitted by iNOS decreases major histocompatibility complex class II expression, alters the TCR configuration and inhibits T-cell expansion (61). In addition, increased ROS production not only diminishes TCR chain expression but also hampers the antigen-specific response of $CD8^+$ T cells. Under hypoxic conditions, MDSCs exhibit increased PD-L1 expression to initiate 'immunological braking'. Furthermore, expression of the immunostimulatory receptor, CD40, by MDSCs halts T-cell proliferation. Consequently, T-cell proliferation and functionality are compromised, allowing MDSCs to successfully suppress T-cell immunity (131).

TGF-β and IL-10 are two soluble cytokines secreted by MDSCs that are involved in T cell and NK cell suppression and macrophage polarization, respectively. TGF-β influences the differentiation of CD4 helper T cells into Th1 and Th2 phenotypes by suppressing the expression of the transcription factors, T-bet (also termed TBX21) and GATA3 (132-134). In the context of early gastrointestinal cancer, CD1d-restricted NK T cells induce MDSCs to produce TGF-β through the IL-13/IL4R/STAT6 signalling pathway. This mechanism is evident in the CT26 colon tumour model, where the depletion of this cell group leads to a partial enhancement of the antitumour immune response (135). Furthermore, MDSCs have been noted to thwart antigen-specific $CD4^+$ T cells by secreting TGF-β and IL-10, thereby facilitating the development of inducible $CD4^+CD25^+Foxp3^+$ Tregs in the MCA26 colon tumour model (136). Consequently, immunosuppressive Tregs augment MDSC function, creating an environment favourable for tumour proliferation (136). Additionally, research indicates that IL-10 produced by MDSCs attenuates the T-cell activation typically mediated by DCs (137,138).

Interactions with other immune cells. In patients with CRC, MDSCs play a role in cultivating the immunosuppressive environment. T cell suppression by MDSCs is merely one aspect of this. A spectrum of immune cells, including NK cells, DCs, Tregs, Th17 cells and TAMs, have all been implicated in interactions with MDSCs, as extensively documented in the literature (47).

MDSCs diminish the antitumour activity of NK cells by suppressing NK cell function. This suppression occurs through the downregulation of the NK cell activation receptors natural killer group 2, member D and NKp30, or by curtailing the production of IFN and perforin in a manner dependent on direct cell contact (139). Furthermore, extended periods of inflammation intensify the inhibitory impact of MDSCs on antitumour-activated NK cells through inflammatory mediators, such as IL-10 and PEG2, or soluble factors, such as iNOS, ROS, ARG-1, adenosine and IDO (140).

In addition, MDSCs influence macrophage dynamics, transitioning into M2-type macrophages by downregulating STAT3 and increasing HIF1α levels or by secreting S100A8/9 proteins. This secretion promotes the polarization of TAMs from M1-type to M2-type, with these reoriented M2-type macrophages exhibiting elevated levels of CD206, CD204, VEGF, CD163 and ARG-1 (141,142).

Accordingly, MDSCs have a substantial domino effect on diverse immune cell types within the TME, cumulatively fostering an immunosuppressive milieu conducive to tumour proliferation.

Pre-metastatic niche formation. A critical role of MDSCs is their contribution to cancer metastasis. Liver metastases occur in 20-70% of patients with CRC, whereas lung metastases are present in 10-20% of patients (143). The 'seed-soil' hypothesis suggests that prior to cancer cell dissemination, a favourable microenvironment (or premetastatic niche) is established in tissues prone to metastatic disease (144). Emerging research indicates that MDSC recruitment to the premetastatic niche

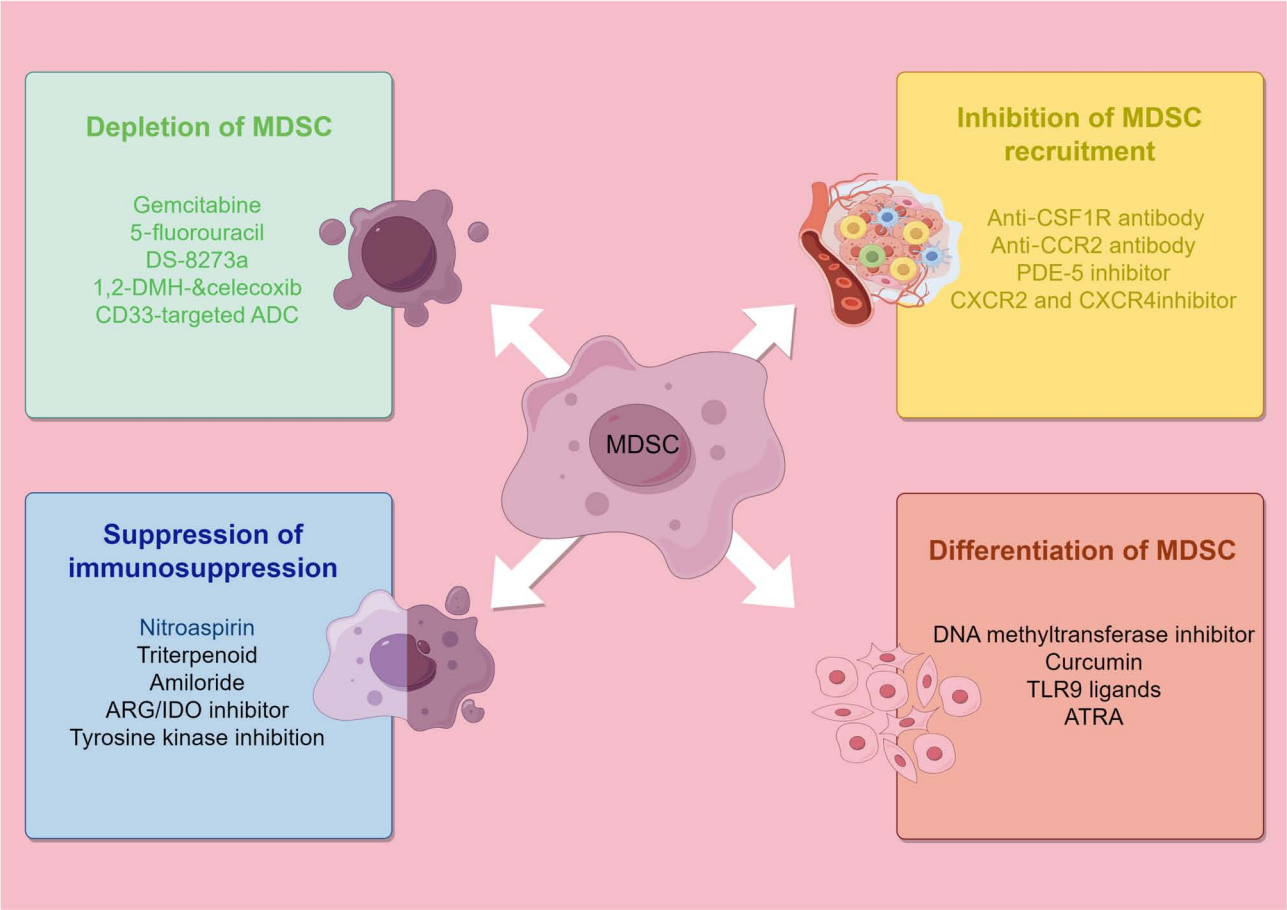

Figure 3. Strategies for targeting MDSCs. The main approaches for targeting MDSCs include: Depleting MDSC populations, preventing MDSC recruitment and migration to the tumour microenvironment, attenuating the immunosuppressive mechanisms of MDSCs and promoting the differentiation of MDSCs into mature non-suppressive myeloid cells such as macrophages and dendritic cells. By Figdraw (https://www.figdraw.com/). MDSC, myeloid-derived suppressor cell; CD33-targeted ADC, CD33-targeted antibody-drug conjugate; CSF1R, colony stimulating factor 1 receptor; CCR2, C-C motif chemokine receptor 2; PDE-5, phosphodiesterase 5; CXCR2, chemokine C-X3-C motif receptor 2; CXCR4, chemokine C-X3-C motif receptor 4; ARG, arginase; IDO, indoleamine 2,3-dioxygenase; TLR9, toll like receptor 9; ATRA, trans-retinoic acid.

of future metastatic target organs is driven by primary tumour cells. For instance, VEGFα secreted by CRC cells prompts TAMs to produce CXCL1 (143), which subsequently attracts circulating CXCR2$^+$ neutrophils and MDSCs to target organs. Additionally, CCL9 from CRC epithelial cells summons IMCs via the CCR1 receptor (145), and CCL2 elicits MDSC recruitment via CCR7 (43).

Amplified MDSCs within target organs increase micro (mi) RNA101 expression in cancer cells, suppressing C-terminal binding protein-2. This mechanism targets key stem cell genes, enhancing cancer cell stemness, inherent tumorigenicity, metastatic potential and drug resistance (146). Moreover, MDSCs directly aid in the survival of metastatic cancer cells (143) and secrete IL-1 receptor antagonists to counteract cancer cell senescence (147). MDSCs also facilitate the establishment of aberrant vascular systems by accumulating matrix metalloproteinases (148), significantly decreasing IFN-γ production and fostering a proinflammatory milieu conducive to EMT (106,149,150). This orchestration remodels the TME, engenders an inflammatory and proliferative state in the target organ, compromises immune defence and supplies preconditioning support for CRC cell colonization, thus supporting cancer cell survival and expansion within the host organ.

5. Targeted MDSC therapy

The inhibitory effects of MDSCs on T-cell responses and multiple cellular functions are critical for antitumour immune responses. MDSCs are positively correlated with the development and spread of cancer, and their presence typically decreases the effectiveness of immunotherapy (151). Given that the accumulation of MDSCs in the TME is considered to be a major obstacle to tumour immunotherapy (152), targeting MDSCs has become a new strategy for tumour immunotherapy. Current clinical studies have focused on four directions (153,154): Depletion of MDSCs, inhibition of MDSC recruitment, suppression of MDSC immunosuppressive function, induction of MDSC differentiation (Fig. 3).

Depletion of MDSCs. The most direct therapeutic strategy for targeted MDSC therapy is MDSC depletion. The selective MDSC inhibitor, gemcitabine, decreases the peripheral blood levels of TGF-β1, PMN-MDSCs and circulating Tregs but has minimal effect on M-MDSCs, which is beneficial for effector T cell proliferation and the recovery of antitumour ability (155,156).

Both subtypes of MDSCs are sensitive to 5-fluorouracil (5-FU), whereas other immune cells, such as T cells, B cells, DCs and NK cells, are not significantly affected (157). In a mouse EL4 (loaded mouse) model, 5-FU enhanced T cell-dependent antitumour responses by inducing the apoptosis of MDSCs in the TME and spleen and by promoting the production of high levels of IFNγ by tumour-infiltrating T cells (158). Patients with CRC may experience less immunosuppression and improved clinical results if they follow the FOLFOX (folinic acid, 5-FU and oxaliplatin) regimen, which may be linked to a decrease in MDSC counts and the restoration of antitumour immunity (159). The administration of celecoxib, a selective COX-2 inhibitor, significantly reduces the frequency of $Gr1^+CD11b^+$ immature myeloid suppressor cells during 1,2-dimethylhydrazine diHCl chemotherapy in CRC mice, while increasing splenic lymphocyte numbers and tumour lymphocyte infiltration (160). In addition, the administration of bevacizumab (anti-VEGF) therapy to patients with CRC results in a decrease in the concentration of immature progenitor cells, with a moderate increase in the number of DCs in the peripheral blood (161). Notably, the use of a TNF-related apoptosis-inducing ligand receptor 2 agonistic antibody (DS-8273a) decreased the number of MDSCs in the peripheral blood of patients with CRC without affecting the proportions of myeloid and lymphoid cell populations. Unfortunately, MDSC numbers were restored to pretreatment levels by day 42 in most patients (162). Gemtuzumab ozogamicin, an anti-CD33 immunotoxin agent, was effective in eliminating MDSCs and reactivating T cells and chimeric antigen receptor T cells in a wide range of cancer types, including CRC (163).

Inhibition of MDSC recruitment. By preventing MDSCs from responding to chemokines, the inhibition of MDSC recruitment can effectively reduce the proportion of MDSCs in the TME and periphery (164,165). Chemokine antagonists help prevent MDSCs from entering the tumour site, thus modifying the immunosuppressive microenvironment (166). As an essential chemokine receptor for MDSC transport (167,168), CXCR2 inhibitors interrupt the CXCR2/CXCL pathway, effectively reducing MDSC infiltration and improving cytotoxic T-cell function (58,169). Additionally, the CCR5/CCL5 axis is essential for tumour progression as it promotes tumour invasion and MDSC migration to the tumour site (170). Targeting the CCR5/CCL axis inhibits the progression and invasiveness of a wide range of tumours (171-174). mCCR5-Ig reduces the migration of MDSCs and Tregs without affecting effector T-cell recruitment to the TME (170). The CSF-1 receptor (CSF-1R), a well-defined target of MDSC recruitment, induces the formation of MDSCs and their transport to the tumour site (175). CSF-1R inhibitors interrupt the CSF-1R signalling pathway, resulting in MDSC ablation or inhibition of their tumour-promoting function and reprogramming of TAMs (154,176-178). A study demonstrated that in an azomethane/dextran sulfate sodium-induced model of colon carcinogenesis, the phosphodiesterase-5 inhibitor, sildenafil, directly inhibited MDSC infiltration into tumour tissues, modulating inflammation in the TME (179). In addition, Liang *et al* (180) reported that anti-CCR2 antibody treatment reduced radiotherapy-induced M-MDSC infiltration in colon cancer.

Suppression of the immunosuppressive function of MDSCs. Inhibiting the immunosuppressive mechanisms of MDSCs is the main therapeutic approach for restoring T-cell activity and successful immunotherapy. MDSCs suppress the immune system by affecting L-arginine metabolism through the production of ARG and NOS (107). In a CRC mouse model, nitroaspirin modulated the immune status of the tumour host by increasing the number and function of tumour antigen-specific T cells through the inhibition of ARG and NOS activity (181). AT38 (a reactive nitrogen inhibitor) (182) reduced the iNOS and ARG-1 levels in a CRC mouse model while effectively reducing the nitration of MDSC chemokines (81). A study revealed that tyrosine kinase inhibition by sunitinib reduced phosphorylated STAT3 and ARG levels in M-MDSCs, inhibited MDSC function and increased T-cell proliferation (183). Another study showed that methyl bardoxolone, a synthetic triterpenoid, inhibited MDSC function by decreasing ROS in mouse MC38 tumour hosts; however, it did not affect ARG-1 or NO levels (184). Notably, amiloride, a drug used to treat hypertension, inhibits the formation of tumour-derived exosomes and reduces the inhibitory function of MDSCs in human CRC and mouse models (185). The inhibition of MDSC metabolic processes is also a novel idea, and the metabolic reprogramming of glycolysis and oxidative phosphorylation can inhibit the immunosuppressive function of tumour MDSCs. The most common metastatic target organ for CRC tumours is the liver (186). A study of hepatocellular carcinoma showed that IL-37 significantly affected the expression of genes related to ATP synthesis and hydrolysis in MDSCs through metabolic reprogramming in patient-derived tumour xenograft model mice and that the glycolytic and oxidative phosphorylation processes of MDSCs were promoted and ATP release was upregulated (187). Thus, the immunosuppressive ability of MDSCs was weakened and tumour development was suppressed.

Induced differentiation of MDSCs. Induction of MDSC differentiation is another therapeutic approach used to target MDSCs and promoting their continued differentiation into mature myeloid cells can reduce their immunosuppressive effects (106). MDSCs are rapidly differentiated into mature myeloid cells, such as DCs and macrophages, in response to all-trans retinoic acid (ATRA), a metabolic intermediate of vitamin A, and ATRA improves T-cell responses in patients with cancer through specific upregulation of glutathione synthase in MDSCs and reduced ROS production (25,188-190). In a CRC mouse model, curcumin administration reduced the number of PMN-MDSCs, activated STAT3 and NF-κB in MDSCs and induced the differentiation of M-MDSCs into cells with an M1-like phenotype (191,192). Daurkin *et al* (193) demonstrated that in the presence of DNA methyltransferase inhibitors, tumour-infiltrating CD11b myeloid cells differentiate into mature myeloid cells. In addition, the activation of Toll-like receptor-9 by CpG promotes MDSC maturation and differentiation and effectively reduces the proportion of $Ly6G^{high}$ MDSCs in CRC tumour models (194).

Other prospective therapeutic strategies. Immune checkpoint blockade (ICB) therapies targeting PD-1, PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have

revolutionized gastrointestinal tumour treatment options in recent years. In preclinical studies, a decrease in the number of MDSCs was detected in patients who received CTLA4 or PD-1/PD-L1 treatment (195-197). A recently published study indicated that the presence of MDSCs is strongly associated with the transformation of premalignant states, metastasis, recurrence and resistance to digestive malignancies. MDSCs express immunosuppressive ligands such as PD-L1 to antagonize the antitumour response of the immune system; therefore, diminishing MDSCs in the TME enhances the outcome of anti-PD-1 therapy (131). However, immune checkpoint inhibitors demonstrate poor efficacy in patients with CRC with immune checkpoint resistance and microsatellite stable (198). Promising melanoma research indicates that the targeting of the CD300 molecule family member d (CD300ld), a tumour surface immunosuppressive receptor, could be combined with anti-PD1 therapy for the treatment of digestive system cancer. CD300ld is specifically upregulated in PMN-MDSCs, is a pivotal receptor regulating the recruitment and immunosuppressive function of PMN-MDSCs and represents the immune system 'braking site' (199). In mice, targeting CD300-ld remodels the tumour immune microenvironment by suppressing the recruitment and function of PMN-MDSCs, resulting in a broad-spectrum antitumour response. More concretely, CD300ld upregulates S100A8/A9 expression through STAT3 activation, forming the CD300ld/STAT3/S100A8/A9 axis and thereby facilitating the immunosuppressive function of PMN-MDSCs (199).

6. Limitations of therapies targeting MDSCs and the landscape

The establishment of an immunosuppressive TME is one of the key mechanisms by which these CRC cells evade the immune system. In recent years, MDSCs have been shown to play a crucial role as major contributors to this process. Studies targeting MDSCs are mainly focused on the multiple major directions of MDSC expansion, namely migration, activation, recruitment, action and metastasis (131). Based on the studies published thus far, targeting MDSCs has been shown to reduce the tumour load and represent a promising therapeutic strategy for CRC (153). In the present review, the clinicaltrials.gov website was searched and the therapeutic approaches involving MDSCs and different treatment regimens for CRC are selectively summarized in Table I.

Although studies targeting MDSCs have reported notable results, the existence of potential limitations constrains the continued advancement of strategies targeting MDSCs. First, MDSCs have a short half-life (200-202), and the strategy of MDSC depletion in the peripheral blood negatively feeds back to the bone marrow (203,204), which increases the risk of MDSC recurrence and accumulation and promotes CRC development. More effective therapies may aim to block MDSC differentiation in the bone marrow, inhibit MDSC migration to affected tissues or manipulate the tissue microenvironment. Second, current targeted therapies for MDSCs are focused on reducing the number of MDSCs that have been generated or on inhibiting their function, with fewer strategies targeting MDSC-induced migration (33). Third, due to the large phenotypic heterogeneity of MDSCs, complex amplification and functional networks, different subgroups of MDSCs use different mechanisms to suppress the immune system, making current therapeutic strategies targeting MDSCs only partially effective. Therefore, further investigations into the molecular phenotypes of MDSCs and their mechanisms in tumour tissues are urgently needed, and the development of therapeutic strategies targeting MDSC subgroups is essential for improving the effectiveness of tumour therapy (12). In addition, based on the summary provided in the present review, cancer cells and MDSCs in primary tumours can directly or indirectly promote metastatic premetastatic niche formation, but the mechanistic similarities and differences in the interactions between the TME and the premetastatic niche remain topics worth exploring (143). Moreover, the TME is very complex and is composed of multiple immune cells and cytokines that form a complex network. It is therefore difficult to achieve the expected effect by exclusively targeting MDSCs, and a more desirable therapeutic effect may be achieved by co-targeting other cells or targets to enhance the immune system or utilizing special contact modalities such as exosomes (33).

Iron-mediated death is a unique form of cell death driven by the accumulation of lipid peroxides. A study on iron death induction and gastric cancer reported that inhibition of the Wnt/β-catenin signalling pathway reduced the expression of the transcription factor, TCF4, inhibited glutathione peroxidase 4 gene transcription and promoted iron death, resulting in a decrease in both tumour weight and volume (205), suggesting the feasibility of the induction of iron-mediated death for the treatment of gastrointestinal tumours. The triple combination of MDSC blockade with iron-mediated death induction and ICB therapy greatly restored tissue immune surveillance and promoted a normal immune response. This treatment inhibited tumour growth and represented a promising strategy for targeted therapy of CRC (206).

Exosomes in the TME act as carriers of molecular delivery exerting indirect effects on MDSC expansion, formation of an immunosuppressive environment (48), cancer cell growth and invasion (207,208) and therapy resistance (209), and direct promotion of CRC cell stemness through S100A9 (210). Under IL-6 induction, PMN-MDSCs synthesize increased exosomal miR-93-5p, which promotes the differentiation of M-MDSC into M2 macrophages and increases CRC risk (211). Compared with healthy individuals, patients with CRC have significantly increased exosomal miR-19a levels in the serum and have a poorer prognosis (212,213). This suggests that exosomes in the TME have the potential to be another potential target in treating CRC.

Therefore, from the perspective of patients with CRC, the strategy of targeting MDSCs requires more comprehensive and refined research and clinical trials, but it remains a promising class of therapeutic strategy due to its special immunosuppressive effects in the TME.

7. Summary and conclusions

In the present review, the nomenclature history of MDSCs along with the two main subtypes, PMN-MDSCs and M-MDSCs, were systematically and comprehensively reviewed and the recruitment, role and metastatic mechanisms of MDSCs in the CRC microenvironment were revealed. Mutations in genes

Table I. Clinical trials targeting MDSCs in colorectal cancer.

First author/s, year	Compound	Therapeutic target	Combination drug	ClinicalTrials.gov ID	Clinical phase	Trial status	Study type	(Refs.)
Javle *et al*, 2021	[a]INCB001158	Arginase	Pembrolizumab	NCT02903914	Phase 2	Completed	Interventional	(218)
Lorentzen *et al*, 2022	Arginase-1 peptide vaccine	Arginase-1	N/A	NCT03689192	Phase 1	Completed	Interventional	(219)
/	Vicriviroc (MK-7690)	CCR5	Pembrolizumab	NCT03631407	Phase 2	Completed	Interventional	/
/	PLX3397	CCR5	N/A	NCT01349036	Phase 2	Completed	Interventional	/
Zeng *et al*, 2022	Maraviroc	CCR5	N/A	NCT01736813	Phase 1	Completed	Observational	(220)
/	Pexidartinib	CSF-1R	Durvalumab	NCT02777710	Phase 1	Completed	Interventional	/
Snajdauf *et al*, 2021	DS-8273a	TRAIL-R2 (DR5)	Nivolumab	NCT02991196	Phase 1	Terminated	Interventional	(221)
Isambert *et al*, 2018	Anakinra	IL-1R + VEGF	LV5FU2 + Bevacizumab	NCT02090101	Phase 2	Completed	Interventional	(222)
Schmitz-Winnenthal *et al*, 2018	VXM01	VEGFR2	N/A	NCT02718430	Phase 1	Completed	Interventional	(223)
Johnson *et al*, 2022	SX-682	CXCR1/2	Nivolumab	NCT04599140	Phase 2	Recruiting	Interventional	(224)
/	Tecemotide (L-BLP25)	MUC1	CPA	NCT01507103	Phase 2	Completed	Interventional	/
Hanna *et al*, 2021	Avelumab	PD-L1	Capecitabine	NCT03854799	Phase 2	Completed	Interventional	(225)
Lizardo *et al*, 2020	Anti-PD-1	PD-L1	Radiotherapy	NCT04001101	Phase 2	Withdrawn	Interventional	(226)
Hull *et al*, 2023	EPA	Gut bacteria	N/A	NCT04682665	Phase 3	Recruiting	Observational	(227)

[a]An arginase inhibitor; CCR5, C-C motif chemokine receptor 5; CSF-1R, colony-stimulating factor 1 receptor; TRAIL-R2 (DR5), human tumour necrosis factor related apoptosis inducing ligand 2; IL-1R, interleukin 1 receptor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; CXCR1/2, chemokine C-X3-C motif receptor 1/2; MUC1, mucin 1; CPA, cyclophosphamide; PD-L1, programmed cell death ligand 1; EPA, eicosapentaenoic acid; N/A, not applicable.

such as KRAS, adenomatous polyposis coli, BRAF and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (214,215), epigenetic modifications of m6A, chemokines in the CC and CXC families, inflammatory mediators, alterations in intestinal microbes and hypoxic environments may cause local aggregation of MDSCs and increase the risk of CRC.

The present review proposes that MDSCs possess two main features: Immunosuppression and metastasis. MDSCs achieve immunosuppressive functions by generating RONS, degrading L-arginine, secreting immunosuppressive cytokines via intercellular contact, paracrine or exocrine mechanisms (216), inhibiting T cell and NK cell toxicity and inducing other immunosuppressive cells, such as Tregs, to achieve immunosuppressive functions and provide favourable conditions for cancer cell survival and growth (217). MDSCs are recruited and expanded to support immunosuppression. MDSCs inhibit normal T cell proliferation in patients with CRC, resulting in poor prognosis. The recruitment of expanded MDSCs enhances cancer stem cell gene expression, directly promotes metastatic cancer cell survival, antagonizes cancer cell senescence and acts as a crossroads between tumour angiogenesis and immunosuppression to provide precursor support for CRC metastasis; therefore, the presence of MDSCs is important for CRC cells to colonize, survive and grow in target organs. Increased MDSC and tumour miRNA101 expression also predicts poor survival.

In addition, the present review comprehensively summarized four types of potential therapeutic strategies for CRC: Depletion of produced MDSCs, inhibition of MDSC recruitment, suppression of MDSC immunosuppression and induction of MDSC differentiation. The primary TME can promote premetastatic niche formation, but the mechanism underlying the interaction between the primary TME and premetastatic niche formation during the process of metastasis initiation requires further investigated.

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Authors' contributions

WZ and SJ wrote the manuscript. HL and YM drew all the figures and tables of the article. WZ, HY, ZZh and WH revised the article. HY, ZZh and MW provided many suggestions for the writing of the article. ZZo designed the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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