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The immunosuppressive role of MDSCs in HCC: mechanisms and therapeutic opportunities

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Abstract

Hepatocellular carcinoma (HCC) is a prevalent malignancy with a significant global burden. Despite substantial advancements in HCC treatment in recent years, therapeutic efficacy remains constrained by immune evasion mechanisms within the tumor microenvironment (TME). Myeloid-derived suppressor cells (MDSCs), as critical immunosuppressive elements of the TME, have garnered increasing attention for their role in tumor progression. Recent studies emphasize their central involvement in promoting immune evasion, tolerance, and immunosuppression in HCC. This review examines the contributions of MDSCs to HCC pathogenesis, elucidates their underlying mechanisms, and discusses ongoing clinical trials, emphasizing their potential as therapeutic targets for improving clinical outcomes.

Introduction

Liver cancer is the sixth most prevalent malignancy globally and the third leading cause of cancer-related mortality. Hepatocellular carcinoma (HCC) accounts for 75-85% of all primary liver cancers, making it the most common type [1]. In recent years, substantial advancements have been achieved in HCC treatment, including chemotherapy, Transcatheter Arterial Chemoembolization (TACE) treatment, surgery, liver transplantation, and immunotherapy [2–5]. Despite these innovations, challenges such as drug resistance, metastasis, and recurrence continue to impede significant improvements in patient outcomes, with the underlying mechanisms remaining poorly understood [6–9]. A large number of studies have shown that the TME plays a crucial role in therapy resistance [10, 11]. It not only influences the outcome of treatment but also undergoes continuous remodeling and adaptation influenced by the treatment process [10]. As a result, understanding the role and mechanisms of the tumor immune microenvironment becomes particularly important.

Multiple immunosuppressive cell populations within the TME have been identified to drive tumor growth and metastasis. For instance, regulatory T cells (Tregs), MDSCs, and tumor-associated macrophages (TAMs) are strongly associated with poor prognosis in HCC [12–15]. As a key component of the TME, MDSCs have attracted increasing attention in recent years due to their unique immune suppressive mechanisms [16, 17]. Increasing evidence highlights the pivotal role of MDSCs in regulating both innate and adaptive immune responses.

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Specifically, It can directly inhibit effector T cells and NK cells through various mechanisms, and further potentiate immune suppression by promoting the differentiation of other inhibitory immune cells, such as Tregs and TAMs [18–20]. Our previous clinical studies demonstrated that the frequency of MDSCs in HCC patients was significantly higher compared to that in chronic hepatitis B patients and healthy individuals [21, 22]. This observation has been corroborated by subsequent studies, which collectively show a marked elevation of MDSCs levels in HCC patients, particularly in advanced stages. Moreover, MDSC infiltration scores are negatively correlated with the survival time of HCC patients [23, 24]. Thus, targeting MDSCs represents a promising strategy for preventing HCC progression.

MDSCs are also closely associated with the treatment of HCC. For instance, radiofrequency ablation (RFA), as an effective curative method, is recommended for early-stage HCC treatment. However, studies have shown that after RFA treatment, peripheral blood PMN-MDSC significantly proliferate, promoting the progression of residual HCC, which is closely associated with poor prognosis [25]. And in TACE treatment, changes in eMDSC are not significant, but mononuclear mMDSC significantly decrease [26]. On the other hand, targeted therapy and immunotherapy have made better progress. For example, the combined use of bevacizumab and atezolizumab significantly reduces MDSC numbers and markedly improves progression-free survival in HCC patients [27]. Given the different roles of MDSCs in treatment, studying them is highly meaningful.

In this review, we provided a comprehensive summary of the currently identified marker genes of MDSCs and elucidated their mechanisms of action in driving immunosuppression and tumor immune evasion in HCC. Additionally, we compiled in vivo and in vitro studies related to MDSCs, highlighting their potential as therapeutic targets. Furthermore, we collected ongoing clinical trials involving MDSCs, aiming to offer insights for future research and the development of novel therapeutic strategies.

The origin and phenotype of MDSCs

MDSCs originate from the differentiation of common myeloid progenitors (CMPs). Hematopoietic progenitor cells (HPCs) first differentiate into CMPs, which further differentiate into immature myeloid cells (IMCs). In healthy individuals, IMCs continue to mature into neutrophils, macrophages, or dendritic cells. However, under pathological conditions, the normal differentiation of IMCs can be blocked by inflammatory mediators or tumor-derived cytokines, inducing their transformation into MDSCs [28–30]. The main controversy and technical challenge in studying MDSCs lies in the lack of unique identification markers, as their phenotype and morphology are highly similar to those of monocytes and neutrophils [31]. Traditionally, MDSCs are identified by $CD33^+$, $CD11b^+$ and $HLA\text{-}DR^-$ markers and are further classified into monocytic MDSCs and polymorphonuclear MDSCs based on $CD14^+$ and $CD15^+$ expression [32, 33]. MDSC classification in mice is relatively well-established, characterized by the expression of myeloid markers such as CD11b and Gr-1 [34]. Specifically, M-MDSCs are typically identified as $CD11b^+$ $Ly6C^{high}$ $Ly6G^-$, while PMN-MDSCs are recognized as $CD11b^+$ $Ly6C^{low}$ $Ly6G^+$ cells [35]. In contrast, the definition of MDSCs in human remains debated. The most widely accepted classification currently recognizes three major subgroups: M-MDSCs, characterized as $CD14^+CD15^-$, and PMN-MDSCs, characterized as $CD15^+CD14^-$, both of which exhibit $CD11b^+HLA\text{-}DR^-$ expression [34, 36]. Additionally, there is a subgroup called eMDSC, consisting of incompletely differentiated precursor cells, with molecular markers including $CD11b^+Lin^-HLA\text{-}DR^-CD33^+CD14^-CD15^-$ [37]. In recent years, with the rise of high-throughput sequencing technologies, several new markers have emerged, offering promising avenues for further research and understanding of MDSCs (Fig. 1).

New markers for PMN-MDSCs

In recent years, there have been significant breakthroughs in identifying markers for PMN-MDSCs. Lectin-like oxidized LDL receptor-1 (LOX-1) was first reported as a novel marker for PMN-MDSCs [38]. $LOX\text{-}1^+$ PMN-MDSCs exhibit elevated levels of NADPH oxidase NOX2 and arginase I. These cells are capable of suppressing T cell activity by reducing T cell proliferation and interfering with interferon-gamma (IFN-γ) production [39]. Compared to healthy controls and patients with other liver diseases (such as chronic hepatitis B and cirrhosis), HCC patients exhibited a significant increase in $LOX\text{-}1^+$ $CD15^+$ PMN-MDSCs, and this increase was also strongly associated with poorer overall survival [39]. Moreover, study by Wang et al. revealed CD300ld as a new functionally highly conserved tumor immune inhibitory receptor that is specifically highly expressed on PMN-MDSCs. CD300ld promotes the migration of PMN-MDSCs to tumors and enhances their T cell-suppressive function through the STAT3-mediated regulation of downstream S100A8/A9 proteins. Furthermore, blocking CD300ld can reshape the tumor immune microenvironment, and showing synergy with anti-PD1 antibody treatment [40]. Thus, CD300ld serves as a novel marker for PMN-MDSCs and provides a promising new target for cancer immunotherapy. A recent

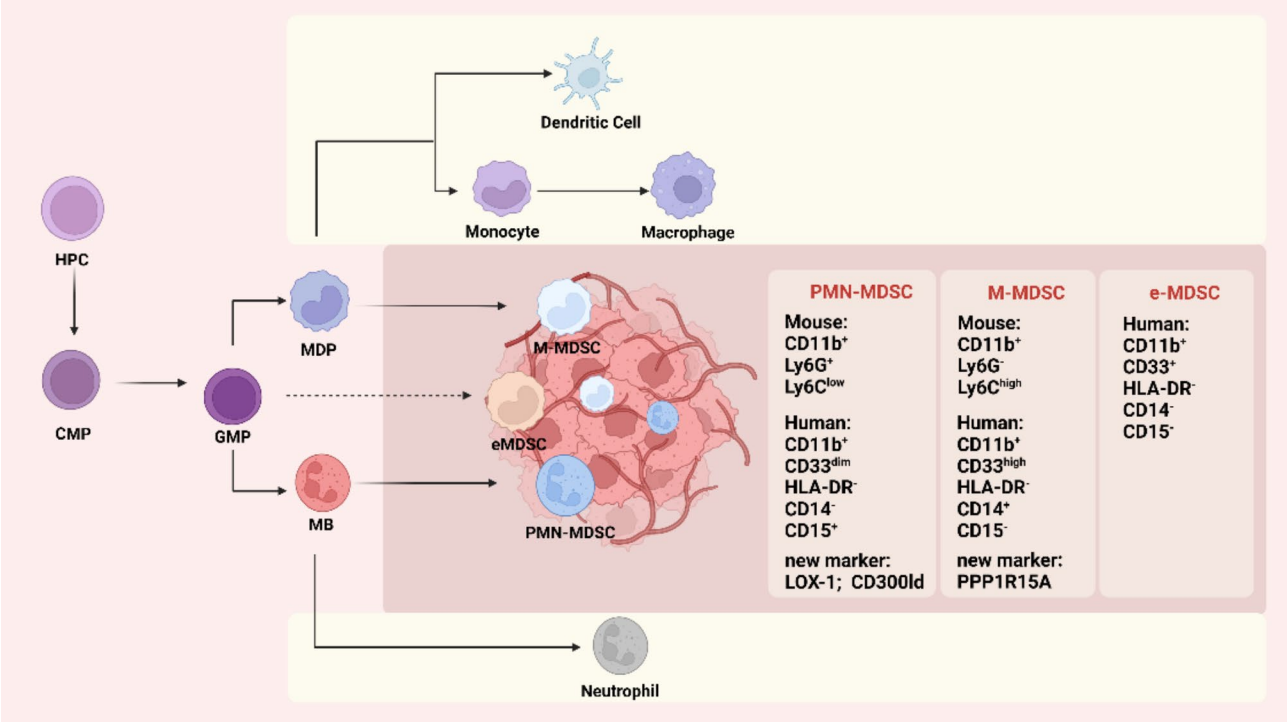

Fig. 1 Origins and markers of MDSCs. HPC: hematopoietic progenitor cell; CMP: Common Myeloid Progenitor; GMP: Ganulocyte-Monocyte Progenitor; MDP: Monocyte-Dendritic cell progenitor; MB: Myelocyte; M-MDSC: monocytic MDSC; PMN-MDSC: polymorphonuclear MDSC; e-MDSC: early-stage MDSC

scRNA-seq study reveals that CD84 may serve as a new marker for PMN-MDSCs. CD84 is highly expressed in MDSCs isolated from primary breast tumors in mice. In human PMN-MDSCs, CD84 is co-expressed with LOX-1, and these cells exhibit elevated ROS production and potent T cell-suppressive capacity [41]. However, whether CD84 also serves as a common marker for MDSCs in HCC remains to be further investigated.

New markers for M-MDSCs

Although significant progress has been made in identifying new markers for PMN-MDSCs, research on M-MDSCs remains relatively limited. Currently, the identification of M-MDSCs mainly relies on monocyte-related markers, in combination with the immunosuppressive features of MDSCs. PPP1R15A, a protein involved in endoplasmic reticulum stress, may serve as a potential new marker for M-MDSCs. In HCC patients with liver fibrosis, PPP1R15A expression is significantly upregulated in M-MDSCs, which enhances the immunosuppressive capacity on T cells by promoting ARG1 and S100A8/9 expression. Furthermore, PPP1R15A^{+} M-MDSCs are closely associated with poor prognosis and low response to ICB therapy in HCC patients. Selective inhibition of PPP1R15A can disrupt the immunosuppressive barrier formed by M-MDSCs [42].

Markers for eMDSCs

Studies on the surface markers for eMDSCs remain lacking. As a newly defined type of MDSC, existing studies have only shown that it maintains a consistently undifferentiated state [43]. Typically, eMDSCs in humans are identified by the markers CD11b^{+}Lin^{-}HLA-DR^{-}CD33^{+}CD14^{-}CD15^{-} [44]. Under this identification standard, studies have shown that eMDSCs are the primary immunosuppressive cells in the tumor immune microenvironment of breast cancer tissues, capable of promoting EMT of tumors and inducing immune evasion [43]. However, an earlier study found that after undergoing microsphere transarterial chemoembolization (mTACE) treatment, the frequency of M-MDSCs in HCC patients significantly decreased, while the frequency of eMDSCs remained stable [26]. A similar conclusion was observed in ovarian cancer [45]. How can these contrasting results be explained? It has been suggested that the markers of eMDSCs overlap to some extent with those of basophils, ovarian cancer patient blood contained 58% of cells with e-MDSC surface markers, and 36% in ascites, which researchers identified as basophils based on CD123^{high} expression and cytology. Therefore, the precise quantification of eMDSCs in circulation should be approached with caution [37]. This viewpoint undoubtedly provides a new approach to eMDSC

research and prompt a reevaluation of the validity of surface markers for eMDSCs. Therefore, eMDSCs should not be defined solely by surface markers but should also consider the presence of basophils and their functional characteristics.

In summary, due to the high heterogeneity of MDSCs in tumor progression, the identification of new biomarkers for MDSCs remains essential. However, the shared genetic features between MDSCs and normal monocytes and neutrophils pose significant challenges for their phenotypic identification. To some extent, it is still necessary to evaluate their immunosuppressive functions to accurately determine the cell type. Although recent advances in emerging technologies, such as single-cell sequencing and spatial transcriptomics, have contributed to progress in MDSC biomarker research, studies on MDSC biomarkers in HCC remain relatively limited. In the future, it will be necessary to integrating multi-omics data, functional validation, and dynamic studies to further explore specific biomarkers of MDSCs, thereby offering more precise targets for tumor immunotherapy.

Recruitment, accumulation, and activation of MDSCs

The recruitment, accumulation, and activation of MDSCs have long been central topics in MDSC research. The tumor creates a highly favorable survival environment for MDSCs, including factors such as hypoxia, nutrient deprivation, acidosis, endoplasmic reticulum (ER) stress, and chronic inflammation [46–48]. Growth factors (e.g., GM-CSF, M-CSF, G-CSF), cytokines (e.g., IL-6, IL-1β, TNF), DAMPs, and PAMPs exploit this environment to promote the generation, recruitment, and activation of MDSCs [44, 49] (Fig. 2).

Key factors driving MDSC recruitment

Hypoxia is one of the key distinguishing features between the TME and peripheral lymphoid organs [50]. MDSCs often accumulate in the hypoxic regions of HCC, and hypoxia-inducible factors (HIF) are key regulatory factors

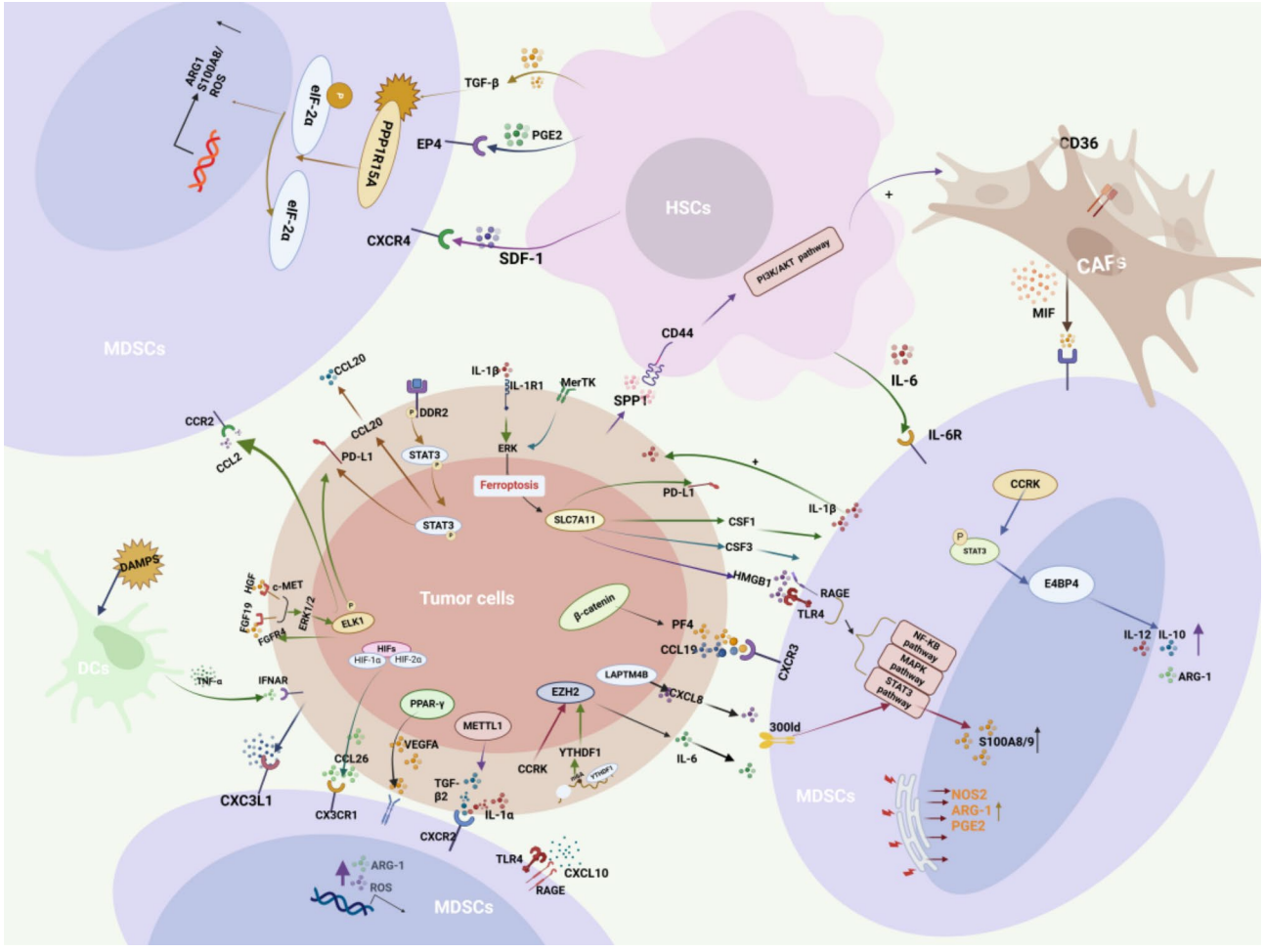

Fig. 2 Recruitment and activation of MDSCs. HSCs: Hepatic Stellate Cells; CAFs: cancer-associated fibroblasts; DCs: Dendritic Cells

for MDSC recruitment [51]. Previously, it was believed that HIF-1α regulates MDSC function via a STAT3-dependent pathway [52, 53]. It can also promote MDSC differentiation and proliferation by enhancing the expression of glycolytic enzymes and lactate transporters [54]. Recent study has reveal that CCL26 is the major hypoxia-induced chemokine. It interacts with the CX3CR1 receptor on MDSCs to promote their recruitment [55]. In addition to inducing the expression of chemokines, hypoxia also stimulates the enhanced expression of ENTPD2, promoting the conversion of extracellular ATP to 5'-AMP, thereby inhibiting MDSC maturation and differentiation [56].

The primary factors driving the recruitment of PMN-MDSCs and M-MDSCs to the tumor are similar to those regulating the recruitment of granulocytes and monocytes. M-MDSCs and monocytes are primarily recruited by chemokines such as CCL2 and CCL5 [57], while PMN-MDSCs are recruited by CXCL1, CXCL5, CXCL6, CXCL8, and CXCL12 [58, 59]. Recent studies have shown that the CXCR family plays a significant role in cancer progression and MDSC migration in HCC patients. It was found that PF4 and CCL9 can promote the recruitment of MDSCs to the TME by binding to the CXCR3 chemokine receptor on their surface [60, 61]. Similarly, CXCR2 also demonstrates significant potential, and it may promote MDSC accumulation through the CXCL1-CXCR2 axis [62], [63]. In addition to mediating communication between tumor cells and MDSCs, chemokines also mediate crosstalk between stromal cells and MDSCs. Tumor-associated fibroblasts (TAFs) can induce the conversion of $CD14^+$ monocytes to $CD14^+HLA\text{-}DR^{-/low}$ MDSCs through the interaction of stromal-derived factor (SDF-1) and CXCR4 [64], while activated hepatic stellate cells can also regulate MDSC migration via the SDF-1-CXCR4 axis [65].

Signaling pathways and ER stress in MDSC activation

The recruitment to the TME is only the first step in the function of MDSCs, others signals are needed to activate them and enable their immunosuppressive properties. These signals are typically mediated by signal transducers and transcriptional activators such as STAT1, STAT3, STAT6, and NF-κB transcription factors [66, 67], and it has been further demonstrated in recent studies [68, 69]. Moreover, the CXCL10-TLR4-MMP14 signaling pathway also may exacerbate HCC recurrence by promoting M-MDSC mobilization [70]. HMGB1, a potent MDSC recruitment factor, has traditionally been understood to promote MDSC function by binding to TLR4 and RAGE receptors, activating NF-κB, MAPK, STAT3, and other signaling pathways [69]. It is important to note that, in previous studies, HMGB1 was primarily considered an extracellular cytokine that activates cell membrane receptors [71]. However, recent research has found that nuclear HMGB1 is crucial for the maintenance of CD8 T cells and IFN-γ production, contributing to anti-tumor immunity [72]. Therefore, the role of nuclear HMGB1 in HCC and its ability to balance the interaction between MDSCs and CD8 T cells remains an area of active research. Moreover, recent studies have shown that Galectin-8 can also induce the expansion of M-MDSCs and bind to the LILR4 receptor on MDSCs, promoting their proliferation through the STAT3 and NF-κB pathways [67].

Several studies have shown that ER stress is involved in the suppressive behavior of MDSCs in tumor-bearing hosts. It has been found that $LOX\text{-}1^+$ $CD15^+$ PMN-MDSCs display higher levels of ER stress markers, and ER stress is also involved in the immunosuppressive activity of $PPP1R15A^+$ M-MDSCs [40, 42]. Based on these studies, ER stress appears to have some regulatory effect on both PMN-MDSCs and M-MDSCs. However, it is important to note that an earlier study found that ER stress did not affect M-MDSC function in chronic infection. In a gene knockout study targeting three typical ER stress pathways: PERK, IRE1α, and ATF6 [73], and there was no change observed in the immunosuppressive capacity of M-MDSCs in chronic infection. In contrast, knockout of IRE1α and ATF6 affected the suppressive function of PMN-MDSCs, modulating their immunosuppressive activity by regulating the expression of Nos2, Arg1, and PGE2 [41]. In summary, while the regulatory role of ER stress in PMN-MDSC function is well-recognized, it remains unclear whether ER stress also affects M-MDSC function and through which pathways, warranting further investigation.

Gut microbiota and stromal cells in MDSC regulation

In recent years, an increasing number of studies have demonstrated a close relationship between the gut microbiota and HCC, involving dysbiosis, abnormal bacterial metabolites, and immune system disorders [74]. One study found that Gram-negative bacteria/LPS controls hepatocytes to establish an immunosuppressive microenvironment by inducing $CXCR2^+$ PMN-MDSC accumulation through TLR4-dependent CXCL1 production, thus promote liver tumor growth [75]. Interestingly, in advanced liver cancer patients with bacterial infections, antibiotics are typically used. However, early use of antibiotics significantly reduced the number of tumor-infiltrating T cells and NK cells in the liver, while increasing the proportion of MDSCs and γδT cells [76]. It is evident that the gut microbiota and its interactions with the immune system play a dual role in the progression of HCC, and further research is needed to better understand its mechanisms.

In addition to the CXCR family, CCL19, CCL20, SIRPα, YTHDF1, DDR2, and others have been found to promote the recruitment and activation of MDSCs [23, 77–79]. It is worth noting that many earlier studies focused on tumor cell-secreted factors mediating the accumulation and function of MDSCs, while more recent studies have extended to the direct or indirect influence of stromal cells on MDSCs. Tumor cells secrete cytokines and growth factors to activate HSCs, inducing their conversion into CAFs [80]. The interactions among these three cell types synergistically promote the recruitment and activation of myeloid-derived suppressor cells (MDSCs). For example, in HCC patients, $CD36^+$ CAFs promote MDSC expansion by secreting MIF, a process mediated through the CD74 receptor on MDSCs [14]. Another study showed that CAFs influence the recruitment of G-MDSCs by secreting chemokines such as CXCL2 [81]. Plasmacytoid dendritic cells also can upregulate interferon regulatory factor 1 (IRF1) by secreting IFN-α, promoting hepatocytes to express the chemokine CX3CL1, thereby recruiting $CX3CR1^+$ M-MDSCs [82]. Activated hepatic stellate cells (HSCs) promote MDSC accumulation by secreting PGE2 [83], and induce M-MDSC development through the p38 MAPK signaling pathway, leading to enhancer reprogramming [84], [85]. Overall, the recruitment and differentiation of MDSCs in the TME are complex and require further investigation to better understand the factors driving the differentiation of M-MDSCs and PMN-MDSCs within the TME.

MDSC immunosuppression and immune evasion

MDSCs play a critical role in immune suppression and tumor immune evasion through both direct and indirect mechanisms. They not only directly inhibit the activation and function of T cells and NK cells by secreting immunosuppressive factors such as IL-10, TGF-β, ROS, and PGE2 but also enhance immunosuppressive effects by promoting the expansion of Tregs [86–88]. Furthermore, MDSCs enhance tumor immune evasion and invasiveness by upregulating PD-L1 expression and promoting EMT [89] (Fig. 3). These multifaceted roles highlight the complexity of MDSC-mediated immune regulation and reinforce their potential as critical therapeutic targets in cancer treatment.

Interaction between MDSCs and immune cells

The primary target of MDSCs is T cells, and different MDSC subsets employ unique mechanisms to suppress T cell function. Generally, M-MDSCs primarily achieve non-specific T cell inhibition by expressing higher levels of TGFβ, Arg1 and iNOS [85, 87, 90]. PMN-MDSCs mediate immune suppression by producing high levels of ROS and engaging in direct cell-to-cell contact with T cells, reducing antigen-specific T cell responses without affecting responses to non-specific stimuli [91, 92]. Additionally, PMN-MDSCs can also upregulate Arg1 activity, which has been confirmed in recently discovered $LOX\text{-}1^+$ PMN-MDSCs. Notably, $LOX\text{-}1^+$ PMN-MDSCs can also inhibit T cell activity in a dose-dependent manner by interfering with IFN-γ production, whereas $LOX\text{-}1^-$ PMN-MDSCs cannot [39]. MDSCs also induce T cell apoptosis by expressing galectin-9, which binds to TIM-3 on T cells [93]. It is widely believed that MDSCs can evade immune surveillance by upregulating the expression of PD-L1, which binds to PD-1 on infiltrating T cells [77, 94, 95]. However, it remains unclear which subset of M-MDSCs or PMN-MDSCs expresses PD-L1 at a higher level. If it can be clarified, it could potentially improve the precise application of current PD-L1 immune checkpoint inhibitors. In addition to their direct interaction with activated T cells, MDSCs can also induce Tregs, a type of immunoregulatory cells, by secreting factors such as IL-10, TGF-β, CD73, and IDO, thereby indirectly suppressing tumor-specific T cell activity and leading to immune escape [86, 96, 97].

Some studies have shown that MDSCs can suppress NK cell activity by downregulating the expression of activation receptors such as NKG2D and NKp30, or by reducing the production of IFN-γ and perforin [96, 98–100]. MDSCs also suppress NK cell function through soluble factors such as iNOS, ROS, ARG1, and adenosine [101]. Similar to T cells, recent study found that HCV-induced MDSCs can deplete local L-arginine by releasing arginase-1. This process inhibits the mTOR signaling pathway, thereby reducing NK cell production of IFN-γ [88], and MDSCs can also inhibit NK cell function by binding to PD-1 on NK cell surfaces. STAT family transcription factors, as important components of the TME, also play a critical role in the interaction between MDSCs and NK cells. STAT1 may not be the primary signaling pathway mediating MDSC-induced NK cell inhibition in HCC [98], but STAT3 can induce NF-κB activation, leading to the release of IDO, which is produced by MDSCs. IDO regulates the catabolism of tryptophan to kynurenine, thereby inhibiting NK cell proliferation [102].

In addition to inhibiting T and NK cells, MDSCs can also suppress other immune cells. For example, MDSCs hinder B cell function by producing IL-7 and activating the STAT5 signaling pathway [103]. They also inhibit DC maturation and suppress antigen cross-presentation [104, 105].

Metabolic changes in MDSCs and immunosuppression

Lipid metabolism, lactate metabolism, and glycolysis in MDSCs play critical roles in their differentiation and function. For instance, fatty acid transport protein 2 (FATP2) is responsible for the uptake of arachidonic acid

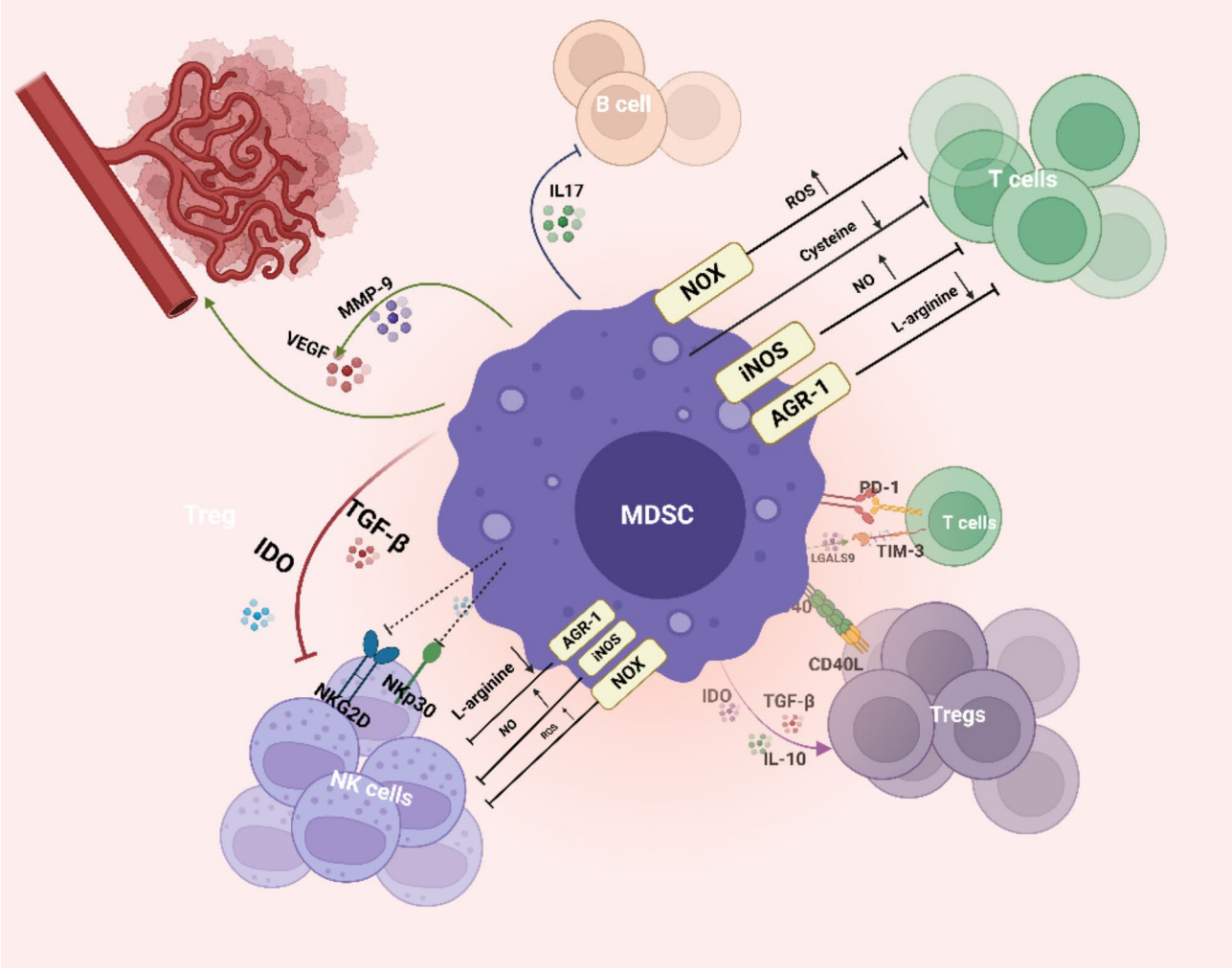

Fig. 3 The role of MDSCs in angiogenesis and immune suppression

and the synthesis of PGE2, contributing to the acquisition of PMN-MDSC suppressive activity [106, 107]. SQLE, a key enzyme in cholesterol synthesis, induces cholesterol accumulation, which enhances the immunosuppressive capacity of MDSCs [87, 108]. PAF, a lipid mediator secreted by tumor cells, interacts with its receptor (PAFR) in the TME, inducing the differentiation of neutrophils into immunosuppressive PMN-MDSCs [109]. Moreover, Baumann et al. demonstrated that MDSCs can transfer acetaldehyde to T cells, impairing their metabolic function and temporarily "stunning" them, preventing them from responding to T cell activation signals [110]. Glycolysis is the main glucose metabolic pathway in MDSCs, mediating their function under both aerobic and anaerobic conditions. In hypoxic environments, HIF-1α expression increases, leading to increased expression of glycolytic enzymes and lactate transporters in MDSCs, which promotes their differentiation and proliferation [111]. Additionally, the elusive MDSCs produce phosphoenolpyruvate through aerobic glycolysis, which exhibits antioxidant activity, mitigating the self-damage caused by ROS production [36].

Ferroptosis is a form of regulated cell death distinct from apoptosis [112]. Studies have shown that the ferroptosis agonist IKE enhances the immunosuppressive function of PMN-MDSCs. This enhancement is associated with ferroptosis-induced release of oxygenated lipids, which act as signaling molecules to further promote the immunosuppressive activity of PMN-MDSCs [69, 107]. In an HCC model resistant to anti-PD-L1 treatment, overexpression of MerTK significantly increased the proportion of MDSCs, while also inhibiting the antitumor activity of $CD8^+$ T cells. MerTK inhibits ferroptosis in tumor cells by upregulating SLC7A11, a ferroptosis suppressor, thereby promoting tumor cell survival and increasing resistance to PD-L1 therapy [113]. Similarly, in another mouse model of HCC, the TLR2 agonist Pam3CSK4 was found to regulate MDSC polarization through Runx1, and Runx1 may exert its effect via the ferroptosis pathway [82].

Table 1 Clinical trials of MDSC-regulated therapies in HCC

Year	Drug	Combination partner	Mechanism of Action	Phase	Trial number
2016	Anti-SIRPα antibody	N/A	Blocking the interaction between SIRPα and CD47 can promote the differentiation of MDSCs.	N/A	NCT02868255
2016	Modified Vaccinia Virus Ankara Vaccine Expressing p53	Pembrolizumab	Reducing the secretion of CXCR3, CCR2-related chemokines, and CSF-1 can decrease the recruitment of MDSCs.	I	NCT02432963
2018	Invariant NKT cells (iNKT) infusion	TAE/TACE	iNKT can interact with circulating MDSCs and reduce their numbers.	II	NCT04011033
2018	Immuncell-LC	N/A		II	NCT02856815
2019	MTL-CEBPA	Pembrolizumab	MTL-CEBPA inhibits the immunosuppressive activity of MDSC by upregulating C/EBP-α.	I	NCT04105335
2024	Icaritin	TACE	Icaritin downregulates the tumor-associated splenic EMH, thereby reducing the generation and activation of MDSCs.	II	NCT06285149
2024	Radiotherapy	Atezolizuma and Bevacizumab	Bevacizumab inhibits the action of VEGF, reducing the generation of tumor blood vessels, thereby suppressing the proliferation and activity of MDSCs.	II	NCT06605664

In addition to their immunosuppressive functions, MDSCs can also further differentiate into M2-type TAMs, and these TAMs express S100A8/9 proteins, exhibiting stronger immunosuppressive functions [114]. Moreover, MDSCs contribute to the remodeling of TME and tumor angiogenesis, directly promoting tumor progression and metastasis. For example, MDSCs promote tumor angiogenesis by producing high levels of matrix metalloproteinase 9 (MMP9), vascular endothelial growth factor (VEGF), and other factors, improving the tumor's nutrient and oxygen supply, further promoting tumor growth and metastasis [115, 116].

Therapeutic strategies for targeting MDSCs

There is strong evidence supporting a close correlation between MDSCs accumulation and clinical outcomes in HCC patients, as previously demonstrated by our group [21, 22].

Several preclinical and clinical trials also have incorporated MDSCs as observational markers, including common therapies such as TACE and radiotherapy [26, 117] (Table 1). A large body of research indicates that inhibiting the recruitment of MDSCs to tumor sites has the potential to overcome chemotherapy resistance and improve immunotherapy responses [118–120]. Currently, most in vitro and in vivo studies focus on the following aspects, aiming to provide new perspectives for clinical targeting of MDSCs: [1] the recruitment and activation of MDSCs; [2] the metabolism of MDSCs; [3] the role of MDSCs in stromal cell interactions and angiogenesis.

Targeting MDSC generation, recruitment, and activation

As mentioned earlier, chemokines are key factors in MDSC recruitment. Thus, blocking the interaction between chemokine receptors and their ligands to inhibit MDSC recruitment to tumor sites is considered an effective therapeutic strategy. This has been confirmed in some studies, where the combination of anti-PD-L1 antibodies with antibodies targeting CCL19 [78], CCL20 [61], and CCL5 [121] significantly inhibited the recruitment of MDSCs, thereby improving T cell activity and inhibiting oxaliplatin resistance [121]. Furthermore, a study discovered a non-cell-autonomous protumorigenic function of CCRK in driving the expansion and activation of MDSCs via NF-κB-mediated production of IL-6, and inhibition of CCRK or IL-6 can enhance the effect of PD-L1 blockade, thereby significantly improving the immune therapeutic efficacy in HCC [122]. Unlike strategies that inhibit MDSC recruitment, Icalitin directly downregulates extramedullary hematopoiesis (EMH) in the spleen, reducing MDSC generation and activation, and it shows synergistic enhancement of efficacy when combined with immune checkpoint inhibitors (such as anti-PD-1 antibodies) [123]. In addition to targeting generation, accumulation and activation, promoting MDSC maturation is also a viable strategy. TLR2 agonists can promote the polarization of MDSCs in HCC via Runx1 [124]. Based on the above studies, most strategies still tend to favor combination with existing immune checkpoint inhibitors. CAR-T is a novel precision-targeted therapy for cancer, but it often loses its tumor control function due to in vivo exhaustion [125]. A study designed a new GPC3-targeted CAR, GPC3-IL7-CCL19, which reverses the tumor immunosuppressive microenvironment by reducing the infiltration of PMN-MDSCs and Treg cells [78].

Targeting MDSC metabolism

Based on the metabolic characteristics of MDSCs in the TME, some therapeutic strategies aim to regulate the suppressive functions of MDSCs through metabolic reprogramming. For instance, by targeting ferroptosis, MerTK can regulate the upregulation of ferroptosis to recruit MDSCs, a MerTK inhibitor, sitravatinib, can

sensitize drug-resistant HCC to PD-L1 therapy by promoting tumor ferroptosis and reducing MDSC infiltration into the TME [113]. Similarly, by targeting lactate metabolism, dichloroacetate (DCA) in Newcastle disease virus (NDV)-mediated HCC indirectly affects MDSC numbers by reducing lactate production and inhibiting STAT3 activation, thereby improving the anti-tumor efficacy in the HCC mouse model and prolonging the survival [126]. Additionally, research conducted on a mouse HCC model has found that IL-37 promotes the glycolysis and oxidative ph EMT phorylation of MDSCs, leading to an upregulation of ATP release, thereby weakening the immunosuppressive capacity of MDSCs [127].

Targeting MDSC-stromal interactions and angiogenesis

The crosstalk between MDSCs and stromal cells, as well as microvascular formation, are equally important for reshaping the tumor immune microenvironment. In recent years, the communication between HSCs and MDSCs has received increasing attention. In a mouse orthotopic HCC model, HSCs promoted PMN-MDSC expansion via COX2-PGE2-EP4 signaling, and inhibiting HSC-derived PEG2 with a COX-2 inhibitor reduced tumor grow and MDSCs accumulation [83]. Activated HSCs can also induce intrinsic p38 MAPK signaling in monocytes, promoting M-MDSC development and immunosuppression, and studies have shown that treatment with p38 MAPK inhibitors eliminates the HSC/M-MDSC crosstalk, preventing HCC growth [84]. Furthermore, VEGF-A can drive the accumulation of MDSCs, which in turn promote angiogenesis and contribute to the formation of pre-metastatic niches [128]. Therefore, targeting angiogenesis represents a promising therapeutic strategy. The upregulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) in tumor cells promotes the production of vascular endothelial growth factor-A (VEGF-A), thereby driving MDSC expansion. However, the use of the selective PPAR-γ antagonist T0070907 significantly reduces MDSC levels and enhances HCC sensitivity to PD-L1 therapy [129]. All-trans retinoic acid can also significantly inhibit HCC progression by targeting myeloid-derived suppressor cells and suppressing tumor angiogenesis [130].

Potential applications of TCM and natural products in HCC via targeting MDSCs

In addition to some commonly used clinical drugs, traditional Chinese medicine (TCM) has also shown significant potential in inhibiting HCC by regulating MDSCs. Isoquercitrin targets USP7 and promotes the ubiquitin-dependent degradation of YY1, thereby inhibiting YY1-mediated MDSC recruitment and activation. A research team developed HMSN-ISO@ProA-PD-L1 Ab dual-functional nanoparticles, which inhibit YY1 and reduce MDSC levels [131]. Additionally, curcumin has been found to inhibit the secretion of factors associated with MDSC expansion, such as GM-CSF and G-CSF. Treatment with curcumin notably reduces the number of MDSCs in tumor tissues [132]. Gansui Banxia Decoction can also exhibit its effect on MDSC accumulation and differentiation by downregulating the AKT/STAT3/ERK signaling pathway and inhibiting IL-1β and IFN-γ [133]. A clinical study on the combination of icariin and TACE as treatment for HCC patients (NCT06285149) is also ongoing. This study investigates the potential of icariin to modulate the tumor immune microenvironment by reducing the secretion of TNF-α and IL-6, and inhibit PD-L1 expression by decreasing the proportion of MDSC cells, offering a promising avenue for immunotherapeutic strategies in HCC treatment.

Currently, there are no targeted therapies specifically aimed at MDSCs approved for use in HCC. Although chemotherapy agents such as 5-fluorouracil, carboplatin, and paclitaxel have been reported to reduce the number of circulating MDSCs in other tumors, their effects on MDSCs are not specific [134]. Notably, the monoclonal anti-CD33 antibody gemtuzumab has shown promising results in depleting $CD33^+$ MDSCs [32]. Additionally, small molecule inhibitors like ruxolitinib, through inhibition of the JAK-STAT signaling pathway, can reduce MDSC accumulation [135, 136]. CSF1R inhibitors, such as PLX3397, target the CSF1 receptor on myeloid cells, thereby reducing MDSC generation and enhancing immune responses [137, 138]. However, these therapies still require further research and optimization to confirm their clinical efficacy in HCC.

Challenges and opportunities

The expansion of MDSCs undoubtedly plays a crucial role in the ability of tumors to evade immune surveillance, promote tumor progression, and impair the function of specific immune cell populations. However, research on MDSCs continues to face significant challenges.

First, the classification and biomarkers of MDSCs remain poorly defined. Currently, the most widely recognized subtypes are M-MDSCs, PMN-MDSCs, and eMDSCs. However, due to the overlap in biomarkers between MDSCs and monocytes or neutrophils, many MDSC-targeting biomarkers lack specificity. Further refinement of phenotypic definitions is required to minimize the impact on conventional monocytes and neutrophils. Additionally, as previously mentioned, eMDSCs markers may overlap with those of eosinophils and are not correlated with prognosis. However, eMDSCs exhibit contrasting behavior in breast cancer and, compared to traditional M-MDSCs and PMN-MDSCs, display distinct phenotypic biomarkers and consistently show poor differentiation status [43]. These opposing findings open up

significant possibilities for the phenotypic identification of eMDSCs in HCC.

The immunosuppressive mechanisms underlying MDSCs remain incompletely understood. S100A9 has been implicated in the activation of multiple signaling pathways, including NF-κB, MAPK, and STAT3, through binding to TLR4 and RAGE receptors. This interaction leads to the conversion of monocytes into immunosuppressive MDSCs [139]. Notably, recent studies utilizing the S100A9 signaling inhibitor Paquinimod have demonstrated that inhibition of S100A9 signaling unexpectedly promotes tumor progression and diminishes the efficacy of anti-PD-L1 therapy [140]. Consequently, a more nuanced understanding of the roles certain molecules play in modulation is essential.

Finally, the current therapies are not completely effective. For instance, in mouse models, the combination of 5-fluorouracil (5-FU) and anti-PD-L1 antibodies showed that 5-FU actually induced the accumulation of MDSCs in the tumor [141]. In early HCC with incomplete microwave ablation, the glycolytic capacity of MDSCs is significantly enhanced [142]. Moreover, most therapeutic approaches are still in the early stages of development, with limited research specifically targeting MDSCs. The true potential of targeting MDSCs may lie in their combination with other immunotherapeutic strategies.

Conclusion

In recent years, various therapies have significantly improved the condition of HCC patients. However, due to the profound immune suppression within TME, the full therapeutic potential has not been realized. MDSCs play a pivotal role in immune evasion in HCC, driving tumor growth and metastasis through multiple mechanisms. Despite this, the specific biomarkers and mechanisms of action remain poorly understood, and targeted therapies for MDSCs are still in the early stages of development. Future research should utilize emerging technologies, such as single-cell sequencing and high-throughput screening, to identify potential MDSC biomarkers, elucidate the mechanisms of MDSC action at various stages of tumor progression, and refine MDSC-targeted therapies to provide new insights for HCC treatment.

Abbreviations

ANG-2	Angiopoietin-2
Arg-1	Arginase 1
CAFs	Cancer-associated fibroblasts
CAR-T cells	Chimeric Antigen Receptor T-cells
CCR2	C-C Motif Chemokine Receptor 2
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CTLs	Cytotoxic $CD8^+$ T-cells
CXCR2	C-X-C Motif Chemokine Receptor 2
DCA	Dichloroacetate
DCs	Dendritic Cells
e-MDSC	Early-stage MDSC
EMT	Epithelial-Mesenchymal Transition
ER	Endoplasmic reticulum
FATP2	Fatty acid transport protein 2
FGF-2	Fibroblast growth factor-2
HCC	Hepatocellular carcinoma
HIF-1α	Hypoxia-Inducible Factor 1 Alpha
HIF	Hypoxia-inducible factors
ICB	Immune Checkpoint Blockade
IDO	Indole amine 2, 3-dioxygenase
IFN-γ	Interferon Gamma
IL-1β	Interleukin-1 Beta
IL-10	Interleukin-10
IMCs	Immature myeloid cells
iMWA	Incomplete microwave ablation
IRF1	Interferon regulatory factor 1
LOX-1	Lectin-like oxidized LDL receptor-1
M-MDSCs	Monocytic myeloid-derived suppressor cells
MDSCs	Myeloid-derived suppressor cells
MMP-9	Matrix metalloprotease-9
NDV	Newcastle disease virus
NK cells	Natural Killer cells
NO	Nitric Oxide
NOS2	Inducible Nitric Oxide Synthase
NOX2	NADPH Oxidase 2
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PGE2	Prostaglandin E2
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
PPARγ	Peroxisome proliferator-activated receptor-gamma
PPAR-γ	Peroxisome proliferator-activated receptor-γ
ROS	Reactive oxygen species
SDF-1	Stromal-derived factor
SDF-1	Stromal Cell-Derived Factor 1
STAT3	Signal Transducer and Activator of Transcription 3
TACE	Transcatheter Arterial Chemoembolization
TAMs	Tumor-associated Macrophages
TCM	Traditional Chinese medicine
TGF-β	Transforming Growth Factor Beta
TME	Tumor microenvironment
Tregs	Regulatory T Cells
VCAM-1	Vascular cell adhesion molecule-1
VEGF-A	Vascular endothelial growth factor-A
VEGF	Vascular Endothelial Growth Factor

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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Competing interests

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