Immune Surveillance by Myeloid-Derived Suppressor Cells in Liver Diseases

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Keywords

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Abstract

Background: Myeloid-derived suppressor cells (MDSCs) are immunosuppressive in nature, originate in the bone marrow, and are mainly found in the blood, spleen, and liver. In fact, liver acts as an important organ for induction and accumulation of MDSCs, especially during infection, inflammation, and cancer. In humans and rodents, models of liver diseases revealed that MDSCs promote regeneration and drive the inflammatory processes, leading to hepatitis, fibrogenesis, and cirrhosis, ultimately resulting in hepatocellular carcinoma. **Summary:** This brief review is focused on the in-depth understanding of the key molecules involved in the expansion and regulation of MDSCs and their underlying immunosuppressive mechanisms in liver diseases. **Key Message:** Modulated MDSCs can be used for therapeutic purposes in inflammation, cancer, and sepsis.

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Introduction

“Myeloid-derived suppressor cells (MDSCs)” were identified almost 13 years back and faced a lot of alterations since the beginning due to their resemblance with

other myeloid cells. However, they are recognized as a separate subset of immature innate immune cells that are closely related to neutrophils and monocytes. MDSCs carry progenitor and precursor markers of mature dendritic cells, macrophages, and granulocytes.

Under physiological state, myelopoiesis differentiates immature myeloid cells into mature immune cells and can alter adaptive immunity. However, during inflammation, sepsis, or cancer, these immature myeloid cells are not able to differentiate into mature immune cells, and instead convert into immature MDSCs [1]. Many human and rodent studies have demonstrated a key role of MDSCs in the regulation and modulation of immune responses leading to progression of liver diseases. Antigen-specific and nonspecific stimulation of MDSCs is carried by a variety of pro- and anti-inflammatory molecules, growth factors, transcription factors, signaling pathways, epigenetic regulations, and miRNAs. In this review, we have discussed about the origin, mechanism of expansion, and the suppressive functions of MDSCs, and therapeutic interventions to modulate MDSCs for the benefit of liver diseases.

Markers of MDSCs

The lack of homogeneous phenotypical characterization of MDSCs has made understanding of the cells unclear even after many years of their origin. In both humans and mice, MDSCs are considered as a heterogeneous population of cells and their origin is linked with

Fig. 1. Generation of MDSCs. Various growth and transcription factors such as GM-CSF, G-CSF, IL-6, PGE2, STAT3, and C/EBP β provide signals to HSCs for the expansion and mobilization of IMCs in the bone marrow. During normal physiological condition, DCs, neutrophils, and macrophages are generated from IMCs; however, in case of any infection, trauma, or cancer, a milieu of pro-inflammatory stimuli, for example, LPS, IL-1 β , and

S100A8/A9, induces generation of activated MDSCs (G-MDSCs and M-MDSCs) with increased ARG1, iNOS, and immunosuppressive cytokines. MDSCs, myeloid-derived suppressor cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCs, hematopoietic stem cells; IMCs, immature myeloid cells; DCs, dendritic cells; G-MDSCs, granulocytic-MDSCs; M-MDSCs, monocytic-MDSCs; ARG1, arginase 1.

monocytic and granulocytic lineages. In humans, MDSCs are categorized as monocytic (M-MDSCs) and granulocytic (G-MDSCs) MDSCs in the peripheral blood on the basis of expression of few markers such as CD14, CD15, CD11b, CD33, and HLADR. M-MDSCs are CD14⁺ with CD11b^{high}CD33⁺HLADR^{lo}, while G-MDSCs are CD14⁻CD15⁺CD11b^{high}CD33⁺HLADR^{lo} cells [2, 3]. G-MDSCs lack the expression of CD14 marker but gain the expression of CD15.

In mice, MDSCs are categorized with dual expression of Gr-1 and CD11b, where M-MDSCs have Gr-1^{low}

expression and are characterized as CD11b⁺Ly6C^{hi}Ly6G^{-/dim}, while G-MDSCs show Gr-1^{hi} expression and are characterized as CD11b⁺Ly6C^{lo}Ly6G^{hi} [4] (Fig. 1, 2).

MDSC Accumulation in Organs

Liver is considered as an immune-tolerant organ, and mostly MDSCs with activity of suppressing antigen-specific immune response are accumulated in the liver fol-

lowed by the lung, spleen, and other lymphoid organs [5]. Recruitment and differentiation of MDSCs are mainly dependent on both liver parenchymal and nonparenchymal cells under the influence of various secretory mediators such as hepatocyte growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), and hepatic acute-phase proteins [6, 7]. Hepatocyte growth factor, being a noninflammatory molecule, engages its receptor c-Met, and with downstream phosphorylation of STAT3 causes expansion and recruitment of MDSCs. GM-CSF also plays a major role in emergency myelopoiesis in response to infection and significantly modulates innate and adaptive immune responses by recruiting MDSCs. In tumor microenvironment, secreted GM-CSF recruits programmed cell death ligand 1 expressing MDSCs which have profound ability of immunosuppression and differentiation. It is observed that knockdown or blocking of GM-CSF reduced indoleamine 2, 3-dioxygenase and programmed cell death ligand 1 expression in liver MDSCs [8, 9]. Therefore, the GM-CSF/JAK2/STAT3 axis supports liver MDSC differentiation and immunosuppression in metastasis.

During any infection or inflammation of the liver, acute-phase proteins such as serum amyloid P and serum amyloid A are released from the liver, which promotes the development and accumulation of MDSCs, especially M-MDSCs, and their suppressive activity [10, 11]. Other than soluble factors, cellular compartment of the liver such as hepatic stellate cells (HSCs) also facilitates MDSC accumulation and differentiation. HSCs, a class of unique liver stromal cells, usually remain in a quiescent state and participate in immunomodulatory activities. During liver injury, HSCs are activated and help in facilitating the trafficking of MDSCs from the bone marrow via COX2-PGE2-EP4 or via p38 MAPK signaling [12, 13]. It is also evidenced that HSCs differentiate MDSCs via a contact-dependent mechanism [14, 15]. In vitro studies showed that primary HSCs induce circulating PBMCs for differentiation to CD14⁺HLADR^{lo} MDSCs which suppress T-cell responses by arginase 1 (ARG1) [14, 15]. Other studies revealed that HSCs help in differentiation of MDSCs using IFN- γ signaling and complement component C3 [16, 17] (Fig. 3).

Mechanisms of Immunosuppression by MDSCs

MDSCs are known for their immunosuppression properties which are due to the secretion of ARG1 and NO. M-MDSCs have low expression of ARG1 with high

Fig. 2. Markers and major accumulation of MDSCs in humans and mice. MDSCs, myeloid-derived suppressor cells.

production of NO, while G-MDSCs show high expression of ARG1 with ROS production [1, 3]. Both types of MDSCs have different ways to induce immunosuppression, while M-MDSCs use both antigen-specific and non-specific mechanisms to suppress specific responses via iNOS-mediated STAT1 nitration and blocking of IFN- γ downstream signaling [18].

On the other hand, G-MDSCs function in an antigen-specific manner via the activation of NO and superoxide-producing peroxynitrite and directly nitrating T-cell receptors. These changes further reduce antigen-specific sensitivity to MHCs, leading to change in T-cell responses [19].

But in mice, M-MDSCs are known for their highly immunosuppressive nature in an antigen nonspecific manner with an increase in the expression of F4/80, CSF-1R, and CD192 [20]. Several studies in mice revealed that overexpression of VEGF along with ARG1 and iNOS leads to the expansion of Treg population [21, 22] mediating an immunosuppressive environment. Furthermore, conversion of cGMP to GMP via PDE-5 enhances the immunosuppressive activity of MDSCs via inflating the ARG1 and NOS2 expression. Inhibition of the PDE-5 activity also reduces the MDSC-mediated T-cell suppression activity [23] (Fig. 3).

Fig. 3. Factors and pathways involved in the suppressive activity of M-MDSCs and G-MDSCs. a) Cellular stress: it activates ER stress proteins such as IRE1 and PERK, which increase the expression of CHOP. Increase in CHOP enhances the suppressive activity of M-MDSCs more than that of G-MDSCs. b) TLR and IL-1 β : interaction with their receptors stimulates NF- κ B, which enhances the activity of both G-MDSCs and M-MDSCs. c) Interaction of TNF- α with its receptor, that is, TNFR, enhances the suppressive activity of M-MDSCs via NF- κ B. d) Interaction of IL-6 with gp130 activates the JAKs-STAT3 pathway, which increases the suppressive

activity of G-MDSCs with the help of C/EBP β and S100A9. e) PGE2-COX2 signaling increases the activity of ARG1 and NOS2. f) Conversion of cGMP to GMP via PDE-5 enhances the activity of ARG1 and NOS2. g) IFN- γ signaling increases the activity of STAT1 and enhances the suppressive activity of M-MDSCs but suppresses the activity of G-MDSCs. h) NOTCH pathway: suppresses the differentiation of both M-MDSCs and G-MDSCs. MDSCs, myeloid-derived suppressor cells; G-MDSCs, granulocytic-MDSCs; M-MDSCs, monocytic-MDSCs; ARG1, arginase 1; PGE5, phosphodiesterase 5; CHOP, C/EBP homologous protein.

Immune Surveillance by MDSCs during Liver Inflammation and Fibrosis

The role of MDSCs is not well established in liver inflammation, fibrosis, and chronic liver diseases (Fig. 4). However, rodent models of liver inflammation such as ConA and D-gal suggested that accumulation of MDSCs during liver diseases prevents extreme damage to the organ. In a ConA-induced hepatitis model, adoptive transfer of MDSCs suppressed the proliferation of CD4⁺CD69-activated T cells and protected mice further from ROS-generated damage [24]. Mainly, G-MDSCs were observed in these mice models which rendered protection independent of Tregs [24]. Similarly, in a D-gal/LPS mice model, MDSCs controlled T-cell

activation in controlling liver damage [24]. This clearly suggests that MDSCs help in preventing liver damage via ROS and iNOS.

However, in fulminant hepatitis, CXCL1- and CXCL2-mediated MDSC accumulation is suggested to be the cause of impaired T-cell responses in an arginase-dependent manner [25].

In primary biliary cholangitis, damaged cholangiocytes and hepatocytes secrete cysteine-rich protein 61 (CCN1). CCN1 along with GM-CSF binds to the integrin α 5 β 2 receptor expressed on MDSCs and inhibits T cells via STAT3 phosphorylation and iNOS [26]. CCN1 is a matrix protein which regulates cell adhesion and cell death, and boosts the functions of HSCs during inflammation and hepatic steatosis in nonalcoholic steatohepatitis patients [27, 28].

Fig. 4. Role of MDSCs in various liver diseases. MDSCs, myeloid-derived suppressor cells; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

There are limited studies available which explain the involvement of MDSCs in chronic liver injury along with the expansion of liver fibrosis. Infusion of bone marrow cells containing MDSCs in patients and mice with hepatic fibrosis enhances fibrosis via production of IL-10 and suppresses the pro-fibrotic function of activated HSCs [29].

Immune Surveillance by MDSCs in Hepatotropic Viral Infections

In acute hepatitis B virus (HBV) infection, arginase-expressing G-MDSCs expand with an increase in viremia and remain in inverse correlation with liver inflammation and suppress T-cell responses [2], while M-MDSCs regulate acute HBV infection using PD-1-induced IL-10 [30]. A surge in the number of MDSCs decreased the proliferation of HBsAg-specific lymphocytes in a mice model [31].

But in chronic HBV infection, it is observed that both circulating and arginase-expressing G-MDSCs are increased, and L-arginine is found to be decreased. In the “immunotolerant” phase of chronic HBV infection, arginase-expressing G-MDSCs increase with an rise in the concentration of ARG1 [32], which alters T-cell functionality and inhibits T-cell proliferation. This is achieved by MDSCs by affecting the CD3- ζ chain of TCR and eventually impairing immune response [33].

In the immune-active phase of chronic HBV infection, $\gamma\delta$ T cells help in the recruitment of ARG1-expressing MDSCs in the liver, which further causes exhaustion of effector CD8 T cells. However, the immunosuppres-

sive phenotype of M-MDSCs (CD14⁺HLADR^{low}PD-1⁺) correlates well with an increase in PD-1 expression and additionally requires IL-10 for T-cell exhaustion [34].

In chronic hepatitis C virus (HCV) infection also, MDSCs were found to be associated with high viral loads and immune tolerance [34]. HCV core protein triggers the generation of MDSCs, which suppresses both CD4⁺ and CD8⁺ T cells by generating ROS and IFN- γ [35]. MDSCs also help in the persistence of HCV by decreasing the expression of TCR ζ chain in CD8 T cells [36]. An increase in ARG1-producing MDSCs correlated with poor prognosis, but upon antiviral treatment their numbers reduced to a minimum [35].

However, it is observed that MDSC suppressive activity might vary with different HCV genotypes [37]. An increase in MDSC frequencies is observed in genotype-2a patients than in patients with genotype 1. Therefore, genotype 1 patients showed an increased tendency for virological response after treatment with peg-IFN- α /ribavirin, which was related to low MDSCs [36]. In addition, genotype 4’s nonresponse to antiviral treatment in Central Africa (Egypt) was also documented in relation to increased MDSCs. Higher MDSCs (Lin⁺HLADR⁺CD33⁺CD11b⁺) were observed in IFN- α /ribavirin nonresponders than responders, suggesting their role in the failure of the therapy. Therapy responders showed low numbers of MDSCs with an increase in IL-2 production by T cells [38], which clearly concludes the role of MDSCs in clearing the HCV.

Immune Surveillance by MDSCs in Autoimmune Hepatitis

In autoimmune hepatitis (AIH), accumulation of IFN- γ -secreting T cells in the portal tracts induces inflammation, hepatocellular injury, and liver necrosis. Induction of autoimmune liver injury was observed due to the activation of both CD4⁺ and CD8⁺ T cells, which resulted in antibody-dependent cell-mediated cytotoxicity and CTL killing [39].

MDSCs expand in numbers with inflammation in noncirrhotic AIH compared to cirrhotic AIH [39]. In cirrhotic AIH patients, an increase in iNOS-expressing MDSCs in the liver and blood correlated well with ALT and AST [40].

In animal models of AIH, the protective role of TGF- β was interlinked with MDSCs. A TGF- β 1^{-/-} AIH mice model revealed that accumulation of CD11b⁺Gr1⁺ my-

eloid cells in the liver suppressed CD4 T-cell proliferation by cell-cell contact via iNOS and NO [41]. In another murine model of AIH, iPSCs generated MDSCs, which were important in inhibiting CD8⁺ T-cell responses [42].

It is observed that in autoimmune diseases, naive T-cell differentiation to Th17 cells was driven by a transcription factor CREM α [43]. Contradictory to previous findings, the suppressive function of hepatic MDSCs was impaired by CREM α by reducing iNOS and ARG1 expression [43]. It was emphasized that immune-mediated hepatitis aggravates due to overexpression of CREM α . Therefore, this implies that in AIH patients, T-cell functionality can be restored by reducing suppressive MDSCs with overexpression of CREM α .

Immune Surveillance by MDSCs in Sepsis

Decompensated chronic liver injury is mostly associated with bacterial infections and sepsis. During any infection, myelopoiesis in the bone marrow is enhanced with mobilization of myeloid cells to systemic blood. However, in animal models of sepsis or in sepsis patients, it has been observed that G-CSF increased the mobilization of CD34 cells and immunosuppressive MDSCs. Previous studies also showed a positive correlation between the increase in MDSC population with nosocomial infections and longer stay of patients in the ICU [44].

It is important to note that many cytokines and growth factors are involved during systemic inflammation, but TNF- α acts as a key mediator in lethal septic shock [45]. In the TNF family, TNF- α is a major player which can regulate critical cellular functions using its 2 transmembrane receptors available in both secretory and transmembrane forms, that is, TNFR1 and TNFR2. In case of staphylococcal sepsis, TNFR1 modulates MDSC differentiation resulting in loss of functional CD4 T cells which hampered bacterial clearance in the spleen [46]. On the other hand, TNFR2 activates the expression of NF- κ B with increased cellular FLICE-inhibitory protein, a master antiapoptotic regulator for initiating the apoptosis process. TNFR2 not only increases the survival capacity of MDSCs but also enhances their suppressive activity by ARG1, iNOS, ROS, IL-10, and TGF- β [47, 48]. Together, both TNFR1 and TNFR2 play a major role in potentiating the MDSCs; however, it is still not clear which TNF receptor affects G-MDSCs or M-MDSCs the most.

There are not many drugs other than routine antibiotics to control the sepsis. However, recently all-trans-retinoic acid and S100A8/A9 drugs (calcium- or zinc-bind-

ing protein) were found to play a prominent role in regulating the expansion of MDSCs. However, in the late stage of sepsis, the use of S100A9 was not much appreciated as it converted myeloid precursors to more immunosuppressive MDSCs [49]. Other agents such as cyclophosphamide and 5-fluorouracil were also found to decrease the frequency of MDSCs and Tregs [50].

Many miRNAs are also being considered for therapeutic modulation of MDSCs (Table 1, includes Ref. [51–63]). miR-21 and 181b were observed to positively regulate the differentiation of MDSCs via Nrf2 and NFI-A transcription factors [49, 64]. At the same time, miR-375 impairs the JAK2-STAT3 pathway and decreases the MDSC numbers [65]. However, it is also reported that in sepsis, increased expression of NFI-A-C/EBP β ultimately activates the NF- κ B, leading to impaired myelopoiesis [56, 66]. These findings clearly suggest that inflammation in sepsis can be controlled by modulating MDSCs.

Immune Surveillance and MDSCs in Liver Cancer

HCC is the second leading cause of cancer-related death worldwide. Patients with chronic liver disease due to HBV, HCV infection, or alcohol consumption and NASH develop HCC [67]. It is well known that soluble factors of the tumor microenvironment, including IL-6, IL-13, GM-CSF, G-CSF, M-CSF, VEGF, and SCF, differentiate MDSCs in the tumor.

MDSCs have a perpetuating role in many other cancers with involvement of distinct pathways including cell cycle, autophagy, IL-3 activation, G-protein, GnRH, mTOR, IFN- γ , MAPK, CSF1, and CREB signaling [68, 69]. But the role of MDSCs, in particular in HCC, is not well documented.

Tumor-associated MDSCs were found to be significantly upregulated in HBV-infected HCC and correlated well with tumor volume. After tumor resection, the liver showed decreased or abrogated accumulation of MDSCs and clearly altered the functions of CD8 T cells, but no effect was evident on CD4 T cells [70]. However, it was observed that the presence of MDSCs even after resection caused early recurrence of cancer [70]. The presence of MDSCs increased vascular invasion and the systemic immune-inflammation index (SII) in HCC with curative resection [71]. SII is being used as a prognostic tool to determine the outcome and host inflammatory status after resection [72]. Patients with solid tumors having a high SII show poor tumor differentiation and prognosis [72].

Table 1. Role of miRNAs and MDSCs

Type of miRNA	Effect on MDSCs	Model (mice/human)	Ref.
miRNA-9	Targets RUNX1 which regulates the differentiation and function of MDSCs	Mice tumor model	[51]
miR-29a	Induces the expansion of myeloid progenitors by affecting myelopoiesis	Mice and humans	[52]
miRNA-30a	Targets SOCS3 which increases MDSC differentiation and immunosuppressive function	B cell lymphoma model mice	[53]
miRNA-155 and miRNA-21	Promotes the expansion of functional MDSCs	Mice model	[54]
miRNA-146a		Murine sepsis	[55]
miR-21 and miR-181b	Activation by STAT3 causes the expansion of MDSCs via NF- κ B	Mice and humans	[56, 57]
miR-17-5p, miR-20a, and miR-106a	Helps in MDSC accumulation and regulates their immunosuppressive activity	Mice model	[58]
miRNA-210	Upregulated miR-210 via HIF-1 α under hypoxia modulates the function of MDSCs by increasing arginase and NO production	Mice tumor model	[59]
miRNA-223	Helps in granulocytic differentiation and accumulation during stress; represses NFI-A	Mice tumor model	[60]
miRNA-494	Targets PTEN and helps in accumulation and functionality	Mice tumor model	[61]
miRNA-424	Its interaction with myeloid transcription factors, that is, NFI-A, influences myeloid differentiation	Mice and humans	[62]
miRNA-690	Regulates activation, expansion, and maturation by targeting C/EBP- α	Mice model	[63]

MDSCs, myeloid-derived suppressor cells; HIF-1 α , hypoxia-inducible factor 1 α .

The hypoxic environment of HCC is very crucial for MDSCs, as hypoxia-inducible factor 1 (HIF-1) helps in the infiltration of CXCR1-expressing MDSCs in tumors by activating chemokine ligand 26 [73]. It is also evident that higher expression of HIF-1/2 α is correlated with poor outcome in HCC patients. HIF-1 also stimulates the expression of ENTPD2/CD39L1, which helps in the maintenance of undifferentiated MDSCs in a tumor environment [74].

In both HCC patients and an orthotopic HCC mice model, it was observed that fibrosis mediates an increased influx of MDSCs, leading to aggressive growth of tumors [13]. Furthermore, it was proved that activated HSCs induce the accumulation of MDSCs by activating COX2-PGE2-EP4 and p38 MAPK pathways. HSC-activated MDSCs regulate their immunosuppressive activity via iNOS, ARG1, and IL-4R α [12]. MDSCs also suppress the T cells by inhibiting their proliferation and inducing cell death. Inhibition of either of the pathways suppresses the HSC-MDSC axis, which enhances the infiltration of tumor antigen-specific lymphocytes to restrict tumor growth [75]. The switch between apoptosis and necrosis is regulated by intracellular ATP, NO, and RIP3, which decreases the release of intracellular ATP and converts apoptotic stimuli to necrosis [76], where low or deficient RIP3 helps in the accumulation and homing of MDSCs in HCC [46]. It was evident in colorectal cancer where RIP3 deficiency initiated the COX-2/PGE₂ pathway, which boosted the accumulation of immunosuppressive MDSCs [77].

Recently, few new molecules were also identified as modulators of MDSCs. Retinoic-acid-related orphan receptor (RORC1), C/EBP homologous protein (CHOP), and paired immunoglobulin-like receptor B (PIR-B) or immunoglobulin-like receptor subfamily B member 3/Ig-like transcripts (ILTs) were observed to help immunosuppressive MDSCs. During emergency hematopoiesis, in response to G-CSF, GM-CSF, and M-CSF, RORC1/RORY supports the development of G-MDSC, M-MDSCs, and tumor-associated M2 macrophage differentiation [20]. It is suggested that depletion of RORC1 may restrict MDSC recruitment and impair the development of tumors. Another cellular stress sensor protein, CHOP was also found to be increased in M-MDSCs, but its existence in G-MDSCs is still unclear. Expression of CHOP was increased in MDSCs due to ROS and iNOS production in tumors. In the absence of CHOP, MDSCs were decreased in tumors, and T cells were modulated through C/EBP- β by decreasing IL-6 and phospho-STAT3 [78]. In fact, heterodimer C/EBP- β modulates the expression of various immunosuppressive genes, including ARG1, NOS2, and H3K4me3, to enhance the immunosuppressive activity of MDSCs in HCC [79].

Several long noncoding (lnc) RNA are found to be involved in the development of HCC. Recently, the role of lnc RNA was found to be associated with MDSCs [79]. IL-6-rich tumor environment induced the expression of lnc RNA which interacts with CHOP and liver-enriched inhibitory protein, and ultimately promotes the expression

Table 2. Role of HDAC family members

	Regulating the human biological processes	Ref.	Role in regulation of MDSCs	Ref.
HDAC1	It acts as a neurotoxin which depends on GSK3 β activity and is inhibited by the activation of PI3K-Akt signaling, while it is neuroprotective when it interacts with HDAC3	[92]	Not known	
HDAC1/2	Regulation of liver regeneration, as its loss inhibits Ki67 expression, resulting in defective hepatocyte mitosis and impaired liver regeneration Regulators of proliferation and tumorigenesis Promotes the repair of double-strand DNA breaks	[93] [93] [94]	Not known	
HDAC2	Negatively controls the learning and memory formation, as well as modulates the plasticity of synapsis	[95]	Rb1 expression inhibited by recruitment of HDAC2 to Rb1 promoter in PMN-MDSCs Caused Rb1 gene silencing, which converts M-MDSCs to G-MDSCs	[83]
HDAC3	Stimulates liver regeneration and cancer cells via STAT3 Helps in the renewal of liver cancer stem cells Promotes gluconeogenesis in liver	[96] [97] [98]	Not known	
HDAC4	Activates HSCs to cause fibrosis with the help of the HDAC4-miR-206-MRTF-A axis Absence of PHB-1 encourages the chances of cholestatic liver injury Regulates HIF-1 α cancer cell response to hypoxia	[99] [100] [101]	Not known	
HDAC5	Regulates lipogenesis process via liver X receptor Helps in maintaining fatty acid oxidation in liver via ER stress and fasting signals	[102]	Not known	
HDAC6*	Acts as tumor suppressor by activating JNK/Beclin-1-dependent autophagic cell death in HCC Promotes the progression of HCC by inhibiting P53 transcriptional activity	[103] [104]	Not known	
HDAC7	Proper B-cell development Promotes TLR4-dependent pro-inflammatory gene expression in macrophages	[105]	Repress myeloid genes whose downregulation is mainly required for the development of macrophages from pre-B cells	[105]
HDAC8	Activates β -catenin which enhances NAFLD-associated HCC Its overexpression enhances tumor growth with inhibition of apoptosis	[106] [106]	Not known	
HDAC9	HDAC9-FoxO1 signaling maintains gluconeogenesis and type 2 diabetes due to HCV Regulates adipogenesis and fat diet-related metabolic diseases	[107] [108]	Not known	
HDAC10	Associated with DNA mismatch repair gene Regulates PD-L1 expression and immune tolerance mediated by APCs	[109]	Not known	
HDAC11	Regulator of metabolism and obesity miR-155 and HDAC11 help Kupffer cells respond to LPS Regulates production of IL-10 and immune tolerance by APCs Lineage differentiation and expansion of immune cells	[110] [111] [112]	Epigenetic regulator of MDSC expansion and function	[113]

PHB-1, prohibitin-1; MDSCs, myeloid-derived suppressor cells; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; G-MDSCs, granulocytic-MDSCs; M-MDSCs, monocytic-MDSCs; PD-L1, programmed cell death ligand 1; HIF-1 α , hypoxia-inducible factor 1 α . *HDAC6 shows diverse roles and distinctly regulates different cellular processes.

of liver-enriched activator protein [79]. PIR-B in mice and ILTs in humans were also recently discovered as regulators of MDSCs. In PIR-B-deficient (*Lilrb3*^{−/−}) mice, MDSCs showed decreased suppressive function and Treg activity, resulting in less tumor growth [80], while in hu-

mans, higher ILT expression in G-MDSCs correlated well with increased survival of cancer patients [81].

Together, all these studies conclude that many factors in a tumor environment increase the MDSC population, which promotes immune escape and thereby causes

HCC growth. Blocking or suppressing these factors may lead to the reduction in growth and proliferation of the tumor.

Epigenetics Regulation in MDSCs

Epigenetic modifications are found to regulate the genomic functions, with no changes to the DNA sequence. These modifications were histone posttranslational modifications and DNA methylation. DNA or CpG methylation is a common modification at cytosine nucleotides in promoter regions which mainly influence gene expression levels [82]. DNA methylation depends on the activity of DNA methyltransferase (DNMT), which is altered in various cancers.

It has also been studied that epigenetic regulators modulate the expansion of MDSCs via RB1 expression in cancer [83]. Low expression of RB1 enhanced the ability of M-MDSCs to differentiate into G-MDSCs. DNA methylation in MDSCs causes the downregulation of MDSC-specific hyper-methylated genes, that is., RUNX1, S1PR4, and FAS, which affects not only the differentiation and suppressive activity of MDSCs but also the switching of immunogenic MDSCs to tolerogenic MDSCs [84]. In tumor MDSCs, the NOS2 promoter carries an excess amount of H3K4me3, the key target of SETD1B, and it was observed that silencing of SETD1B diminishes iNOS expression in MDSCs [85].

In addition, the role of HDACs was also documented in the regulation of MDSCs. HDACs remove acetyl groups from ϵ -N-acetyl lysine amino acids on histone and mainly regulate the chromatin structure by wrapping histones tightly to DNA. Classical HDACs are zinc-dependent, which involves class 1, 2, and 4 HDACs; however, class 3 HDACs are called as sirtuins, which basically require NAD⁺ for their function [86, 87].

DNMT enzymes are known to catalyze the transfer of a methyl group to DNA. They are of 2 main types, that is, DNMT1 and DNMT3, with the same kind of architecture and regulatory region attached to a catalytic domain. During defective myelopoiesis, differentiation of myeloid cells is known to require modification in DNA methylation depending on the expression of DNMT3A which is induced by PGE2 [84, 88]. Li et al. [89] observed that DNMT3A upregulated the expression of HDAC9 and activated antiviral innate immunity.

Inhibition of HDACs enhances both MDSC development and expansion. It was observed that HDAC inhibition via sodium butyrate and suberoylanilide hydroxam-

ic acid influenced the process of GM-CSF-mediated expansion of MDSCs both in vitro and in vivo [90], while inhibition of HDACs by entinostat and ricolinostat causes inactivation of the immunosuppressive activity of both major subsets of MDSCs [91]. The role of many HDACs in MDSC regulation is presented in Table 2 (includes Ref. [92–113]).

Out of all HDACs, HDAC6 was found to help in the phosphorylation of STAT3, which in turn accelerated MDSC generation and expansion. But the direct role of HDAC6 in the generation and expansion of MDSCs is not yet studied. In addition, HDAC11 deficiency was also noticed to regulate the expansion and suppressive activity of MDSCs [113, 114]. From these results, it can be concluded that epigenetic modifications by inactivation of HDACs may be helpful in the differentiation of MDSCs to normal myeloid cells.

Future Perspectives for MDSCs

MDSCs expand from myeloid cells and in immunosuppressive nature, which suppresses all cells but majority effector T cells. In chronic liver diseases, sepsis, and liver cancer, improving effector functions of T cells will not be sufficient until the immunosuppressive environment consisting of MDSCs is improved. Therefore, existing MDSC modulators and few pathways should be fine-tuned to control MDSC differentiation and expansion. By modulation of few HDAC inhibitors, MDSC functionality can be fine-tuned in various liver diseases. Therefore, modulated MDSCs can be used for therapeutic purposes in inflammation, cancer, and sepsis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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