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REVIEW

Noncoding RNA-Mediated Regulation of Myeloid-Derived Suppressor Cells in Cancer

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Abstract: Myeloid-derived suppressor cells (MDSCs) arise from myeloid progenitors in the bone marrow and, under the influence of tumor- and immune-cell-derived cytokines, chemokines, and growth factors, enhance immunosuppressive activity within the tumor microenvironment (TME). Noncoding RNAs (ncRNAs)—including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs)—have emerged as critical regulators of MDSCs biology. Recent evidence has shown that ncRNAs are intimately involved in MDSCs recruitment, differentiation, and suppressive function by modulating key signaling pathways, including STAT3, NF-κB, and PI3K/AKT. Mechanistically, ncRNAs act through epigenetic control (eg, histone modifications and chromatin remodeling), post-transcriptional regulation (eg, miRNA sponging), and fine-tuning of gene networks. These insights highlight RNA-based strategies that target ncRNAs to disrupt MDSCs-mediated immune suppression and potentiate antitumor immunity, while acknowledging ongoing challenges such as delivery specificity, stability, and off-target effects. This review synthesizes current understanding of how ncRNAs regulate MDSCs via major signaling axes and discusses implications for cancer progression and therapeutic development.

Keywords: ncRNAs, MDSCs, tumor, tumor microenvironment, tumor immunity

Introduction

Cancer remains a leading cause of mortality worldwide. According to GLOBOCAN 2022, nearly 20 million new cases and 9.7 million deaths were reported in that year alone.[1] Despite advances in serological testing, imaging, and endoscopy, the limited specificity of current diagnostic methods often results in late-stage detection. Likewise, standard therapeutic approaches such as neoadjuvant radiotherapy, adjuvant chemotherapy, and surgery have achieved only modest improvements in patient outcomes. These limitations underscore the urgent need for innovative strategies that target the biological mechanisms underpinning tumor progression and immune evasion.

A primary mechanism driving these clinical challenges is the tumor's ability to create a profoundly immunosuppressive tumor microenvironment (TME). This complex ecosystem allows cancer cells to evade immune surveillance and resist immunotherapy. Among the key architects of this immunosuppressive network are myeloid-derived suppressor cells (MDSCs). While their foundational biology was defined in a seminal review,[2] our current understanding continues to evolve, particularly regarding their complex roles in the human tumor microenvironment.[3] Initially described in tumor-bearing hosts as immature myeloid cells with potent suppressive activity, MDSCs have been progressively consolidated under consensus criteria, with refinements to their markers, developmental routes, and functional boundaries.[4,5] Driven by tumor- and immune-derived signals, MDSCs exert profound immunosuppressive effects, thereby facilitating tumor immune escape and resistance to conventional therapies.[5,6] Their central role has made MDSCs attractive targets for next-generation precision oncology. At the same time, unresolved complexity remains in their markers, developmental routes, and functional states.[4] In parallel with advances in tumor immunology, a deeper understanding of gene regulation has revealed noncoding RNAs (ncRNAs) as essential regulators of virtually all cellular processes.[7] These molecules—

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including long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), microRNAs (miRNAs), and PIWI-interacting RNAs (piRNAs)—are now recognized to constitute the majority of the human transcriptome.[7,8] Beyond their regulation of tumor-intrinsic processes such as proliferation, migration, and apoptosis, ncRNAs also fine-tune immune-cell function and fate decisions. Through these roles, ncRNAs help shape the tumor microenvironment, influencing immune escape and therapeutic sensitivity.[9,10] Recent studies have highlighted a direct intersection between ncRNAs and MDSCs.[11] For example, miR-155 has been implicated in modulating MDSC function and has been explored in combination delivery platforms,[12] whereas lncRNA HOTAIR recruits EZH2 to drive histone modifications that affect MDSC differentiation and function.[13] Other ncRNAs regulate tumor–immune interactions via chromatin remodeling, miRNA sponging, or exosome-mediated communication.[14–16] Notably, several regulatory effects appear context dependent, and contradictory findings have been reported across tumor types; these limitations are summarized in the sections below. Collectively, these findings position ncRNAs not only as biomarkers for cancer diagnosis but also as potential therapeutic targets for modulating MDSC activity.[17] Beyond ncRNA-mediated regulation, MDSC programs are shaped by cytokine/chemokine cues and pharmacologic or metabolic interventions. Tumor-derived GM-CSF/G-CSF/IL-6–STAT3 signaling, arginase-1/iNOS-driven metabolic rewiring, and nanoparticle-based drug delivery systems have each demonstrated MDSC-suppressive activity in preclinical models.[2,3,15] These strategies provide a complementary framework against which ncRNA-centered approaches can be interpreted. This review therefore summarizes the molecular mechanisms by which ncRNAs regulate MDSCs across diverse tumor contexts, highlighting their implications for cancer progression and therapy.

MDSCs: Key Roles in Tumor Biology

The Origin and Development of MDSCs

MDSCs are pivotal immunosuppressive cells originating from myeloid progenitors in the bone marrow. Under normal physiological conditions, these progenitor cells differentiate into essential immune effectors, including monocytes, macrophages, dendritic cells, and granulocytes, forming the frontline defense of the host.[18] However, pathological states such as chronic inflammation or cancer disrupt this orderly differentiation, leading instead to the abnormal accumulation of immunosuppressive MDSCs.[19] This disrupted maturation significantly facilitates immune evasion by tumors and is involved in various other pathological scenarios, as illustrated in Figure 1.

The differentiation of MDSCs is intricately governed by diverse inflammatory signals, notably granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), which play key roles in their regulation.[20] These cytokines often accumulate excessively within the tumor microenvironment, inducing myeloid progenitors to adopt immunosuppressive characteristics.[21] Additionally, other cytokines like interleukins (IL-6, IL-1β), chemokines, and tumor necrosis factor-alpha (TNF-α) significantly contribute to this differentiation process.[22–24] The combined action of these factors promotes aberrant differentiation of myeloid progenitors, ultimately leading to the enhanced production of immunosuppressive MDSCs under pathological conditions.

Subtypes of MDSCs

MDSCs represent a pathological state of activated monocytes and relatively immature neutrophils. In murine models, MDSCs are generally divided into two main subsets, distinguished by the hallmark surface markers GR-1 and CD11b: monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (G-MDSCs), also referred to as polymorphonuclear MDSCs (PMN-MDSCs). M-MDSCs are characterized by the surface markers $CD11b^{+}Ly6C^{high}Ly6G^{low/-}$, while PMN-MDSCs are defined by $CD11b^{+}Ly6C^{low/-}Ly6G^{+}$.[25] Unlike murine MDSCs, human MDSCs lack the expression of GR-1, resulting in distinct classification criteria. In human peripheral blood mononuclear cells, MDSCs are typically identified by the phenotype $CD33^{+}$, $CD11b^{+}$, and $HLA\text{-}DR^{low/-}$. Based on the expression of CD15 and CD14 markers, human MDSCs are classified into granulocytic MDSCs (G-MDSCs) and monocytic MDSCs (M-MDSCs).[26] Additionally, a distinct subset of bone marrow progenitor cells with MDSC-like characteristics, termed "early-stage myeloid-derived suppressor cells" (eMDSCs), has been identified exclusively in humans. This population primarily comprises bone marrow progenitor and precursor cells, accounting for less than 5% of the total MDSC population. eMDSCs are defined by the surface markers

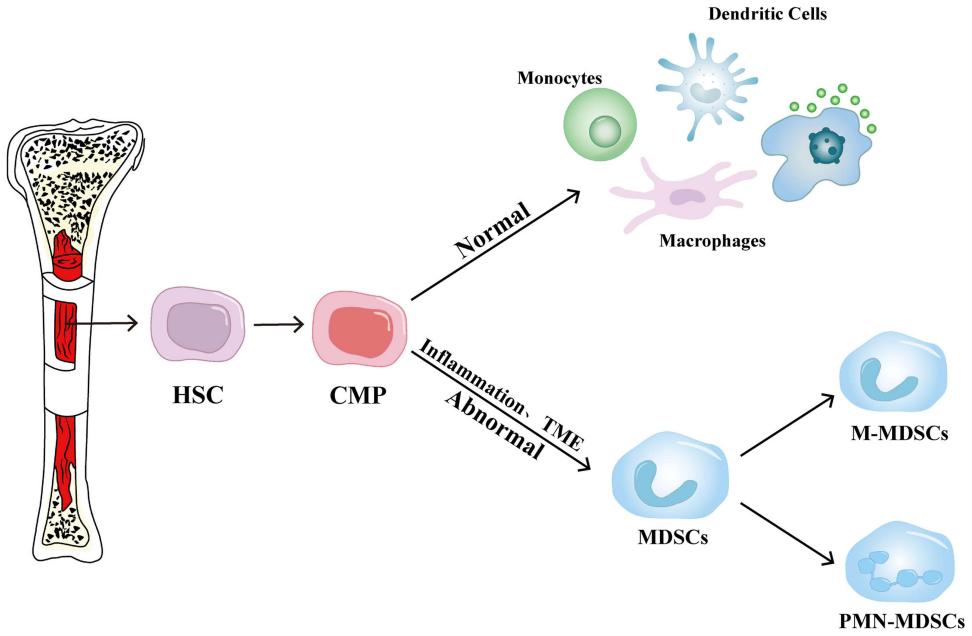

Figure 1 Origin and development of MDSCs. Under normal physiological conditions, hematopoietic stem cells (HSCs) and common myeloid progenitors (CMPs) differentiate into monocytes, dendritic cells, and macrophages. However, in the presence of inflammation or abnormalities in the tumor microenvironment (TME), CMPs give rise to immature MDSCs. These MDSCs further differentiate into monocytic MDSCs (M-MDSCs) or polymorphonuclear MDSCs (PMN-MDSCs), both of which play a key role in mediating immunosuppression within the TME.

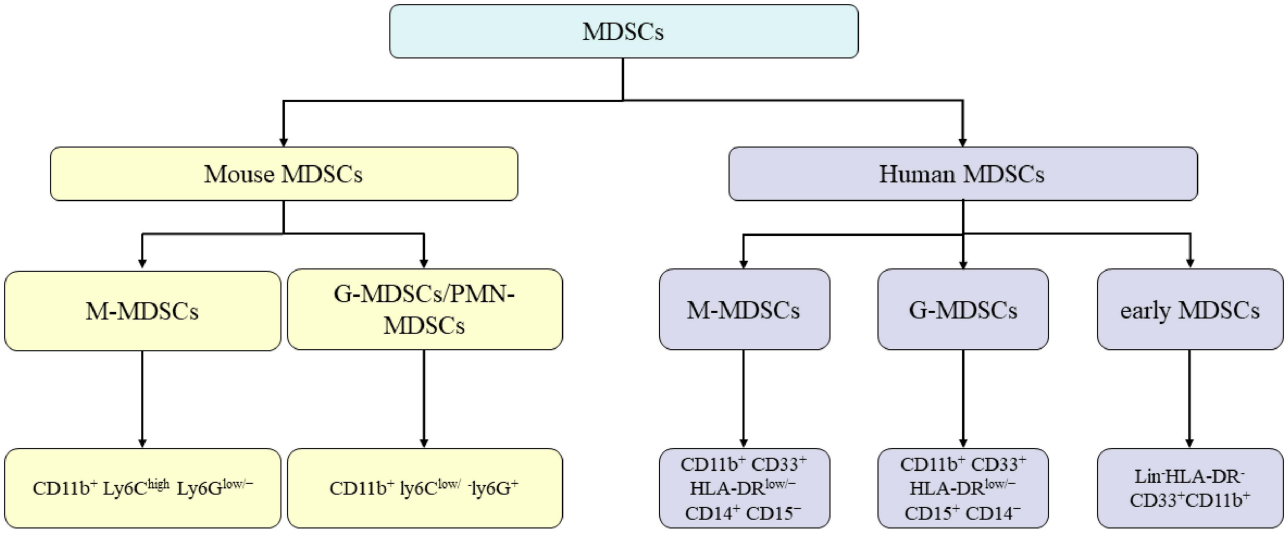

Figure 2 The Classification and Characteristics of MDSCs. MDSCs are broadly classified into monocytic MDSCs (M-MDSCs) and granulocytic/polymorphonuclear MDSCs (G-MDSCs/PMN-MDSCs) in both mice and humans. In mice, M-MDSCs are identified by the surface markers $CD11b^+$ $Ly6C^{high}$ Ly6G $^{low/-}$, while G-MDSCs/PMN-MDSCs are characterized as $CD11b^+$ $Ly6Cl^{low/-}$ $Ly6G^+$. In humans, M-MDSCs are $CD11b^+$ $CD33^+$ HLA-$DR^{low/-}$ $CD14^+$ $CD15^-$.and G-MDSCs are $CD11b^+$ $CD33^+$ HLA-$DR^{low/-}$ $CD15^+$ $CD14^-$. An additional subset, early-stage MDSCs (eMDSCs), is identified in humans by the markers Lin− HLA-DR− $CD33^+$ $CD11b^+$.

$Lin^-HLA\text{-}DR^-CD33^+$ $CD11b^+$, where "Lin" refers to a lineage-negative panel that includes CD3, CD14, CD15, CD19, and CD56[27–29] (Figure 2).

Mechanisms of MDSCs Formation

MDSCs are pivotal in establishing the TME and play an essential role in immune evasion and tumor progression. Key signaling pathways such as STAT3, NF-κB, and PI3K/AKT play crucial roles in regulating MDSCs recruitment, differentiation, and expansion. These pathways are activated by cytokines and growth factors within the TME and

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work synergistically to promote MDSCs function. STAT3, for example, promotes MDSCs proliferation and survival, contributing to their expansion within the TME.[30,31] NF-κB signaling enhances MDSCs differentiation and facilitates their immune suppressive function.[32] PI3K/AKT signaling is involved in metabolic reprogramming, supporting MDSCs survival and immune suppression.[33] Together, these signaling pathways orchestrate the formation of an immune-suppressive niche that not only facilitates tumor growth but also promotes resistance to immune checkpoint inhibitors and other cancer therapies.

The recruitment, differentiation, and expansion of MDSCs are regulated by a sophisticated interplay of cytokines, chemokines, and growth factors secreted by tumor and immune cells.[3] Tumor-derived chemokines such as CXCL8 (in humans) and CXCL5 (in mice) are key regulators of MDSCs recruitment, directing these cells to the tumor site, where they suppress the infiltration and function of effector immune cells, including T cells and natural killer (NK) cells.[34] Furthermore, signaling through B7H3 and CXCR4 is integral to MDSCs recruitment, with tumor-derived exosomes activating the TLR2/NF-κB pathway, thereby enhancing MDSCs infiltration and fostering immune suppression within the TME.[35,36]

Upon entering the TME, MDSCs differentiate into various immunosuppressive cell types, such as regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs), all of which contribute to the tumor's ability to escape immune detection.[37] The differentiation of MDSCs is primarily driven by cytokines such as G-CSF, IL-6, and GM-CSF, which facilitate the conversion of MDSCs into Tregs and TAMs, thereby promoting the establishment of an immunosuppressive microenvironment conducive to tumor growth.[38,39] In addition, netrin-1, secreted by tumor cells, significantly facilitates the differentiation of MDSCs via its receptor A2BR, thereby amplifying immune escape and accelerating tumor progression.[40]

The expansion of MDSCs is primarily driven by persistent inflammation and the continuous secretion of growth factors such as G-CSF, GM-CSF, and IL-6, alongside activation of the CXCR2/CXCL1 signaling axis. This not only facilitates MDSCs migration into the tumor site but also enhances their proliferative capacity, resulting in a significant accumulation of MDSCs within the TME.[41] The increased presence of MDSCs exacerbates immune suppression, further promoting tumor metastasis and resistance to both conventional and immunotherapies.[42] Moreover, MDSCs maintain an immunosuppressive niche in the TME through the secretion of cytokines such as IL-10 and TGF-β, which dampen effector immune responses and allow tumor cells to evade immune detection and resist therapeutic interventions.[43,44]

Importantly, targeting MDSCs recruitment, differentiation, and expansion holds significant therapeutic potential, as it may enhance the efficacy of immune-based therapies and improve patient outcomes in cancer treatment.

Mechanisms of Action of MDSCs

MDSCs are a population of myeloid-derived cells with potent immunosuppressive properties, and they are commonly found in the majority of cancer types.[45] The key mechanisms underlying their activity can be outlined as follows:

Initially, MDSCs suppress immune responses through a variety of mechanisms, exerting multiple effects on T cell function. By secreting immunosuppressive molecules, including arginase and nitric oxide synthase, MDSCs directly interfere with T cell activity. These molecules deplete critical amino acids, such as L-arginine, in the local microenvironment, thereby restricting T cell proliferation and activation.[46] Moreover, MDSCs indirectly suppress T cell activation and function by secreting immunosuppressive cytokines, notably TGF-β and IL-10.[47] These factors collectively dampen T cell responsiveness, significantly weakening the overall immune defense.

In addition to direct suppression of T cells, MDSCs enhance immune suppression indirectly by stimulating the expansion and function of Tregs. The increased number and activity of Tregs restrict the activation of other immune populations, further suppressing immune responses.[48] Direct cell-to-cell interactions between MDSCs and T cells, involving inhibitory surface molecules such as PD-1 ligands, have also been shown to suppress T cell functions, thus intensifying the immune-suppressive environment.[49]

Furthermore, MDSCs actively support tumor progression and metastasis by modulating the TME. They release multiple cytokines and chemokines, such as VEGF, IL-6, and IL-1β, exacerbating local inflammation and creating conditions favorable for tumor growth. Additionally, MDSCs facilitate tumor angiogenesis, enhancing blood vessel formation to supply nutrients, further promoting tumor expansion and dissemination.[50]

Lastly, MDSCs boost tumor invasiveness by supporting metastatic processes. They secrete enzymes like matrix metalloproteinases (MMPs), which degrade and remodel the extracellular matrix (ECM), facilitating tumor cell invasion and spread.[51] MDSCs also migrate to distant pre-metastatic sites, where they produce cytokines such as CXCL12, establishing an immunosuppressive microenvironment conducive to metastatic tumor cell colonization and growth, thus significantly aiding tumor metastasis and progression.[52]

Together, these mechanisms position MDSCs as critical factors in tumor growth, immune suppression, and metastasis (Figure 3).

Regulation of MDSCs by miRNAs in Tumors

Digestive System Tumor

In digestive system tumors, miRNAs play a pivotal role in modulating the immunosuppressive functions of MDSCs through various signaling pathways, including STAT3, PI3K/AKT, TGF-β/SMAD, NF-κB, and PD-L1-mediated immune evasion. These pathways regulate MDSC recruitment, differentiation, and activation, thus facilitating tumor progression and immune escape.

The STAT3 pathway is a central regulator of MDSC activity. It is crucial for MDSC proliferation, survival, and immune suppression. miR-155 enhances MDSC immunosuppressive functions in colorectal cancer by targeting SOCS1,

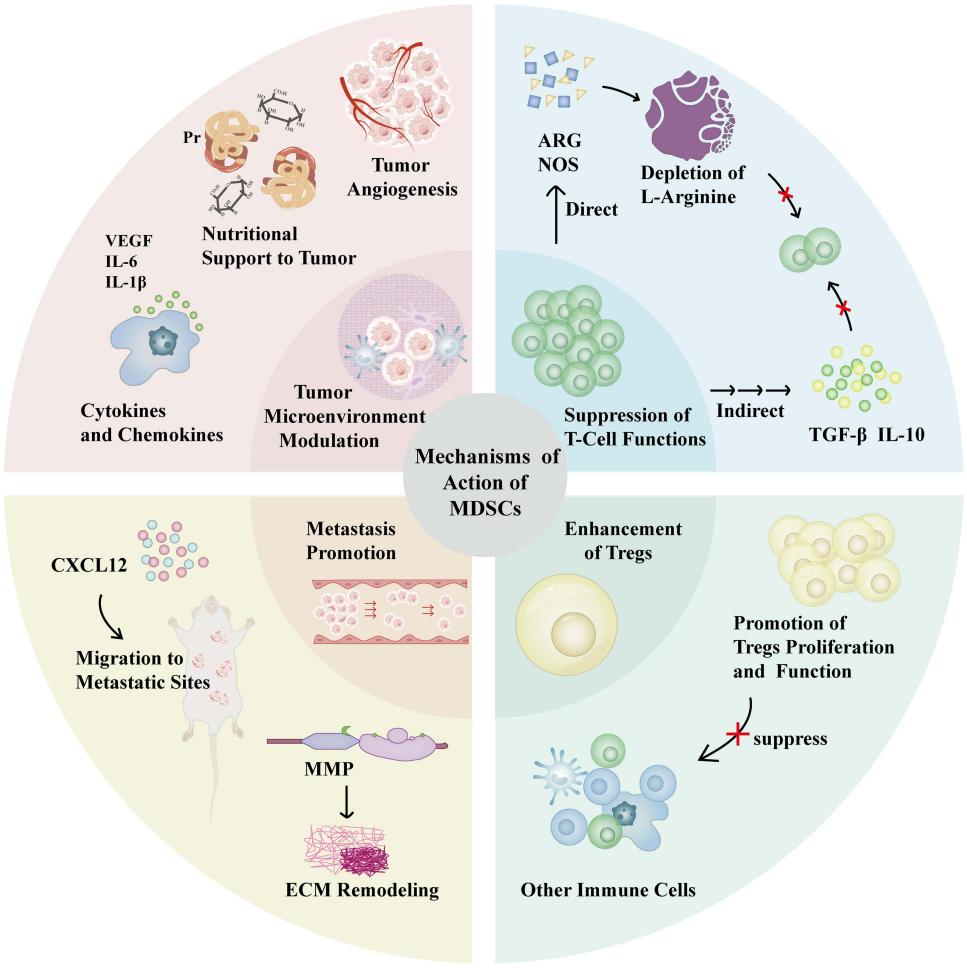

Figure 3 Schematic representation of the functional roles of MDSCs in the TME. MDSCs utilize multiple mechanisms to suppress immune responses and facilitate cancer progression. They secrete immunosuppressive molecules (eg, ARG, NOS, TGF-β, IL-10), which suppress T-cell function both directly and indirectly. MDSCs also promote the proliferation and activity of Tregs and release cytokines (eg, VEGF, IL-6, IL-1β) to remodel the TME and drive inflammation. In addition, MDSCs contribute to tumor angiogenesis by supporting vascular development, facilitate ECM remodeling through the secretion of MMPs, and migrate to pre-metastatic sites, where they secrete chemokines such as CXCL12 to establish an immunosuppressive niche. Collectively, these mechanisms enhance tumor growth, immune evasion, and metastasis.

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which amplifies STAT3 activation and accelerates tumor progression.[53] In esophageal cancer, CAFs secrete IL-6 and exosomal miR-21, which activate STAT3 signaling, inducing M-MDSC generation and promoting the secretion of immunosuppressive cytokines like IL-10 and TGF-β, which inhibit CD8+ T cell activity and contribute to chemotherapy resistance.[54]

The PI3K/AKT pathway is another critical signaling mechanism in MDSCs regulation. miR-494 in gastric cancer is regulated by tumor-secreted TGF-β, which upregulates miR-494 expression, leading to PTEN downregulation and PI3K/AKT activation. PTEN is a tumor suppressor gene that negatively regulates the PI3K/AKT pathway. In its absence or reduced expression, this pathway becomes hyperactivated, which promotes MDSCs-mediated inhibition of T cell proliferation and interferon-γ production, further promoting immune suppression.[55] Likewise, miR-26b-5p promotes differentiation and immunosuppressive activities of MDSCs in esophageal cancer by targeting PTEN, facilitating immune evasion and metastatic progression.[56]

The TGF-β/SMAD signaling pathway significantly influences MDSC function, driving their differentiation, improving survival, and enhancing their immunosuppressive capacity. In hepatocellular carcinoma, decreased expression of miR-101-3p and miR-490-3p elevates TGFBR1 levels, resulting in increased infiltration and immunosuppressive potential of MDSCs.[57] Moreover, in gastric cancer, CAF-derived TGF-β further amplifies MDSC-mediated immune suppression via miR-494, forming a self-reinforcing loop that strengthens TGF-β/SMAD signaling.[55]

The NF-κB pathway represents another critical route through which MDSCs are regulated, particularly under inflammatory and immunosuppressive conditions. For instance, in gastric cancer, miR-130b enhances NF-κB activity by targeting CYLD, boosting the immunosuppressive functions of $SLFN4^+$ MDSCs. This activation promotes gastric epithelial cell proliferation and the initiation of premalignant lesions.[58] NF-κB signaling further amplifies the release of pro-inflammatory cytokines and immunosuppressive mediators, thus supporting tumor immune escape.

Additionally, miRNAs regulate immune evasion mechanisms involving PD-L1. For example, in colorectal cancer, miR-570 expression is suppressed by ZnC, thereby enhancing the immunosuppressive role of MDSCs and accelerating tumor progression.[59] miR-93 and miR-106b also influence the bone marrow microenvironment by repressing CXCL12 expression, reducing stem cell migration and diminishing MDSC-mediated suppression of T cells via the inhibition of PD-L1.[60]

Gynecological Tumor

miRNAs significantly influence MDSCs activity in gynecological tumors through various signaling cascades, including SOCS3-JAK/STAT, NF-κB, HIF-1α, and oxidative stress pathways. These pathways collectively regulate MDSCs recruitment, differentiation, and immunosuppressive functions, facilitating immune evasion and tumor progression.

The SOCS3/JAK/STAT pathway represents a critical regulatory mechanism in gynecological cancers mediated by miRNAs. miR-9 targets SOCS3, a known suppressor of JAK/STAT signaling, promoting MDSC recruitment and increasing their suppressive capacity within the breast cancer microenvironment, thus supporting tumor growth and immune evasion.[61] Exosomal miR-9 and miR-181a secreted by breast cancer cells also intensify JAK/STAT activation by targeting SOCS3 and PIAS3, significantly expanding eMDSCs and enhancing their immunosuppressive effects, further enabling tumor progression and immune escape.[62] Similarly, miR-155 aids the recruitment and activity of MDSCs in tumors, contributing to immune suppression. Delivery systems using miR-155 inhibitors have demonstrated potential in reducing MDSC populations, impairing their suppressive functions, and boosting antitumor $CD8^+$ T cell responses.[12]

NF-κB signaling is another essential miRNA target in gynecological cancers. miR-146a suppresses NF-κB signaling in breast cancer, reducing immunosuppressive factor secretion by MDSCs and promoting their polarization toward an M1 phenotype. This shift diminishes MDSC numbers and enhances $CD8^+$ T cell-mediated antitumor immunity.[63] Furthermore, miR-146a and miR-155 regulate MDSC function via the NF-κB pathway, modulating the activities of effector T cells and Tregs.[64] In ovarian cancer, miR-211 inhibits both NF-κB and STAT3 signaling through targeting CHOP, thus disrupting MDSC differentiation and immunosuppressive functions. CHOP, an ER stress-related transcription factor, regulates cellular stress responses and apoptosis pathways. Through downregulating CHOP, miR-211 impairs MDSC immunosuppression, enhancing $CD4^+$ and $CD8^+$ T cell antitumor responses.[65,66]

The HIF-1α pathway also critically modulates MDSC functions in gynecological malignancies via miRNAs. Specifically, miR-210 enhances MDSC immunosuppression by influencing HIF-1α expression, suppressing effector T cell activity, and increasing IL-10 and TGF-β production, thereby supporting immune evasion and tumor progression.[67]

Finally, miRNAs regulate oxidative stress pathways affecting MDSC activity. In ovarian cancer, miR-17-5p and miR-20a downregulate STAT3 and NADPH oxidase subunits (p47phox, gp91phox), decreasing ROS and H_2O_2 production. This reduction mitigates MDSC-mediated suppression of antigen-specific $CD4^+$ and $CD8^+$ T cells, impeding tumor advancement.[68]

Hematologic Tumor

In lymphoma, the upregulated expression of miR-30a enhances the immunosuppressive capabilities of MDSCs and inhibits T cell function by increasing the secretion of immunosuppressive molecules, including Arg-1 and IL-10, thereby facilitating tumor immune evasion.[69] Similarly, miR-21 and miR-155 intensify MDSCs functions through the activation of multiple signaling pathways such as TGF-β, IL-6, and JUN, further promoting immune suppression in the tumor microenvironment. Conversely, miR-130b influences MDSCs activity via the IGF1 signaling pathway, aiding in immune suppression and tumor advancement. Additionally, decreased miR-28 expression is linked to reduced MDSCs numbers and diminished immunosuppressive function, suggesting its critical role in modulating immune responses.[70]

Lung Cancer

Within lung cancer, miR-300 facilitates tumor immune evasion and progression by regulating the KLF9/GADD34 signaling axis, thereby promoting the expansion and immunosuppressive phenotype of MDSCs in the TME.[71] Additionally, the receptor complex LILRB4/gp49B strengthens MDSCs immunosuppressive functions by suppressing miR-1 family expression, thus favoring MDSC differentiation into the immunosuppressive M2 subtype.[72] MDSC-derived exosomal miR-126a critically modulates the TME, significantly enhancing MDSC-mediated immunosuppression and promoting tumor growth.[73] Furthermore, miR-143-3p boosts MDSCs immunosuppressive activity by targeting the tumor suppressor gene ITM2B, resulting in the activation of PI3K/Akt signaling.[74] miR-21 regulates MDSCs stability and survival by downregulating SORBS1 expression, promoting MDSC accumulation and their immunosuppressive capacity in the TME.[75] Finally, miR-21a enhances MDSC-driven immune suppression through suppression of PDCD4, increasing autocrine IL-6 production and subsequent activation of STAT3 phosphorylation, further consolidating immune evasion in lung cancer.[76]

Glioma

In glioma, MSC-derived exosomes containing miR-21 significantly enhance MDSC immunosuppressive functions through activation of the PTEN/PI3K/AKT/HIF-1α signaling pathway.[77,78] Tumor-derived exosomes enriched with miR-1246 induce differentiation and activation of monocytic MDSCs (M-MDSCs) via the DUSP3/ERK pathway, thus increasing their suppressive capacity.[79] Under hypoxic conditions, glioma-derived exosomes (H-GDEs) carrying miR-10a and miR-21 notably enhance MDSC expansion and their immunosuppressive function. Specifically, miR-10a targets the RORA gene to activate IκBα/NF-κB signaling, while miR-21 inhibits PTEN to enhance PI3K/AKT pathway activity.[78] Exosomal miR-1298-5p derived from glioma cells significantly promotes MDSC immunosuppressive functions by targeting MSH2 and activating NF-κB signaling, leading to increased NOS2 and TGF-β expression. Further experimental evidence indicates these miR-1298-5p-loaded exosomes markedly augment MDSC suppression of T cell proliferation.[80] miR-29a enhances MDSCs proliferation by targeting the Hbp1 gene, whereas miR-92a augments their immunosuppressive functions by repressing Prkar1a, activating the PKA/p-STAT3 signaling cascade.[81]

Melanoma

In melanoma, tumor-derived exosomes carry miRNAs (including miR-146a, miR-155, miR-125b, miR-100, etc.) that target and regulate key signaling pathways such as STAT3, NF-κB, and PI3K/AKT. These miRNAs promote MDSCs expansion and activation, while suppressing the proliferation and function of effector T cells.[82] In $CD133^+$ melanoma stem cells, downregulation of miR-92 leads to upregulation of integrins αV and α5, enhancing TGF-β activation. This, in

turn, increases the immunosuppressive effects of MDSCs via the SMAD2 signaling pathway.[83] Under tumor conditions, activation of the CXCR2 signaling pathway significantly upregulates the expression of miR-449c, which inhibits STAT6 translation. This shift alters the differentiation balance of bone marrow progenitor cells, promoting the expansion of M-MDSCs.[84]

Other Tumors

In thyroid cancer, miR-486-3p has been seen as a target of the NF-κB2 gene. Downregulation of miR-486-3p contributes to the excessive activation of the NF-κB2 signaling pathway, which in turn promotes cancer cell metastasis and invasion. Restoration of miR-486-3p expression significantly inhibits PMN-MDSC-mediated activation of NF-κB2, thereby reducing thyroid cancer cell migration and invasion.[85] Additionally, miR-142-3p regulates the immunosuppressive function of MDSCs by targeting the C/EBPβ pathway. Downregulation of C/EBPβ reduces the number of TAMs in fibrosarcoma, while simultaneously promoting the accumulation of M-MDSCs, thereby enhancing immune suppression.[86] Under hypoxic conditions, exosomes secreted by oral squamous cell carcinoma cells exhibit significantly upregulated expression of miR-21, which promotes the expansion of MDSCs and further enhances their immunosuppressive function.[87]

In summary, miRNAs play a critical role in regulating the recruitment, differentiation, and immunosuppressive functions of tumor-associated MDSCs across various cancer types (Figure 4) (Table 1).

Regulation of MDSCs by lncRNAs in Tumors

Digestive System Tumor

Recent study has shown that lncRNA Lnc-17 Rik enhances the immunosuppressive functions of MDSCs by increasing Arg-1 activity in M-MDSCs and boosting H_2O_2 production inPMN-MDSCs.[88] Zheng et al demonstrated that Pvt1 is upregulated by HIF-1α under hypoxic conditions, thereby modulating the function and differentiation of G-MDSCs.[89] MIR4435-2HG, a long non-coding RNA previously identified as oncogenic, was reported by Zhang et al to facilitate

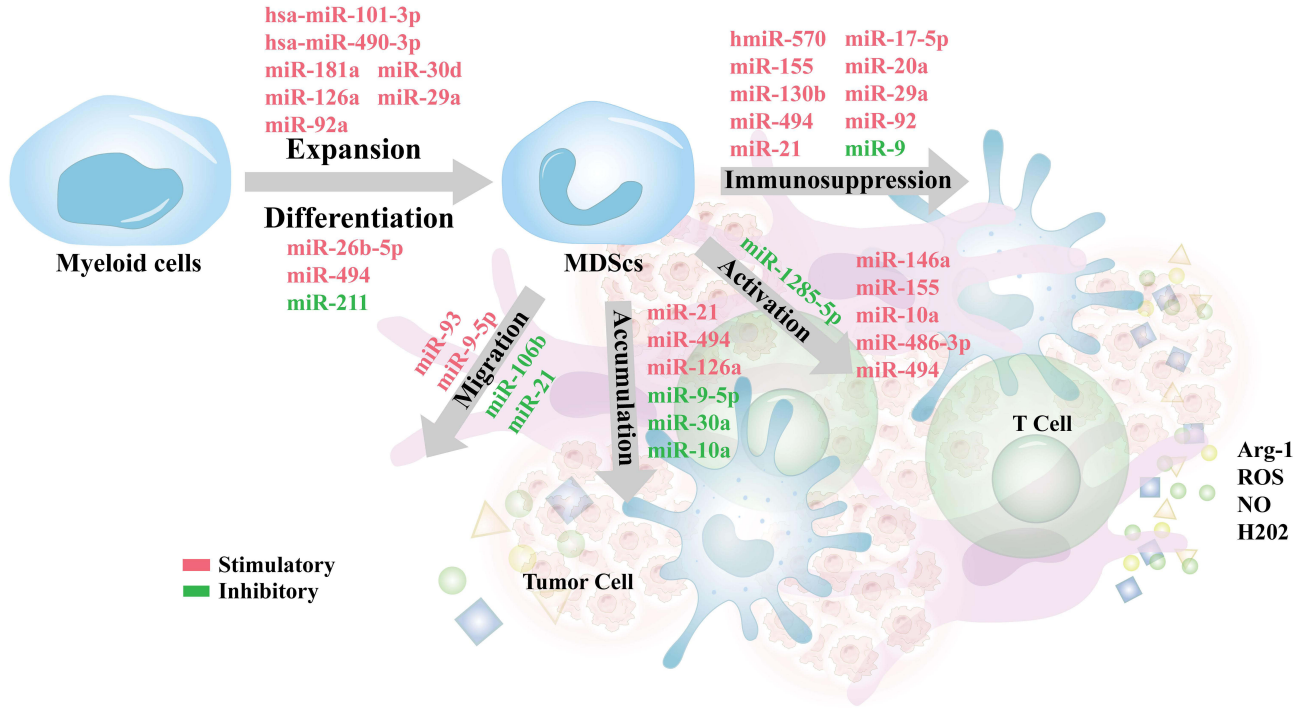

Figure 4 Regulatory roles of miRNAs in MDSCs expansion, differentiation, accumulation, activation, and immunosuppressive functions within the tumor microenvironment. miRNAs such as miR-101-3p, miR-490-3p, and miR-30d promote MDSCs expansion, while miR-494 and miR-211 regulate their differentiation. The accumulation of MDSCs is influenced by miRNAs including miR-21, miR-494, and miR-126a. Activation of MDSCs is driven by miRNAs such as miR-155, miR-9, and miR-146a, which enhance their immunosuppressive capacities through the production of Arg-1, ROS, NO, and H2O2, ultimately suppressing effector T cell function.

Table 1 Mechanisms of miRNAs Regulation of Tumor MDSCs

Tumor	miRNAs	miRNAs Regulation (Up/Down)	Mechanism	Impact On MDSCs	Impact On Cancer	miRNAs main Source	Reference
Digestive system tumor	miR-101-3p, miR-490-3p	Upregulated	Upregulate TGFBR1 and activate the TGF-β/SMAD pathway	Enhance the infiltration and immunosuppressive function of MDSCs	Promote cancer	CAFs	[57]
	miR-93,miR-106b	Downregulated	Downregulate CXCL12, affecting the homing and migration capabilities of stem cells in the bone marrow microenvironment, while simultaneously inhibiting the expression of PD-L1	Weaken the suppressive effect of MDSCs on T cell activation	Suppress cancer	Tumor cells	[60]
	miR-570	Upregulated	Enhances PD-L1-mediated immune escape capacity	Promotes the immunosuppressive function of MDSCs	Promote cancer	Tumor Cells	[59]
	miR-155	Upregulated	Inhibits SOCS1 expression and enhances STAT3 activity	Promotes the immunosuppressive function of MDSCs	Promote cancer	Host immune cells and tumor exosomes	[53]
	miR-130b	Upregulated	Targets CYLD, and activates the NF-κB signaling pathway	Regulates the immunosuppressive function of SLFN4+ MDSCs	Promote cancer	SLFN4+ MDSCs	[58]
	miR-494	Downregulated	Downregulates PTEN levels and activates the PI3K/Akt signaling pathway in gastric cancer	Promotes the immunosuppressive function of MDSCs	Promote cancer	Tumor-infiltrating MDSCs	[55]
	miR-26b-5p	Downregulated	Targets PTEN and activates the PI3K/AKT signaling pathway	Promotes the differentiation and immunosuppressive capacity of MDSCs	Promote cancer	Exosomes from apoptotic tumor cells	[56]
	miR-21	Upregulated	Activates the STAT3 signaling pathway	Induces the generation of M-MDSCs and enhances their immunosuppressive function	Promote cancer	CAF-derived exosomes	[54]
Gynecological tumor	miR-9	Upregulated	Downregulates SOCS3 expression	Promotes the immunosuppressive function of MDSCs	Promote cancer	Tumor cells	[61]
	miR-146a	Upregulated	Inhibits the NF-κB signaling pathway.	Reduces the proportion of MDSCs	Suppress cancer	ICAM-1-decorated exosomes	[63]
	miR-155	Downregulated	Directly targets MDSCs	Reduces the proportion of MDSCs in the tumor and inhibits their immunosuppressive function	Suppress cancer	Host immune cells and tumor exosomes	[12]
	miR-9,miR-181a	Upregulated	Targets SOCS3 and PIAS3 to activate the JAK/STAT signaling pathway	Enhances the expansion and immunosuppressive function of eMDSCs	Promote cancer	Tumor-derived exosomes	[62]
	miR-146	Upregulated	Targets key nodes such as the NF-κB signaling pathway	Regulates the function of MDSCs	Promote cancer	ICAM-1-decorated exosomes	[64]
	miR-210	Upregulated	Targets and regulates the HIF-1α signaling pathway	Promotes the immunosuppressive function of MDSCs	Promote cancer	Hypoxic tumor microenvironment	[67]
	miR-211	Upregulated	Targets the CHOP gene and inhibits the NF-κB and STAT3 signaling pathways	Weakens the differentiation and immunosuppressive function of MDSCs	Suppress cancer	MDSCs	[65]
	miR-21,miR-21b,miR-181b	Upregulated	Induce expression through the STAT3/C/EBPβ pathway and inhibits its expression by targeting the 3' untranslated region (UTR) of Wdr5, Ash2l, and Mll1, thereby disrupting the function of the MLL1 complex	Promotes the accumulation and enhanced immunosuppressive function of MDSCs	Promote cancer	PMN-MDSCs	[66]
	miR-17-5p, miR-20a	Downregulated	Inhibits the translation of STAT3 and reduces NADPH oxidase	Weakens the suppressive capacity of MDSCs on antigen-specific $CD4^+$ and $CD8^+$ T cells	Suppress cancer	MDSCs	[68]

(*Continued*)

Table 1 (Continued).

Tumor	miRNAs	miRNAs Regulation (Up/Down)	Mechanism	Impact On MDSCs	Impact On Cancer	miRNAs main Source	Reference
Hematological tumor	miR-30a	Upregulated	Directly targets MDSCs	Promotes the immunosuppressive function of MDSCs	Promote cancer	Tumor cells	[69]
	miR-21,miR-155, miR-130b, miR-28	Upregulated	Exerts their effects through the TGF-β, IL-6, IGF1, and JUN signaling pathways	Enhances the activity of MDSCs and regulates their function	Promote cancer	Tumor cells	[70]
Lung tumor	miR-300	Upregulated	Regulates the KLF9/GADD34 axis	Enhances the expansion and immunosuppressive function of MDSCs	Promote cancer	Tumor cells	[71]
	miR-1 family	Downregulated	Directly targets MDSCs	Promotes the immunosuppressive function of MDSCs	Promote cancer	MDSC-derived exosomes	[72]
	miR-126a	Upregulated	Plays a key role in the tumor microenvironment through MDSC-derived exosomes	Promotes the immunosuppressive function of MDSCs	Promote cancer	MDSC-derived exosomes	[73]
	miR-143-3p	Upregulated	Targets and inhibits the tumor suppressor ITM2B, activating the PI3K/Akt signaling pathway	Promotes the immunosuppressive function of MDSCs	Promote cancer	G-MDSCs-derived exosomes	[74]
	miR-21	Downregulated	Targets and inhibits the expression of SORBS1	Regulates the stability and survival of MDSCs and reduces their accumulation in the tumor microenvironment	Suppress cancer	Tumor cells	[75]
	miR-21a	Upregulated	Targets PDCD4, downregulates its expression, thereby activating autocrine IL-6 production and promoting STAT3 phosphorylation	Promotes the immunosuppressive function of MDSCs	Promote cancer	Exosomes from Lewis lung carcinoma cells	[76]
Glioma	miR-21	Upregulated	Activates the PTEN/PI3K/AKT/HIF-1α pathway	Enhances the immunosuppressive function of MDSCs.	Promote cancer	Glioma-derived exosomes	[77,78]
	miR-1246	Upregulated	Regulates the DUSP3/ERK signaling pathway, driving the differentiation and activation of M-MDSCs	Promotes the immunosuppressive function of M-MDSCs	Promote cancer	Glioma patient body fluids	[79]
	miR-10a	Upregulated	Targets the RORA gene and activates the IκBα/NF-κB signaling pathway	Promotes the expansion and immunosuppressive function of MDSCs	Promote cancer	Glioma-derived exosomes	[78]
	miR-1298-5p	Downregulated	Targets the MSH2 gene and activates the NF-κB signaling pathway, promoting the expression and secretion of NOS2 and TGF-β in MDSCs	Enhances the ability of MDSCs to suppress T cell proliferation	Promote cancer	Glioma-derived exosomes	[80]
	miR-29a, miR-92a	Upregulated	Target the Hbp1 and Prkar1a genes, activating the PKA/p-STAT3 signaling pathway	Promote MDSC cell cycle progression and enhances their immunosuppressive function	Promote cancer	Glioma-derived exosomes	[81]
	miR-146a,miR-155.miR-125b, miR-100	Upregulated	Target and regulates key signaling pathways, such as the STAT3, NF-κB, and PI3K/AKT pathways	Promote the expansion and activation of MDSCs	Promote cancer	Tumor cells, MDSC-derived exosomes	[82]
	miR-92	Downregulated	Leads to the upregulation of integrin αV and α5 expression, enhancing TGF-β activation, and further exerting its effects through the SMAD2 signaling pathway	Promotes the immunosuppressive function of M-MDSCs	Promote cancer	Tumor-derived exosomes	[83]
Other tumors	miR-449c	Upregulated	Inhibits the translation of STAT6, thereby altering the differentiation balance of bone marrow precursor cells	Promotes the expansion of M-MDSCs	Promote cancer	Tumor cells	[84]
	miR-486-3p	Downregulated	Directly targets the NF-κB2 gene,its downregulation leads to excessive activation of the NF-κB2 pathway	Promotes PMN-MDSC-mediated NF-κB2 activation	Promote cancer	Peripheral blood circulation MDSCs	[85]
	miR-142-3p	Upregulated	Targets the C/EBPβ pathway	Regulates the immunosuppressive function of MDSCs	Suppress cancer	Tumor cells	[86]
	miR-21	Upregulated	Directly targets MDSCs	Promotes the expansion of MDSCs and enhances their immunosuppressive function	Promote cancer	Tumor-derived exosomes	[87]

tumor initiation and progression in models of colitis-associated cancer and spontaneous intestinal adenomatous polyposis. This pro-tumorigenic effect is associated with the loss of MIR4435-2HG, which results in an increased infiltration of PMN-MDSCs into the tumor microenvironment and augments their immunosuppressive functions, rather than directly affecting cancer cell proliferation, migration, or invasion.[90] Furthermore, Lnc-C/EBPβ modulates the expression of C/EBPβ LIP and WDR5, leading to the downregulation of IL4i1, which in turn impacts MDSC differentiation. The reduced IL4i1 levels may impair the immunoregulatory function of MDSCs, thereby influencing tumor immune evasion.[91] Overexpression of lncRNA 57Rik not only upregulates key immunosuppressive genes, including Arg-1 and NOS2, thereby enhancing the suppressive function of MDSCs, but also promotes the release of metabolic byproducts such as Arg-1, NO, and H2O2, which inhibit T cell proliferation and function.[92] Recent studies have shown that Olfr29-ps1, a lncRNA, is upregulated in MDSCs in response to the tumor-associated factor IL6. This upregulation results in the suppression of miR-214-3p expression, which leads to increased MyD88 levels. Consequently, elevated MyD88 expression enhances both the immunosuppressive function and differentiation of MDSCs.[93] Studies have shown that lncRNA HOTAIR (Hox antisense intergenic RNA), a member of the HOXC gene cluster, promotes CCL2 secretion through its overexpression, which in turn induces the proliferation of monocytes and MDSCs.[13] CRNDE (Colorectal Neoplasia Differentially Expressed), a long non-coding RNA implicated in tumor promotion, has been detected across multiple cancer types. Li et al revealed that CRNDE upregulates CXCL3 expression, leading to the recruitment of G-MDSCs into the TME, which subsequently suppresses CD8+ T cell infiltration and function.[94]

Lung Cancer

Studies have shown that lncRNA RUNXOR is upregulated in the peripheral blood of lung cancer patients, while its target gene RUNX1 is downregulated in these patients. Knockdown of RUNXOR reduces Arg1 expression in MDSCs.[95] Another Study has shown that lncRNA Snhg6 promotes the differentiation of $CD11b^{+}Ly6G^{-}Ly6C^{high}$ M-MDSCs, while having no effect on the differentiation of $CD11b^{+}Ly6G^{+}Ly6C^{low}$ PMN-MDSCs.[96] In the tumor microenvironment, lncRNA AK036396 is highly expressed in PMN-MDSCs. Further investigation reveals that silencing lncRNA AK036396 significantly reduces the immunosuppressive functions of PMN-MDSCs, including decreased Arg1 activity and ROS production, while promoting their maturation. Additionally, lncRNA AK036396 directly interacts with the Fcnb protein, and its silencing destabilizes Fcnb, thereby further reducing the immunosuppressive capacity of PMN-MDSCs. Furthermore, silencing Fcnb also attenuates the immunosuppressive function of PMN-MDSCs and delays tumor progression.[97] HOTAIRM1 (HOXA Transcript Antisense RNA, Myeloid-Specific 1) is a myeloid-specific lncRNA located between the HOXA1 and HOXA2 genes in humans. Research by Tian et al demonstrated that HOTAIRM1 expression is significantly downregulated in the tumor tissues of lung cancer patients. Overexpression of HOTAIRM1 inhibits the immunosuppressive functions of MDSCs. Furthermore, HOTAIRM1 regulates MDSC function by modulating HOXA1 expression, thereby affecting the immune microenvironment and tumor progression in lung cancer.[98]

Other Tumors

Beyond the aforementioned cancers, lncRNAs have also been shown to regulate MDSCs in other tumors. Notably, inhibition of Malat1 in the primary TME of triple-negative breast cancer (TNBC) has been reported to promote a more immune-stimulatory environment. This is achieved by reducing the immunosuppressive effects of TAMs and MDSCs on T cells, thereby enhancing T cell responses.[99] Another study emphasized that lnc-chop promotes the expression of key enzymes associated with the immunosuppressive function of MDSCs, including ARG-1, NOS2, NOX2, and COX-2, thereby playing a pivotal role in tumor and inflammatory microenvironments.[100] The expression of PROM1, CCAT1, HOTAIR, and MUC19 has been reported to be closely associated with the recruitment of MDSCs in HPV-positive head and neck squamous cell carcinoma (HNSCC).[101] Recent studies have identified a novel lncRNA, LncOVM, which forms a complex with the protein PPIP5K2. This complex promotes the proliferation and metastasis of ovarian cancer cells. Notably, PPIP5K2 plays a role in regulating the secretion of complement C5, which in turn influences tumor microenvironment remodeling and facilitates the recruitment of neutrophil- MDSCs.[102] Research has shown that Lnc-H19, via its encoded protein H19-IRP, facilitates the formation of an immunosuppressive microenvironment, thereby promoting the proliferation of GBM cells and their immune evasion. Additionally, H19-IRP enhances the accumulation of MDSCs

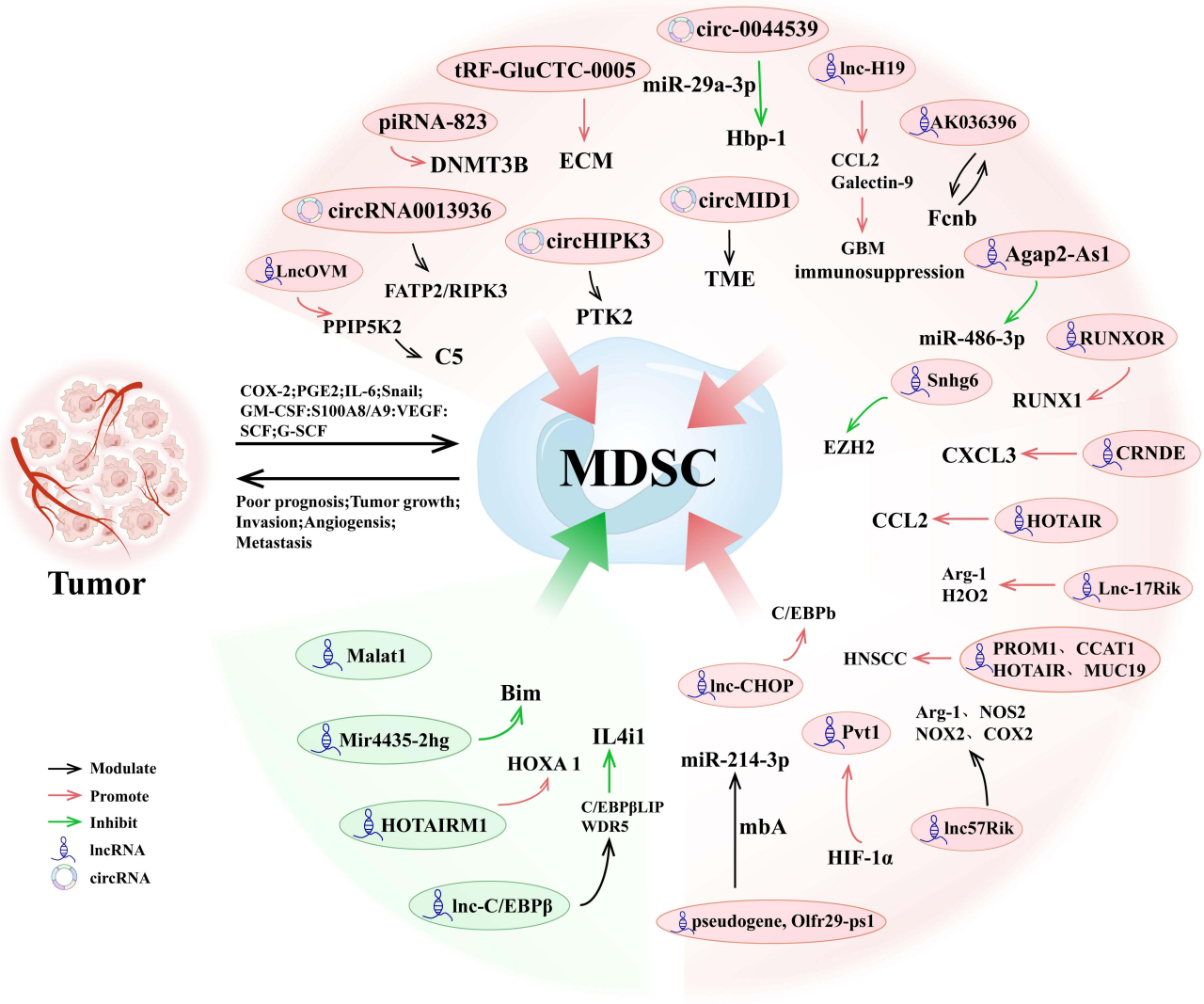

Figure 5 Regulation of MDSCs by ncRNAs in Tumors. This figure illustrates the roles of various ncRNAs in regulating MDSCs and promoting tumor immune evasion within the tumor microenvironment. Key ncRNAs, including lncRNAs, circRNAs, miRNAs, and piRNAs, modulate MDSC activation, differentiation, and immunosuppressive functions via pathways such as FAT2/RIPK3 (circHIPK3), CXCL3/CCL2 (HOTAIR), and Hbp-1 inhibition (miR-29a-3p).

by regulating the transcription of CCL2 and Galectin-9, which exacerbates tumor-induced immune suppression and drives tumor metastasis and growth.[103] Studies have shown that Lnc-AGAP2-AS1 exacerbates the immunosuppressive effects within the TME by regulating the secretion of TGF-β1 from MDSCs. This, in turn, inhibits effector T cell function and promotes tumor metastasis.[104] In summary, lncRNAs play a pivotal role in regulating tumor-associated MDSCs across various cancers, and are closely linked to tumor initiation, progression, and prognosis (Figure 5). This section reviews the current research on the involvement of lncRNAs in modulating MDSCs in tumors, as summarized in Table 2.

Regulation of MDSCs by Other ncRNAs in Tumors

Digestive System Tumor

Circ-0044539 modulates the immunosuppressive activity of MDSCs through exosomal signaling and plays a pivotal role in lymph node metastasis of hepatocellular carcinoma. It exerts its effects by targeting miR-29a-3p to inhibit Hbp-1, which enhances the levels of Arg1 and NO in PMN-MDSCs and suppresses T cell proliferation, thereby establishing an immunosuppressive pre-metastatic lymph node microenvironment.[105] tRF-GluCTC-0005 activates hepatic stellate cells via exosomes, upregulating WDR1 expression and promoting the production of ECM components and the secretion of

Table 2 Mechanisms of lncRNAs Regulation of Tumor MDSCs

Tumor	lncRNAs	lncRNAs Regulation (Up/Down)	Mechanism	Impact On MDSCs	Impact On Cancer	lncRNAs main Source	Reference
Digestive system tumor	lnc-17Rik	Upregulated	Not only enhances the activity of Arg-1 in M-MDSCs, but also increases the production of H_2O_2 in PMN-MDSCs	Enhances the immunosuppressive functions of MDSCs	Promote cancer	Tumor cells	[88]
	Pvt1	Upregulated	HIF-1α upregulates the expression of PVT1 in MDSCs under hypoxic stress	Enhances the immunosuppressive functions of MDSCs	Promotes cancer	Tumor cells, MDSCs	[89]
	Mir4435-2hg	Upregulated	Reprograms neutrophils by inhibiting apoptosis	Promotes neutrophil survival, altering PMN-MDSCs	Neutral	Neutrophils	[90]
	lnc-C/EBPβ	Upregulated	Regulates the expression of C/EBPβLIP and WDR5, downregulating the levels of IL4i1	Attenuates the immunosuppres-sive function of MDSCs	Suppress cancer	Tumor cells	[91]
	lnc57Rik	Upregulated	Enhances the expression of immunosuppressive genes, including Arg-1, NOS2, NOX2, and COX2	Enhances the immunosuppressive function of MDSCs.	Promote cancer	Tumor cells, MDSCs	[92]
	Olfr29-ps1	Upregulated	Promotes the immuno-suppressive function and specialization of MDSCs by forming Mir-214-3p after mbA modification	Enhances the immunosuppressive function and differentiation of MDSCs	Promote cancer	M-MDSCs	[93]
	HOTAIR	Upregulated	Recruits TAN/MDSCs by releasing CCL2	Facilitates the immunosuppressive function and differentiation of MDSCs	Promote cancer	Tumor cells	[13]
	CRNDE	Upregulated	Mediates the secretion of CXCL3	Recruit abundant G-MDSCs	Promote cancer	Tumor cells	[94]
Lung cancer	RUNXOR	Upregulated	Recruits RUNX1 protein at the 3' end and binds to the promoter and enhancers to regulate the expression of RUNX1	Increase the production of MDSCs and enhance their im-munosuppressive effects	Promote cancer	Tumor cells	[95]
	Snhg6	Upregulated	Inhibit EZH2 expression through the ubiquitination pathway	Promotes MDSCs differentiation and function without enhancing their immunosuppressive function	Neutral	MDSCs	[96]
	AK036396	Upregulated	Regulates the maturation status and metabolic pathways of PMN-MDSCs, as well as their interaction with Fcnb protein	Enhances the immunoregulatory function of MDSCs	Promote cancer	PMN-MDSCs	[97]
	HOTAIRM1	Downregulated	Enhances the expression of HOXA1 in MDSCs	Weakens the immunosuppressive function of MDSCs	Suppress cancer	Tumor cells, MDSCs	[98]
Other tumors	Malat1	Upregulated	Directly targets MDSCs	Weakens the immunosuppressive function of MDSCs	Suppress cancer	Tumor cells	[99]
	lnc-CHOP	Upregulated	Binds to CHOP and C/EBPβ iso-form LIP to induce the activity of C/EBPβ isoform LIP	Promotes the generation of MDSCs and their immunosup-pressive effects	Promote cancer	Tumor cells, MDSCs	[100]

(*Continued*)

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Table 2 (Continued).

Tumor	lncRNAs	lncRNAs Regulation (Up/Down)	Mechanism	Impact On MDSCs	Impact On Cancer	lncRNAs main Source	Reference
	PROM1,CCAT1, HOTAIR and MUC19	Upregulated	Associated with the recruitment of MDSCs in HPV-positive HNSCC	Recruit MDSCs	Promote cancer	Tumor cells	[101]
	lncOVM	Upregulated	Forms complex with PPP6C and regulates secretion of complement C5, regulating tumor microenvironment	Promotes the differentiation, pro-liferation, and function of MDSCs	Promote cancer	MDSCs	[102]
	lnc-H19	Upregulated	Regulates the transcription of CCL2 and Galectin-9 through its encoded protein H19-IRP	Promotes the accumulation of MDSCs	Promote cancer	Tumor cells	[103]
	Agap2-As1	Upregulated	Regulates the secretion of TGF-β1 from MDSCs	Promotes the accumulation of MDSCs and enhance their immunosuppressive activity	Promote cancer	Tumor cells, MDSCs	[104]

factors such as IL-6. This process recruits MDSCs and establishes an immunosuppressive pre-metastatic niche, thereby facilitating liver metastasis of pancreatic cancer.[106]

Urinary System Tumor

Exosomes derived from bladder cancer containing circRNA_0013936 have been shown to enhance the immunosuppressive activity of PMN-MDSCs by modulating the expression of fatty acid transporter protein 2 (FATP2) and receptor-interacting protein kinase 3 (RIPK3).[107] MDSCs transfer the S100A9 protein via exosomes, promoting the generation of circMID1 in prostate cancer. Through the circMID1/miR-506-3p/MID1 axis, MDSCs regulate the tumor microenvironment, enhancing their immunosuppressive activity and accelerating tumor progression.[108]

Other Tumors

The circHIPK3/PTK2 signaling axis facilitates the conversion of M-MDSCs into M2 macrophages in lung cancer, thereby strengthening the immunosuppressive characteristics of the tumor microenvironment.[109] In the multiple myeloma tumor microenvironment, G-MDSCs amplify the immunosuppressive function of MDSCs by inducing the expression of piRNA-823. This piRNA activates DNMT3B and triggers widespread DNA methylation, indirectly maintaining MDSC-mediated suppression and facilitating immune evasion.[110] This section summarizes current research on the roles of other ncRNAs in modulating MDSCs in tumors, as presented in Table 3.

Therapeutic Strategies Targeting ncRNAs in MDSCs

Targeting oncogenic ncRNAs with antisense oligonucleotides (ASOs) or small molecule inhibitors represents a promising therapeutic strategy.[111,112] For instance, targeting HOTAIR or circHIPK3 can diminish MDSC-driven immunosuppression and bolster antitumor immune responses.[109,113]

In addition to suppressing oncogenic ncRNAs, delivering synthetic mimics of tumor-suppressive ncRNAs holds potential for reprogramming MDSCs into a less suppressive phenotype. This approach can complement existing therapies by reducing the immunosuppressive barrier created by MDSCs.[111,114]

Integrating ncRNA-targeted strategies with immune checkpoint blockade, such as anti-PD-1/PD-L1 therapies, can potentiate antitumor immune responses.Additionally, integrating these strategies with chemotherapies or targeted therapies, such as CSF1R inhibitors, can further disrupt MDSC activity and improve treatment efficacy.[112,115]

To achieve effective delivery, novel platforms such as nanoparticle-based systems have been developed to specifically target ncRNAs in MDSCs. For instance, dual-responsive PEG-lipid polyester nanoparticles enable precise siRNA delivery to the TME, reducing MDSC-mediated immunosuppression while enhancing T cell activation.[114] These advances highlight the potential of ncRNA-targeting strategies as a transformative approach to modulate MDSCs activity and improve the outcomes of cancer immunotherapy.

Conclusion

Recent studies have notably enhanced the comprehension of how ncRNAs regulate MDSCs within the tumor microenvironment (TME). Various ncRNAs, such as miRNAs, lncRNAs, and circRNAs, influence MDSC recruitment, differentiation, and immunosuppressive activities by modulating essential signaling pathways, including STAT3, NF-κB, and PI3K/AKT, thus promoting immune escape and tumor progression. Moreover, ncRNAs impact tumor-immune interactions via processes such as histone modification, chromatin remodeling, and modulation of miRNA functions, thereby intensifying immune suppression and facilitating tumor growth.

MDSC regulation involves intricate networks comprising cytokines, chemokines, and growth factors secreted by tumor cells as well as immune cells. Collectively, these molecules strengthen the immunosuppressive environment, accelerating tumor advancement. Additionally, Tregs interact with MDSCs, further consolidating immune suppression.

Targeting oncogenic ncRNAs through antisense oligonucleotides (ASOs) or small molecule inhibitors represents a promising therapeutic approach to disrupting MDSC-induced immune suppression. Additionally, strategies aiming to reprogram MDSCs into less immunosuppressive phenotypes using synthetic mimics of tumor-suppressive ncRNAs could complement existing cancer treatments. Integrating these interventions with immune checkpoint blockade therapies, such

Table 3 The Mechanisms of Other ncRNAs Involvement in Regulating Tumor MDSCs

Tumor	miRNAs	ncRNAs Regulation (Up/Down)	Mechanism	Impact On MDSCs	Impact On Cancer	Main Source	Reference
Digestive system tumor	circ-0044539	Upregulated	Targets and inhibits Hbp-1 through miR-29a-3p	Enhances the levels of Arg1 and NO in PMN-MDSCs	Promote cancer	Tumor cells, Exosomes	[105]
	tRF-GluCTC-0005	Upregulated	Promotes ECM production and the secretion of factors such as IL-6	Recruits MDSCs	Promote cancer	Exosome-derived tRNA fragments	[106]
Urologic tumor	circRNA_0013936	Upregulated	Regulates the expression of fatty acid transport protein 2 (FATP2) and receptor-interacting protein kinase 3 (RIPK3)	Enhances the immunosuppressive activity of PMN-MDSCs	Promote cancer	Bladder-cancer-derived exosomes	[107]
	circMID1	Upregulated	Regulates the tumor microenvironment through the circMID1/miR-506-3p/MID1 axis	Promotes the immunosuppressive function of MDSCs	Promote cancer	MDSC-derived exosomes	[108]
Other tumors	circHIPK3	Upregulated	Exerts its effects through the circHIPK3/PTK2 axis	Promotes the differentiation of M-MDSCs into M2 macrophages	Promote cancer	Tumor cells, Exosomes	[109]
	piRNA-823	Upregulated	Activates DNMT3B and its mediated global DNA methylation	Indirectly maintains the suppressive activity of MDSCs	Promote cancer	MDSCs	[110]

as anti-PD-1/PD-L1 antibodies, or targeted agents like CSF1R inhibitors, might enhance anti-tumor immune responses and clinical efficacy. Collectively, ncRNAs converge on a limited set of myeloid programs-prominently STAT3, NF-κB, and PI3K/AKT-to influence MDSC specification, maintenance, and suppressive function. Mechanistically, epigenetic writers/readers (eg, EZH2), post-transcriptional control (miRNA sponging), and exosome-mediated transfer act in combination and are context dependent across tumor types. Therapeutically, ncRNA-directed strategies (sense/antisense, siRNA, miRNA mimics, and delivery via nanoparticles or exosomes) are promising adjuncts to immunotherapy but face challenges in cell-type–specific delivery, durability, and off-target effects. We outline testable priorities: (i) pathway-centric triage, comparing JAK/STAT pathway-dominant tumors, which are often associated with immune dysregulation and tumor progression, with TGF-β pathway-dominant tumors, which are frequently linked to immune suppression and tumor metastasis; (ii) cell-selective delivery platforms for MDSCs; (iii) paired biomarker panels (circulating ncRNAs and exosomal ncRNAs associated with myeloid states); and (iv) rigorous cross-species standards for MDSC definition. In line with the synthesis above, future work should prioritize pathway-centric triage, MDSC-selective delivery platforms for ncRNA agents, paired biomarker panels integrating circulating/exosomal ncRNAs with myeloid states, and cross-species standards for MDSC definition.

A compelling example of the challenges that lie ahead is the paradoxical nature of key regulators like miR-155. While widely explored as a therapeutic agent due to its immunostimulatory properties—such as enhancing dendritic cell maturation—its net effect in the tumor microenvironment can be profoundly pro-tumorigenic. Seminal studies have revealed that this is because the dominant role of miR-155 in supporting MDSCs and Tregs can outweigh its beneficial anti-tumor functions. This functional dichotomy, where a single ncRNA can be both friend and foe, underscores the complexity of targeting these pathways.

Therefore, despite the promising developments outlined above, several critical challenges remain. These include not only further clarifying the context-dependent regulatory mechanisms of ncRNAs in MDSCs, but also improving delivery specificity and overcoming barriers for effective clinical translation of RNA-based treatments. Continuous research into ncRNA mechanisms and advances in targeted therapeutic strategies hold considerable promise for enhancing the efficacy of cancer immunotherapy.

Abbreviations

ncRNAs, non-coding RNAs; miRNAs, microRNA; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; piRNAs, PIWI-interacting RNAs; MDSCs, myeloid-derived suppressor cells; M-MDSCs, monocytic MDSCs; G-MDSCs, granulocytic MDSCs; PMN-MDSCs, polymorphonuclearMDSCs; eMDSCs, early-stage myeloid-derived suppressor cells; TME, tumor microenvironment; Tregs, regulatory T cells; TAMs, tumor-associated macrophages; CAFs, cancer-associated fibroblasts; ceRNA, competitive endogenous RNA; SOCS3, Suppressor of Cytokine Signaling 3; TNF-α, tumor necrosis factor-alpha; ECM, extracellular matrix; MMP, matrix metalloproteinases.

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Disclosure

The authors declare no conflicts of interest in this work.

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