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REVIEW

Converting "cold" to "hot": epigenetics strategies to improve immune therapy effect by regulating tumor-associated immune suppressive cells

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Abstract

Significant developments in cancer treatment have been made since the advent of immune therapies. However, there are still some patients with malignant tumors who do not benefit from immunotherapy. Tumors without immunogenicity are called "cold" tumors which are unresponsive to immunotherapy, and the opposite are "hot" tumors. Immune suppressive cells (ISCs) refer to cells which can inhibit the immune response such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T (Treg) cells and so on. The more ISCs infiltrated, the weaker the immunogenicity of the tumor, showing the characteristics of "cold" tumor. The dysfunction of ISCs in the tumor microenvironment (TME) may play essential roles in insensitive therapeutic reaction. Previous studies have found that epigenetic mechanisms play an important role in the regulation of ISCs. Regulating ISCs may be a new approach to transforming "cold" tumors into "hot" tumors. Here, we focused on the function of ISCs in the TME and discussed how epigenetics is involved in regulating ISCs. In addition, we summarized the mechanisms by which the epigenetic drugs convert immunotherapy-insensitive tumors into immunotherapy-sensitive tumors which would be an innovative tendency for future immunotherapy in "cold" tumor.

KEYWORDS
DNA methylation, epigenetics strategy, histone modification, immune suppressive cell, noncoding RNA

List of abbreviations: 3'-UTR, three prime untranslated region; 5caC, 5-carboxylcytosine; 5fC, 5-formylcytosine; 5mC, 5-methylcytosine; ACT, adoptive cell transfer; AKT, protein kinase B; ALDH1A3, aldehyde dehydrogenase 1 family member A3; ALL, acute lymphoblastic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APCL, APC regulator of WNT signaling pathway 2; Arg1,

1 | BACKGROUND

Cancer cells and the resulting tumor progression are greatly affected by metabolic stress within various regions of the tumor microenvironment (TME) [1]. The TME is composed of diverse cell types that either support or restrain tumorigenesis, which include immune cells and immune suppressive cells (ISCs). Immunotherapy is the next great breakthrough in antitumor drug research after chemotherapy. Immunotherapy, including cancer vaccines, adoptive cell transfer (ACT), and immune checkpoint inhibitors (ICIs), has obtained durable clinical responses, but their efficacies vary and only specific subsets of cancer patients can benefit from them [2]. Patients with non-immunogenic tumors ("cold" tumors)

arginase-1; ARID3B, AT-rich interaction domain 3; ATM, ataxia telangiectasia-mutated gene; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma-extra large; BLIMP1, B lymphocyte-in-duced maturation protein-1; BMF, B-cell lymphoma-2; c-MET, cellular-mesenchymal epithelial transition factor; c-Myc, myelocytomatosis viral oncogene homolog; C/EBPa, CCAAT/enhancer-binding protein alpha; CAF, cancer-associated fibroblast; CaMKKβ, $Ca2^{+}$/calmodulin-dependent protein kinase kinase; CCL17, C-C motif chemokine ligand 17; CCL18, C-C motif chemokine ligand 18; CCL20, C-C motif chemokine ligand 20; CCL22, C-C motif chemokine ligand 22; CCL28, C-C motif chemokine ligand 28; CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; CCND1, cyclin D1; CDK2, cyclin dependent kinase 2; CGI, CpG island; circRNA, circular RNA; CMGT, canine mammary gland tumor; CMML, Chronic myelomonocytic leukaemia; CNS, conserved non-coding sequence; COX-2, cyclooxygenase-2; CPEB4, cytoplasmic polyadenylation element binding protein 4; CRC, colorectal cancer; CRLM, colorectal liver metastasis; CSF-1R, colony stimulating factor-1 receptor; CTCL, central T cell lymphoma; CTL, cytotoxic lymphocytes; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CXCL10, C-X-C motif chemokine ligand 10; CXCL12, C-X-C motif chemokine ligand 12; CXCL13, C-X-C motif chemokine ligand 13; CXCL9, C-X-C motif chemokine ligand 9; CXCR1, C-X-C motif chemokine receptor 1; CXCR2, C-X-C motif chemokine receptor 2; CXCR5, C-X-C chemokine receptor type 5; DC, dendritic cell; DKK3, Dickkopf WNT signaling pathway inhibitor 3; DNMT1, DNA methyltransferase 1; DNMT3A, DNA methyltransferase 3 alpha; DNMT3B, DNA methyltransferase 3 beta; DNMTi, DNA methyltransferase inhibitor; dsRNA, double-stranded RNA; DUSP3, dual specificity protein phosphatase 3; E2F1, E2 promoter binding factor 1; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EOC, epithelial ovarian cancer; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESCC, esophageal squamous cell cancer; eTreg, effector regulatory T; ETS1, ETS proto-oncogene 1; exo, exosomes; EZH2, enhancer of Zeste homolog 2; EZH2i, enhancer of Zeste homolog2 inhibitor; FOXM1, Forkhead box M1; FOXO3a, forkhead box O3; FOXP3, forkhead box P3; G-MDSC, granulocytic-MDSC; GADD45B, growth arrest and DNA damage inducible protein beta; GC, gastric carcinoma; GITR, glucocorticoid induced tumor necrosis factorreceptor; GSK2, glycogen synthase kinase 2; GSK3β, glycogen synthase kinase-3β; H3K4Me3, histone H3 lysine 4; HAT, histone acetyltransferases; HCC, hepatocellular carcinomas; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HDM, histone demethylase; HGF, hepatocyte growth factor; HIF-1α, hypoxia inducible factor-1; HLA-DR, human leukocyte antigen – DR; HMT, histone methyltransferase; HOTAIR1, HOX transcript antisense RNA; HOXA1, homeo box A1; I-MDSC, immature-MDSC; IBD, inflammatory bowel disease; IC, immune checkpoint; ICI, immune checkpoint inhibitor; ICOS, inducible co-stimulator; ICOSL, inducible co-stimulator ligand; IDH1i, isocitrate dehydrogenase 1 inhibitor; IDH2i, isocitrate dehydrogenase 2 inhibitor; IDH, isocitrate dehydrogenase; IFN-γ, Interferon-gamma; IGF2BP3, insulin like growth factor 2 mrna binding protein 3; IL-10, interleukin 10; IL-16, Interleukin 16; IL-17, interleukin 17; IL-4, Interleukin-4; IL-6, Interleukin 6; IMC, immature myeloid cells; INI1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1; iNOS, Inducible nitric oxide synthase; IRF7, Interferon regulatory factor 7; IRF8, Interferon regulatory factor 8; ISC, immune suppressive cell; ITM2B, Integral Membrane Protein 2B; ITP, immune thrombocytopenia; iTreg, induced Treg; K-RAS, kirsten Rat Sarcoma Viral Oncogene Homolog; KLF2, Kruppel-like factor; KLF4, Krüppel-like factor 4; KLF6, Kruppel-like factor 6; LC3B, light-chain 3B; LLC, Lewis lung cancer; lncRNA, long non-coding RNA; LNP, Lipid-like nanoparticle; M-MDSC, monocytic MDSC; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MAVS, mitochondrial antiviral signaling protein; MDA5, melanoma differentiation-associated gene 5; MDM2, mouse doubleminute 2 homolog; MDM2, mouse doubleminute 2 homolog; MDS, myelodysplastic syndromes; MDSC, myeloid-derived suppressor cell; me1, monomethylation; me2, dimethylation; me3, trimethylation; MGL1, Macrophage galactose-C type lectin; MHC-II, class II major histocompatibility complex; MIF, macrophage migration inhibitory factor; miRNA, microRNA; MMP, matrix metalloproteinase; MMSC, multiple myeloma stem cell; mTOR, mammalian target of rapamycin; MV, microvesicle; MYC, myelocytomatosis; MYCN, BHLH transcription factor; NEDD4-1, Neural precursor cell expressed, developmentally down-regulated 4, E3 ubiquitin protein ligase; NK, nature killer; NKTCL, Natural killer/T-cell lymphoma; NO, nitric oxide; NOS2, nitric oxide synthase 2; NOX2, NADPH-oxidase 2; NPR3, nuclear factor erythroid 2-like 3 receptor; Nrp1, neuropilin-1; NSCLC, non-small cell lung carcinoma; OPN, osteopontin; PABP, poly(A)-binding protein; PBMC, peripheral blood mononuclear cell; PCa, prostate cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDAC, pancreatic ductal adenocarcinoma; PDCD4, programmed cell death 4; PDCD4, Programmed cell death protein 4; PGC-1α, Peroxisome proliferator-activated receptor γ coactivator 1α; PGC1-α, Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PGE2, prostaglandin E2; PGE2, prostaglandin E2; PI3K-AKT, Phosphatidylinositol 3-kinases-protein kinase B; PI3K, phosphoinositide-3 kinase; PIP3, phosphatidylinositol-3,4,5-triphosphate; PMN-MDSC, polymorphonuclear MDSC; PPARγ, peroxisome proliferator-activated receptor γ; PRDM1, PR/SET Domain 1; PTBP1, polypyrimidine tract-binding protein; PTCL, peripheral T-cell lymphoma; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PTM, post-translational modifications; pTreg, peripherally induced Treg; RBP, RNA-binding proteins; RORγt, retinoid-related orphan receptor gamma t; ROS, reactive oxygen species; Runx1, runt-associated transcription factor 1; RUNXOR, runt-related transcription factor 1 overlapping RNA; SAM, S-adenosylmethionine; SAPK, stress activated protein kinase; SETDB1, SET domain bifurcated 1; siRNA, small interfering RNA; SMARCA4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4; snoRNA, small nucleolar RNA; SOCS1, suppressor of cytokine signaling 1; SOSC1, suppressor of cytokine signal 1; SOX4, SRY-related high-mobility-group box 4; SPCA2, ATPase secretory pathway $Ca2^{+}$ transporting 2; STAT3, signal transducer and activator of transcription 3; STAT6, Signal

can't respond or slightly respond to immunotherapy. Converting "cold" into "hot" is always a pivotal objective in immunotherapy. A large number of past researches have predominantly focused on immune cells. However, we found that ISCs play an essential part in tumor immunotherapies. A comprehensive understanding of ISCs in the TME is essential for deciphering the mechanisms of immunotherapies, defining predictive biomarkers, and identifying novel therapeutic targets.

Epigenetics refers to heritable changes in cellular phenotype independent of DNA sequence alterations, which include DNA methylation, histone modifications, and non-coding RNAs. Regulators synergistically regulate chromatin structure and gene expression through various covalent modifications of histones, proteins, and nucleic acids. Epigenetic alterations lead to carcinogenesis by regulating oncogenic and tumor suppressor gene pathways [3, 4], and by affecting the activation, differentiation, and function of immune cells and ISCs [5, 6]. Since epigenetics plays an important role in the process of ISCs affecting tumors, therapeutic strategies implementing epigenetic modulating drugs are expected to significantly impact the TME through inhibition of ISCs (such as myeloid-derived suppressor cells [MDSCs], regulatory T [Treg] cells and so on), resulting in converting "cold" into "hot" and increasing the sensibility of tumors to immunotherapy.

In this review, we discussed the diverse mechanisms of epigenetic regulation in ISCs and summarized the epigenetic modulation of ISCs to regulate the TME, resulting in converting "cold" tumors into "hot" tumors for improved therapeutic outcomes, which is considered a huge breakthrough in tumor immunotherapies.

transducer and activator of transcription 6; TAM, tumor-associated macrophages; TCF7, transcription factor 7; TCR, T cell antigen receptor; TET2, Tet methylcytosine dioxygenase 2; TET, ten-eleven translocation; TGF-β, transforming growth factor-β; TGFBI, transforming growth factor beta Induced; TGFBR1, Transforming growth factor beta receptor type 1; TGFBR3, Transforming growth factor beta receptor type 3; Th17, T helper cell 17; Th1, T helper cell 1; THBS1, thrombospondin 1; THC, tetrahydrocannabinol; TIM-3, T cell immunoglobulin domain and mucin domain-3; TIP, Tat-Interactive protein; TLR4, Toll-like receptor 4; TLR, Toll-like receptor; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; TNF-R1, TNF receptor 1; TNFR2, TNF receptor 2; TNFSF10, TNF superfamily member 10; TNRC6, trinucleotide repeat containing 6; TRAIL-R2, TNF-related apoptosis-inducing ligand receptor 2; TRAILR1, TNF-related apoptosis-inducing ligand receptor 1; Treg, regulatory T cell; TSDR, Treg specific demethylated region; tTreg, thymic-derived Treg; UBE2C, ubiquitin conjugating enzyme E2 C; UPR, unfolded protein response; UTR, untranslated region; VEGF, vascular endothelial growth factor; WD, tryptophan-aspartic acid; WDR5, WD repeat domain 5; YAP1, Yes Associated Protein 1; ZEB1, zinc finger E-box binding homeobox 1; ZEB2, zinc finger E-box binding homeobox 2.

Yijia Tang, Guangzu Cui, and Haicong Liu contributed equally to the article.

2 | ISCs

The activation and maintenance of the immune system is regulated both positively and negatively. ISCs mainly refer to a class of cells that can release inhibitory factors in the body, suppress immune response, and maintain immune homeostasis which include Treg cells, MDSCs, tumor-associated macrophages (TAMs), fibroblasts, and tumor cells themselves. Since Treg cells, MDSCs, and TAMs are the most representative and infiltrated ISCs in the tumor immune microenvironment, we start from these three cells to deeply introduce its mechanism. (Figure 1)

Under physiological conditions, ISCs can negatively regulate the body's immune response, maintain immune homeostasis, and prevent autoimmune diseases and excessive inflammation by secreting immunosuppressive factors, expressing immunomodulatory molecules, or directly contacting other immune cells to inhibit the activation, proliferation, and effector functions of T cells, B cells, nature killer (NK) cells, etc.

The effect of ISCs on the TME is mainly to inhibit the immune surveillance and killing of tumor cells, and promote tumor growth, invasion, and metastasis. ISCs suppress the activation, proliferation, and effector functions of cytotoxic lymphocytes (CTL), NK cells, and other immune cells by secreting immunosuppressive factors (such as transforming growth factor-β [TGF-β] [7], interleukin 10 [IL-10] [8], prostaglandin E2 [PGE2] [9], etc.), expressing immune regulatory molecules (such as programmed death-ligand 1 [PD-L1] [10], cytotoxic T lymphocyte-associated antigen-4 [CTLA-4] [11], T cell immunoglobulin domain and mucin domain-3 [TIM-3] [12], etc.), or directly contacting other immune cells [13]. ISCs also affect the processes of angiogenesis, lymphangiogenesis, extracellular matrix (ECM) remodeling, and others in the TME, further altering the biological characteristics of the tumor [14] (Figure 2).

2.1 | TAMs

It is currently thought that TAMs may originate from bone marrow-derived monocyte precursors or from tissue-specific embryonic-derived macrophages [15–17]. TAMs are similar to M2 macrophages in a sense, but TAMs are not considered to be an independent subset of macrophages, and the presence of TAMs is closely related to tumors [18]. TAMs and M2 macrophages have some similar characteristics, such as the expression of some "overlapping" marker molecules, such as CD206, CD163, and similar to M2 macrophages, TAMs can also secrete some immunosuppressive cytokines such as IL-10, TGF-β, etc. [19]. Unlike

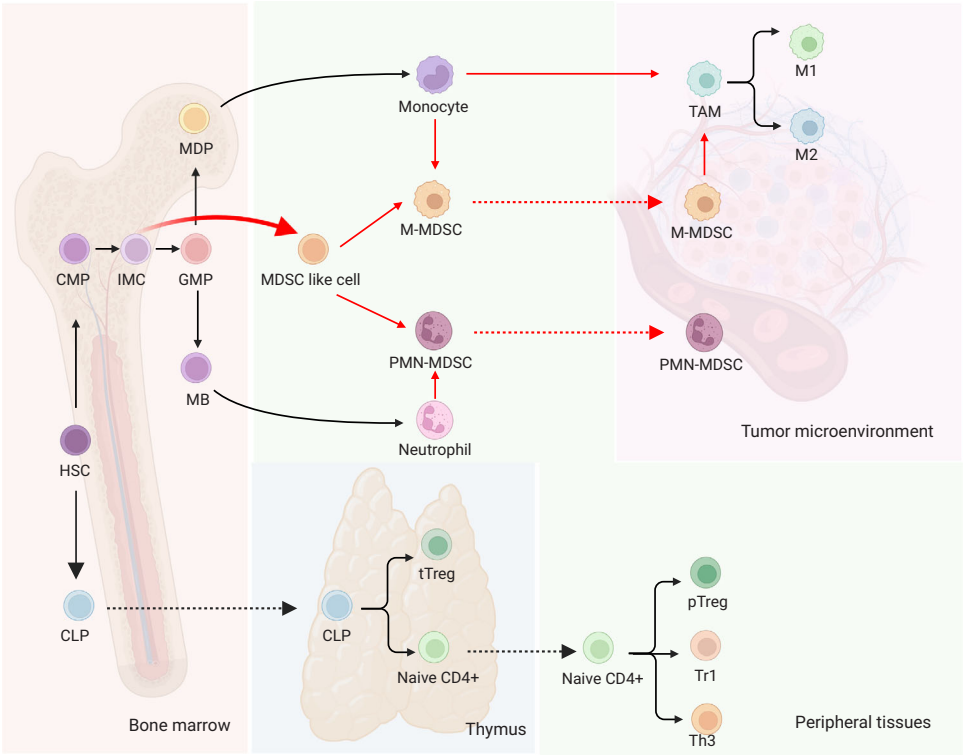


FIGURE 1 Schematic diagram of TAMs, MDSCs, and Treg cells development. The activation and maintenance of the immune system is regulated both positively and negatively. ISCs are capable of suppressing the immune response of the body and include mainly Treg cells, MDSCs, and TAMs in the tumor immune microenvironment. Treg cells have two developmental pathways: tTreg and pTreg cells. MDSCs can be further divided into monocytic MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSC or G-MDSC), according to their surface markers and functions, and TAM can acquire M1 or M2 phenotypes. Abbreviations: CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; HSC, hematopoietic stem cell; IMC, immature myeloid cell; ISC, immune suppressive cell; MB, myeloblast; MDP, macrophage/dendritic cell progenitor; MDSC, myeloid-derived suppressor cell; pTreg, peripherally induced Treg; TAM, tumor-associated macrophage; Th3, helper 3 T; Tr1, type 1 regulatory T; Treg, regulatory T; tTreg, thymic-derived Treg.

M2 macrophages, TAMs highly express surface marker molecules, such as CD68, CD163, Macrophage galactose-C type lectin (MGL1), Dectin-1, CD81, class II major histocompatibility complex (MHC-II), and scavenger receptor A. Movahedi *et al.* [20] reported that the tumor-infiltrating monocyte pool is mainly Ly6C^{+} CX3CR1^{low}, and showed that Ly6C^{high} monocytes are direct precursors of TAMs [18, 21]. Some studies have found that TAM differentiation depends on Notch signaling, transcriptional regulation of RBPJ [22, 23].

2.1.1 | Tumor-promoting effect of TAMs

TAMs can promote tumor growth, metastasis, angiogenesis, immunosuppression, drug resistance, and many other biological behaviors of tumor cells [19, 24]. TAMs can express a variety of chemokines (such as C-C motif chemokine ligand 2 [CCL2], C-C motif chemokine ligand 5 [CCL5], C-C motif chemokine ligand 17 [CCL17], etc.), cytokines (such as vascular endothelial growth factor [VEGF], IL-10, Interleukin-4 [IL-4], and TGF-β), and enzymes (such as cyclooxygenase-2 [COX-2], matrix metalloproteinase [MMP], and cathepsin K) to inhibit the killing defense of the human immune system against tumor tissue function, thereby promoting tumor development, metastasis, and resistance to chemotherapy and immunotherapy [25]. TAMs can promote the maintenance of tumor stem cell properties by secreting some related factors (such as TGF-β [26]), and tumor stem cells can also activate TAMs by some signals (such as the Wnt pathway [27]).

Studies have shown that TAMs play an important role as tumor-promoting cells in the occurrence and development of breast cancer [28–30]. An animal experiment had previously shown that targeting colony-stimulating factors with drugs to reduce TAMs infiltration can reduce tumor growth and metastasis [31]. TAMs can enhance ECM destruction and invasion by tumor cells through the production of MMPs, cysteine cathepsins, and serine proteases, cysteine-rich acidic proteins, and C-C motif chemokine ligand 18 (CCL18), among other substances [32–34]. TAMs can promote tumor drug resistance by

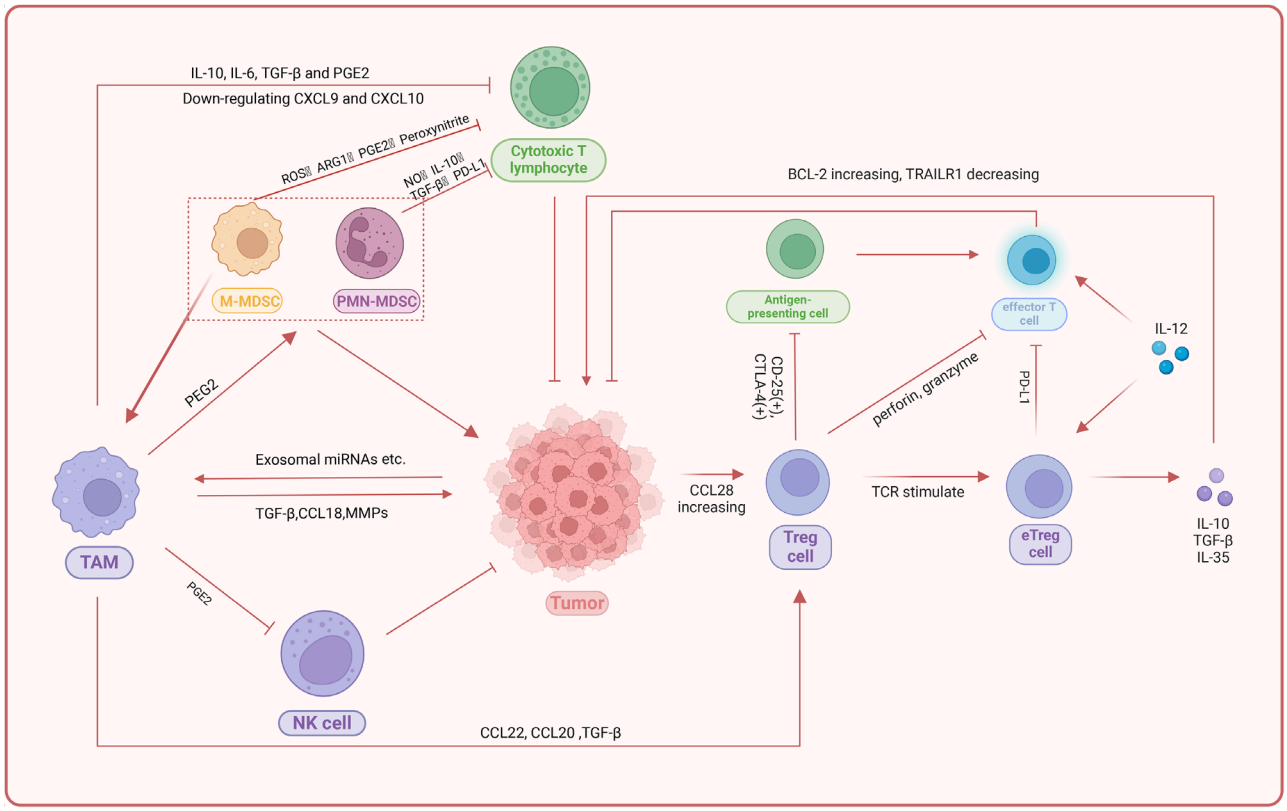


FIGURE 2 The mechanism of TAMs, MDSCs, and Treg cells affecting tumor cells. The TME is composed of many different cells that support or restrain tumorigenesis which includes ISCs, such as TAMs, MDSCs, and Treg cells. These cells may promote or inhibit the development of tumors through different mechanisms. Abbreviations: ARG1, arginase1; BCL-2, B-cell lymphoma-2; CCL18, chemokine ligand 18; CCL20, chemokine ligand 20; CCL22, chemokine ligand 22; CCL28, chemokine ligand 28; CXCL10, C-X-C motif chemokine ligand 10; CXCL9, C-X-C motif chemokine ligand 9; IL-10, interleukin 10; IL-12, interleukin 12; IL-35, interleukin 35; IL-6, interleukin 6; ISC, immune suppressive cell; M-MDSC, monocytic MDSC; MDSC, myeloid-derived suppressor cell; MDSC, myeloid-derived suppressor cell; NK, nature killer; PD-L1, programmed cell death 1 ligand 1; PGE2, prostaglandin E2; PMN-MDSC, polymorphonuclear MDSC; ROS, reactive oxygen species; TAM, tumor-associated macrophage; TCR, T cell antigen receptor; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TRAILR1, (TNF)-related apoptosis-inducing ligand receptor 1; Treg, regulatory T.

metabolic reprogramming, promoting tumor angiogenesis, producing multiple cytokines, and releasing exosomal miRNAs [30, 35, 36]. In addition, TAMs play an important role in various tumor tissues, such as glioma [15, 37], endometrial adenocarcinoma [38, 39], and so on.

2.1.2 | Tumor-inhibiting effect of TAMs

Even though many of the above studies have shown that TAMs have a tumor-promoting effect in tumor tissue, however, a study of patients with stage III colon cancer who received folinic acid, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy found that a high volume of TAMs was associated with a better prognosis [21]. In the TME, due to reasons such as hypoxia, nutrient deficiency, metabolic disorders, and stress, cells in the TME die, so that TAMs gather and generate M1 polarization to clear dead cells in the TME, resulting in a pro-inflammatory and anti-tumor effect. However, with the development of tumors and the chronicity of inflammation, anti-inflammatory signals and some substances produced by tumor cells make TAMs turn to M2 polarization. At this time, TAMs produce some anti-inflammatory molecules, thereby promoting angiogenesis and immunosuppression, thereby leading to tumor progression [40]. All in all, the specific TME determines the roles of TAMs in tumorigenesis and development.

2.1.3 | TAMs in immune TME

As previously mentioned, immunosuppression is an important factor in the tumor-promoting effects of TAMs. TAMs can produce many cytokines, such as IL-10, IL-6, TGF-β, and PGE2, to limit the function of cytotoxic T cells to achieve tumor-promoting effects [41]. During cold tumor formation, TAMs can achieve this by reducing

the infiltration of anti-tumor immune cells and increasing the recruitment of tumor-promoting immune cells. TAMs reduce $CD8^+$ T cell infiltration by producing TGF-β and down-regulating C-X-C motif chemokine ligand 9 (CXCL9) and C-X-C motif chemokine ligand 10 (CXCL10) expressions to achieve immunosuppression [42, 43]. PGE2 produced by TAMs reduces dendritic cell (DC) and NK infiltration and activation in tumor tissue by inhibiting DC and NK cell differentiation and maturation [44, 45]. TAMs can enhance their immunosuppressive effects by secreting secretory C-C motif chemokine ligand 22 (CCL22), C-C motif chemokine ligand 20 (CCL20), and TGF-β to recruit and activate Treg cells and by secreting PGE2 to enhance infiltration and activation of MDSCs [42, 46].

2.2 | MDSCs

MDSCs are the heterogeneous population of immature myeloid cells (IMCs) that suppress immunity in tumors and chronic inflammation [47]. Under physiological conditions, IMCs produced in the bone marrow migrate to different peripheral organs and rapidly differentiate into mature granulocytes, macrophages or DC. Under pathological conditions, such as TME or acute and chronic infections, factors are produced that promote the accumulation of IMC at these sites, prevent their differentiation and induce their activation, known as MDSCs [48].

Immunophenotype of human MDSCs defined by the expression of CD11b, CD33 and the negative or low expression of human leukocyte antigen – DR (HLA-DR) [49]. Based on phenotypic and morphological features, they were subdivided into polymorphonuclear MDSCs (PMN-MDSC) and monocytic MDSCs (M-MDSC), which led to their different (although partially overlapping) functions in immunosuppression [50]. A small group of myeloid progenitor cells and precursors with MDSC characteristics and a potent immunosuppressive effect is named "early MDSC", accounting for less than 5% of the total population of MDSCs [51].

2.2.1 | Tumor-promoting effect of MDSCs

Activated MDSCs secrete chemokines, cytokines, and enzymes that contribute to tumor cell invasion, proliferation, survival, adhesion, and chemoattraction, resulting in tumor progression, invasion, and metastasis [52]. MDSCs are recruited into premetastatic niches and promote tumor metastasis through the chemokine receptors C-X-C motif chemokine receptor 1 (CXCR1), and C-X-C motif chemokine receptor 2 (CXCR2) [53]. During metastasis, tumor cells promote survival by forming heterotypic plugs that interact with bone marrow cells and platelets. When tumor cells extravasate, their growth is regulated by the cellular and growth factors of the microenvironment like MDSCs, referred to as the metastatic ecotone [54]. MDSCs promote tumor infiltration by secreting MMPs, which play an important role in ECM degradation [55]. Research conducted on breast cancers lacking type II TGF-β receptors has demonstrated that $Gr\text{-}1^+$ $CD11b^+$ cells enhance tumor cell invasion and metastasis, which are MMP dependent [56]. In addition, MDSCs are associated with tumor angiogenesis and promote tumor growth [57–59]. Comprehending the tumor-promoting mechanisms of MDSCs is pivotal for developing therapeutic interventions aimed at tumor transformation.

2.2.2 | Tumor-inhibiting effect of MDSCs

Current studies all point to MDSC promoting tumor progression by exerting immunosuppressive effects. Nevertheless, stories before cancer are noteworthy. Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC) [60]. Mammalian target of rapamycin (mTOR) inhibitors attenuate IBD via Treg expansion promoted by MDSCs [61]. Histone methyltransferase (HMT) inhibitors have been shown to improve the condition of IBD and delay the development of colitis-associated cancer. These inhibitors achieve this by promoting the accumulation of immunosuppressive MDSCs in the colon [62]. Interestingly, in a simulated skin inflammation model using S100A9 transgenic mice, IMC triggers the generation of $CD4^+$ T cells capable of producing interleukin 17 (IL-17) through the production of CCL4 [63]. Indeed, the role of MDSCs in promoting tumorigenesis during chronic inflammation is multifaceted and warrants extensive exploration.

2.2.3 | MDSCs in immune TME

MDSCs convert "hot" tumors into "cold" ones by suppressing anti-tumor immunity. MDSCs inhibit immune responses mediated by B cells and NK cells, especially T cells. The identical mechanisms by which M-MDSCs and PMN-MDSCs suppress immune responses include upregulation of signal transducer and activator of transcription 3 (STAT3) expression, induction of endoplasmic reticulum (ER) stress, expression of arginase 1 and expression of S100A8/A9 [64]. Distinctively, PMN-MDSCs preferentially use reactive oxygen species (ROS), peroxynitrite, arginase 1, and PGE2 to mediate immune suppression, whereas M-MDSCs use nitric oxide (NO), immunosuppressive cytokines, such as IL-10 and TGF-β, and the

expression of immune regulatory molecules like PD-L1 [65]. Despite the predominance of PMN-MDSCs in circulating MDSCs, they are less immunosuppressive than M-MDSCs at the individual cellular level [66]. In most cases, the expansion of PMN-MDSC populations is much greater than that of M-MDSC [67]. In addition, M-MDSC can differentiate into TAM in the tumor environment, and these macrophages have a different phenotype and function from MDSCs [67]. The development of epigenetic drugs targeting MDSCs holds promise for reversing "cold" tumors into "hot" ones.

2.3 | Treg cells

Treg cells are key regulators of inflammation and are important for immune tolerance and homeostasis [68]. Treg cells develop into thymic-derived Treg (tTreg) cells under the induction of the transcription factor forkhead box P3 (FOXP3), which plays a crucial role in the differentiation, maintenance, and function of Treg cells [69, 70]. Forkhead box O3 (FOXO3a) can also be produced by naïve T cells in the presence of TGF-β and IL-2, and these Treg cells are termed induced Treg (iTreg) cells in vitro and peripherally induced Treg (pTreg) cells in vivo [68]. Compared with iTreg, the function and structure of tTreg are more stable. Several groups have used microarrays to analyze developmental and functional differences between tTregs and iTreg cells [71] and have shown that the expression of neuropilin-1 (Nrp1) is increased in tTregs. Nrp1 increases the nuclear localization of FOXP3through AKT phosphorylation, thereby promoting the stability of pTreg cells and playing its role in anti-tumor immunity [72].

Treg cells, as important immune cells, also play an important role in TME. However, a large number of studies have shown that the final effect of Treg cells on tumors has not been determined [73–75], and their tumor-promoting or anti-tumor functions may not be mutually exclusive but depend on time and background.

2.3.1 | Tumor-promoting effect of Treg cells

A large number of studies have found that the infiltration of a large number of Treg cells into tumor tissues is usually associated with a poor prognosis for cancer patients [76]. Treg cells participate in tumor immune escape and promote the occurrence and development of tumors by blocking effector T cells responses to cancer cells and cytokines secretion [77, 78]. At the same time, Betts *et al.* [79] found that Treg cells inhibit immune surveillance during sarcoma formation, and under hypoxic conditions. Tumor cells can recruit Tregs by upregulating the expression of C-C motif chemokine ligand 28 (CCL28) to enhance tumor immune tolerance and promote angiogenesis [80].

At present, the mechanism of how Treg cells inhibit tumor cells death has not been clearly elucidated, and some studies believe that the inhibitory effector regulatory T (eTreg) cells are inseparable from the cell contact-dependent inhibition mechanism [81–83]. Infiltrating Treg cells in mouse and human tumors highly express CD25 and CTLA-4 [84]. One of the key functions of CTLA-4 is to down-regulate the expression of CD80/86 in antigen-presenting cells and inhibit the activation of conventional T cells [78], thus producing immunosuppressive effects.

In addition, because Treg cells do not produce IL-2 themselves, they require exogenous IL-2 captured by the high-affinity IL-2 receptor (CD25 as a component of the receptor) to survive, and this uptake of IL-2 from the surrounding environment may limit the amount of IL-2 available to activate and proliferate nearby conventional T cells [85]. Ohue *et al.* [86] found that after T cell antigen receptor (TCR) stimulation in draining lymph nodes, naive Treg cells proliferate dramatically and differentiate into highly suppressive eTreg cells, which consume IL-2 through high-affinity IL-2 receptors and secrete inhibitory cytokines (including IL-10, IL-2, TGF-β, and IL-35) and ATP degradation to show their inhibitory activity. These inhibitory mechanisms work in an antigen-nonspecific manner: Studies have shown that Treg cells in the bone marrow and blood of patients with hematological malignancies secrete elevated levels of the cytokines IL-10, TGF-β, and IL-35 [87–89]. Experiments have shown that IL-35 can promote the proliferation of paraffin-embedded human pancreatic cancer cells. It can also inhibit tumor cell apoptosis by inducing Bcl-2 and reducing the expression of (TNF)-related apoptosis-inducing ligand receptor 1 (TRAILR1) [90]. At the same time, eTreg cells can also inhibit the maturation of antigen-presenting cells, such as DCs, in an antigen-specific manner. TCR transgenic animal models have shown that antigen-specific Treg cells show superior immunosuppressive function compared with antigen-nonspecific Treg cells, and antigen-specific Treg cells show stronger immunosuppressive function [86].

On the other hand, cytotoxic substances produced by Treg cells, such as perforin and granzyme, kill effector T cells [91]. In addition, activated eTreg cells and effector T cells may express programmed cell death protein 1 (PD-1). In the TME, PD-1 may enhance the activation and immunosuppressive function of Treg cells, inhibit the excessive activation of conventional T cells and make them dysfunctional or depleted by inhibiting TCR and costimulatory CD28 signaling [92].

2.3.2 | Tumor inhibition of Treg cells

In addition to tumor promotion, Treg cells have recently been found to play a role in inhibiting tumor development at the early stage of cancer development. Cytokines secreted by T helper cell 17 (Th17) cells are highly expressed in both human colon cancer and mouse polyposis [93]. Studies have shown that the persistent inflammatory response mediated by Th17 can lead to enteritis and ultimately to CRC [93–95]. Treg cells can inhibit the Th17 cell-mediated inflammatory response through an IL-10-dependent pathway and prevent the occurrence of Th17 cell-mediated chronic enteritis in a mouse model [96]. On the other hand, functional analysis of Treg cells in mice has shown that Treg cells naturally activated by TCR will exert suppressive functions through cell-cell contacts, such as CTLA-4 and/or glucocorticoid – induced tumor necrosis factorreceptor (GITR) signaling. Studies in tumor-bearing mice have shown that the use of antibodies against Treg cells can significantly improve their anti-tumor effects, and their combination with PD-1 antibodies can produce anti-tumor synergistic effects [97].

The meta-analysis by Shang *et al.* [98] showed that while high FOXP3 Tregs infiltration was significantly associated with poor prognosis in most solid tumors studied, tumor-infiltrating FOXP3 Tregs were associated with favorable prognosis in colorectal, head and neck, and esophageal cancers. This may be related to the suppression of the excessive inflammatory response of epithelial cells by Treg cells. As mentioned above, Treg cells can express cytokines, such as IL-10, and the results of Poutahidis *et al.* [99] showed that exogenous IL-10 supplementation helped down-regulate IL-6 and oncogenic *K-ras* expression in epithelial cells. In addition, treatment with IL-10 also significantly reduced Gr-1$^+$ 7/4$^+$ (neutrophil) cells, which were shown to be required for cancer, as tumor invasion was reversed using anti-LY-6G (Gr-1) antibodies. Together with these studies, it may be hypothesized that Treg cells prevent the development and growth of related cancers by releasing IL-10.

2.3.3 | Treg cells in the immune TME

FOXP3-expressing Treg cells are abundant in TME. Treg cells abundantly infiltrate into tumor tissues, which is often associated with poor prognosis in cancer patients [100]. Researches had found that targeting at Treg cells has been found to improve the efficacy of immunotherapy [75, 101], in other words, converting cold into hot. Tanaka *et al.* [100] found that depletion of Treg cells is an effective way to evoke anti-tumor immunity. A previous experiment showed that a removal of CD25 Treg cells from tumor-bearing mice by anti-CD25 monoclonal antibody (mAb) administration increased tumor-infiltrating CD8 T cells with a resultant eradication of syngeneic tumors [102]. The reason might be that Treg depletion is likely to possess an antigen-non-specific "adjuvant effect" because the depletion activates APCs and up-regulates CD80/86 expression to facilitate strong presentation of tumor-antigens to tumor-reactive CD4 and CD8 T cells [103]. One of the recent breakthroughs in cancer immunotherapy is the clinical use of anti-CTLA-4 antibody, often referred to as the checkpoint blockade therapy [75]. Recent studies have suggested the possibility that anti-CTLA-4 mAb predominantly affects Treg cells [11, 104], thereby enhancing anti-tumor immune responses which means Treg might be a target spot to increase the sensitivity of the tumor to immunotherapy. What is said above reminds that Treg plays an essential role in the sensitivity of the tumor to immunotherapy.

3 | EPIGENETICS

3.1 | Non-coding RNAs

Less than 3% of the sequences in the human genome encode proteins, and more than 90% of the sequences are transcribed into RNA but do not encode proteins. These RNA molecules that cannot encode proteins are called non-coding RNAs. Non-coding RNAs are not by-products of transcription but have regulatory functions. According to the size of non-coding RNA molecules, they are often divided into short non-coding RNA, small non-coding RNA, long non-coding RNA (lncRNA), and circular RNA (circRNA). Among them, small non-coding RNAs include microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), and other types" [105]. More and more studies have shown that non-coding RNAs play a very important regulatory role in the occurrence and development of tumors.

3.1.1 | miRNA

miRNA is widely found in animals, plants, and some viruses. miRNA exerts a negative regulatory effect on gene expression at the mRNA level [106, 107]. Regarding the mechanism of miRNA action, on the one hand, miRNAs can cause mRNA cleavage and thus play a negative regulatory role [108]. On the other hand, miRNAs can exert their biological functions through translational repression [109, 110]. It is currently believed that miRNAs inhibit cap-dependent translation in the initiation phase [111]. The interaction of trinucleotide repeat containing 6 (TNRC6) with poly(A)-binding protein (PABP) disrupts

the function of PABP in protein translation [105]. This may be the mechanism by which miRNAs exert their effects.

miRNA has been shown to be an important factor in the development of a variety of diseases, including cancer, cardiovascular disease, metabolic endocrine disorders, etc [112]. Many studies have confirmed the important role of miRNAs in various cancers. Drosha and Dicer are two RNase III endonucleases responsible for the formation of pre-miRNA and miRNA dimers during miRNA maturation. Loss of function of Drosha and Dicer leads to down-regulation of miRNAs in cancer, which has a significant impact on embryonic development and cancer development and metastasis [113, 114]. Some miRNAs exhibit pro-cancer effects. It has been shown that miR-155-5p upregulates RhoA mRNA levels and translation, thereby promoting the development and metastasis of colon cancer [115]. Let-7 miRNA inhibits tumor progression by targeting and down-regulating the expression of many oncogenes, including E2 promoter binding factor 1(E2F1), AT-rich interaction domain 3 (ARID3B), Kirsten Rat Sarcoma Viral Oncogene Homolog (K-RAS), and Myelocytomatosis viral oncogene homolog (c-Myc) [116]. However, multiple studies have shown that the same miRNAs have different roles in different tumors. It has been shown that miR-126 can reduce cell proliferation in the breast cancer cell line (MCF7), induce apoptosis, and inhibit tumor angiogenesis by downregulating the VEGF-A signaling pathway [117]. miR-126 inhibits glioma progression by targeting and regulating the Phosphatase and tensin homolog deleted on chromosome 10 (PTEN)/Phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT) and mouse doubleminute 2 homolog (MDM2)-p53 pathways [118]. Another study showed that miR-126 expression was significantly increased in esophageal cancer. miR-126 inhibited cell death by targeting STAT3 three prime untranslated region (3'-UTR) and down-regulating the expression of two autophagic signals, light-chain 3B (LC3B) and p62 protein [119].

3.1.2 | LncRNA

LncRNAs are a highly diverse group of non-coding RNAs larger than 200 nt that do not have the ability to encode proteins [120]. Different mechanisms of action of lncRNAs with different subcellular localizations [121]. For intranuclear lncRNA, its main mechanism of action is involved in transcriptional regulation, epigenetic modifications, and nuclear structure regulation. The same lncRNA may exert its effects in different tissues through different mechanisms. For example, lncRNA FIRRE can stabilize BECN1 mRNA by binding to polypyrimidine tract-binding protein (PTBP1) to promote tumor development [122]. LncRNAs localized in the cytoplasm are mainly involved in post-transcriptional gene regulation. LncRNA can function as miRNA sponges. For example, lncRNA FENDRR targets miR-362-5p by promoting nuclear factor erythroid 2-like 3 receptor (NPR3) and inactivating the p38-mitogen-activated protein kinase (MAPK) pathway to inhibit hepatocellular carcinomas (HCC) cell viability while promoting apoptosis [123].

Similar to miRNAs, the development of many diseases is also related to lncRNA. In cancer development, lncRNA also has two effects: tumor suppressor and tumor promoter [124]. SET domain bifurcated 1 (*SETDB1*) is an oncogene that encodes an HMT. LncRNA FENDRR silences survivin through SETDB1-mediated methylation of H3K9, thereby inhibiting proliferation, migration, and invasion of cholangiocarcinoma cells [125]. LncRNA Pvt1b is a p53-dependent long-stranded non-coding RNA isoform. It can inhibit the expression of the oncogene Myc without altering the genomic chromosome, thus inhibiting tumor growth [126].

3.1.3 | circRNA

circRNA is a single-stranded closed-loop RNA that is conserved and tissue-specific. circRNA is currently considered to function as a post-transcriptional regulator by binding RNA or RNA-binding proteins (RBPs) or even encoding proteins under certain conditions to regulate transcription and translation [127–130]. circRNA can act as miRNA sponges [131, 132]. circRNA can be translated in a cap-independent manner [130]. In addition, circRNA can interact with proteins through a variety of mechanisms, such as affecting protein-protein associations, blocking or facilitating the binding of proteins and other molecules, recruitment, forming complexes with proteins and nucleic acids to regulate mRNA stability and translation processes, and transporting and reassigning proteins to their localization in the cell [130]. For example, hsa_circ_001783 can act as a miRNA sponge to target and inhibit miR-200c-3p, thereby enhancing the expression of miR-200c-3p's target genes zinc finger E-box binding homeobox 1 (*ZEB1*), zinc finger E-box binding homeobox 2 (*ZEB2*), and ETS proto-oncogene 1 (*ETS1*) and promoting breast cancer progression [133].

Similar to the two previously mentioned noncoding RNAs, circRNAs are also involved in the development and progression of cancer. circRNA are involved in tumor invasion and metastasis, angiogenesis, and immune regulation. For example, hsa_circ_0003204 promotes proliferation and invasion of cervical cancer cells by activating the MAPK signaling pathway [134]. circ3823 binds to and inhibits miR-30c-5p and deregulates miR-30c-5p from its target transcription factor 7 (*TCF7*), thereby upregulating

Myc and cyclin D1 (CCND1) and thereby promoting proliferation, invasion, and angiogenesis in CRC cells [135]. circUHRF1 produced by HCC cells promotes immunosuppression by degrading miR-449c-5p to upregulate TIM-3 expression, leading to reduced tumor necrosis factor-α (TNF-α) and Interferon-gamma (IFN-γ) secretion by NK cells [136]. Of course, some circRNAs exist that inhibit tumor progression. circRNA_0005075 can inhibit gastric cancer cell growth and metastasis by promoting the function of miR-431, upregulating p53 expression, and thus inhibiting epithelial mesenchymal transition [137].

3.2 | Histone modification

DNA is packaged in the form of chromatin in eukaryotic cells with nucleosomes as functional units, each of which is composed of an octamer of four core histones (H3, H4, H2A, and H2B). The core of the nucleosome is formed by globular regions of histones, while the N-terminal tail protrudes from the nucleosome and is enhanced by various post-translational modifications (PTMs). Histone tails are altered by a large group of non-histone chromatin-related proteins called chromatin-modifying enzymes. These enzymes are present in cells as multicomponent protein complexes that are regularly recruited to chromatin along with DNA-binding transcription factors [138]. Many covalent PTMS in histone and DNA-related regions play a key role in genomic function by binding specific transcription factors and coactivators and altering the structural properties of chromatin [139]. Based on their functions, chromatin-modifying enzymes are classified into four groups: acetylated histone acetyltransferases (HAT), histone deacetylase (HDAC), HMT, and histone demethylase (HDM) [140]. The resulting PTM can act in concert or alone to promote chromatin-mediated activation or repression of inflammatory cytokine gene expression [141], cell cycle arrest [142], senescence [143], apoptosis [144], growth factors [145], and antioxidants [146].

Histone methylation, which occurs at the lysine residue of histone H3 or H4, is one of the most common histone modifications. This modification is mediated by HMT using S-adenosylmethionine (SAM) as the substrate [147]. Histone methylation can be divided into monomethylation (me1), dimethylation (me2), and trimethylation (me3). In general, methylation of H3K4, H3K36, and H3K79 is thought to promote gene expression, whereas methylation of H3K9, H3K27, and H4K20 is inversely associated with gene silencing expression and chromatin condensation [148].

Acetylation of histones is considered a marker of active chromatin. The acetylation state of chromatin is a dynamic process that is regulated by HAT and HDAC. Acetylated histone lysine side chains no longer carry a positive charge, thus losing the ability to bind tightly to DNA and facilitating the binding of transcriptional regulators [149]. H3 and H4 are the main histones modified by proteases. There are many lysine residues in histones that can be acetylated, including H3K9, H3K14, H3K18, H3K23, H3K27, etc.

Aberrant histone lysine methylation patterns have been identified in various human cancers. For example, low levels of H3K4me2 correlated with low survival rates in both lung and kidney cancers [150] and were also associated with adverse prognosis in non-small cell lung carcinoma (NSCLC) [151], HCC [152], and breast cancer [153] Moreover, aberrant histone lysine acetylation patterns have been reported as a common hallmark of human cancer. Increased expression of HDAC family proteins has been observed in many cancers, including B cell acute lymphoblastic leukemia (ALL) and T cell ALL [154].

3.3 | DNA methylation

DNA methylation is the dominant epigenetic marker. 5-methylcytosine (5mC) was the primary and extensive DNA covalent modification [155]. In the mammalian genome, 5mC exists mostly in the CpG dinucleotide context, with 70%-80% of CpGs being methylated, while CpG-rich regions, known as CpG islands (CGIs), are present in more than half of the vertebrate genes [156]. Mammalian gene CGIs transcription start site methylation represses gene transcription. In mammals, DNA methyltransferases, include DNA methyltransferase 1 (DNMT1), DNA methyltransferase 3 alpha (DNMT3A), and DNA methyltransferase 3 beta (DNMT3B), of which DNMT3A and DNMT3B are necessary for the maintenance of methylation [157]. 5mC can be demethylated by either passive or active processes. Passive DNA demethylation is thought to deplete 5-hydroxymethylcytosine through DNA replication [158]. Active DNA demethylation in mammals is achieved through ten-eleven translocation (TET)-mediated oxidation of 5mC to 5-hydroxymethylcytosine, 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC), followed by replication-dependent dilution of oxidized 5mC or thymine DNA glycosylase-mediated excision of 5fC and 5caC coupled with base excision repair [159].

Tumor cells are characterized by a different methylome from that of normal cells. The methylation status of immune genes influences the tumor immune response in the TME and correlates with the density of tumor-infiltrating lymphocytes [160]. Investigation of colon cancer-derived tumor-infiltrating lymphocytes demonstrated that hypermethylation of the IFN-γ gene can prevent the maturation of T helper cell 1 (Th1) lymphocytes [161]. This may be the epigenetic mechanism for

TABLE 1 Mechanisms of epigenetic therapy targeting immunosuppressive cells.

Title	Year of publication	Main findings
Targeting the epigenetic regulation of antitumor immunity [163]	2020	1. MDSC: Reducing the frequency of MDSC in tumoral tissues with DNA methyltransferase inhibitors may improve the efficacy of immune therapy responses in the context of immune checkpoint blockade or adoptive cell therapy. 2. Treg cell: Targeting P300/CBP and TIP60 acetylation-dependent regulation of FOXP3 expression may affect the differentiation of T cells into Treg cells.
Cancer epigenetics, tumor immunity, and Immunotherapy [164]	2020	The epigenetic inhibitors DNMT and KMT6A (EZH2) both directly inhibit the expression of Th1-type chemokines, such as CXCL9 and CXCL10, which are essential for T-cell recruitment and infiltration.
Epigenetic modulation of antitumor immunity for improved cancer immunotherapy [165]	2021	1. MDSC: The epigenetic component p66a regulates MDSC by modifying STAT3 activity. Inhibition of EZH126 by GSK2 has been shown to suppress antitumor immunity by enhancing MDSC content in tumors. 2. Treg: Phosphoric acid-modified vitamin C induces hypomethylation of the FOXP3 gene promoter region in Treg cells.
Histone deacetylase inhibitors as anticancer drugs [166]	2017	Treg cell: Inhibition of HDAC6 activates naive T cells, while class II HDAC inhibitors enhance Treg number and function.
Tumor microenvironmental signals reshape chromatin landscapes to limit the functional potential of exhausted T cells [167]	2022	Terminal depletion of T cells: Enforced expression of H3K27 histone demethylase Kdm6b can restore the antitumor effects of depleted T cells.
Targeting pancreatic cancer immune evasion by inhibiting histone deacetylases [168]	2022	Treg cell: The HDAC inhibitor Entinostat reduced the ratio of Treg cells in tumor tissues.
Lysine acetylation/deacetylation modification of immune-related molecules in cancer immunotherapy [169]	2022	1. Treg cell: Low-dose HDAC inhibitors can regulate the expression of CTLA-4, promote the natural generation of FOXP3 Treg cells, and restore the suppressive function of Treg cells by regulating histone H3K27 acetylation in ITP. 2. MDSC: Etinostat, a class I HDAC inhibitor, contributes to the positive antitumor effect of PD-1 inhibitors in lung and renal-cell carcinoma syngeneic mouse models by inhibiting the tumor suppressive effect of MDSC cells.

Abbreviations: CXCL, C-X-C motif chemokine ligand; DNMT, DNA methyltransferase; FOXP3, Forkhead box protein P3; GSK2, glycogen synthase kinase 2; HDAC, histone deacetylase; ITP, immune thrombocytopenia; KMT6A (EZH2), Enhancer of zeste homologue 2; MDSC, Myeloid-derived suppressor cells; TAM. Tumor-associated macrophage; TIP, Tat-Interactive Protein; Treg, Regulatory T cells.

tumor-induced immunosuppression. Meanwhile, DNA methylation alterations implicate epigenetic modulation in precision immunotherapy. Jung *et al.* [162] reported that low DNA methylation is expected to decrease tumor immunity and undermine the clinical benefit of immunotherapy. All of the above has proven that DNA methylation has a deep relationship with tumors.

4 | MECHANISMS IN ISCs

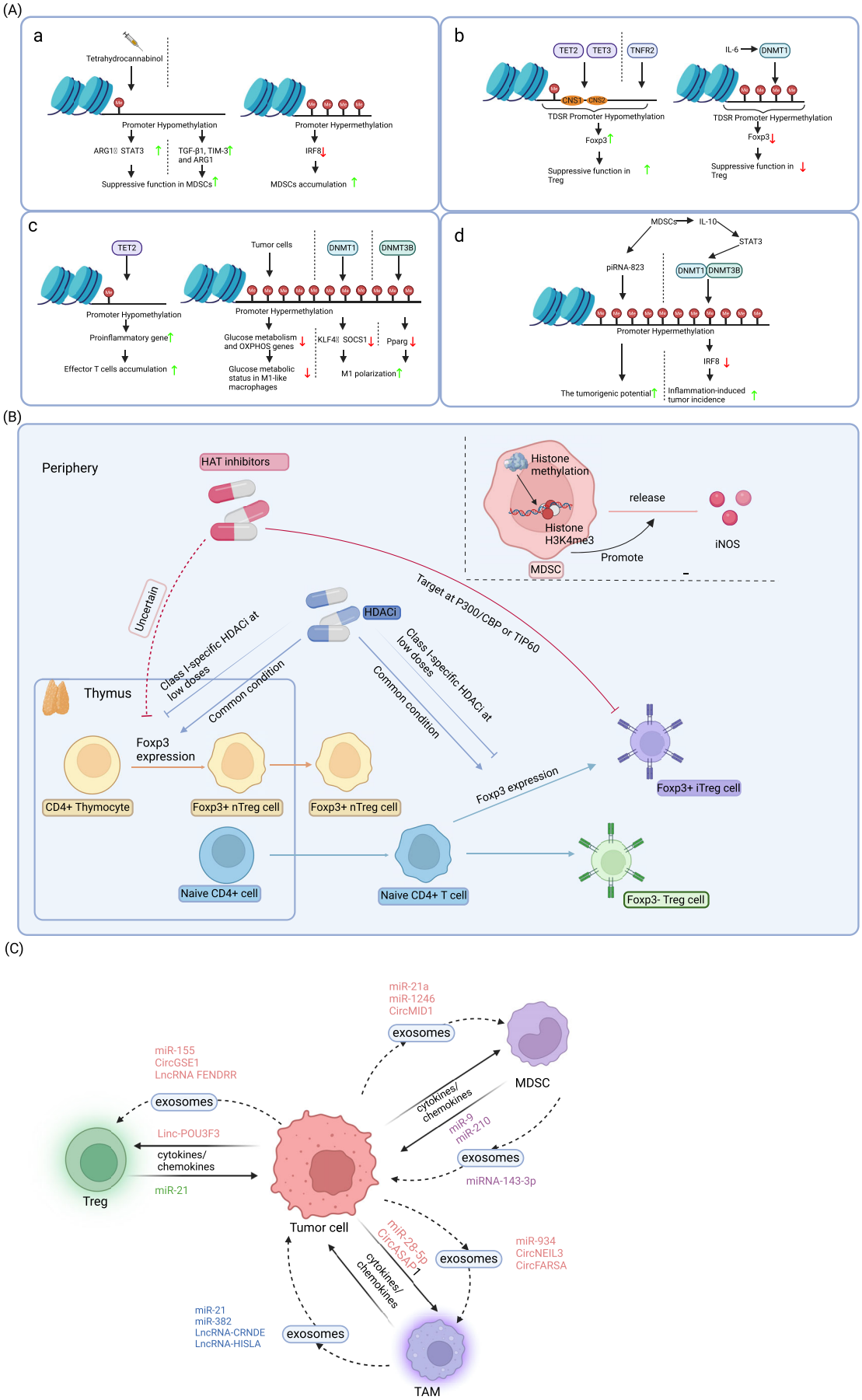
Some existing studies have reported the effects of epigenetic therapeutic strategies on immunosuppressive cells (Table 1), and the mechanism of epigenetic modification on immunosuppressive cells will be introduced in detail below (Figure 3).

4.1 | Noncoding RNA in ISCs

4.1.1 | The roles of Noncoding RNA in TAM

Non-coding RNAs can affect the occurrence and development of tumors by regulating the function and biological behavior of TAMs.(Table 2) Tumor cell-derived lncRNAs, circRNAs, and miRNAs function as oncogenes by regulating macrophage polarization and immunosuppression, promoting tumor cell proliferation, cell cycle, invasion, and metastasis [170].

The study of Lai *et al.* [188] found that lncRNA-NBR2 can promote tumor progression by regulating TAM M2 polarization. Zong *et al.* [191] found that knockdown of LncRNA SNHG1 inhibited M2 macrophage polarization by inhibiting Signal transducer and activator of transcription



6 (STAT6) phosphorylation, suggesting that lncRNA-SNHG1 could promote breast cancer progression by affecting TAMs. Another study showed that LincRNA-p21 can directly target p53 or indirectly target p53 through an hnRNP-K-dependent mechanism, thereby promoting the maintenance of the TAM phenotype in breast cancer tissues [198]. LncRNA-p21 knockdown significantly reversed the functional phenotype of TAM and enhanced its antitumor ability [189]. Xie *et al.* [182] showed that circSMARCC1 disrupts the crosstalk between TAM and prostate cancer (PCa) cells via the CCL20-CCR6 axis, including TAM recruitment and mediates M2 macrophage polarization, thereby promoting PCa progression. Studies have shown that the CCL20-CCR6 axis can promote tumor progression by stimulating the release of inflammatory modulators from TAM [199]. Zhu *et al.* [200] found that knockdown of circMERTK resulted in attenuated apoptosis of $CD8^+$ T cells in a co-culture assay, suggesting that circMENTK may have an effect on the immunosuppressive activity of TAM-like cells. TAM-like cells can exert immunosuppressive activity through the circMERTK/miR-125a-3p/IL-10 axis, suggesting that circMERTK may play an important role in TAM activation and may serve as a potential therapeutic target for CRC [183]. Zhou *et al.* [171] showed that the miR-285p-interleukin 34 (IL-34) macrophage feedback loop regulates HCC metastasis. IL-34 may promote TAM polarization and infiltration through IL34/colony stimulating factor-1 receptor (CSF-1R) [201]. Zhao *et al.* [202] showed that Xist regulates the expression of CCAAT/enhancer-binding protein alph (C/EBPa) and Kruppel-like factor 6 (KLF6) by competing with miR-101, in which KLF6 can inhibit M2 polarization by reducing the expression of peroxisome proliferator-activated receptor γ (PPARγ), and C/EBPa and its target gene SPl1 participate in the activation of Toll-like receptor (TLR) ligand-induced M1 macrophages. This mediates the polarization of macrophages and affects the proliferation and migration of breast and ovarian cancer cells [190]. Another study showed that the miR-144/miR-451a cluster promotes macrophage M1 polarization and antitumor activity by targeting hepatocyte growth factor (HGF) and macrophage migration inhibitory factor (MIF) [172]. HGF regulates AMPK phosphorylation through upstream regulators of Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKKβ), and promotes macrophage M2 polarization through HGF/c-met signaling pathway [203]. miR-934 induces M2 macrophage polarization by downregulating PTEN expression and activating the PI3K/AKT signaling pathway, and polarized macrophages can also promote the formation of M2 macrophages through a C-X-C motif chemokine ligand 13 (CXCL13)/C-X-C chemokine receptor type 5 (CXCR5)/NFκB/p65/miR-934 positive feedback loop by secreting CXCL13 liver metastases from rectal cancer [173]. Zhou *et al.* [176] found that tumor cells induce decreased expression of mir-382 in TAMs, thereby reducing the downstream inhibition of Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) to further induce M2 polarization, thereby enhancing the ability of TAMs to promote EMT and distant metastasis of breast cancer cells. PGC-1α activates PPARγ, which plays an important role in TAM polarization. This may be the mechanism that makes it work.

In addition, TAM-derived lncRNAs also promote tumor proliferation, metastasis, and drug resistance [204]. Studies have shown that TAM-derived exosomes containing lncCRNDE or miR-21 can enhance the resistance of gastric cancer cells to cisplatin chemotherapy. The mechanism may be that the exosome transfer of miR-21 leads to the downregulation of PTEN, the increase of AKT activation and the up-regulation of Bcl-2, a gene related to apoptosis [174, 193]. The vesicular miRNAs produced by TAM also promote the malignant behavior of tumor cells [205].

As far as the current research goes, there are a variety of non-coding RNAs that can be used as tumor markers for tumor diagnosis and prognosis, and are also good targets for tumor treatment by converting tumors from cold to hot. For example, lncRNA, as an important regulatory substance, can also be used as tumor markers, such as

FIGURE 3 The mechanism of epigenetic strategies in ISCs. (A) The pathway of non-coding RNA acting between tumor cells and ISCs. (B) The mechanism of histone modification in ISC. (C) The mechanism of DNA methylation in ISC.Epigenetics refers to heritable changes in cellular phenotype independent of DNA sequence alterations, with major regulators including DNA methylation, histone modifications, and non-coding RNAs. Since epigenetics plays an important role in the process of ISCs affecting tumors, therapeutic strategies implementing epigenetic modulating drugs are expected to significantly impact the TME through inhibition of ISCs (such as MDSCs, Treg cell and so on) resulting in turning "cold" to "hot" and increase the sensibility of tumor to immunotherapy. Abbreviations: ARG1, arginase 1; CBP, CREB-binding protein; DNMT1, DNA methyltransferase 1; DNMT3B, DNA methyltransferase 3B; Foxp3, forkhead box protein P3; H3K4me3, histone H3 lysine 4 trimethylation; HAT, histone acetyltransferases; HDACi, histone deacetylase inhibitor; iNOS, inducible nitric oxide sythase; IRF8, interferon regulatory factor 8; ISC, immune suppressive cell; KLF4, Kruppel-like factor 4; MDSC, myeloid-derived suppressor cells; Pparg, peroxisome proliferator-activated receptor gamma; SOCS1, suppressor of cytokine signaling 1; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TET2, tet methylcytosine dioxygenase 2; TET3, tet methylcytosine dioxygenase 3; TGF-β1, transforming growth factor beta-1; TIM-3, T cell immunoglobulin domain and mucin domain-3; TME, tumor microenvironment; TNFR2, tumor necrosis factor receptor 2; Treg, regulatory T.

TABLE 2 Non-coding RNAs affecting TAMs.

Noncoding RNAs	Origin cell	Expression in tumor cell	Way of crosstalk	Role in tumor cells or immunosuppressive cells	Reference
miR-28-5p	HCC cell	Downregulated	Cytokine	Downregulate miR-28-5p: mediate TAM infiltration through IL-34, induce TAM to produce TGF-β1, and further inhibit the expression of miR-28-5p, forming a feedback loop to promote tumor growth and metastasis.	[171]
miR-144/miR-451a cluster	HCC cell	Downregulated	Cytokine	Paracrine pathways targeting HGF and MIF induce M1-like repolarization of TAMs.	[172]
miR-934	CRC cell	Upregulated	Exosome	Down-regulation of PTEN expression and activation of PI3K/AKT signaling pathway induces the polarization of M2 macrophages, and M2 macrophages can promote CRLM through CXCL13/CXCR5/NFκB/p65/miR934 positive feedback loop.	[173]
miR-21	TAM	Upregulate	Exosome	Inhibit apoptosis by down-regulating PTEN, enhance the activation of PI3K/AKT signaling pathway, thereby increasing the drug resistance of gastric cancer, breast cancer, and bladder cancer.	[174, 175]
miR-382	TAM	Downregulated	Exosome	Targets PGC-1α, reduces PGC-1α inhibition, thereby altering metabolic state and promoting M2 polarization of TAMs.	[176]
miR-221-3p	TAM	Upregulate	Exosome	Decreased expression of the epithelial marker E-cadherin induced EMT, triggering a switch to a CSC-like phenotype and MDR, thereby promoting EOC cell proliferation, adhesion, migration, and resistance.	[177]
miR-223	TAM	Upregulate	Exosome	Promoted drug resistance in EOC cells through the PTEN-PI3K/AKT pathway.	[178]
miRNA-501-3p	TAM	Upregulated	Exosome	Inhibits tumor suppressor TGFBR3 gene and facilitates the development of PDAC by activating the TGF-β signaling pathway.	[179]
miR-95	TAM	Upregulated	Exosome	Regulation of JunB promotes PCa cell proliferation, invasion, and EMT pathway activation.	[180]
miR-125a/b	TAM	Upregulated	Exosome	Downregulation of CD90 promotes cell proliferation and stem cell properties of HCC cells.	[181]
circSMARCC1	PCa cell	Upregulated	Chemokine	Blockade of crosstalk between prostate cancer cells and TAMs via the miR-1322/CCL20/CCR6 signaling pathway promotes tumor progression.	[182]
circMERTK	TAM	Upregulated	Cytokine	Exerts immunosuppressive activity through the CircMERTK/miR-125a-3p/IL-10 axis.	[183]
circASAP1	HCC cell	Upregulated	Chemokine	Regulation of miR-326/miR-532-5p-CSF-1 signaling pathway mediates TAM infiltration.	[184]
circ0048117	ESCC cell	Upregulated	Exosome	Serves as a sponge for miR-140, which competes with TLR4 to promote M2 macrophage polarization.	[185]
circNEIL3	Glioma cell	Upregulated	Exosome	circNEIL3 stabilizes IGF2BP3 protein by preventing hinted4-mediated ubiquitination, enabling TAMs to acquire immunosuppressive properties.	[186]

(Continues)

TABLE 2 (Continued)

Noncoding RNAs	Origin cell	Expression in tumor cell	Way of crosstalk	Role in tumor cells or immunosuppressive cells	Reference
circFARSA	NSCLC cell	Upregulated	Exosome	circFARSA induces M2 polarization through PTEN ubiquitination and degradation, further activating the PI3K/AKT signaling pathway.	[187]
LncRNA-NBR2	CRC cell	Downregulated	Cytokine	Upregulates TNF-α and HLA-DR expression, promotes M1 polarization and inhibits M2 polarization.	[188]
LincRNA-p21	TAM	N/A	N/A	Inhibit the interaction between p53 and MDM2, inhibit the activation of NF-κB and STAT3 signaling pathways, promote the transformation of macrophages into TAMs, and promote tumor progression.	[189]
LncRNA-Xist	TAM	Upregulated	N/A	LncRNA-Xist mediates macrophage polarization and affects breast and ovarian cancer cell proliferation and migration by competing with miR-101 to regulate the expression of C/EPBα and KLF6.	[190]
LncRNA-SNHG1	TAM	Downregulated	N/A	Inhibition of M2 macrophage polarization by inhibiting STAT6 phosphorylation.	[191]
LncRNA-GAS5	EC cell	Upregulated	N/A	Transformation of TAMs from a pro-tumor phenotype to an anti-tumor phenotype mediated by activation of the miR-21-PTEN-AKT pathway and inhibition of YAP1.	[192]
LncRNA-CRNDE	TAM	Downregulated	Exosome	CRNDE facilitates NEDD4-1-mediated PTEN ubiquitination. PTEN dephosphorylates PIP3, which suppresses the activation of the PI3K/Akt signaling pathway and ultimately represses PI3K/Akt pathway-mediated cancer cell proliferation, invasion, and drug resistance.	[193]
LncRNA-HISLA	TAM	Upregulated	Exosome	Stabilize the expression of β-catenin by inhibiting the interaction between GSK3β and β-catenin, thereby promoting the activation of EMT and tumor metastasis.	[194]
LncRNA-MMPA	TAM	Upregulated	Exosome	Polarized M2 macrophages interact with miR-548s as a microRNA sponge to increase ALDH1A3 mRNA levels, thereby promoting glucose metabolism and cell proliferation in HCC.	[127]
LncRNA-PACERR	PDAC cell	Upregulated	N/A	LncRNA-PACERR binds to IGF2BP2 to enhance the stability of KLF12 and c-Myc in the cytoplasm in an m6a-dependent manner. The promoter of LncRNA-PACERR is the target of KLF12, and LncRNA-PACERR interacts with KLF12 in the nucleus to recruit EP300 to increase histone acetylation. Thereby promoting M2 polarization of TAMs.	[195, 196]
LncRNA RP11-361F15.2	OS cell	Upregulated	N/A	Promotion of CPEB4-mediated tumorigenesis and M2-like polarization of TAMs by miR-30c-5p	[197]

Abbreviations: ALDH1A3, aldehyde dehydrogenase 1 family member A3; CPEB4, cytoplasmic polyadenylation element binding protein 4; CRLM, colorectal liver metastasis; CSF, Colony stimulating factor; EMT, Epithelial-Mesenchymal Transition; EOC, Epithelial ovarian cancer; GSK3β, glycogen synthase kinase-3β; HGF, Human growth factor; IGF2BP3, Insulin Like Growth Factor 2 mRNA Binding Protein 3; MDM2, mouse doubleminute 2 homolog; MIF, Macrophage Migration Inhibitory Factor; N/A, not applicable; NEDD4-1, Neural precursor cell expressed, developmentally down-regulated 4, E3 ubiquitin protein ligase; PDAC, pancreatic ductal adenocarcinoma; PGC1-α, Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PIP3, phosphatidylinositol-3,4,5-triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome ten; STAT3, Signal Transducer and Activator of Transcription 3; TAM. Tumor-associated macrophage; TGFBR3, Transforming growth factor beta receptor type 3; TLR4, Toll-like receptors; YAP1, Yes Associated Protein 1.

CR936218.2, SREBF2-AS1, TMEM220-AS1, LINC00205, LUCAT, AL049840.2, AL139260.1, DCST1-AS1, INC01232, etc [206]. For the treatment of TAM epigenetics, Xu *et al.* [207] showed that SRY-related high-mobility-group box 4 (SOX4) is a direct target gene of miR-204-5p in TAMRs. SOX4 silencing significantly inhibited the proliferation, migration, and clone formation of TAMRs. The expression of lnc-42060 and SOX4 in canine mammary gland tumours (CMGT) tissues was significantly positively correlated. Lnc-42060 positively regulates the expression of SOX4 at both mRNA and protein levels in TAMRs. Further cell biology experiments showed that lnc-42060 promoted drug resistance, proliferation, and metastasis of TAMRs through the miR-204-5p/SOX4 axis. That is, lnc-42060 and miR-204-5p were regarded as ceRNAs regulating SOX4 expression. Certain non-coding RNAs, such as miR-122-5p, can increase radiation sensitivity and may amplify radiation damage during therapy [208, 209]. Other adverse effects are still being explored.

Furthermore, exosomal miR-21 targeting TAM may be a promising adjuvant therapy strategy for gastric cancer patients, especially those with cisplatin-resistant gastric carcinoma (GC) [174]. Currently, there exist diverse well-established approaches for RNA delivery, including lipid nanoparticles and other techniques, in addition to the aforementioned exosomes [210]. Similarly, the delivery of non-coding RNA can also adopt a similar route. The use of exosomes to deliver miRNAs has been achieved in many fields. Studies have shown that the use of exosomes to encapsulate miRNA let-7a and inject it can target breast cancer cells and exert anti-tumor effects [211]. Another study showed that the use of mesenchymal stem cell-derived exosomes can deliver LNA-antimiR-142-3p to breast cancer stem cells to reduce their tumorigenicity [212]. Liposome particles can also serve as carriers for non-coding RNA. Lipid-like nanoparticles (LNPs) have been shown to deliver small interfering RNA (siRNA) to muscle cells, liver cells, and neurons [213]. In addition to these, some new methods are gradually being discovered. It has been found that miR-29b-5p can be delivered by stem cell-homing hydrogel to inhibit the progression of arthritis and promote cartilage repair in rats [214].

4.1.2 | The roles of noncoding RNA in MDSCs

Epigenetic modifications can lead to the remodeling of MDSC characteristics, thereby regulating their antitumor immunity and the ability to promote tumor metastasis (Table 3). The inhibitory effect of MDSC on tumor immunity is regulated by miRNAs produced by various tumor cells [215]. Zhang *et al.* [216] found that both miR-17-5p and miR-20a could reduce the immunosuppressive ability of MDSCs by downregulating STAT3 expression. STAT3-mediated S100A9 protein regulates DC differentiation and MDSC infiltration in cancer [216]. Noman *et al.* [217] demonstrated that hypoxia inducible factor-1 (HIF-1α)-induced overexpression of miR-210 enhanced the tumor-promoting function of MDSCs by increasing arginase activity and NO production. Overexpression of miR-210 enhances MDSC-mediated T cell suppression in vivo. miR-210 regulates the expression levels of arginase-1 (Arg1), Interleukin (IL-16), and C-X-C motif chemokine ligand 12 (CXCL12) in MDSC, thereby affecting T cell function [217]. Tian *et al.* [218] found that inhibition of miR-9 promoted the differentiation of MDSCs and significantly reduced their immunosuppressive function, while overexpression of miR-9 significantly enhanced the function of MDSCs in in vitro studies. miR-9 enables MDSC differentiation by targeting runt-associated transcription factor 1 (Runx1), an essential transcription factor that regulates MDSC differentiation and function. Zhang *et al.* [219] showed that miR-21a in Lewis lung cancer(LLC) exosomes(exo) is able to target programmed cell death 4 (PDCD4) through IL-6 and phosphorylation of the STAT3 signaling pathway), thereby promoting functional expansion of MDSCs, which in turn will prevent the activation of cytotoxic $CD8^+$ T cells, thereby promoting tumor growth. Wang *et al.* [220] found that miR-34a could inhibit the transformation of tumor cells into $CD11b^+Gr1^+$ cells with immunosuppressive function by reducing TGF-β and IL-10. Another study found that miRNA deletion may promote the migration ability of MDSCs and their ability to promote tumor angiogenesis [221] These experimental results also indicate that the regulation of miRNAs on MDSCs is not always positive.

In addition to miRNAs, lncRNAs expressed in tumor tissues are also involved in the regulation of MDSCs. Zheng *et al.* [230] reported that HIF-1α upregulated the expression of lncRNA Pvt1 in granulocytic-MDSCs (G-MDSCs) under hypoxia. Pvt1 knockdown reduced the levels of Arg1 and ROS in G-MDSCs and restored antitumor T cell responses. Targeting Pvt1 attenuates G-MDSC-mediated immunosuppression. This could be further confirmed as a potential therapeutic strategy. Tian *et al.* [229] found that runt-related transcription factor 1 overlapping RNA (RUNXOR) knockdown reduced the expression of arginase Arg1 in MDSCs, indicating that RUNXOR was significantly associated with MDSC-induced immunosuppression in lung cancer patients and may be a target for anti-tumor immunotherapy. Tian *et al.* [227] also confirmed that the lncRNA HOTAIRM1 can enhance the expression of homeo box A1 (HOXA1) in MDSCs and that high levels of *HOXA1* (the target gene of HOX transcript antisense RNA [HOTAIR1]) can delay tumor progression and enhance anti-tumor immune responses by reducing

TABLE 3 Non-coding RNAs affecting MDSC.

Noncoding RNAs	Origin cell	Expression in tumor cell	Way of crosstalk	Role in tumor cells or immunosuppressive cells	Reference
miR-21	CAF	Upregulated	Exosome	Autocrine activation of STAT3 by IL-6 promotes the generation of M-MDSCs.	[222, 223]
miR-21a	LLC	Upregulated	Exosome	Induction of MDSC expansion by downregulation of PDCD4.	[219]
miR-1246	Glioma cell	Upregulated	Exosome	Drives differentiation and activation of MDSCs in a DUSP3/ERK-dependent manner.	[224]
miR-155	MDSC	Downregulated	N/A	Downregulated miR-155 targets and upregulates the expression of HIF-1a, thereby upregulating the expression of CXCL1, CXCL3, and CXCL8 in MDSCs, contributing to enhanced recruitment of MDSCs to tumors.	[221, 223]
miRNA-143-3p	G-MDSC	Upregulated	Exosome	targeting the 3'-UTR region, activation of the PI3K/Akt signaling pathway by inhibiting the transcription of ITM2B to promote proliferation.	[225]
miR-210	MDSC	Upregulated	Cytokine	Increase arginase activity and nitric oxide production, downregulate the expression of IL-16 or CXCL12, thereby enhancing its tumor-promoting effect.	[217]
miR-9	MDSC	Upregulated	Chemokine	Target the runt-related transcription factor 1, levels of CD11c, F4/80, CD40, CD80, CD86, and MHC class II molecules were reduced. Arginase activity as well as iNOS and ROS levels were also enhanced.	[218]
CircMID1	PCa cell	Upregulated	Exosome	Exosome S100A9 from MDSC promotes the expression of circMID1 in PC3 cells, and circMID1 acts as a ceRNA to regulate the expression of MID1 through miR-506-3p.	[226]
HOTAIRM1	MDSC	Downregulated	N/A	HOTAIRM1 can enhance the expression of HOXA1 in MDSCs, and the high level of HOXA1, the target gene of HOTAIRM1, can delay tumor progression and enhance anti-tumor immune response by down-regulating the immunosuppression of MDSCs.	[227]
LncRNA MALAT1	PBMC	Upregulated	N/A	Directly regulates the proliferation of MDSCs and increases their ARG1 expression.	[228]
RUNXOR	MDSC	Upregulated	N/A	Down-regulate RUNX1 expression; down-regulate ARG1 expression.	[229]
Pvt1	MDSC	Upregulated	N/A	Elevated ARG1 and ROS levels in G-MDSCs suppressed antitumor T cell responses.	[230]
LncRNA AK036396	PMN-MDSC	Upregulated	N/A	Enhances the stability of ficolin B, thereby facilitating its complex formation with mannose-binding lectin-associated serine proteases and activation of complement through the lectin pathway in granulocytes. Activation of complement can promote MDSCs to produce ROS and ARG1, and accelerate the migration of MDSCs to tumor site 559.	[231]
Lnc-C/EBPβ	MDSC	Upregulated	N/A	Regulate a series of target transcripts such as ARG1, NOS2, NOX2, COX2, IL4i1, etc. To control the immunosuppressive function and differentiation of MDSCs. Lnc-C/EBPβ may bind to C/EBPβ and WDR5 to promote the differentiation of PMN-MDSCs but inhibit the differentiation of Mo-MDSCs.	[232, 233]

(Continues)

TABLE 3 (Continued)

Noncoding RNAs	Origin cell	Expression in tumor cell	Way of crosstalk	Role in tumor cells or immunosuppressive cells	Reference
LncRNA RNCR3	MDSC	Upregulated	N/A	RNCR3 may act as a ceRNA to promote the expression of Chop by infiltrating miR-185-5p, increasing the levels of ARG1 and iNOS; regulating the level of KLF2 in endothelial cells.	[234]
LINC00978 (MIR4435-2HG)	PMN-MDSC	Downregulated	N/A	Reduction of miR-4435-2HG enhances the immunosuppressive ability of PMN-MDSCs by interfering with fatty acid metabolism.	[235]
Lnc57Rik	MDSC	Upregulated	N/A	Lnc57Rik can not only bind with the C/EBPb isoform liver-enriched activator protein to activate C/EBPb, but also with the methyltransferase WD repeat-containing protein 5 that enables the enrichment of histone H3 trimethylated lysine 4 marks on the promoter regions of ARG1, NOS2, NOX2, and COX2, eventually resulting in their transcriptional activation.	[235]

Abbreviations: ARG1, Arginase-1; COX2, cyclooxygenase-2;WD, tryptophan-aspartic acid; DUSP3, dual specificity protein phosphatase 3; ERK, extracellular signal-regulated kinase; HOXA1, Homeo box A1; iNOS, inducible nitric oxide synthase; ITM2B, integral membrane protein 2B; KLF2, Kruppel-like factor; MDSC, Myeloid-derived suppressor cells; N/A, not applicable; NOX2, NADPH-Oxidase 2; PDCD4, Programmed cell death protein 4; ROS, reactive oxygen species; RUNX1, Runt-related transcription factor 1; STAT3, Signal Transducer and Activator of Transcription 3; UTR, Untranslated Region.

the immunosuppressive ability of MDSCs, indicating that HOTAIRM1/HOXA1 downregulates the immunosuppressive function of MDSCs and may be a potential therapeutic target for lung cancer. The study by Zhou *et al.* [228] found that the lncRNA MALAT1 negatively regulates MDSCs and is reduced in peripheral blood mononuclear cells (PBMCs) of lung cancer patients.

In addition, it was found that cancer-associated fibroblasts (CAFs) induce MDSC production through activation of STAT3 signaling, which is achieved through secretion of IL-6 and exosome miR-21 by CAFs, thereby increasing the risk of cisplatin resistance in esophageal cancer [222]. Another study showed that G-MDSCs can also derive exosomal miR-143-3p, which can counteract lung cancer cells and inhibit the transcription of Integral Membrane Protein 2B (ITM2B) to activate the PI3K/AKT signaling pathway to enhance proliferation [225].

Currently, there are few studies on the epigenetic therapy of MDSC. Some studies have shown that lnc-RNA which targets STAT3 can reduce the infiltration of M-MDSCs, restore drug sensitivity, and further induce tumor regression [222].

4.1.3 | The roles of noncoding RNA in Tregs

Noncoding RNAs produced by tumor cells can affect the function of Treg cells through different pathways, thereby affecting the occurrence and development of tumors (Table 4). miR-155, miR-146a, miR-17-92, and other miRNA molecules are involved in the development and function of Treg cells [236]. Yao *et al.* [237] and Zhang *et al.* [238] found that miR-155 was involved in the occurrence and development of cervical cancer by inhibiting suppressor of cytokine signal 1 (SOSC1) expression and inducing a Th17/Treg imbalance. Zheng *et al.* [239] found that gastrectomy altered the balance of Th17/Treg cells, accompanied by an increase in PD-1/PD-L1 expression and a decrease in miR-21 expression, resulting in an increase in the proportion of Th17 cells but a decrease in the proportion of Treg cells, which suggested that miR-21 could be used as a predictor for the postoperative outcome of gastric cancer. LncRNA also has regulatory effects on the function of Treg cells. Yu *et al.* [240] found that the low expression of lncRNA FENDRR and GADD45B and the high expression of miR-423-5p in HCC not only reduced cell proliferation and tumenicity but also promoted apoptosis of HCC cells, thus regulating the Tregs-mediated immune escape of HCC. lncRNA FENDRR inhibited Treg-mediated escape of HCC cell immunity through sponge miR-423-5p upregulation of GADD45B

In addition, not only ncRNAs produced by tumor cells can affect Treg cell function, but also exosomal miR-29a-3p and miR-21-5p secreted by TAMs can directly inhibit STAT3 and regulate Treg/Th17 cells, leading to an imbalance [253]. For the treatment of Tregs, Yin *et al.* [243] demonstrated that tumor-secreted miR-215 induced Treg-mediated immunosuppression by microvesicle (MV) delivery of functional anti-miR-214 (ASOs) into $CD4^+$ T cells is a new and effective cancer treatments. Zhou *et al.* [253] found that TAM-derived exosomes transferred STAT3-targeting miRNAs to T cells and regulated T cell

TABLE 4 Non-coding RNAs affecting Treg.

Noncoding RNAs	Origin cell	Expression in tumor cell	Way of crosstalk	Role in tumor cells or immunosuppressive cells	Reference
miR-21	Treg	Upregulated	Chemokine	miR-21 induces the expression of ICOS on Treg cells. Promotes Treg differentiation to promote CRC progression by activating the PI3K-AKT pathway; cross-tracks with Treg cells via ICOSL, activates endothelial cells, stimulates Bcl-2 expression and angiogenesis.	[241, 242]
miR155	Cervical cancer cell etc.	Upregulated	Exosome	Inhibit the expression of the target gene SOCS1, promote the differentiation of Th17, increase the levels of IL-17, RORγt and STAT3, inhibit the conversion of Treg to Th17, induce Th17/Treg imbalance; activate IL-2/STAT5 and IL-6/STAT3 signaling pathways, and induce Treg/Th17 cell differentiation and Th17 function, increase IL-17A production.	[237, 238]
miR-214	Lung cancer cell etc.	Upregulated	Microvesicle	Downregulated PTEN and promoted Treg expansion, induced Tregs to secrete higher levels of IL-10.	[243]
miR-24-3p	NPC cell	Upregulated	Exosome	Increased the expression of P-ERK, P-STAT1, and P-STAT3, but decreased the expression of P-STAT5. By inhibiting the expression of FGF11 to regulate the phosphorylation of ERK and STAT proteins to inhibit the proliferation and differentiation of T cells and increase the level of Treg.	[244]
CircGSE1	HCC cell	Upregulated	Exosome	Promotes HCC progression by inducing expansion of Tregs by modulating the miR-324-5p/TGFBR1/Smad3 axis.	[245]
CircRNA has_circ_0069313	OSCC cell	Upregulated	Exosome	Inhibition of miR-325-3p-induced FOXP3 degradation promotes immune escape and Treg function by maintaining FOXP3 levels.	[246]
LncRNA FENDRR	HCC cell	Downregulated	Exosome	Acts as a miR-423-5p sponge, it inhibits Treg-mediated immune escape in HCC cells by infiltrating miR-423-5p and upregulating GADD45B.	[240]
RP11-357H14.17	GC cell	Upregulated	N/A	Associated with ATF2 signaling pathway; promote the expression of FOXP3 and promote the entry of Treg into tumor tissue.	[247]
Linc-POU3F3	GC cell	Upregulated	Cytokine	Recruit TGF-β and activate TGF-β signaling pathway, increase the phosphorylation of SMAD2/3, promote the distribution of Tregs in peripheral blood T cells, thereby promoting the proliferation of gastric cancer cells.	[248]
RP11-323N12.5	HCC cell	Upregulated	Cytokine and Chemokine	Promote the transcription of YAP1 by binding to c-Myc in the YAP1 promoter, YAP1 induces naïve T cells to differentiate into Treg cells by up-regulating TGFBR2 and up-regulates various molecules and chemokines related to Treg recruitment, thereby promoting the enhancement of Treg differentiation.	[249, 250]
LncRNA SNHG16	BC cell	Upregulated	Exosome	SNHG16 served as a ceRNA by sponging miR-16-5p, which led to the derepression of its target gene SMAD5 and resulted in potentiation of the TGF-β1/SMAD5 pathway to upregulate CD73 expression in Vδ1 T cells.	[251]
HOXA-AS2	Glioma cell	Upregulated	N/A	LncRNA HOXA-AS2 promotes the expression of KDM2A/JAG1 in glioma by combining with miR-302a, and promotes Treg cell proliferation and immune tolerance.	[252]

Abbreviations: CRC, colorectal cancer; ERK, extracellular signal-regulated kinase; GADD45B, Growth Arrest And DNA Damage Inducible Protein Beta; ICOS, Inducible Co-Stimulator; ICOSL, Inducible Co-Stimulator ligand; N/A, not applicable; PTEN, phosphatase and tensin homolog deleted on chromosome ten; RORγt, retinoid-related orphan receptor gamma t; SOCS1, Suppressor of Cytokine Signaling 1; STAT3, Signal Transducer and Activator of Transcription 3; TGFBR1, Transforming growth factor beta receptor type 1; Treg, Regulatory T cells PI3K-AKT, (Phosphatidylinositol 3-kinases)(Protein Kinase B); YAP1, Yes Associated Protein 1.

subset polarization, resulting in a Treg/Th17 imbalance that promoted tumor progression. Targeting exosomes or these miRNAs could be a way to treat cancer.

4.2 | Histone modification in ISCs

4.2.1 | Histone modifications in TAM

There is not enough evidence to prove that histone deacetylase inhibitor (HDACi) is closely related to TAM. Meredith *et al.*[254] found that after the addition of HDACi to the original treatment of ovarian cancer, the number of infiltrated TAM was significantly reduced, and the tumor load was further reduced. This suggests that HDACi may inhibit tumor development by reducing TAM invasion. However, we have not found direct evidence of how HDACi affects TAM, which may be the focus of future research.

4.2.2 | Histone modifications in MDSCs

Studies have shown that histone modifications contribute to the accumulation and function of MDSCs [255–257]. Analysis of CRC tissues revealed that HDAC related genes were up-regulated in tumor-infiltrating immature-MDSC (I-MDSC), while HAT-related genes were down-regulated in CRC patients. In contrast, HDAC-related genes were downregulated in tumor-infiltrating PMN-MDSC [257]. All of the above evidence points to the importance of HDAC activation in mediating MDSC inhibitory function and chemotaxis.

In addition, histone methylation is also involved in the regulation of MDSC function. Inducible nitric oxide synthase (iNOS) is a key mediator of the inhibitory function of M-MDSC. HMT SETD1B mediates the methylation of histone H3 lysine 4 (H3K4Me3) at the nitric oxide synthase 2 (NOS2) promoter to stimulate the expression of iNOS in tumor-derived MDSC and exerts the inhibitory effect of MDSC [258]. At the same time, osteopontin (OPN) is highly expressed in M-MDSC, and OPN is closely related to the poor prognosis of human pancreatic cancer. The WD repeat domain 5 (WDR5)-H3K4me3 epigenetic axis can inhibit pancreatic tumor immune escape by blocking OPN expression in M-MDSC. These results indicate that histone methylation affects tumor response to immunotherapy by regulating the suppressive effect of MDSC [259].

HDACi can exert a range of effects on MDSCs [165]. Some studies showed that several HDACi delete or inhibit MDSCs in tumors. Wang *et al.* [260] showed that HDACi SAHA eliminated MDSCs in a breast carcinoma model by inducing apoptosis of Gr1 cells. This is mainly due to the increase in intracellular ROS content caused by HDACi. Besides, HDACi CG-745 can also reduce MDSCs content, thereby promoting anti-tumor immunity within the TME of CT26 colon cancer in mice [261]. In another study involving epigenetic therapy, treatment with HDACi resulted in significant reductions in tumor-associated MDSCs [262].

4.2.3 | Histone modifications in Treg cells

Histone modification is also a key determinant of Treg cell development and function. One strategy to epigenetically regulate Treg cell function by altering the acetylation status may be to target P300/CBP and TIP60 acetylation-dependent regulation of FOXP3 expression [263]. Small molecules targeting the P300/CBP bromodomain can reduce the acetylation level of FOXP3 and affect the differentiation of Treg cells, suggesting that targeting the P300/CBP bromodomain may be a potential target for alleviating Treg mediated immunosuppression. However, although P300/CBP bromodomain inhibition can effectively reduce the differentiation of pTreg cells, this strategy is not effective for tTreg cells and therefore does not affect the number of Treg cells that are dominated by tTreg cells in the TME [264]. This lack of efficacy may be related to the use of different transcription factors by tTreg cells and pTreg cells. In addition, Tao *et al.* [265] found that HDACi treatment increased Treg expression of CTLA-4, GITR, and PD-1, leading to an increase in the number of Treg cells in vivo. However, other HDACi may also have immunostimulatory effects. Class I-specific HDACi (entinostat) can down-regulate FOXP3 transcription/expression in Tregs when applied at low doses, leading to the loss of Treg suppressive function without affecting the intrinsic activity of T effector cells [266]. All in all, it refers to the fact that histone modifications did influence the function of Treg cells in a good or bad sense.

Inhibition of histone acetylation is one of the first therapeutic strategies to be applied to epigenetics. We concluded that the anti-tumor effects of HDACi are mainly through regulating the release of inflammatory cytokines, the expression of cell signal receptors, and the expression of NF-κB, JAK2/STAT3 and other signal axes [267, 268]. At present, HDACi has not been studied in the treatment of Treg, but it may be a future treatment strategy. Diarrhea, myelosuppression and cardiovascular toxicity are the main side effects of HDACi. The existing drugs still have problems, such as poor pharmacokinetics, off-target binding and drug resistance. At present, the research direction of HDACi is ZBG-free HDACi, dual-target HDACi, and HDACi combining nano and photosensitive materials,

which can solve the problems of side effects and drug effects to a certain extent [269, 270].

4.3 | DNA methylation in ISCs

4.3.1 | DNA methylation in TAM

The DNMT family and its inhibitors in inflammation and tumors are interesting and worthy of consideration. In a mouse model of ovarian cancer, an experiment revealed that the combined administration of a DNMT inhibitor and an ornithine decarboxylase inhibitor led to a notable reduction in immunosuppressive cells, particularly M2-polarized macrophages, and a concurrent elevation in tumor-killing M1 macrophages compared to the administration of either drug alone [271, 272]. Notably, this effect was found to be attenuated upon the administration of an antibody targeting the CSF-1R. In this process, DNMT inhibitors may induce a polarity shift in macrophages by eliciting an interferon response and promoting IFN-γ production, thereby modulating the immune microenvironment. This experiment underscores the potential synergistic effects of combining epigenetic modulators for therapeutic interventions in ovarian cancer.

Tet methylcytosine dioxygenase 2 (TET2), a protein regulating the DNA methylation landscape, may influence the function of TAM. Contrary to the recognized role of TET2 as a tumor suppressor, Pan *et al.* [273] found that TET2 expression is increased in intertumoral myeloid cells both in mouse models of melanoma and in melanoma patients. Ablation of TET2 in myeloid cells suppressed melanoma growth in vivo and shifted the immunosuppressive gene expression program in TAM to a proinflammatory one, with a concomitant reduction of the immunosuppressive function. This resulted in increased numbers of effector T cells in the tumor, and T cell depletion abolished the reduced tumor growth observed upon myeloid-specific deletion of TET2. The result means that TET2 may mediate immunosuppressive function of TAM and melanoma tumor progression.

In addition, DNMT1 has been shown to play crucial roles in M1 activation by suppressing the expression of Krüppel-like factor 4 (KLF4) and suppressor of cytokine signaling 1 (SOCS1), and DNMT1 overexpression enhances the secretion of proinflammatory cytokines, such as TNF-α and IL-6 [274, 275]. Similarly, a high level of DNMT3B promotes M1 polarization by methylating the promoter region of peroxisome proliferator activated receptor γ in murine adipose tissue macrophages [276]. At present, the research on the treatment direction of TAM by DNA methyltransferase inhibitors (DNMTi) is still shallow, and new treatment strategies are explored through in-depth research.

4.3.2 | DNA methylation in MDSCs

Among a host of immune checkpoints (ICs), IC ligands, and immunosuppressive molecules implicated in MDSC function, CGIs in the promoter regions of TGF-β1, TIM-3, and Arg1 were highly unmethylated in MDSCs, suggesting that DNA methylation is one of the key mechanisms that regulate their expression [277]. Sasidharan *et al.* [278] found HDAC inactivation and DNA demethylation mediate upregulation of genes involved in cell migration and recruitment of MDSCs in tumor-infiltrating PMN-MDSCs. Rodríguez-Ubreva *et al.* [279] reported an MDSC-specific DNMT3A upregulation, which is PGE2 dependent, that is required for the acquisition of their immunosuppressive capacity, providing a novel target for therapeutic intervention.

Administration of tetrahydrocannabinol (THC) into wild-type mice caused increased methylation at the promoter region of DNMT3A and DNMT3B in THC-induced MDSCs, resulting in reduced expression of DNMT3A and DNMT3B. At the same time, promoter region methylation was decreased at arginase-1 and STAT3 in THC-induced MDSCs, and consequently, these two genes were actively transcribed in MDSCs [280]. The high expression of arginase-1 and STAT3 resulted in increased tumor progression and suppressive function in MDSCs. It is noteworthy that Interferon regulatory factor 8 (IRF8) is frequently silenced in the MDSCs of human cancer patients [281]. Under pathological conditions such as cancer, IRF8 is silenced by its promoter DNA hypermethylation, resulting in the accumulation of PMN-MDSCs and M-MDSCs in mice [281]. All of the above proves that epigenetics influences the effect of MDSC on tumors.

Interestingly, MDSC can also regulate the function of tumor cells via epigenetics. Ai *et al.* [282] study showed that G-MDSCs triggered piRNA-823 expression, which then promoted DNA methylation and increased the tumorigenic potential of multiple myeloma stem cells (MMSCs). Furthermore, silencing of piRNA-823 in MMSCs reduced the stemness of MMSCs maintained by G-MDSCs, resulting in decreased tumor burden and angiogenesis in vivo. Ibrahim *et al.* [283] reported that inflammation induces the accumulation of MDSCs that express high levels of IL-10 in colon tissue. IL-10 induces the activation of STAT3 which directly binds to the DNMT1 and DNMT3B promoters to activate their expression, resulting in DNA hypermethylation at the IRF8 promoter to silence IRF8 expression in colon epithelial cells. Mice with *Irf8* deleted in colonic epithelial cells exhibit significantly higher inflammation-induced tumor incidence [283]. Human colorectal carcinomas have significantly higher DNMT1 and DNMT3B and lower IRF8 expression, and they exhibit significantly

higher IRF8 promoter DNA methylation than normal colon [283].

DNA methylation were the one of earliest epigenetic targets for drug development. Epigenetic drugs such as DNMT inhibitors have been approved by the Food and Drug Administration (FDA) for clinical use in hematological malignancies and other cancers [284]. The traditional mechanism of the role of DNMT inhibitors is similar to the traditional pathway of HDACi. However, we also found that DNMTi may have influences on tumors by affecting ISCs. Similar to HDACi, in one study, DNMTi treatment was similarly found to result in a significant reduction in tumor-associated MDSCs [262]. Decitabine, a DNMT inhibitor with immunomodulatory effects, depletes MDSCs in vivo by inducing apoptosis at relatively low doses [285]. Daurkin *et al.* [286] demonstrated that tumor-infiltrated MDSCs can be enriched and differentiated in the presence of Decitabine into mature tumor-derived APCs whose function is opposite to MDSCs, which means Decitabine can inhibit the development of tumors by decreasing MDSCs.

Indeed, a major obstacle to epigenetic therapies is the inability to target specific cells, particularly due to the lack of specificity in targeting methyltransferases, which can result in genome-wide hypomethylation [287]. The main side effects of DNMTi are bleeding, anemia and infection due to myelosuppression (thrombocytopenia, anemia, and granulocytopenia).

4.3.3 | DNA methylation in Treg cells

Epigenetics regulation by CpG methylation at specific gene sites in T cells controls the differentiation of Treg cells [288]. The methylation status of Treg specific demethylated region (TSDR) is important because it allows or prevents the binding of the methylation-sensitive transcription factor ETS1 which controls the stability of FOXP3 expression in $CD4^+$ T cells [289]. Demethylation of the TDSR is required for long-term FOXP3 maintenance and Treg cell functional suppression [290].

A mass of studies showed that DNA methylation is closely related to the function of Treg cells. Yue *et al.* [291] show that during Treg cell development in the thymus, TET proteins mediate the loss of 5mC in Treg cell-specific hypomethylated regions, including "conserved non-coding sequences" (CNS) CNS1 and CNS2, and intronic cis-regulatory elements in the FOXP3 locus. TET2 and TET3 are guardians of Treg cell stability and immune homeostasis. The stability of FOXP3 expression is markedly compromised in Treg cells from TET2/TET3 double-deficient mice [292, 293]. Tseng *et al.* [294] also showed that TNF receptor 2 (TNFR2) maintained FOXP3 expression in Treg cells by restricting DNA methylation at the FOXP3 promoter, although the mechanism by which TNFR2 regulates DNA methylation is unclear. Moreover, IL-6 suppresses the development and function of Tregs by enhancing the activity of DNMT1 and repressing FOXP3 expression [295, 296].

The therapeutic strategy of DNMTi for Treg remains to be explored. Notably, it has been shown that DNMT1 is crucial for a core genetic program maintaining Treg development and function. In the Treg lineage, its deletion, but not DNMT3A's, leads to lethal autoimmunity. Therefore, caution is warranted in considering the use of DNMT inhibitors in developing Treg-based cellular therapies [297].

5 | DISCUSSION

All of the above suggests that epigenetic drugs may also work by affecting ISCs. We listed some of the FDA-approved drugs (Table 5) and some of the clinical trials currently underway (Table 6). However, these drugs are not specific for ISCs, which means they have two sides: they may promote the action of immune cells or ISCs. The final result of affecting tumors may depend on the dose of drugs. Meanwhile, the present epigenetic drugs are not accurate to a certain site, and it is difficult to achieve precise treatment. This means that existing epigenetic drugs can have significant side effects. When the target gene is suppressed, it may over active the remaining cancer-related genes leading to genomic instability. Besides, considering the cytotoxicity of these drugs and the sensitivity of the reproductive system to them, special groups should use with caution to prevent the occurrence of fetal malformation and fertility decline.

Furthermore, there is still considerable room for further development of drugs targeting other epigenetic mechanisms, such as isocitrate dehydrogenase (IDH) protein inhibitors and enhancer of Zeste homolog2 (EZH2) inhibitors, whose downstream products may affect histone modification and other mechanisms that influence tumor development. In addition to traditional drugs, some studies have shown that dietary therapy may also reverse tumor progression by affecting epigenetic mechanisms. Ishak Gabra *et al.* [323] found that dietary glutamine-derived α-KG levels in vivo led to H3K4me3 hypomethylation, thereby inhibiting epigenetically activated oncogenic pathways in melanoma. This may suggest that diet and drug therapy can work together to increase efficacy through epigenetic pathways. In general, this review summarized the epigenetic mechanisms in ISCs affecting tumors and hopes to find the specific biomarkers of ISCs, aiming at promoting clinical drug development and increasing the specificity of drugs.

TABLE 5 Mechanism and clinical application of FDA-approved drugs.

Drug of epigenetic therapy	Molecular target of drug therapy	Related signaling pathways	Related molecules	Clinical applications
Azacitabine	DNMTi	TNF-R1 and TRAIL-R2 (Genotoxic Carcinogen-Induced Bladder Cancer) [298]. IL-6 receptor-alpha and IL-6, phospho-STAT3 and Bcl-xl, NF-kappaB (multiple myeloma) [299].	dsRNA/Type I Interferon [300].	AML; CMML; MDS
Decitabine	DNMTi	dsRNA/MDA5/MAVS/IRF7 (CRC-initiating cells) [301]. p16, THBS1, and cancer testis antigens [302]. TGFBI-MAPK (urothelial carcinoma) [303].		AML; CMML; MDS
Vorinostat	HDACi	UBE2C (cervical cancer) [304]. PI3K/Akt (cervical cancer) [305].	Bcl-2 (lymphomas) [306].	CTCL
Romidepsin	HDACi	SPCA2/Wnt/Ca^{2+} (breast Cancer) [309].	TRAIL (Apo10L, TNFSF10) [307] and BMF [308].	CTCL; PTCL
Belinostat	HDACi	SAPK/JNK, UPR, PI3K-AKT-mTOR, Wnt/β-catenin (PTCL) [310].		PTCL
Panobinostat	HDACi	Type I Interferon (AML) [311]. JAK2/STAT3 (PanNET) [312]. Akt/FOXM1 (gastric Cancer) [313]. APCL-Wnt/β-catenin (breast cancer) [314].		Multiple myeloma
Chidamide	HDACi	NOTCH1-MYC (T-ALL) [315]. c-MET-/HGF (NSCLC) [316]. AKT/mTOR, MAPK, ATM-Chk2-p53-p21 (NKTCL) [317]. MYCN/DKK3-Wnt/β-catenin (B-ALL) [318]. Hedgehog signaling-miRNA-338-5p (glioma cells) [319]. HDAC3-AKT-P21-CDK2 (AML) [320].		PTCL
Enasidenib	IDH2i	N/A	2-HG (AML) [321].	AML
Ivosidenib	IDH1i	N/A		AML
Tazemetostat	EZH2i	PRDM1/BLIMP1 (NHL) [322].		Epithelioid sarcoma and follicular lymphoma

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APCL, APC regulator of WNT signaling pathway 2; ATM, ataxia telangiectasia-mutated gene; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma-extra-large; BLIMP1, B lymphocyte-in-duced maturation protein-1; BMF, B-cell lymphoma-2; c-MET, cellular-mesenchymal epithelial transition factor; CDK2, cyclin dependent kinase 2; CMML, Chronic myelomonocytic leukaemia; CRC, colorectal cancer; CTCL, central T cell lymphoma; DKK3, Dickkopf WNT signaling pathway inhibitor 3; DNMTi, DNA methyltransferase inhibitors; dsRNA, double-stranded RNA; EZH2i, enhancer of Zeste homolog2 inhibitor; FOXM1, Forkhead box M1; HDACi, histone deacetylase inhibitor; HGF, hepatocyte growth factor; IDH1i, isocitrate dehydrogenase 1 inhibitor; IDH2i, isocitrate dehydrogenase 2 inhibitor; IL-6, Interleukin 6; IRF7, Interferon regulatory factor 7; MAPK, mitogen-activated protein kinase; MAVS, mitochondrial antiviral signaling protein; MDA5, melanoma differentiation-associated gene 5; MDS, myelodysplastic syndromes; mTOR, mammalian target of rapamycin; MYC, myelocytomatosis; MYCN, BHLH transcription factor; N/A, not applicable; NKTCL, Natural killer/T-cell lymphoma; NSCLC, non-small cell lung cancer; PI3K, phospoinositide 3-kinases; PRDM1, PR/SET Domain 1; PTCL, peripheral T-cell lymphoma; SAPK, stress activated protein kinase; SPCA2, ATPase secretory pathway Ca2+ STAT3, signal transducer and activator of transcription 3; TGFBI, transforming growth factor beta Induced; THBS1, thrombospondin 1; TNF-R1, TNF receptor 1; TNFSF10, TNF superfamily member 10; TRAIL-R2, TNF-related apoptosis-inducing ligand receptor 2; transporting 2; UBE2C, ubiquitin conjugating enzyme E2 C; UPR, unfolded protein response.

6 | CONCLUSIONS AND FURTHER PERSPECTIVES

Since TAMs, MDSCs, and Treg cells are the most representative ISCs in TME, this review started with these three cell types and respectively introduced the roles of them in oncogenesis. Recently, people have paid more attention to the epigenetic mechanism. We specially focused on TME and tried to explore the epigenetic mechanism of ISCs. Based on this, we hope to find the specific biomarkers of ISCs, aiming at promoting clinical drug development. Besides, we combined with the approved epigenetic therapy and tried to explore the mechanisms of its curative effect and expand the scope of indications. Or, combined epigenetic therapy with other clinical therapies to alleviate the related side effects, perhaps.

TABLE 6 Ongoing clinical trials combining epigenetic therapies with immunotherapies.

Drug of epigenetic therapy	Drug of immunotherapy	Condition or disease (identifier, estimated enrollment)
DNMT inhibitor		
Azacitidine	Pembrolizumab (anti-PD-1)	Pancreatic cancer (NCT03264404, 31), AML (NCT04284787, 76), MDS (NCT03094637, 40), melanoma and other malignant neoplasms of skin (NCT02816021, 24), Hodgkin's lymphoma (NCT05355051, 24)
	Nivolumab (anti-PD-1)	Squamous cell carcinoma of head and neck (NCT05317000, 50), AML (NCT03092674, 1670), Hodgkin lymphoma (NCT05162976, 30), Osteosarcoma (NCT03628209, 51), AML (Childhood) (NCT03825367, 13)
	Nivolumab (anti-PD-1) + Lpilimumab (anti-CTLA-4)	AML (NCT02397720, 182), leukemia / MDS (NCT02530463, 160)
	Nivolumab (anti-PD-1) + Relatlimab (anti-LAG-3)	AML (NCT04913922, 30)
	Nivolumab (anti-PD-1) + Entinostat	NSCLC (NCT01928576, 101)
	Tislelizumab (anti-PD-1)	NK/T cell lymphoma (NCT04899414, 50), NK/T cell lymphoma (nasal and nasal-type) (NCT05058755, 62)
	Sintilimab (anti-PD1)	PTCL (NCT04052659, 30)
	Durvalumab (anti-PD-L1) + Romidepsin	PTCL (NCT03161223, 148)
	Sabatolimab (anti-TIM-3)	AML (NCT04623216, 59), leukemia (NCT03066648, 242), MDS (NCT05201066, 70)
	IO-202 (anti-ILT-3)	AML (NCT04372433, 119)
	PF-04518600 (anti-OX40)	AML (NCT03390296, 138)
Decitabine	Pembrolizumab	Triple-negative breast carcinoma (NCT02957968, 47), solid tumor / lymphoma (NCT03445858, 21), NSCLC (NCT03233724, 85), AML / MDS (NCT03969446, 54), triple-negative breast carcinoma (NCT05673200, 24), PTCL / CTCL (NCT03240211, 37)
	Nivolumab	AML (NCT04277442, 13), malignant melanoma (NCT05089370, 30), NSCLC (NCT02664181, 13), B-cell lymphoma (NCT05272384, 27), AML / MDS (NCT03092674, 1670)
	Lpilimumab	AML / MDS (NCT02890329, 48)
	Durvalumab	Head and neck cancer (NCT03019003, 13)
	Camrelizumab (anti-PD-1)	Hodgkin lymphoma (NCT04510610, 100; NCT03250962, 280)
	Camrelizumab + Chidamide	Hodgkin lymphoma (anti-PD-1 antibody resistant) (NCT04514081, 200), Hodgkin lymphoma (NCT04233294, 100), non-Hodgkin lymphoma (NCT04337606, 100)
	Spartalizumab (anti-PD1) + Sabatolimab	AML / MDS (NCT03066648, 242)
Guadecitabine	Pembrolizumab	Fallopian tube carcinoma / ovarian cancer / primary peritoneal carcinoma (NCT02901899, 45), prostatic cancer / NSCLC (NCT02998567, 34)
	Durvalumab	Clear cell renal cell carcinoma (NCT03308396, 57)
	Atezolizumab (anti-PD-L1)	CML / MDS (NCT02935361,33), fallopian tube carcinoma / ovarian cancer / primary peritoneal carcinoma (NCT03206047, 75)
	Nivolumab + Lpilimumab	Melanoma / NSCLC (NCT04250246, 184)

(Continues)

TABLE 6 (Continued)

Drug of epigenetic therapy	Drug of immunotherapy	Condition or disease (identifier, estimated enrollment)
BET inhibitor		
ZEN-3694	Pembrolizumab	Prostate small cell carcinoma (NCT04471974, 54), triple-negative breast carcinoma (NCT05422794, 45)
	Nivolumab + Lpilimumab	Malignant solid neoplasm (ovarian cancer) (NCT04840589, 66)
HDAC inhibitor		
Vorinostat	Pembrolizumab	Breast cancer (NCT04190056, 65), NSCLC (NCT02638090, 124), renal cell carcinoma / urinary bladder neoplasms (NCT02619253, 57), diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin lymphoma (NCT03150329, 52), squamous cell carcinoma (NCT04357873, 112), head and neck squamous cell carcinoma (NCT02538510, 50)
Romidepsin	Pembrolizumab	PTCL (NCT03278782, 39)
	Nivolumab	Triple-negative breast cancer (NCT02393794, 51)
Belinostat	Durvalumab + Tremelimumab (anti-CTLA-4)	Infiltrating urothelial carcinoma, sarcomatoid variant (NCT05154994, 9)
Entinostat	Pembrolizumab	Bladder cancer (NCT03978624, 20), melanoma (NCT03765229, 11), metastatic uveal melanoma (NCT02697630, 29), MDS (NCT02936752, 27), lymphoma (NCT03179930, 47)
	Atezolizumab	Extensive stage small cell lung cancer (NCT04631029, 36)
	Nivolumab	CNS tumor, solid tumor (NCT03838042, 128)
	Nivolumab + Lpilimumab	Breast adenocarcinoma (NCT02453620, 45), renal cell carcinoma (NCT03552380, 18)
Valproic acid	Avelumab (anti-PD-L1)	Cancer that is associated with chronic viral infection (NCT03357757, 39)
Tinostamustine	Nivolumab	Malignant melanoma (NCT03903458, 21)
Chidamide	Anti-PD-1 antibody	NK/T cell lymphoma of the nasal cavity (NCT04414969, 35)
	Nivolumab	Melanoma, renal cell carcinoma, NSCLC (NCT02718066, 96)
	Tislelizumab	PTCL (NCT05675813, 264)
	Toripalimab (anti-PD-1)	ESCC, Adenocarcinoma of esophagogastric junction, gastric adenocarcinoma (NCT05163483, 87), cervical cancer (NCT04651127, 40)
	Zimberelimab (anti-PD-1)	Triple-negative breast cancer (NCT05632848, 47)
	Sintilimab	PTCL (NCT04831710, 83), PTCL (NCT04052659, 30), angioimmunoblastic T cell lymphoma (NCT04831710, 83), PTCL (NCT04512534, 51), CTCL (NCT04296786, 52)
IDH inhibitor		
Ivosidenib	Nivolumab	Advanced solid tumor (IDH1 mutation glioma) (NCT04056910, 35)
EZH2 inhibitor		
Tazemetostat	Pembrolizumab	Urothelial carcinoma (NCT03854474, 30), small cell lung cancer (NCT05353439, 60), NSCLC (NCT05467748, 66)
	Durvalumab	Advanced solid tumor (NCT04705818,173)
	Nivolumab + Lpilimumab	INI1-Neg/SMARCA4-Def Tumors (NCT05407441, 49)

Abbreviations: AML, acute myeloid leukemia; CNS tumor, central nervous system tumor; CTCL, central T cell lymphoma; ESCC, Esophageal squamous cell cancer; INI1, (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1); MDS, myelodysplastic syndromes; N/A, not applicable; NSCLC, non-small cell lung cancer; PTCL, peripheral T-cell lymphoma; SMARCA4, (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4).

DECLARATIONS

AUTHOR CONTRIBUTIONS

Yijia Tang, Guangzu Cui, and Haicong Liu contributed to the conception of the review. Yijia Tang, Guangzu Cui, and Haicong Liu performed the literature search and finished the manuscript. Yijia Tang, Guangzu Cui, and Haicong Liu prepared the figures and the tables. Ying Han and Changjing Cai made critical revisions. Shan Zeng, Ziyang Feng, and Hong Shen proofread the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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