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J Clin Invest. 2024;134(12):e178540. <https://doi.org/10.1172/JCI178540>.

Review

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Epigenetic regulation of tumor immunity

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Introduction

Tumor microenvironment (TME) heterogeneity is recognized as a cancer hallmark (1–4). Studies using mass cytometry, single-cell RNA-Seq (scRNA-Seq), and spatial transcriptomics/proteomics revealed a dynamic and heterogeneous TME, consisting of supporting extracellular matrix, T cells, and various myeloid cells, including macrophages, myeloid-derived suppressor cells (MDSCs), and neutrophils (5–7). T cells (e.g., CD8⁺ cells) play an important anti-tumor role across cancer types by inducing granzyme- and perforin-mediated apoptosis. Myeloid cells are usually polarized toward a protumor and immunosuppressive phenotype in response to specific stimuli in the TME (8), thus promoting tumor progression, suppressing T cell-mediated antitumor immunity, and facilitating cancer cell immune escape. Genetic modification, metabolic reprogramming, and epigenetic alteration are the key factors that determine the TME landscape during tumor progression (9–11).

Compared with nonmalignant cells, cancer cells exhibit distinct epigenetic features with regard to histone posttranslational modification, DNA methylation, and RNA modification (1, 12, 13). These epigenetic changes control tumor growth by affecting the biology of oncogenes and/or tumor suppressor genes (12, 14). In addition to these cell-intrinsic effects, cancer cell epigenetic alterations induce immunotherapy resistance by regulating distinct immune cell populations in the TME (15, 16). Recent studies using scRNA-Seq and single-cell sequencing assay for transposase-accessible chromatin sequencing (scATAC-Seq) revealed the association between immune cell composition and chromatin accessibility in cancer cells (17, 18). Notably, cancer cell epigenetic plasticity highly associates with genes located in open chromatin

regions that are essential for intercellular communications (19). Epigenetic enzymes and transcriptional mediators in cancer cells can regulate the expression of genes that encode ligands, receptors, and cytokines responsible for immune cell differentiation, migration, and activation (1, 15, 19, 20).

Once infiltrating into the TME, epigenetic reprogramming confers a fitness advantage for these immune cells during tumor progression (21, 22). Certain therapies (e.g., immunotherapy) are also strong stimuli for histone and RNA modifications in tumor-associated immune cells (23–25). Targeting the epigenetic enzymes and factors might potentiate antitumor immunity and synergize with immunotherapies, including immune checkpoint inhibitors (ICIs) (16, 26–28). Given the critical role of immune cells in cancer development (1, 29), understanding the mechanism of epigenetically mediated tumor-immune symbiosis may provide new insights into the discovery of new therapeutic targets. In this Review, we explore the mechanisms for how epigenetic changes in cancer cells affect immune cell biology and how the aberrant epigenome of immune cells affects tumor progression. We also highlight the therapeutic potential of targeting epigenetically dependent tumor-immune communication and its influence on antitumor efficiency of ICI therapy.

Epigenetic modulation in cancer

Depending on the targets, epigenetic modulation can be classified as chromatin modification, DNA methylation, and RNA modification. Chromatin remodeling is driven by various histone-modifying enzymes, such as histone acetyltransferase, histone deacetylase (HDAC), histone methyltransferase, and histone demethylase (30). These enzymes play an essential role in remodeling chromatin toward an active or repressive state that is accessible or inaccessible to other regulatory factors (12). DNA methylation is catalyzed by DNA methyltransferases (DNMTs) that introduce cytosine at position C5 in CpG dinucleotides. Hypermethylation of pericentromeric heterochromatin and CpG islands in cancer cells contributes to genomic instability and transcription of tumor suppressor genes, allowing cancer cells to better adapt to the TME (31). RNA modification could rapidly rewire the transcriptome and proteome of cancer cells and immune cells

Authorship note: LP and FZ contributed equally to this work and are co-first authors.

Conflict of interest: ABH serves on the advisory boards of Caris Life Sciences and WCG Oncology; is supported by research grants from Alnylam and AbbVie; and receives consulting fees from Novocure and Istari Oncology. Additionally, she has active granted patents (no. 9,675,633, no. 9,399,662) and a pending patent (international applications PCT/US2022/019435 and US 63/158,642).

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Reference information: *J Clin Invest.* 2024;134(12):e178540.

<https://doi.org/10.1172/JCI178540>.

in the TME. m⁶A is the most common type of RNA modification that can affect oncogenic networks and tumor immunogenicity (32, 33). Mechanistically, m⁶A modification is regulated by three types of factors, including methyltransferases (writers, e.g., METTL3 and METTL4), demethylases (erasers, e.g., FTO and ALKBH5), and m⁶A binding proteins (readers, e.g., YTHDC1 and YTHDF1). In the nucleus, a writer complex installs m⁶A, a process that can be removed by erasers. The m⁶A nuclear readers recognize m⁶A-modified RNAs, thus regulating mRNA splicing and other nuclear processes. Once mRNAs translocate to cytoplasm from nucleus, m⁶A binds to cytosolic readers, regulating mRNA stability and cancer progression (34).

Cancer cell epigenetic reprogramming regulates TME biology

Although many patients with cancer benefit from ICIs, their antitumor efficacy can be limited by the immunosuppressive TME (1). Insufficient CD8⁺ T cell infiltration, low PD-L1 expression in cancer cells, and downregulation of major histocompatibility class I (MHC-I) antigen processing and presentation result in a “cold” (immunological ignorance) TME that typically does not respond to ICI therapy (16, 35, 36). These cold tumor properties are associated with epigenetic alterations in cancer cells (27, 37–39). Specifically, these epigenetic alterations suppress the proliferation and activation of T cells and promote the infiltration and immunosuppressive activation of macrophages, MDSCs, and neutrophils by upregulating the expression and secretion of various cytokines and factors (40–42), resulting in immunosuppression and tumor progression in a context-dependent manner (40, 43).

Cancer cell epigenetics affect T cell biology. Cancer cells are more easily adapted to the dynamic TME than normal cells because of their epigenetic instability (12, 14, 15, 44). Increasing evidence shows that cancer cell amplification of epigenetic regulators (e.g., H3K36 methyltransferase NSD1, H3K9 methyltransferase SETDB1, histone deacetylase HDAC8, and H3K4 mono-methyltransferase MLL4) is associated with immune modulation (26, 37, 45, 46). These histone-modifying enzymes profoundly regulate cancer cell biology to reshape the immune landscape. In context of cancer cell and T cell crosstalk, SETDB1 mediates intrinsic immunogenicity of cancer cells by catalyzing H3K9 trimethylation and repressing IFN genes (45); HDAC8 in hepatocellular carcinoma cells inhibits CD8⁺ T cell infiltration by reducing H3K27 acetylation and silencing chemokine gene *CCL4* (26); and MLL3 and MLL4 ablation in cancer cells promotes CD8⁺ T cell activation and cytotoxicity by decreasing H3K4me1 and H3K27ac marks and inhibiting *GSDMD* expression (46). Together, cancer cells may take advantage of epigenetics to avoid T cell-mediated immune surveillance (Figure 1).

In contrast to genetic alterations, chromatin-modifying enzymes can target a wide range of domains through thousands of discrete accessible chromatin regions for regulating T cell infiltration and activation (35, 36, 38, 45, 47). SETDB1 is one of such enzymes that exhibits aberrant activity in cancer cells. Amplification of *SETDB1* is associated with segmental duplication events in repression domains of cancer cells that are enriched for immune gene clusters (e.g., IFN gene, Fcγ receptor gene, and ULBP1/RAET1 family gene clusters).

Setdb1 knockout in lung cancer cells or melanoma cells reduces H3K9me3 marks, where about one-third of segmental duplications are enriched for immune-related genes (45). As such, a discrete single epigenetic modification in cancer cells can impact multiple immune-related processes simultaneously (36, 45). Recent advances with CRISPR screening improve the feasibility of identifying vital epigenetic regulators (e.g., MLL4 and SETDB1) that mediate the interplay between cancer cells and T cells (36, 45, 46, 48). scRNA-Seq has also emerged as a powerful technique for evaluating and validating the effect of epigenetic regulators in shaping the immune landscape (49). With the help of this approach, *SETDB1* has been identified in lung carcinoma cells that can regulate CD8⁺ T cell infiltration and recognition and MHC-I presentation (45).

Epigenetic regulators can also mediate tumor immunity independent of their catalytic activity (Figure 1) (50). Lysine-specific demethylase 5B (KDM5B) is such an example (50). Deletion of *Kdm5b* in melanoma cells extends the survival of tumor-bearing mice and increases CD8⁺ T cell infiltration into the TME. Mechanistically, KDM5B represses endogenous retroelements (e.g., *MMVL30*) by recruiting H3K9 methyltransferase SETDB1. Reexpression of either wild-type KDM5B or catalytically inactive KDM5B in *Kdm5b*^{-/-} melanoma cells rescues this phenotype (50). Similarly, KDM5D, located on the Y chromosome, has been found to be a critical epigenetic regulator for inhibiting MHC-I antigen presentation in male colon cancer through a demethylase-independent manner (51). In metastatic cancer cells, KDM5D interacts with the Sin3-HDAC1/2 complex to escape CD8⁺ T cell-mediated tumor killing by downregulating H3K27ac and superenhancer activity (51). Given that certain epigenetic regulators are specifically encoded by X or Y chromosome genes, or regulated by sex hormones (e.g., androgen/pY-SREBF1/H2A-K130ac signaling), these regulators may dictate sex differences in controlling T cell biology in tumors (51, 52).

Cancer cell epigenetics regulate macrophage biology. Macrophages are one of the most prominent immune cell populations in tumors across cancer types (53). The density of tumor-associated macrophages (TAMs) is highly correlated with tumor progression and patient survival (53–58). Although many studies have focused on elucidating the relationship between cancer cell genetic alterations (e.g., mutation and deletion of *IDH*, *PTEN*, *TP53*, *NF1*, and *RBI*) and TAM biology (59–62), recent findings suggest that epigenetic reprogramming also regulates the biology (e.g., infiltration and immunosuppressive polarization) of TAMs (20, 57). Mechanistically, epigenetic regulators directly modulate the expression of soluble factors (e.g., cytokines and chemokines), which are responsible for TAM recruitment and immunosuppression (Figure 2). Acetyl-lysine reader CECR2 is such an example that can promote macrophage immunosuppressive polarization by increasing chromatin accessibility and the expression of *CSF1*, *CSF2*, *CSF3*, and *CXCL1* (56). CLOCK has been identified as another epigenetic regulator highly expressed in glioblastoma stem cells, which promotes microglia infiltration and immunosuppressive polarization by transcriptionally upregulating chemokines OLFML3 and LGMN (63, 64).

Another nonnegligible mechanism underpinning TAM regulation is the indirect function of epigenetic regulators on affecting immune regulatory factors. For instance, *CREBBP/EP300*

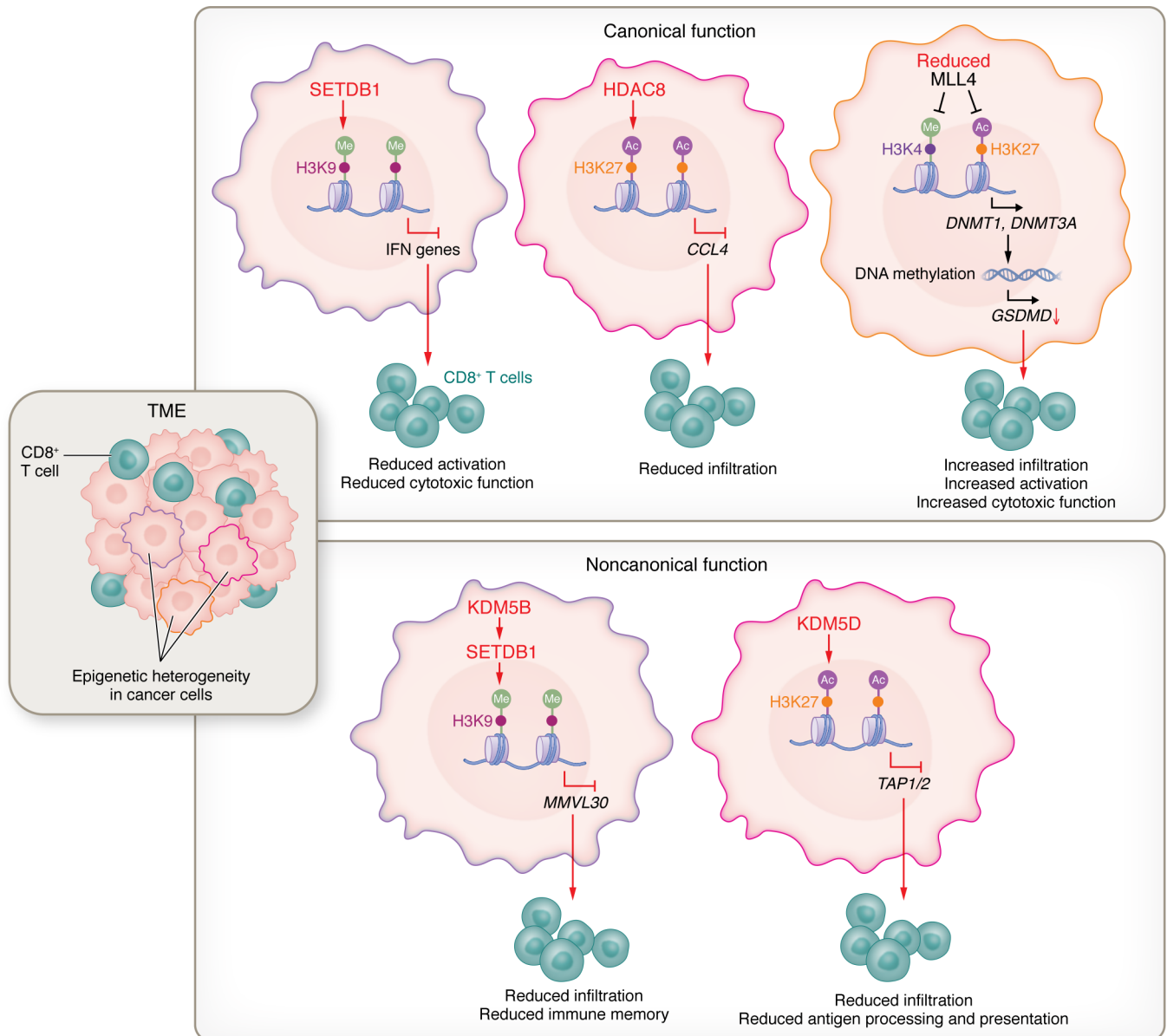


Figure 1. Epigenetic modulations in cancer cells regulate T cell biology. Under selective pressure in the tumor microenvironment (TME), cancer cells exhibit high epigenetic heterogeneity. Aberrant expression of epigenetic enzymes (e.g., SETDB1, HDAC8, and MLL4) in cancer cells regulate the expression of immunomodulatory genes (e.g., *IFN* genes, *CCL4*, and *GSDMD*) by catalyzing their classical substrates (e.g., H3K9, H3K27, and H3K4), which, in turn, affect the infiltration, activation, and cytotoxic function of T cells in the TME. Additionally, epigenetic regulators (e.g., KDM5B and KDM5D) in cancer cells also affect T cell antitumor immunity through noncanonical functions. Cancer cells take advantage of these epigenetic modulations to avoid CD8⁺ T cell surveillance, resulting in adaptive clonal expansion. Ac, acetyl group; *CCL4*, chemokine ligands 4; DNMT1/3a, DNA methyltransferases 1/3a; *GSDMD*, gasdermin D; HDAC8, histone deacetylase 8; KDM5B/D, lysine demethylase 5B/D; Me, methyl group; MLL4, mixed-lineage leukemia 4; MMVL30, virus-like 30S; SETDB1, SET domain bifurcated histone lysine methyltransferase 1; TAP1/2, transporter associated with antigen processing 1/2.

mutations in cancer cells inhibit H3K27 acetylation to downregulate NOTCH suppressor FBXW7, which, in turn, upregulates the expression of CSF1 and CCL2. Consequently, these factors promote macrophage immunosuppressive polarization and tumor growth (Figure 2) (65). Additionally, depletion of m⁶A demethylase ALKBH5 in glioblastoma cells significantly decreases the expression of chemokine CXCL8 under hypoxic conditions. CXCL8 is not a m⁶A target gene. Instead, ALKBH5 erases m⁶A deposition from the lncRNA NEAT1, accelerating paraspeckle assembly and

SFPQ relocation from the CXCL8 promoter (57). Thus, certain epigenetic modulations in cancer cells may hijack other pathways to regulate TAM biology. Given the importance of TAMs in tumor progression, targeting epigenetically driven TAM biology holds great promise for cancer treatment. Experimental findings from cancer mouse models demonstrate that genetic and pharmacologic inhibition of distinct epigenetic factors, such as CECR2, ALKBH5, and EZH2, impairs tumor progression by reducing TAM infiltration and immunosuppressive polarization (27, 56, 57).

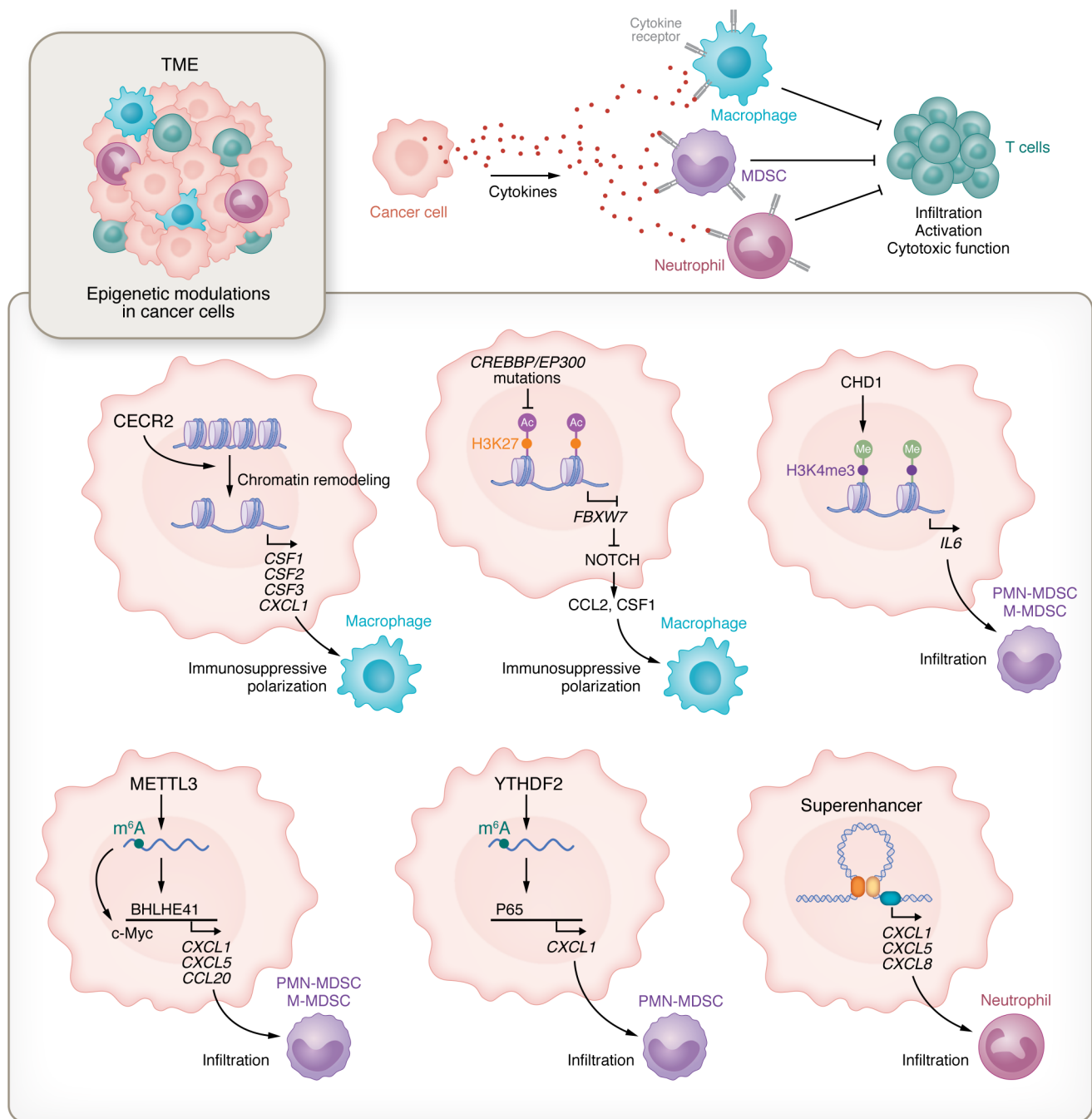


Figure 2. Epigenetic modulations in cancer cells regulate the biology of macrophages, MDSCs, and neutrophils. Epigenetic alterations in cancer cells lead to secretion of various cytokines, chemokines, and factors into the TME. Mechanistically, certain epigenetic modulations (e.g., chromatin remodeling and superenhancer formation) can directly regulate cytokine and chemokine expression. In addition, epigenetic alterations (e.g., histone acetylation and m⁶A mRNA modification) promote cytokine expression through indirect mechanisms, in which other pathways (e.g., NOTCH pathway and NF- κ B pathway) control the expression of downstream targeted genes. Cancer cell-secreted cytokines bind to specific cytokine receptors on myeloid cells (e.g., macrophages, MDSCs, and neutrophils), promoting their tumor infiltration and immunosuppressive polarization. Consequently, immunosuppressive myeloid cells inhibit the infiltration, activation, and cytotoxic function of T cells, resulting in immune escape. BHLHE41, basic helix-loop-helix family member e41; CCL20, chemokine ligands 20; CECR2, cat eye syndrome chromosome region candidate 2; CHD1, chromodomain helicase DNA binding protein 1; c-Myc, cellular Myc; CREBBP/EP300, CREB-binding protein and E1A-binding protein P300; CSF1, colony-stimulating factor 1; CXCL1/5/8, C-X-C motif chemokine ligand 1/5/8; m⁶A, N⁶-methyladenosine; MDSC, myeloid-derived suppressor cell; METTL3, methyltransferase like 3; PTEN, phosphatase and tensin homolog; YTHDF2, YTH N6-methyladenosine RNA binding protein 2.

Cancer cell epigenetics regulate MDSC biology. MDSCs, including polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs), are another critical component of the TME that exhibit potent protumor and immunosuppressive functions.

Increasing evidence demonstrates that MDSC biology is modulated by distinct epigenetic regulators in the TME (Figure 2). In *PTEN*-deficient prostate cancer, the expression of epigenetic regulators (e.g., subunit of SWI/SNF chromatin remodeling complex

ARID1A and chromatin-remodeling factor CHD1) is positively correlated with MDSC abundance (40, 43, 66, 67). Mechanistically, *PTEN* loss inhibits the degradation of CHD1, which specifically interacts with H3K4me3 to upregulate IL-6, resulting in infiltration of both M-MDSCs and PMN-MDSCs. In contrast to CHD1, ARID1A tends to specifically mediate PMN-MDSC chemotaxis without affecting M-MDSCs. m⁶A appears to be one of the most well-studied epigenetic factors in regulating tumor-MDSC symbiosis (41, 68, 69). Genetic or pharmacologic inhibition of m⁶A writer METTL3 reduces the infiltration of MDSCs in lung cancer (70) and PMN-MDSCs in colorectal cancer (40) by reducing the expression of chemokines CXCL1, CXCL5, and CCL20. METTL3 promotes the translation of transcriptional factor BHLHE41 (40) or increases the stability of *c-Myc* (70), which, in turn, transcriptionally upregulates the expression of these chemokines to trigger M-MDSC and PMN-MDSC infiltration into the TME (Figure 2). In contrast to m⁶A writers, erasers remove m⁶A decoration from RNA. A scRNA-Seq analysis of intrahepatic cholangiocarcinoma tumors demonstrated that knockdown of eraser ALKBH5 upregulates MDSC infiltration (69). However, the opposite effect is observed in colorectal cancer, showing that ALKBH5 promotes the infiltration of PMN-MDSCs and M-MDSCs by directly demethylating AXIN2 messenger RNA (41). These findings suggest that ALKBH5-mediated MDSC infiltration is context and cancer type dependent. Further investigations revealing this context-dependent TME may offer insights into the role and underlying mechanism of ALKBH5 in triggering MDSC infiltration.

In addition to writers and erasers, the expression of m⁶A readers is correlated with tumor immunity (68). Recent studies integrating MeRIP-Seq, RNA-Seq, and Ribo-Seq demonstrated that the NF- κ B pathway plays a key role in m⁶A-mediated MDSC accumulation into the TME (25, 55, 68, 71, 72). More specifically, NF- κ B subunit p65/Rela is the direct target of YTHDF1 that upregulates chemokine CXCL1 expression in colorectal cancer cells, promoting the infiltration of PMN-MDSCs into the TME (68). The NF- κ B pathway may serve as a central hub connecting other epigenetic signals with MDSC chemotaxis (43, 73). For example, ARID1A can induce a positive feedback loop with the NF- κ B pathway, resulting in further chemokine expression and PMN-MDSC infiltration (25, 43). Targeting these epigenetic regulators and the downstream signaling of NF- κ B pathway has been shown to reduce tumor growth and MDSC infiltration (25, 38, 43, 68).

Cancer cell epigenetics regulate neutrophil biology. Neutrophils are the most abundant innate immune cell populations in the circulatory system that can drive immunosuppression. Although neutrophils share many similarities with their immature counterparts PMN-MDSCs (70), they may respond to different cancer cell epigenetic signals. For instance, IDH1 mutation epigenetically upregulates G-CSF expression in glioma cells by increasing H3K4me3 marks on the *CSF3* promoter region, resulting in infiltration of neutrophils, but not PMN-MDSCs (74). In renal cancer cells, epigenetic remodeling promotes the infiltration of mature neutrophils from bone marrow into the TME without affecting myelopoiesis or immature PMN-MDSCs (75). In contrast to tumor-MDSC symbiosis that predominantly contributes to tumor growth (40, 41, 43), recent findings highlight the criti-

cal role of epigenetic modulation in neutrophil-induced cancer metastasis (42, 75, 76). DNA methylation and superenhancer (SE) formation in renal cancer cells are required for chemokine (e.g., CXCL8) expression to increase neutrophil infiltration (Figure 2). Inhibition of SE-driven chemokine transcription with BET inhibitor in murine tumor models reduces lung metastasis and prolongs survival in a neutrophil-dependent manner (75). Likewise, histone methyltransferase EZH2 and histone H3K36 trimethyltransferase SETD2 have been reported as vital epigenetic factors regulating neutrophil infiltration during cancer metastasis (42, 77). Unlike its enzymatic function in primary tumors (76), EZH2 promotes melanoma and breast cancer brain metastasis independent of its methyltransferase activity but relying on neutrophils (77). Specifically, tyrosine kinase Src phosphorylates EZH2 at Y696 in brain metastatic cancer cells, which upregulates G-CSF to increase the infiltration of PD-L1⁺ neutrophils, inhibiting CD8⁺ T cell proliferation and promoting metastasis (77, 78). Together, these findings highlight that cancer cell epigenetics plays an important role in regulating neutrophil infiltration and activation in the TME.

Immune cell epigenetic remodeling affects tumor malignancy

The interplay between cancer cells and immune cells is a two-way street. After infiltrating into the TME that has been engineered by cancer cell signaling (e.g., epigenetic regulators), immune cells reciprocally affect tumor progression and therapy efficiency. Increasing evidence shows that epigenome rewiring in immune cells supports their infiltration, activation, differentiation, antigen presentation, immunosuppression, and exhaustion, resulting in a new TME that drives cancer cell immune escape (21) and facilitates tumor progression (79–81). Here, we discuss how immune cell epigenetics affect tumor progression (Figure 3).

T cell epigenetics regulate cancer cell biology. Due to the epigenetic vulnerability and functional dynamics of tumor-infiltrating lymphocytes, targeting epigenetic factors in T cells has emerged as a promising strategy for restoring antitumor immunity (79–81). Depending on the chromatin accessibility, CD8⁺ T cells in the TME can be divided into two epigenetic states: fixed dysfunctional state (marked by high CD38, CD30L, and CD101) and plastic dysfunctional state (marked by high CD5), which are enriched in late-stage and early-stage tumors, respectively (82). Since plastic dysfunctional CD8⁺ T cells are more easily reprogrammed to express immunostimulatory cytokines (82), investigating the mechanisms underlying epigenetic regulation in these T cells might provide vital insight into cancer therapy.

Hypoxia is a hallmark of cancer that drives T cell epigenetic reprogramming (1). The correlation between hypoxia and T cell exhaustion has been shown in many types of solid tumors (79, 80, 83). Hypoxia-inducible factors (HIFs), especially HIF-1 α , are the key factors that activate T cell exhaustion program under the hypoxic TME (84, 85). In breast cancer, hypoxia epigenetically downregulates the expression of cytotoxic cytokines (e.g., IFN- γ , TNF- α , and granzyme B) in T cells and promotes them toward an exhaustion-like state without affecting proliferation (80). This inhibitory effect largely depends on the interaction among HIF-1 α , PRC2, and HDAC1, which induces chromatin remodeling,

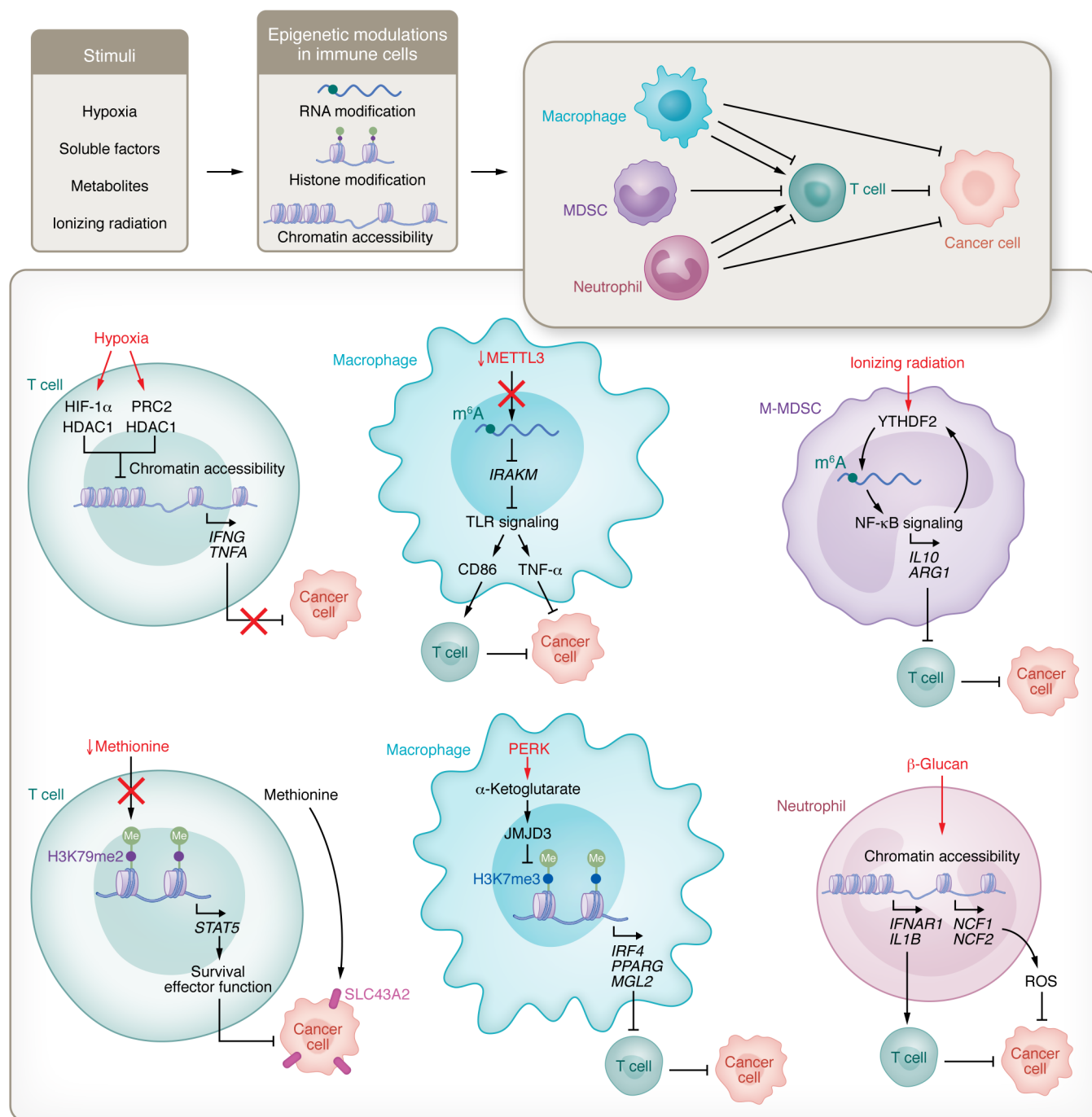


Figure 3. Epigenetic modulations in immune cells regulate cancer cell biology. Various stimuli (e.g., hypoxia, soluble factors, metabolites, and therapeutic interventions) trigger epigenetic alterations in tumor-infiltrating immune cells. These global epigenetic changes upregulate the expression of cytokines or functional molecules (e.g., IFN- γ and TNF- α) in immune cells directly suppressing cancer cell growth. Additional epigenomic changes in innate immune cells regulate cancer cell biology through modulating T cell function. Epigenetic modifications in macrophages, MDSCs, and neutrophils are essential for regulating the expression of genes that encode immunosuppressive factors (e.g., *IL10* and *ARG1*) or proinflammatory cytokines (e.g., *IL1B*). These innate immune cell-derived molecules further induce T cell activation or dampen T cell antitumor function. ARG1, arginase 1; HIF-1 α , hypoxia-inducible factor α ; IFNAR1, IFN α and β receptor subunit 1; IRAKM, IL-1 receptor-associated kinase 3; IRF4, IFN regulatory factor 4; MGL2, macrophage galactose N-acetyl-galactosamine-specific lectin 2; NCF1/2, neutrophil cytosolic factor 1/2; PERK, protein kinase RNA-like ER kinase; PRC2, polycomb-repressive complex 2; SLC43A2, solute carrier family 43 member 2.

resulting in epigenetic suppression of these tumor-killing cytokines (Figure 3) (80). Moreover, exhausted CD8⁺ T cells exhibit an impaired cytotoxic activity, as they harbor fewer active (e.g., H3K27ac) and more repressed chromatin marks (e.g., H3K27me3)

(79). This may explain the recent observations that distinct chromatin features are present in T cell progenitors and terminally exhausted tumor-infiltrating T cells under hypoxic conditions (79). Targeting hypoxia-induced chromatin remodeling with HIF-

1 α inhibitor PX478, deletion of hypoxia-related gene *Ndufs4*, or overexpression of H3K27 histone demethylase KDM6B improves T cell-mediated antitumor efficiency (79, 80).

T cell exhaustion is also attributed to the production of immunosuppressive factors and metabolites in the TME (21, 86–89). Genome-wide CRISPR screening revealed that BAF chromatin remodeling complex is an essential epigenetic regulator for T cell persistence in tumors (81). Depletion of BAF complex member ARID1A or SMARCD2 prevents the terminal exhaustion of T cells and increases memory T cells (81, 90). Given that ARID1A is also a critical epigenetic factor in cancer cells (38, 91), targeting ARID1A may gain dual benefits that simultaneously cause cancer cell death and enhance T cell-mediated antitumor activity. Distinct metabolites in the TME can alter the T cell epigenetic landscape (21, 86, 92). Cancer cells uptake exogenous methionine to maintain their high proliferation rate by overexpressing the methionine transporter SLC43A2. Through this mechanism, cancer cells out-compete T cells for methionine, which can maintain H3K79me2 in tumor-infiltrating lymphocytes (21). Due to scarce methionine in the TME, loss of H3K79me2 damages the antitumor immunity of T cells by downregulating the STAT5 pathway (Figure 3) (21). Rewiring metabolic exhaustion of CD8⁺ T cells by supplementation of methionine prevents epigenetic reprogramming and activates T cells for tumor killing (21). Beyond methionine metabolism, m⁶A reader YTHDF1 upregulates the immunosuppressive function of Tregs by maintaining cell hyperglycolysis (86). IDH1 is a metabolic enzyme that catalyzes isocitrate to α -ketoglutarate, a cofactor for histone and DNA demethylases, generating a unique epigenetic landscape to affect antitumor immunity (93–95). On the other hand, the IDH1 mutant can enhance DNA damage response by epigenetically upregulating H3 hypermethylation and ATM signaling (96). As a result, the immune TME is reshaped by DNA damage-induced activation of the cGAS/STING pathway (97–99). Notably, recent findings show that IDH1-mutant cancer cell-derived oncometabolite 2-hydroxyglutarate (2HG) could directly affect CD8⁺ T cell biology in the TME (88, 100). Thus, metabolism may act as a central hub connecting epigenetic alteration and antitumor function in T cells.

Macrophage epigenetics regulate cancer cell biology. Given that exhausted T cells and macrophages in the TME are spatiotemporally associated (101), macrophage epigenetic regulators may affect cancer cell biology by regulating T cell functional status. Indeed, TAMs exhibit high MHC-II expression due to chromatin accessibility changes at the early tumor stage (102). These TAMs promote the expansion of Tregs that protect lung cancer cells from adaptive immunity (102). Integration of scRNA-Seq data with cell-cell communication analytical tools and trajectory analysis highlighted the crucial role of m⁶A methylation in TAM-CD8⁺ T cell crosstalk (103). Through this codependency, activated macrophages induce a feedback circuit aligned to protect cancer cells from T cell-mediated tumor killing (101, 103). In addition to this indirect mechanism, CRISPR screening of RNA binding proteins demonstrated that epigenetic alteration in macrophages is critical for tumor progression (104). m⁶A writer METTL3 is a key regulator for macrophage activation (104). METTL3 deficiency in TAMs downregulates m⁶A modification on IRAKM, which, in turn, slows down its degradation and suppresses TLR signaling-mediated

TAM activation, inhibiting proinflammatory cytokine expression and promoting tumor progression (Figure 3) (104). YTHDF1 is an essential reader for METTL3-mediated macrophage reprogramming. Depleting the macrophage METTL3-YTHDF1 axis promotes tumor growth and metastasis (55). However, YTHDF1 in dendritic cells (105) and YTHDF2 in macrophages (106) and METTL3 in cancer cells (40, 70) show an opposite effect. Together, these findings highlight the importance of targeting the context-dependent METTL3-YTHDF axis.

In addition to m⁶A modification, metabolism-dependent histone modification regulates TAM immunosuppressive reprogramming. TAMs usually occupy a high lactate microenvironment due to the “Warburg effect” of cancer cells (107). During TAM glycolysis, glucose is converted into pyruvate, which is incorporated into the TCA cycle for citrate production (108). Mitochondria-secreted citrate is further cleaved by ATP-citrate lyase, generating acetyl-coenzyme A for histone acetylation (109). Depleting ATP-citrate lyase decreases the immunosuppressive activity of TAMs (110). Hence, factors controlling metabolic reprogramming may epigenetically regulate TAM activation and its protumor function. An example supporting this hypothesis is the protein kinase RNA-like ER kinase (PERK) signaling cascade, which epigenetically promotes TAM immunosuppression by upregulating serine biosynthesis and mitochondrial function (54). Mechanistically, activated PERK increases α -ketoglutarate production in mitochondria, resulting in upregulation of immunosuppressive genes (e.g., *Irf4*, *Pparg*, and *Mgl2*) by enhancing JMJD3-dependent histone demethylation in TAMs (Figure 3) (54). Finally, DNA methylation enzymes play a fundamental role in macrophage phenotypic changes (111, 112). Tet2 is a typical DNA methylcytosine dioxygenase that catalyzes 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) for DNA demethylation (111). Genome-wide 5hmC DNA immunoprecipitation (5hmC-DIP) revealed that Tet2 is required to maintain the low 5mC level at the *Arg1* gene locus (111). Thus, Tet2 supports TAM immunosuppressive polarization to promote tumor progression in melanoma mouse models (111). Together, these findings support the idea that epigenetic reprogramming of TAMs affects tumor progression.

MDSC epigenetics regulate cancer cell biology. MDSCs exhibit a potent immunosuppressive and protumor activity by secretion of immunoregulatory factors (25, 113, 114), which are regulated by epigenetic factors, such as H3K27ac regulator CBP/EP300-BRD. Inhibition of CBP/EP300-BRD impairs tumor growth by reducing the migration, differentiation, and function of M-MDSCs and PMN-MDSCs (114). Consistent with these findings, METTL3 is highly enriched in PMN-MDSCs and M-MDSCs of human colon tumors (115). The elevated METTL3-YTHDF1 axis promotes *JAK1* mRNA translation in polysome, upregulating STAT3 signaling in MDSCs to increase the expression of immunosuppressive factors (e.g., IL-6 and IL-10), thus promoting tumor growth by reducing T cell infiltration and activation (115).

Despite these observations, M-MDSCs and PMN-MDSCs may exhibit different roles during tumor progression. Compared with PMN-MDSCs, M-MDSCs are more relevant for promoting lung metastasis in tumor mouse models (116). This finding is consistent with an early study showing that M-MDSCs exhibit stronger immunosuppressive activity than PMN-MDSCs (117). Given that

M-MDSCs are sensitive to DNMT inhibitor (118), epigenetic therapy with 5-azacytidine shows a potent antimetastasis activity by downregulating M-MDSC migration, activation, and differentiation (116). Another great example is *Olfir29-ps1*, a m⁶A-regulated pseudogene, that governs MDSC differentiation (119). Upon the epigenetic regulation, *Olfir29-ps1* increases the percentage of M-MDSCs by regulating the *miR-214-3p*/MYD88 signaling axis but decreases the differentiation of PMN-MDSCs (119). Additionally, epigenetic changes induced by therapy, such as ionizing radiation (IR), are critical for MDSC differentiation in the TME. In detail, IR upregulates m⁶A reader YTHDF2 in MDSCs, which, in turn, promotes m⁶A-modified RNA degradation at genes that encode negative regulators of NF- κ B signaling. The activated NF- κ B/RELA signaling further upregulates YTHDF2 expression in M-MDSCs. This positive circuit between NF- κ B and YTHDF2 amplifies the expression of multiple cytokines in M-MDSCs, which promote MDSCs infiltration/differentiation and inhibit T cell function to promote tumor growth (Figure 3) (25). Inhibition of YTHDF2 using its specific inhibitor DC-Y13-27 potentiates radiotherapy by reducing M-MDSC infiltration/differentiation in colon cancer and melanoma mouse models (25). However, DC-Y13-27 alone has a limited antitumor effect (25), suggesting that the function of NF- κ B-YTHDF2 feedback loop in MDSCs is context dependent.

Neutrophil epigenetics regulates cancer cell biology. Neutrophils are a heterogeneous population of innate immune cells in the TME (120, 121). Epigenetic mediators (e.g., METTL3 and KDM6B) are essential for neutrophil development and activation (122–124). By modifying the mRNA of TLR4, m⁶A writer METTL3 promotes neutrophil migration and production of proinflammatory cytokines (e.g., TNF- α , IL-6, and IL-1 β). However, it is still unclear how neutrophils respond to METTL3 inhibition in the TME. Myeloid-specific deletion of *Kdm6b* reduces the abundance of neutrophils in glioblastoma tumors (124), indicating that histone demethylation might promote neutrophil infiltration. Infiltrated neutrophils secrete various cytokines to suppress T cell activation and proliferation, thus promoting tumor progression (120). Neutrophils may also exhibit antitumor effects independent of T cell-mediated immunity (125). For example, pretreatment with β -glucan in mice can reprogram circulating neutrophils into an antitumor phenotype that suppresses tumor growth irrespective of adaptive immunity in the host (126). While type I IFN signaling activation is required for this phenotype switch, β -glucan-induced trained immunity increases chromatin accessibility of ROS-producing genes (e.g., *NCF1/2*) in neutrophils (126). Functional studies demonstrated that adoptive transfer of β -glucan-pretreated neutrophils into recipient mice inhibits tumor growth (Figure 3) (126). As epigenetic rewiring of granulopoiesis reprograms neutrophils to an antitumor phenotype (126), it is conceivable that epigenetically modulated neutrophils represents a promising avenue for immunologically cold tumors.

Targeting epigenetic regulators for cancer immunotherapy

Cancer immunotherapies, including ICIs, have undergone remarkable advancement over the years. However, the TME poses a challenge for developing effective immunotherapies owing to its heterogeneous and immunosuppressive nature (127, 128). Epigenetic

reprogramming is critical for governing the formation of such TMEs, resulting in impaired T cell activation and accumulated immunosuppressive cells, including Tregs, TAMs, and MDSCs (56). Given the symbiotic interaction between cancer cells and immune cells, epigenetic reprogramming in each cell component can reshape the TME to affect immunotherapy efficiency (129, 130). Therefore, targeting pivotal epigenetic modulators may change the TME to overcome the limited effects of cancer immunotherapies (131).

DNMT and HDAC inhibitors are the most widely used drugs for cancer treatment, with the potential to improve the antitumor efficiency of immunotherapy (132–134). Decitabine (DAC) is an FDA-approved DNMT inhibitor that has been approved for hematological malignancy treatment (135). Despite DAC's limited efficacy on solid tumors as a monotherapy, a recent study revealed that DAC significantly enhanced the antitumor effect of anti-PD1 or anti-VISTA in pancreatic ductal adenocarcinoma (136). Similarly, inhibition of HDAC1 synergized with anti-PD1 by preventing T cell exhaustion in breast cancer (80), and treatment with HDAC8 inhibitor PCI-34051 combined with anti-PD-L1 induced a robust antitumor effect in liver cancer (26). Inhibiting EZH2 using DZNep or EPZ can turn the tumor from cold to hot by activating the dsRNA/STING/IFN axis or downregulating the expression of protumor inflammatory cytokine G-CSF, resulting in upregulation of activated CD8⁺ T cells and downregulation of immunosuppressive neutrophils. As a result, EZH2 inhibition synergized with anti-PD1 therapy in prostate and breast cancer (27, 77). Additionally, pharmacologic inhibition of other methyltransferases (e.g., PRMT5, SMYD3, or MLL4 methyltransferase) or specific deletion of these epigenetic regulators in cancer cells has also been found to specifically increase the antitumor efficacy of anti-PD1 therapy across cancer types (46, 137–140). Apart from inhibitors aiming at inhibiting histone modification and DNA methylation, targeting the chromatin remodeling regulator CECR2 using its specific inhibitors (e.g., GNE-886 and NVS-CECR2-1) can effectively enhance antitumor immunity (56). Targeting chromatin remodeling complex ARID1A or its downstream effector NF- κ B can also reshape the immunosuppressive TME by inducing IFN expression and reducing PMN-MDSC recruitment, thereby offering benefits to anti-PD1/CTLA-4 for cancer treatment (38, 43). Together, these findings suggest that targeting epigenetics can greatly improve ICI antitumor efficiency (Table 1).

Because T cells can eliminate cancer cells (141), directly targeting the epigenome in tumor-infiltrating CD8⁺ T cells to preserve their effector functions is another strategy being explored in combination with ICIs (Table 1) (81, 142–144). Suv39h1, a histone methyltransferase, has been found to promote T cell exhaustion by downregulating IFN- γ and granzyme B in effector CD8⁺ T cells. Treatment with the Suv39h1 inhibitor ETP-69 combined with anti-PD1 induced an increased proportion of effector CD8⁺ T cells and impaired tumor growth (23). Furthermore, treatment with histone demethylase LSD1 inhibitor GSK2879552 induced a long-lasting response of anti-PD1 in colon cancer by reinvigorating exhausted CD8⁺ T cells in the TME (142). Treatment with KDM6B inhibitor GSK-J4 enhanced the efficacy of anti-PD1 therapy in glioblastoma by decreasing CD14⁺Ly6c2⁺CXCL2⁺VEGFA⁺ monocytic macrophages and increasing CD8⁺GZMB⁺IFN- γ ⁺ cytotoxic T cells (124). Moreover, hypoxia-activated epigenetic machinery (e.g., HDAC1)

Table 1. Targeting epigenetic regulators for reshaping the TME

	Epigenetic alteration	Epigenetic target	Cancer type	Working mechanism and rationale of combination with ICI	Synergistic effect when combining with ICI	Refs.
Target cancer cell epigenetics						
Cancer cell	Histone methylation	Enhancer of zeste homolog 2 (EZH2)	Prostate cancer	EZH2 inhibition increases T cell infiltration by activating dsRNA/STING/CXCL10/CXCL11 signaling	Anti-PD1	27
			Brain metastases	EZH2 inhibition decreases tumor-associated neutrophil infiltration by activating c-JUN/G-CSF signaling	Anti-PD1 and/or anti-CTLA-4	77
		Mixed-lineage leukemia 4 (MLL4)	Melanoma	MLL4 inhibition increases T cell infiltration by activating DNMT1/DNMT3A-GSDMD axis-mediated pyroptosis	Anti-PD1	46
		Protein arginine methyltransferase 5 (PRMT5)	Melanoma	PRMT5 inhibition increases T cell and NK cell infiltration by activating IFI16-cGAS/STING-TBK1-IRF3-CCL5/CXCL10 signaling	Anti-PD1	137
	Histone demethylation	Set and mynd domain-containing protein 3 (SMYD3)	Melanoma	SMYD3 inhibition promotes T cell priming and activation by activating CSDE1/STAT1/MHCI signaling	Anti-PD1	139
		Lysine demethylases 5B (KDM5B)	Melanoma	KDM5B inhibition increases T cell infiltration by activating SETDB1/MMVL30/RIG-I/IFN-I signaling	Anti-PD1	50
		Histone deacetylase 8 (HDAC8)	Hepatocellular carcinoma	HDAC8 inhibition increases T cell infiltration by activating CCL4	Anti-PD-L1	26
	Chromatin remodeling	At-rich interaction domain 1A (ARID1A)	Prostate cancer	ARID1A inhibition increases T cell infiltration by activating A20/NF-κB/CXCL2/CXCL3 signaling	Anti-PD1 and/or anti-CTLA-4	43
Target immune cell epigenetics						
CD8 ⁺ T cell	Histone methylation	SUV39H1 histone lysine methyltransferase (SUV39H1)	Melanoma	SUV39H1 inhibition promotes T cell activation by activating IFN-I signaling	Anti-PD1	23
	Histone demethylation	Lysine demethylase 1A (LSD1)	Colon carcinoma	LSD1 inhibition promotes T cell survival by activating TCF1-IL7Rα/SLAMF6 signaling	Anti-PD1	142
		Lysine demethylase 6B (KDM6B)	Melanoma	KDM6B inhibition promotes T cell activation by activating IL-2/BCL6/SLAMF6 signaling	Anti-PD1	79
	Histone deacetylation	Histone deacetylase 1 (HDAC1)	Triple-negative breast cancer	HDAC1 inhibition increases T cell infiltration by activating PCR2/IFNG signaling	Anti-PD1	80
Treg	Chromatin remodeling	Basic leucine zipper atf-Like transcription factor (BATF)	Non-small cell lung cancer	BATF inhibition suppresses Treg activation by activating CCR8/CTLA4 signaling	Anti-PD1	145
MDSC	RNA modification	Yth n6-methyladenosine RNA binding protein F2 (YTHDF2)	Colon adenocarcinoma	YTHDF2 inhibition decreases MDSC infiltration by activating ADRB2/METRNL/SMPDL3B/NF-κB signaling	Anti-PD1	25

in CD8⁺ T cells suppressed immune effector activity by downregulating IFN-γ. HDAC1 inhibition using its inhibitor entinostat dramatically boosted the antitumor efficiency of anti-PD1 therapy in breast cancer (80). Targeting BATF in Tregs inhibited chromatin accessibility and reduced the expression of CTLA4, ICOS, GITR, and PD-1, suppressing Treg activation and providing a stronger antitumor effect when combined with anti-PD1 therapy (145). Besides targeting aberrant epigenome alterations in T cells, modulators affecting other immune cells such as macrophages and MSDCs can also synergize with ICIs (Table 1). CN133, a novel HDAC inhibitor that impairs the function of PMN-MDSCs by reducing the expression of immunosuppressive enzymes, has been found to markedly improve the antitumor efficacy of anti-PD1 treatment in prostate cancer (146). Considering these epigenetic regulators' pivotal role in immune cell activation and exhaustion, coinhibiting "epigenetic checkpoints" and classical immune checkpoints (e.g., PD1 or CTLA-4) may achieve a synergistic antitumor effect (27, 80, 147).

In addition to solid tumors, epigenetic drugs (e.g., DNMT inhibitor azacytidine) show clinical benefits in hematologic malignancies, including acute myeloid leukemia (AML) (148, 149). It

should be noted that the effectiveness of epigenetic therapies in AML is context dependent. AML cells harboring somatic mutations in *DNMT3A* appear more susceptible to azacytidine treatment (150). Conversely, AML cells expressing high levels of ubiquitin ligase RNF5 show less sensitivity to HDAC inhibitors (151). Given that epigenetic changes in AML cells can modulate cell-intrinsic immune response (152), it is reasonable to develop epigenetic immunotherapies by combining epigenetic drugs with chimeric antigen receptor (CAR) T cell therapies (153). Indeed, preclinical studies showed that treatment with azacytidine increases CD123 expression, resulting in enhanced recognition and elimination of AML cells in response to anti-CD123 CAR T cells (153). Together, these findings highlight that epigenetic immunotherapies may hold great promise for hematologic malignancy treatment.

Concluding remarks

Immunotherapy, including ICI, has revolutionized current oncology treatment (1, 16, 154). However, a plethora of clinical trials have shown that many patients with cancer ultimately develop resistance to ICIs (155–157). The TME is now recognized as a critical

barrier impairing the efficacy of ICI (5, 158, 159). Given the heterogeneity of the TME across cancer types, specifically targeting this context-dependent interplay between the TME and cancer cells is a recognized strategy for sensitizing nonresponder tumors to ICIs (11, 26, 27, 160). In addition to genetic alterations, epigenetic remodeling plays an important role in regulating TME heterogeneity (36, 161, 162). Because cancer cells have a more plastic and unstable epigenome than nonmalignant cells, they can easily adapt to the selection pressures and exhibit a distinct epigenetic state that can further allow them to activate alternative gene regulatory programs (12, 35, 163, 164), including genes for controlling T cell immunity (Figure 1) (51, 138). This theory may explain the significant correlation between epigenetic alterations in cancer cells and T cell dysfunction (79, 165). Additionally, cancer cells that have undergone epigenome alteration release various cytokines and chemokines within the TME, recruiting and activating tumor-associated myeloid cells (e.g., macrophages, MDSCs, and neutrophils). These cells further shape an immunosuppressive TME by limiting the proliferation and function of cytotoxic T cells (Figure 2). Given the heterogeneity and plasticity of the myeloid cells in the TME, future studies are still needed to elucidate the role and underlying mechanism of cancer cell epigenetic change—driven immune landscape in a context-dependent manner.

Furthermore, epigenetic changes in immune cells contribute to tumor progression (22, 145). Unlike cancer cell epigenetics that are mainly attributed to genetic stimuli (166), immune cell epigenetics are primarily triggered by stimuli from the TME, such as hypoxia and cancer cell-derived factors or metabolites (Figure 3) (80, 110, 167, 168). Tumor-associated myeloid cells (e.g., TAMs) exhibit a superior sensitivity to metabolite changes (107, 110, 169, 170) and can switch their phenotypes upon epigenetic reprogramming (54, 107, 110, 111, 169, 171). Thus, targeting the altered epigenetic states of myeloid cells may inhibit tumor growth and improve T cell activ-

ity to yield new therapeutic strategies for overcoming ICI resistance (Table 1) (55, 106, 124). Of note, cancer treatments are also able to drive epigenetic modifications in cancer cells and immune cells (12, 24, 25). Myeloid cells, such as MDSCs, take advantage of this mechanism to further impede tumor immunity even in the presence of such treatment (25). Despite these important findings, it is still unclear whether epigenetic regulators affect myeloid cell lineage plasticity and dynamics in the TME and how this connection consequently regulates cancer cell survival and ICI resistance.

Single-cell approaches have emerged as powerful tools to decipher different layers of epigenome in cancer cells and immune cells simultaneously (18, 22, 49, 172). We postulate that the integration of these techniques with CRISPR screening may help identify unforeseen epigenetic elements that are crucial for tumor-immune interplay. Despite the progress, single-cell epigenetic technologies are still limited by low throughput, poor coverage, and lack of multiplexing capabilities (18). Developing epigenetic long-read single-cell sequencing may provide new insights into how epigenomic heterogeneity is related to the codependency between immune cells and cancer cells (173). Given the dynamic epigenomic landscape of immune cells (174–176), we are optimistic that a deeper understanding of mechanisms connecting epigenetic modifications to tumor immunity will advance the development of novel immunotherapies.

Acknowledgments

This work was supported in part by NIH grant R01 NS124594 (to PC), NIH grant R01 NS127824 (to PC), and Department of Defense Career Development Award W81XWH-21-1-0380 (to PC).

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