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REVIEW

Targeting the cytokine-epigenetic axis: a new paradigm and prospects for disease treatment

Yuyue Luo[1,#], Yikan Zheng[2,#], Jie Qin[1,#], Jinwei Liu[2], Yuhan Ma[2], Jingda Li[3], Jun Li[4], Wenlong Sun[1,*], Qian Zhang[2,*] and Mengyao Li[5,6,*]

[1]School of Life Sciences and Medicine, Shandong University of Technology, Zibo, China
[2]First Clinical Medical College, Inner Mongolia Medical University, Hohhot, China
[3]College of Life Science, Yangtze University, Jingzhou, China
[4]College of Pharmacy, Inner Mongolia Medical University, Hohhot, China
[5]State Key Laboratory of Systems Medicine for Cancer, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[6]Shanghai Key Laboratory for Cancer Systems Regulation and Clinical Translation, Shanghai Jiading District Central Hospital, Shanghai, China

*Corresponding Authors: Wenlong Sun. Email: wenlongsun0814@163.com; Qian Zhang. Email: bioqzhang@immu.edu.cn; Mengyao Li. Email: limy@sioc.ac.cn
[#]These authors contributed equally to this work as the first author

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ABSTRACT: Cytokines, as key signaling molecules, are involved in the regulation of physiological and pathological processes such as inflammation, immunity, and cell growth. Epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs, enable precise control of gene expression without changing the DNA sequence. Recent studies have revealed that cytokines interact with epigenetic regulation to form a dynamic and complex "cytokine-epigenetic axis". Through metabolic reprogramming and regulation of epigenetic enzyme activity, this axis affects gene expression patterns at both transcriptional and post-transcriptional levels, thereby contributing to the initiation and progression of various diseases, including autoimmune diseases, neurodegenerative diseases, neuropsychiatric disorders, metabolic diseases, and cancer. Targeting this regulatory axis by combining interventions on upstream cytokine signaling and downstream epigenetic enzymes represents a new precision therapeutic strategy for overcoming resistance to monotherapy and achieving disease-modifying treatment. This review describes how cytokines regulate epigenetic modification substrates through metabolic reprogramming and directly regulate epigenetic enzyme activity via JAK-STAT, NF-κB, and TGF-β/Smad pathways; how this axis drives disease chronicity and therapy resistance across autoimmune, neurodegenerative, metabolic, and neoplastic diseases by establishing long-lasting functional reprogramming; and emerging strategies targeting this axis through combined interventions, precision medicine, and disease memory reprogramming.

KEYWORDS: Cytokines, epigenetics, DNA methylation, histone modifications, immunometabolism, targeted therapy

1 Introduction

Dysregulation of cytokine networks is a pivotal characteristic in numerous major diseases, entailing disruption of the intricate equilibrium between pro-inflammatory and anti-inflammatory signals. Cytokines are not merely "messengers" of inflammation, but also "programmers" that shape immune memory through epigenetic coding, serving as a double-edged sword in infections, autoimmune diseases, atherosclerosis, and cancer. Epigenetic mechanisms provide a fundamental layer of regulation for cytokine network homeostasis by precisely controlling the spatiotemporal patterns of inflammatory gene expression through reversible chromatin modifications, including DNA methylation, histone modifications and chromatin remodeling. Together, these cytokine-driven and epigenetic regulatory processes form a "cytokine-epigenetic axis" that underlies disease pathogenesis and provides critical targets for developing precise therapeutic strategies.

Research on the cytokine-epigenetic regulation axis aims to understand the mechanisms of this complex biological process in disease initiation and development, providing new ideas for prevention, diagnosis, and treatment. Cytokines participate in inflammatory responses, immune regulation, cell proliferation, etc., by activating specific signaling pathways, which are precisely regulated by epigenetic mechanisms. Mechanistically, cytokines bind to their receptors and activate the MAPK pathway and transcription factors NF-κB and AP-1, which recruit histone acetyltransferases (HATs) and deacetylases (HDACs) to modify chromatin and regulate gene transcription. Similarly, the

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PI3Kβ–mTOR axis integrates cytokine signals to control immune cell activation and inflammatory gene expression through epigenetic remodeling [1,2]. These pathways can quickly respond to stimuli but have inherent limitations, such as difficulty in promoting cell differentiation, lack of immune memory formation, and inability to promote tissue remodeling. In contrast, cytokines can induce long-lasting and stable epigenetic changes, thereby "reprogramming" cellular functions and significantly affecting disease occurrence, development, and outcomes. In addition to being acute mediators of immune responses, cytokines are also major drivers of epigenetic reprogramming. By continuously activating metabolism-epigenetic coupling pathways, they leave lasting and heritable molecular imprints on innate immune cells and their precursors, leading to profound functional remodeling [3,4].

This review aims to elucidate the molecular mechanisms by which key cytokines regulate epigenetic modifications and summarize the central pathological roles of this regulatory axis in disease initiation and progression. We will analyze how cytokines, through signaling pathways such as JAK-STAT, NF-κB, and SMAD, specifically regulate the expression and activity of DNA methyltransferases (DNMTs), histone modifiers, and chromatin remodeling factors. This regulation induces alterations in the methylation patterns of specific gene promoter regions, restructures histone acetylation and methylation modifications, and reprograms the expression of non-coding RNA networks, ultimately leading to stable transcriptional memory and disease phenotypes. Furthermore, we will focus on summarizing the key roles of this regulatory mechanism in major diseases, including inflammatory diseases, autoimmune diseases, malignant tumors, and organ fibrosis. This reveals how the cytokine-epigenetic axis drives imbalances in the immune microenvironment, promotes malignant transformation from chronic inflammation, regulates tumor immune escape, and leads to abnormal tissue repair [5,6]. Finally, we will discuss challenges associated with existing combination therapies, particularly regarding precise delivery, toxicity control, and temporal optimization. We will also outline future directions for developing personalized dual-target therapeutic systems using advanced technologies such as dynamic epigenetic-immunological monitoring, AI-assisted drug combination prediction, and gene-edited epigenetic regulation. This will provide an innovative theoretical framework and translational pathway for the development of disease-modifying therapies.

2 Core Mechanisms of Cytokine Regulation of Epigenetics

Pro-inflammatory and anti-inflammatory cytokines can differentially regulate the same histone modification or DNA methylation, leading to distinct transcriptional changes in a context-dependent manner. In systemic lupus erythematosus, IFN-α upregulates IDH2 and increases α-ketoglutarate levels, which enhance KDM6A/B histone demethylase activity and reduce H3K27me3 at interferon-stimulated genes (ISGs). TNF-α increases citrate-derived acetyl-CoA production, thereby promoting histone acetylation at inflammatory gene promoters. It also disrupts HDAC5-mediated deacetylation of NF-κB p65, which helps sustain NF-κB transcriptional activity [7,8]. By contrast, TGF-β can recruit DNMTs such as DNMT3A and increase repressive histone marks such as H3K9me2 and H3K27me3 to silence target genes [9,10]. These effects are also different across tissue environments. In synovial fibroblasts from rheumatoid arthritis, TNF-α amplifies inflammation via coordinated histone acetylation and α-ketoglutarate-dependent demethylation. In the tumor microenvironment (TME), TGF-β can promote immunosuppressive memory through epigenetic silencing. In the placenta from gestational diabetes mellitus (GDM), hypomethylation of the TNF-α promoter is associated with activation of NF-κB and aggravated insulin resistance [11]. Thus, the same cytokine can have different effects on gene expression in different tissues and cell types.

2.1 Modulation of Epigenetic Substrates via Metabolic Reprogramming

2.1.1 Regulatory Roles of the TCA Cycle and Metabolic Intermediates

The tricarboxylic acid (TCA) cycle serves as a central hub for cellular energy metabolism and biosynthesis. It produces intermediates, including α-ketoglutarate (α-KG), succinate, and citrate, which are essential not only for energy conversion but also function as key signaling molecules directly involved in epigenetic modifications. These intermediates thus establish a molecular bridge between metabolic state and gene expression regulation, precisely coordinating the interplay between metabolism and gene expression.

α-Ketoglutarate [12], a key intermediate metabolite of the TCA cycle, is not only an important carrier in cellular energy metabolism, but also an essential cofactor for Jumonji C-domain histone demethylases (KDM2-7) and TET family DNA demethylases. The intracellular concentration of α-KG directly affects the activity of these enzymes, thereby regulating chromatin modifications and gene transcription processes. In SLE, this metabolically driven epigenetic regulatory mechanism is significantly disrupted. Abnormally activated interferon-α (IFN-α) in monocytes from SLE patients simultaneously enhances glycolysis flux and oxidative phosphorylation levels to meet the energy demands of immune cell hyperactivation, while also increasing intracellular α-KG concentrations by upregulating isocitrate dehydrogenase 2 (IDH2) expression. As the main mitochondrial enzyme responsible for converting isocitrate into α-KG, increased IDH2 expression leads to elevated α-KG accumulation, which specifically enhances the enzymatic activity of histone demethylases KDM6A/B. Under the combined action of α-KG, KDM6A/B efficiently removes the repressive histone mark H3K27me3 from promoter regions of ISGs, relieving chromatin compaction and maintaining sustained transcriptional activation of ISGs. This cytokine-mediated regulatory loop reveals how

cytokines in SLE reprogram TCA cycle metabolic flux, utilize metabolic intermediates to regulate chromatin modifications, and ultimately establish a "trained immunity" environment within immune cells to sustain chronic inflammation.

Metabolic-epigenetic regulation mediated by TCA cycle intermediates is not unique to SLE but exhibits a high degree of mechanistic conservation in various inflammatory diseases. Liu et al. [13] demonstrated that the metabolic reprogramming of the TCA cycle was also deeply involved in regulating epigenetic modifications in macrophages infected with *Mycobacterium tuberculosis* (Mtb). Mtb infection induces succinate accumulation, which stabilizes hypoxia-inducible factor-1α (HIF-1α) and promotes pro-inflammatory factors such as IL-1β expression; meanwhile, fluctuations in α-KG levels, which act as cofactors for TET2 enzymes, affect DNA methylation status, thereby regulating macrophage polarization and antimicrobial function. Similarly, Wen et al. [7] revealed in their study on rheumatoid arthritis that TNF-α-mediated metabolic reprogramming in patients' synovial fibroblasts led to increased citrate efflux, which enhanced the transcriptional activity of inflammatory genes by promoting histone acetylation and synergized with demethylated regulation mediated by α-KG, forming a metabolic-epigenetic network that amplified inflammation. Furthermore, Kusnadi et al. found that Systemic IFN-γ directly signaled through cardiomyocyte IFNGR to suppress oxidative phosphorylation and fatty acid oxidation while enhancing glucose uptake and glycolysis, driving cardiac metabolic rewiring independent of confounding inflammatory disease [14]. Taken together, these studies demonstrate that metabolite-epigenetic regulation mediated by TCA cycle intermediates is a pervasive cellular regulatory mechanism in various pathological settings. In SLE, the IFN-α–IDH2/α-KG/KDM6A/B regulatory axis not only reveals the crosstalk mechanisms among cytokines, metabolic reprogramming, and epigenetic modifications in autoimmune diseases but also provides novel molecular targets for disease intervention. In the future, it is anticipated that targeting the regulation of IDH2 enzyme activity, intracellular α-KG levels, or KDM6A/B function will disrupt the vicious circle of "metabolic reprogramming, epigenetic modification, and inflammatory gene activation" and provide potential therapeutic strategies for SLE and other chronic inflammatory disorders.

2.1.2 Acetyl-CoA and Histone Acetylation

Histone acetylation is a key epigenetic modification that regulates the structural flexibility of chromatin and gene transcriptional activity. The balance between histone acetylation and deacetylation depends on substrate availability and signal transduction from cellular metabolic networks, forming a cross-domain regulatory axis from metabolism to epigenetic modifications and then to gene expression. As the main substrate for this modification, acetyl-CoA is synthesized in conjunction with the central metabolic pathways of cells [15]. Citrate from the TCA cycle is transported into the cytoplasm via the mitochondrial citrate carrier (CIC), where ATP-citrate lyase (ACLY) cleaves it into acetyl-CoA and oxaloacetate, providing direct substrates for nuclear histone acetylation. Meanwhile, pyruvate derived from glycolysis enters the mitochondria, where it is oxidatively decarboxylated by the pyruvate dehydrogenase complex (PDC) to generate acetyl-CoA. Some of this acetyl-CoA can be transported to the perinuclear region, participating in chromatin-associated acetylation modifications. This close relationship between metabolic pathways and epigenetic modifications allows cells to precisely control chromatin accessibility and gene transcription efficiency through substrate supply.

Short-chain fatty acids (SCFAs) such as butyrate and valerate produced by gut microbiota are important metabolite-derived epigenetic regulators that modulate immune cell functions through multiple mechanisms, especially the effector activation of $CD8^+$ T cells [16]. Cytokines including IL-1β and IL-6 can influence the production and availability of SCFAs by modulating gut microbial composition, thereby indirectly regulating the epigenetic landscape [17]. SCFAs can directly inhibit HDAC activity. by preventing the deacetylation of lysine residues on histones, HDAC inhibition significantly increases local and global levels of histone acetylation, leading to a relaxation of chromatin compaction and transcriptional activation of effector molecules including IL-2 receptor α chain (CD25), IFN-γ, and TNF-α, thereby enhancing the cytotoxic activity and immune memory formation of $CD8^+$ T cells. In addition, SCFAs activate mTOR signaling, which upregulates key glycolytic enzymes including hexokinase 2 (HK2), 6-phosphofructokinase/fructose-2,6-diphosphatase 3 (PFKFB3), and pyruvate kinase M2 (PKM2). This enhances glycolytic metabolic flux in immune cells, providing abundant substrates for acetyl-CoA production and subsequent histone acetylation. Together, these processes form a positive feedback loop consisting of SCFAs, mTOR, glycolysis, acetyl-CoA, and histone acetylation. Notably, this regulatory mechanism is consistent across different pathological contexts, as demonstrated in Mtb-infected macrophages and synovial fibroblasts from patients with rheumatoid arthritis.

More importantly, SCFAs can further enhance the substrate supply capacity by regulating acetylation modification of the metabolic enzyme itself; inducing ACLY acetylation and activation to enhance its catalytic activity and promote acetyl-CoA production. This mechanism establishes a multilevel interactive network between metabolic flux and epigenetic modifications, providing stable molecular support for sustained activation of immune cell effector function. The above cross-domain regulatory mechanisms mediated by microbial metabolites not only reveal an in-depth dialogue among gut microbiota, metabolic status, and immune functions but also provide a dual-pronged strategy of synergistic intervention through "metabolic regulation" and "epigenetic modification" for targeted therapy of immune-related diseases.

2.1.3 DNA Methylation

DNA methylation, a crucial epigenetic modification that regulates gene expression, is intrinsically connected to cellular metabolic states through cross-regulatory mechanisms. This process depends on the functional integrity of one-carbon metabolism pathways. The methionine cycle and folate metabolism interact synergistically within this pathway to produce S-adenosylmethionine (SAM), the primary methyl donor for DNA methylation. Methionine is converted into SAM under the catalysis of methionine adenylyltransferase (MAT). After donating a methyl group, SAM is converted into S-adenosylhomocysteine (SAH). Simultaneously, 5-methyltetrahydrofolate, generated by folate metabolism, acts as a methyl donor to regenerate methionine via the homocysteine remethylation pathway, thereby ensuring a steady supply of the SAM pool. The efficiency of methionine uptake, the bioavailability of folate, and the activity of key enzymes in one-carbon metabolism collectively affect the intracellular ratio of SAM to SAH. This ratio subsequently influences the catalytic efficiency of DNMTs and impacts the establishment and maintenance of the genome-wide DNA methylation profile.

A further study [18] has revealed that epigenetic reprogramming mediated by methionine metabolism is a key regulatory factor in Th cell fate determination and one of the core mechanisms shaping adaptive immune responses. Methionine metabolism not only provides energy and biosynthetic precursors for Th cell differentiation but also precisely regulates the expression of key transcription factors through its metabolite SAM, which regulates histone methylation modifications and DNA methylation status. When methionine supply is limited or when the one-carbon metabolic pathway is disrupted, the level of SAM in Th cells decreases, leading to a significant reduction in the activation-related histone mark H3K4me3, thereby inhibiting the expression of Th17-related genes and limiting the pathogenic function of Th17 cells. Conversely, sufficient methionine supply enhances H3K4me3 modifications, thereby supporting Th17 cell effector function and promoting cytokine secretion such as IL-17. These findings suggest that methionine metabolism flexibly regulates the balance of Th cell subsets through epigenetic reprogramming, making it a potential target for immunological intervention.

Furthermore, in metabolic diseases such as GDM, abnormal DNA methylation in the mother and placenta is closely linked to one-carbon metabolic disorders [12]. In placental tissues of GDM patients, the promoter regions of IGFBP-1 and IGFBP-2 show increased methylation, silencing their transcription and downregulating protein expression. Loss of these inhibitors of IGF-1 removes suppression on the IGF-1 pathway, promoting trophoblast proliferation and abnormal angiogenesis, ultimately leading to fetal overgrowth and macrosomia. Meanwhile, the TNF-α gene promoter in peripheral blood mononuclear cells and placenta is hypomethylated, correlating with increased TNF-α secretion. Wang et al. identified that methylation status of five CpG sites (COPS8, PIK3R5, HAAO, CCDC124, C5orf34) in peripheral blood can serve as GDM biomarkers [19]. Valencia-Ortega et al. found that GDM mediates the impact of pre-pregnancy obesity on LEP methylation in the placenta [20]. As a pro-inflammatory cytokine, TNF-α activates NF-κB, exacerbating insulin resistance and disrupting placental metabolic homeostasis, forming a vicious cycle between inflammation, epigenetic modification, and metabolic dysfunction. Furthermore, the MTHFR C677T polymorphism, which affects SAM production, intensifies abnormal DNA methylation in GDM, suggesting that genetic and metabolic factors synergistically promote GDM via epigenetic regulation.

2.2 Direct Regulation of the Expression and Activity of Epigenetic Modification Enzymes

2.2.1 TGF-β/Smad Pathway

The TGF-β/Smad pathway, a central hub of cellular signaling, not only establishes an epigenetic regulatory network for gene silencing through dynamic interactions with DNMTs and histone modifiers but also plays a crucial role in the development of immune-mediated cellular memory. Collectively, these mechanisms exert synergistic effects on chronic inflammation and autoimmune disease progression. Specifically, this pathway contains an intrinsic epigenetic feedback mechanism wherein TGF-β induces DNMT3A to participate in gene silencing, whereas the histone methyltransferase SETDB2 suppresses Smad3 expression by catalyzing H3K9me3 modification within the Smad3 promoter region, thereby negatively regulating pathway activity. It is this imbalanced bidirectional interaction rather than simple pathway activation that drives chronic inflammation and autoimmune disease progression. For instance, in diabetic nephropathy, impaired epigenetic repression of Smad3 by SETDB2 leads to feedback loop collapse, which synergizes with training-induced immune-mediated inflammatory memory to accelerate kidney damage. Furthermore, the TGF-β/Smad pathway can establish long-term cellular memory akin to trained immunity through DNMT3A-mediated DNA methylation, suggesting its causal role in programming innate immune memory.

At the level of epigenetic regulation, the TGF-β/Smad pathway can recruit DNMTs to participate in gene silencing. For example, DNMT3A subtype b upon induction by TGF-β can cooperate with repressive histone modifications such as H3K9me2 and H3K27me3 to silence key genes such as E-cadherin Through combined regulation of DNA methylation and histone modification, thereby driving the process of epithelial-mesenchymal transition (EMT). At the same time, histone methyltransferase SETDB2 can inhibit Smad3 expression and activation by catalyzing H3K9me3 modification at the promoter region of Smad3, thus negatively regulating excessive activation of the TGF-β/Smad pathway and maintaining cellular homeostasis [11]. This crosstalk between pathways and epigenetic enzymes provides a multilayered regulatory mechanism for precise silencing of gene expression.

In addition, the abnormal activation of TGF-β/Smad pathway can also affect gene methylation status

by regulating DNMT activity. In lung adenocarcinoma, after YTHDF1-mediated m6A modification, DUSP5 promotes the EMT process by activating TGF-β/Smad pathway [21]; in hepatocellular carcinoma, HBx-induced upregulation of MAP1S promotes nuclear translocation of the Smad complex through MAP1S/Smad/TGF-β1 loop and enhanced expression of downstream oncogenes of TGF-β, and DNA methylation mediated by DNMT3A may be involved in the regulation of this loop. In chronic kidney disease, excessive activation of TGF-β/Smad pathway is a key driving factor of renal fibrosis [22], while miR-10a/b could inhibit this pathway by targeting TGFBR1; its expression was regulated by XRN2, which further explained the synergistic regulatory network between this pathway and epigenetic modifications [23].

Trained immunity, a form of memory in the innate immune system, relies on cytokines such as IL-1β and GM-CSF to induce histone modifications, endowing myeloid cells with long-term activation [24]. IL-1β can activate downstream signaling pathways to increase the enrichment level of H3K4me3 in the promoter regions of inflammatory genes in myeloid cells, while also increasing the modification level of H3K27ac, promoting chromatin relaxation, and enhancing the transcriptional activity of inflammatory genes. This change is stable and not easily altered even after stimulus withdrawal, enabling myeloid cells to rapidly initiate a strong inflammatory response upon re-exposure, thereby forming persistent inflammatory memory [25].

GM-CSF, on the other hand, is involved in establishing trained immunity by regulating histone-modifying enzyme activity [26]. Specifically, it programs myeloid-committed progenitors by strongly activating STAT5, ERK, and Akt-mTOR signaling pathways, which are essential for establishing a training program that promotes sustained expression of training-associated genes and enhanced cytokine responsiveness upon restimulation [27].

Notably, there is a complex cross-regulation between the TGF-β/Smad pathway and trained immunity. Under pathological conditions, abnormal activation of the TGF-β/Smad pathway may affect IL-1β- and GM-CSF-mediated histone modification patterns by regulating DNMTs and histone modifier activity, thereby exacerbating myeloid cell hypertrained status [22]. Conversely, histone modifications induced by trained immunity can also negatively regulate the expression of key molecules in pathways such as Smad3, thus driving the development of chronic inflammation and autoimmune diseases [19,20]. Collectively, these mechanisms reveal profound epigenetic interactions between the TGF-β/Smad pathway and trained immunity, providing new insights into understanding the underlying mechanisms of chronic inflammation and developing targeted intervention strategies.

2.2.2 JAK-STAT Pathway

STAT proteins, as crucial transcriptional regulators, play a significant role in the dynamic epigenetic regulation of chromatin. They accomplish this by precisely recruiting HATs or HDACs to the promoter regions of target genes, thereby meticulously managing gene transcription efficiency. This process is vital for physiological adaptation and pathological transformation. The JAK-STAT pathway, a rapid signaling module that extends from the cell surface to the nucleus, can promote cancer progression and metastasis when abnormally activated. The specificity of STAT protein recruitment of HATs and HDACs forms the fundamental mechanism that underpins the function of this pathway.

During β-cell adaptation to pregnancy, maternal pancreatic β-cells undergo proliferation and functional remodeling to meet the metabolic demands of pregnancy. STAT3-mediated epigenetic regulation is a key mechanism in this process. Zhang et al. [28] found that STAT3 specifically binds with p300 (a major member of the HAT family) to form a complex, which is recruited to regulatory regions of pregnancy-associated genes to promote activating acetylation modifications such as histone H3K27ac, thereby increasing chromatin accessibility and relieving transcriptional inhibition, ultimately promoting the expression of genes related to β-cell proliferation and insulin secretion function adaptation. The binding ability of STAT3 combined with p300 reaches its peak during mid-pregnancy. More than two-thirds of STAT3 binding sites overlap with p300, directly participating in the epigenetic activation of pregnancy-associated genes. Acetyl-CoA synthetase 2 provides substrate for p300 acetyltransferase activity by producing acetyl-CoA, further enhancing the epigenetic regulation effect of the STAT3-p300 complex on gene transcription, thus ensuring sufficient β-cell proliferation during mid-pregnancy while maintaining functional balance. ACSS2 is highly enriched in the β-cell nucleus, and its expression progressively increases during pregnancy; β-cell-specific knockout of Acss2 reduces global H3K27ac levels, directly affecting the efficiency of acetylation regulation by the STAT3-p300 complex. However, when pregnant mice are exposed to a high-fat diet, the synergistic effect between STAT3 and p300 becomes abnormally activated, leading to excessive histone acetylation at open chromatin regions specific to pregnancy. This induces abnormal overexpression of genes related to metabolic stress, ultimately disrupting functional homeostasis of β-cells and increasing susceptibility to gestational diabetes. In contrast, β-cell-specific knockout of Acss2 effectively reversed this pathological process, restoring insulin secretion and glucose tolerance in β-cells.

In the context of cancer stem cell regulation [29], STAT3 constructs complex transcriptional regulatory networks by selectively binding to different HAT or HDAC complexes to drive tumor progression. The C-terminal phosphorylated p27 as a key cofactor forms a trimeric complex with STAT3 and CBP from the HAT family. This complex is recruited to the promoter regions of stemness self-renewal driver genes such as MYC and JAG1, where it strongly activates target gene transcription by specifically enhancing histone H3K27 acetylation levels to maintain the stemness characteristics of CSCs. This complex is particularly prominent in triple-negative breast cancer, where enrichment for H3K27ac at its binding sites positively correlates with the spheroid-forming ability of CSCs. At the same

time, STAT3 can also switch its mode of regulation by binding to SIN3A- or HDAC1-containing complexes to target the PTPN12 gene promoter region, thereby inhibiting its expression through histone deacetylation. As a specific inhibitor of Pyk2, downregulation of PTPN12 leads to sustained activation of Pyk2, which in turn phosphorylates STAT3 to form a Pyk2–STAT3 positive feedback loop that continuously amplifies proliferative signals in CSCs, ultimately promoting tumorigenesis, invasion, and metastasis. Dysregulated recruitment of HATs and HDACs mediated by STAT3 not only drives expansion of the CSC population but is also closely associated with poor patient outcomes. in breast cancer patients, for example, a genetic signature of STAT3 activation combined with high expression of phosphorylated p27 predicts shorter relapse-free survival.

These mechanisms corroborate each other and reveal that the recruitment of HATs and HDACs by STAT proteins is strictly cell type- and milieu-dependent, a feature that makes them key molecular switches connecting physiological and pathological states [28–30]. In addition to β-cell adaptation to pregnancy, members of the STAT family regulate functional remodeling in different cell types through similar mechanisms under physiological conditions.

2.2.3 NF-κB Pathway

As a central signaling hub in inflammation and tumorigenesis, the NF-κB pathway plays a crucial role in the epigenetic regulatory network through precisely regulating HDACs and histone methyltransferases activities as well as their nuclear translocation, thereby exerting profound effects on gene transcriptional homeostasis and disease progression. Dysregulation of these enzymes is closely associated with pathological processes such as pancreatic cancer and inflammation-associated diseases whose regulation mechanisms depend on signal-dependent modifications and complex assembly mediated by the NF-κB pathway [31–33]. The pathological significance of this axis lies in the causal effect of signal persistence. Under acute TNF-α stimulation, p65 phosphorylation is transient and HDAC5 can reassociate with p65 after the signal subsides to restore homeostasis; however, under conditions of persistent stimulation such as chronic inflammation or obesity, HDAC5 is chronically excluded from p65, resulting in constitutive hyperacetylation of p65, sustained PD-L1 expression, and immune evasion. Therefore, the duration of HDAC5–p65 dissociation is the causal determinant for pathological transformation.

Regarding the regulation of HDACs, the interaction between class IIa HDAC5 and p65 core subunit of NF-κB pathway is a key node. Studies have shown that HDAC5 can directly bind to p65 subunit and specifically mediate deacetylation of lysine 310 on p65 through its DAC domain, which significantly inhibited the transcriptional activity of p65, thereby downregulating the expression of immune checkpoint molecule PD-L1 [9]. TNF-α induces phosphorylation of p65 at serine 311, which disrupts its binding ability, lifts the inhibition of HDAC5 on PD-L1 transcription, and provides a molecular basis for tumor immune escape. The nucleocytoplasmic shuttle of class IIa HDACs depends on the cycle of phosphorylation-mediated cytoplasmic retention and dephosphorylation-induced nuclear import. Although the phosphorylation state of HDAC5 does not affect its binding ability to p65, it directly regulates its enrichment in the nucleus, thereby affecting the efficiency of histone deacetylase in the promoter region of target genes. Under physiological conditions, the NF-κB pathway maintains gene expression homeostasis by regulating the balance between HDACs and HATs; however, under pathological conditions such as high-fat diet-induced β-cell dysfunction, abnormal activation of the NF-κB pathway destroys the synergistic balance between HDACs and HATs, leading to excessive histone acetylation and disruption of cellular homeostasis. In colorectal cancer research, miR-34a affects immune suppression by regulating the SIRT1/NF-κB axis, which also indirectly reflects the network characteristics of HDAC family members and NF-κB pathway in coordinating the regulation of gene expression [31].

The activity of HMTs is regulated by cofactor binding, post-translational modifications and complex assembly that are mediated by the NF-κB pathway, while nuclear translocation processes are regulated by NF-κB-induced signaling to recruit chromatin-binding targets [32]. HMTs participate in gene transcription regulation by catalyzing the methylation of specific lysine or arginine sites on histones, thereby forming activating or repressive chromatin marks. In inflammatory and TMEs, activation of NF-κB signaling can induce recruitment of specific HMTs to promoter regions of inflammation-related genes, which activates target gene expression through enhanced histone methylation modification, thus forming an inflammatory amplification loop [33]. Notably, there is extensive functional crosstalk between HMTs and HDACs, which generate synergistic or antagonistic effects under the regulation of the NF-κB pathway. During immune cell polarization, HDAC-mediated histone deacetylation and HMT-catalyzed methylation jointly regulate the transcription of M1- and M2 macrophage polarization-associated genes, affecting the intensity and duration of inflammatory responses; in tumor cells, this interplay can reshape the epigenetic state of tumor-associated genes, promoting tumor cell proliferation, invasion, and immune evasion.

The regulation of HDACs and HMTs by the NF-κB pathway is highly cell type- and microenvironment-dependent. During β-cell adaptation to pregnancy, the NF-κB pathway regulates the balance between HDACs and HATs to maintain histone acetylation levels, thereby ensuring β-cell proliferation and functional adaptation. In contrast, in cancer stem cells, the NF-κB pathway mediates the formation of a complex comprising HDAC1 and HMTs, which are involved in activating genes that maintain stemness and silencing tumor suppressor genes, respectively, thereby driving cancer stem cell expansion and tumor progression [33]. In bone diseases with inflammation, an imbalance in the regulation of HDACs and HMTs by the NF-κB pathway disrupts bone metabolic homeostasis, exacerbating bone damage and inflammatory responses.

In autoimmune diseases such as rheumatoid arthritis, abnormal activation of the NF-κB pathway leads to dysregulation of HDAC and HMT functions, intensifying synovial tissue inflammatory proliferation and joint damage.

In therapeutic applications, HDACs and HMTs targeting the NF-κB pathway have demonstrated significant potential. The HDAC5 inhibitor LMK235 elevates p65 acetylation levels and promotes its nuclear accumulation by inhibiting deacetylase activity, leading to upregulated CXCR4 surface expression and enhanced hematopoietic stem cell homing and engraftment [34]. By specifically regulating the activity of HMTs such as Setdb2, which trimethylates histone H3 at NF-κB binding sites on inflammatory cytokine gene promoters to suppress transcription, it is possible to disrupt the transcriptional activation of inflammation-related genes, offering a novel therapeutic approach for inflammatory disease [35]. To address the functional imbalance between HDACs and HMTs due to aberrant NF-κB pathway activation, IKK inhibitors like aspirin and sulfasalazine can indirectly modulate HDAC and HMT functions by suppressing NF-κB pathway activity, presenting additional treatment avenues for inflammation-associated disorders. In essence, these mechanisms underscore the pivotal role of the NF-κB pathway in mediating physiological adaptation and pathological transitions through precise modulation of HDACs and HMTs, establishing a robust theoretical basis for disease intervention strategies centered on this regulatory axis.

Figure 1 integrates the signaling and metabolic arms of the cytokine-epigenetic axis. On the signaling side, TGF-β/Smad, JAK-STAT, and NF-κB pathways directly regulate epigenetic enzyme activity. For example, TGF-β/Smad promotes E-cadherin silencing and trained immunity through modulation of histone methylation and acetylation; the JAK-STAT pathway drives STAT acetylation and dimerization; and upon TNF-α stimulation, HDAC5-mediated deacetylation of NF-κB p65 is relieved to allow for p65/p50 nuclear translocation and recruitment of histone methyltransferases to drive PD-L1 expression. On the metabolic side, SCFAs derived from gut microbiota and TCA cycle intermediates provide key substrates and cofactors for DNA methylation and histone acetylation or demethylation to remodel chromatin states via metabolite-epigenetic coupling. Together, these two arms coordinate epigenetic reprogramming to regulate immune responses and immune evasion. The following sections examine how this unified framework manifests in specific disease contexts and can be therapeutically exploited.

3 The Role of the Cytokine-Epigenetic Axis in Major Diseases

The "cytokine-epigenetic axis", a regulatory network comprising cytokines and epigenetic modifications, facilitates sustained functional reprogramming across various cellular levels. This encompasses immune cells, parenchymal cells, and stem cells, achieved through meticulous regulation of epigenetic mechanisms such as DNA methylation, histone alterations, and chromatin remodeling. Consequently, transient inflammatory stimuli are transformed into enduring changes in cellular function. Notably, this mechanism is deeply intertwined with the pathological advancement of autoimmune diseases, neurodegenerative disorders, neuropsychiatric conditions, metabolic diseases, and cancer. It stands at the core of these diseases' chronic progression, contributes to treatment resistance, and influences disease heterogeneity. This paper will methodically explore the specific mechanisms and recent research developments related to this axis within diverse pathological contexts, adopting a disease-centric viewpoint. *Figure 2* illustrates the extensive regulatory role of epigenetic modifications as a core mechanism in autoimmune and inflammatory diseases, metabolic disorders, neurodegenerative and psychiatric disorders, and cancer. In rheumatoid arthritis and systemic lupus erythematosus, cytokines such as TNF and IFN drive aberrant immune cell activation, chronic inflammation, and treatment resistance by reshaping DNA methylation patterns and glycolysis-associated epigenetic states. In Alzheimer's disease, Parkinson's disease, and schizophrenia, peripheral LPS stimulation or metabolites influence disease progression through regulation of microglial activation, neuroinflammation, and DNA methylation levels. In metabolic disorders such as obesity, type 2 diabetes, and NAFLD, inflammatory factors regulate metabolic homeostasis and liver infiltration via epigenetic–immune axes including SIRT1/ADAM17, p53/miR-22, and CD47-SIRPα. In tumor microenvironment, the NF-κB/p53/miR-34b-5p signaling axis and chronic antigen stimulation respectively promote tumor proliferation and $CD8^+$ T cell functional exhaustion through epigenetic reprogramming. In summary, this diagram reveals that epigenetic regulation serves as an intersection hub connecting immune, metabolic, neural, and oncologic networks, playing a critical role in the pathological mechanisms of various major diseases.

3.1 Autoimmune and Inflammatory Diseases

Autoimmune and inflammatory diseases are distinct pathological conditions that share a close relationship. Autoimmune diseases arise from the immune system's aberrant recognition and attack on self-antigens, while inflammatory diseases can be triggered by various factors such as infection, tissue damage, or immune dysregulation. These conditions often overlap in clinical practice, contributing to a shared pathological basis for chronic inflammatory damage. In both types of diseases, a dysregulated cytokine milieu drives epigenetic reprogramming of immune cells, which serves as the central mechanism underlying disease chronicity and persistent immune dysfunction.

Study has demonstrated that IFN-γ not only boosts pro-inflammatory gene expression and resistance to tolerance via the STAT1-IRF axis but also induces the "dismantling" of enhancers associated with anti-inflammatory and tissue repair genes by inducing the repressive histone mark H3K27me3 or downregulating the key transcription factor MAF, leading to sustained cellular function remodeling [36]. This identifies a dual

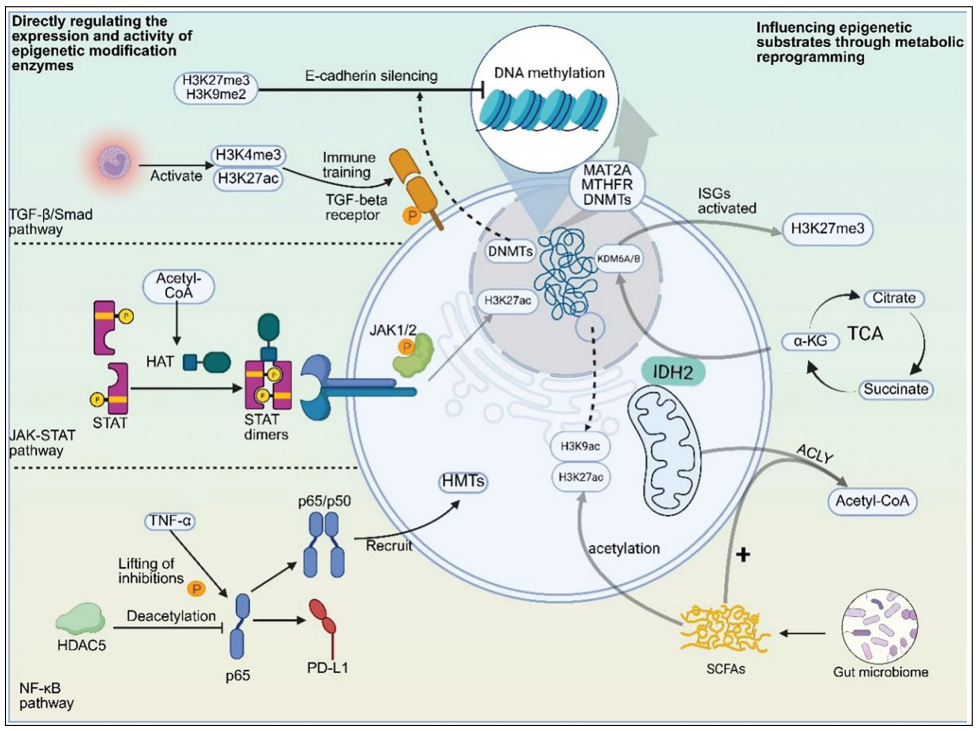

Figure 1: Core Mechanisms of Cytokine Regulation of Epigenetics. On the signaling side, the TGF-β/Smad, JAK-STAT, and NF-κB pathways directly regulate epigenetic enzyme activity. TGF-β/Smad promotes E-cadherin silencing and trained immunity through modulation of histone methylation and acetylation. The JAK-STAT pathway drives STAT acetylation and dimerization. Upon TNF-α stimulation, HDAC5-mediated deacetylation of NF-κB p65 is relieved, allowing p65/p50 nuclear translocation and recruitment of histone methyltransferases to drive PD-L1 expression. On the metabolic side, short-chain fatty acids derived from gut microbiota and TCA cycle intermediates provide key substrates and cofactors for DNA methylation and histone acetylation or demethylation, remodeling chromatin states via metabolite-epigenetic coupling. Together, these two arms coordinate epigenetic reprogramming to regulate immune responses and immune evasion. ACLY: ATP-citrate lyase; α-KG: alpha-ketoglutarate; DNMTs: DNA methyltransferases; HAT: histone acetyltransferase; HDAC5: histone deacetylase 5; HMTs: histone methyltransferases; IDH2: isocitrate dehydrogenase 2; ISGs: interferon-stimulated genes; JAK: Janus kinase; KDM6A/B: lysine demethylase 6A/B; MAT2A: methionine adenosyltransferase 2A; MTHFR: methylenetetrahydrofolate reductase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PD-L1: programmed death-ligand 1; SCFAs: short-chain fatty acids; STAT: signal transducer and activator of transcription; TCA: tricarboxylic acid; TGF-β: transforming growth factor-beta; TNF-α: tumor necrosis factor-alpha.

epigenetic strategy through which a single cytokine simultaneously activates and represses distinct gene programs at separate genomic loci. These studies precisely delineate the key pathways by which cytokine signaling induces epigenetic alterations that result in cellular functional reprogramming, offering a molecular basis for understanding the persistence of abnormal immune responses.

In the clinical course of autoimmune diseases such as rheumatoid arthritis, the regulatory role of the cytokine-epigenetic axis extends to multiple levels, including disease stratification, progression, and treatment response. Studies have shown that this axis not only drives immune activation and initiates disease but also contributes to the maintenance of pathological states and mediates therapeutic resistance. For example, interferon-α induces DNA demethylation reprogramming at enhancer regions in B cells and T cells from patients with early rheumatoid arthritis, creating a persistent inflammatory epigenetic memory associated with resistance to conventional therapy [37]. This finding is consistent with observations that an inflammatory microenvironment can induce alterations in DNA methylation within specific immune-regulatory regions of monocytes [38]. These epigenetic signatures are significantly associated with disease activity and prognosis, providing evidence at the cellular level for the long-term capacity of cytokines to shape the epigenome. At the therapeutic intervention level, blockade of tumor necrosis factor-α not only alleviated inflammatory symptoms but also systemically reversed the overall aberrant methylome in the peripheral blood of patients with rheumatoid arthritis. Moreover, pretreatment epigenetic signatures could predict patient responses to anti-TNF agents, revealing the reversibility and predictive value of this axis for therapeutic modulation [39]. Collectively, these findings highlight the central role of various cytokines in sustaining pathogenic phenotypes in the synovium and immune cells of rheumatoid arthritis by regulating HDACs, DNMTs, and noncoding RNA networks [40].

In addition, several studies have focused on specific immune cell types and revealed how the cytokine milieu shapes their epigenetic landscape to influence functional differentiation and therapeutic responsiveness. A Cell-type resolved analysis of whole blood methylomes showed that methotrexate treatment response was associated with dynamic changes in methylation within an enhancer region near KRT19 in $CD4^+$ T cells, $CD8^+$ T cells, and NK cells, suggesting that cytokines may modulate cell type-specific epigenetic marks to impact drug sensitivity [41]. Innate immune cells undergo persistent epigenetic and metabolic reprogramming upon inflammatory stimulation to form a "trained immunity" state,

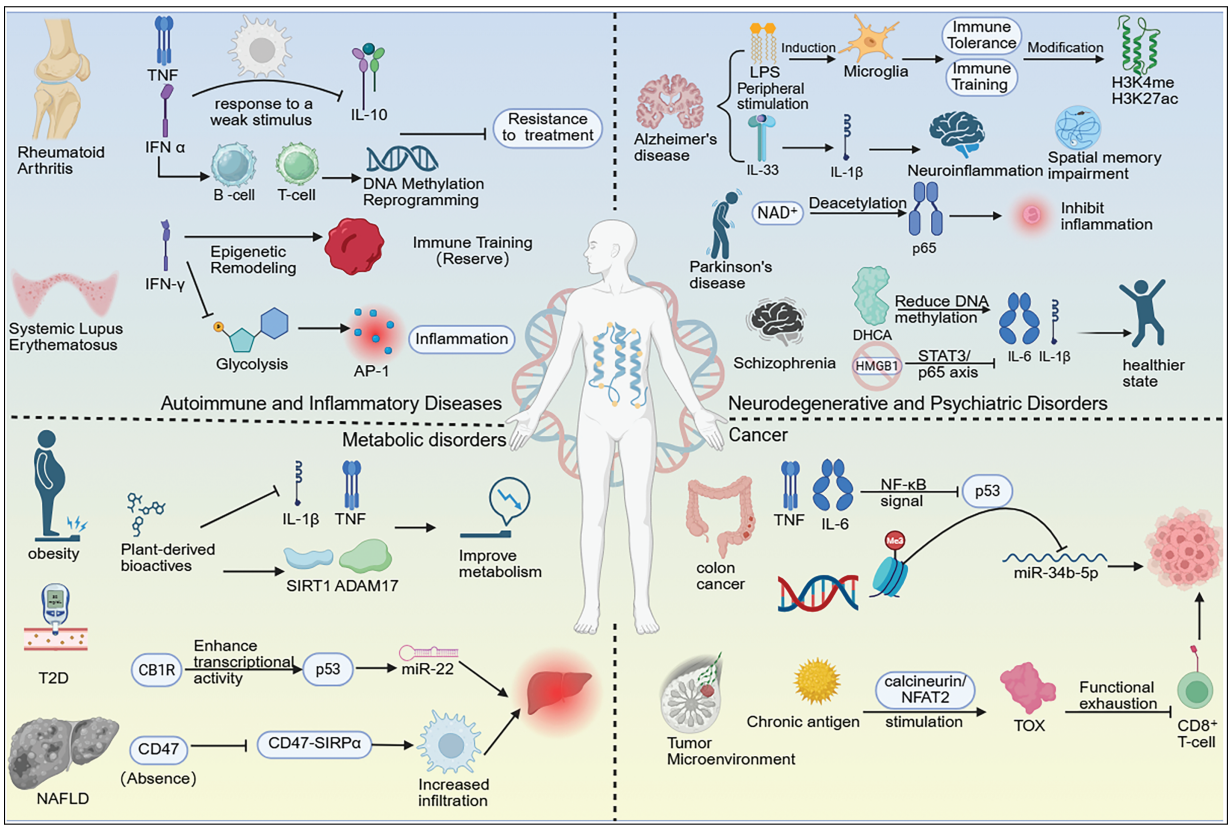

Figure 2: The role of the cytokine-epigenetic axis in major diseases. In autoimmune and inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus, cytokines including TNF and IFN reshape DNA methylation and glycolysis-associated epigenetic states, driving aberrant immune activation, chronic inflammation, and treatment resistance. In neurodegenerative and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, and schizophrenia, peripheral LPS stimulation or metabolites influence disease progression by regulating microglial activation, neuroinflammation, and DNA methylation levels. In metabolic disorders such as obesity, type 2 diabetes, and NAFLD, inflammatory factors regulate metabolic homeostasis and liver infiltration through epigenetic–immune axes including SIRT1/ADAM17, p53/miR-22, and CD47–SIRPα. In tumor microenvironment, the NF-κB/p53/miR-34b-5p axis and chronic antigen stimulation promote tumor proliferation and $CD8^+$ T cell exhaustion via epigenetic reprogramming. Overall, epigenetic regulation acts as an intersection hub connecting immune, metabolic, neural, and oncogenic networks across major diseases. AP-1: activator protein-1; CD: cluster of differentiation; DHCA: dehydroepiandrosterone derivative (or as contextually defined); H3K4me: histone H3 lysine 4 methylation; H3K27ac: histone H3 lysine 27 acetylation; HMGB1: high mobility group box 1; IFN: interferon; IL: interleukin; LPS: lipopolysaccharide; miR: microRNA; NAFLD: non-alcoholic fatty liver disease; NAD^+: nicotinamide adenine dinucleotide; NF-κB: nuclear factor kappa B; NFAT2: nuclear factor of activated T-cells 2; SIRPα: signal regulatory protein alpha; STAT3: signal transducer and activator of transcription 3; T2D: type 2 diabetes; TOX: thymocyte selection-associated HMG box; TNF: tumor necrosis factor.

providing a mechanistic explanation for maintenance of chronic inflammatory states [42]. Analysis of single-cell chromatin accessibility maps showed that distinct cellular states in rheumatoid arthritis synovium share a "chromatin super-state" controlled by transcription factors such as AP-1, suggesting that cytokines may maintain pathogenic cellular phenotypes through regulation of such conserved open chromatin patterns [43]. Together, these studies demonstrate that the cytokine–epigenetic axis plays a central role in regulating immune cell-specific responses, mediates therapy resistance, and sustains chronic inflammatory feedback loops.

The impact of this mechanism even extends to the stem cell level [44]. It has been shown that in chronic autoimmune inflammatory conditions such as systemic lupus erythematosus, a microenvironment consisting of cytokines like interferon-γ can induce persistent epigenetic reprogramming of long-lived hematopoietic stem cells. Animal models and transplantation experiments have revealed that hematopoietic stem cells exposed to such an inflammatory environment can serve as a long-term reservoir for "trained immunity". Although macrophages differentiated from these cells retain enhanced capacity for secretory activity of cytokines, their key glycolytic metabolic activity is uncoupled from this function. Mechanistically, this functional-metabolic disassociation arises from decreased chromatin accessibility at promoter regions of genes involved in glycolysis and the mTOR pathway in both hematopoietic stem cells and their myeloid progeny, while pro-inflammatory gene programs are independently activated via factors such as AP-1. This study demonstrates that the cytokine-epigenetic axis can program immune cells at their origin and drive disease chronicity and proposes a novel perspective that effector functions and supportive metabolic programs of immune cells can be dissociated at the epigenetic level under pathological conditions.

Current research is uncovering the complex regulatory networks of the cytokine-epigenetic axis and its translational potential in a broader range of immune cell types, disease spectrums, and molecular dimensions [45]. Studies have shown that various immune cells driven by an inflammatory microenvironment commonly exhibit dysregulation of DNA methylation, histone modification, and noncoding RNA expression

in rheumatoid arthritis; these reprogramming events collectively lead to functional disorders, and an integrated strategy for targeted intervention was proposed in this study. Research on systemic autoinflammation diseases highlighted that abnormalities in DNA methylation and miRNA are key to explaining phenotypic heterogeneity among patients with identical gene mutations, thereby constructing a gene-epigenome-environment interaction model [46]. Another study introduced the metabolic dimension into this axis, elucidating that metabolites such as ikoic acid and α-ketoglutarate can act as signaling molecules to influence immune cell differentiation by directly regulating the activity of epigenetic enzymes such as TET and HDAC, thus directly coupling cytokine-mediated metabolic reprogramming with epigenetic modifications [47]. A specific example was provided in studies of fibroblast-like synovial cells in rheumatoid arthritis [48], where the proinflammatory factor TGF-β was shown to upregulate CDH6 expression by increasing chromatin accessibility and H3K27ac modification, driving cell migration and survival. This revealed the epigenetic regulatory mechanism of this gene in this type of cell and its potential therapeutic value. These advances expand the scope of the cytokine-epigenetic axis at multiple levels, which together point to its role as a central hub for understanding disease mechanisms and developing new therapies.

3.2 Neurodegenerative Diseases and Neuropsychiatric Disorders

3.2.1 Neurodegenerative Diseases

Neurodegenerative diseases are a class of pathological conditions characterized by the progressive structural and functional loss of specific neuronal populations in the central nervous system. They often manifest clinically as cognitive decline or motor control disorders, with Alzheimer's disease and Parkinson's disease being typical examples [49,50]. Among their complex pathological networks, the cytokine milieu driven by chronic neuroinflammation is a key mechanism underlying the progressive deterioration of the disease through the induction of epigenetic reprogramming of glial cells. Studies have shown that microglia and other cells can undergo persistent epigenetic changes in response to central pathological stimuli, thereby maintaining pro-inflammatory states and accelerating neurodegeneration. However, it remains unclear whether and how peripheral immune signals could exert a lasting influence on brain pathology via such reprogramming [51].

To investigate this mechanism [52], the authors established models of microglial 'immune training' or 'immune tolerance' by administering single or repeated low-dose lipopolysaccharide (LPS) stimuli to mice. They showed that such peripheral immune experiences can alter the epigenetic landscape of microglial enhancers through remodeling H3K4me1 and H3K27ac modifications, which persist for at least six months and ultimately determine the degree of β-amyloid deposition in Alzheimer's disease models. The mechanism lies in the fact that the 'trained' state promotes proinflammatory and glycolytic metabolism in microglia via activation of pathways such as HIF-1α, thereby exacerbating plaque deposition; whereas the 'tolerant' state favors phagocytosis-related gene programs and enhances Aβ clearance. This study addresses the critical question of how peripheral inflammation achieves long-term directional regulation of central pathology, with its core innovation being the first *in vivo* demonstration that tissue-resident macrophages have functional innate immune memory and can directly shape neurodegenerative pathological outcomes. This establishes a complete causal chain of 'peripheral stimulation, microglial epigenetic reprogramming, disease modification', providing a new paradigm for intervention in neurodegenerative processes through immune reprogramming and demonstrating that peripheral inflammatory experiences can determine central neuropathology through microglial enhancer reprogramming. However, the mechanistic interpretation of the study still relies primarily on LPS as a single pathogen-associated molecular pattern, and the specific transcriptional regulatory networks linking particular histone modifications to downstream pathological phenotypes have not yet been fully elucidated, which constitutes the main limitation to current understanding of the precision of function along this axis.

The brain's endogenous cytokine network can also deeply shape the progression of AD pathology through direct or indirect epigenetic mechanisms [53]. One study found that direct injection of recombinant IL-33 into the mouse hippocampus activated microglia and promoted IL-1β expression, resulting in neuroinflammation and spatial memory deficits; This mechanism was blocked in IL-1α/β deficient mice, clarifying an independent pathogenic role for a local IL-33 and IL-1 axis in the hippocampus. Another study [54] found that astrocyte-derived IL-3 could reprogram microglia to enhance their ability to migrate to and clear Aβ plaques via upregulation of TREM2-dependent receptors, exerting a protective effect in disease models and revealing a positive example of functional reprogramming of microglia by cytokines. Further research [55] directly established an "epigenetic-cytokine" axis by finding that low DNA methylation upstream of CASP4 in AD drives its expression, which in turn promotes IL-1β release via a non-canonical inflammasome pathway to exacerbate Aβ deposition, constructing a clear pathway from epigenetic modification to inflammatory amplification. Another study identified KChIP3 as a key node whose expression is triggered by NLRP3, Caspase-1, and IL-1β inflammatory signaling and subsequently acts as a transcription factor to suppress synaptic genes and promote pro-inflammatory genes, amplifying both neuroinflammation and synaptic dysfunction in disease models [56]. These studies confirm from different perspectives that endogenous cytokine signaling can become a central driver of AD pathology by regulating the expression of key effector molecules such as IL-1β, CASP4, and KChIP3 or by directly reprogramming glial cell function. Their novelty lies in the direct link between cytokine action and specific epigenetic changes or transcriptional reprogramming, providing a new mechanism accounting for the persistence and specificity of neuroinflammation.

Neuroinflammation is also deeply embedded in a cytokine-epigenetic regulatory axis during the pathological progression of Parkinson's disease. Studies have shown that inflammatory activation of microglia is closely coupled with glycolytic reprogramming, and the activation of NAD^+ and SIRT1 pathways mediates deacetylation of key transcription factor p65 to inhibit expression of pro-inflammatory factors, which directly reveals the pathway by which metabolic changes influence inflammatory outcomes through epigenetic regulator SIRT1 [57]. Further studies found that pattern recognition receptor NLRC5 and transcription factor NF-κB1 can profoundly affect glial cell cytokines such as IL-1β and TNF-α at the transcription level by regulating signaling pathways including NF-κB. Among them, NF-κB1 has been shown to directly bind to and activate the promoter of inhibitory receptor CD200R1, providing an epigenetic explanation at the level of transcription factor-promoter interaction for how the cytokine environment is regulated via specific transcription programs [58,59]. Another study [60] more systematically proposed the "epigenetics and DAT endocytosis" axis, clarifying that pro-inflammatory cytokines such as IL-1β and TNF-α may regulate the expression of genes related to dopamine transporter function by influencing epigenetic mechanisms such as DNA methylation and histone modification, thereby converting inflammatory signals into persistent neuronal dysfunction. The above studies enriched our understanding of the "cytokine-epigenetic" axis in Parkinson's disease from multiple dimensions ranging from metabolic enzymes and transcription factors to chromatin modifications.

3.2.2 Neuropsychiatric Disorders

In contrast to neurodegenerative diseases, the core pathology of neuropsychiatric disorders is not characterized by a substantial structural loss of neurons. Instead, it is characterized by the functional dysregulation of circuits that govern affective, cognitive, and behavioral homeostasis. Clinical disorders within this category encompass depression, anxiety disorders, and schizophrenia. Although these two types of disorders vary in their pathological morphology, an increasing amount of evidence indicates that neuroinflammation and the cytokine-epigenetic regulatory axis it drives are also profoundly involved in the onset and maintenance of psychiatric symptoms.

Research [61] has shown that IL-1β knockdown in the hippocampus attenuates LPS-induced memory deficits and anxiety- and depressive-like behaviors in mice. The mechanism involved suppressed oxidative stress and neuroinflammation, as well as restored expression of neurotrophic factors such as brain-derived neurotrophic factor, suggesting a central role for IL-1β in these processes. In addition, developmental model studies have found that maternal immune activation leads to genome-wide remodeling of 5hmC and 5mC in offspring prefrontal cortex, thereby persistently upregulating genes associated with neuronal activity and inducing anxiety-like behaviours [62].

Further studies have elucidated microglial-specific signaling pathways, showing that high mobility group box 1 drives the release of proinflammatory factors such as IL-1β and IL-6 via activation of the STAT3 and p65 signaling axis to promote depressive-like behaviors [63]. In addition, maternal immune activation is closely associated with anxiety-like behavior in female offspring, which was strongly linked to upregulation of a long noncoding RNA, AU020206. This lncRNA increases cytokine production, such as IL-6 and IL-1β, in the brain through interferon regulatory factor and STAT1 signaling axis [64].

At the level of clinical translation, chronic inflammation markers based on DNA methylation were significantly associated with widespread brain structural abnormalities, suggesting that epigenetic mechanisms may mediate long-term effects of inflammation on brain structure [65]. Meanwhile, cross-diagnostic studies have shown that severity in mental disorders is correlated with specific peripheral inflammatory protein profiles, supporting the view that immune dysregulation serves as a transdiagnostic dimension for mental disorders [66]. A meta-analysis further identified key genes expressed in peripheral blood leukocytes whose altered expression was associated with major depressive disorder and thus linked genetic risk to neuroimmune conversational mechanisms [67]. Numerous studies suggest that cytokines can persistently alter the expression of neuroimmunological- and synaptic plasticity-related genes by influencing epigenetic mechanisms such as DNA methylation, histone modification, and noncoding RNAs, thereby playing an important role in the pathological processes of psychiatric disorders.

3.3 Metabolic Diseases

Metabolic diseases, characterized by an imbalance in energy metabolism, include chronic pathological conditions such as obesity, type 2 diabetes and non-alcoholic fatty liver disease. The incidence of these diseases is increasing with changes in lifestyle. Although metabolic disorders are the main manifestations of these diseases, more and more studies have shown that chronic low-grade inflammation and epigenetic regulation play a central role in their pathogenesis [68,69]. Recent studies have found that inflammatory cytokines interact closely with epigenetic mechanisms to form the "cytokine-epigenetic axis", which promotes the imbalance of metabolic homeostasis.

The liver is a key organ in which this regulatory axis exerts its effects. Studies have shown that under long-term high-fat diet conditions, CD47 deficiency inactivates the CD47–SIRPα signaling pathway, leading to increased macrophage infiltration, enhanced NF-κB activation and upregulation of proinflammatory factors such as IL-1β and TNF-α, while downregulating PPARα and SIRT1 expression, thereby synergistically exacerbating steatohepatitis [70]. Another important pathway involves NAD^+ metabolism; inhibition of NAMPT, the rate-limiting enzyme for its synthesis, reduces intracellular NAD^+ levels, thereby inhibiting the deacetylase activity of SIRT1 and causing activation of SREBP1, a master regulator of lipid synthesis [71]. In relation to this, miR-122, which is highly expressed in

nonalcoholic fatty liver disease, can directly target and inhibit Sirt1 mRNA, thereby suppressing downstream LKB1 and AMPK signaling pathways and promoting lipogenesis-related gene expression [72]. However, studies using hepatocyte-specific TNFR1 knockout models found that although loss of TNFR1 in hepatocytes improved insulin resistance, it did not alleviate hepatic steatosis, inflammation and fibrosis induced by a high-fat and high-fructose diet [73], suggesting that regulation of liver inflammation involves complex cell type specificity.

Environmental factors can have long-term effects on metabolism through epigenetic mechanisms. Studies have shown that activation of peripheral cannabinoid receptor 1 enhances the transcriptional activity of p53, which in turn upregulates miR-22; the latter directly targets and inhibits SIRT1 and PPARα, leading to dysregulation of hepatic lipid metabolism [74]. A feedback regulatory loop exists among AMPK, inflammation, and epigenetics. The pro-aging miR-146a reduces NAD^+ levels and SIRT1 activity by specifically inhibiting NAMPT, while AMPK activation suppresses NF-κB to downregulate miR-146a [75]. Relevant studies have elucidated the mechanism underlying the formation of epigenetic memory: a high-salt diet persistently increases histone H3K27 acetylation levels at the promoter region of the Sirt3 gene in the liver [76]. This study showed that a dietary factor could induce sustained epigenetic changes that maintain hepatitis independent of the original dietary exposure. High levels of H3K27ac inhibited the binding of transcription factor NRF2 to the promoter, resulting in persistent low expression of SIRT3, which in turn triggered hepatosteatosis, inflammation, and ultimately cardiovascular damage.

This axis also plays an important role in diabetes and its complications. Study has shown that *Berberis brandisiana* can upregulate SIRT1, downregulate ADAM17, reduce TNF-α and IL-6 levels, and comprehensively improve the metabolic and inflammatory state of diabetic rats [77]. Clinical studies have found that long-term mortality risk in patients with type 2 diabetes is significantly associated with accelerated aging derived from DNA methylation age and inflammatory protein methylation predictors such as CXCL10 and CRP [78]. High glucose or renal ischemia stimuli can induce persistent histone modifications at TNF and TGF-β1 gene loci (including H3K4me3 and H3K9ac), forming a "metabolic memory" or "hypoxic memory", which maintains pro-inflammatory and pro-fibrotic programs even after the initial stimulus disappears [79,80].

3.4 Cancer

Cancer is a complex disease characterized by abnormal cell proliferation, genomic instability and the ability to undergo malignant transformation. Its initiation and progression are not only determined by genetic alterations of oncogenes and tumor suppressor genes but also significantly influenced by inflammatory signals and epigenetic regulatory networks within the TME. During cancer progression, persistent cytokine stimulation from the chronic inflammatory milieu can induce epigenetic reprogramming in both tumor cells and infiltrating immune cells, thereby translating inflammatory cues into stable changes in gene expression that promote immune evasion, metastasis, colonization and therapeutic resistance. The cytokine-epigenetic axis represents an important route through which extracellular signaling is translated into sustained intracellular changes in gene expression in the TME, playing a key role in driving tumor progression, immune evasion and therapy resistance.

The cytokine-epigenetic axis plays a key role in the development of T cell exhaustion, which is a central barrier to antitumor immunity [81]. It has been shown that under chronic antigen stimulation, calcineurin and NFAT2 signaling induce expression of the transcription factor TOX [82]. In turn, TOX programs $CD8^+$ T cell exhaustion by regulating chromatin accessibility at genes associated with exhaustion and effector genes through recruitment of chromatin remodeling complexes. This finding identified TOX as a transcription factor that actively programs the epigenetic landscape of exhausted T cells.

At the level of tumor cells themselves, inflammatory cytokines can drive malignant progression through multiple epigenetic pathways. In colitis-associated cancers [83], for example, the inflammatory cytokines IL-6 and TNF-α suppress p53 function via NF-κB signaling and cooperate with DNA methylation to downregulate miR-34b-5p expression, thereby relieving its inhibition on c-MYC and activating downstream oncogenic pathways. Further studies have shown that inflammatory mediators prostaglandin E2 and IL-6 in the metastatic niche induce expression of the DNMT3B by activating NF-κB and STAT3 signaling [84]. DNMT3B in turn activates multiple metastasis-promoting pathways through genome-wide reprogramming of methylation patterns, facilitating the establishment of tumor cells at distant organ sites. Notably, in breast cancer, DNMT3B expression is heterogeneous within primary tumors; highly expressing subpopulations exhibit greater metastatic potential, and this expression is upregulated by the prostaglandin E2-STAT3-NF-κB inflammatory signaling axis [85].

Tumor-associated fibroblasts, a key component of the TME, are significantly regulated by the cytokine-epigenetic axis. A study has shown that these fibroblasts can activate the JAK-STAT pathway through the secretion of LIF, leading to the acetylation of STAT3 and subsequent epigenetic silencing of the SHP-1 gene [86]. Further research has demonstrated that TGF-β1 induces the deposition of repressive modifications H3K9me3 and H3K27me3 in tumor-associated fibroblasts by activating histone methyltransferases G9a and EZH2 [87]. This process results in the silencing of the transcription of chemokines CXCL9 and CXCL10, thereby inhibiting the recruitment of T cells to tumor tissues. The cytokine-epigenetic axis also plays an important role in shaping the function of different immune cell populations. Studies have shown that TGF-β and IL-2 regulate Foxp3 transcription and histone acetylation status of its enhancer regions through the SMAD and STAT5 pathways, thereby affecting the differentiation and function of regulatory T cells [88]. In glioma research, it was found

that TGF-β and IL-10 secreted by myeloid suppressor cells can affect DNA methylation and histone modification to silence the expression of immune-related genes [89]. It is worth noting that endogenous PD-L1 in lung cancer cells can enter the nucleus, bind to phosphorylated Stat3, and co-localize with promoters of genes such as IL-6 to enhance their transcription and promote immunosuppression mediated by myeloid-derived suppressor cells [90,91]. Conversely, blocking the interaction between GARP and TGF-β1 can lift the transcriptional inhibition of the E-selectin gene by TGF-β1, thus promoting T cell infiltration [92]. In hematologic malignancies, oncogenes activated by STAT5 induce OSM expression; OSM acts on OSM receptors on stroma cells to activate STAT3, reprogram their metabolic state and cytokine secretion profile, and shape an immunosuppressive microenvironment [93].

The cytokine-epigenetic axis is also a key driver of resistance to various therapies. It has been shown that circadian dysregulation, which leads to increased IL-6 levels and is associated with Per2 gene promoter downregulation by methylation, promotes chemoresistance in ovarian cancer through activation of the PI3K and Akt pathways [94]. Bioinformatic studies suggest that high PRC1 expression correlates with a TH2 type cytokine milieu and the methylation status of specific CpG sites and may be involved in this regulatory network in an indirect manner [95]. A relevant review highlights that immunosuppressive cytokines such as TGF-β can induce epigenetic silencing of antigen presentation-related genes while epigenetic regulators such as EZH2 can reciprocally shape a suppressive cytokine milieu [96]. In A recent study on melanoma, it was demonstrated that the transcriptional coactivator IκBζ recruits HDAC3 and EZH2 to the promoter regions of chemokines such as CXCL9 and CXCL10 where they mediate histone deacetylation and methylation to suppress their expression, resulting in immune cell exclusion and anti-PD-1 resistance [97].

As shown in *table 1*, the cytokine-epigenetic axis exhibits highly consistent patterns of action across autoimmune diseases, neurodegenerative diseases, neuropsychiatric disorders, metabolic disease and cancer. Although pathological features and affected cell types differ widely between these disease classes, core mechanisms of this axis are shared. A pathological cytokine milieu establishes persistent functional reprogramming at multiple levels including immune cells, parenchymal cells and stem cells by regulating epigenetic mechanisms such as DNA methylation, histone modifications and chromatin accessibility. This process translates transient inflammatory stimuli into long-term changes in cellular function. This reprogramming can manifest either as sustained amplification and maintenance of pro-inflammatory states or as profound suppression of anti-inflammatory repair functions. Together, these processes drive chronic disease progression, mediate treatment resistance and shape clinical heterogeneity of the disease.

It is important to note that this axis possesses the crucial attribute of bidirectional reversibility. Targeted interventions against pathological cytokines or their downstream epigenetic regulatory factors can, to a certain degree, reverse the established abnormal epigenetic imprinting and restore normal cellular function. This characteristic offers a robust theoretical foundation for the development of new therapeutic strategies. In the future, through a comprehensive elucidation of the finely-tuned regulatory network of the cytokine and epigenetic axis in various diseases, it is anticipated that effective intervention in disease progression can be achieved, thus paving the way for novel precision treatment methods centered on epigenetic reprogramming.

4 Targeted Treatment Strategies and Their Significance

4.1 Combined or Synergistic Treatment Strategies

Emerging therapeutic strategies targeting the cytokine-epigenetic axis offer a novel approach to overcome treatment barriers in cancer and inflammatory diseases. The progression and development of drug resistance in these conditions are often linked with abnormal activation of cytokine networks and significant disruptions in epigenetic regulation. This dual-targeted strategy, which simultaneously addresses gene transcription and signal transduction, aims to surpass the limitations of monotherapy, thereby providing new potential for improving clinical outcomes in refractory diseases.

In the development of therapeutic strategies for hematologic malignancies, this approach has shown considerable promise in various contexts. For example, in multiple myeloma, the combination of HDAC inhibitor palbociclib with bortezomib and dexamethasone effectively induces tumor cell apoptosis through synergistic effects involving epigenetic reprogramming and NF-κB signaling inhibition [98]. Subsequent studies have confirmed that combining HDAC inhibitors or DNA methyltransferase inhibitors (DNMTis) with chemotherapy or tumor vaccines can reverse the epigenetic silencing of antigen-presentation-related genes in tumor cells, thereby enhancing immune recognition and clearance efficiency [99,100]. In myelofibrosis treatment, the combination of BET inhibitor pelabresib and JAK inhibitor ruxolitinib significantly improves splenomegaly and reduces pro-inflammatory cytokine levels by simultaneously inhibiting both inflammatory gene transcription and JAK-STAT signaling pathway activation [101].

The Treatment strategy for solid tumors also reflects the core value of this axis. In hepatocellular carcinoma and gastric cancer, HDAC inhibitors elevate histone acetylation levels across the genome and at specific loci, leading to the up-regulation of chemokine expression, such as CXCL9 and CXCL10. These chemokines promote the infiltration of $CD8^+$ T cells into the TME and significantly enhance the anti-tumor efficacy of PD-1 and PD-L1 blockade [102,103]. This mechanism reveals a synergistic relationship between epigenetic regulation and immune checkpoint blockade.

The application of this combined strategy has been extended from cancer treatment to the field of infectious diseases. Studies have demonstrated that Panobinostat in combination with interferon α-2a can selectively eliminate latent HIV infection by establishing a synergistic “epigenetic activation-immune

Table 1
The role of the cytokine-epigenetic axis in various diseases

Disease type	Key molecules	Mechanism	References
Autoimmune and Inflammatory Diseases	IFN-α	Induces DNA methylation reprogramming in B-cell or T-cell enhancer regions, leading to the formation of inflammatory memory associated with treatment resistance	[37]
	IFN-γ	Enhances pro-inflammatory genes via the STAT1/IRF axis; causes the "disassembly" of anti-inflammatory gene enhancers by inducing H3K27me3 or downregulating MAF	[36]
	TNF-α	Blocking the TNF-α systemically reverses abnormal methylation patterns in the peripheral blood of RA patients	[39]
	TGF-β	In RA fibroblast-like synoviocytes, TGF-β upregulates CDH6 expression by increasing H3K27ac	[48]
	AP-1	Maintain the pathogenic cell phenotype	[43]
Neurodegenerative Diseases and Neuropsychiatric Disorders	LPS	Peripheral LPS stimulation determines the extent of Aβ deposition by reshaping the microglial landscape	[52]
	IL-33	Local IL-33 in the hippocampus induces neuroinflammation and memory impairment by activating microglia and promoting IL-1β	[53]
	IL-3	IL-3 derived from astrocytes enhances the migration and clearance of Aβ plaques by microglia through upregulation of TREM2	[54]
	CASP4	Low methylation of the DNA upstream of the CASP4 gene in AD drives its expression, promotes IL-1β release via a non-canonical inflammasome, and exacerbates Aβ deposition	[55]
	NFKB1	NFKB1 binds to and activates the promoter of the inhibitory receptor CD200R1, thereby regulating the inflammatory state of glial cells	[59]
	IL-1β	IL-1β knockdown in the hippocampus alleviates LPS-induced anxiety- and depression-like behaviors and restores BDNF expression	[61]
	HMGB1	Activation of the STAT3/p65 axis drives the release of IL-1β and IL-6, promoting depression-like behavior	[63]
Metabolic Diseases	NAMPT	Inhibition of NAMPT reduces NAD^+, which in turn inhibits SIRT1, leading to the activation of the lipid synthesis factor SREBP1	[71]
	miR-122	Targeted inhibition of Sirt1 mRNA promotes adipogenesis	[72]
	Sirt3	A high-salt diet continuously increases H3K27ac levels in the Sirt3 promoter region of the liver, inhibits NRF2 binding, and results in sustained low Sirt3 expression	[76]
	H3K4me3/H3K9ac	High sugar or renal ischemia stimulates persistent histone modifications at pro-inflammatory or pro-fibrotic gene loci, creating a metabolic memory	[79,80]
	IL-6/TNF-α	NF-κB inhibits p53, which, in synergy with DNA methylation, downregulates miR-34b-5p, thereby lifting the repression of c-MYC	[83]
Cancer	TGF-β1	Activation of G9a/EZH2 leads to the deposition of H3K9me3/H3K27me3, silencing CXCL9/CXCL10 and inhibiting T-cell recruitment	[87]
	TGF-β, IL-10	Silences immune-related genes by influencing DNA methylation and histone modifications	[89]
	PD-L1	PD-L1 binds to p-Stat3 within the nuclei of tumor cells, enhancing the transcription of IL-6 and other molecules, thereby promoting MDSC-mediated immune suppression	[91]
	TGF-β1	Lift the transcriptional repression of the E-selectin gene by TGF-β1, thereby promoting T-cell infiltration	[92]

Note: IFN-α: interferon-alpha; IL-10: interleukin-10; STAT1: signal transducer and activator of transcription 1; IRF: interferon regulatory factor; H3K27me3: trimethylation of histone H3 at lysine 27; MAF: musculoaponeurotic fibrosarcoma oncogene homolog; TNF-α: tumor necrosis factor-alpha; RA: rheumatoid arthritis; TGF-β: transforming growth factor-beta; H3K27ac: acetylation of histone H3 at lysine 27; CDH6: cadherin-6; AP-1: activator protein-1; LPS: lipopolysaccharide; Aβ: amyloid beta; IL-33: interleukin-33; IL-1β: interleukin-1β; IL-3: interleukin-3; TREM2: triggering receptor expressed on myeloid cells 2; CASP4: caspase 4; AD: Alzheimer's disease; NFKB1: nuclear factor kappa B subunit 1; CD200R1: CD200 receptor 1; BDNF: brain-derived neurotrophic factor; HMGB1: high mobility group box 1; STAT3: signal transducer and activator of transcription 3; p65: nuclear factor kappa B p65 subunit; NAMPT: nicotinamide phosphoribosyltransferase; NAD+: nicotinamide adenine dinucleotide; SREBP1: sterol regulatory element-binding protein 1; miR-122: microRNA-122; Sirt1: sirtuin 1 (gene); Sirt3: sirtuin 3; NRF2: nuclear factor erythroid 2-related factor 2; H3K4me3: trimethylation of histone H3 at lysine 4; H3K9ac: acetylation of histone H3 at lysine 9; IL-6: interleukin-6; p53: tumor protein p53; c-MYC: MYC proto-oncogene; TGF-β1: transforming growth factor-beta 1; G9a: euchromatic histone lysine methyltransferase 2; EZH2: enhancer of zeste homolog 2; H3K9me3: trimethylation of histone H3 at lysine 9; CXCL9: C-X-C motif chemokine ligand 9; CXCL10: C-X-C motif chemokine ligand 10; PD-L1: programmed death-ligand 1; p-Stat3: phosphorylated signal transducer and activator of transcription 3; MDSC: myeloid-derived suppressor cell.

clearance" axis, providing new insights into functional cure strategies [104].

In the adoptive cell immunotherapy field, this strategy has shown unique value *in vitro*. By combining mTOR inhibitors with interferon-α to genetically reprogram T cells *ex vivo*, it is possible to specifically induce their differentiation into functionally enhanced Th1 cytokine profile cells (RAPA-201 cells). This

Table 2
Synergistic treatment strategies targeting the Cytokine-Epigenetic axis

Disease area	Treatment strategies	Mechanisms or pathways	References
Multiple myeloma	Panobinostat + Bortezomib + Dexamethasone	Regulates chromatin structure and synergistically induces apoptosis	[98]
	RAPA-201 ± low-intensity chemotherapy	Enhance the antitumor activity of T cells	[105]
Advanced colorectal cancer	Guadecitabine + GVAX vaccine + cyclophosphamide	Enhance tumor antigen expression and synergistically enhance T-cell recognition	[100]
Myelofibrosis	Pelabresib + Ruxolitinib	Pelabresib and ruxolitinib inhibit BRD4-mediated downregulation of pro-inflammatory cytokine transcription and synergistically inhibit JAK-STAT signaling	[101]
	Panobinostat + Ruxolitinib	Inhibiting JAK-STAT signaling reduces pro-inflammatory cytokines and regulates the expression of fibrosis- and inflammation-related genes	[106]
Hepatocellular carcinoma	CXD101+ PD-1/PD-L1 Inhibitor	Enhanced IFN-γ/STAT1 signaling and chromatin accessibility	[102]
Stomach cancer	HDACi + PD-L1 inhibitor	Restore histone acetylation levels and re-engage $CD8^+$ T cells	[103]
Latent HIV-1 infection	Panobinostat + pegylated IFN-α2a	Increased integration sites and immune clearance	[104]
NK/T-cell lymphoma	HDACi + PD-1 inhibitor	Upregulates CXCL9/CXCL10 expression, promotes $CD8^+$ T cell infiltration, and synergistically enhances IFN-γ signaling	[107]
	Chidamide + JAK inhibitor	Restore drug sensitivity	[108]
Solid tumor	HDACi + PD-1/PD-L1 inhibitors ± cytokine modulators	Upregulates the expression of immune molecules and modulates PD-L1, synergistically enhancing immune cell function	[109]

Note: HDACi: histone deacetylase inhibitor; JAKi: Janus kinase inhibitor; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; IFN-γ: interferon-γ; CXCL9: C-X-C motif chemokine ligand 9; CXCL10: C-X-C motif chemokine ligand 10; STAT1: signal transducer and activator of transcription 1; BRD4: bromodomain-containing protein 4; GVAX: granulocyte-macrophage colony-stimulating factor-secreting tumour vaccine.

cellular product induced significant clinical remissions in relapsed and refractory multiple myeloma, demonstrating that synergy between cytokines and epigenetic regulation can be achieved at the level of cell manufacturing [105].

As shown in *table 2*, several combinatorial therapeutic strategies targeting the cytokine-epigenetic axis have already entered clinical investigations covering a wide range of fields including hematologic malignancies, solid tumors, infectious diseases and cellular therapy, thus providing systematic clinical evidence to understand the translational value of this axis.

4.2 Precision and Personalized Medicine

In the immunotherapy of solid tumors, stratifying patients based on specific cytokine profiles and epigenetic characteristics in the TME has become a key approach to precision medicine. In particular, an exhausted CD8-positive T cell signature comprising chemokine genes CCL5, CXCL9, and CXCL13 can effectively predict the response of hepatocellular carcinoma patients to anti-PD-1 or anti-PD-L1 therapy. This signature score was negatively correlated with WNT or β-catenin pathway activity, revealing the underlying mechanism by which abnormalities in tumor cell epigenetics affect treatment efficacy through shaping an inhibitory cytokine milieu [110]. Furthermore, researchers constructed a three-gene immune activation signature comprising CXCL10, IDO1, and IFI44L [111]. This signature reflects the interferon signaling axis downstream of DNA damage response deficiency and can effectively predict patient responses to immune checkpoint blockade therapy. Subsequent multicohort analysis further revealed that a predictive model comprising M1 macrophage-derived chemokine CXCL9 and RNA epigenetic modification enzyme APOBEC3G was significantly associated with better immunotherapeutic response when highly expressed [112]. In cholangiocarcinoma, high CXCL9 expression is associated with favorable responses to chemotherapy combined with immunotherapy, while loss-of-function mutations in the epigenetic regulator ARID1A are associated with poorer prognosis and an immunosuppressive microenvironment, suggesting that integrating cytokine expression with epigenetic features enables more precise patient stratification [113].

At the therapeutic strategy level, targeted intervention in cytokine signaling pathways combined with epigenetic regulation provides a new approach to improve the efficacy of immunotherapy. In metastatic uveal melanoma, clinical studies on HDAC inhibitor entinostat plus pembrolizumab have shown that epigenetic drugs can remodel the immune

microenvironment by upregulating tumor antigen presentation and regulating secretion of suppressive immune cells and their associated cytokines IL-10 and TGF-β, thereby enhancing the antitumor effects of PD-1 inhibitors [114]. Similarly, in the treatment of myelofibrosis, the BET inhibitor palprecelib plus JAK inhibitor ruxolitinib simultaneously inhibited both the cytokine JAK-STAT pathway and the epigenetic BET or NF-κB axis, significantly reducing levels of proinflammatory cytokines such as IL-6 and IL-8 and improving the clinical course of myelofibrosis [101].

The development of non-invasive or minimally invasive biomarkers that integrate multidimensional information is a key approach to achieving personalized therapy. Analysis of the liquid immune profile based on peripheral blood immune cell subsets revealed that protective plasmacytoid dendritic cells and NKT cells were associated with type I interferon production and Th1 cytokines, respectively, whereas PD-1$^+$ CD8$^+$ T cells, which are risk factors, corresponded to an environment rich in inhibitory cytokines. This profile was able to predict patient survival independently [115]. In hepatocellular carcinoma, CD38 has been identified as a co-exhaustion marker for CD8$^+$ tissue-resident memory T cells [115]; its high expression depletes NAD$^+$, thereby inhibiting sirtuin deacetylase activity and inducing metabolic and epigenetic levels of T cell dysfunction. This suggests that combining a CD38 inhibitor with an anti-PD-1 agent could be useful for personalized therapy [116].

4.3 Reprogramming Disease Memories

Targeting the cytokine-epigenetic axis provides a new dimension to reverse pathological processes by directly erasing or rewriting disease-associated cellular memory states through intervention in key epigenetic nodes and downstream cytokine signaling. Studies have shown that BRD4 maintains the differentiated state of CD8-positive T cells by regulating terminal effector T cell-specific superenhancers; its inhibition can shift these cells toward memory precursor cells, thus presenting an epigenetic target for reversing functional memory of T cells [117]. Further studies have found that EGFR signaling promotes secretion of chemokines such as CCL2 and CCL5 by upregulating ILT4, thereby contributing to immunosuppressive microenvironmental memory. Targeting ILT4 effectively disrupted this axis and enhanced the antitumor efficacy of PD-L1 inhibitors [118]. In addition, using the TME evaluation tool TMEscore, it was suggested that epigenetic mechanisms including TGF-β signaling, IDO1-mediated kynurenine metabolism, and DNA methylation are closely related to the formation of immunosuppressive memory states [119].

In both hematologic and solid tumors, the cytokine-epigenetic axis is particularly important in regulating disease memory. In acute myeloid leukemia, leukemic stem cells integrate the ATF4 stress axis, NKG2D immune escape axis, and HOXA9 and MEIS1 transcriptional memory axis to synergistically maintain their stemness and drug resistance memory [120]. In triple negative breast cancer, MYC epigenetically silences STING, thereby inhibiting downstream chemokine expression and impairing T cell recruitment; MYC inhibition can reverse this state and enhance immune cell infiltration, but this strategy remains at the pre-clinical exploration stage [121]. Phase Ib clinical trial of colorectal cancer showed that a DNA methylation inhibitor combined with an HDAC inhibitor and PD-1 antibody could reduce intratumoral regulatory T cells and regulate the immunosuppressive microenvironment, but the clinical response was limited, suggesting that the combination strategy needs further optimization [122].

Recent preclinical investigations further explored strategies to reprogram immune cell memory through the cytokine-epigenetic axis. It has been shown that the combined use of DNA demethylating agents and HDAC inhibitors can reverse M2 tumor-associated macrophages into an M1-like phenotype by upregulating miR-7083-5p expression, thereby altering their cytokine secretion profile and disrupting a tumor-promoting memory state [123]. In CAR T cell models, Class I HDAC inhibitors were found to promote differentiation towards a central memory phenotype and reduce exhaustion marker expression via enhanced H3K27 acetylation and activation of Wnt/β-catenin pathways, resulting in improved capacity for cytokine secretion and persistence [124]. Other studies have suggested that mature migratory dendritic cells identified in human melanoma specimens may support T cell memory features through secretion of cytokines such as IL-15 and whose abundance is significantly associated with patient response to immune checkpoint inhibitors and improved survival [125]. Taken together, these findings illustrate the potential of cytokine-based epigenetic reprogramming but the strategies outlined remain largely experimental or preclinical; the ability to durably erase disease-associated memory in patients has not been established. *Figure 3* integrates the three therapeutic concepts discussed above. Combination therapy illustrates how combining epigenetic modifiers (HDACi/DNMTi) with ICI or JAKi enhances tumor immunogenicity and effector cell recruitment. Personalized treatment shows how biomarker-directed stratification (APOBEC3G, CXCL9, ARID1A) and exhaustion-based selection can direct alternative therapies. Reprogramming memory depicts a transition from a PD-1$^+$/IL-10/TGF-β-enriched pathological state to a reprogrammed memory pool where BETi/HDACi restore T cell function, promote M1 polarization, and induce IFN-γ/IL-15 providing a mechanism for durable immune memory.

4.4 Feasibility of Treatment Strategies

Relevant research in recent years has provided evidence supporting the therapeutic feasibility of targeting the "cytokine-epigenetic axis" from delivery systems to mechanistic foundation.

In terms of drug delivery, Schelker et al. demonstrated the feasibility of co-delivery of HDACIs and TKIs via liposome to maintain a synergistic ratio *in vivo* [126]. Others have elucidated mechanisms by which DNMT inhibitors and HDAC inhibitors can remodel the immune microenvironment through induction of immunogenic cell death in tumor cells, activation of

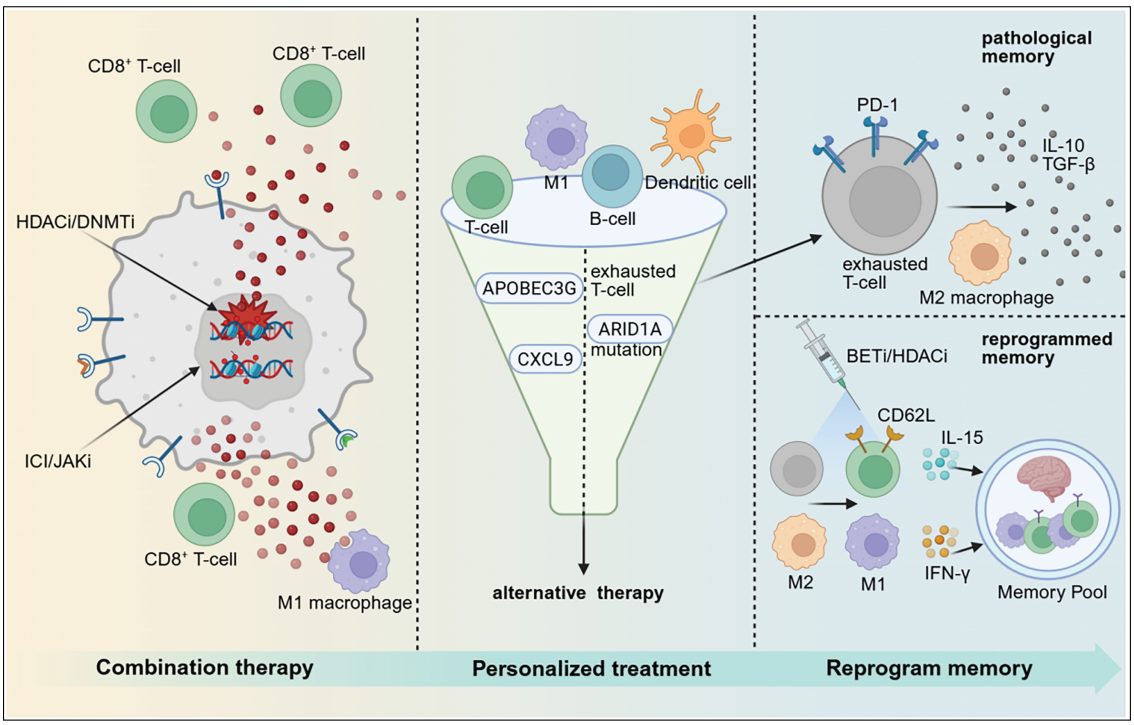

Figure 3: Therapeutic Strategies Targeting the Cytokine-Epigenetic Axis. Combination therapy involves combining epigenetic modifiers (HDACi/DNMTi) with ICI or JAKi to enhance tumor immunogenicity and effector cell recruitment. Personalized treatment uses biomarker-directed stratification (APOBEC3G, CXCL9, ARID1A) and exhaustion-based selection to direct alternative therapies. Reprogramming memory illustrates a transition from a PD-1^{+}/IL-10/TGF-β-enriched pathological state to a reprogrammed memory pool, where BETi/HDACi restore T cell function, promote M1 polarization, and induce IFN-γ/IL-15, providing a mechanism for durable immune memory. HDACi: histone deacetylase inhibitor; DNMTi: DNA methyltransferase inhibitor; ICI: immune checkpoint inhibitor; JAKi: Janus kinase inhibitor; APOBEC3G: apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G; CXCL9: C-X-C motif chemokine ligand 9; ARID1A: AT-rich interaction domain 1A; PD-1: programmed cell death protein 1; TGF-β: transforming growth factor-β; BETi: bromodomain and extra-terminal motif inhibitor; CD62L: L-selectin; IFN-γ: interferon-γ; M1/M2: type 1/type 2 macrophage.

dendritic cells, inhibition of the function of MDSCs and Tregs, and lifting HDAC3-mediated suppression of cytotoxic programs in CD8^{+} T cells, as well as reviewed epigenetic regulatory mechanisms for key cytokines such as IFN-γ, IL-2, and IL-12 [127]. Recent advances in targeted drug delivery have begun to address this challenge. For instance, a rationally designed nanocarrier platform was developed for the targeted co-delivery of the epigenetic drug CM-272 to tumor cells and the small molecule inhibitor Ibrutinib to myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment [128]. This study demonstrates that precise, cell-type-specific delivery of epigenetic agents is clinically feasible. Together, these findings support the viability of therapeutic strategies targeting the cytokine-epigenetic axis.

4.5 Current Challenges and Limitations

Combined strategies targeting the cytokine-epigenetic axis have shown promise in theoretical studies and early clinical trials, but their clinical translation is still challenging. This difficulty stems not only from the inherent complexity of both cytokine networks and epigenetic regulatory systems, but also from the unpredictability introduced by their interactions, which greatly impact treatment efficacy, safety, and precision.

The complexity and functional redundancy of cytokine networks are the main obstacles to precise intervention. As a highly interconnected and functionally overlapping dynamic network, the cytokine system often involves a single cytokine in multiple signaling pathways, with complex synergistic or antagonistic relationships between different cytokines. This characteristic means that blocking a specific cytokine may activate compensatory bypasses, leading to suboptimal treatment outcomes. For example, although the combination of HDAC inhibitors and JAK inhibitors can reduce pro-inflammatory cytokine levels such as IL-8 and MCP-1 in myelofibrosis treatment, the correlation between these changes and clinical symptom improvement remains unclear, suggesting the existence of untargeted compensation pathways or more intricate network regulatory mechanisms [108]. In addition, the cytokine profile within the TME exhibits significant spatiotemporal heterogeneity. In hepatocellular carcinoma, lung metastases have higher CD8-positive T cell exhaustion scores than primary liver cancer, indicating that different organ microenvironments have unique cytokine profiles [110]. Most patients with metastatic uveal melanoma present with liver metastases, which may affect the representativeness of efficacy evaluations [114]. In gastric cancer, combined blockade of TGF-β and IL-1β can reprogram myeloid cell immune training in the TME, yet chronic *H. pylori* infection means that complete inhibition of IL-1β-driven training could weaken mucosal immunity against secondary infection [129]. The dynamic evolution of cytokine profiles during treatment further complicates the selection

of intervention targets. Intervention strategies based on static biopsy samples struggle to address the dynamic changes in cytokine networks, representing a core bottleneck for precision intervention.

The lack of tissue specificity and off-target effects of epigenetic drugs is another key limiting factor. Most epigenetic drugs in widespread clinical use today, such as HDAC inhibitors and DNMTis, lack cell or tissue selectivity; their effects are not restricted to tumor cells or target immune cells but also broadly impact the epigenome of normal cells throughout the body. While HDAC inhibitors increase the immunogenicity of tumor cells, they may exert bidirectional regulatory effects on the function of immune effector cells such as T cells and dendritic cells. In CAR-T cell therapy, Class I HDAC inhibitors can promote a central memory phenotype and reduce exhaustion [124], but their effects on immune cells are dose dependent. Although BET inhibitors disrupt inflammatory gene expression in tumor cells or macrophages, they also affect transcriptional programs in normal cells such as cardiomyocytes and hematopoietic stem cells. BRD4 plays an important role in $CD8^+$ T cell differentiation; its inhibition can bias toward precursors of memory cells [117], but its effects on other cell types may cause adverse events such as thrombocytopenia and cardiotoxicity. The wide range of this effect results in an extremely narrow therapeutic window, making it difficult to balance efficacy and toxicity. It also obscures the precise cellular targets of treatment, hindering mechanistic elucidation and drug optimization.

While dual-targeting strategies are designed to achieve synergy, they also risk additive toxic side effects and novel safety concerns. The combination of interventions targeting both the cytokine pathway and epigenetic regulation is intended to increase efficacy through a synergistic effect; however, the toxicities of both drugs may accumulate. Clinical studies indicate that while HDAC inhibitors combined with JAK inhibitors have reduced splenomegaly and improved symptoms in some patients, overall efficacy has not reached statistical significance and long-term safety and tolerability of this treatment remain to be evaluated [108]. More critically, excessive suppression of inflammatory signaling and epigenetic regulation could impair fundamental immune and gene expression programs essential for host defense against infection or tissue repair. In a study of HIV-1 latency, although HDAC inhibitors combined with interferon α-2a activated latent virus, proviruses integrated into regions of epigenetic repression persisted and treatment may selectively enrich reservoirs of drug resistant virus [104]. In clinical trials combining DNMTis or HDAC inhibitors with PD-1 inhibitors in colorectal cancer patients with intact mismatch repair function, regimens were generally safe and well tolerated and reductions in regulatory T cells were observed; however, objective response rates were extremely limited and clinical responses were poor [122].

The lack of in-depth mechanistic understanding further hinders the development of this field. Most studies on combination therapy remain at a descriptive level, and there is no clear answer to core questions such as how epigenetic drugs regulate cytokine networks, how cytokine signaling affects epigenetic states, and what is the molecular basis of their synergistic effects. In uveal melanoma research, although HDAC inhibitors combined with PD-1 antibodies have shown clinical activity, the specific regulatory mechanism of HDAC inhibitors on immune cells still needs to be further elucidated [114]. In the study of CD38 in hepatocellular carcinoma, functional experiments have not yet fully revealed the specific molecular mechanisms by which CD38 directly causes or aggravates T cell exhaustion [116]. These mechanistic uncertainties make the design of combination regimens highly dependent on empirical exploration. At the same time, these knowledge gaps also hinder the establishment of reliable pharmacodynamic biomarkers. For example, increased blood histone acetylation levels following administration of HDAC inhibitors merely reflect the drug's action on systemic targets and cannot demonstrate that it produces the desired epigenetic remodeling on specific immune cells within the TME. Furthermore, the Janus-faced function of STAT3 poses another obstacle: systemic inhibition may impair tissue regeneration while blocking tumor progression. An ideal strategy would selectively block Y705 phosphorylation while preserving S727 phosphorylation, but current chemical tools cannot achieve this distinction. Even a highly selective STAT3 inhibitor like YY002 simultaneously inhibits both phosphorylation sites and remains preclinical, underscoring that no drug capable of such selective modulation has entered clinical validation [130].

These challenges collectively indicate a core problem in clinical translation: the absence of integrated biomarkers capable of guiding precise patient stratification. Single, static biomarkers struggle to predict dynamic changes triggered by combination therapy. In hepatocellular carcinoma, although $CD8^+$ T cell depletion can forecast the response to immune checkpoint inhibitors, studies have neither directly measured nor manipulated the epigenetic regulation of these genes. Moreover, they have not integrated gene expression profiles with epigenetic data such as DNA methylation and chromatin accessibility [110]. In cholangiocarcinoma, loss-of-function mutations in ARID1A are linked to a poorer prognosis. These mutations may impede interferon responses by restricting the chromatin accessibility of interferon-responsive genes. However, the identification and application of such multitasking biomarkers are still in their early stages [113]. In gastric cancer, VAMP8 methylation is correlated with low scores for TME signatures, while ATG7 demethylation is associated with immunologic exclusion, suggesting that methylation regulates immune-related gene expression [119]. Nevertheless, no personalized treatment algorithms based on these biomarkers have been developed. Current biomarker studies mainly involve retrospective analyses with limited sample sizes and lack validation through prospective, multicenter clinical trials.

5 Conclusions

Dysregulation of cytokine networks and epigenetic regulation are central to the development and progression of many major diseases. This review explores how cytokines modulate the availability of substrates for epigenetic modifications through metabolic reprogramming and directly affect the activity of epigenetic enzymes via signaling pathways, including JAK-STAT, NF-κB, and TGF-β/Smad. Together, these mechanisms constitute the molecular basis of a "cytokine-epigenetic axis." Building on this knowledge, we discuss the prominent pathological roles of this axis in autoimmune diseases, neurodegenerative and psychiatric disorders, metabolic diseases, and cancer, uncovering the underlying mechanisms by which it contributes to disease chronicity and treatment resistance through persistent functional reprogramming. We then provide an overview of emerging therapeutic strategies targeting this axis, focusing on the potential of combination interventions, precision medicine, and disease memory resetting, as well as major challenges for clinical translation. A detailed understanding of the regulatory mechanisms of the cytokine-epigenetic axis not only provides a new theoretical framework for understanding imbalances in immune and metabolic homeostasis but also identifies potential targets for developing countermeasures against persistent chronic diseases.

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