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Epigenetic Regulation of Immune Cells in Health and Disease: A Comprehensive Review

Serunjogi Ruth

Faculty of Pharmacy Kampala International University Uganda

Email: ruth.serunjogi@studwc.kiu.ac.ug

ABSTRACT

Epigenetic regulation plays a crucial role in the development, differentiation, and function of immune cells. Mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA interactions dynamically shape gene expression, enabling immune cells to adapt to environmental stimuli and mediate appropriate immune responses. Aberrant epigenetic regulation is implicated in a range of diseases, including autoimmune disorders, cancer, and chronic inflammatory conditions. In autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, altered DNA methylation and histone modifications contribute to immune dysregulation and tissue damage. In cancer, immune cells in the tumor microenvironment often exhibit epigenetic changes that facilitate immune evasion. Emerging therapeutic strategies targeting epigenetic pathways, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, and CRISPR-based epigenome editing, offer promising approaches for treating immune-mediated diseases. This review provides a comprehensive overview of the epigenetic mechanisms governing immune cell behavior, their dysregulation in disease, and the potential of epigenetic therapies to restore immune homeostasis and improve patient outcomes.

Keywords: Epigenetics, immune cells, DNA methylation, histone modifications, non-coding RNAs, autoimmune diseases, immunotherapy

INTRODUCTION

Epigenetics refers to the study of heritable changes in gene function that occur without alterations to the underlying DNA sequence [1]. These changes are largely mediated by mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA activity. Together, these processes regulate the structure of chromatin and gene expression patterns in response to internal and external stimuli. The immune system, a complex network of cells and molecules that protect the host from pathogens, relies on tightly regulated gene expression programs for proper development, differentiation, and function [2]. Immune cells such as T cells, B cells, macrophages, and dendritic cells must undergo precise epigenetic changes to perform their roles in immune defense, tolerance, and memory formation [3]. Dysregulation of these epigenetic processes can lead to immune-related diseases, including autoimmunity, chronic inflammation, and cancer. In this review, we explore the various epigenetic mechanisms that govern immune cell behavior under normal and disease conditions. We also examine how epigenetic therapies are emerging as promising strategies for modulating immune responses in the treatment of diseases.

MECHANISMS OF EPIGENETIC REGULATION IN IMMUNE CELLS

DNA Methylation

DNA methylation involves the covalent addition of a methyl group to the 5th carbon position of cytosine residues, particularly within CpGdinucleotides [4]. This process is catalyzed by DNA methyltransferases (DNMTs), which transfer methyl

groups from the donor molecule S-adenosyl methionine (SAM) to cytosine [5]. DNA methylation can either activate or silence gene transcription depending on its location and context. Promoter region methylation typically results in gene repression, whereas methylation within gene bodies may enhance transcription. In immune cells, DNA methylation patterns are critical for maintaining cellular identity and controlling the expression of key immune-related genes [6]. Methylation marks are dynamically altered during immune cell differentiation, and they play an essential role in the development and function of various immune cell types.

Immune Cell Development and Differentiation

During hematopoiesis, the differentiation of multipotent hematopoietic stem cells (HSCs) into distinct immune lineages is associated with specific DNA methylation patterns. For example, DNMT3A and DNMT3B, two de novo DNA methyltransferases, are highly expressed in progenitor cells, allowing them to establish new methylation patterns that drive lineage commitment [7]. In regulatory T cells (Tregs), the FOXP3 gene, which is a master regulator of Treg function, is tightly controlled by DNA methylation [8]. Demethylation of a conserved CpG island within the FOXP3 promoter is essential for its stable expression and for Treg differentiation. FOXP3 expression and subsequent Treg formation are critical for maintaining immune tolerance and preventing autoimmune responses. In autoimmune diseases such as systemic lupus erythematosus (SLE), altered DNA methylation patterns, including hypomethylation of immune-related genes, contribute to the dysregulated immune response [9]. In B-cell development, the immunoglobulin heavy-chain (IgH) locus undergoes demethylation during V(D)J recombination, allowing B cells to diversify their antibody repertoire [10]. Additionally, activation-induced cytidinedeaminase (AID) is regulated by DNA methylation during class-switch recombination, a process that enables B cells to produce different antibody isotypes.

Histone Modifications

Histones are core proteins around which DNA is wrapped to form nucleosomes, the basic units of chromatin [11]. Histone modifications include acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, all of which regulate the accessibility of chromatin to the transcriptional machinery. These post-translational modifications are catalyzed by specific enzymes, including histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases, and demethylases [12].

Histone Acetylation and Deacetylation

Histone acetylation generally promotes an open chromatin structure, facilitating transcription. HATs such as p300 and CBP (CREB-binding protein) add acetyl groups to lysine residues on histones, neutralizing their positive charge and reducing their interaction with DNA [13]. This allows transcription factors and RNA polymerase to access gene promoters and initiate transcription. In contrast, HDACs remove acetyl groups, leading to chromatin condensation and transcriptional repression. In immune cells, histone acetylation is essential for gene activation during immune responses. For example, during macrophage activation, pro-inflammatory cytokine genes such as TNF-α, IL-6, and IL-12 become highly acetylated at their promoter regions, resulting in their rapid transcription and release of cytokines to combat infection [14]. HDACs also play critical roles in immune cell differentiation and function. In T-cell development, the deletion of specific HDACs, such as HDAC1 and HDAC2, results in impaired T-cell development and altered thymocytematuration [15]. HDAC inhibitors, which have been explored as therapeutic agents, have shown the ability to modulate immune responses by repressing the expression of pro-inflammatory genes.

Histone Methylation and Immune Regulation

Histone methylation can lead to either gene activation or repression depending on the specific residue that is modified. For example, trimethylation of histone H3 at lysine 4 (H3K4me3) is a mark of active transcription, whereas trimethylation at lysine 27 (H3K27me3) is associated with gene silencing [16]. Methylation marks are established by histone methyltransferases such as EZH2 (Enhancer of Zeste Homolog 2), which is part of the Polycomb Repressive Complex 2 (PRC2), and are removed by demethylases such as KDM6B [17]. In the immune system, histone methylation regulates the expression of key cytokines and transcription factors involved in immune cell differentiation. For instance, the differentiation of Th1 cells, which produce interferon-gamma (IFN-γ), is dependent on the acquisition of H3K4me3 at the IFN-γ promoter [18, 19]. Conversely, Th2 differentiation is promoted by GATA3, which recruits histone-modifying enzymes to activate the expression of Th2-specific cytokines like IL-4, IL-5, and IL-13, while repressing Th1 genes [20].

Histone Modifications in Disease

Aberrant histone modifications contribute to immune dysregulation in various diseases. In autoimmune diseases, such as multiple sclerosis (MS), histone deacetylation at specific gene loci is associated with the persistent activation of pro-inflammatory genes, leading to chronic immune activation and tissue damage. In cancer, tumor-associated macrophages (TAMs) and other immune cells within the tumor microenvironment often exhibit altered histone modification patterns that promote an immunosuppressive phenotype [21]. EZH2, which catalyzes H3K27me3, has been found to be overexpressed in TAMs and contributes to their ability to suppress anti-tumor immune responses.

Chromatin Remodeling

Chromatin remodeling involves the ATP-dependent restructuring of nucleosomes to expose specific DNA regions for transcription or other processes. Chromatin remodeling complexes, such as the SWI/SNF complex, are essential for regulating gene accessibility in response to environmental cues. In immune cells, chromatin remodeling plays a critical role during activation and differentiation. For instance, during T-cell activation, the SWI/SNF complex is recruited to the promoter regions of cytokine genes such as IL-2, facilitating their rapid expression [22].

Chromatin Remodeling in Disease

Mutations in chromatin remodeling genes have been implicated in various diseases, including cancer and immunodeficiency syndromes. For example, mutations in ARID1A, a component of the SWI/SNF complex, have been linked to poor outcomes in patients with certain cancers [23]. In immune cells, defects in chromatin remodeling complexes can impair antigen presentation, leading to immune evasion by tumor cells.

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small, non-coding RNA molecules (~22 nucleotides in length) that regulate gene expression post-transcriptionally by binding to the 3' untranslated region (UTR) of target mRNAs, leading to mRNA degradation or translational repression [24]. miRNAs have emerged as critical regulators of immune cell development, differentiation, and function. In T cells, miR-155 is essential for Th1 differentiation and the production of IFN-γ, while miR-146a acts as a negative regulator of inflammation by targeting key signaling molecules such as IRAK1 and TRAF6 in the NF-κB pathway [25].

Long Non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that regulate gene expression through diverse mechanisms, including chromatin remodeling, transcriptional regulation, and interaction with miRNAs. lncRNAs are increasingly recognized as important regulators of immune cell function. One example is NEAT1, a lncRNA that promotes the activation of macrophages by enhancing the assembly of paraspeckles, subnuclear structures that regulate gene expression during inflammation [26]. Another example is lincR-Ccr2-5'AS, which controls the migration of Th2 cells during allergic inflammation by regulating the expression of chemokine receptors [27].

EPIGENETIC REGULATION IN IMMUNE CELL DEVELOPMENT AND FUNCTION

T-cell Differentiation and Plasticity

T-cell differentiation is a highly plastic process that is regulated by both transcription factors and epigenetic modifications. Naïve CD4+ T cells can differentiate into several effector subsets, including Th1, Th2, Th17, and Tregs, depending on the cytokine environment and antigenic stimulation [28]. Epigenetic modifications such as DNA methylation and histone modifications play a critical role in determining T-cell fate. For instance, during Th1 differentiation, the T-bet transcription factor recruits HATs to the IFN-γ locus, leading to increased histone acetylation and active transcription [29].

B-cell Differentiation and Function

B-cell differentiation and antibody production are tightly regulated by epigenetic mechanisms. During B-cell maturation, key transcription factors such as Pax5 and Bcl6 establish B-cell identity by recruiting chromatin-modifying enzymes to activate B-cell-specific genes and repress genes associated with alternative lineages [30]. In response to antigenic stimulation, B cells undergo somatic hypermutation and class-switch recombination, processes that are regulated by DNA methylation and histone modifications. AID, the enzyme responsible for initiating these processes, is epigenetically regulated, and its dysregulation can lead to impaired antibody responses or B-cell malignancies.

EPIGENETIC DYSREGULATION IN IMMUNE-RELATED DISEASES

Autoimmune Diseases

Autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS), are characterized by the loss of immune tolerance and the destruction of self-tissues [31]. Epigenetic dysregulation plays a critical role in the pathogenesis of these diseases. In SLE, global DNA hypomethylation of CD4+ T cells leads to the overexpression of immune-related genes, contributing to the hyperactivation of T cells and the production of autoantibodies [32]. Similarly, in RA, aberrant histone modifications and miRNA expression patterns promote chronic inflammation and joint destruction.

Cancer

Epigenetic alterations in immune cells are also a hallmark of cancer. Tumor cells often exploit epigenetic mechanisms to evade immune surveillance. For instance, tumor-associated macrophages (TAMs) undergo epigenetic reprogramming that promotes an immunosuppressive phenotype, allowing tumors to grow unchecked [33].

Chronic Inflammatory Diseases

Chronic inflammatory diseases, such as inflammatory bowel disease (IBD), asthma, and psoriasis, are driven by persistent immune activation and tissue damage. Epigenetic mechanisms contribute to the maintenance of chronic inflammation by regulating the expression of pro-inflammatory cytokines and other immune-related genes. For example, in IBD, histone modifications at the promoter regions of pro-inflammatory genes such as IL-6 and TNF-α lead to their sustained expression in macrophages, contributing to the chronic inflammatory response in the gut [34].

EMERGING EPIGENETIC THERAPIES IN IMMUNE-MEDIATED DISEASES

Given the central role of epigenetic regulation in immune cell function and disease, there is growing interest in developing epigenetic therapies for immune-mediated diseases. Epigenetic drugs, including DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), are being investigated for their ability to modulate immune responses and restore immune homeostasis [34, 35].

DNA Methylation Inhibitors

DNMT inhibitors, such as azacitidine and decitabine, are approved for the treatment of hematologic malignancies [37]. These agents work by inhibiting DNA methylation, leading to the reactivation of tumor suppressor genes and the induction of immune responses against cancer cells. Recent studies have shown that DNMT inhibitors can also enhance the efficacy of immune checkpoint blockade by upregulating the expression of immune-related genes in tumor cells [38].

HDAC Inhibitors

HDAC inhibitors, such as vorinostat and romidepsin, have shown promise in the treatment of both cancer and autoimmune diseases. By inhibiting HDACs, these drugs increase histone acetylation and promote the expression of genes involved in immune activation. HDAC inhibitors have been shown to suppress inflammation in animal models of autoimmune diseases such as RA and MS, suggesting their potential as therapeutic agents for immune-related disorders [39].

CRISPR-Based Epigenome Editing

CRISPR-Cas9 technology has revolutionized gene editing, and recent advances in epigenome editing offer the potential to precisely modify epigenetic marks at specific loci [40]. CRISPR-based tools can be used to target DNA methylation, histone modifications, or non-coding RNAs, allowing for the precise regulation of gene expression in immune cells. This approach holds promise for the development of targeted therapies for diseases characterized by epigenetic dysregulation.

BET Inhibitors

Bromodomain and extra-terminal (BET) proteins are chromatin readers that recognize acetylated histones and promote transcriptional activation [41]. BET inhibitors, such as JQ1, disrupt the interaction between BET proteins and acetylated histones, leading to the suppression of pro-inflammatory genes. BET inhibitors have shown promise in preclinical models of cancer, autoimmune diseases, and chronic inflammation [42].

CONCLUSION

Epigenetic regulation is integral to the proper functioning of the immune system, governing processes such as immune cell differentiation, activation, and memory formation. The dynamic and reversible nature of epigenetic modifications allows immune cells to rapidly respond to environmental cues while maintaining the plasticity necessary for effective immune responses. However, dysregulation of epigenetic processes contributes to the pathogenesis of various diseases, including autoimmunity, cancer, and chronic inflammation. As our understanding of epigenetic mechanisms in

immune cells continues to expand, novel therapeutic strategies targeting epigenetic regulators are emerging as promising approaches for the treatment of immune-mediated diseases. Epigenetic therapies, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, and CRISPR-based epigenome editing tools, have the potential to reshape immune responses and restore immune homeostasis. Ongoing research into the mechanisms of epigenetic regulation in immune cells will undoubtedly lead to new insights and therapeutic opportunities for combating immune-related disorders.

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