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Genetic and Epigenetic Modifiers of Immune Dysregulation: A Comprehensive Review

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ABSTRACT

Immune dysregulation arises from a complex interplay between genetic predisposition, environmental exposures, and dynamic epigenetic modifications that collectively shape immune cell development, signaling, and responsiveness. Over the past two decades, rapid advances in genomics and epigenomics have elucidated key mechanisms by which inherited variants, somatic mutations, DNA methylation, histone modifications, microRNAs, and chromatin remodeling contribute to abnormal immune activation or suppression. These mechanisms underlie a wide spectrum of disorders, including autoimmunity, chronic inflammation, immunodeficiency, cancer-associated immune escape, and aberrant responses to infection. This review synthesizes current knowledge on major genetic and epigenetic determinants of immune dysregulation, highlighting the molecular pathways involved, their clinical significance, and the interplay between developmental and environmental influences. Emerging insights into gene-environment interactions, including the effects of diet, stress, xenobiotics, and the microbiome on immune epigenetics, reveal new therapeutic opportunities. Understanding how diverse layers of regulation converge on immune homeostasis provides a foundation for precision medicine approaches aimed at diagnosing, predicting, and treating diseases associated with immune imbalance.

Keywords: Immune dysregulation, genetic variants, epigenetic regulation, DNA methylation, microRNAs

INTRODUCTION

The immune system maintains a delicate balance between tolerance and activation, enabling protection against pathogens while preventing excessive or misguided responses that result in tissue damage [1,2]. Immune dysregulation arises when this balance is disturbed, manifesting as heightened inflammation, impaired pathogen clearance, autoimmunity, allergy, or immunodeficiency. A growing body of evidence demonstrates that both genetic susceptibility and epigenetic modifications play central roles in shaping the immune landscape [3]. Genetic variants alter protein structure, signaling pathways, or receptor function, while epigenetic marks dynamically regulate gene expression without altering the underlying DNA sequence [4]. Together, these determinants orchestrate immune cell differentiation, responsiveness to stimuli, and the magnitude of inflammatory or regulatory responses. Modern genomic technologies, including genome-wide association studies, epigenome mapping, chromatin accessibility profiling, and single-cell multi-omics, have uncovered a vast network of gene-environment interactions that contribute to immune dysfunction [5,6]. These findings underscore the complexity of immune regulation and suggest that immune dysregulation rarely arises from a single defect but rather from combined perturbations in multiple regulatory layers [7]. This review explores the major genetic and epigenetic mechanisms that influence immune dysregulation, discusses their functional consequences, and examines their relevance across a spectrum of human diseases.

2. Genetic Determinants of Immune Dysregulation

Genetic contributions to immune dysregulation are rooted in inherited or acquired alterations that modify immune cell development, receptor recognition, signal transduction, or effector functions. These determinants can be broadly categorized into single-gene mutations, polymorphisms affecting immune function, and structural variations such as copy number alterations [8].

2.1 Single-Gene Mutations and Monogenic Immune Disorders

Monogenic disorders provide some of the clearest examples of how genetic defects can lead to severe immune dysregulation. Mutations in genes such as FOXP3, CTLA4, STAT1, STAT3, RAG1, and RAG2 impair immune tolerance, lymphocyte development, or cytokine signaling, leading to conditions such as IPEX syndrome, immune

dysregulation with polyendocrinopathy, autoimmune cytopenias, recurrent infections, and early-onset autoimmunity [9]. While individually rare, these disorders have illuminated essential regulatory pathways in immune biology. For example, FOXP3 mutations disrupt regulatory T cell development, resulting in uncontrolled T cell activation and widespread autoimmunity [10]. Similarly, gain-of-function mutations in STAT3 drive excessive inflammatory signaling, predisposing affected individuals to autoimmunity and chronic inflammation.

2.2 Common Genetic Variants and Immune Susceptibility

Beyond rare monogenic diseases, common genetic variants influence immune responsiveness across populations. Genome-wide association studies have identified hundreds of loci associated with autoimmune conditions, allergies, and inflammatory diseases [11]. Many of these variants map to genes involved in antigen presentation, cytokine signaling, or immune cell differentiation. Notable examples include polymorphisms in the HLA region, PTPN22, IL23R, and TNFAIP3. HLA alleles strongly influence the peptides presented to T cells, shaping the risk of diseases such as type 1 diabetes, rheumatoid arthritis, and celiac disease [12]. PTPN22 variants alter T cell receptor signaling thresholds, increasing susceptibility to autoimmunity.

2.3 Somatic Mutations and Age-Associated Immune Dysregulation

Immune dysregulation is also influenced by somatic mutations accumulated over the lifespan. Clonal hematopoiesis of indeterminate potential, driven by mutations in genes such as DNMT3A, TET2, and ASXL1, alters immune cell function and has been linked to chronic inflammation, cardiovascular disease, and increased mortality [13]. These mutations skew immune cell composition and may promote inflammatory cytokine production. Additionally, somatic mutations in immune receptors and signaling molecules contribute to lymphoid malignancies and aberrant immune activation [14].

3. Epigenetic Regulation of Immune Homeostasis

Epigenetic modifications govern gene activity through reversible biochemical changes that influence chromatin structure and transcriptional potential. Unlike genetic alterations, epigenetic changes respond dynamically to environmental stimuli, allowing immune cells to adapt to infections, nutritional cues, toxins, and stress [15]. The principal epigenetic mechanisms include DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling complexes.

3.1 DNA Methylation

DNA methylation, the covalent addition of a methyl group to cytosine residues, plays a crucial role in establishing lineage-specific immune programs. During hematopoiesis, methylation patterns guide the differentiation of progenitors into specialized immune cell subsets [16]. Aberrant methylation contributes to immune dysregulation by altering the expression of cytokines, receptors, transcription factors, and costimulatory molecules. Hypomethylation of pro-inflammatory gene promoters can drive excessive cytokine production, while hypermethylation of regulatory genes, such as FOXP3, impairs tolerance mechanisms [17]. In autoimmune diseases such as systemic lupus erythematosus, global DNA hypomethylation in T cells enhances autoreactivity and promotes type I interferon responses [18].

3.2 Histone Modifications

Histone proteins undergo post-translational modifications including acetylation, methylation, ubiquitination, and phosphorylation. These marks influence chromatin accessibility and thereby regulate transcriptional activity [19]. Histone acetylation generally promotes gene expression by relaxing chromatin structure, whereas histone deacetylation represses transcription. Dysregulation of histone-modifying enzymes, such as histone acetyltransferases, deacetylases, and methyltransferases, can disrupt immune balance. For example, increased histone acetylation at inflammatory gene loci enhances cytokine expression in macrophages, contributing to chronic inflammatory diseases [20]. Defects in histone methylation have been implicated in T helper cell polarization abnormalities, affecting susceptibility to allergy or autoimmunity.

3.3 Non-Coding RNAs

MicroRNAs, long non-coding RNAs, and circular RNAs represent another critical layer of immune regulation. MicroRNAs act as post-transcriptional regulators by binding to mRNA transcripts and modulating their stability or translation [21]. Immune-specific microRNAs, such as miR-155, miR-146a, and miR-21, play essential roles in controlling inflammatory responses, T cell activation, and macrophage polarization. Dysregulation of these microRNAs has been linked to autoimmunity, chronic inflammation, and cancer-associated immune suppression [22]. Long non-coding RNAs interact with chromatin regulators, transcription factors, and signaling molecules, enabling fine-tuned control of immune pathways.

3.4 Chromatin Architecture and Accessibility

Chromatin remodeling complexes adjust the structural configuration of chromatin, allowing transcriptional machinery to access specific genomic regions. Improper remodeling contributes to immune dysregulation by altering the expression of genes involved in antigen processing, cytokine signaling, and apoptosis [23]. High-resolution chromatin profiling has shown that inflammatory stimuli can rapidly reconfigure chromatin landscapes in innate

immune cells, establishing either primed or tolerant states. These epigenetic memory effects influence long-term immune behavior and contribute to phenomena such as trained immunity [24].

4. Gene-Environment Interactions in Immune Dysregulation

The fine balance between genetic predisposition and environmental exposure determines whether an individual develops immune dysfunction. Environmental agents induce epigenetic modifications that can exacerbate underlying genetic susceptibility [25].

4.1 Microbiome Interactions

The gut microbiome plays a pivotal role in shaping immune development. Dysbiosis alters microbial metabolites such as short-chain fatty acids, which act as epigenetic modulators through inhibition of histone deacetylases. In genetically susceptible individuals, dysbiosis can trigger or worsen autoimmune diseases [26].

4.2 Diet and Metabolism

Dietary components influence immune regulation through epigenetic pathways. Nutrients such as folate and methionine modulate DNA methylation, while polyphenols and fatty acids regulate histone modifications. Caloric excess and metabolic syndrome further promote pro-inflammatory epigenetic signatures [27].

4.3 Environmental Toxicants

Xenobiotics, heavy metals, particulate matter, and endocrine-disrupting compounds induce oxidative stress and epigenetic drift. These exposures can modify DNA methylation profiles, alter microRNA expression, and impair chromatin structure, resulting in persistent immune dysregulation [28].

4.4 Stress and Neuroendocrine Influences

Psychological stress induces hormonal changes that modulate epigenetic regulators in immune cells. Chronic stress is associated with altered methylation of genes controlling inflammation, potentially contributing to increased susceptibility to inflammatory diseases [29].

5. Clinical Implications and Disease Associations

Genetic and epigenetic modifiers have profound clinical implications because they shape susceptibility, progression, and therapeutic responsiveness across a wide array of immune-mediated diseases [30]. In autoimmunity, variants in genes controlling antigen presentation, cytokine signaling, or regulatory T cell function frequently interact with epigenetic abnormalities such as DNA hypomethylation or aberrant histone acetylation to promote persistent self-reactivity [31]. Epigenetic drift also contributes to the onset of allergic disorders by skewing T helper cell differentiation toward IgE-mediated responses. In primary and secondary immunodeficiencies, both inherited mutations and environmentally induced epigenetic alterations impair immune cell development or effector functions, increasing vulnerability to infections and malignancy [32].

Epigenetic signatures are emerging as powerful biomarkers capable of distinguishing disease subtypes, predicting flare risk, and monitoring therapeutic response, particularly in autoimmune and inflammatory disorders [33]. Genetic testing, including whole-exome and targeted panel sequencing, improves early diagnosis of monogenic immune dysregulation syndromes and guides personalized treatment strategies. Therapeutically, drugs that modulate epigenetic states, such as histone deacetylase inhibitors, DNA methylation inhibitors, or microRNA-based therapeutics, offer promising approaches for recalibrating dysregulated immune pathways [34,35]. These interventions, combined with precision medicine strategies that integrate genetic and epigenomic profiles, hold significant potential for improving outcomes in patients with complex immune-related diseases.

CONCLUSION

Immune dysregulation arises from a multifaceted interplay between genetic predisposition and dynamic epigenetic regulation. Together, these layers orchestrate immune tolerance, activation thresholds, cytokine responses, and cellular differentiation. Advances in multi-omics technologies continue to reveal the deep integration of these pathways and their contributions to human disease. A comprehensive understanding of both genetic and epigenetic determinants will be essential for developing precision therapies aimed at restoring immune homeostasis and preventing chronic inflammation or immunodeficiency.

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