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Opinion Article

DNA Methylation Alterations in Autoimmune Conditions

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DESCRIPTION

Autoimmune diseases, encompassing conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and type 1 diabetes, affect millions of people worldwide and present significant clinical. These diseases arise when the immune system mistakenly attacks healthy tissues, leading to chronic inflammation and progressive organ damage. While genetic predisposition plays a role in susceptibility, it does not fully account for the variable onset, severity and progression observed among individuals. Increasing evidence points to epigenetics the study of heritable changes in gene expression without alterations in the underlying DNA sequence as a critical factor in mediating the interplay between genetics, environment and immune dysregulation. Epigenetic mechanisms, including DNA methylation, histone modifications and non coding RNAs, function as molecular switches that regulate gene expression in response to external and internal signals. In autoimmune diseases, these mechanisms can alter the expression of genes responsible for immune cell activation, cytokine production and tolerance to self antigens. DNA methylation, the addition of methyl groups to cytosine residues in CpG islands, is one of the most studied epigenetic modifications in autoimmunity. Hypomethylation in immune cells can lead to aberrant overexpression of genes involved in immune activation, contributing to autoantibody production and tissue damage. For instance, hypomethylation of the *CD40L* gene in T cells has been linked to systemic lupus erythematosus, promoting excessive T cell help to B cells and enhanced autoantibody formation. Conversely, hypermethylation of regulatory genes that suppress inflammation can impair immune tolerance and exacerbate disease activity. Peripheral blood methylation profiles are being investigated as potential biomarkers for early detection, disease monitoring and prognosis, offering a non invasive tool for precision medicine in autoimmune conditions.

Histone modifications, including acetylation, methylation, phosphorylation and ubiquitination, influence chromatin structure and transcriptional accessibility, thereby modulating gene expression. In autoimmune disorders, altered histone acetylation patterns can enhance the transcription of pro inflammatory cytokines, such as TNF alpha, IL-6 and IFN-gamma, perpetuating chronic inflammation. Pharmacological agents targeting histone Deacetylases (HDACs) have demonstrated immunomodulatory effects in preclinical models, reducing disease severity in conditions like rheumatoid arthritis and lupus. Similarly, histone methylation marks can either activate or repress genes crucial for immune tolerance, influencing T cell differentiation, B cell function and the balance between pro and anti inflammatory responses. Non coding RNAs, including MicroRNAs (miRNAs) and Long Non Coding RNAs (lncRNAs), represent another layer of epigenetic regulation with profound implications for autoimmune diseases. miRNAs can fine tune the expression of multiple target genes involved in immune pathways. miR-155 is known to promote T cell activation and pro inflammatory cytokine production, while miR-146a acts as a negative regulator of immune signaling, limiting excessive inflammation. Dysregulation of these miRNAs has been observed in multiple autoimmune conditions, suggesting their potential as diagnostic biomarkers or therapeutic targets. lncRNAs, though less well characterized, are emerging as critical regulators of immune cell differentiation, cytokine networks and epigenetic feedback loops, providing novel insights into disease pathogenesis.

The influence of environmental and lifestyle factors on autoimmune disease epigenetics cannot be overstated. Viral infections, smoking, diet, microbiome composition and exposure to chemical pollutants can all modify DNA methylation histone marks, and non coding RNA expression, thereby modulating immune responses. For instance, certain viral infections can trigger epigenetic changes that activate autoreactive T and B cells, initiating disease onset in genetically susceptible individuals. Similarly, dietary components such as folate, vitamin B12 and polyphenols provide methyl donors or influence histone modifying enzymes, potentially mitigating harmful epigenetic alterations and supporting immune regulation. Epigenetic modifications are often tissue specific and influenced by age and environmental exposures, complicating biomarker identification and therapeutic targeting. Moreover, most human studies rely on peripheral blood samples, which may not fully reflect epigenetic changes in affected organs such as the kidney, joints or central nervous system.

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