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Insight of Epigenetics in Autoimmunity and Allergies

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Abstract:- Epigenetic processes include DNA methylation, chromatin changes, and micro RNA-based signaling all play a role in controlling genome activity. Epigenetic regulation is present in practically every component of immunity, whether for host defense or in the form of interference resistance. These cycles are crucial in mediating dynamic reactions to the environment over the life span of an individual, although we are only beginning to grasp how dysregulation in these pathways may play a role in autoimmune disorders. The epigenetic mechanisms that affect immune development and, by extension, an individual's health and the course of disease, are covered in a clear and succinct manner here.

Keywords:- *Autoimmune Diseases, Epigenetics, DNA Methylation, Histone Modification, and mRNA*

I. INTRODUCTION

To explain how cells with a very small number of genes [30,000] may specialize into multiple cell types and how a phenotype can be passed down from parent to offspring [1], the field of epigenetics was founded. Changes in gene expression that are epigenetically inherited but do not involve changes to the DNA sequence are called "epigenetics." Hence, the epigenetic cycle plays a crucial role in controlling changes in gene expression during the cell cycle, development, and in response to external factors. This is the idea that changes to the epigenome, such as those that occur during the cell cycle or in response to environmental stimuli, can be undone, and that they can occur quickly. The fact that epigenetics changes with age and can be affected by environmental factors clarifies the relationship between environmental variables, advanced age, and the development of autoimmune illnesses [AID] [2]. Furthermore, X chromosome inactivation may be a critical epigenetic process that helps to explain the female predisposition for autoimmunity [3]. Epigenetic modifications caused by AIDS are reversible and cell-type specific, affecting predominantly CD4 T cells, regulatory T cells [Treg], and B cells in SLE [4, 5], lymphocytes in addition, synovial fibroblasts in RA [6, 7], and lymphocytes and skin fibroblasts in individuals with SSc [6, 7]. Furthermore, organ-specific AIDS, including type 1 diabetes, MS, idiopathic thrombocytopenic purpura (ITP), and celiac disease, are influenced by epigenetic changes. To sum up, epigenetic dysregulations are present in both idiopathic and chemical/drug-induced AIDS [8].

II. EPIGENETIC LINKS TO ALLERGIC AND AUTOIMMUNE ILLNESSES:

In both allergy disorders, in which the immune system reacts inappropriately to innocuous environmental allergens, and autoimmune diseases, in which the immune system reacts inappropriately to the body's own antigens, the immune system itself is at fault. These complex immunological disorders have their roots in a genetic predisposition, but the exponential growth in disease incidence cannot be attributed solely to hereditary factors [9]. The epigenetic process has emerged as an important part of disease in recent years due to its environmental responsiveness and capacity to affect disease probability in a manner similar to polymorphisms [10].

Not enough research has been done on humans and animals [11] to pinpoint the epigenetic factors and environmental determinants that influence the immune response in allergies and autoimmune diseases. Differential epigenetic programming of immune cells and tissue-derived cells in the damaged organs has been uncovered through studies of monozygotic twins discordant for various illnesses. Other regions of the genome that experience unique epigenetic alterations have been uncovered by genome-wide case-control investigations [10, 12–17]. Dietary habits,

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environmental pollutants, and medicines are just some of the environmental elements that might affect an individual's susceptibility to autoimmunity and allergies through epigenetic pathways. DNA methylation and histone alterations are two examples of epigenetic processes that they can influence. Methyl donor intake and environmental cigarette smoke exposure are particularly pivotal (ETS). DNA methylation and the risk of asthma and autoimmune diseases like MS are mostly influenced by dietary methyl donors [18, 19]. ETS is linked to an increased risk of acquiring asthma or MS [20, 21], and it appears to alter DNA methylation and histone changes. In infants less than 5 years of age [n = 56] [22], methylation changes at the ACSL3 gene promoter [measured in cord blood] were associated with maternal airborne polycyclic aromatic hydrocarbon (PAH) exposure and parent-reported asthma. Another research revealed that exposure to maternal PAH was linked to increased DNA methylation in the IFNG promoter [23]. Increased IFNG methylation and decreased IFNG expression were confirmed after in vitro exposure of lung cancer cell lines to non-cytotoxic PAH components. These results lend credence to the idea that epigenetic changes in the mother may have important consequences for the developing fetus.

One of the most challenging aspects of studying epigenetic links between diseases is establishing causality. The creation of causation is clouded by the fact that epigenetic alterations are dynamic, fluctuate over time, and vary cell- or tissue-specifically. The etiology of a disease may be the direct or indirect result of an epigenetic variation. Long-term alterations in blood cell production in immunological illnesses may be one example of this. Demonstrating the importance of epigenetics in disease will need finding evidence of variation before symptoms appear [24]. One of the many ways this can be tackled is by comparing case and control groups' tissue and cell types of interest. Distinguishing disease-related epigenetic variation across various organs of varying ancestry [25] shows that these imprints were likely created very early in development.

Recent advances in technology have paved the way for studies of epigenetics on a genomic scale. While DNA methylation is the primary focus of these epigenome-wide association studies [EWAS], other epigenetic markers can also be screened for on a massive scale. The possibility for genetic influences on epigenetic modifications like DNA methylation necessitates a honest depiction of these influences. Methylation can be prevented by polymorphisms at CG dinucleotides, which could be misunderstood as a prolonged balanced epigenetic process. As well as evaluating several tissues at various time points, modern EWAS study designs require specific sequencing data [26]. Hence, these studies are exceedingly complex, but they have the potential to reveal extremely important insights about human population epigenetics.

III. EPIGENETIC MODIFICATIONS OBSERVED DURING AUTOIMMUNE DISEASES*:*

A. DNA methylation:

Gene transcription dysregulation, chromosomal instability, and the development of AIDS-related conditions like SLE have all been linked to deficiencies in CpG methylation caused by a lack of enzymatic activity of DNMTs [27]. Inadequate DNA methylation was also accounted for [28] in rheumatoid arthritis, systemic sclerosis, and dermatomyositis. Liver hypomethylation precedes kidney hypomethylation in the development of type 1 diabetes, and both are linked to anomalies in rodent SAM and homocysteine metabolism [29]. One such piece of evidence connecting DNA methylation and diabetes is the widely held but unproven assumption that DNA methylation regulates the insulin promoter [30]. For DNMT transcripts, researchers have found conflicting evidence. Januchowski [31] found that the mRNA levels of DNMT1 and DNMT3a were reduced in the CD4 T cells of SLE patients. However, Balada et al. ignored any difference between CD4 T cells from SLE patients and those from healthy people. B cells from SLE patients are distinguished by an abnormal activation of DNMT1 in response to IgM stimulation [5]. To clarify these disparate findings, researchers looked at the expression of the two DNA methyltransferase enzymes in question (MBD2 and MBD4) and found that MBD4 is up-regulated in CD4 and CD8 T cells from SLE patients, but not in B cells [32, 33]. Patients with ITP had lower levels of DNMT3a and DNMT3b expression in their PBMC, as described in [34].

B. Histone modifications:

CD4 T cells from SLE patients can be widely distinguished by their hypoacetylation and hypermethylation of H3 and H4 [H3k9me2/3 and H3K4me] [35]. Moreover, histone H3 and H4 are hypoacetylated and hypermethylated in MRL/lpr splenocytes. Patients with systemic lupus erythematosus (SLE) have CD4 T cells with reduced HDAC expression [35]. It has been shown that HDACs are upregulated in RA synovial cells at the transcriptional level, and that HDAC-specific siRNA has shown that HDACs play a vital role in synoviocyte cell proliferation and death. Hyperacetylation in synoviocytes was linked to a reduction in HAT action but no change in HDAC activity, according to a different study [37]. HDACi appear to be counterproductive in human AIDS, despite their efficacy in cancer, mental health, and animal models of the disease. DNA demethylation and the induction of AID-encoding genes are two additional potential effects of HDACi. We also don't know much about how well it works with other AIDS drugs or whether there are any potential side effects from using it.

C. miRNA:

Increased expression of microRNAs miR-146a, miR-155, miR-132, and miR-16 were found in RA PBMCs compared to healthy controls and patients with other autoimmune diseases [38]. Both miR-146a and miR-16 have been linked to the development of RA. In RA fibroblast-like synoviocyte, miR-155, miR-146a, and miR-124a expression is elevated. Furthermore, miR-146 was found in monocytes and subsets of B and T cells in RA synovial tissue [34]. MiR-

146 is increased in RA [38, 39], and studies of its effect on cytokine pathways have shown that it controls the IFN pathway but not the TNFa pathway. Because miR-146 is downregulated in PBMC from SLE patients, this may explain why there is an increase in IFN- expression in these individuals [39]. A study of peripheral blood mononuclear cells (PBMC) from SLE patients found nine up-regulated and seven down-regulated miRNAs [40], suggesting that miR-146 is not the only miRNA of interest in SLE. There were 66 miRNAs that were found to have altered expression in SLE kidney tissue samples. Vinuesa claims that 50% of lupus genes can be targeted by just 3 microRNAs [miR-181a, miR-186, and miR-590-3p] [42]. Liver miRNA expression is also changed in PBC patients, with some miRNAs being downregulated (miR-122a and miR-26a) and others being upregulated (miR-328 and miR-299-5p). [43]; in the salivary glands and PBMC of patients with primary sclerosing sialadenitis. [44]; and [miR-146a], [miR-203], and [miR-125b] in the skin of psoriasis patients. [45]. This data demonstrates that a potential biomarker can be developed by studying the atypical miRNA expression pattern in AID.

D. Epigenetics modifications and autoantibodies:

There is evidence that the structure of DNA and post-translational changes of histones can influence antigenicity and immunogenicity. Some of these variations are overt, and it has been argued that this makes them ideal candidates for use as biomarkers [46]. DNA, U1-snRNP, Sm, Sp100, La/SSB, and cytoplasmic Ro52 are just a few examples of autoantigens that need to be added to this list. In addition to histones, over 200 other proteins have been shown to be substrates for HDAC.

IV. CONCLUSION AND FUTURE PERSPECTIVE:

The epigenome will likely serve as diagnostic and prognostic indications, and it will also provide future therapeutic targets, despite our limited understanding of epigenetic processes at present. To further our knowledge of the epigenome, however, we need to create three-dimensional guides to help us grasp the atomic compartmentalization and intergene interactions that take place during the active-to-inactive and inactive-to-active phases of loci. Although genetic SNP maps provide a more precise estimate of how the locus should be packaged, recognized, and expressed, epigenetic guidelines will still allow us to select target destinations that may affect the development of autoimmune illnesses. Now being developed by epigenetic major researchers, these new methods and the data they produce will surely be tested and authorized in AID, thereby changing the field of autoimmunity [47]. Since epigenetics seems to be involved in many diseases, including malignancies and tumors, insights gained from studying these other diseases can have a significant impact on autoimmune diseases. Researchers in the fields of epigenetics, autoimmune diseases, malignant growth and cancer, and others will need to work together more closely in the future to share insights and form businesses that capitalize on their combined expertise.

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