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Epigenetics in systemic lupus erythematosus (Review)

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Abstract. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, with mechanisms that remain to be elucidated. Previous studies have proposed that genes and environments are required for lupus to develop and flare. It has been found that epigenetics have a significant influence on SLE. The present review will concentrate on epigenetics in SLE. There are a number of studies reporting that autoreactive T cells and B cells in patients with SLE have evidence of altered patterns of DNA methylation, modifications of histones and microRNA (miRNA). Long noncoding RNAs (lncRNAs) are another type of noncoding RNAs, which have an important role in epigenetics. lncRNAs may possibly become a new hotspot in SLE.

Contents

1. Introduction

Autoimmune diseases arise from the dysfunction of the immune system, which results in the inflammation and the damage of tissues and organs. Innate and adaptive immunity contribute to the mechanism of diseases (1). Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that is characterized by immune complex accumulation in blood vessels and connective tissue (2).

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The etiology and pathogenesis of SLE remain to be elucidated. It is believed that the etiological factors include the genetic susceptibility, environmental factors and epigenetics. Recent genome-wide association studies (GWAS) and fine mapping of candidate genes or regions have considerably broadened the understanding of this complex autoimmune disease. At present, >100 gene variations/alleles from different ethnicities are known, which are genetic risk factors for lupus (3). Another study of GWAS of several thousand allelic variants (single nucleotide polymorphisms) in case-control studies have identified >30 genes involved in SLE (4). Environmental factors, such as ultraviolent light, smoking and alcohol, have an important role in the pathophysiology of SLE (5). The combination of genetic abnormalities, environmental factors and their interactions contribute to the induction of SLE (6,7). Epigenetic dysregulation has recently been reported to have a critical role in the pathogenesis of SLE (8).

2. Epigenetics

Epigenetic information is carried chiefly by DNA itself, histones and noncoding RNAs (ncRNAs). It has been found that epigenetic dysregulation occurs generally in lupus.

3. DNA methylation abnormalities

DNA methylation is one of the epigenetic mechanisms. It suppresses gene expression by methylating the deoxycytosine base at the 5' position to form deoxymethylcytosine (9). DNA hypomethylation, an epigenetic modification, can influence gene expression and has been implicated in the pathogenesis of SLE. The gene can lead to decreased or silenced gene expression by the methylation of C-G dinucleotides (CpG) (10,11). Lupus patients exhibit global T-cell hypomethylation (12). The genes include a number of autoimmune-related genes, such as ITGAL [cluster of differentiation 11a (CD11a)] and TNFSF7 (CD70) (13,14). CD11a, perforin and the KIR genes were overexpressed in patients with active, but not inactive, lupus, and the same sequences demethylated in proportion to disease activity and gene overexpression in these patients (15,16). $CD4^+$ T cells from idiopathic SLE patients are significantly hypomethylated compared to healthy control $CD4^+$ T cells (17). The X chromosome of SLE women is demethylated, which may be the reason of the predominance of SLE in women (18,19). A genome-wide DNA methylation study in $CD4^+$ T cells in lupus patients compared to normal healthy controls identified that there are 105 hypermethylated

and 236 hypomethylated CG sites in the 27,578 CG sites located within the promoter regions of 14,495 genes (20). There is another study regarding genome-wide DNA methylation study in two independent sets of lupus patients and matched healthy controls, which characterized the DNA methylome in naïve $CD4^+$ T cells in lupus. The study quantified for >485,000 methylation sites across the genome, and identified and replicated 86 differentially methylated CG sites between patients and controls in 47 genes, with the majority being hypomethylated through gene expression analysis from the same cells to investigate the association between the DNA methylation changes observed and mRNA expression levels. Significant hypomethylation has been observed to interfere on regulated genes in naïve T cells from lupus patients, including IFIT1, IFIT3, MX1, STAT1, IFI44L, USP18, TRIM22 and BST2, which suggested epigenetic transcriptional accessibility in these genetic loci (21). Hypomethylation of CpG sites within genes from different pathways has also been reported to be associated with anti-double stranded DNA (dsDNA), anti-SSA, anti-Sm and anti-ribonucleoprotein production in SLE (22). The plasma DNA of active SLE patients showed decreased methylation densities. The extent of hypomethylation correlated with SLEDAI and the anti-dsDNA antibody level. SLE patients had higher concentrations of immunoglobulin G (IgG)-bound DNA in plasma (23). The hypomethymethylation of plasma DNA may be accessible for IgG to bind DNA. DNA methylation mechanisms are involved in SLE.

4. Histone modifications and SLE

Histones are a group of proteins wrapping the DNA to form the chromosomal structure nucleosome. The post-translational modifications of histone proteins have been identified as one of the major epigenetic mechanisms in government of chromatin remodeling and gene expression through phosphorylation, acetylation, and methylation and so on (24). In $CD4^+$ T cells of SLE patents, it has been identified that global histone H3 and H4 are hypoacetylated and global histone H3K9 is hypomethylated. The results indicated that the modifications of histones are involved in the pathogenesis of SLE (25,26). Acetylated histones contribute to the immunostimulatory potential of neutrophil extracellular traps (NETs) in systemic lupus erythematosus (27). It was found that the histone acetyltransferases (HATs) and histone deacetylases (HDACs) were abnormal in patients with active SLE (25). In another study, isoaspartic acid (isoAsp) was reported as a modification that triggers B- and T-cell autoimmunity to otherwise inert self-peptides and T-cell autoimmunity to otherwise inert self-peptides (28). H2B is the only histone that has isoAsp modification, which has contributed to recognition of H2B by B cells and development of the antibodies to this particular histone (29). The specific post-translational histone modifications of NETs could be immunogens and potential targets of lupus autoantibodies (30). Protein phosphatase 2A is involved in the regulation of the interleukin (IL)-17 locus by enhancing histone H3 acetylation through a mechanism that involves activation of interferon regulatory factor 4. This process contributes to the pathogenesis of SLE (31). The inhibition of histone deacetylase can upregulate B-cell microRNAs (miRNAs) that silence AICDA/Aicda (AID) and PRDM1/Prdm1 (Blimp-1), contributing to B-cell differentiation processes that underpin antibody and autoantibody responses in lupus MRL/Faslpr/lpr mice (32). HDAC inhibitors are also able to ameliorate renal lesions in lupus nephritis (LN) (33). A clinical study also showed that mycophenolic acid could upregulate the level of histone H3/H4 global acetylation by regulating HATs and HDACs in lupus $CD4^+$ T cells and affected the histone H4 acetylation and histone H3K4 tri-methylation levels in the CD40L promoter region that inhibited the expression of CD40L, which indicates the potential epigenetic mechanism of therapeutic effects in SLE (34). The structural alterations and immunogenicity of histones following glycation and oxidation reactions are involved in the pathological process of SLE (35). Peroxynitrite-modified H1 histone induced high titre antibodies and binding of SLE autoantibodies involved in SLE etiopathogenesis (36). 4-Hydroxy-2-nonenal modified histone H2A may also become an antigenic stimulus for SLE autoantibodies (37). DNA methylation and histone modifications can regulate gene expression together. The transcription factor cAMP-responsive element modulator-α represses IL-2 expression through histone deacetylation and CpG-DNA methylation in SLE T cells (21).

5. Noncoding RNAs and SLE

ncRNA were previously regarded as 'junk and noise'; however, recently it was suggested that ncRNA has a critical role in physiological processes that maintain cellular and tissue homeostasis (38-40). ncRNAs are grouped into two major classes according to the transcript size: Small ncRNAs [<200 nucleotides (nt)], such as miRNAs, and long ncRNAs (≥200 nt). miRNAs have a role in regulating protein coding genes, such as the binding of transcription factors or enhancers to the cis-regulatory elements, DNA methylation or histone modification status of the promoter (41). There are a number of studies regarding miRNAs in SLE. The peripheral blood mononuclear cells from patients with SLE exhibited increases in certain miRNAs (miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198 and miR-298) and decreases in others (miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112 and miR-184) (42). Profiling of the miRNAs expressed in the peripheral blood mononucleated cells (PBMCs) from lupus patients revealed that miR-146a was underexpressed in SLE. A further study found that STAT1 was another target of miR-146a, and there was a reverse correlation of miR-146a levels with the expression of interferon-inducible genes and SLE disease activity (43). miR-3148 could target TLR7 through binding to its 3-untranslated region (3'UTR), which may explain why the 3'UTR of TLR7 mRNA affects its expression in SLE (44). miR-125a was significantly downregulated in PBMCs from SLE patients and promote the secretion of CCL5 by SLE T cells (45). Recent studies showed that distinct expression patterns of miRNAs in peripheral blood leukocytes of SLE patients were associated with different autoantibodies in those SLE patients (46). Another study reported that there were aberrant expression of miRNAs (particularly hsa-miR-371-5p, hsa-miR-423-5p, hsa-miR-638, hsa-miR-1224-3p and hsa-miR-663) in the PBMCs of LN patients across different patients with different

ethnicities (47). miRNAs -21, -126 and -148a were upregulated in $CD4^+$ lupus T cells and there was decreased Dnmt1 expression (48,49). miR-21 was increased in $CD4^+$ T cells from lupus-prone mice. In SLE123 mice models bearing three lupus susceptibility loci from the NZM2410 lupus-prone strain, backcrossed onto a C57BL/6 (B6) background, blocking miR-21 expression decreased splenomegaly (50). A 27-miRNA signature was identified in patients with SLE; 19 miRNAs correlated with disease activity. A total of 8 miRNAs were deregulated specifically in T cells and 4 in B cells. miR-21 was upregulated and strongly correlated with SLE disease activity (51).

Long noncoding RNAs (lncRNAs) are another type of noncoding RNA, which have been studied recently. lncRNAs are defined as transcripts that are non-protein coding transcripts >200 nt (52). lncRNA are classified into five categories, which are the sense, antisense, intronic, bidirectional lncRNAs and long intergenic ncRNAs (lincRNAs) (53). The functions of lncRNAs in the immune system have been found to be important regulators of the various biological processes in recent studies. lncRNAs have an important role in innate and adaptive immunity (54). SLE is a type of systemic autoimmune diseases, which involves a complicated interaction between the innate and the adaptive immune system loss of immunological tolerance to self-nuclear antigen, and antibody production (55). While there are less lncRNAs reported in SLE, the locations of certain lncRNAs have suggested their involvement in SLE. There are altered expression levels of certain lncRNAs in SLE. For example, linc0949 and linc0597 were significantly decreased in patients with SLE compared with patients with RA and healthy control subjects. Linc0949 was associated with the SLEDAI-2K score, complement component C3 level and organ damage. Linc0949 was decreased in LN patients (56). This lincRNA may become a biomarker of SLE. The BXSB mouse strain is an important model of glomerulonephritis observed in SLE. In this mice model, the Gas5 gene was underexpressed. Suppressed GAS5 may inhibit the cell cycle and apoptosis. Therefore, it is implicated in autoimmune diseases by leading promotion antigen exposure and production of autoantibodies (57). The GWAS have identified a region on chromosome 1q25 that is associated with SLE. The Gas5 gene is an lncRNA, which is a prime candidate for the chromosome 1q25 SLE locus. Therefore, the genetic evidence demonstrated that GAS5 is associated with the susceptibility of SLE (58,59). Gas5 binds to the DNA-binding domain of the glucocorticoid receptor (GR) by acting as a decoy 'glucocorticoid response element (GRE)', thus, competing with DNA GREs for binding to the GR (59). Therefore, we presume that Gas5 lncRNA may have an important role in the SLE patients who are insensitive to glucocorticosteroid treatments. GAS5 lncRNA is itself required for mTOR inhibitor action (60). It may be involved in the effects of the tacrolimus treatment for SLE. NeST, formally known as Tmevpg1, is a lincRNA gene located adjacent to the IFN-γ-encoding gene in mice (Ifng) and humans (IFNG) (61). lincRNA NeST can upregulate the expression of the IFN-γ gene in Th1 cells by recruiting H3K4 methyltransferase to the IFN-γ locus (61). A previous study showed that the activity index for diffuse proliferative lupus nephritis (DPLN) was correlated with the value of the IFN-γ/IL-4 ratio. This indicates that IFN-γ has a principal role in the development of DPLN (62). Another study showed that the expression of IFN-γ was significantly higher in patients with DPLN (63). We hypothesized that NeST would be involved in the pathomechanism of proliferative LN.

6. Conclusion

Evidence has clearly suggested that epigenetic mechanisms are involved in the pathogenesis of SLE. Although significant progress has been made in the field of epigenetics in SLE in the past decades, a number of questions remain to be elucidated. There are numerous studies regarding DNA methylation, histone modification and miRNAs. lncRNAs, which are relatively new, are important for discovering the different expression levels of lncRNAs and the mechanisms in patients with SLE.

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