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Epigenetic mechanisms in lupus

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Abstract

Purpose of review—Epigenetic mechanisms regulate gene expression, and epigenetic gene dysregulation is implicated in the pathogenesis of a growing number of disorders. Of the autoimmune diseases, epigenetic mechanisms are most clearly involved in human systemic lupus erythematosus (SLE). Herein, we summarize earlier work on epigenetic mechanisms contributing to human SLE. We first focus on the roles of DNA demethylation and DNA methyltransferase enzyme dysregulation, and we then review recent and important advances in this field.

Recent findings—Many advances in the past year have been made. The importance of DNA demethylation in SLE was confirmed through twin studies. New T lymphocyte immune genes that are activated by DNA demethylation, and that may participate in autoreactivity, were identified. Finally, novel mechanisms contributing to DNA demethylation in SLE were discovered.

Summary—A comprehensive understanding of the epigenetic mechanisms contributing to SLE will likely enable development of new therapeutic agents and strategies that target the dysregulated genes or correct the aberrant epigenetic modifications. Although specific agents have not yet been tested in SLE, the studies reviewed hold promise that these approaches will be useful in the treatment of human lupus.

Keywords

chromatin; DNA methylation; epigenetics; histone; lupus

Introduction

Epigenetics is defined as heritable changes in gene expression not due to changes in the DNA sequence. Epigenetic mechanisms regulate multiple aspects of chromatin structure and function, allowing transcriptionally repressive or permissive configurations for gene expression. Recent reports have confirmed and extended the earlier work demonstrating the significance of epigenetic mechanisms in the pathogenesis of systemic lupus erythematosus (SLE). New mechanisms contributing to DNA demethylation have been identified, and epigenetic effects on the expression of additional and important immune molecules have been discovered. The following sections review these studies, focusing on an epidemiologic study, DNA methylation, and histone modifications.

General mechanisms of epigenetics

Methylation of deoxycytosine (dC) bases in CG pairs, referred to as DNA methylation, and various covalent histone modifications, including acetylation and methylation, are the most common epigenetic mechanisms of gene regulation. DNA methylation is a biochemically

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stable modification that promotes a transcriptionally repressive chromatin structure inaccessible to transcription factors. Genes unnecessary for the function of any given cell are often silenced by DNA methylation. DNA methylation patterns are established during development by the *de novo* DNA methyltransferases Dnmt3a and Dnmt3b. Silencing is then maintained in proliferating cells by replicating these methylation patterns during mitosis, via the maintenance DNA methyltransferase Dnmt1, thus making them 'heritable' [1]. In contrast, histone modifications regulate multiple chromatin processes and functions, and they are dynamic [2,3]. Importantly, the enzymatic reactions creating and removing epigenetic marks from chromatin can be disrupted by environmental factors. This can then cause heritable changes in gene expression. The pathologic significance of epigenetic gene dysregulation is well established in tumor biology [4]. Now, errors in epigenetic regulatory mechanisms are being implicated in other environmentally sensitive diseases, including SLE [5].

Epigenetics in lupus

Two primary observations indicate that both genetic and environmental factors contribute to human SLE pathogenesis. First, some drugs cause a lupus-like disease in genetically predisposed people [6]. Second, the concordance rate of lupus in identical twins is greater than in the general population, but it is still incomplete [7••]. The nature of the environmental factors has been unclear. Evidence accumulated over more than 20 years indicates that the environment can contribute to human SLE through epigenetic mechanisms, and in particular by inhibiting the replication of DNA methylation patterns during mitosis. This is in contrast to murine models such as the MRL/lpr, BXSB, and New Zealand black/white strains, where lupus is primarily, if not completely, determined by genetic changes [8]. This review therefore focuses on human SLE, where epigenetic mechanisms appear to be required for disease causation. Animal models are cited when they have been created to confirm pathogenicity of epigenetic changes found in human SLE, but the traditional murine genetic models have been excluded.

In 1988 Cornacchia *et al*. [9] reported that medications inhibiting DNA methylation, including the irreversible DNA methyltransferase inhibitor 5-azacytidine and the lupus-inducing drugs hydralazine and procainamide, make human CD4+ T cells autoreactive. Experimentally demethylated murine CD4+ T cells were also found to become autoreactive when treated with these drugs, and they caused a SLE-like disease when transferred into syngeneic, nonlupus prone mice [10,11]. These experiments thus demonstrated that epigenetically modified T cells are sufficient to cause lupus-like autoimmunity.

CD4+ T cells from patients with SLE were found to have hypomethylated DNA [12], and further studies showed that both experimentally demethylated human CD4+ T cells and CD4+ T cells from SLE patients share demethylation of the same DNA sequences and overexpression of the same genes, including CD11a [13], perforin [14], CD70 [15,16], and CD40 ligand [17]. LFA-1 (CD11a/CD18) over-expression, caused by transfection or inhibition of DNA methylation, makes CD4+ T cells autoreactive *in vitro*. They respond to and kill autologous or syngeneic macrophages in the absence of added antigen, and transfected cells caused a lupus-like disease *in vivo* [10]. Aberrant perforin expression in experimentally demethylated CD4+ T cells or in CD4+ T cells from SLE patients also contributes to autoreactive killing of macrophages [14], whereas over-expression of CD70 or CD40L stimulates B cell IgG overproduction [15–17]. These studies thus provide an explanation as to how normal T cells might become pathogenic in SLE.

Mechanistic studies revealed that CD4+ T cells from patients with active SLE had lower Dnmt1 levels than controls, due to decreased ERK pathway signaling [18], and suggested

that a failure to replicate DNA methylation patterns during mitosis might contribute to lupus pathogenesis. This was confirmed with a transgenic mouse model in which expression of a dominant negative MEK was selectively induced in T cells using the tetracycline-inducible gene under the control of a CD2 promoter. Adding doxycycline to the drinking water of these mice decreased Dnmt1 in T cells, increased expression of the methylation sensitive genes CD11a and CD70, and induced lupus-like autoimmunity with anti-dsDNA antibodies and an 'interferon signature' [19].

DNA methylation

Twin studies confirmed the importance of DNA demethylation in human lupus. Javierre *et al.* [7••] compared leukocyte DNA methylation in identical twins discordant for SLE, rheumatoid arthritis and dermatomyositis. Only twins discordant for lupus had widespread changes in DNA methylation, with 49 genes demethylated in the twin with lupus. Demethylation was associated with decreased DNA methyltransferase levels. Since genetically identical twins were studied, this study supports the importance of both epigenetic and genetic elements in lupus pathogenesis. Though shifts in leukocyte subsets could potentially contribute to the observed differences, this represents an important contribution to the field by eliminating concerns of genetic variability as a cause of lupus discordance between siblings.

GADD45a

The mechanisms causing DNA demethylation in SLE are incompletely understood. Li *et al.* [20••] showed that GADD45a may contribute. GADD45a is induced by growth arrest and DNA damage, and it removes methylation marks in genomic DNA [21]. GADD45a was found to be increased in CD4+ T cells from SLE patients compared with healthy controls. GADD45a mRNA levels correlated directly with the SLEDAI and CD11a and CD70 transcript levels, and inversely with overall DNA methylation [20••]. UV-B radiation also increased GADD45a, CD11a, and CD70 mRNAs, and it decreased overall DNA methylation, in normal CD4+ T cells. Furthermore, control CD4+ T cells transfected with GADD45a developed hypomethylated DNA and over-expression of CD11a and CD70. They also had increased proliferative capacity, and they caused increased IgG production from co-cultured B cells. Conversely, suppressing GADD45a in CD4+ SLE T cells with siRNAs decreased GADD45a, CD11a, and CD70 expression, increased overall DNA methylation levels, decreased their proliferative capacity, and decreased their ability to stimulate B cells [20••]. This report thus suggests that ultraviolet (UV) light and perhaps other environmental agents may trigger lupus flares by stimulating GADD45a overexpression.

RFX1

The enzymes responsible for epigenetic chromatin modifications are recruited by transcription factors that bind to DNA. Zhao *et al.* [22••], identified RFX1 as a transcription factor required for epigenetic modifications in SLE. RFX1 was downregulated in SLE CD4+ T cells. Transfecting control CD4+ T cells with RFX1 siRNAs increased CD11a and CD70 expression by decreasing DNA methylation and increasing histone acetylation at each gene's promoter. RFX1 in SLE CD4+ T cells decreased CD11a and CD70 expression by increasing methylation and decreasing acetylation of their promoters. Both HDAC1 and DNMT1 bind RFX1 in control CD4+ T cells. In Jurkat T cells, HDAC1 and DNMT1 require RFX1 and intact X-box elements for binding to the CD11a and CD70 promoters [22••]. Dysregulation of this transcription factor may thus also contribute to epigenetic abnormalities in lupus T cells.

Protein phosphatase 2

Protein phosphatase 2Ac (PP2Ac) dephosphorylates serine and threonine residues, and it has many cellular functions [23–25]. PP2Ac expression and enzymatic activity are increased in SLE CD3+ T cells through unknown mechanisms [26]. Sunahori *et al.* [27••] demonstrated that increased PP2Ac expression in CD4+ T cells is mediated by a region containing cAMP response element (CRE) and Sp1 binding sites located 240 bp 5′ to its promoter. Methylation of this region blocked binding of phosphorylated CRE binding protein (CREB), but not Sp1. CREB binding, and subsequent PP2Ac expression, were increased *in vitro* by treatment with the DNA methylation inhibitor 5-azacytidine [27••]. Although lupus patients were not studied, this adds a signaling molecule to the growing list of T cell genes affected by DNA methylation. SLE is characterized by signaling abnormalities [28], so PP2Ac dysregulation could participate in disease pathogenesis by modulating the expression of other genes involved in immune function is also characterized by signaling abnormalities [28].

KIR genes

Killer immunoglobulin like receptors (KIRs) are clonally expressed on natural killer (NK) cells. They either stimulate or suppress cytotoxicity and the release of inflammatory cytokines, depending on the specific KIR member. Normal T cells do not express KIRs [29]. Basu *et al.* [30••] demonstrated increased expression of the KIR gene family on experimentally demethylated CD4+ T cells and on CD4+ T cells from SLE patients. This was caused by demethylation of the KIR gene promoters. KIR overexpression correlated with SLE disease activity. Crosslinking stimulatory KIRs promoted IFN-γ release while crosslinking inhibitory KIR prevented autoreactive, cytotoxic responses. As normal T cells do not express KIR genes, targeting KIR molecules may be therapeutically useful in lupus.

CD5

B cells from SLE patients express less CD5 and more IL-6 than B cells from controls [31]. CD5 has two isoforms, CD5-E1A on the cell surface and CD5-E1B in the cytoplasm. Garaud *et al.* [32••] showed that the CD5-E1B promoter is preferentially hypomethylated in lupus B cells, leading to increased CD5-E1B transcription at the expense of CD5-E1A. This decreases cell surface CD5 expression [32••]. Methylation of the E1B promoter was increased by blocking IL-6 signaling. The relative hypomethylation and overexpression of intracellular CD5 was reinforced by signaling through the B cell and IL-6 receptors. Interestingly, the CD5-E1B promoter hypomethylation in SLE may be due to decreased DNMT1 expression secondary to IL-6 signaling [32••]. DNMT1 levels in SLE B cells decreased when the cells were treated with anti-IL-6 antibodies [32••], and IL-6 is overexpressed by SLE T cells [33]. As cell surface CD5 negatively regulates signaling through the B cell receptor, decreased CD5 levels could result in activation and expansion of autoreactive B cells in SLE.

Histone modifications

Dimers of four histone proteins, H2A, H2B, H3, and H4, combine to bind DNA and form the nucleosome, and the nucleosomes are then assembled to make chromatin fibers [34]. Histone ‘tails’ protrude from the nucleosome, and they are modified by the covalent addition of methyl, acetyl, or other moieties. These modifications provide signals referred to as the ‘histone code’ that direct structural chromatin modifications [3]. There have been several new reports describing histone acetylation and methylation in lupus.

Histone acetylation

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate chromatin accessibility by adding or removing, respectively, acetyl groups to lysine residues in the N-terminal histone domains [35]. Acetylation neutralizes the positive charge of histone lysines, weakening electrostatic DNA-histone interactions and increasing DNA accessibility for gene expression [36]. Conversely, deacetylation strengthens DNA-histone interactions, thus decreasing DNA accessibility and subsequent gene expression [37].

T cells from SLE patients express different patterns and levels of cytokines and other molecules compared to T cells from controls [38]. Hu *et al.* [39] showed that SLE CD4+ T cells had decreased overall acetylation of both H3 and H4, and the degree of H3 hypoacetylation correlated inversely with SLE disease activity. This raises the possibility that decreased histone acetylation might contribute to lupus pathogenesis by promoting silencing of some genes. However, the genes affected are unclear.

Monocytes are also implicated in SLE pathogenesis [40]. Zhang *et al.* [41•] analyzed H4 acetylation in monocytes from control and SLE patients. Out of 11 000 genes, 179 had increased H4 acetylation as measured by chromatin immunoprecipitation (ChIP) from SLE monocytes. Consistent with the known IFN-α overexpression in SLE [40], binding sites for interferon regulatory factor 1 (IRF1) were found in over two thirds of the genes with hyperacetylated histones. Again, the significance of these changes is unclear. Overall, the importance of histone acetylation changes in human SLE remains uncertain.

Histone methylation

Histone methylation also affects gene expression. Promoters of actively transcribed genes are marked by methylation of lysine 4 on histone H3 (H3K4), and an actively transcribed gene is also methylated at lysine 36 on H3 (H3K36) [42]. In contrast, inactive genes are methylated at H3K27 and permanently silenced genes are frequently methylated at H3K9 [43]. Hu *et al.* [39] reported hypomethylation at H3K9 in SLE CD4+ T cells, compared with healthy controls. Correspondingly, mRNA levels of the histone methyltransferases SUV39H2 and EZH2 were also decreased in SLE CD4+ T cells [39]. As is the case with histone acetylation, the functional significance of changes in histone methylation remains uncertain.

Conclusion

Significant advances have been made in our understanding of epigenetic mechanisms in lupus. Despite this, many unanswered questions remain. A growing body of literature supports the concept that impaired CD4+ T cell DNA methylation, caused by environmental influences, contributes to SLE pathogenesis by altering gene expression in genetically predisposed people. This suggests that preventing or correcting the altered methylation patterns, or designing therapies directed at cells expressing the modified genes, may be therapeutic in SLE. Histone modifications are another important epigenetic mechanism, but the significance of altered histone acetylation and methylation in lupus is not well understood. Epigenetic changes unique to SLE must be more fully characterized before treatment strategies targeting these changes can be identified and then tested.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 610–611).

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