



## Similarities and Differences of Epigenetic Mechanisms in Lupus and Sjögren's Syndrome

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### Abstract

Systemic lupus erythematosus (SLE) and primary Sjögren's syndrome are two systemic autoimmune diseases, which are believed to develop when genetically predisposed individuals undergo epigenetic modifications in response to environmental factors. Recent advances in the understanding of the pathophysiology of these two diseases suggest a multi-step process involving environmental factors leading to distinct cell specific deregulation of the epigenetic machinery, and the effect is reinforced in those patients with risk variants mapping to epigenetically-controlled immune regulators. Finally, it was observed that the PKC-delta/Erk/DNMT1 pathway was altered in both diseases and the effects could be reversed thus providing arguments to suggest that therapeutic strategies targeting this pathway would be effective in both diseases.

**Keywords:** Systemic lupus erythematosus; Sjögren's syndrome; Epigenetics; DNA methylation; Histone acetylation; Endogenous retrovirus

### Abbreviations

HERV: Human Endogenous Retroviruses; MSG: Minor Salivary Glands

### Introduction

Recent advances in our comprehension of the pathophysiology of Autoimmune diseases (AID) strongly suggest a multi-step process that involves environmental factors (e.g. viruses, tobacco, drugs), followed by deregulation of the epigenetic machinery (e.g. DNA demethylation, histone modifications), which in turn specifically affects the immune system and/or the target organs and, last but not least, this process is amplified in the case of genetic mutations [1,2]. As a consequence, autoreactive lymphocytes and autoantibodies (Abs) are produced leading to development of the disease [3]. At the crossroads of environmental and genetic factors, epigenetic processes are deregulated and, in order to highlight important similarities and differences between AID, we have selected systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) as models (Table 1).

### Environmental factors

Several lines of evidence strongly support a critical and pathogenic role for environmental factors and subsequent epigenetic deregulation

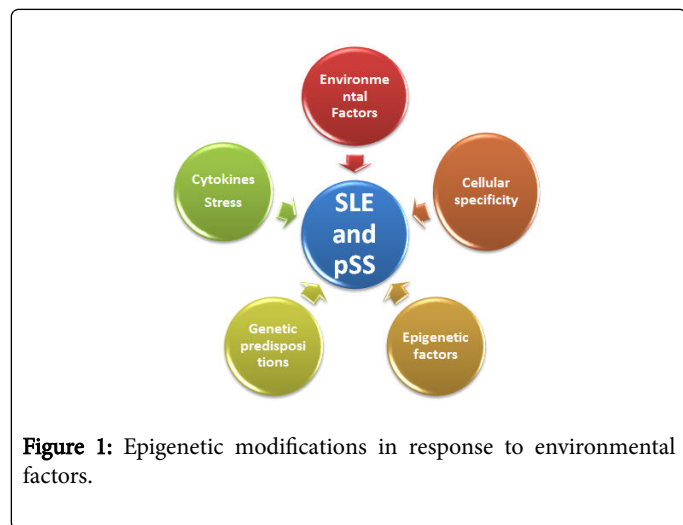
in SLE and pSS development. Such assertion is based on the determination of the disease concordance rates (CR) for monozygotic twins (MZ) revealing a CR of 24-57% for SLE and a CR of 15-25% for pSS, thus supporting an intermediate scenario in which genetics and environmental factors are both involved [1]. Geoepidemiology Analysis has given results that highlight differences between the two diseases since the highest rate of pSS is reported in northern countries while the worldwide distribution of SLE is more homogeneous [4]. Sunlight exposure, smoking, and industrial pollution were associated with SLE, while viruses and psychological stress are reported as contributing factors in pSS [5]. Direct evidence has been provided that UV light, cigarette smoking, and chemicals can induce important epigenetic changes. Regarding drug-induced AID, hydralazine and procainamide, two drugs known to interfere with DNA methylation are well known to induce SLE and SS in both humans and mice. As a whole, these observations strongly suggest a key role-played by DNA methylation and DNA demethylation inducers in the development of these two diseases [6,7].

### Retrotransposons

Another argument to consider, with regards to epigenetic deregulation in AID, is to the detection of abnormal levels of retrotransposons and, among these, human endogenous retroviruses (HERV) [8]. Inserted within the human genome (8%), HERVs are controlled at the epigenetic level by DNA methylation and, when such control is impaired, they can affect the human genome in different ways. One example is related to the human T cell leukaemia related endogenous retrovirus (HRES-1) that is inserted in the long arm of chromosome 1 at position 1q42. DNA methylation controls HRES-1 expression [9], and when expressed, HRES-1 produces a p38gag protein that can induce the development of Abs as observed in 29% of patients with SLE, and 10% of patients with pSS in contrast to 1.5% in healthy donors [10]. An association between SLE and HRES-1 polymorphisms has been described [11]. In minor salivary glands from pSS patients, several HERV-E elements were reported including the SLE T cell provirus HERV-E 4.1 [12]. Another example is HERV-CD5 that is integrated into chromosome 11 upstream of the host cd5 gene exon 1 and downstream of the cd6 gene [13]. This integration occurred just prior to the divergence of hominoids from old world monkeys 25 million years ago [14]. In SLE B cells, defective DNA methylation at HERV-CD5 promoter introduces an alternative promoter for the cd5 gene, and enables transcription of a fusion transcript with the consequence of an intracellular variant of CD5 [15,16], which could, in turn, promote B cell autoreactivity [17,18].

	SLE	pSS
Environmental factors	Drugs (procainamide, isoniazide)	Drugs (procainamide, isoniazide)
	UV lights, smoking	Virus, stress
Monzygotic twins	24-57% concordance rate	15-25% concordance rate
Retrotransposons	HRES-1 (T and B cells)	
	HERV-E 4.1 (T cells)	HERV-E 4.1 (minor salivary glands)
	HERV-E CD5 (B cells)	
DNA methylation	↓Pkc delta-Erk	↓Pkc delta-Erk
	↓DNMT1, DNMT3a	↓DNMT1
	↑Gadd 45 alpha, MBD4	↑Gadd 45 alpha
Histone modifications	↑H3-H4 hypoacetylation	unknown
	↑H3k9 trimethylation	unknown
Genetic risk variants	Long range regulatory sequences	Long range regulatory sequences
	B cells>T cells	B cells>monocytes
Reversibility	Anti-CD20 (B cells)	Anti-IL-6R (epithelial cells)

**Table 1:** Similarities and differences influencing epigenetic factors in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS).



### Epigenetic modifications and cellular specificity

In SLE, T cells, B cells and monocytes are demethylated due to a decrease in the protein kinase (PKC)-delta/Erk/DNA methyl transferase (DNMT)1 pathway, and an increase in the enzymatic activity of Gadd45alpha and MBD4 [19]. T cell PKC-delta inactivation induces a lupus-like disease in mice [20]. A similar scenario is reported in pSS, as DNA demethylation results from a reduction of the PKC-delta/Erk/DNMT1 pathway and an increase of Gadd45alpha, but with the notable exception that the target cell is different and concerns minor salivary gland epithelial cells (SGEC) in pSS [21]. Changes in histone modifications are also detected in CD4 T cells from SLE patients, with global H3 and H4 hypoacetylation and hyper H3k9 trimethylation [22].

### Genetics

Upto forty non-HLA genetic associations were characterized in SLE and pSS, and the list is growing with development of genome wide association studies (GWAS) and next-generation sequencing (NGS) technologies which contribute to the characterization of rare single nucleotide polymorphisms (SNPs), new copy number variations (CNV) and microsatellites [23]. The development of the ENCODE (Encyclopedia of DNA elements) and roadmap Epigenomic programs were decisive for our comprehension of the associated causal genetic risk-factors revealing that they are present predominantly within cell-specific long range gene-regulatory sequences which are located outside promoters, protein coding regions, splice junctions, and 3' UTRs [24]. Histone acetylation is effective to control long-range regulatory sequences by controlling transcription factor binding and in turn transcription. However, such control may be altered in the case of genetic risk variants and such effect would predominantly affect B cells in both SLE and pSS [23], while it is T cells that are affected in nearly all AID [1].

### Reversibility and cytokines

The anti-CD20 monoclonal antibody (mAb) B-cell-depleting agent rituximab is effective in both SLE and pSS [25-27] and targeting cytokines such as BAFF and IL-6 is also effective in management of SLE [28]. Part of this activity may be attributed to the powerful influence of the biotherapies on the epigenetic machinery. In pSS, treating patients with anti-CD20 mAb therapy restores global DNA methylation in SGEC [21], and the utilization of the anti-IL6 receptor mAb itolizumab in SLE B cells repairs the defective Erk/DNMT1 pathway and DNA methylation [16,29].

## Conclusion

The arguments presented here indicate that epigenetic changes (DNA demethylation, histone modifications) confer a risk for SLE and pSS suggesting a strong argument for epigenetic causality in genetically predisposed individuals (Figure 1). Another important point is related to the cellular specificity, which concerns mainly lymphocytes in the case of SLE and epithelial cells in the case of pSS. However, it was also observed that the process was reversible, and that both diseases could be induced by DNA demethylating drugs and are related to a defective PKC-delta/Erk/DNMT1 pathway. As a consequence it can be postulated that drugs controlling this pathway would undoubtedly have benefits for SLE and pSS prevention and treatment [30,31].

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