Review

The epigenetic impact of the exposome on Sjögren's disease. A systematic review

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ABSTRACT

Objectives. *Sjögren's disease (SjD) is a complex systemic autoimmune disorder with a multistep pathogenesis driven by the interplay of genetic, epigenetic, hormonal, and environmental factors. Even though genetic predisposition is clearly associated with disease susceptibility, it cannot fully explain its pathophysiology. Hormonal fluctuations and various components of the exposome are also considered critical contributors to disease onset and progression. Environmental exposures can induce heritable changes that modulate gene expression without affecting the underlying DNA sequence, known as epigenetic alterations.*

Methods. *A comprehensive literature search was conducted across major databases (PubMed, MEDLINE, Embase and Web of Science). No publication date restrictions were applied, but only articles written in English were considered. Studies were eligible for inclusion if they investigated any environmental exposure in association with epigenetic modifications in SjD, using human, animal (e.g., mice), or in vitro/in vivo models.*

Results. *Epigenetic mechanisms, including DNA methylation, histone modifications, and dysregulation of non-coding RNAs (nc-RNAs), are increasingly recognised as central to SjD pathogenesis. These alterations may serve as a crucial link between the exposome and the onset of autoimmune processes by mediating the immune system's response to external stimuli. Consequently, they may promote aberrant immune activation, leading to both glandular and extra-glandular manifestations, and may increase the risk of lymphomagenesis through chronic B-cell stimulation within affected issues.*

Conclusions. *Despite notable advances, further research is warranted to elucidate how specific environmental and epigenetic factors interact in genetically susceptible individuals. This systematic review also highlights the potential of epigenetic modifications as biomarkers to enhance diagnostic accuracy and design targeted, individualised therapies based on precision medicine approaches.*

Introduction

Sjögren's disease (SjD) is a chronic systemic autoimmune disorder typified by lymphocytic infiltration and dysfunction of the salivary and lacrimal glands (1). The disease frequently shows a multifaceted clinical presentation. It may be asymptomatic, especially in early stages, or present with symptoms of xerostomia and xerophthalmia known as sicca symptoms. Additionally, SjD may also manifest with a broad spectrum of extra-glandular and systemic features, potentially involving the joints, skin, kidneys, lungs and other internal organs. Furthermore, SjD is associated with a higher risk of lymphomagenesis in comparison with other autoimmune diseases, probably due to chronic stimulation of B-cells within the affected tissues (2).

Although its exact aetiopathogenesis remains unclear, SjD is widely recognised as a multistep process triggered by environmental, hormonal and epigenetic factors in genetically predisposed individuals, requiring sustained interactions between the innate and adaptive immune systems (3-5). Several genetic susceptibility regions, mainly within but also outside of the major histocompatibility complex (MHC) -including human leukocyte antigen (HLA) and non-HLA genes- have been

associated with SjD (6). However, genetic predisposition alone, even if different genetic regions are combined in polygenic scores, appears to be insufficient for disease onset and progression (7, 8). Indeed, no absolute concordance rate for SjD in monozygotic twins has been reported, whereas estimates based on different studies for overlapping autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) suggest a concordance rate of approximately 20 percent (20%). These findings emphasise the importance of additional cofactors, especially environmental, hormonal and epigenetic influences, in the pathogenesis of SjD.

Among these, epigenetic modifications, particularly those driven by environmental exposures, are thought to play a substantial role in disease pathophysiology (9, 10). By modulating intracellular signalling pathways, they may contribute to aberrant activation of lymphocytes within glandular or extra-glandular tissues, promoting the release of cytokines, such as interferon (IFN)-gamma, interleukin-17 (IL-17), B-cell activating factor (BAFF), as well as the production of SjD specific autoantibodies (anti-Ro/SSA, anti-La/SSB) (11-13). Each epigenetic mechanism exerts a distinct influence on immune dysregulation in SjD, leading to the activation of diverse molecular pathways and the emergence of phenotypic heterogeneity observed among the patients.

This review provides an overview of recent literature focusing on new insights into epigenetic studies and underscoring how components of the exposome -including infections, diet, smoking, alcohol, pollutants and hormonal fluctuations- may influence gene expression and immune regulation in the context of SjD.

Methods

Electronic searches were performed across major databases: PubMed, MEDLINE, Embase and Web of Science. No restrictions were applied regarding publication date, but only articles written in English were considered. The following search string was used and adapted appropriately for each database: ("Sjogren" OR "Sjogren's" OR "Sjogren's Disease" OR "Sjogren's Syndrome" OR "Sjögren" OR "Sjögren's" OR "Sjögren's Syndrome" OR "SjD") AND ("environment" OR "environmental factors" OR "environmental exposure" OR "alcohol" OR "smoking" OR "pollution" OR "air pollution" OR "solvents" OR "environmental pollutants" OR "PM2.5" OR "PM10" OR "particulate matter" OR "pesticides" OR "toxins" OR "heavy metals" OR "chemical exposure" OR "diet" OR "nutrition" OR "drug-induced" OR "virus" OR "viral" OR "infection" OR "infections" OR "viral infection" OR "viral infections" OR "EBV" OR "Epstein-Barr" OR "Epstein-Barr virus" OR "CMV" OR "Cytomegalovirus" OR "HCV" OR "Hepatitis C" OR "HTLV-1" OR "HSV" OR "Herpes simplex virus" OR "Hormone Replacement Therapy" OR "hormone therapy" OR "HRT" OR "Estrogen Therapy" OR "ERT" OR "Estrogen Replacement Therapy" OR "stress" OR "psychological stress" OR "chronic stress") AND ("epigenetics" OR "epigenetic" OR "epigenetic modification" OR "epigenetic factors" OR "methylation" OR "hypomethylation" OR "hypermethylation" OR "CpGs" OR "CpG" OR "micro-RNA" OR "micro-RNAs" OR "miRNA" OR "miRNAs" OR "non-coding RNA" OR "noncoding RNA" OR "non-coding RNAs" OR "noncoding RNAs" OR "ncRNA" OR "nc-RNA" OR "ncRNAs" OR "nc-RNAs" OR "histone" OR "histones" OR "histone modification" OR "histone modifications" OR "histone acetylation" OR "histone hyperacetylation" OR "histone hypoacetylation" OR "histone methylation" OR "histone hypermethylation" OR "histone hypomethylation").

Studies were eligible for inclusion if they investigated any environmental exposure in association with epigenetic modifications in SjD, using human, animal (*e.g.*, mice), or *in vitro*/*in vivo* models. Both descriptive (observational) and interventional designs were considered. Articles were excluded if they did not examine epigenetic effects or were not related to environmental exposure. All retrieved references were initially screened for duplicates. Then, titles and abstracts were assessed for relevance, followed by full-text evaluation of potentially eligible publications. Two independent reviewers performed the screening process, and any disagreements were resolved by consensus. The workflow of the present review is presented in Figure 1.

Epigenetics in Sjögren's disease

Recently, researchers have increasingly highlighted the significant influence of epigenetic mechanisms in the development of autoimmune diseases, including SjD (9, 14, 15).

The term "epigenetics" was first introduced by Conrad Waddington in 1942 within the field of developmental biology, to describe the interactions between genes and their products that result in the expression of a phenotype (16, 17). Since then, the concept has been adopted across various disciplines, leading to some ambiguity regarding its precise definition in the literature. In more recent years, however, "epigenetics" has been more specifically defined as the study of heritable changes that alter gene expression and can potentially influence the phenotype without affecting the underlying DNA sequence. Such changes include DNA methylation, histone modifications, notably via methylation or acetylation, and non-coding RNAs (ncRNAs).

These mechanisms constitute semi-stable alterations -sufficiently stable to maintain cell identity over time, yet dynamic enough to respond to external stimuli (18, 19). Importantly, epigenetic regulation allows for the coordinated control of multiple genes, enabling cells to activate genes that are necessary for their specific function, while silencing those that are not. This modulation helps maintain stable gene expression patterns within each cell type and supports overall tissue homeostasis. Nevertheless, these patterns are not fixed and can change in response to various environmental factors, including infections, smoking, chemical exposure, and others.

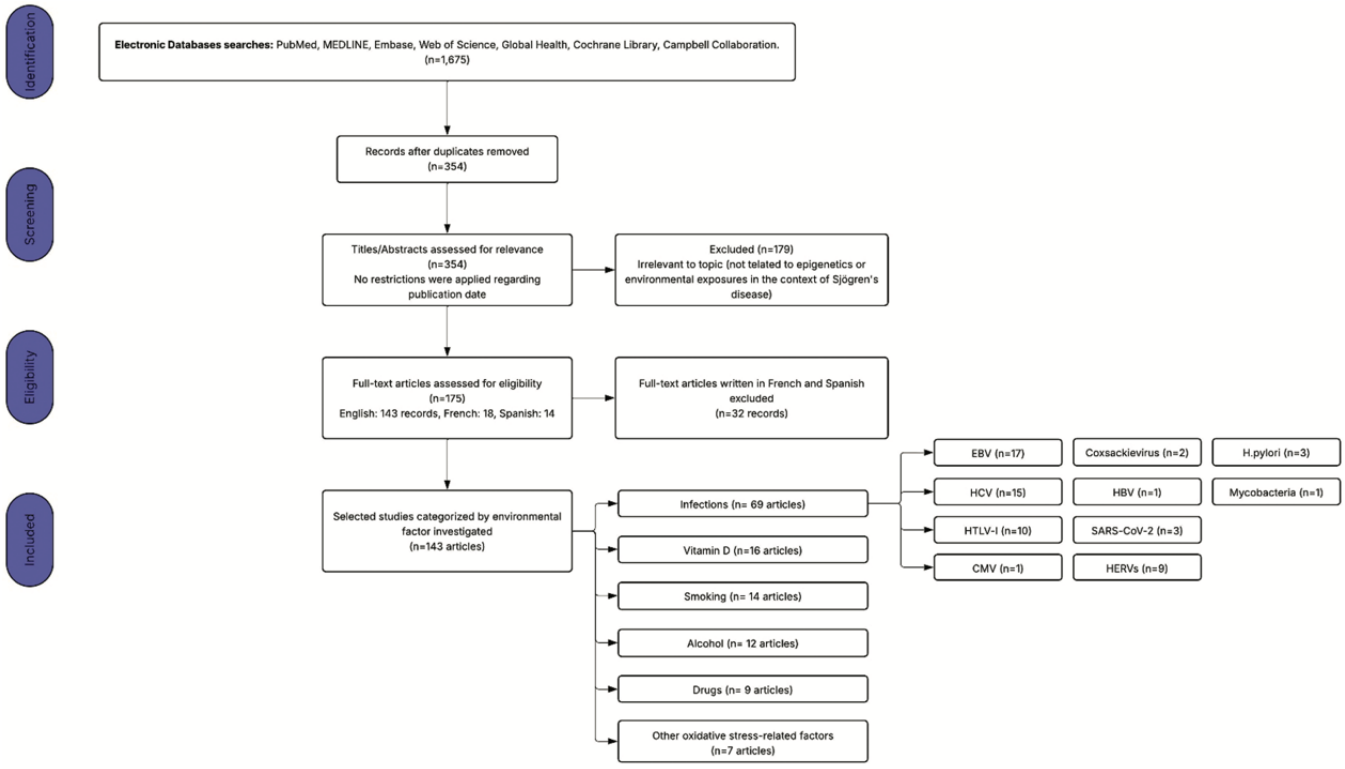

Fig. 1. Workflow of the present review.

DNA methylation

The most extensively studied and well-characterised epigenetic mark is DNA methylation. Its primary mechanism involves the inhibition of transcription factors binding to regulatory DNA regions, thereby leading to transcriptional suppression. This process entails the covalent addition of a methyl (CH3) group to cytosine residues within CpG dinucleotides (where a cytosine is followed by a guanine) (19). CpG dinucleotides are not evenly distributed across the genome and tend to cluster in regions known as "CpG islands", which are typically located in gene promoter areas. In somatic cells, promoters of active genes are generally unmethylated, whereas promoters of inactive genes are often hypermethylated (20). In mammalian DNA, methylation takes place almost exclusively at cytosines within CpG contexts and is catalysed by DNA methyltransferases (DNMTs). There are three phylogenetically conserved DNMTs in mammals; DNMT1, DNMT3a and DNMT3b. De novo DNA methylation is established by DNMT3a and DNMT3b, while DNMT1 maintains these modifications during DNA replication (20).

Beyond endogenous regulation, DNA methylation patterns can also be modulated by external environmental factors. Specifically, exposure to environmental toxins can directly inhibit DNMTs activity, potentially resulting in hypomethylation or hypermethylation of multiple genes (14). These epigenetic alterations can influence gene expression, with downstream effects on both transcriptional and post-transcriptional levels.

Teruel *et al*. demonstrated that DNA methylation affects many cell types implicated in SjD pathophysiology, including $CD19^+$ B and $CD4^+$ T lymphocytes, $CD14^+$ monocytes and salivary gland epithelial cells (SGECs) (21). Investigations in these cells from SjD patients employed various methods to assess DNA methylation at specific CpG sites in selected target genes or determined global methylation without single CpG site resolution (19). Epigenome-wide association studies (EWAS) in patients with SjD have consistently revealed a global reduction in DNA methylation levels at CpG sites. Notably, this hypomethylation was observed within genes involved in type I IFN -such as STAT1, IFI44L, IFITM1 and USP18- signalling across various cell types, particularly in comparison between tissue samples from patients with SjD and healthy individuals. At the molecular level, it was associated with decreased expression of the methyltransferase DNMT1 and increased expression of the demethylating partner Gadd45 alpha (15). Consequently, IFN-inducible genes were upregulated in SjD patients, with a more pronounced signature in individuals exhibiting elevated titres of anti-Ro/SSA and anti-La/SSB autoantibodies (22-24).

In addition, CD70 promoter hypomethylation has been shown to lead to overexpression of CD70 in CD4+ T lymphocytes from patients with SjD (25). This epigenetic alteration promotes aberrant T cell activation and enhanced B cell help, ultimately resulting in autoantibody production. Collectively, these findings underscore the role of DNA hypomethylation in disrupting immune tolerance and the broader contribution of epigenetic dysregulation in the pathogenesis and progression of SjD.

Histone modifications

Modifications of histone proteins represent another epigenetic mechanism. Histones are small globular proteins (11-15 kD) that participate in the formation of a multi-subunit core around which DNA can be wrapped to create a nucleosome. This structure constitutes the first level of DNA compaction, essential for packaging linear DNA into highly condensed chromosomes, while also being important in gene transcription by modifying chromatin accessibility to the transcriptional machinery (20, 26).

Histones are subject to a wide range of covalent post-translational alterations, among which methylation, acetylation, ubiquitination, phosphorylation being the most prevalent. These modifications have been reported at multiple amino acid residues, although the most common region is the N-terminal tail. As a result, changes of their flexible N-terminal tails can modulate their interactions with adjacent histones, DNA and various nuclear proteins, ultimately impacting gene transcription (27).

The most widely studied histone modifications are the methylation and acetylation of lysine (K) residues, particularly on histones H3 and H4 (28). Histone methylation exerts diverse effects on chromatin structure and cellular processes, including transcriptional activation or repression, as well as involvement in DNA replication and repair. In contrast, histone acetylation is generally associated with a relaxed chromatin conformation that facilitates transcription, whereas deacetylation promotes chromatin condensation and transcriptional repression (28, 29).

Additionally, environmental factors can lead to post-translational histone alterations such as phosphorylation, methylation, or ubiquitination (30). These changes can create binding sites for regulatory proteins that modulate chromatin architecture and gene expression, thereby contributing to the pathogenesis of autoimmune diseases.

As reported by Imgenberg-Kreuz *et al*., CpG sites hypomethylated in whole blood from patients with SjD compared to healthy controls were notably abundant in enhancer regions by histone 3 lysine 4 methylation (H3K4me1) and histone 3 lysine 27 acetylation (H3K27ac), while hypermethylated CpG cites were depleted in these areas and primarily localized within genes marked by histone 3 lysine 36 methylation (H3K36me3), indicative of active transcription (19, 31). At present, there are no studies available analysing histone modifications directly in primary cells from patients with SjD. Nevertheless, efforts to integrate multiple layers of genome-wide datasets, including SNP genotyping, DNA methylation and histone marks, offer significant potential to enhance our understanding of the functional impact of variants associated with SjD.

Non-coding RNAs (ncRNAs)

Among the mechanisms of epigenetic regulation are also non-coding RNAs (ncRNAs), a diverse group of RNA molecules that do not encode functional proteins; however, they act as regulatory RNAs, essential for the post-transcriptional control of mRNA expression (32, 33). NcRNAs include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Their transcription from intronic or intergenic regions plays a critical role in biological processes such as tissue differentiation, development, proliferation and cell metabolism.

MiRNAs are a class of evolutionary highly conserved small (19-25 nucleotides), non-coding, single-stranded RNA molecules that play a pivotal role in gene silencing by acting as negative modulators of gene expression (34-36). They perform this function by binding to complementary sequences of their target mRNA in the 3' untranslated region (UTR) (36). By this mechanism, miRNAs induce either translational inhibition or destabilization of the target mRNA (37). LncRNAs, on the other hand, are defined as ncRNAs with a length above 200 nucleotides, localized in both the nucleus and the cytoplasm (38, 39). They participate in a range of molecular pathways, including epigenetic regulation, transcription and translation, although their precise mechanisms of action are still elusive. It has been observed that lncRNAs can interact with other ncRNAs, such as miRNAs. Specifically, they may function as "miRNA sponges", binding to miRNAs and thus preventing them from targeting mRNAs (40). Moreover, lncRNAs can compete with the 3' UTR regions of mRNAs for miRNA binding, which can indirectly inhibit the miRNA-mediated repression of these mRNAs (41).

Emerging evidence suggests that dysregulation of ncRNAs may contribute to SjD pathogenesis by modulating immune responses and inflammatory signaling pathways (42). Aberrant expression of both miRNAs and lncRNAs has been identified across multiple autoimmune disorders, including SjD (37, 43, 44). Indeed, recent studies in peripheral blood cells, minor salivary gland tissue and SGECs from patients with SjD revealed numerous differentially expressed miRNAs (45). Nevertheless, the exact functional implications and target genes of these molecules remain only partially understood in many cases (45-50).

Owing to their participation in fundamental cellular regulation, alterations in expression of ncRNAs can significantly affect their target molecules. One of the most extensively studied and well-characterised miRNAs, has-miR-146a, is known to have a key role in both innate and adaptive immunity by suppressing inflammatory responses (51). Investigations into the expression profile of this miRNA in peripheral blood mononuclear cells (PBMCs) from individuals with SjD have consistently demonstrated its upregulation (47). Consequently, has-miR-146a is thought to participate in early disease pathogenesis by promoting phagocytic activity and reducing the production of pro-inflammatory cytokines (47).

Additionally, recent findings have shown that downregulation of miR-574 and miR-17-92, along with upregulation of miR-768-3p,miR-150 and miR-155, are also associated with the pathogenesis of SjD (52, 53). Bruno *et al*. observed miR-155 upregulation in SjD patients who experienced non-Hodgkin's lymphoma (NHL), that was correlated positively with focus score, BAFF-R, and IL-6R levels- biomarkers

of aberrant B cell activation and lymphomagenesis (54).

Environmental exposures have been shown to modulate the transcription of miRNAs and lncRNAs through various mechanisms, including direct effects on transcription factor effectiveness, epigenetic modifications or disruptions in intracellular signalling pathways (55). Moreover, the gut microbiota, which is dynamically shaped by diet and other environmental elements, can modulate ncRNA expression, indirectly affecting immune system regulation and the initiation or progression of autoimmune disorders (56, 57).

Environmental factors in the pathogenesis of Sjögren's disease

Viral infections

Viral infections have long been considered potential triggers for initiating the autoimmune process in SjD (58). As a result, they have been the subject of ongoing investigation. Thus far, three different viruses have been extensively studied in relation to their impact on the pathogenic pathways of SjD; Epstein-Barr virus (EBV), hepatitis C virus (HCV) and human T cell lymphotropic virus type I (HTLV-1) (58, 59). However, there are many other viruses that are thought to be associated with SjD development, which will be further examined below (60-63). The mechanisms by which viruses can induce modifications in infected cells are still debated but may involve abnormal gene transcription resulting from viral genome insertion into the host cell DNA, or virus-induced epigenetic alterations.

Epstein-Barr virus (EBV). Although it should be noted that EBV is highly prevalent, being present in up to 95% of the general population, it appears to exhibit a marked tropism for the salivary glands, suggesting a potential association with SjD. Indeed, several studies have shown that EBV DNA is detected at increased levels in the salivary glands of patients with SjD compared with healthy individuals. Moreover, patients positive for anti-SSA/Ro and/or anti-SSB/La autoantibodies have been found to have higher immunoglobulin G (IgG) titres against the EBV early antigen in contrast to those with negative autoantibodies. On the same prism, Hudson *et al.* studied previously healthy females with primary EBV infection and concluded that anti-Ro52 and anti-Ro60 autoantibodies were detectable as early as seven days after infection, undergoing class switching from IgM to IgG (64). These findings suggest that EBV infection may directly promote the production of SjD-associated autoantibodies.

Recently, Kaberdoos *et al.* found that genes such as SLAM7, RUNX3, BCL2, FAS and CD247, which are involved in the immune response to EBV, were observed to be hypomethylated in labial salivary gland (LSG) tissue of patients with SjD (65). Specifically, SLAM7 has been identified as a marker expressed on $CD4^+$ cytotoxic T lymphocytes (CTLs). In SjD, elevated levels of $CD4^+$ CTLs have been reported in both peripheral blood and SGECs, correlating with disease progression and severity (66). Notably, $CD4^+$ CTLs comprise approximately 20% of all T lymphocytes in the salivary glands of affected individuals. Recent investigations proved that increased expression and hypomethylation of the RUNX3 gene in minor salivary gland tissue have demonstrated excellent diagnostic performance with an area under the curve (AUC) of 1.0 for distinguishing SjD patients (67). Additionally, overexpression of BCL2, FAS and FASL in LSG of SjD has been confirmed by immunohistochemistry, with BCL2 upregulation correlating with a reduction in acinar cell numbers (68). Complementary findings from genome-wide DNA methylation analyses reported CD247 hypomethylation in $CD4^+$ T lymphocytes of SjD patients, suggesting epigenetic regulation may contribute to disease pathogenesis (8, 22, 69). The observed increase in B-cell populations and hypomethylation of EBV-related genes underscore their involvement in the development of ectopic lymphoid structures within the salivary glands of SjD patients and, consequently, in disease pathogenesis (70). Importantly, EBV is detectable within these structures in a subset of patients, whereas it is absent in glandular tissue lacking these structures.

As previously mentioned, miRNAs expression plays also a central role in SjD pathogenesis. One study reported that levels of the EBV-derived miRNA, ebv-miR-BART13-3p, were elevated in the salivary glands of patients with SjD compared to healthy controls (71). Of note, ebv-miR-BART13-3p has been proposed to suppress the expression of stromal interaction molecule 1 (STIM1), a key regulator in the secretory function of acinar cells. This finding provides a compelling mechanistic link between EBV infection and reduced saliva production. Furthermore, this miRNA has been reported to mediate intercellular communication by transferring between B lymphocytes -the primary targets of EBV- and SGECs via microvesicles.

Moreover, latent transcripts of EBV [such as EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs)] exert epigenetic control over viral oncoprotein expression through mechanisms including CpG methylation, histone deacetylation, miRNA interactions, and activation of super enhancers (72). These same epigenetic pathways may also lead to the immortalisation of host cells and to abnormal cell behaviour that might result in malignancy. In addition, EBV encodes two ncRNAs, EBER-1 and EBER-2, which have been associated with B cell lymphomagenesis. These findings suggest that EBV may influence the SjD pathogenesis through epigenetic reprogramming of B lymphocytes, resulting in both chronic immune activation and lymphoproliferative disorders.

Hepatitis C virus (HCV). HCV has been increasingly implicated in autoimmune manifestations that resemble or potentially overlap with SjD (73, 74). In addition to its well-established hepatotropism, it exhibits both lymphotropism and sialotropism, infecting immune cells and salivary glands -tissues central to SjD pathology (75).

Chronic HCV infection has been associated with systemic immune activation, particularly B-cell hyperactivity mediated by elevated BAFF levels,

which may lead to features commonly observed in SjD, such as cryoglobulinemia, vasculitis, polyneuropathy and lymphoproliferative disorders (76, 77). These extrahepatic manifestations, alongside clinical symptoms like xerostomia and arthralgia, have led to ongoing debate over whether HCV acts as a direct etiological factor in SjD or simply mimics its clinical presentation. Nonetheless, it should be noted that active HCV infection is an exclusion criterion in the 2016 American College of Rheumatology/European League Against Rheumatism (currently European Alliance of Associations for Rheumatology) classification criteria for SjD (78).

Recent findings suggest that HCV may exert epigenetic effects on host cells, possibly altering gene expression profiles involved in immune pathways and epithelial cells function, further reinforcing its potential relevance in SjD pathogenesis (79). Although such epigenetic marks, namely DNA methylation, histone modifications and miRNA dysregulation, have been documented in HCV-infected hepatocytes and lymphoid cells, direct evidence of these alterations in SGECs remains lacking (80).

Human T Lymphotropic virus type I (HTLV-I). Investigations using transgenic mouse models have demonstrated that retroviral infection increases susceptibility to autoimmune diseases, including SjD, polymyositis and RA, compared to non-infected controls (81). In this context, HTLV-I, through the expression of its regulatory Tax and HBZ (HTLV-I bZIP factor), can infect SGECs, resulting in elevated levels of proinflammatory mediators, such as ICAM-1, IP-10, and chemokines like RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) (82). During HTLV-I infection, B cell activity appears to be downregulated, leading to reduced production of autoreactive antibodies (83).

Green *et al*. reported that transgenic mice with the HTLV-1 Tax gene developed an exocrinopathy resembling human SjD (84). Additionally, Mariette *et al*. identified the HTLV-I Tax gene within salivary gland cells of SjD patients (85). Nakamura *et al*. observed that SjD patients co-infected with HTLV-I and HAM had significantly lower anti-SAA/Ro antibody titres, despite more pronounced lacrimal gland involvement; however, Focus scores in minor salivary gland biopsies were comparable between HTLV-I-positive and -negative groups (83). Terada *et al*. demonstrated that HTLV-I-seropositive SjD patients often have IgA-class HTLV-I antibodies in saliva (86). In follow-up research, the same group noted reduced glandular destruction in HTLV-I-positive SjD patients, suggesting that HTLV-I may inhibit apoptotic pathways and promote cell proliferation (87).

A Brazilian cohort of 129 HTLV-I-seropositive individuals showed that, although many exhibited sicca (46 with xerostomia, 18 with xerophthalmia, 8 with confirmed hyposalivation), only one had SjD-specific autoantibodies; minor salivary gland biopsies in six cases showed SjD-characteristic mononuclear infiltrates (88).

Overall, these findings suggest a dual role for HTLV-I; in some individuals, it may trigger a full-blown autoimmune response culminating in SjD, while in others it may cause nonspecific salivary gland inflammation manifesting as sicca symptoms. Notably, HTLV-I-positive SjD patients tend to have fewer ectopic germinal centres and reduced CXCL13 expression in infiltrating mononuclear cells in contrast to HTLV-I-negative SjD patients (89). Nevertheless, according to the current literature, there is no evidence to date indicating that HTLV-I induces epigenetic modifications in SGECs. Therefore, more in-depth investigation is warranted in this context of SjD pathogenesis.

Other viruses

As previously stated, several other viruses have been implicated in the potential pathogenesis of SjD, including, among others, cytomegalovirus (CMV), coxsackievirus, hepatitis B virus (HBV) and SARS-CoV-2 virus. The salivary glands are recognised as target organs of CMV, with cases of parotitis and sialadenitis being described during the course of infection (90). Triantafyllopoulou *et al*. detected evidence of coxsackie virus VP1 antigen in minor SGECs of SjD patients, an infection not observed in secondary SjD, other rheumatic conditions or healthy controls (60). The authors also reported cross-reactivity between anti-SAA/Ro60 and a homologous peptide in coxsackievirus 2B protein, suggesting virus-induced immune activation (61). Additionally, HBV has been associated with SjD through observational data indicating a potential protective effect of antiviral therapy (62). Despite these findings, current evidence is insufficient to establish a clear link between these viral infections and SjD development. This field remains unexplored, and it is currently unknown whether and how these viruses may contribute to SjD pathophysiology, particularly via epigenetic mechanisms.

According to current studies, the prevalence of Coronavirus disease-19 (COVID-19) has been found to be significantly higher in patients with SjD compared to general population. In the study by Lee *et al*., the comparison between COVID-19-positive and COVID-19-negative individuals identified three differentially methylated CpG sites with a false discovery rate (FDR) below 0.05: cg22399236, cg03607951, and cg09829636 (91). Notably, a search of these CpGs in the EWAS Atlas revealed multiple associations between hypomethylation of cg03607951, located in IFI44L gene, and several autoimmune disorders, including SLE, SjD, and mixed connective tissue disease, among others. The persistence hypomethylation of IFI44L three months post-infection may indicate that the reversal of infection-induced immune responses is a prolonged process, potentially reflecting the lasting impact of SARS-CoV-2 on the epigenetic regulation of immune-related genes. In this context, longitudinal studies assessing the persistence of methylation changes after infection could provide valuable insights into the possible long-term epigenetic consequences of COVID-19 and their role in the development of autoimmune diseases (63, 69).

Human endogenous retroviruses (HERVs). HERVs, which comprise approximately 8% of the human genome, are normally silenced by epigenetic mechanisms, primarily DNA methylation (92). Disruption of this regulation can lead to the expression of HERV elements and retroviral proteins with immunogenic potential. In SLE and SjD, specific HERV loci, such as HRES-1, HERV3-1 and HERV-E 4.1 p30 gag protein, are overexpressed in lymphocytes and SGECs, and antibodies against HRES-1-derived p38 gag protein have been found in a subset of patients with both autoimmune diseases (93). Furthermore, DNA hypomethylation of HERV-CD5 promoter in B lymphocytes results in the expression of an intracellular CD5 variant, which may drive autoreactive responses (94, 95).

At the molecular level, both SLE and SjD share a defective protein kinase (PKC)-delta/ERK/DNA methyltransferase (DNMT)1 pathway -affecting lymphocytes in SLE and SGECs in SjD- which leads to global DNA hypomethylation (96). Histone modifications are also detected in CD4 T cells from SLE patients, with global H3 and H4 hypoacetylation and hyper H3k9 trimethylation (97). Methylation inhibitors such as 5-azacytidine (5-aza-C) or procainamide seem to enhance HERV transcription by downregulating DNMT1, a phenomenon observed both in PBMCs and in animal models. Moreover, experimental agents, including cycloheximide (a protein synthesis inhibitor) and benzopyrene diol epoxide (a DNA-damaging compound), have been shown to synergistically upregulate ERV RNA expression *in vitro*. Remarkably, the epigenetic dysregulation underlying HERV activation appears to be reversible. In SjD, treatment with anti-CD20 monoclonal antibody (rituximab) has been shown to restore methylation profiles in SGECs and correct pathway defects (96). Similarly, in SLE, anti-IL-6 receptor therapy (tocilizumab) reactivates DNMT1 expression through the ERK pathway in B lymphocytes (98, 99). These findings strongly support a model in which epigenetically driven HERV dysregulation contributes to the pathogenesis of autoimmune diseases like SLE and SjD, particularly in genetically predisposed individuals.

Other infections

Helicobacter pylori. H.pylori infection may play a role in SjD pathogenesis; however, its contribution remains controversial due to conflicting reports (100). A recent meta-analysis of nine studies examining H.pylori infection rates among SjD patients reported a weak association between the two entities, reaching an odds ratio (OR) of 1.24 (95% CI 1.03-1.50) (101). Notably, six out of the nine included studies used outdated classification criteria for SjD, while only two confirmed H.pylori infection via biopsy; the remaining seven relied on serological testing. Therefore, the findings from this meta-analysis should be interpreted with caution. Additionally, a more recent investigation showed a higher prevalence of past H.pylori infection among newly diagnosed SjD patients, compared to controls.

MiRNA-mediated immune modulation and impaired apoptosis observed in H.pylori-associated gastric MALT lymphoma raise the possibility of similar epigenetic dysregulation in SjD. Specifically, H.pylori infection appears to affect the expression of certain miRNAs, such as 21a, 135b, 142a, 150, and 155, which modulate cell proliferation, B cell hyperactivity, and survival. These miRNAs have been shown to inhibit the transcription of the gene encoding the proapoptotic protein TP53INP1 (tumour protein p53-inducible nuclear protein 1) (102). Thus, it is plausible that H.pylori, through epigenetic alterations, may be involved in SjD pathogenesis and potentially lead to complications such as lymphoma.

Mycobacterial infection. Recent findings suggest that infection with non-tuberculosis mycobacteria (NTM), such as *Mycobacterium avium* subsp. paratuberculosis (MAP), may contribute to the pathogenesis of SjD through mechanisms involving molecular mimicry and epigenetic modulation of immune responses. In genetically predisposed individuals, including those carrying polymorphisms in the TNFAIP3 gene, which encodes the A20 protein, dysfunction of A20 may amplify macrophage inflammatory responses to mycobacteria, increasing exposure to mycobacterial antigens. MAP, widely present in the environment and the diet, expresses heat shock proteins (*e.g.*, hsp65) that share epitope homology with host autoantigens Ro and La, supporting a molecular mimicry mechanism in autoimmunity. Moreover, the BCG vaccine -known to modulate both innate and adaptive immunity via epigenetic reprogramming- has been proposed to exert protective or therapeutic effects against SjD, underscoring a potential role of infection-driven epigenetic alterations in the initiation or development of the disease (103).

Vitamin D

In SjD, several studies have suggested a potential role for vitamin D in the disease pathogenesis (104-106). The primary natural source of vitamin D (1,25-dihydroxyvitamin D3) is its synthesis in the skin, which occurs through a process dependent on ultraviolet radiation (UV). Reduced exposure to UV, often recommended as part of the management of cutaneous manifestations, has been proposed as a contributing factor to vitamin D deficiency (107).

Recently, increasing attention has been given to the role of vitamin D in modulating epigenetic mechanisms, primarily in the context of cancer, as well as in the pathogenesis of autoimmune disorders (108, 109). Among these, SLE is the most extensively studied in relation to epigenetic dysregulation, with vitamin D deficiency being implicated in disrupted DNA methylation -particularly through reduced availability of methyl donors and impaired DNMT1 activity- leading to gene hypomethylation and immune imbalance (112). Furthermore, focus has been placed on the methylation status of specific genes in T lymphocytes, such as CD11a (ITGAL), perforin (PRF1), CD70 (TNFSF7), and CD40LG (TNFSF5), as key contributors to the pathogenesis and progression of SLE (14). Histone

modifications and ncRNAs in SLE have received less research attention compared to DNA methylation.

In contrast, in RA, vitamin D deficiency has been linked to higher disease activity, and certain polymorphisms and methylation changes in vitamin D genes (such as VDR and CYP27B1) have been associated with disease susceptibility.

In SjD, although low vitamin D levels have been correlated with disease manifestations and complications, evidence for a direct epigenetic mechanism remains limited. Conflicting results from other studies underscore the need for further investigation. Of note, a vitamin D-related SNP, VDR rs7975232, has been proposed as a potential risk factor for SjD, although its relevance appears to be population-specific (113). Therefore, additional large-scale, multi-ethnic genetic studies are urgently warranted to unravel the interaction between vitamin D, genetic susceptibility and disease progression. Comparable limitations are observed in systemic sclerosis and inflammatory bowel disease, where vitamin D status influences immune function and epithelial barrier integrity, but its role in epigenetic regulation is not yet clearly defined (114, 115).

Smoking

Despite its well-established role as a risk factor in autoimmune diseases, such as RA and multiple sclerosis, the impact of smoking on SjD remains insufficiently investigated. Nevertheless, Jin *et al*. (116), in their systematic review and meta-analysis on risk factors for SjD, examined the association between smoking and SjD in detail. According to their findings, current smoking was negatively associated with the development of SjD, with all reported ORs being less than 1 (<1) (117-120).

Although several studies have suggested that smoking may have a protective effect against SjD (59, 119), Jin *et al*. did not reveal any clear association between either former or current smoking and the disease (116). Of note, Olsson *et al*. reported that individuals who later developed SjD smoked at similar levels during early life as the general population but were more likely to quit smoking over time (117).

Cigarette smoking leads to the inhalation of toxic substances, including tars, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons, and free radicals. This toxic exposure induces oxidative stress, which can disrupt normal epigenetic regulation. One proposed mechanism involves the inhibition of MEK-ERK kinase signalling pathway, which may alter gene expression in immune and inflammatory pathways, thereby contributing to the pathogenesis of autoimmune diseases (123-125). Inhibition at any point in this molecular pathway may ultimately result in the downregulation of DNMTs. The consequent DNA hypomethylation can lead to the upregulation of pro-inflammatory genes, potentially driving clinical manifestations that resemble those observed in SLE (126).

These alterations may also affect additional components of the ERK signalling pathway, as well as its regulatory proteins, including specific phosphatases. For example, protein phosphatase 2A (PP2A) directly inactivates MEK, leading to inhibition of ERK. Other phosphatases involved include PPS and DUSP23, the latter of which being notably overexpressed in patients with SLE. Furthermore, several proteins can modulate the activity of DNMTs. One such protein is EZH2, the catalytic subunit of the Polycomb Repressive Complex 2; elevated EZH2 expression in $CD4^+$ T lymphocytes has been associated with DNMT3A repression, resulting in epigenetic dysregulation in autoimmune disorders (127).

There is evidence suggesting that some of these methylation modifications may be reversible following tobacco cessation (125, 128). However, the interplay between gene polymorphisms, epigenetic marks, and smoking exposure remains incompletely understood and requires further investigation.

As mentioned above, such epigenetic influences have been observed in SLE, where smoking-related alterations in DNA methylation have been linked to disease susceptibility and severity (129, 130). This raises the possibility that similar mechanisms may also be involved in SjD pathogenesis, indicating a need for further research to explore whether tobacco-induced epigenetic changes contribute to disease onset or progression in SjD as well.

Alcohol

Alcohol consumption has been shown to induce epigenetic modifications, including DNA methylation and histone acetylation (131). These alterations can disrupt immune homeostasis and may contribute to the initiation or progression of autoimmune disorders (132). Although most existing data focus on SLE, similar epigenetic pathways are thought to be involved in SjD, which shares overlapping immunopathogenic mechanisms (133, 134). Antioxidant compounds found in alcoholic beverages, most notably resveratrol in wine and humulones in beer, may further modulate these epigenetic processes, possibly inhibiting inflammatory pathways (135-137). Moreover, interindividual variability in alcohol metabolism, such as polymorphisms in genes like N-acetyltransferase 2 (NAT2), has been associated with altered risk for SLE (138).

Given the shared molecular features between SLE and SjD, including T cell DNA hypomethylation and IFN-regulated gene signatures, it is plausible that alcohol-induced epigenetic alterations -modulated by metabolic genotypes like NAT2- could similarly affect disease susceptibility or activity in SjD. Future research integrating epigenomic and pharmacogenomic data is needed to elucidate these interactions and their potential relevance in disease modulation or prevention.

Drug-induced SjD

Hydralazine, procainamide and isoniazid have been implicated in the development of autoimmune responses through their capacity to disrupt normal epigenetic regulation in T lymphocytes (139-141). Both agents inhibit DNA methylation, particularly in $CD4^+$ T lymphocytes, promoting the expression of normally silenced immune-related genes. *In vitro* studies

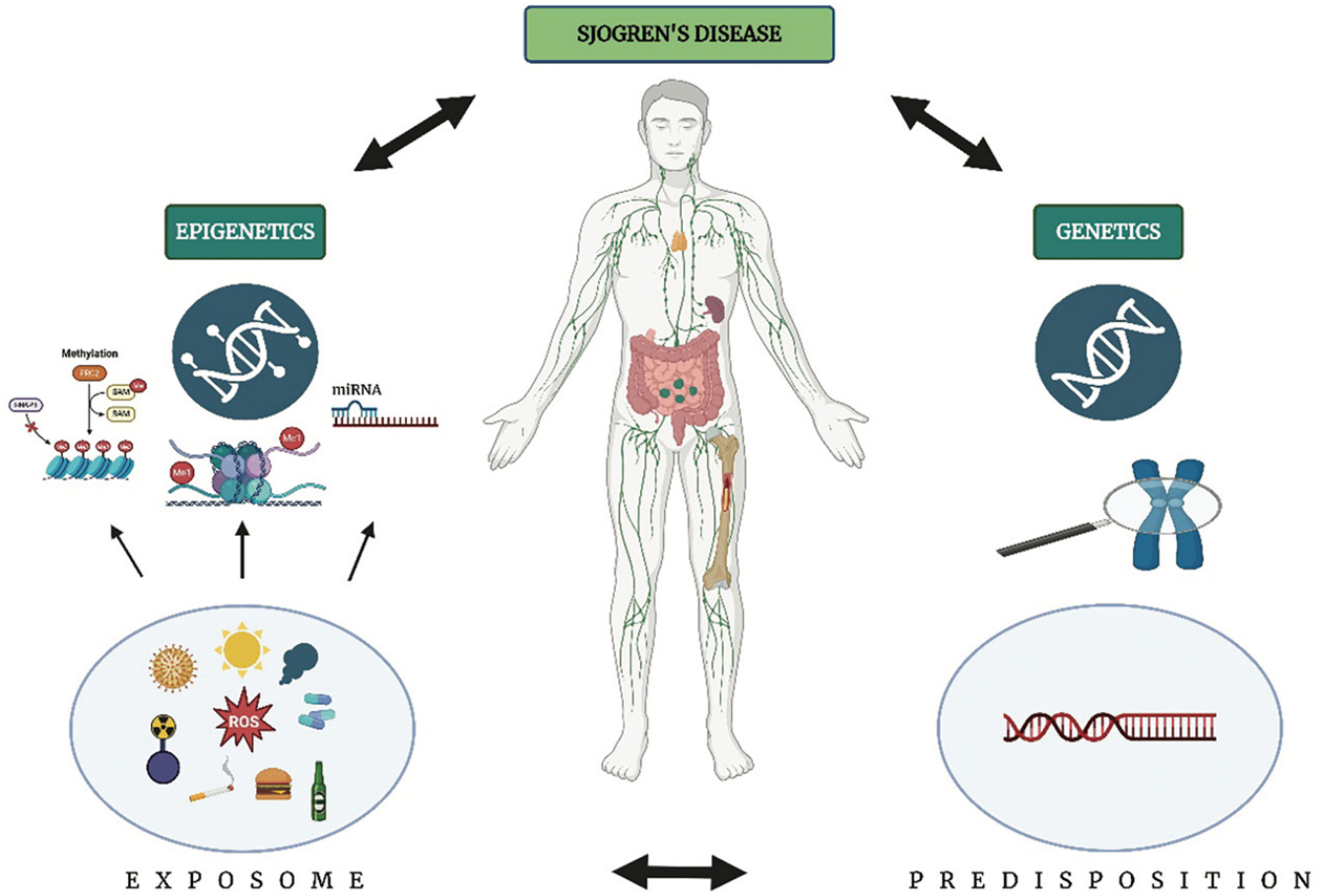

Fig. 2. Genetics and epigenetics in Sjögren's disease (SjD).

demonstrate that exposure of human T cell clones to these drugs results in autoreactive phenotypes (142). Similarly, murine models receiving $CD4^+$ T lymphocytes treated with these drugs develop autoimmune manifestations, including glomerulonephritis and production of autoantibodies such as anti-dsDNA and anti-histone antibodies (130).

Mechanistic investigations reveal that these drugs reduce DNMT1 activity and lead to overexpression of genes such LFA-1, CD70, and CD40L. These changes have been observed both in patients with SLE and in drug-induced lupus animal models, underscoring a shared pathogenic mechanism (143). Considering the similarities in DNA methylation alterations reported in both SLE and SjD, notably the hypomethylation of IFN-stimulated genes and CD70, emerging recent studies suggest that comparable epigenetic modifications may play a role in the onset or progression of SjD.

Oxidative stress

Oxidative stress represents a key environmental factor that influences gene expression through epigenetic mechanisms and plays a pivotal role in the pathogenesis of autoimmune diseases, including SLE and SjD.

In addition to smoking, various environmental exposures contribute to oxidative stress (144). These include, among others, diet, UV radiation (especially UVB; 290-320 nm) (113), air pollution (*e.g.*, nitrogen dioxide, ozone), industrial solvents, pesticides, silica dust, and toxic heavy metals like cadmium and arsenic. All these factors promote the excessive production of reactive oxygen species (ROS), leading to oxidative damage of cellular components and disruption of intracellular signalling pathways.

Importantly, oxidative stress also affects the function of epigenetic enzymes, especially DNMT1. Reduced DNMT1 activity results in global DNA hypomethylation, particularly in T lymphocytes, allowing aberrant expression of normally silenced immune-related genes. This process may enhance immune hyperactivity and cause the loss of self-tolerance, leading to lupus-like disease in genetically predisposed individuals (140, 145, 146).

Moreover, certain dietary components, such as folate and choline, constitute essential methyl donors for DNA methylation. Insufficient intake or impaired metabolism of these nutrients can disrupt the biochemical supply of methyl groups necessary for DNMT function, thereby promoting aberrant DNA methylation patterns (147). A diet poor in methyl donors may aggravate DNA hypomethylation caused by oxidative stress, leading to immune dysregulation and potentially contributing to the development of autoimmune disorders, including SLE and SjD.

A recent genome-wide methylation analysis of SLE patients identified an association between living near major highways, an indicator of long-term

Table I. Environmental factors and their epigenetic influences in Sjögren's disease (SjD) and other autoimmune conditions.

DNA methylation			
Environmental factor	**Main findings in SjD**	**Main findings in other autoimmune conditions**	**References**
Epstein-Barr virus (EBV)	-RUNX3 hypomethylation in minor salivary glands -CD247 hypomethylation in CD4+ T lymphocytes		(8, 22, 65, 67)
SARS-CoV-2 virus	Hypomethylation of cg03607951 in IFI44L gene	**SLE, mixed connective tissue disease** Hypomethylation of cg03607951 in IFI44L gene	(63, 69, 92)
HERVs	-DNA hypomethylation of HERV-CD5 promoter in B lymphocytes -Defective PKC-δ/ERK/DNMT1 & global DNA hypomethylation -Reversibility (rituximab)	**SLE** -Defective PKC-δ/ERK/DNMT1 & global DNA hypomethylation -Reversibility (tocilizumab)	(95, 96, 97, 99, 100)
1,25-dihydroxyvitamin D3 & Methyl-donor-poor diet	-Impaired DNMT1 activity - VDR rs7975232 as a potential risk factor	**SLE** -Impaired DNMT1 activity -Hypomethylation of CD11a (ITGAL), PRF1, CD70 (TNFSF7) and CD40LG (TNFSF5) in T lymphocytes **RA** Methylation changes in vitamin D genes (including VDR & CYP27B1) and disease susceptibility	(14, 112-115, 147, 151)
Smoking	-Oxidative stress -Inhibition of MEK-ERK kinase signalling pathway -Downregulation of DNMTs & DNA hypomethylation -Upregulation of pro-inflammatory genes -Potential association with SjD susceptibility and severity -Need for further research in SjD pathogenesis	**SLE** -Oxidative stress -Inhibition of MEK-ERK kinase signalling pathway -Downregulation of DNMTs & DNA hypomethylation -Upregulation of pro-inflammatory genes -PPS & DUSP23 overexpression -Association of EZH2 overexpression in CD4+ T lymphocytes with DNMT3 inhibition	(123-125) (126) (127) (128) (129, 130)
Hydralazine, procainamide, isoniazid (INH)	-Downregulation of DNMT1 -DNA hypomethylation of IFN-stimulated genes in CD4+ T lymphocytes -Overexpression of LFA-1, CD70, and CD40L genes	**SLE** -Downregulation of DNMT1 -DNA hypomethylation of IFN-stimulated genes in CD4+ T lymphocytes -Overexpression of LFA-1, CD70, and CD40L genes	(94, 130, 139-141, 142, 152)
Oxidative stress: -UV radiation -Air pollution -Industrial solvents -Pesticides -Silica dust -Heavy metals (*e.g.*, cadmium, arsenic)	-Excessive production of ROS -Reduced DNMT1 activity -Global DNA hypomethylation, particularly in T lymphocytes	**SLE** -Excessive production of ROS -Reduced DNMT1 activity -Global DNA hypomethylation, particularly in T lymphocytes -Association of long-term exposure to traffic-related air pollution with UBE2U gene hypomethylation	(140, 145, 146, 148)
Histone modifications			
Environmental factor	**Main findings in SjD**	**Main findings in other conditions**	**References**
Epstein-Barr virus (EBV)		EBNAs & LMPs, histone deacetylation and activation of super enhancers (B cell lymphomagenesis)	(72)
HERVs	-Global H3 & H4 hypoacetylation -Hyper H3k9 trimethylation		(98)
Non-coding RNAs (nc-RNAs)			
Environmental factor	**Main findings in SjD**	**Main findings in other conditions**	**References**
Epstein-Barr virus (EBV)	Elevation of EBV-miR-BART13-3p in salivary glands of SjD patients	Association of EBER-1 and EBER-2 ncRNAs with B cell lymphomagenesis	(71)
Helicobacter pylori	Dysregulation of miR-21a, miR-135b, miR-142a, miR-150, miR-155 Inhibition of TP53INP1		(103)

exposure to traffic-related air pollution, and hypomethylation of the UBE2U gene (148). This gene encodes an enzyme involved in protein and histone ubiquitination, as well as DNA repair, suggesting the environmental pollutants may influence epigenetic regulation of key cellular pathways. Further studies are needed to confirm these findings related specifically to SLE patients. Similar research is also warranted in SjD in order to determine whether environmental exposures such as air pollution induce comparable epigenetic alterations.

Conclusive remarks

Epigenetics is emerging as a crucial area of research in SjD, offering significant insights into the underlying mechanisms of the disease. By revealing how dynamic and potentially reversible modifications regulate gene expression, epigenetic studies open promising avenues for clinical innovation. These alterations hold potential not only as diagnostic biomarkers but also therapeutic targets, creating new opportunities for precision medicine approaches in the treatment of SjD (149, 150).

Recent studies have identified epigenetic changes in both immune cells and SGECs affected by SjD, emphasising their key role in disease pathophysiology through the dysregulation of intracellular signalling pathways. As a consequence, they may drive immune dysfunction and result in glandular damage. Moreover, various components of the exposome, such as viral infections, smoking, alcohol consumption, and exposure to pollutants or toxins, appear to influence these epigenetic mechanisms, potentially contributing to the onset and progression of autoimmune diseases, including SjD.

Despite notable progress, substantial investigation is still needed to clarify how specific epigenetic and environmental factors interact in genetically predisposed individuals, leading to SjD development and heterogeneity. Continued exploration in this field could significantly improve diagnostic accuracy, prognostic assessment, and therapeutic precision in SjD through individualised, mechanism-driven strategies.

A summary of the epigenetic modifications influenced by specific environmental factors in SjD and other autoimmune conditions is presented in Table I.

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