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Review

Sjogren's syndrome: Everything you always wanted to know about genetic and epigenetic factors

Carlo Perricone [a,*,1], Lorenza Bruno [a,1], Giacomo Cafaro [a], Andrea Latini [b], Fulvia Ceccarelli [c], Paola Borgiani [b], Cinzia Ciccacci [d], Dimitrios Bogdanos [e], Giuseppe Novelli [b], Roberto Gerli [a], Elena Bartoloni [a]

[a] Rheumatology, Department of Medicine, University of Perugia, Piazzale Giorgio Menghini, 1, 06129 Perugia, Italy
[b] Department of Biomedicine and Prevention, Genetics Section, University of Rome Tor Vergata, 00133 Rome, Italy
[c] Division of Rheumatology, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University, 00133 Rome, Italy
[d] UniCamillus, Saint Camillus International University of Health Sciences, 00131 Rome, Italy
[e] Department of Rheumatology and Clinical Immunology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Thessaly, Greece

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease characterized by a wide spectrum of glandular and extra-glandular features. Genetic and epigenetic factors play an important role in the disease susceptibility and phenotype. There are a multitude of genes that have been identified as implicated in the pathogenesis of pSS, both in HLA and extra-HLA regions with a strong contribution given by genes in interferon signalling pathways. Among the HLA alleles, the most consistent associations have been found with DR2 and DR3 alleles at the DRB1 locus. Moreover, several gene variants outside the MHC locus are in genes involved in NF-κB signalling, B- and T-cell function and methylation processes possibly responsible for lymphomagenesis. There is still a lack of knowledge on precise genetic patterns and prediction models of diseases, and data on pharmacogenetics is scarce. A comprehensive summary of the common genetic factors and an extensive analysis of novel epigenetic aspects is provided, together with a view on the relationships between novel therapeutic agents for pSS and genetic targets in signalling pathways, aiming at improving tailored treatment strategies in the view of a more personalized medicine.

1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease characterized by a wide spectrum of glandular and extra-glandular features. As a result, the clinical presentation is heterogeneous and can vary from sicca symptoms (xerostomia and xerophtalmia) to systemic disease that may affect virtually any organ system [1]. pSS has been closely associated with an enhanced risk of developing lymphoma which can occur in around 2–5 % of cases and represents the most severe complication that a patient may develop [2].

The histological hallmarks are a lymphocytic infiltration of the exocrine glands and B-cell hyperactivity [3]. Antinuclear antibodies (ANA) are the most frequently detected autoantibodies, anti-Ro/SSA the most specific [4]. The disease affects predominantly women, suggesting a hormonal influence on the pathogenesis. Other contributors include genetic, environmental, and immune factors. It is likely that in a genetically predisposed individual an environmental trigger - including certain infections – may determine epigenetic modifications [5]. These factors may result in a progressive dysfunction of the salivary gland cells which will be the main site of chronic inflammation linked to the hyperactivity of B lymphocytes and antibodies [6]. The contribution of genetic factors is supported by the evidence that about 35 % of patients with pSS have at least one relative with the same syndrome or another related autoimmune disease and that twins have a further increased risk of diseases [7]. There are a multitude of pathways that have been implicated in the pathogenesis of pSS, involving genes both in HLA and extra-HLA regions, with a strong contribution of interferon signalling pathways. Despite novel biological agents are being tested and more frequently adopted in severe cases according to organ involvement, disease activity and the presence and extent of extragrandular

* Corresponding author.
E-mail addresses: carlo.perricone@unipg.it (C. Perricone), bogdanos@med.uth.gr (D. Bogdanos).
[1] These authors equally contributed

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manifestations [8], the treatment is still not satisfactory in a relevant percentage of patients, and markers of response are lacking. Few pharmacogenetics studies may provide substantial contribution to improve treatment strategies in the view of personalized medicine [9].

2. Common genetic factors-susceptibility and phenotype: HLA

By the late 1940s, it has been recognized a genetic susceptibility in the development of SS [10]. Thirty years later, it has been confirmed the association between specific human leukocyte antigens (HLA) and the pathogenesis of SS and recent genome-wide association studies (GWAS) have confirmed that the HLA locus still represents the strongest genetic factor to SS predisposition [11]. Indeed, among the HLA alleles, to date, the most consistent associations have been found with DR2 and DR3 alleles at the DRB1 locus in Caucasian populations [12,13]. Strong associations with anti-Ro/SSA and/or anti-La/SSB were found in patients carrying DRB1*03 and DQB1*02 alleles or heterozygous for DQw1 and DQw2 [14,15]. A recent meta-analysis of 1166 cases and 6470 controls of different ethnic backgrounds, derived from 23 studies, confirmed a significant risk of SS development with HLA class II alleles DRB1*03:01, DQA1*05:01 andDQB1*02:01, while DQA1*02:01, DQA1*03:01 and DQB1*05:01 alleles seem to have a protective effect [16]. In detail, over time, several studies have analyzed specific HLA associations in different ethnic groups: the results revealed that in North American Caucasians the risk predicted haplotype was HLA-DRB1*0301-DRB3*0101-DQA1*0501-DQB1*0201, in Japanese HLA-DRB1l*O405-DRB4*0101 -DQA1*0301-DQB1*0401 and DRw53s [17], while in Chinese SS patients DRB1*0803-DQAl*0103-DQB1*0601. Another study examining Chinese pSS patients found HLA-DR3, DR52 and DR2 to be significantly higher than in controls [18]. A study on Mexican SS patients found HLA-DRB1*01:01 and HLA-B*35:01 more present in patients than in controls, even confirming the HLA association with the production of anti-Ro/SSA [19]. In the Columbian population, HLA-DRB1*0301-DQB1*0201 associations were statistically significant for patients with advanced histopathological features. In addition, they demonstrated that HLA-DRB1*0301-DQB1*0201 positively correlated with autoantibodies production [20]. Furthermore, Roitberg-Tambur et al. examined the HLA genes that contribute to the predisposition of SS in a cohort of patients with Jewish Israel ancestry and Greeks, non-Jewish patients. They confirmed the role of HLADQA1*001-DQA1*0201-DQB1*0501 in Israelite Jews and of HLA-DQA1*050 in Greeks [21]. Significant associations were also found in pSS patients from Southern Spain with HLA-Cw7, HLA-DR3 and HLA-DR11 [22]. In the French population, the leading association was observed with HLADRB1* 15-DRB1*0301 [23]. Furthermore, a study examining a pSS Italian cohort identified DR3 as correlated with autoantibodies and extra-glandular manifestations [24]. Two studies from Denmark analyzed the role of HLA alleles and SS: the first study found HLA-Dw2 frequency to be significantly increased [25], and the second study found DQA1*0501-DQB1*0201-DQA1*0301 to have positive association [26]. In a Finnish study the significant haplotypes were HLA-DRB1*0301-DQA1*0501-DQB1*0201 [27]. Two Norwegian studies published in 2001 showed HLA DRB1*03-DQB1*02-DQA1*0501, DRB1*0301 and DRB3*0101 as the alleles that had association with SS patients with anti-SSA and/or anti-SSB [28,29]. Finally, other associations were seen in United Kingdom (HLA-DR3, and HLA-DRw52) [30], Hungary (HLA-DQB1*0201-DRB1*03-DQB1*0501) [31] and Australia (DR3-DQA1*0501-DQB1*02) and the haplotypes were primarily associated to La/Ro ribonucleoproteins [32,33].

Overall, HLA variability plays a major role in genetic predisposition to SS. Moreover, there are common susceptibility variants in pSS shared with other autoimmune diseases that support a common genetic background. The identification of several peptides, including Ro/SSA and La/SSB, that bind to the HLA alleles associated with SS emphasizes the mechanistic biological aspects of the association between SS and different HLA genes, especially in terms of the biochemical characteristics of critical amino acids. In Table 1 the described associations between HLA genes with pSS are summarized.

Table 1
Reported associations between HLA and SS susceptibility.

Susceptibilty Genes	Population(S)	Protective Genes
B*35:01	Mexicans [19]	
DQA1*001	Israeli Jews [21]	
DQA1*0201	Israeli Jews [21]	DQA1*02:01[16]
DQA1*0301	Japanese, Danish, Finnish, Norwegian [17, 26, 27, 29]	DQA1*03:01[16]
DQA1*050	Greeks [21no]	
DQA1*0501	North Americans, Danish, Finnish, Norwegian, Australian [12, 26, 27, 29, 32]	
DQA1*15	Chinese [18]	
DQA1*103	Chinese [18]	
DQB1*020	Finnish, Norwegian [27,17]	
DQB1*0201	North America, Columbian, Danish, Hungarian, Australian; associated with Autoantibodies [12, 20, 26, 31, 32]	
DRB1*03	Hungarian [31]	
DQB1*0501	Israeli Jews, Hungarian [21, 31]	DQB1*05:01[16]
DQB1*0601	Chinese [18]	
DRB1*0101	Mexicans [19]	
DRB3*0101	North Americans, Norwegian [12,17]	
DRB1*0301	North America, Columbian, French, Finnish; associated with severe histology [12, 20, 23, 27]	
DRB1*15	French [23]	
DRB1*0405	Japanese [17]	
DRB4*0101	Japanese [17]	
DQB1*0401	Japanese [17]	
DRB1*0803	Chinese [18]	
DRw52	UK [30]	
DRw53s	Japanese [17]	

3. The role of non-HLA genes

Until few years ago, most studies on the SS genetics relied on candidate gene analysis and investigated mainly the HLA system. Since genome wide association study (GWAS) started to be available, several new non-HLA genes and polymorphisms predisposing to the development of the disease were found, involving both innate, adaptive immune systems or acting as a bridge between them.

It was found that a preponderant role in the pathogenesis of pSS is played by type I interferon (IFN). In fact, the IFN system is often overexpressed in both salivary glands and peripheral blood of pSS patients, and the prominent overexpression of IFN-regulated genes leads to the so-called IFN signature [34]. Consequently, it is not surprising that most of the non-HLA pSS susceptibility gene variations involve the IFN pathway or IFN specific inducible genes (ISGs) [35–37]. Among the ISGs investigated, various single gene polymorphisms (SNPs) were identified as risk factors for the development of pSS, such as the IFN regulatory factor 5 (IRF5), signal transducer and activator of transcription 4 (STAT4), interleukin 12 A (IL12A) and 2′-5′ oligoadenylate synthetase 1 (OAS1) genes [38].

IRF5 gene encodes for a transcription factor promoting innate as well as the cell-mediated immune responses, involving both type I IFN and the toll-like receptor signalling pathways.

Both the 5-bp CGGGG insertion/deletion in the promoter of IRF5, which leads to an increased IRF5 transcription in peripheral blood mononuclear cells (PBMCs), and the rs10488631 SNP downstream of IRF5 were associated to pSS development with odds ratios (ORs) >1.4. Similar results were obtained with STAT4 rs7582694 and an additive effect between IRF5 and STAT4 alleles have been proposed [39,40]. Although STAT4 is not considered a direct member of the type I IFN pathway, it is a transcription factor mainly activated by IL-12 which promotes IFN-γ secretion and T-helper 1 cell differentiation. Consequently, it could represent a bridge between innate and adaptive immune responses, and it is considered a shared risk factor for the development of autoimmune diseases [41]. In fact, the relationship

between SNPs of IRF5, STAT4 and IL12A genes with pSS and other autoimmune diseases has been confirmed by several independent studies, though not in all the populations tested [42–48].

OAS1 is another ISG, and it encodes for a protein with enzymatic activity involved in viral clearance. This gene may have various functional isoforms (e.g. p42, p44, p46, p48) with consequently various protein expressions and different enzymatic activities. Considering that viral infections are one of the supposed triggers of pSS, this could explain why OAS1 polymorphisms, like rs10774671 have been identified and confirmed as a risk factor for the development of the disease [49]. Regarding the genetic polymorphisms linked to the adaptive immunity, most of them involves B lymphocytes differentiation and activation, like early B cell factor 1 (EBF1) gene, B lymphocyte kinase (BLK) (rs12677843) and family with sequence similarity 167 (FAM167) (rs12549796) [46].

Various other gene polymorphisms have been described as risk factors for the development of the disease, such those of cluster of differentiation 28 (CD28)(CD28 GC haplotype OR 2.5- folds, $P < 0.001$), cytotoxic T-lymphocyte–associated antigen 4 (CTLA4), the protein tyrosine phosphatase non-receptor type 22 (PTPN22W), tumor necrosis factor (TNF) α (308 A allele), interleukin 10 (IL-10)(1082 G allele) and C-X-C chemokine receptor type 5 (CXCR5) [50–52].

All of them are involved at various levels in the lymphocytes activities like tissue migration (CXCR5), activation or proliferation (CD28, CTLA4), receptor responsiveness (PTPN22W), immunoglobulin secretion (IL-10). For example, CTLA4 acts as an inhibitory molecule, inhibits cellular cycle progression and transcription factors such as nuclear factor kappa-light-chain enhancer of activated B cells (NK-kB), avoiding non-physiological T cell proliferation.

It has been observed that CTLA4 haplotypes resulting in a deregulation of CTLA4 activity, increase the risk of pSS [50,53,54].

One of the most studied genes, whose polymorphisms have been confirmed as a risk factor for the disease, is the tumor necrosis factor ligand superfamily member 4 (TNFSF4). This encodes for the cytokine ligand TNFSF4, also called OX40L, which influences both innate and adaptive immunity. In fact, it regulates the activity of dendritic cells, B and T lymphocytes and it is important for antibody production [55]. Therefore, TNFSF4 is a bridge between innate and adaptive immune systems as well as the Wnt/β-catenin signalling pathway. It is therefore not surprising that the TNFSF4 rs2205960 polymorphism and the several variants in the Wnt/β-catenin signalling pathway, such as rs606989 in LRP5, rs409238 in FRZB, rs2037547in GSK3B and rs2241766 in ADIPOQ, have been found linked to pSS susceptibility [56–58]. In a case-control study from Mexico, an association between TNFSF4 rs1234315C/T and pSS was observed (OR 1.28, $p = 0.04$), however, after Bonferroni correction, this association was lost [59].

Nevertheless, there are some polymorphisms which mostly influence the disease phenotype more than the disease susceptibility. For instance, lymphotoxin α (LTA) and lymphotoxin β (LTB) are essential in lymphoid organogenesis and the maintenance of tertiary lymphoid tissues, and some variants have been associated with anti-SSA and anti-SSB antibody-positive pSS [60,61]. Differently, some genetic variants are associated with the risk of lymphoma development: the three-prime repair exonuclease 1 (TREX1) (OR [95 % CI]: 0.4 [0.2–0.9], p-value: 0.02), the methylene-tetrahydrofolate reductase (MTHFR), the B-cell activating factor (BAFF), or TNF alpha induced protein 3 (TNFAIP3).

In addition, specific BAFF variants seem to represent a risk factor for higher disease activity and the presence of autoantibodies [62–64], and it was demonstrated that rs12583006 was significantly related to pSS susceptibility in Chinese population [65].

TNFAIP3 gene encodes for the A20 protein, exerting a negative feedback regulation on nuclear factor kB (NF-kB) and consequently on adaptive immune response. Moreover, it may serve as an important onco-suppressant. Polymorphisms of TNFAIP3 and functional abnormalities of A20 increase the risk of several autoimmune diseases [66] and rs2230926 variant allele marked up the risk of lymphoma in pSS in Caucasian and Asiatic cohorts, despite it does not correlate with an increased risk of pSS alone (odds ratio, 3.36 [95 % confidence interval, 1.34–8.42) [67]. Interestingly, in an Italian cohort, TNFAIP3 gene rs2230926 SNP does not seem to associate with the risk of pSS, differently from the rs6920220 SNP [68]. Other distinct genetic variants have been found to be associated with the presence of glandular germinal centre- like structures, including SNPs in CCL11, AICDA, BANK1, BCL2 IL17A, ICA1, PKN1 and SNPs in the NF-κB pathway genes CARD8, IKBKE and TANK. A higher focus score was associated with the presence of the minor allele of the rs11575837 polymorphism within the promoter of Natural Cytotoxicity Triggering Receptor 3 (NCR3)/ NKp30, which normally encodes a natural killer (NK) specific receptor regulating the cross talk between NK and dendritic cells as well as type II IFN secretion [69,70].

Several other SNPs in different genes (GTF2I, PTTG1, MBL2, TAP2, CFLAR, NFKBIE, APOM and NOTCH4) have been already reported as associated with pSS and other various autoimmune diseases, such as rheumatoid arthritis and SLE, and others showed suggestive associations (PTTG1, PRDM1, DGKQ, FCGR2A, IRAK1BP1, ITSN2, and PHIP), although further evidence are needed [38,44].

In the last year, a relevant contribution came from a GWAS conducted by Khatri et al. [71] They identified ten genome-wide significant regions in Sjögren's cases of European ancestry: CD247, NAB1, PTTG1-MIR146A, PRDM1-ATG5, TNFAIP3, XKR6, MAPT-CRHR1, RPTOR-CHMP6-BAIAP6, TYK2, SYNGR1. These genes are involved in several pathways of immunity including abovementioned TNFAIP3 and intracellular signalling.

In conclusion, several genetic polymorphisms may increase the risk of pSS development. However, it could be hard to understand the true functional impact of these genetic variants. More studies, especially functional as well as studies of genes interactions are still required.

4. Epigenetics

Over the last decade, many studies have been published with the aim of explaining the correlation between epigenetic modifications and the development of autoimmune diseases. Epigenetic modifications are heritable and reversible alterations that induce upregulated or downregulated gene expression, without changes in the sequence of bases in the DNA. They play a role in silencing or promoting the expression of coding sequences. Typical epigenetic modifications are DNA methylation, modifications of histones, and the expression of non-coding RNAs (ncRNAs). Moreover, they act by regulating the aberrant differentiation and activation of immunocytes and promoting the production of pro-inflammatory cytokines in autoimmune disease, including primary pSS [72,73].

4.1. DNA methylation

DNA methylation is a mechanism that transfers a methyl group by DNA methyltransferases (DNMTs) from S-adenosyl-methionine (SAM) to the carbon-5 position of the cytosine residue in CpG dinucleotides, generating 5-methyl cytosine (5-mC). Methylated CpG sites induce the structural changes of chromatin, making it difficult for transcriptional factor binding. CpG islands enriched in CpG base pairs are mainly distributed in the promoter and first exon regions of genes. Thus, DNA methylation is a signal of gene silencing. Demethylation of DNA is the removal of a methyl group from cytosine through a serial process starting from the oxidation of 5mC to 5-hydroxymethylcytosine (5hmC), and demethylation of genes indicates enhanced gene expression [74]. Many alterations in DNA methylation have been described in minor salivary gland (MSG) epithelial cells and lymphocytes in SS patients.

For example, Yin et al. determined the methylation status of the TNFS7 promoter region [75] and reported hypomethylation at the TNFSF7 promoter, which correlated with CD70 overexpression in pSS CD4+ T cells. Demethylation of the CD70 promoter regulatory elements

contributes to CD70 overexpression in pSS CD4(+) T cells and may contribute to autoreactivity [76].

A genome-wide DNA methylation study in naïve CD4+ T cells in patients with pSS identified 553 hypomethylated CpG sites and 200 hypermethylated CpG sites. The hypomethylated genes in patients with pSS included LTA, CD247, TNFRSF25, PTPRC, GSTM1, and PDCD1. The IFN signature pathway was involved by hypomethylation of STAT1, IFI44L, USP18, and IFITM1. In addition, the transcription factor gene RUNX1, that regulates the differentiation of hematopoietic stem cells into mature cells and has been linked to cancer predisposition, was hypermethylated in patients with pSS, suggesting a possible connection to lymphoma predisposition. This is the first epigenome-wide DNA methylation study in patients with pSS [77].

Luo X et al. [78] identified in monocytes from pSS patients 2819 differentially methylated positions (DMPs), comprising 1977 hypomethylated- and 842 hypermethylated-DMPs, corresponding to 1313 unique genes when compared with controls. It was shown that, among many, the most differentially hypomethylated genes were the IFN-related genes and those involved in the Notch signalling pathway. Chi et al. [79] observed a total of 19 DMR-MeQTL pairs that exhibited strong evidence for a causal mediation relationship. Close to half of these DMRs reside in the MHC and their corresponding meQTLs are in the region spanning the HLA-DQA1, HLA-DQB1, and HLA-DQA2 loci.

4.2. Histone modifications

Aberrant histone acetylation plays important role in the pathogenesis of autoimmune diseases. Histone proteins are essential for nuclear architecture, and they are involved in regulatory processes of gene transcription by modifying the accessibility of chromatin for the transcription machinery. Histones are enriched with basic lysine and arginine residues, especially in the N-terminal tails, which are feasible for several post-translational modifications (PTMs), like methylation, acetylation, phosphorylation and ubiquitination. These modified histones lead to altered chromatin structures or act as binding sites for non-histone regulators, resulting in varied gene expression [80]. Multiple enzymes are involved in histone modifications, such as histone deacetylases (HDACs), histone acetyltransferases (HATs) and histone methyltransferase (HMTs). They have been reported to be involved in T- and B-cell responses. Histone modifications studies in pSS patients are still quite elusive. Lv et al. investigated whether there was abnormal histones acetylation in patients with pSS. This study found that the messenger (mRNA) expression of p300, CREBBP and PCAF (histone acetyltransferase genes) in PBMCs from pSS patients was decreased in comparison with healthy controls and HAT activity and histone H3/H4 acetylation were reduced [81].

4.3. ncRNAs

Non-coding RNAs (ncRNAs) are single-strand RNA molecules transcribed from the genome. They do not encode functional proteins but are regulatory RNAs. Small non-coding RNAs (miRNAs) are 19–22 nucleotides in length, whereas long non-coding RNAs (lncRNAs) are longer than 200 nucleotides. MicroRNAs act as negative modulators of gene expression by binding to complementary sequences of their target mRNAs while the mechanism of action of lncRNAs is still unclear [82].

Many dysregulated miRNAs have been found in SS patients and the most investigated is miR-146. Pauley et al. [83] examined the expression of miR-146a in the PBMCs of pSS patients. The miR-146a expression was significantly increased in pSS patients compared to healthy controls. In addition, functional analysis revealed the role of miR-146a in stimulating phagocytic activity and suppressing inflammatory cytokine production. Zilahi et al. [84] measured both the expression of miR-146 and its target genes IRAK1, IRAK4 and TRAF6 in the PBMCs of SS patient and healthy controls using qPCR. They founded that both miR146 and TRAF6 were significantly overexpressed in pSS patients, whereas the expression of IRAK1 gene was significantly decreased and the expression of IRAK4 did not differ significantly. Finally, Shi et al. [85] demonstrated an overexpression of miR-146a in PBMCs of the patients with SS. Furthermore, the expression levels of this miRNAs correlated with patients' clinical features. More recently, Zhang et al. [86] investigated the role of miR-155-5p in SS. Stimulation of salivary gland epithelial cells (SGECs) with IFN-γ increased the levels of miR-155-5p, while also inducing apoptosis, these effects were reversed by miR-155-5p knockdown. This response seems to be mediated by an overactivation of NF-kB pathway through the elimination of one of its inhibitors, arrestin β2. A study conducted by Peng et al. [87] on a Chinese population, using microarray analysis, has shown miR-181a as the miRNA that most profoundly differed between PBMCs of patients with pSS and healthy individuals. In particular, miR-181a levels were highly increased in SS patients.

Jara et al. [88] showed that pSS is characterized by an overactivation of type I IFN pathway. They demonstrated that type I IFNs decrease expression of hsa-miR-145-5p, a miRNA with anti-inflammatory roles, leading to upregulation of MUC1 and TLR4, two relevant gene targets that are overexpressed in pSS patients and contribute to SG inflammation and dysfunction.

Non-Hodgkin's lymphoma (NHL) is the major and the worst adverse outcomes of Sjogren's syndrome. Kopsogeorgou et al. [89], using qPCR, investigated the expression of miR200b-5p in the minor salivary gland of three groups of patients (without lymphoma, pre-lymphoma and SS-associated lymphoma). They showed that long before the clinical onset of the lymphoma, miRNA miR-200b-5p is found to be significantly downregulated in the minor SGs of pSS patients, indicating that this epigenetic regulation may be involved in the progression to non-Hodgkin B-cell lymphoma. Unlike miRNAs, research regarding the differential expression and putative functional role of lncRNAs has not received extensive attention in SS. One of the first studies considered the expression of TMEVPG1, a lncRNA that contributes to IFN-γ expression. Using qPCR, Wang J et al. [90] investigated the expression of TMEVPG1 in CD4+ T cells of SS patients, showing its up regulation. In addition, the level of expression of TMEVPG1 was correlated with the level of SSA, ESR and IgG.

In a recent study, Chen et al. [91] investigated differentially expressed long non-coding RNA in PBMCs in patients with pSS to search for lncRNAs that could affect pSS pathogenesis. The results were validated by RT-qPCR and they showed that GABPB1-AS1 was significantly up-regulated in pSS patients, and its expression level is positively correlated with the percentage of B cells and IgG levels.

All these findings highlight a role of epigenetic modifications in pSS. Accordingly, it could be considered the possibility of taking epigenetic targets as a strategy for SS therapy.

In Fig. 1 are summarized potential epigenetic mechanisms of immune system activation leading to tissue damage in SS.

5. Transcriptomics

In the last decades, *−omic* approaches have become one of the main strategies to investigate the pathogenesis of pSS, due to their ability to provide a comprehensive picture of the biology in multiple cell populations and tissues. Their power is further amplified by advanced bioinformatics approaches.

It is beyond the purpose of this review to provide a detailed insight on all the evidence on the topic. Most data derived from transcriptomic studies demonstrated the so-called IFN signature, especially in anti-SSA/Ro and anti-SSB/La positive subjects [92]. In fact, a large proportion of differentially expressed genes (DEG) in SS patients compared to healthy controls (HC) are involved in signal pathways regulated by type I and II IFN. Analysis of DEGs have been performed in multiple tissues, fluids, and cell populations, including salivary glands, saliva, circulating B cells, dendritic cells, and monocytes.

DEGs identified in SS are involved in a large number of biological

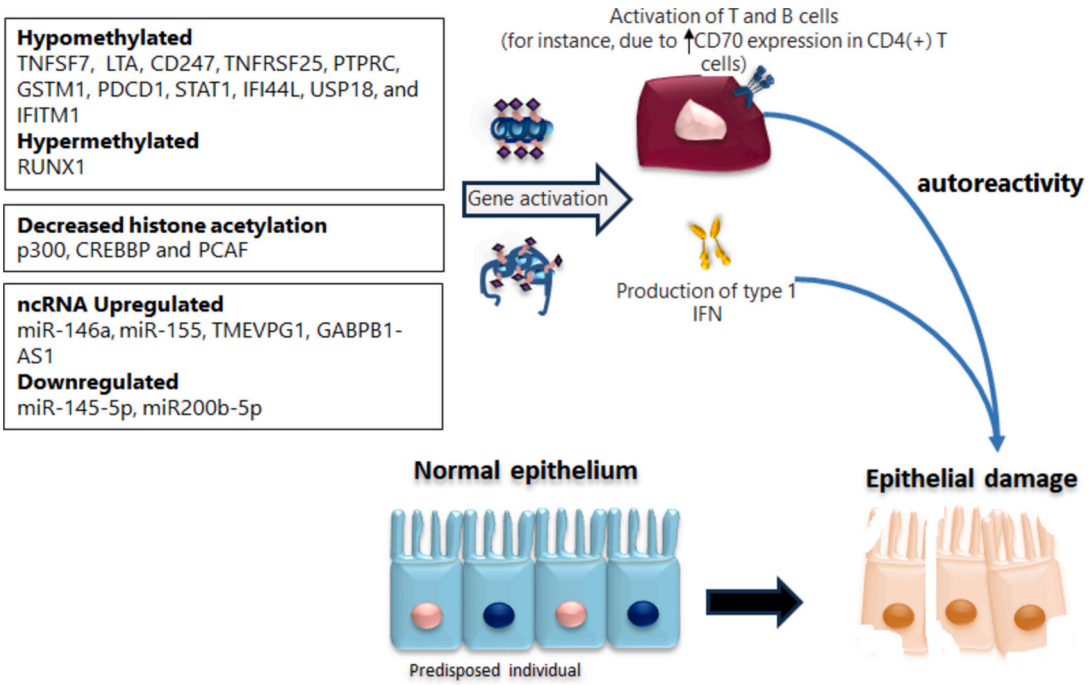

Fig. 1. Potential epigenetic mechanisms of immune system activation leading to tissue damage in SS. An appropriate genetic background is believed to trigger pSS. Epigenetic factors can modify genetic expression in key pathways through several mechanisms. Genes that appear hypomethylated are negative regulators or suppressors of immune responses while hypermethylation of RUNX1, a regulator of the differentiation of hematopoietic stem cells into mature blood cells, possibly promotes lymphomagenesis. mRNA expression of p300, CREBBP and PCAF, that are histone acetyltransferase genes, seems decreased in pSS and could be implicated in abnormal T and B cell responses. Further dysregulation of ncRNAs may alter the expression of target genes implicated in the immune response finally leading aberrant homing and activation of T cells and B cells, possibly for instance through increased expression of CD70 on T lymphocytes. Promotion of autoimmunity, further enhanced by plasmocytoid dendritic cells which produce high levels of type I interferon, is the key step to sustaining epithelial damage.

processes, ranging from the initial dysregulation of the immune system to salivary gland infiltration, damage and function.

5.1. *Immune system regulation and activation*

Among the multiple DEGs described, some may be of particular significance, due to their key role in the regulation of the immune response. As an example, the gene SAMD9L is involved in the innate immune response, along with DTX3L and TAP2 (antigen presentation), PLSCR1 (enhances IFN-mediated response), FCGR2A (IgG Fc fragment receptor) and multiple toll-like receptors that have been described as upregulated in plasmacytoid dendritic cells (pDC) [93,94]. Genes involved in lymphocyte activation such as CD53, PTPRC and IFI16 were also found to be upregulated in SS SGs [93–95]. Very interestingly, significant differences of the transcriptome between pSS and healthy controls SG samples seem to be evident only when inflammatory infiltrates and periductal areas are compared, while no significant differences in acinar tissue were found. This observation is in line with the preferential involvement of periductal areas as clearly described in pathologic specimens of SS salivary glands [96]. Studies focused on circulating B cells confirmed the type I and II IFN signature and found numerous genes upregulated in SS, including numerous TNF superfamily members and Janus kinase(JAK)/STAT pathway regulators [97,98]. Moreover, salivary gland endothelial cells under-expression of peroxisome proliferator activated receptor (PPAR)γ, especially in patients with severe inflammatory infiltrates and higher prevalence of lymphoma, may confirm its anti-inflammatory function and aberrant activity in SS, thus suggesting a pathogenic role [99].

5.2. *Immune cell migration*

An upregulation of the SELL gene, encoding a cell adhesion molecule involved in leukocyte migration and homing towards lymphoid organs, has been demonstrated in SS salivary glands, along with the upregulation of chemokines, such as CCL21, CXCL10, CXCL12 and several receptors (CCR)1, CCR5, CCR7 [100]. Additionally, signal transduction and activator of transcription (STAT)1 and arachidonate 5-lipoxygenase were demonstrated to be involved in the inflammatory response [101].

5.3. *Cell apoptosis*

As an additional altered mechanism in pSS, an increased expression of apoptosis-associated genes (such as FAS, CASP1) and proteasome subunits has been demonstrated in PBMCs and pDCs [93–95,100], along with molecules involved in the regulation of oxidative stress and metabolic processes [100].

The analysis of transcriptome through bioinformatics techniques may also allow to identify and stratify SS patients into distinct subgroups, according to gene expression. As an example, analysing SG transcriptome, Min et al. were able to identify two clusters of SS patients, the first included patients with a high inflammatory status, characterized by an upregulation of genes involved in B and Th1 cell activation; the second cluster included subjects with a low inflammatory signature and some activation of Th17-related genes. Subjects in cluster one were resistant to rituximab, unlike those in cluster 2 [102]. These observations seem to fit very well with real-life experience, where these distinctions are almost universally accepted. Even more interestingly, transcriptomics allowed to find an association between actin-related signalling pathways and fatigue [103]. Moreover, some investigations found significant differences of the transcriptome between male and female SS patients [104,105]. Future studies on this topic may represent a key to further understand the mechanisms underlying the sex-related differences in terms of disease incidence and prevalence.

5.4. MicroRNAs

Transcriptomic analysis is not necessarily limited to mRNA. In fact, the first paper analysing microRNAs (miRNA) in SS was published in 2011, when the authors analyzed minor SG tissue and found that differentially expressed miRNAs in SS compared to HC were essentially involved in the control of inflammation and of exocrine gland function. Even more interestingly, miRNA profiling could effectively stratify SS patients according to low or high focus score (FS), being miR-768-3p and has-miR-574 the most informative transcripts [106]. Numerous other data on miRNAs followed, describing a dysregulation of miRNAs involved in the expression of the autoantigens SSA/Ro and SSB/La, that may even have a pathogenic function [107], the upregulation of miRNA-181a in SS PBMCs, possibly involved in the autoreactivity of B cells [108] and of miR-30, miR-17/92, miR-200, miR-let-7 families and has-miR-5100, whose levels inversely correlate with salivary flow, possibly through the modulation of the enzyme GALNT1 [109–112].

Shaw et al. [113] detected major differences in the regulation of X-linked genes from pSS patients and control subjects. In pSS female minor salivary gland-derived mesenchymal stromal cells (MSCs), X-linked genes exhibited preferential expression from one of the two X chromosomes. pSS MSCs show decreased levels of miR6891-5p, a HLA-expressed miRNA, this inhibition causes allelic skewing and H3K27me3 dysregulation.

Gong et al. demonstrated that mesenchymal stem cells negatively regulate CD4+ T cell activation through the miRNA 125b and miRNA 155 TCR pathway. So, expression levels of miRNA-125b-5p and miRNA-155 in CD4+ T cells are associated with disease activity [114].

Instead, Zhang et al. found that overexpression of miR-155-5p promoted IFN-γ-induced inflammation [115].

Additionally, predictive target analysis suggests that the dysregulation of miRNA expression in SS monocytes may contribute to the pathogenesis of the disease by inhibition of the transforming growth factor (TGF)β pathway, rather than modulating pro-inflammatory signals. Many other differentially expressed miRNAs have been identified, however their function remains unknown and further research is required in order to enrich the complex picture of SS pathogenesis. Moreover, the finding of co-expression of specific couples of non-genetically linked miRNAs in SS monocytes may represent a potential diagnostic biomarker of the disease.

5.5. Long non-coding RNA

Long non-coding RNAs (lncRNA) are transcripts of >200 nucleotides that do not code for peptides but can interact with other molecules, such as mRNA and DNA exerting modulatory functions. Some lncRNAs were found to be differentially expressed in SS compared to HC. Although the functions of numerous lncRNAs are still largely unknown, differential expression of transcripts involved in the regulation of IFN-inducible genes, regulators of IFNγ and TNFα may be significant findings [116]. Additionally, the correlation of some lncRNAs expressed in MSGs with β2-microglobulin, erythrocyte sedimentation rate (ESR), IgA levels and RF positivity may suggest some pathogenic mechanisms of lncRNAs, such as a contribution to the inflammatory status and autoimmunity [117].

For example, a lncRNA called LINC01871 that is IFNγ inducible, influences expression of many immune cell genes and growth factors and regulated by calcineurin signalling and TCR ligand engagement. Altered LINC01871 expression may influence the dysregulated T cell inflammatory pathways implicated in pSS [118].

Instead, Amezcua-Guerra et al. [119] analyzed the expression levels of an IFN-α-inducible lncRNA, MALAT1, and several kinds of IFN-stimulated genes and chemokines in the PBMCs of the patients with SS. They showed an unusually high capacity of PBMC to express ISG and to produce interferon-responsive chemokine, suggesting a possible benefit from therapies targeting these molecules in patients with pSS.

Despite the analysis of transcriptome is a valuable tool to investigate the biology of SS, it will unlikely be enough to fully unravel the complex pathogenesis of the disease. In fact, the status at the time of diagnosis is not necessarily representative of pathogenic changes, which may take place months to years before SS becomes clinically evident. Studies performed on mouse models of SS have in fact demonstrated that the transcriptome changes profoundly during the development of the disease and significant differences can be appreciated between salivary and lachrymal glands [120,121].

6. Pharmacogenomics

Pharmacogenomics is a field of research that studies the relationship between inter-individual genetic variability and the variability in the response to drugs, both in term of efficacy and toxicity. The study of the genomic profile can give an important contribution to improve effective drug selection to avoid adverse drug reactions and to maximize drug efficacy [122]. There are very few studies conducted on patients with pSS to evaluate the genomic profile and the response to treatment and unfortunately the application of pharmacogenomics in clinical practice is still limited [123,124]. Moreover, so far there are no approved biological drugs for the treatment of pSS.

Several studies were performed in patients with rheumatoid arthritis treated with anti-CD20 rituximab (RTX) treatment [125]. The presence of specific variations in FCGR3A, FCGR2A, TGFβ1, IL-6, IRF5, BAFF genes could be used to predict response to this drug [126,127]. Pharmacogenetic analysis of belimumab failed to identify robust genetic predictors of efficacy in patients with systemic lupus erythematosus [128]. In a post hoc meta-analysis of belimumab trials BLISS-52 and BLISS-76, a tendency towards improved response to add-on intravenous belimumab 10 mg/kg versus standard of care alone in patients with high baseline BLyS protein and IFN-1 mRNA levels and medium/high BLyS mRNA levels were demonstrated [129]. Only one study was performed on patients with pSS by Quartuccio et al. [130] The authors suggested that type I IFN signature may affect the magnitude of biological effect of belimumab on immunoglobulin production, including rheumatoid factor, thus possibly reducing the risk of lymphoma [130].

So far, there is no approved biologic for the treatment of pSS [131]. Nonetheless, several trials are ongoing on molecules with different targets, including B and T cell signalling, B cell depletion, inhibition of key cytokines (Fig. 2).

Considering B cell depletion, besides anti-CD20 rituximab, also obinutuzumab has been tested in patients with pSS immunized against rituximab [133] but conclusive data are lacking. More data are available on epratuzumab (anti-CD22) which showed in a phase I/II study 50 % of response on Schirmer's test, unstimulated whole salivary flow, fatigue as measured on a VAS, and laboratory parameters including erythrocyte sedimentation rate and IgG titres [134]. Notably, despite promising results, the drug is no longer tested. Considering B cells as a target, belimumab acts inhibiting BAFF, while ianalumab is an anti-BAFF-R monoclonal antibody and iscalimab is an anti-CD40. All these molecules can inhibit (and can deplete B cells), ianalumab being the only to have reached the primary end points (Improvement in SGUS and in ESSDAI) in a phase II clinical trial [131]. Several genes can modulate this pathway, including BAFF and CD40, but also Jak1 and TNFSF13B [135]. Considering other targets, seletalisib by inhibiting PI3kδ could regulate T and B cell responses while among BTK inhibitors, remibrutinib seems promising having achieved primary end point in phase II clinical trial, differently from tirabrutinib that failed to meet primary end point in a similar RCT. Some drugs which are well known for treatment of other diseases, such as the anti-TNF infliximab, the anti-IL-6 tocilizumab, and the anti-IL12/23 ustekinumab have shown no significant improvement or a paucity of data [131]. The question arises whether a pharmacogenetic tailored approach could have improved results from these drugs. Trials on JAK inhibitors including tofacitinib are still ongoing. These are interesting molecules given the broad

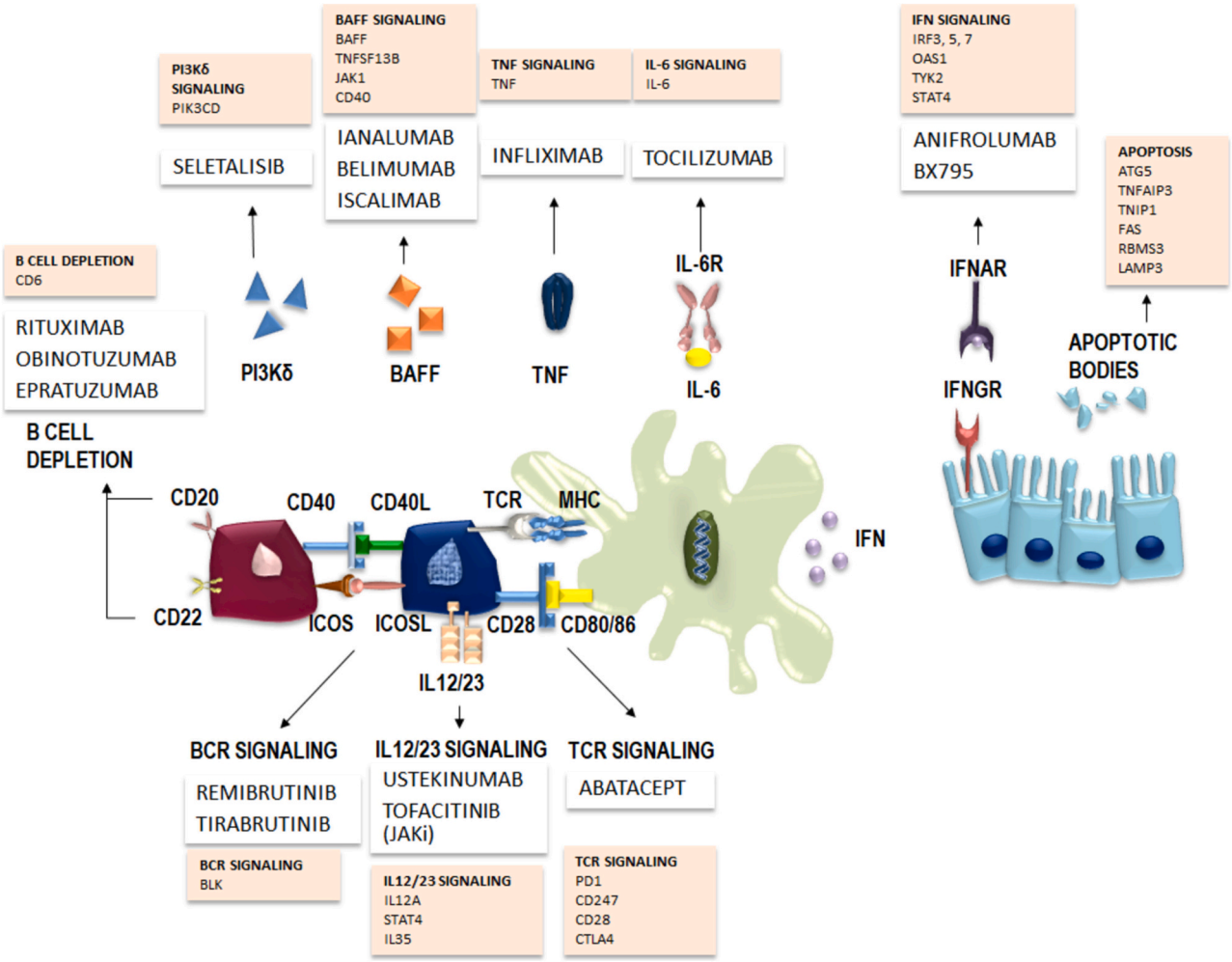

Fig. 2. Biologic or targeted synthetic agents currently evaluated in primary Sjögren syndrome with their respective targets and genes associated to the relative signalling pathway. Randomized controlled trials evaluating the effectiveness of novel drugs in pSS showed a potential for agents acting through several mechanisms targeting both innate and adaptive immune pathways. In the figure, the signalling pathway or the target cytokine is shown, in the white boxes is referred to the drugs acting on each specific pathway or cytokine. In coloured boxes the most relevant genes for each pathway are reported. These genes may a) be themselves a target for treatment, b) represent a possible modulator of therapeutic response. BAFF, B cell-activating factor; BCR, B cell receptor; TCR, T cell receptor (modified from [132]).

spectrum of molecules that they can modulate. Moreover, SNPs in JAK1, JAK2, JAK3 or in STAT signalling pathway could influence and predict treatment response of these drugs. Finally, anti-interferon strategies, which include anifrolumab, an inhibitor of type I IFN receptor (IFNAR1), and BX795, a TBK1 inhibitor that downregulates IRF3 and IRF7 signalling, are other promising strategies in pSS given the strong influence of the IFN signature in these patients. BX795 in an in vitro study showed that was able to reduce the expression of IFN-stimulated genes in PBMCs from pSS patients with a type I IFN signature [136]. Furthermore, OAS1, TYK2 and STAT4 are possible genes that, together with those of the IFN signature, may regulate the efficacy of these drugs.

Being pSS an autoimmune epithelitis, the epithelium itself is another potential target of novel therapies. A dysregulated apoptosis of salivary gland epithelial cells is believed to fuel the initial stages of autoimmunity. There are several genes that regulate apoptosis and that can be abnormally expressed in pSS including ATG5, TNFAIP3, FAS, LAMP3 and RBMS3 [137,138], and there is evidence that their mRNA expression can be a marker of response to treatment as shown for hydroxychloroquine [139].

Thus, we eagerly wait for the approval of novel treatment for pSS that could be possibly tailored also on the basis of genetic or epigenetic individual signatures.

7. Genetic and Sjogren: another link to ASIA syndrome

In 2011 Yehuda Shoenfeld and Nancy Agmon-Levin coined the term Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) to describe an “umbrella” of clinical conditions namely siliconosis, Gulf war syndrome, macrophage myophasciitis syndrome, sick building syndrome and post-vaccination phenomena which share similar signs or symptoms [140]. Since then, several diseases have been possibly ascribed to be, at least in some circumstances, associated with ASIA if not another branch of the same tree [141]. In 2014 we described the possible associations between ASIA and pSS since these two conditions share clinical and pathogenic aspects [142]. Xerostomia and xerophtalmia are among proposed classification criteria for ASIA syndrome and there are experimental animal models in which adjuvants, specifically alum, may induce a Sjogren's like disease [143]. Borba et al. included pSS in the classical prototypes of ASIA syndrome [144]. It is now clearer that some genetic predisposition factors could be responsible for susceptibility to both these conditions. Among HLA haplotypes, [145], the DRB1*03 seem to be a possible link among the two conditions [146]. When considering non-HLA genes, PTPN22 variants do not seem to be associated with pSS but patients with pSS may present markedly increased expression of this molecule especially in patients with active disease and elevated levels of anti-SSA/Ro and anti-SSB/La

autoantibodies [147]. Moreover, a genetic interaction between TRAF1-C5 and TNFAIP3 or TNFAIP3, PTPN22, and TRAF1-C5 SNPs may represent a risk factor for pSS [148]. Appreciating the correct depiction of susceptible individuals to ASIA and pSS and the functional implications of related gene-variants could provide further insights into our understanding of diseases mechanisms and heterogeneity.

8. Conclusions

To conclude, the multitude of factors contributing to the pathogenesis of pSS are also capable of determining the clinical manifestations and the response to treatment. A better knowledge of these factors will allow us to earlier detect and diagnose the patients and to implement more effective and individualized treatments in the perspective of precision medicine.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

References

[1] Manfrè V, Chatzis LG, Cafaro G, Fonzetti S, Calvacchi S, Fulvio G, et al. Sjögren's syndrome: one year in review 2022. Clin Exp Rheumatol 2022 Dec;40(12):2211–24. https://doi.org/10.55563/clinexprheumatol/43z8gu.

[2] Retamozo S, Brito-Zerón P, Ramos-Casals M. Prognostic markers of lymphoma development in primary Sjögren syndrome. Lupus 2019 Jul;28(8):923–36. https://doi.org/10.1177/0961203319857132.

[3] Mavragani CP, Moutsopoulos HM. Sjögren syndrome. CMAJ 2014 Oct 21;186(15):E579–86. https://doi.org/10.1503/cmaj.122037.

[4] Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X. Primary Sjogren syndrome. BMJ 2012 Jun 14;344:e3821. https://doi.org/10.1136/bmj.e3821.

[5] Jonsson R, Brokstad KA, Jonsson MV, Delaleu N, Skarstein K. Current concepts on Sjögren's syndrome - classification criteria and biomarkers. Eur J Oral Sci 2018 Oct;126(Suppl. 1):37–48. https://doi.org/10.1111/eos.12536.

[6] Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren's syndrome: beyond the dryness - from pathophysiology to diagnosis and treatment. Int J Med Sci 2017 Feb 23;14(3):191–200. https://doi.org/10.7150/ijms.17718.

[7] Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dörner T. The diagnosis and treatment of Sjögren's syndrome. Dtsch Arztebl Int 2017 May 26;114(20):354–61. https://doi.org/10.3238/arztebl.2017.0354.

[8] Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis 2020 Jan;79(1):3–18. https://doi.org/10.1136/annrheumdis-2019-216114.

[9] Giacomelli R, Afeltra A, Bartoloni E, Berardicurti O, Bombardieri M, Bortoluzzi A, et al. The growing role of precision medicine for the treatment of autoimmune diseases; results of a systematic review of literature and Experts' Consensus. Autoimmun Rev 2021 Feb;20(2):102738. https://doi.org/10.1016/j.autrev.2020.102738.

[10] Coverdale H. Some unusual cases of Sjogren's syndrome. Br J Ophthalmol 1948 Sep;32(9):669–73 [PMID: 18170503].

[11] Fye KH, Terasaki PI, Michalski JP, Daniels TE, Opelz G, Talal N. Relationshipp of HLA-Dw3 and HLA-B8 to Sjögren's syndrome. Arthritis Rheum 1978 Apr;21(3):337–42. https://doi.org/10.1002/art.1780210308.

[12] Cobb BL, Lessard CJ, Harley JB, Moser KL. Genes and Sjögren's syndrome. Rheum Dis Clin North Am 2008 Nov;34(4):847–68. vii, https://doi.org/10.1016/j.rdc.2008.08.003.

[13] Harley JB, Reichlin M, Arnett FC, Alexander EL, Bias WB, Provost TT. Gene interaction at HLA-DQ enhances autoantibody production in primary Sjögren's syndrome. Science 1986 May 30;232(4754):1145–7. https://doi.org/10.1126/science.3458307.

[14] Gottenberg JE, Busson M, Loiseau P, Dourche M, Cohen-Solal J, Lepage V, et al. Association of transforming growth factor beta1 and tumor necrosis factor alpha polymorphisms with anti-SSB/La antibody secretion in patients with primary Sjögren's syndrome. Arthritis Rheum 2004 Feb;50(2):570–80. https://doi.org/10.1002/art.20060.

[15] Gottenberg JE, Busson M, Loiseau P, Cohen-Solal J, Lepage V, Charron D, et al. In primary Sjögren's syndrome, HLA class II is associated exclusively with autoantibody production and spreading of the autoimmune response. Arthritis Rheum 2003 Aug;48(8):2240–5. https://doi.org/10.1002/art.11103.

[16] Cruz-Tapias P, Rojas-Villarraga A, Maier-Moore S, Anaya JM. HLA and Sjögren's syndrome susceptibility. A meta-analysis of worldwide studies. Autoimmun Rev 2012 Feb;11(4):281–7. https://doi.org/10.1016/j.autrev.2011.10.002.

[17] Moriuchi J, Ichikawa Y, Takaya M, Shimizu H, Uchiyama M, Sato K, et al. Association between HLA and Sjögren's syndrome in Japanese patients. Arthritis Rheum 1986 Dec;29(12):1518–21. https://doi.org/10.1002/art.1780291215.

[18] Wang J, Jiang M, Qiu C. Study on the relationship between primary Sjögren syndrome and HLA-DRbeta gene. Zhonghua Nei Ke Za Zhi 1997 Jun;36(6):398–401. Chinese. PMID: 10374300.

[19] Hernández-Molina G, Vargas-Alarcón G, Rodríguez-Pérez JM, Martínez-Rodríguez N, Lima G, Sánchez-Guerrero J. High-resolution HLA analysis of primary and secondary Sjögren's syndrome: a common immunogenetic background in Mexican patients. Rheumatol Int 2015 Apr;35(4):643–9. https://doi.org/10.1007/s00296-014-3143-7.

[20] Anaya JM, Correa PA, Mantilla RD, Arcos-Burgos M. TAP, HLA-DQB1, and HLA-DRB1 polymorphism in Colombian patients with primary Sjögren's syndrome. Semin Arthritis Rheum 2002 Jun;31(6):396–405. https://doi.org/10.1053/sarh.2002.32557.

[21] Roitberg-Tambur A, Friedmann A, Safirman C, Markitziu A, Ben-Chetrit E, Rubinow A, et al. Molecular analysis of HLA class II genes in primary Sjögren's syndrome. A study of Israeli Jewish and Greek non-Jewish patients. Hum Immunol 1993 Apr;36(4):235–42. https://doi.org/10.1016/0198-8859(93)90130-s.

[22] García Portales R, Belmonte Lope MA, Camps García MT, Ocón Sánchez P, Alonso Ortiz A, Guil García M, et al. Inmunogenética del síndrome de Sjögren en el sur de España [Immunogenetics of the Sjogren's syndrome in southern Spain]. An Med Interna 1994 Feb;11(2):56–61. Spanish. PMID: 8193233.

[23] Jean S, Quelvennec E, Alizadeh M, Guggenbuhl P, Birebent B, Perdriger A, et al. DRB1*15 and DRB1*03 extended haplotype interaction in primary Sjögren's syndrome genetic susceptibility. Clin Exp Rheumatol 1998 Nov-Dec;16(6):725–8 [PMID: 9844767].

[24] Vitali C, Tavoni A, Rizzo G, Neri R, D'Ascanio A, Cristofani R, et al. HLA antigens in Italian patients with primary Sjögren's syndrome. Ann Rheum Dis 1986 May;45(5):412–6. https://doi.org/10.1136/ard.45.5.412.

[25] Manthorpe R, Morling N, Platz P, Ryder LP, Svejgaard A, Thomsen M. HLA-D antigen frequencies in Sjögren's syndrome. Differences between the primary and secondary form. Scand J Rheumatol 1981;10(2):124–8. https://doi.org/10.3109/03009748109095284.

[26] Morling N, Andersen V, Fugger L, Georgsen J, Halberg P, Oxholm P, et al. Immunogenetics of rheumatoid arthritis and primary Sjögren's syndrome: DNA polymorphism of HLA class II genes. Dis Markers 1991 Sep-Oct;9(5):289–96. PMID: 1686751.

[27] Kerttula TO, Collin P, Polvi A, Korpela M, Partanen J, Mäki M. Distinct immunologic features of Finnish Sjögren's syndrome patients with HLA alleles DRB1*0301, DQA1*0501, and DQB1*0201. Alterations in circulating T cell receptor gamma/delta subsets. Arthritis Rheum 1996 Oct;39(10):1733–9. https://doi.org/10.1002/art.1780391017.

[28] Bolstad AI, Wassmuth R, Haga HJ, Jonsson R. HLA markers and clinical characteristics in Caucasians with primary Sjögren's syndrome. J Rheumatol 2001 Jul;28(7):1554–62 [PMID: 11469461].

[29] Nakken B, Jonsson R, Brokstad KA, Omholt K, Nerland AH, Haga HJ, et al. Associations of MHC class II alleles in Norwegian primary Sjögren's syndrome patients: implications for development of autoantibodies to the Ro52 autoantigen. Scand J Immunol 2001 Oct;54(4):428–33. https://doi.org/10.1046/j.1365-3083.2001.00993.x.

[30] Pease CT, Shattles W, Charles PJ, Venables PJ, Maini RN. Clinical, serological, and HLA phenotype subsets in Sjögren's syndrome. Clin Exp Rheumatol 1989 Mar-Apr;7(2):185–90 [PMID: 2786788].

[31] Kovács A, Endreffy E, Petri I, Kovács L, Pokorny G. HLA class II allele polymorphism in Hungarian patients with primary Sjögren's syndrome. Scand J Rheumatol 2006 Jan-Feb;35(1):75–6. https://doi.org/10.1080/03009740500287517.

[32] Rischmueller M, Lester S, Chen Z, Champion G, Van Den Berg R, Beer R, et al. HLA class II phenotype controls diversification of the autoantibody response in primary Sjögren's syndrome (pSS). Clin Exp Immunol 1998 Feb;111(2):365–71. https://doi.org/10.1046/j.1365-2249.1998.00504.x.

[33] Teos LY, Alevizos I. Genetics of Sjögren's syndrome. Clin Immunol 2017 Sep;182:41–7. https://doi.org/10.1016/j.clim.2017.04.018.

[34] Cafaro G, Croia C, Argyropoulou OD, Leone MC, Orlandi M, Finamore F, et al. One year in review 2019: Sjögren's syndrome. Clin Exp Rheumatol 2019 May-Jun;37(Suppl. 118):3–15 (3). Epub 2019 Jul 16. PMID: 31464675.

[35] Mavragani CP, Crow MK. Activation of the type I interferon pathway in primary Sjogren's syndrome. J Autoimmun 2010 Nov;35(3):225–31. https://doi.org/10.1016/j.jaut.2010.06.012.

[36] Rizzo C, Grasso G, Destro Castaniti GM, Ciccia F, Guggino G. Primary Sjogren syndrome: focus on innate immune cells and inflammation. Vaccines (Basel) 2020 Jun 3;8(2):272. https://doi.org/10.3390/vaccines8020272.

[37] Vakaloglou KM, Mavragani CP. Activation of the type I interferon pathway in primary Sjögren's syndrome: an update. Curr Opin Rheumatol 2011 Sep;23(5):459–64. https://doi.org/10.1097/BOR.0b013e328349fd30.

[38] Lessard CJ, Li H, Adrianto I, Ice JA, Rasmussen A, Grundahl KM, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are

associated with Sjögren's syndrome. Nat Genet 2013 Nov;45(11):1284–92. https://doi.org/10.1038/ng.2792.
[39] Nordmark G, Kristjansdottir G, Theander E, Appel S, Eriksson P, Vasaitis L, et al. Association of EBF1, FAM167A(C8orf13)-BLK and TNFSF4 gene variants with primary Sjögren's syndrome. Genes Immun 2011 Mar;12(2):100–9. https://doi.org/10.1038/gene.2010.44.
[40] Gestermann N, Mekinian A, Comets E, Loiseau P, Puechal X, Hachulla E, et al. STAT4 is a confirmed genetic risk factor for Sjögren's syndrome and could be involved in type 1 interferon pathway signaling. Genes Immun 2010 Jul;11(5):432–8. https://doi.org/10.1038/gene.2010.29.
[41] Liaskou E, Patel SR, Webb G, Bagkou Dimakou D, Akiror S, Krishna M, et al. Increased sensitivity of Treg cells from patients with PBC to low dose IL-12 drives their differentiation into IFN-γ secreting cells. J Autoimmun 2018 Nov;94:143–55. https://doi.org/10.1016/j.jaut.2018.07.020.
[42] Li Y, Zhang K, Chen H, Sun F, Xu J, Wu Z, et al. A genome-wide association study in Han Chinese identifies a susceptibility locus for primary Sjögren's syndrome at 7q11.23. Nat Genet 2013 Nov;45(11):1361–5. https://doi.org/10.1038/ng.2779.
[43] Song IW, Chen HC, Lin YF, Yang JH, Chang CC, Chou CT, et al. Identification of susceptibility gene associated with female primary Sjögren's syndrome in Han Chinese by genome-wide association study. Hum Genet 2016 Nov;135(11):1287–94. https://doi.org/10.1007/s00439-016-1716-0.
[44] Fang K, Zhang K, Wang J. Network-assisted analysis of primary Sjögren's syndrome GWAS data in Han Chinese. Sci Rep 2015 Dec 21;5:18855. https://doi.org/10.1038/srep18855.
[45] Miceli-Richard C, Gestermann N, Ittah M, Comets E, Loiseau P, Puechal X, et al. The CGGGG insertion/deletion polymorphism of the IRF5 promoter is a strong risk factor for primary Sjögren's syndrome. Arthritis Rheum 2009 Jul;60(7):1991–7. https://doi.org/10.1002/art.24662.
[46] Nordmark G, Kristjansdottir G, Theander E, Eriksson P, Brun JG, Wang C, et al. Additive effects of the major risk alleles of IRF5 and STAT4 in primary Sjögren's syndrome. Genes Immun 2009 Jan;10(1):68–76. https://doi.org/10.1038/gene.2008.94.
[47] Dideberg V, Kristjansdottir G, Milani L, Libioulle C, Sigurdsson S, Louis E, et al. An insertion-deletion polymorphism in the interferon regulatory Factor 5 (IRF5) gene confers risk of inflammatory bowel diseases. Hum Mol Genet 2007 Dec 15;16(24):3008–16. https://doi.org/10.1093/hmg/ddm259.
[48] Kristjansdottir G, Sandling JK, Bonetti A, Roos IM, Milani L, Wang C, et al. Interferon regulatory factor 5 (IRF5) gene variants are associated with multiple sclerosis in three distinct populations. J Med Genet 2008 Jun;45(6):362–9. https://doi.org/10.1136/jmg.2007.055012.
[49] Li H, Reksten TR, Ice JA, Kelly JA, Adrianto I, Rasmussen A, et al. Identification of a Sjögren's syndrome susceptibility locus at OAS1 that influences isoform switching, protein expression, and responsiveness to type I interferons. PLoS Genet 2017 Jun 22;13(6):e1006820. https://doi.org/10.1371/journal.pgen.1006820.
[50] López-Villalobos EF, Carrillo-Ballesteros FJ, Muñoz-Valle JF, Palafox-Sánchez CA, Valle Y, Orozco-Barocio G, et al. Association of CD28 and CTLA4 haplotypes with susceptibility to primary Sjögren's syndrome in Mexican population. J Clin Lab Anal 2019 Jan;33(1):e22620. https://doi.org/10.1002/jcla.22620.
[51] Thorlacius GE, Wahren-Herlenius M, Rönnblom L. An update on the role of type I interferons in systemic lupus erythematosus and Sjögren's syndrome. Curr Opin Rheumatol 2018 Sep;30(5):471–81. https://doi.org/10.1097/BOR.0000000000000524.
[52] Vlachogiannis NI, Nezos A, Tzioufas AG, Koutsilieris M, Moutsopoulos HM, Mavragani CP. Increased frequency of the PTPN22W* variant in primary Sjogren's syndrome: association with low type I IFN scores. Clin Immunol 2016;173:157–60. https://doi.org/10.1016/j.clim.2016.10.015.
[53] Schildberg FA, Klein SR, Freeman GJ, Sharpe AH. Coinhibitory pathways in the B7-CD28 ligand-receptor family. Immunity 2016 May 17;44(5):955–72. https://doi.org/10.1016/j.immuni.2016.05.002.
[54] Zhang Q, Vignali DA. Co-stimulatory and co-inhibitory pathways in autoimmunity. Immunity 2016 May 17;44(5):1034–51. https://doi.org/10.1016/j.immuni.2016.04.017.
[55] Kato H, Kojima H, Ishii N, Hase H, Imai Y, Fujibayashi T, et al. Essential role of OX40L on B cells in persistent alloantibody production following repeated alloimmunizations. J Clin Immunol 2004 May;24(3):237–48. https://doi.org/10.1023/B:JOCI.0000025445.21894.e5.
[56] Yang Y, Li X, Li B, Mu L, Wang J, Cheng Y, et al. Associations between TNFSF4 gene polymorphisms (rs2205960 G > A, rs704840 T > G and rs844648 G > A) and susceptibility to autoimmune diseases in Asians: a meta-analysis. Immunol Invest 2021 Feb;50(2–3):184–200. https://doi.org/10.1080/08820139.2020.1718693.
[57] Taylor KE, Wong Q, Levine DM, McHugh C, Laurie C, Doheny K, et al. Genome-wide association analysis reveals genetic heterogeneity of Sjögren's syndrome according to ancestry. Arthritis Rheumatol 2017 Jun;69(6):1294–305. https://doi.org/10.1002/art.40040.
[58] Fernández-Torres J, Pérez-Hernández N, Hernández-Molina G, Martínez-Nava GA, Garrido-Rodríguez D, López-Reyes A, et al. Risk of Wnt/β-catenin signalling pathway gene polymorphisms in primary Sjögren's syndrome. Rheumatology (Oxford) 2020 Feb 1;59(2):418–25. https://doi.org/10.1093/rheumatology/kez269.
[59] Ramírez-Bello J, Jiménez-Morales S, Barbosa-Cobos RE, Sánchez-Zauco N, Hernández-Molina G, Luria-Pérez R, et al. TNFSF4 is a risk factor for rheumatoid arthritis but not for primary Sjögren's syndrome in the Mexican population. Immunobiology 2022 Jul;227(4):152244. https://doi.org/10.1016/j.imbio.2022.152244.
[60] Bolstad AI, Le Hellard S, Kristjansdottir G, Vasaitis L, Kvarnström M, Sjöwall C, et al. Association between genetic variants in the tumour necrosis factor/lymphotoxin α/lymphotoxin β locus and primary Sjogren's syndrome in Scandinavian samples. Ann Rheum Dis 2012 Jun;71(6):981–8. https://doi.org/10.1136/annrheumdis-2011-200446.
[61] Vondenhoff MF, Greuter M, Goverse G, Elewaut D, Dewint P, Ware CF, et al. LTbetaR signaling induces cytokine expression and up-regulates lymphangiogenic factors in lymph node anlagen. J Immunol 2009 May 1;182(9):5439–45. https://doi.org/10.4049/jimmunol.0801165.
[62] Nezos A, Gkioka E, Koutsilieris M, Voulgarelis M, Tzioufas AG, Mavragani CP. TNFAIP3 F127C coding variation in Greek primary Sjogren's syndrome patients. J Immunol Res 2018 Dec 19;2018:6923213. https://doi.org/10.1155/2018/6923213. PMID: 30662920; PMCID: PMC6313987.
[63] Nocturne G, Boudaoud S, Miceli-Richard C, Viengchareun S, Lazure T, Nititham J, et al. Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjogren's syndrome. Blood 2013 Dec 12;122(25):4068–76. https://doi.org/10.1182/blood-2013-05-503383.
[64] Fragkioudaki S, Nezos A, Souliotis VL, Chatziandreou I, Saetta AA, Drakoulis N, et al. MTHFR gene variants and non-MALT lymphoma development in primary Sjogren's syndrome. Sci Rep 2017 Aug 4;7(1):7354. https://doi.org/10.1038/s41598-017-07347-w.
[65] Zheng A, Hu N, Xu J, Yuan Y, Zhang S, Chen W, et al. Associations between TNFSF13B polymorphisms and primary Sjögren's syndrome susceptibility in primary Sjögren's syndrome patients: a meta-analysis. Immun Inflamm Dis 2023 Dec;11(12):e1103. https://doi.org/10.1002/iid3.1103.
[66] Musone SL, Taylor KE, Nititham J, Chu C, Poon A, Liao W, et al. Sequencing of TNFAIP3 and association of variants with multiple autoimmune diseases. Genes Immun 2011 Apr;12(3):176–82. https://doi.org/10.1038/gene.2010.64.
[67] Nocturne G, Tarn J, Boudaoud S, Locke J, Miceli-Richard C, Hachulla E, et al. Germline variation of TNFAIP3 in primary Sjögren's syndrome-associated lymphoma. Ann Rheum Dis 2016 Apr;75(4):780–3. https://doi.org/10.1136/annrheumdis-2015-207731.
[68] Ciccacci C, Latini A, Perricone C, Conigliaro P, Colafrancesco S, Ceccarelli F, et al. TNFAIP3 gene polymorphisms in three common autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, and primary Sjogren syndrome-association with disease susceptibility and clinical phenotypes in Italian patients. J Immunol Res 2019 Aug 27;2019:6728694. https://doi.org/10.1155/2019/6728694.
[69] Wehner R, Dietze K, Bachmann M, Schmitz M. The bidirectional crosstalk between human dendritic cells and natural killer cells. J Innate Immun 2011;3(3):258–63. https://doi.org/10.1159/000323923.
[70] Reksten TR, Johnsen SJ, Jonsson MV, Omdal R, Brun JG, Theander E, et al. Genetic associations to germinal centre formation in primary Sjogren's syndrome. Ann Rheum Dis 2014 Jun;73(6):1253–8. https://doi.org/10.1136/annrheumdis-2012-202500.
[71] Khatri B, Tessneer KL, Rasmussen A, Aghakhanian F, Reksten TR, Adler A, et al. Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. Nat Commun 2022 Jul 27;13(1):4287. https://doi.org/10.1038/s41467-022-30773-y.
[72] Li P, Han M, Zhao X, Ren G, Mei S, Zhong C. Abnormal epigenetic regulations in the immunocytes of Sjögren's syndrome patients and therapeutic potentials. Cells 2022 May 27;11(11):1767. https://doi.org/10.3390/cells11111767.
[73] De Benedittis G, Ciccacci C, Latini A, Novelli L, Novelli G, Borgiani P. Emerging role of microRNAs and long non-coding RNAs in Sjögren's syndrome. Genes (Basel) 2021 Jun 11;12(6):903. https://doi.org/10.3390/genes12060903.
[74] Konsta OD, Thabet Y, Le Dantec C, Brooks WH, Tzioufas AG, Pers JO, et al. The contribution of epigenetics in Sjögren's Syndrome. Front Genet 2014 Apr 3;5:71. https://doi.org/10.3389/fgene.2014.00071.
[75] Yin H, Zhao M, Wu X, Gao F, Luo Y, Ma L, et al. Hypomethylation and overexpression of CD70 (TNFSF7) in CD4+ T cells of patients with primary Sjögren's syndrome. J Dermatol Sci 2010 Sep;59(3):198–203. https://doi.org/10.1016/j.jdermsci.2010.06.011.
[76] Altorok N, Coit P, Hughes T, Koelsch KA, Stone DU, Rasmussen A, et al. Genome-wide DNA methylation patterns in naive CD4+ T cells from patients with primary Sjögren's syndrome. Arthritis Rheumatol 2014 Mar;66(3):731–9. https://doi.org/10.1002/art.38264.
[77] Tessarz P, Kouzarides T. Histone core modifications regulating nucleosome structure and dynamics. Nat Rev Mol Cell Biol 2014 Nov;15(11):703–8. https://doi.org/10.1038/nrm3890.
[78] Luo X, Peng Y, Chen YY, Wang AQ, Deng CW, Peng LY, et al. Genome-wide DNA methylation patterns in monocytes derived from patients with primary Sjogren syndrome. Chin Med J (Engl) 2021 Mar 26;134(11):1310–6. https://doi.org/10.1097/CM9.0000000000001451.
[79] Chi C, Taylor KE, Quach H, Quach D, Criswell LA, Barcellos LF. Hypomethylation mediates genetic association with the major histocompatibility complex genes in Sjögren's syndrome. PloS One 2021 Apr 22;16(4):e0248429. https://doi.org/10.1371/journal.pone.0248429.
[80] Ellmeier W, Seiser C. Histone deacetylase function in CD4$^+$ T cells. Nat Rev Immunol 2018 Oct;18(10):617–34. https://doi.org/10.1038/s41577-018-0037-z.
[81] Lv X, Zhou M, Zhang Q, He Y, Wang Y, Xuan J, et al. Abnormal histones acetylation in patients with primary Sjögren's Syndrome. Clin Rheumatol 2022 May;41(5):1465–72. https://doi.org/10.1007/s10067-021-06036-4.
[82] Imgenberg-Kreuz J, Sandling JK, Nordmark G. Epigenetic alterations in primary Sjögren's syndrome - an overview. Clin Immunol 2018 Nov;196:12–20. https://doi.org/10.1016/j.clim.2018.04.004.

[83] Pauley KM, Stewart CM, Gauna AE, Dupre LC, Kuklani R, Chan AL, et al. Altered miR-146a expression in Sjögren's syndrome and its functional role in innate immunity. Eur J Immunol 2011 Jul;41(7):2029–39. https://doi.org/10.1002/eji.201040757.

[84] Zilahi E, Tarr T, Papp G, Griger Z, Sipka S, Zeher M. Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjögren's syndrome. Immunol Lett 2012 Jan 30;141(2):165–8. https://doi.org/10.1016/j.imlet.2011.09.006.

[85] Shi H, Zheng LY, Zhang P, Yu CQ. miR-146a and miR-155 expression in PBMCs from patients with Sjögren's syndrome. J Oral Pathol Med 2014 Nov;43(10):792–7. https://doi.org/10.1111/jop.12187.

[86] Zhang J, Zhu L, Shi H, Zheng H. Protective effects of miR-155-5p silencing on IFN-γ-induced apoptosis and inflammation in salivary gland epithelial cells. Exp Ther Med 2021 Aug;22(2):882. https://doi.org/10.3892/etm.2021.10314.

[87] Peng L, Ma W, Yi F, Yang YJ, Lin W, Chen H, et al. MicroRNA profiling in Chinese patients with primary Sjögren syndrome reveals elevated miRNA-181a in peripheral blood mononuclear cells. J Rheumatol 2014 Nov;41(11):2208–13. https://doi.org/10.3899/jrheum.131154.

[88] Jara D, Carvajal P, Castro I, Barrera MJ, Aguilera S, González S, et al. Type I interferon dependent hsa-miR-145-5p downregulation modulates MUC1 and TLR4 overexpression in salivary glands from Sjögren's syndrome patients. Front Immunol 2021 Jun 2;12:685837. https://doi.org/10.3389/fimmu.2021.685837.

[89] Kapsogeorgou EK, Papageorgiou A, Protogerou AD, Voulgarelis M, Tzioufas AG. Low miR200b-5p levels in minor salivary glands: a novel molecular marker predicting lymphoma development in patients with Sjögren's syndrome. Ann Rheum Dis 2018 Aug;77(8):1200–7. https://doi.org/10.1136/annrheumdis-2017-212639.

[90] Wang J, Peng H, Tian J, Ma J, Tang X, Rui K, et al. Upregulation of long noncoding RNA TMEVPG1 enhances T helper type 1 cell response in patients with Sjögren syndrome. Immunol Res 2016 Apr;64(2):489–96. https://doi.org/10.1007/s12026-015-8715-4.

[91] Chen X, Cheng Q, Du Y, Liu L, Wu H. Differential long non-coding RNA expression profile and function analysis in primary Sjogren's syndrome. BMC Immunol 2021 Jul 20;22(1):47. https://doi.org/10.1186/s12865-021-00439-3.

[92] Segal BM, Nazmul-Hossain AN, Patel K, Hughes P, Moser KL, Rhodus NL. Genetics and genomics of Sjögren's syndrome: research provides clues to pathogenesis and novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011 Jun;111(6):673–80. https://doi.org/10.1016/j.tripleo.2011.01.040.

[93] Hillen MR, Pandit A, Blokland SLM, Hartgring SAY, Bekker CPJ, van der Heijden EHM, et al. Plasmacytoid DCs from patients with Sjögren's syndrome are transcriptionally primed for enhanced pro-inflammatory cytokine production. Front Immunol 2019 Sep 4;10:2096. https://doi.org/10.3389/fimmu.2019.02096.

[94] Zhang L, Xu P, Wang X, Zhang Z, Zhao W, Li Z, et al. Identification of differentially expressed genes in primary Sjögren's syndrome. J Cell Biochem 2019 Oct;120(10):17368–77. https://doi.org/10.1002/jcb.29001.

[95] Khuder SA, Al-Hashimi I, Mutgi AB, Altorok N. Identification of potential genomic biomarkers for Sjögren's syndrome using data pooling of gene expression microarrays. Rheumatol Int 2015 May;35(5):829–36. https://doi.org/10.1007/s00296-014-3152-6.

[96] Tandon M, Perez P, Burbelo PD, Calkins C, Alevizos I. Laser microdissection coupled with RNA-seq reveal cell-type and disease-specific markers in the salivary gland of Sjögren's syndrome patients. Clin Exp Rheumatol 2017 Sep-Oct;35(5):777–85. Epub 2017 Apr 18. PMID: 28421997.

[97] Imgenberg-Kreuz J, Sandling JK, Björk A, Nordlund J, Kvarnström M, Eloranta ML, et al. Transcription profiling of peripheral B cells in antibody-positive primary Sjögren's syndrome reveals upregulated expression of CX3CR1 and a type I and type II interferon signature. Scand J Immunol 2018 May;87(5):e12662. https://doi.org/10.1111/sji.12662.

[98] Rivière E, Pascaud J, Tchitchek N, Boudaoud S, Paoletti A, Ly B, et al. Salivary gland epithelial cells from patients with Sjögren's syndrome induce B-lymphocyte survival and activation. Ann Rheum Dis 2020 Nov;79(11):1468–77. https://doi.org/10.1136/annrheumdis-2019-216588.

[99] Vakrakou AG, Polyzos A, Kapsogeorgou EK, Thanos D, Manoussakis MN. Impaired anti-inflammatory activity of PPARγ in the salivary epithelia of Sjögren's syndrome patients imposed by intrinsic NF-κB activation. J Autoimmun 2018 Jan;86:62–74. https://doi.org/10.1016/j.jaut.2017.09.007.

[100] Horvath S, Nazmul-Hossain AN, Pollard RP, Kroese FG, Vissink A, Kallenberg CG, et al. Systems analysis of primary Sjögren's syndrome pathogenesis in salivary glands identifies shared pathways in human and a mouse model. Arthritis Res Ther 2012 Nov 1;14(6):R238. https://doi.org/10.1186/ar4081.

[101] Song GG, Kim JH, Seo YH, Choi SJ, Ji JD, Lee YH. Meta-analysis of differentially expressed genes in primary Sjogren's syndrome by using microarray. Hum Immunol 2014 Jan;75(1):98–104. https://doi.org/10.1016/j.humimm.2013.09.012.

[102] Min HK, Moon SJ, Park KS, Kim KJ. Integrated systems analysis of salivary gland transcriptomics reveals key molecular networks in Sjögren's syndrome. Arthritis Res Ther 2019 Dec 19;21(1):294. https://doi.org/10.1186/s13075-019-2082-9.

[103] James K, Al-Ali S, Tarn J, Cockell SJ, Gillespie CS, Hindmarsh V, et al. A transcriptional signature of fatigue derived from patients with primary Sjögren's syndrome. PloS One 2015 Dec 22;10(12):e0143970. https://doi.org/10.1371/journal.pone.0143970.

[104] Michael D, Soi S, Cabera-Perez J, Weller M, Alexander S, Alevizos I, et al. Microarray analysis of sexually dimorphic gene expression in human minor salivary glands. Oral Dis 2011 Oct;17(7):653–61. https://doi.org/10.1111/j.1601-0825.2011.01816.x.

[105] Liang Y, Tsoi LC, Xing X, Beamer MA, Swindell WR, Sarkar MK, et al. A gene network regulated by the transcription factor VGLL3 as a promoter of sex-biased autoimmune diseases. Nat Immunol 2017 Feb;18(2):152–60. https://doi.org/10.1038/ni.3643.

[106] Alevizos I, Alexander S, Turner RJ, Illei GG. MicroRNA expression profiles as biomarkers of minor salivary gland inflammation and dysfunction in Sjögren's syndrome. Arthritis Rheum 2011 Feb;63(2):535–44. https://doi.org/10.1002/art.30131.

[107] Kapsogeorgou EK, Gourzi VC, Manoussakis MN, Moutsopoulos HM, Tzioufas AG. Cellular microRNAs (miRNAs) and Sjögren's syndrome: candidate regulators of autoimmune response and autoantigen expression. J Autoimmun 2011 Sep;37(2):129–35. https://doi.org/10.1016/j.jaut.2011.05.003.

[108] Peng L, Ma W, Yi F, Yang YJ, Lin W, Chen H, et al. MicroRNA profiling in Chinese patients with primary Sjögren syndrome reveals elevated miRNA-181a in peripheral blood mononuclear cells. J Rheumatol 2014 Nov;41(11):2208–13. https://doi.org/10.3899/jrheum.131154.

[109] Tandon M, Gallo A, Jang SI, Illei GG, Alevizos I. Deep sequencing of short RNAs reveals novel microRNAs in minor salivary glands of patients with Sjögren's syndrome. Oral Dis 2012 Mar;18(2):127–31. https://doi.org/10.1111/j.1601-0825.2011.01849.x.

[110] Gallo A, Vella S, Tuzzolino F, Cuscino N, Cecchettini A, Ferro F, et al. MicroRNA-mediated regulation of mucin-type O-glycosylation pathway: a putative mechanism of salivary gland dysfunction in Sjögren syndrome. J Rheumatol 2019 Nov;46(11):1485–94. https://doi.org/10.3899/jrheum.180549.

[111] Williams AE, Choi K, Chan AL, Lee YJ, Reeves WH, Bubb MR, et al. Sjögren's syndrome-associated microRNAs in CD14(+) monocytes unveils targeted TGFβ signaling. Arthritis Res Ther 2016 May 3;18(1):95. https://doi.org/10.1186/s13075-016-0987-0.

[112] Gallo A, Tandon M, Illei G, Alevizos I. Discovery and validation of novel microRNAs in Sjögren's syndrome salivary glands. Clin Exp Rheumatol 2014 Sep-Oct;32(5):761–2. Epub 2014 Sep 5. PMID: 25189219.

[113] Shaw TM, Zhang W, McCoy SS, Pagenkopf A, Carp DM, Garg S, et al. X-linked genes exhibit miR6891-5p-regulated skewing in Sjögren's syndrome. J Mol Med (Berl) 2022 Sep;100(9):1253–65. https://doi.org/10.1007/s00109-022-02205-3.

[114] Gong B, Zheng L, Lu Z, Huang J, Pu J, Pan S, et al. Mesenchymal stem cells negatively regulate CD4+ T cell activation in patients with primary Sjögren syndrome through the miRNA 125b and miRNA 155 TCR pathway. Mol Med Rep 2021 Jan;23(1):43. https://doi.org/10.3892/mmr.2020.11681.

[115] Zhang J, Zhu L, Shi H, Zheng H. Protective effects of miR-155-5p silencing on IFN-γ-induced apoptosis and inflammation in salivary gland epithelial cells. Exp Ther Med 2021 Aug;22(2):882. https://doi.org/10.3892/etm.2021.10314.

[116] Sandhya P, Joshi K, Scaria V. Long noncoding RNAs could be potential key players in the pathophysiology of Sjögren's syndrome. Int J Rheum Dis 2015 Nov;18(8):898–905. https://doi.org/10.1111/1756-185X.12752.

[117] Shi H, Cao N, Pu Y, Xie L, Zheng L, Yu C. Long non-coding RNA expression profile in minor salivary gland of primary Sjögren's syndrome. Arthritis Res Ther 2016 May 17;18(1):109. https://doi.org/10.1186/s13075-016-1005-2.

[118] Peck AB, Nguyen CQ. Transcriptome analysis of the interferon-signature defining the autoimmune process of Sjögren's syndrome. Scand J Immunol 2012 Sep;76(3):237–45. https://doi.org/10.1111/j.1365-3083.2012.02749.x.

[119] Amezcua-Guerra LM, Sánchez-Muñoz F, Pichardo-Ontiveros E, González-Ramírez J, Martínez-Martínez LA, Juárez-Vicuña Y. Interferon-alpha regulates expression of lncRNA MALAT1 and interferon-stimulated genes, as well as chemokine production, in primary Sjögren's syndrome. Clin Exp Rheumatol 2022 Dec;40(12):2275–82. https://doi.org/10.55563/clinexprheumatol/ggkc9t.

[120] Joachims ML, Khatri B, Li C, Tessneer KL, Ice JA, Stolarczyk AM, et al. Dysregulated long non-coding RNA in Sjögren's disease impacts both interferon and adaptive immune responses. RMD Open 2022 Nov;8(2):e002672. https://doi.org/10.1136/rmdopen-2022-002672.

[121] Wang D, Xue L, Yang Y, Hu J, Li G, Piao X. Temporal gene expression analysis of Sjögren's syndrome in C57BL/6.NOD-Aec1Aec2 mice based on microarray time-series data using an improved empirical Bayes approach. Mol Biol Rep 2014 Sep;41(9):5953–60. https://doi.org/10.1007/s11033-014-3471-4.

[122] Weinshilboum RM, Wang L. Pharmacogenomics: precision medicine and drug response. Mayo Clin Proc 2017 Nov;92(11):1711–22. https://doi.org/10.1016/j.mayocp.2017.09.001.

[123] Cecchin E, Stocco G. Pharmacogenomics and personalized medicine. Genes (Basel) 2020 Jun 22;11(6):679. https://doi.org/10.3390/genes11060679.

[124] Lim SH, Kim K, Choi CI. Pharmacogenomics of monoclonal antibodies for the treatment of rheumatoid arthritis. J Pers Med 2022 Jul 31;12(8):1265. https://doi.org/10.3390/jpm12081265.

[125] Leandro M, Isenberg DA. Rituximab - the first twenty years. Lupus 2021 Mar;30(3):371–7. https://doi.org/10.1177/0961203320982668.

[126] Tavakolpour S, Alesaeidi S, Darvishi M, GhasemiAdl M, Darabi-Monadi S, Akhlaghdoust M, et al. A comprehensive review of rituximab therapy in rheumatoid arthritis patients. Clin Rheumatol 2019 Nov;38(11):2977–94. https://doi.org/10.1007/s10067-019-04699-8.

[127] Quartuccio L, Fabris M, Pontarini E, Salvin S, Zabotti A, Benucci M, et al. The 158VV Fcgamma receptor 3A genotype is associated with response to rituximab in rheumatoid arthritis: results of an Italian multicentre study. Ann Rheum Dis 2014 Apr;73(4):716–21. https://doi.org/10.1136/annrheumdis-2012-202435.

[128] St Jean PL, Roth DA, McCarthy LC, Hughes AR. Pharmacogenetic analysis of belimumab fails to identify robust genetic predictors of efficacy in lupus. Pharmacogenet Genomics 2019 Aug;29(6):132–5. https://doi.org/10.1097/FPC.0000000000000378.

[129] Wilkinson C, Henderson RB, Jones-Leone AR, Flint SM, Lennon M, Levy RA, et al. The role of baseline BLyS levels and type 1 interferon-inducible gene signature status in determining belimumab response in systemic lupus erythematosus: a post hoc meta-analysis. Arthritis Res Ther 2020 May 4;22(1):102. https://doi.org/10.1186/s13075-020-02177-0.

[130] Quartuccio L, Mavragani CP, Nezos A, Gandolfo S, Tzioufas AG, De Vita S. Type I interferon signature may influence the effect of belimumab on immunoglobulin levels, including rheumatoid factor in Sjögren's syndrome. Clin Exp Rheumatol 2017 Jul-Aug;35(4):719–20. PMID: 28281461.

[131] Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. Nat Rev Rheumatol 2024 Aug;20(8):473–91. https://doi.org/10.1038/s41584-024-01135-3. Epub 2024 Jul 9. PMID: 38982205.

[132] Thorlacius GE, Björk A, Wahren-Herlenius M. Genetics and epigenetics of primary Sjögren syndrome: implications for future therapies. Nat Rev Rheumatol 2023 May;19(5):288–306. https://doi.org/10.1038/s41584-023-00932-6. PMID: 36914790; PMCID: PMC10010657.

[133] Pezot M, Nocturne G, Belkhir R, Henry J, Pavy S, Seror R, et al. Obinutuzumab in patients with Sjogren's disease immunised against rituximab. Ann Rheum Dis 2024 Feb 15;83(3):407–8. https://doi.org/10.1136/ard-2023-224999 [PMID: 37945315].

[134] Steinfeld SD, Tant L, Burmester GR, Teoh NK, Wegener WA, Goldenberg DM, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. Arthritis Res Ther 2006;8(4):R129. https://doi.org/10.1186/ar2018. PMID: 16859536; PMCID: PMC1779377.

[135] Zheng A, Hu N, Xu J, Yuan Y, Zhang S, Chen W, et al. Associations between TNFSF13B polymorphisms and primary Sjögren's syndrome susceptibility in primary Sjögren's syndrome patients: a meta-analysis. Immun Inflamm Dis 2023 Dec;11(12):e1103. https://doi.org/10.1002/iid3.1103. PMID: 38156381; PMCID: PMC10698818.

[136] Bodewes ILA, Huijser E, van Helden-Meeuwsen CG, Tas L, Huizinga R, Dalm VASH, et al. TBK1: a key regulator and potential treatment target for interferon positive Sjögren's syndrome, systemic lupus erythematosus and systemic sclerosis. J Autoimmun 2018 Jul;91:97–102. https://doi.org/10.1016/j.jaut.2018.02.001. PMID: 29673738.

[137] Song IW, Chen HC, Lin YF, Yang JH, Chang CC, Chou CT, et al. Identification of susceptibility gene associated with female primary Sjögren's syndrome in Han Chinese by genome-wide association study. Hum Genet 2016 Nov;135(11):1287–94. https://doi.org/10.1007/s00439-016-1716-0.

[138] Tanaka T, Warner BM, Michael DG, Nakamura H, Odani T, Yin H, et al. LAMP3 inhibits autophagy and contributes to cell death by lysosomal membrane permeabilization. Autophagy 2022 Jul;18(7):1629–47. https://doi.org/10.1080/15548627.2021.1995150.

[139] Nakamura H, Tanaka T, Ji Y, Zheng C, Afione SA, Warner BM, et al. Salivary gland LAMP3 mRNA expression is a possible predictive marker in the response to hydroxychloroquine in Sjögren's disease. PloS One 2023 Feb 23;18(2):e0282227. https://doi.org/10.1371/journal.pone.0282227.

[140] Shoenfeld Y, Agmon-Levin N. 'ASIA' e autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun 2011;36:4e8.

[141] Watad A, Quaresma M, Bragazzi NL, Cervera R, Tervaert JWC, Amital H, et al. The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. Clin Rheumatol 2018 Feb;37(2):483–93. https://doi.org/10.1007/s10067-017-3748-9. PMID: 28741088.

[142] Colafrancesco S, Perricone C, Priori R, Valesini G, Shoenfeld Y. Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). J Autoimmun 2014 Jun;51:10–6. https://doi.org/10.1016/j.jaut.2014.03.003. PMID: 24774584.

[143] Bagavant H, Nandula SR, Kaplonek P, Rybakowska PD, Deshmukh US. Alum, an aluminum-based adjuvant, induces Sjögren's syndrome-like disorder in mice. Clin Exp Rheumatol 2014 Mar-Apr;32(2):251–5. PMCID: PMC3990870.

[144] Borba V, Malkova A, Basantsova N, Halpert G, Andreoli L, Tincani A, et al. Classical examples of the concept of the ASIA syndrome. Biomolecules 2020 Oct 12;10(10):1436. https://doi.org/10.3390/biom10101436. PMID: 33053910; PMCID: PMC7600067.

[145] Arango MT, Perricone C, Kivity S, Cipriano E, Ceccarelli F, Valesini G, et al. HLA-DRB1 the notorious gene in the mosaic of autoimmunity. Immunol Res 2017 Feb;65(1):82–98. https://doi.org/10.1007/s12026-016-8817-7. PMID: 27435705.

[146] Watad A, Quaresma M, Brown S, et al. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) – an update. Lupus 2017;26(7):675–81. https://doi.org/10.1177/0961203316686406.

[147] Menchaca-Tapia PA, Marín-Rosales M, Salazar-Camarena DC, Cruz A, Oregon-Romero E, Tapia-Llanos R, et al. Analysis of *PTPN22* -1123 G>C, +788 G>A and +1858 C>T polymorphisms in patients with primary Sjögren's syndrome. Diagnostics (Basel) 2023 Feb 27;13(5):899. https://doi.org/10.3390/diagnostics13050899. PMID: 36900045; PMCID: PMC10001387.

[148] Cadena-Sandoval D, Montúfar-Robles I, Barbosa-Cobos RE, Hernández-Molina G, Karen Salas-García A, Sánchez-Zauco N, et al. Interactions between TNFAIP3, PTPN22, and TRAF1-C5 gene polymorphisms in patients with primary Sjögren's syndrome. Arch Rheumatol 2024 Feb 1;39(1):60–70. https://doi.org/10.46497/ArchRheumatol.2024.10108. PMID: 38774701; PMCID: PMC11104759.