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Review article

A comprehensive review of Sjögren's syndrome: Classification criteria, risk factors, and signaling pathways

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ABSTRACT

Sjögren's syndrome (SS) is a chronic autoimmune disease that affects the exocrine glands and may lead to a range of systemic symptoms that impact various organs. Both innate and adaptive immune pathways might trigger the disease. Studying the signaling pathways underlying SS is crucial for enhancing diagnostic and therapeutic effectiveness. SS poses an ongoing challenge for medical professionals owing to the limited therapeutic options available. This review offers a comprehensive understanding of the intricate nature of SS, encompassing disease classification criteria, risk factors, and signaling pathways in immunity and inflammation. The advancements summarized herein have the potential to spark new avenues of research into SS.

1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease whose characteristic hallmark is lympho-plasmocytic infiltration of the salivary and lacrimal glands. The general features of SS are shown in Fig. 1 [1,2]. SS is more commonly observed in middle-aged women, with a higher incidence ratio in females than males (14:1), with the average age of onset ranging from 51.6 ± 13.8 to 62 ± 13 years [3,4]. Primary SS may present without any other autoimmune diathesis. However, approximately 60 % of SS patients have coexisting autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and systemic sclerosis [5]. Systemic involvement is seen in most SS patients [6]. Around half of patients with systemic involvement experience aggravation of the disease over time. The extra-glandular manifestations mainly include active synovitis, severe leukocytopenia, interstitial pneumonia, autoimmune cytopenia, Raynaud's phenomenon, lymphadenopathy, cutaneous vasculitis, renal disease, neurological involvement, and myositis [7–11]. In severe cases, the extra-glandular manifestations can be life-threatening [12,13].

Research has found that SS patients with positive anti-SSA/SSB antibodies are at an increased risk of developing diseases such as hypertension, hypercholesterolemia, venous thromboembolism, interstitial lung disease, cerebral infarction, and multiple myeloma [14–17]. Interstitial lung disease, the most common pulmonary complication in SS, occurs in around 20 % of patients and is associated

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with higher levels of lactic dehydrogenases and anti-Ro52k positivity [18]. Non-Hodgkin lymphoma is a severe complication of SS and may worsen the disease prognosis. It occurs in around 5–10 % of patients—15 to 20 times higher than in the general population [19,20]. Lymphomagenesis may occur when lymphoepithelial sialadenitis is coupled with sustained antigenic stimulation, leading to autoreactive B cell clones in the salivary glands of SS patients.

Although mild benefits are reported for some drugs, conventional systemic immunosuppressive therapy has not demonstrated efficacy in controlling SS [21,22]. SS therefore remains an unresolved challenge for clinicians, with limited therapeutic options. This review provides a comprehensive insight into the complex nature of SS, describing disease classification criteria, risk factors, and signaling pathways in immunity and inflammation. The developments described have the potential to inspire new ideas for SS research.

2. Classification criteria

The understanding of SS has evolved over a century, from initial case reports to research on pathogenesis at the cellular and molecular levels. The history of SS research may be divided into three periods: clinical (1888–1950), immunologic (1950–1980), and molecular (1980–present) (Fig. 2) [23]. Researchers from different regions have proposed multiple classification criteria for the diagnosis of SS. The earliest Bloch criterion was proposed in 1965, followed by several regional standards such as the Shearn standard, the San Francisco standard, the Copenhagen standard, the European classification standard, and the revised Japanese standard [24–27]. Currently, commonly used classification standards include the 2002 American-European Consensus Group (AECG) criteria, the 2012 Sjögren's International Collaborative Clinical Alliance (SICCA) classification standard, and the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria [28–30]. The 2016 ACR/EULAR classification criteria have a high sensitivity and specificity of 96 % and 95 %, respectively, making them suitable for validation analysis of diagnostic criteria and inclusion in clinical trials [30,31]. In recent years, non-invasive and real-time examination techniques such as magnetic resonance imaging, ultrasound elastography, corneal in vivo laser-scanning confocal microscopy, and impression cytology have shown promise, and may potentially improve timely diagnosis and prognostic evaluation of SS [32–36].

3. SS risk factors

3.1. Genetic factors

Although the etiology of SS remains unknown, various factors have been hypothesized to contribute to its development. Among these, the *HLA* genes account for the most significant genetic predisposition to SS [37]. The epithelial expression of *HLA-DP* or *-DQ*,

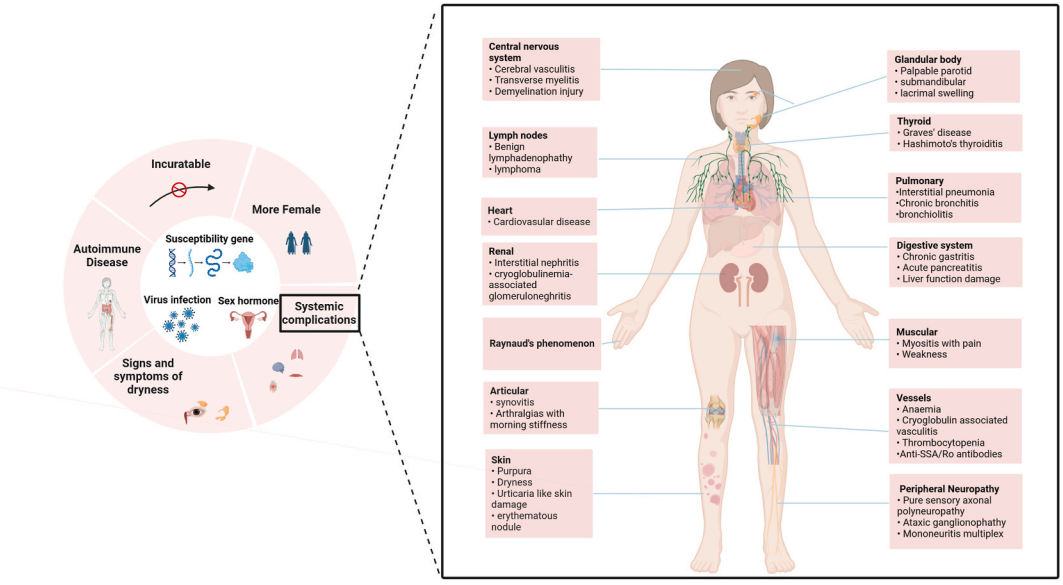

Fig. 1. General features, risk factors and systemic complications of Sjögren's syndrome
Sjögren's syndrome is an incurable autoimmune disease that occurs most frequently in women, usually affecting the lacrimal and salivary glands, with systemic complications. Genetic, viral, and hormonal factors are essential in inducing SS. The extra-glandular manifestations mainly include active synovitis, severe leukocytopenia, interstitial pneumonia, autoimmune cytopenia, Raynaud's phenomenon, lymphadenopathy, cutaneous vasculitis, renal disease, neurological involvement, and myositis. Interstitial lung disease is the most common pulmonary complication in SS. Non-Hodgkin's lymphoma is a severe complication of SS and could worsen disease prognosis. In severe cases, the extra-glandular manifestations of SS may be life-threatening. Created with BioRender.com.

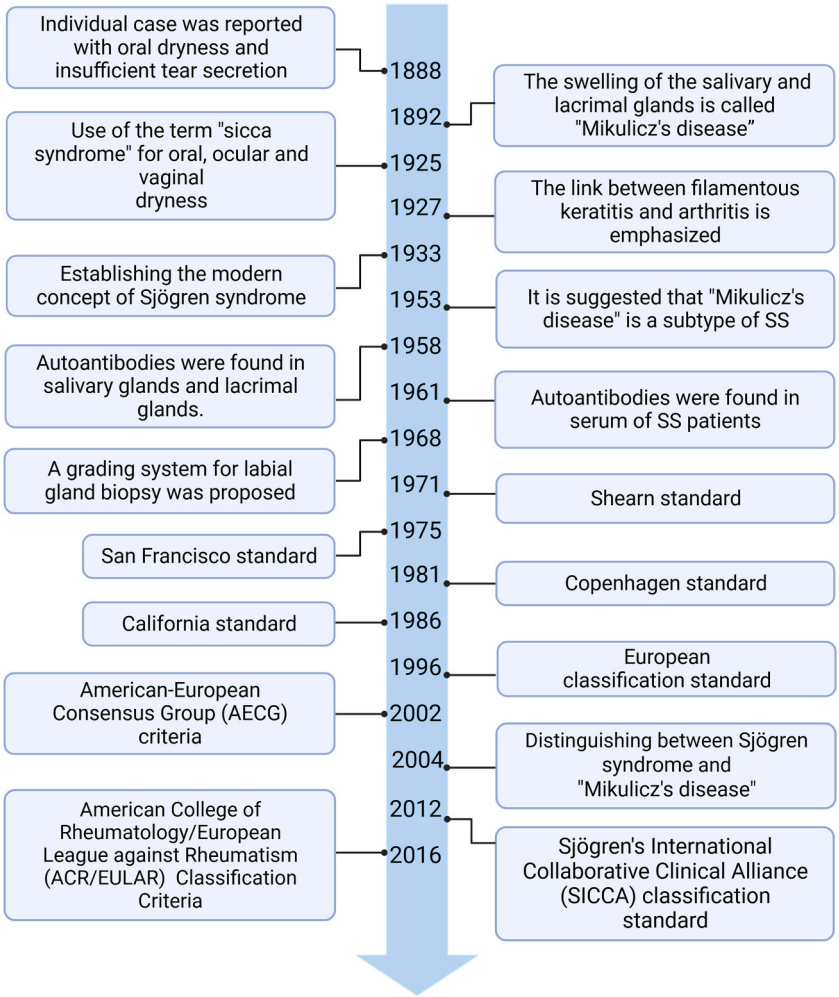

Fig. 2. Milestones in the history of research on Sjögren's syndrome
SS has been studied for over a century, with research progressing from case reports to cellular and molecular studies. The history of SS research may be divided into three periods: clinical (1888–1950), immunologic (1950–1980), and molecular (1980–present). Over time, SS became recognized as a systemic disease by Sjögren in 1933 and auto-antibodies were subsequently discovered by various researchers. The development of lip gland biopsy and the recognition of auto-antibodies have led to notable improvements in the diagnosis and treatment of SS. Various classification standards for the diagnosis of SS have been successively formulated. The earliest of these was the Bloch criterion in 1965, which was followed by several regional standards. The 2002 European criteria, the 2012 Sjögren's International Collaborative Clinical Alliance classification standard, and the 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria are commonly used at present. Created with BioRender.com.

rather than *-DR*, may be a prerequisite for the autoimmune process underlying SS to develop in genetically susceptible individuals [38]. Moreover, the association between *HLA* and SS is limited to patients with anti-SSA and anti-SSB antibodies—*HLA* is not associated with SS in patients without these auto-antibodies [39]. Strong associations with anti-Ro/SSA and anti-La/SSB have been found in patients carrying *DRB1*03* and *DQB1*02* alleles or those heterozygous for *DQw1* and *DQw2* [40]. At the allelic level, *DQB1*02:01*, *DRB1*03:01*, and *DQA1*05:01* alleles are risk factors for SS, whereas *DQA1*02:01*, *DQA1*03:01*, and *DQB1*05:01* alleles are protective factors [41]. MICA, a new non-canonical MHC-linked but HLA-independent susceptibility locus, has a strong association with SS [42]. Weighted gene co-expression network analysis indicates that SS samples with highly expressed *EIF2AK2* or *TDRD7* genes are correlated with inflammatory response, interferon (IFN)-α response, and IFN-γ response [43]. Although the exact genetic factors implicated in SS are not entirely understood, genome-wide association studies have identified several non-*HLA* genes (including *IRF5*, *STAT4*, *BLK*, *PHIP*, *DDX6-CXCR5*, *COL11A2*, *DGKQ*, *PTTG1*, *FCGR2A*, *TNPO3*, *TNFAIP3*, *TNIP1*, *FAM*167-BLK, *GTF2I*, *IL12A*, and *ITSN2*, among others) that appear to be associated with the condition [44–51]. Research has found that individual *TNFAIP3*, *PTPN22*, and *TRAF1-C5* single-nucleotide polymorphisms (SNPs) are not associated with susceptibility or severity of SS, and do not act as serological markers of the disease. However, genetic interactions between TRAF1-C5 and TNFAIP3 or TNFAIP3, PTPN22, and TRAF1-C5 SNPs are risk factors for SS [52]. The rs2069705 SNP in the *IFN-γ* gene acts as a pivotal element in SS susceptibility,

primarily by augmenting IFN-γ transcription, leading to B cell infiltration in the exocrine glands [53]. The rs12583006 SNP is significantly related to SS susceptibility in SS patients [54]. In addition, the presence of multiple X chromosomes are important risk factors for susceptibility to SS [55]. The estimated prevalence of SS in women with the 47, XXX karyotype is ~2.9 times higher than in women with the 46, XX karyotype, and ~41 times higher than that in men with the 46, XY karyotype [56]. Very rare X chromosome abnormalities are present among patients with SS [57]. Among ~2100 women with SS, 1 patient had 45, X/46, XX/47, XXX, with a triplication of the distal p arm of the X chromosome in the 47, XXX cells. These insights provide valuable information for potential future research on SS.

3.2. Viral infection

Infection with viruses or other immune activators may cause abnormal activation of epithelial cells and immune system responses [58]. Direct stimulation by viruses causes salivary gland epithelial cells to secrete chemokines that recruit and activate lymphocytes, resulting in lymphocyte infiltration into the exocrine glands [59]. The epithelial cells of the labial salivary gland were the target of Epstein-Barr virus (EBV) infection [60,61]. Persistent EBV infection may activate polyclonal B cells, inducing the production of auto-antibodies [62,63]. Additionally, a high human T-cell leukemia virus type I viral load in situ is considered to promote the production of transforming growth factor beta, resulting in fibrous changes to the salivary glands in patients with anti-centromere-antibody-seropositive SS [64]. Human T-cell leukemia virus type 1-associated SS may exhibit different immunological patterns to idiopathic SS [65]. In addition, hepatitis C [66–68], cytomegalovirus [69,70], and COVID-19 [71–73] have also been suggested to be closely related to the onset of SS. Although antiviral therapy may help control persistent viral infections that could trigger SS, it may not effectively treat persistent diseases that are no longer dependent on the initial viral infection.

3.3. Hormone abnormality

Estrogen is believed to play a complex role in the occurrence and development of SS by targeting key immune pathways, and increases the risk of the disease in genetically predisposed women [74,75]. Estrogen levels decline during menopause, and lower estrogen levels promote apoptosis in acinar cells [76]. In estrogen-deficient mice, severe autoimmune lesions developed in the salivary and lacrimal glands, and estrogen administration resulted in the recovery of these lesions [77]. Estradiol, a primary form of estrogen, inhibits subcellular structural damage and confers protective effects on the sublingual gland [78]. The salivary gland epithelial cells of patients with SS exhibit significantly reduced responsiveness to 17β-estradiol [79]. A large cohort study has confirmed that women who use estrogen replacement therapy are at an increased risk of dry eye syndrome [80]. In addition, the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, and hypothalamic-pituitary-thyroid axis may also influence the development of SS [81–84].

4. The pathogenesis of SS

As shown in Fig. 3a, the salivary gland epithelium is primarily made up of acinar cells and ductal cells. Acinar cells experience multiple defects in SS, while pathogenic events may occur in the ductal epithelium. SS is characterized by chronic antigen exposure, local production of autoantibodies, accumulation of T cells and B cells, and the formation of lymphoepithelial lesions with basal cell hyperplasia [85]. Epithelial cells undergo abnormal activation, serving as a crucial trigger for an autoimmune response. It may secrete releasing chemokines to attract B cells [86]. In a pro-inflammatory environment, activating B cell-activating factor (BAFF) and proliferation-inducing ligand (APRIL) triggers B cells to produce pro-inflammatory cytokines, potentially resulting in epithelial hyperplasia (Fig. 3b). Follicular helper T (TFH) cells may secrete cytokines to drive B cell proliferation, leading to the differentiation of B cells into plasma cells and the production of numerous autoantibodies, advancing the progression of SS [87,88].

4.1. Altered glandular homeostasis

Altered glandular homeostasis might precede the onset of inflammation and contribute to secretory dysfunction in patients with SS [89,90]. Acinar cells produce and secrete saliva, which is transported through the intercalated and striated ducts to the mouth. However, in individuals with SS, acinar cells tend to have multiple defects [91]. The production of saliva by acinar cells starts with the activation of muscarinic 3 receptors by muscarinic neurotransmitters such as acetylcholine. In patients with SS, auto-antibodies against muscarinic receptors may disrupt this process [85,92]. Under normal physiological conditions, aquaporins (AQPs) facilitate water discharge from the apical membrane of acinar cells. However, in patients with SS, the expression of various AQPs is altered, and the ability of these channels to respond to muscarinic stimuli is significantly reduced [93,94]. Aberrant localization of fusion receptors involved in regulated exocytosis has also been observed in the salivary glands of SS patients [95]. Mucins, produced by mucous acinar cells in the salivary gland, are crucial for lubrication, which aids swallowing [96]. Mucin components such as Mucin 5B/7 are found outside the basal pole of mucous acinar cells, and may contribute to glandular inflammation in SS [97,98]. Maintenance of the polarity of acinar cells is crucial for normal secretory function [99]. During the pathogenesis of SS, the ductal epithelium may also be affected by various pathogenic events such as the activation of innate immune pathways, epithelial cell apoptosis, and senescence [100,101]. In a healthy individual, immune cells are present in the salivary gland epithelium for immune surveillance, which enables a quick response to any injury or infection [102]. However, chronic antigen exposure may lead to the formation of lymphoepithelial lesions in SS.

4.2. Immune cells and salivary gland epithelial cells in SS

4.2.1. Immune cells in SS

In patients with SS, the exocrine glands are infiltrated by various immune cells. T-cell subpopulations play essential roles in SS-related autoimmunity through orchestrating complex immune responses. T helper type 1 (Th1) and T helper type 17 (Th17) cells penetrate the gland in the early stage of the disease, producing inflammatory factors that lead to epithelial cell damage and maintaining the inflammatory response [103,104]. The process of infiltration of TFH and B cells occurs in the late stage of the disease, with

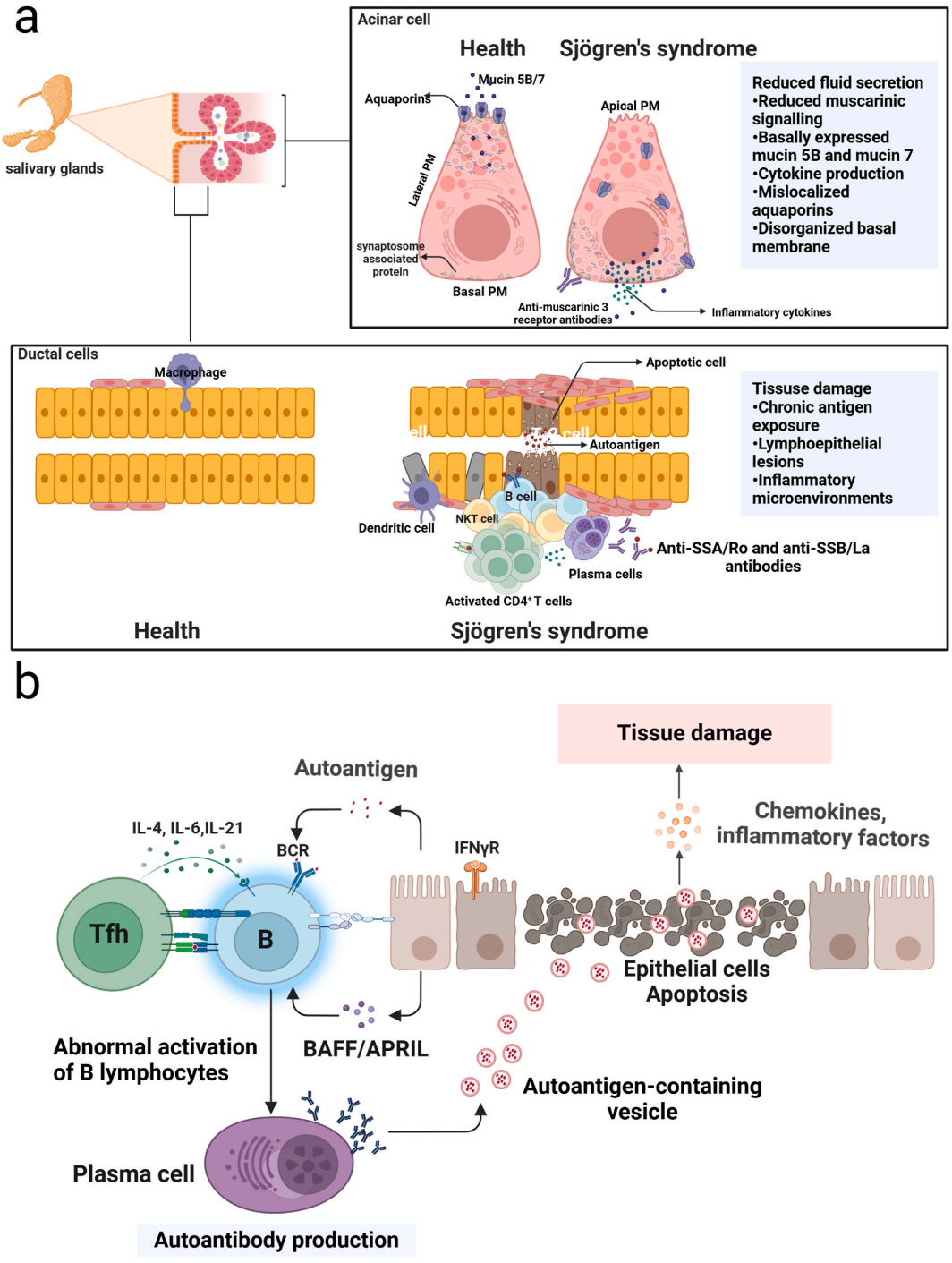

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Fig. 3. The complex pathogenesis of Sjögren's syndrome
(a) Altered glandular homeostasis precedes the onset of inflammation, contributing to secretory dysfunction in patients with SS. In individuals with SS, acinar cells tend to have multiple defects. The expression of different AQPs is altered, and the ability of these channels to respond to muscarinic stimuli is significantly impaired. Aberrant localization of fusion receptors involved in regulated exocytosis has been observed in the salivary glands of SS patients. The ductal epithelium may be affected during SS development because of various pathogenic events such as activation of innate immune pathways, epithelial cell apoptosis, and senescence. Multiple factors could cause chronic antigen exposure, leading to the formation of lymphoepithelial lesions. (b) During immune cell activation, pro-inflammatory factors are released, leading to sustained and persistent inflammatory responses, amplifying tissue damage, and causing progressive functional damage to affected organs. TFH cells secrete cytokines to drive B cell proliferation, leading to the differentiation of B cells into plasma cells and the production of numerous autoantibodies, thus further advancing the progression of SS. The activated infiltrated immune cells are considered to form a complex signaling network with salivary gland cells, leading to impaired secretion. Created with BioRender.com.

TFH promoting B cell differentiation and antibody production [105–107]. Regulatory T cells (Tregs) might play a role in maintaining immune balance and regulating the loss of self-tolerance mechanisms in SS [108]. The levels of forkhead box protein p3-positive (FoxP3 (+)) Tregs in the minor salivary glands lesions of SS patients correlate with inflammation grade during lymphoma development [109]. However, their role in SS is controversial. Studies have identified the distinctive phenotype and possible pathogenic impact of $CD8^+$ T cells in SS [110–112]. $CD8^+$ T cells can contribute to acinar injury in exocrine glands [113]. Studies have confirmed that interleukin (IL)-17-producing $CD4^-CD8^-$ T cells undergo expansion in peripheral blood and infiltrate salivary glands in patients with SS [114]. However, peripheral $CD4^+CD8^+$ double-positive T cells may have a protective role in SS [115]. Almost half of the infiltrating B cells in the peripheral stroma of the glandular lobules of salivary gland tissue are fully differentiated plasma cells [116, 117]. A significant amount of auto-antibodies produced by plasma cells binds to auto-antigens released by damaged host cells, enhancing tissue damage and gland dysfunction. Macrophages—innate immune cells widely present in the glandular tissues of patients with SS—have a bidirectional relationship with the inflammatory microenvironment, which makes them a potential therapeutic target for SS [118]. The pathogenesis of aqueous-deficient dry eye is driven by the concerted action of monocytes/macrophages and infiltrating lymphocytes [119]. In addition, natural killer T-like cells infiltrate the labial salivary glands of patients with SS, putatively playing a role in its pathogenesis [120,121]. However, the potential contribution of immune cells to the pathology of SS remains understudied.

4.2.2. Salivary gland epithelial cells in SS

The exocrine glands of SS patients have an inflammatory microenvironment rich in various proinflammatory cytokines and other factors that can induce an activation status to the surrounding epithelia [122]. Salivary gland epithelial cells can be abnormally activated when stimulated by virus infections or type I interferon, producing chemokines such as CCL7, CCL21, CXCL10, and CXCL13 [123]. These chemokines promote the aggregation of lymphocytes and their focal distribution around the gland ducts. Salivary gland epithelial cells can actively secrete cytokines such as BAFF, IL-21, and IL-7 and promote the proliferation and activation of B lymphocytes and TFH cells [87,88]. Meanwhile, salivary gland epithelial cells are crucial as antigen-presenting cells, which express MHC class II molecules and co-stimulatory molecules like CD86 and CD80 on the cell surface, effectively interacting with CD28 on T lymphocytes to drive T cell activation [124]. In addition to the active presentation of autoantigens, apoptosis also serves as a significant source for releasing autoantigens. Increasing the level of epithelial cell apoptosis can trigger the production of anti-SSA and anti-SSB antibodies [125]. The disruption of the salivary gland epithelium in SS is influenced by critical signaling pathways such as the Toll-like receptor (TLR) and nuclear transcription factor kappa B (NF-κB) signaling, as well as interferons pathways [85,126,127]. Studies have confirmed that the increased vulnerability of SS salivary gland epithelial cells to the injurious effect of TLR-3 ligation is likely associated with the intrinsic activation processes that apparently operate in the epithelia of SS patients [128]. Herein, epithelial cells are actively involved in initiating and driving the autoimmune response in multiple ways, although the underlying cause of its persistent abnormality remains a mystery.

5. Signaling pathways in the pathogenesis of SS

In SS, the activated infiltrated immune cells form a complex signaling network— wherein TLR signaling augments or results in both IFN/cytokine responses and the activation of the other molecular pathways—with salivary gland cells, leading to secretion dysfunction. During immune cell activation, pro-inflammatory factors are released, leading to sustained and persistent inflammatory responses, amplifying tissue damage, and causing progressive functional damage to affected organs and chronic inflammatory environments.

5.1. Toll-like receptor signaling pathway in SS

TLRs are important mediators of inflammatory pathways, mainly involved in innate immunity. The activation of TLR signaling pathways leads to the activation of several factors such as NF-κB, p38 mitogen-activated protein kinase (p38 MAPK), and c-Jun terminal kinase [129]. TLRs are expressed on ductal and acinar epithelial cells in the labial salivary glands of patients with SS [130]. TLR2 plays a role in inducing Th17 cell pathogenicity and driving autoimmune inflammation [131]. TLR2 ligation induces the production of IL-23/IL-17 via IL-6, STAT3, and NF-κB pathways in SS [132]. TLR3-induced apoptosis of salivary gland epithelial cells is mediated through Fas-associated protein with death domain/caspase-8/caspase-3 pathways [130]. TLR4 can initiate a pro-inflammatory

response and attract inflammatory cells to amplify and perpetuate inflammation in epithelial cells [98]. TLR7 is related to the development of sialadenitis in SS. Mononuclear cells from labial/salivary glands in SS patients have been found to show TLR-7-dominant expression [133]. Meanwhile, TLR7 from patients with SS has been reported to stimulate immature B cells, leading to increased plasma cell differentiation and class transition [134]. Additionally, the PBMCs of SS patients demonstrate upregulated levels of *TLR9* mRNA, while patients with SS exhibit the presence of TLR7/TLR9-positive cells in multiple areas of the parotid glands, such as the epithelial islands, lymphocytes, and ductal epithelial cells [135]. Activation of TLR9 signaling may induce phosphorylation of its downstream protein kinases, p38/MAPK and JNK, in a time-dependent manner in SS [136,137].

5.2. NF-κB signaling pathway in SS

NF-κB is positioned at the center of the downstream signaling pathway of TLR. In response to biological stress, NF-κB is activated in cells. The activated NF-κB enters the nucleus to regulate the expression of inflammatory cytokines and initiate immune responses [138]. NF-κB is involved in inflammasome regulation, highlighting its importance in the pathogenesis of inflammatory diseases. Studies have suggested that there are abnormalities with inhibitor of nuclear factor kappa-B kinase ε, NF-kappa-B inhibitor α, and NF-κB in SS [139]. The destruction and exposure of salivary gland close junction structure in SS patients may be related to NF-κB [127]. One possible biomarker for SS is the overexpression of TNF receptor-associated factor 6, which is controlled by the NF-κB pathway [140]. In addition, the dysregulation of the NF-κB pathway may increase susceptibility to SS lymphoma [141,142].

5.3. NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) signaling pathway in SS

The inflammasome is a molecular platform that is formed in the cytosolic compartment to mediate host immune responses to infection and cellular damage [143]. The process of NLRP3 inflammasome activation involves two signals, namely priming and activation. An illustrative instance of priming is the binding of bacterial lipopolysaccharides to TLR4, which initiates NF-κB signaling. This leads to the activation of NF-κB in the nucleus, facilitating the transcription of NF-κB dependent genes. The second signal for inflammasome activation is provided by NLRP3 agonists, which activate NLRP3 to initiate inflammasome assembly and the secretion of mature IL-1β [144]. The NLRP3 inflammasome-mediated inflammation is implicated in the pathogenesis of SS [145]. The occurrence of systemic NLRP3 inflammasome activation has been reported in severe SS [146]. The NLRP3 inflammasome is involved in the onset and development of inflammation in dry eye associated with SS [147]. NLRP3 genotypes potentially influence the progression and clinical outcome of SS [148]. Additionally, inhibiting the NLRP3 inflammasome-related signaling pathway and its mediated pyroptosis can alleviate SS [149].

5.4. The IFN signaling pathway in SS

The IFN signaling pathway is a critical feature of SS. Dysregulation of the IFN pathway often results in tissue damage and inflammation, with the salivary gland being a commonly affected organ [150,151]. IFNs are categorized into three types based on the receptors involved in signal transduction: type I interferons (IFN-Is, mainly including IFN-α, IFN-β and IFN-ω), type II interferon (IFN-γ), and type III interferons (IFN-λs) [152]. TLRs are the primary pattern recognition receptors in the IFN-Is signaling pathway. TLR may induce type I IFN responses by activating IFN-regulatory factor (IRF) family-3 and IRF-7 [153]. Meanwhile, IFN-Is may activate the Janus kinase/signal transducer and activator of the transcription 1 (JAK-STAT1) signaling pathway and induce the expression of inflammatory genes [154]. Inhibition of the JAK-STAT pathway suppresses the expression of IFN-related genes and B-cell activating factor belonging to the TNF family (BAFF, also termed BLyS) in primary salivary gland epithelial cells [155]. Research has found that the expression of IFN-I inducer and IFN-I-related proteins in peripheral blood mononuclear cells (PBMCs) of patients with SS is increased, and the positive rate of IFN-I signaling in the whole blood of these patients ranges from 53 % to 81 % [156]. The abrogation of IFN-I signaling could prevent the occurrence and development of SS [157–159]. IFN-I may also continuously stimulate the secretion of BAFF by salivary epithelial cells, destroying the lacrimal and salivary glands [151,160]. Additionally, in patients with SS, activation of IFN-I in neutrophils causes damage to mitochondria and results in the production of reactive oxygen species, which leads to the creation of neutrophil extracellular traps. The substances released by neutrophil extracellular traps may act as auto-antigens, triggering immune responses and releasing inflammatory substances [156]. IFN-γ has been reported to promote autoimmune germinal centers (GCs) via interaction with the B cell IFN-γ receptor [161,162]. Chronic exposure of the salivary epithelium to IFN-γ alters tight junction integrity, leading to secretory dysfunction [163]. IFN-γ triggers salivary gland epithelial cell ferroptosis by inhibiting cystine-glutamate exchange through the JAK-STAT1 pathway [164]. Moreover, IFN-γ may increase global DNA hydroxymethylation through activation of the JAK-STAT pathway and upregulation of the expression of ten-eleven translocation methylcytosine dioxygenases 3 in the human salivary gland [165]. Studies have shown that IFN-λs are expressed in minor salivary gland tissues in a similar pattern to IFN-I, and their expression is probably subject to micro-environmental regulation [166]. In addition, IFN-λs have a positive regulatory effect on various plasmacytoid dendritic cell functions, including the production of cytokines, survival, and determination of phenotype [167].

5.5. Phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway in SS

The PI3K/AKT/mTOR pathway regulates cell survival, proliferation, growth, metabolism, angiogenesis and metastasis [168,169]. PI3K activation triggers inflammation by enhancing TLR4-mediated NF-κB transactivation through PI3K/Akt signaling [170].

Furthermore, PI3K activation inhibits the activation of downstream transcription factors mediated by TLR and the production of inflammatory factors [171]. The mRNA expression of PI3K, AKT, and mTOR was found to be dramatically increased in a mouse model of SS [172]. PI3K/Akt pathway activation is involved in the TLR3-induced apoptosis of salivary gland epithelial cells [173]. High expression of phosphorylated ribosomal protein S6, a downstream mediator of the PI3Kδ pathway, was found in the salivary glands of patients with SS [174]. The Akt pathway is specifically activated in the minor salivary glands of SS patients [175]. In addition, salivary gland atrophy may be regulated through mTOR [176]. Autophagy is modulated by mTOR kinase and indirectly by the PI3K/AKT survival pathway [177]. Autophagy pathway activation is an essential mechanism for preserving acinar cells during the atrophy of salivary glands after injury [178]. Further research is necessary to understand how the metabolic changes caused by PI3K/Akt pathway activation impact the immune response in SS.

5.6. IL-33/ST2 signaling pathway in SS

The ST2 is a part of the IL-1 receptor/TLR superfamily and has two main subtypes, namely, transmembrane type ST2 (ST2L) and soluble type ST2 (sST2). ST2L represents the longest transcript, whereas sST2 is the truncated, soluble isoform [179]. sST2 levels are significantly increased in SS patients with hematological abnormalities [180]. The ST2-specific ligand is IL-33, which is a tissue-derived nuclear cytokine from the IL-1 family and abundantly expressed in endothelial cells [181]. IL-33 binds to the promoter region of the transcription factor NF-κB subunit p65, inhibiting p65 synthesis. This indirect effect leads to negative regulation of the expression of genes controlled by NF-κB [182]. Moreover, the levels of IL-33 in the tears of SS patients were strongly associated with the severity of ocular involvement [183]. IL-33 is released and acts with IL-12 and IL-23 to favor the secretion of IFN-γ by natural killer and natural killer T cells, forming a vicious auto-inflammatory loop that can contribute to disease perpetuation [184]. Further understanding of the biological activity of IL-33 and the mechanisms underlying its involvement in SS may help clinical drugs effectively block the progression of various immune diseases caused by IL-33.

5.7. Wnt signaling pathway in SS

Wnts are a family of 19 human extracellular secreted glycoproteins that play a crucial role in regulating immune responses and underlie the complexity of the regulatory structure and physiological efficiency of signaling [185]. Wnt may activate the TLR/MyD88 pathway, promoting the synthesis of the anti-inflammatory cytokine IL-10. Meanwhile, the components of the Wnt/β-catenin pathway modulate inflammatory and immune responses via interaction with NF-κB and, thus, significantly influence the progression of inflammation [186]. The Wnt/β-catenin pathway has been shown to play a role in both mesenchymal and ductal maturation of salivary glands [187,188]. A study has confirmed that the *LRP5*, *ADIPOQ*, and *FRZB* genes associated with the Wnt/β-catenin signaling pathway may increase the risk of SS [189]. Additionally, the expression of Wnt1 and Wnt3a in the salivary glands has been found to be elevated in SS [190]. As in the case of all new immune targets, a deeper understanding of Wnt/β-catenin signaling will help determine which treatment pathways and choices may benefit patients with SS the most.

5.8. Other transcription factors and signaling pathways in SS

In regards to SS, there are other transcription factors and signaling pathways worth considering. B7–H3, which belongs to the B7 ligand family, has shown potential as a target for antibody-based immunotherapy. It induces apoptosis in human salivary gland epithelial cells by activating the NF-κB pathway [191,192]. HMGB1, which is a nuclear protein from the alarmin family, plays a role in triggering xerostomia in SS. Suppressing HMGB1 may help alleviate symptoms by reducing TLR4/NF-κB pathway activation and increasing AQP5 expression [193]. A distinct ligand-gated ion channel P2X7 receptor (P2X7R) may mediate activation of the NLRP3 inflammasome in the salivary gland epithelium [194,195]. P2X7R can regulate fluid secretion in the mouse submandibular gland [196]. Studies have confirmed that the P2X7R-NLRP3 inflammasome complex modulates the release of IL-1β and IL-18 in the development of SS [197].

Recent studies have found that cell metabolism, stress response, and the molecular mechanisms involved in cell death are closely related to SS immune inflammation; these processes include ferroptosis, cuproptosis, mtDNA accumulation, pyroptosis, autophagy, gut microbiota, mitochondrial dysfunctions, and endoplasmic reticulum stress [164,198–200]. Herein, the SS signaling pathway highlights a complex network of molecular interactions and signaling cascades. These pathways are crucial for understanding the inflammatory processes, glandular dysfunction, and systemic manifestations associated with SS.

6. Concluding remarks and future perspectives

In SS, genetic markers act in concert with environmental triggers such as viral infections, which may initiate or exacerbate the SS autoimmune response. Although SS may involve a combination of environmental and genetic factors, little is known about the pathogenic mechanisms that lead to the disease. Inflammation and the presence of autoantibodies targeting ribonucleoprotein particles SSA/Ro and SSB/La are the main pathological features of SS; furthermore, the imbalance of immune homeostasis in salivary gland inflammation plays a significant role in the occurrence and development of SS. Epithelial cells may present autoantigens to immune cells, perpetuating the autoimmune response. By unraveling the intricate mechanisms by which immune cells infiltrate and damage the salivary glands, specific targets for immunotherapy can be identified to offer more personalized treatment options for patients.

To improve treatment options for SS, it is essential to address some critical questions. In particular, it is necessary to identify the risk factors that affect SS patients with different systemic complications. A standardized method for evaluating disease activity and outcomes reported in patients with SS must be established. Additionally, the relationship between salivary gland symptoms and extra-glandular manifestations should be investigated, and the mechanisms responsible for fatigue and organ involvement in SS patients explored. By tackling these questions head-on, we may gain a better understanding of SS and develop more effective treatments for patients with the disease.

In conclusion, in this review, we lay the groundwork for novel therapeutic approaches by dissecting the genetic, environmental, and immunological factors contributing to SS and describing the interactions between immune cells and glandular epithelial cells. The elucidation of signaling pathways in SS offers promising targets for immunotherapy. Understanding the association of the epithelium with immune cells opens new avenues for therapeutic strategies to restore glandular function and extra-glandular manifestations of SS. As research in this field continues to evolve, it is hoped that these insights will be translated into more effective and personalized therapies for patients with SS, ultimately improving their quality of life.

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Ethics declaration

Review and/or approval by an ethics committee as well as informed consent was not required for this study because this literature review only used existing data from published studies and did not involve any direct experimentation/studies on living beings.

Data availability statement

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

CRediT authorship contribution statement

Ting Zhao: Writing – original draft, Resources, Data curation, Conceptualization. **Runrun Zhang:** Validation, Supervision, Resources, Investigation. **Zhaofu Li:** Writing – review & editing, Validation, Resources, Formal analysis, Conceptualization. **Dongdong Qin:** Writing – review & editing, Visualization, Validation, Project administration, Formal analysis, Conceptualization. **Xinchang Wang:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Q. Zhan, J. Zhang, Y. Lin, et al., Pathogenesis and treatment of Sjogren's syndrome: review and update, Front. Immunol. 14 (2023) 1127417, https://doi.org/10.3389/fimmu.2023.1127417.
[2] X. Mariette, L.A. Criswell, Primary Sjögren's syndrome, N. Engl. J. Med. 378 (10) (2018) 931–939, https://doi.org/10.1056/NEJMcp1702514.
[3] C.P. Mavragani, H.M. Moutsopoulos, The geoepidemiology of Sjögren's syndrome, Autoimmun. Rev. 9 (5) (2010) A305–A310, https://doi.org/10.1016/j.autrev.2009.11.004.
[4] P. Brito-Zerón, E. Theander, C. Baldini, et al., Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations, Expet Rev. Clin. Immunol. 12 (2) (2016) 137–156, https://doi.org/10.1586/1744666x.2016.1109449.
[5] Y. Yao, J.F. Ma, C. Chang, et al., Immunobiology of T Cells in Sjögren's syndrome, Clin. Rev. Allergy Immunol. 60 (1) (2021) 111–131, https://doi.org/10.1007/s12016-020-08793-7.
[6] M. Bandeira, M. Silvério-António, N. Khmelinskii, et al., Beyond sicca: high prevalence and predictors of baseline and worsening systemic involvement in patients with Sjögren's disease, Rheumatology advances in practice 8 (2) (2024), https://doi.org/10.1093/rap/rkae035 rkae035.
[7] P. Karakasis, D. Patoulias, K. Pamporis, et al., Risk of subclinical atherosclerosis in primary Sjogren's syndrome: a systematic review and meta-analysis, Eur. J. Intern. Med. 122 (2023) 93–101, https://doi.org/10.1016/j.ejim.2023.11.007.
[8] H.E. Konak, K. Gök, B. Armağan, et al., Neurological involvement in patients with primary Sjögren's syndrome: a retrospective cross-sectional study, Ann. Indian Acad. Neurol. 26 (4) (2023) 424–430, https://doi.org/10.4103/aian.aian_138_23.
[9] A.S. Lee, R.H. Scofield, K.M. Hammitt, et al., Consensus guidelines for evaluation and management of pulmonary disease in Sjögren's, Chest 159 (2) (2021) 683–698, https://doi.org/10.1016/j.chest.2020.10.011.
[10] C.S. Santos, R.R. Salgueiro, C.M. Morales, et al., Risk factors for cardiovascular disease in primary Sjögren's syndrome (pSS): a 20-year follow-up study, Clin. Rheumatol. 42 (11) (2023) 3021–3031, https://doi.org/10.1007/s10067-023-06686-6.
[11] V.A. V, S. Narayanan, R. Bhasi, et al., Central pontine myelinolysis and hypokalemic paralysis as presenting manifestations of sjogren's syndrome, Cureus 15 (9) (2023) e45233, https://doi.org/10.7759/cureus.45233.

[12] T.H. Yang, Y.F. Cheng, C.S. Chen, et al., Increased prevalences of head and neck cancers in patients with Sjögren's syndrome, Head Neck 45 (11) (2023) 2874–2881, https://doi.org/10.1002/hed.27518.

[13] P. Witkowski Durand Viel, K. Henry, J. Morel, et al., Chronological interplay, clinical features, and treatments among patients with cancer and primary Sjögren's syndrome, Cancer Immunol. Immunother. : CII. 72 (12) (2023) 4309–4322, https://doi.org/10.1007/s00262-023-03565-6.

[14] J. Mofors, M. Holmqvist, L. Westermark, et al., Concomitant Ro/SSA and La/SSB antibodies are biomarkers for the risk of venous thromboembolism and cerebral infarction in primary Sjögren's syndrome, J. Intern. Med. 286 (4) (2019) 458–468, https://doi.org/10.1111/joim.12941.

[15] J. Mofors, A. Björk, K.E. Smedby, et al., Increased risk of multiple myeloma in primary Sjögren's syndrome is limited to individuals with Ro/SSA and La/SSB autoantibodies, Ann. Rheum. Dis. 79 (2) (2020) 307–308, https://doi.org/10.1136/annrheumdis-2019-216287.

[16] E. Bartoloni, C. Baldini, G. Schillaci, et al., Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study, J. Intern. Med. 278 (2) (2015) 185–192, https://doi.org/10.1111/joim.12346.

[17] D. Bernal-Bello, J. Rodríguez-Rodríguez, M.Á. Duarte-Millán, et al., Anti-synthetase syndrome and the risk of progressive pulmonary fibrosis: weighting of concomitant anti-Ro/SSA antibodies, Clin. Rheumatol. 42 (8) (2023) 2249–2250, https://doi.org/10.1007/s10067-023-06615-7.

[18] G. Sambataro, F. Ferro, M. Orlandi, et al., Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: a systematic review from the Italian Society of Rheumatology, Autoimmun. Rev. 19 (2) (2020) 102447, https://doi.org/10.1016/j.autrev.2019.102447.

[19] A. Alunno, M.C. Leone, E. Bartoloni, et al., Novel insights on lymphoma and lymphomagenesis in primary Sjögren's Syndrome, Panminerva Med. 63 (4) (2021) 491–498, https://doi.org/10.23736/s0031-0808.20.04079-3.

[20] T. Wu, S. Li, J. Chen, et al., A bibliometric analysis of primary Sjögren's syndrome-associated lymphoma from 1991 to 2022, Heliyon 9 (11) (2023) e21337, https://doi.org/10.1016/j.heliyon.2023.e21337.

[21] S. Nakayamada, K. Saito, H. Umehara, et al., Efficacy and safety of mizoribine for the treatment of Sjögren's syndrome: a multicenter open-label clinical trial, Mod. Rheumatol. 17 (6) (2007) 464–469, https://doi.org/10.1007/s10165-007-0627-2.

[22] S. Sugai, H. Takahashi, S. Ohta, et al., Efficacy and safety of rebamipide for the treatment of dry mouth symptoms in patients with Sjögren's syndrome: a double-blind placebo-controlled multicenter trial, Mod. Rheumatol. 19 (2) (2009) 114–124, https://doi.org/10.1007/s10165-008-0141-1.

[23] J.-M. Anaya, N. Talal, Sjögren's syndrome comes of age, Semin. Arthritis Rheum. 28 (6) (1999) 355–359, https://doi.org/10.1016/S0049-0172(99)80001-8.

[24] M.A. Shearn, Sjögren's syndrome, Semin. Arthritis Rheum. 2 (2) (1972) 165–190, https://doi.org/10.1016/0049-0172(72)90008-x.

[25] T.E. Daniels, S. Silverman Jr., J.P. Michalski, et al., The oral component of Sjögren's syndrome, Oral Surg. Oral Med. Oral Pathol. 39 (6) (1975) 875–885, https://doi.org/10.1016/0030-4220(75)90108-5.

[26] C. Vitali, S. Bombardieri, H.M. Moutsopoulos, et al., Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European Study Group on Diagnostic Criteria for Sjögren's Syndrome, Ann. Rheum. Dis. 55 (2) (1996) 116–121, https://doi.org/10.1136/ard.55.2.116.

[27] R. Manthorpe, K. Frost-Larsen, H. Isager, et al., Sjögren's syndrome, Allergy 36 (3) (1981) 139–153, https://doi.org/10.1111/j.1398-9995.1981.tb01829.x.

[28] C. Vitali, S. Bombardieri, R. Jonsson, et al., Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group, Ann. Rheum. Dis. 61 (6) (2002) 554–558, https://doi.org/10.1136/ard.61.6.554.

[29] S.C. Shiboski, C.H. Shiboski, L. Criswell, et al., American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort, Arthritis Care Res. 64 (4) (2012) 475–487, https://doi.org/10.1002/acr.21591.

[30] C.H. Shiboski, S.C. Shiboski, R. Seror, et al., 2016 American College of Rheumatology/European League against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts, Arthritis Rheumatol. 69 (1) (2017) 35–45, https://doi.org/10.1002/art.39859.

[31] M. Ramos-Casals, P. Brito-Zerón, S. Bombardieri, et al., EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies, Ann. Rheum. Dis. 79 (1) (2020) 3–18, https://doi.org/10.1136/annrheumdis-2019-216114.

[32] X. Dai, X. Sui, S. Chen, et al., The diagnostic performance of salivary gland ultrasound elastography in Sjögren's syndrome and sicca symptoms: a systematic review and meta-analysis, Eur. Radiol. 34 (3) (2023) 1545–1555, https://doi.org/10.1007/s00330-023-10166-5.

[33] M.R. Kanavi, S.B. Hosseini, R. Aliakbar-Navahi, et al., Impression cytology in a series of clinically diagnosed ocular surface melanocytic lesions, J. Ophthalmic Vis. Res. 12 (1) (2017) 17–22, https://doi.org/10.4103/jovr.jovr_72_16.

[34] S.P. Weber, R.M. Hazarbassanov, A. Nasaré, et al., Conjunctival impression cytology evaluation of patients with dry eye disease using scleral contact lenses, Contact Lens Anterior Eye : J. Br. Contact Lens Assoc. 40 (3) (2017) 151–156, https://doi.org/10.1016/j.clae.2016.12.008.

[35] T. Zheng, Q. Le, J. Hong, et al., Comparison of human corneal cell density by age and corneal location: an in vivo confocal microscopy study, BMC Ophthalmol. 16 (2016) 109, https://doi.org/10.1186/s12886-016-0290-5.

[36] N. Inanc, S. Jousse-Joulin, K. Abacar, et al., The novel OMERACT Ultrasound Scoring System for salivary glands changes in patients with Sjögren's syndrome is associated with MRI and salivary flow rates, J. Rheumatol. 51 (3) (2023) 263–269, https://doi.org/10.3899/jrheum.2023-0202.

[37] J. Imgenberg-Kreuz, A. Rasmussen, K. Sivils, et al., Genetics and epigenetics in primary Sjögren's syndrome, Rheumatology 60 (5) (2021) 2085–2098, https://doi.org/10.1093/rheumatology/key330.

[38] P.S. Thrane, T.S. Halstensen, H.R. Haanaes, et al., Increased epithelial expression of HLA-DQ and HLA-DP molecules in salivary glands from patients with Sjögren's syndrome compared with obstructive sialadenitis, Clin. Exp. Immunol. 92 (2) (1993) 256–262, https://doi.org/10.1111/j.1365-2249.1993.tb03389.x.

[39] J.E. Gottenberg, M. Busson, P. Loiseau, et al., In primary Sjögren's syndrome, HLA class II is associated exclusively with autoantibody production and spreading of the autoimmune response, Arthritis Rheum. 48 (8) (2003) 2240–2245, https://doi.org/10.1002/art.11103.

[40] J.E. Gottenberg, M. Busson, P. Loiseau, 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. 50 (2) (2004) 570–580, https://doi.org/10.1002/art.20060.

[41] P. Cruz-Tapias, A. Rojas-Villarraga, S. Maier-Moore, et al., HLA and Sjögren's syndrome susceptibility. A meta-analysis of worldwide studies, Autoimmun. Rev. 11 (4) (2012) 281–287, https://doi.org/10.1016/j.autrev.2011.10.002.

[42] R. Carapito, J.E. Gottenberg, I. Kotova, et al., A new MHC-linked susceptibility locus for primary Sjögren's syndrome: mica, Hum. Mol. Genet. 26 (13) (2017) 2565–2576, https://doi.org/10.1093/hmg/ddx135.

[43] Q. Yao, Z. Song, B. Wang, et al., Identifying key genes and functionally enriched pathways in Sjögren's syndrome by weighted gene Co-expression network analysis, Front. Genet. 10 (2019) 1142, https://doi.org/10.3389/fgene.2019.01142.

[44] C.J. Lessard, H. Li, I. Adrianto, et al., Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome, Nat. Genet. 45 (11) (2013) 1284–1292, https://doi.org/10.1038/ng.2792.

[45] I.W. Song, H.C. Chen, Y.F. Lin, et al., Identification of susceptibility gene associated with female primary Sjögren's syndrome in Han Chinese by genome-wide association study, Hum. Genet. 135 (11) (2016) 1287–1294, https://doi.org/10.1007/s00439-016-1716-0.

[46] L.Y. Teos, I. Alevizos, Genetics of Sjögren's syndrome, Clin. Immunol. 182 (2017) 41–47, https://doi.org/10.1016/j.clim.2017.04.018.

[47] C. Miceli-Richard, E. Comets, P. Loiseau, et al., Association of an IRF5 gene functional polymorphism with Sjögren's syndrome, Arthritis Rheum. 56 (12) (2007) 3989–3994, https://doi.org/10.1002/art.23142.

[48] G. Nordmark, G. Kristjansdottir, E. Theander, et al., Additive effects of the major risk alleles of IRF5 and STAT4 in primary Sjögren's syndrome, Gene Immun. 10 (1) (2009) 68–76, https://doi.org/10.1038/gene.2008.94.

[49] C. Miceli-Richard, N. Gestermann, M. Ittah, et al., The CGGGG insertion/deletion polymorphism of the IRF5 promoter is a strong risk factor for primary Sjögren's syndrome, Arthritis Rheum. 60 (7) (2009) 1991–1997, https://doi.org/10.1002/art.24662.

[50] K.E. Taylor, Q. Wong, D.M. Levine, et al., Genome-wide association analysis reveals genetic heterogeneity of Sjögren's syndrome according to ancestry, Arthritis Rheumatol. 69 (6) (2017) 1294–1305, https://doi.org/10.1002/art.40040.

[51] F. Sun, P. Li, H. Chen, et al., Association studies of TNFSF4, TNFAIP3 and FAM167A-BLK polymorphisms with primary Sjogren's syndrome in Han Chinese, J. Hum. Genet. 58 (7) (2013) 475–479, https://doi.org/10.1038/jhg.2013.26.

[52] D. Cadena-Sandoval, I. Montúfar-Robles, R.E. Barbosa-Cobos, et al., Interactions between TNFAIP3, PTPN22, and TRAF1-C5 gene polymorphisms in patients with primary Sjögren's syndrome, Archives of rheumatology 39 (1) (2024) 60–70, https://doi.org/10.46497/ArchRheumatol.2024.10108.

[53] X. Chen, M. Li, H. Li, et al., Implications of IFNγ SNP rs2069705 in primary Sjögren's syndrome: transcriptional activation and B cell infiltration, Am. J. Physiol. Cell Physiol. 326 (5) (2024) C1494–c1504, https://doi.org/10.1152/ajpcell.00661.2023.

[54] A. Zheng, N. Hu, J. Xu, et al., Associations between TNFSF13B polymorphisms and primary Sjögren's syndrome susceptibility in primary Sjögren's syndrome patients: a meta-analysis, Immunity, inflammation and disease 11 (12) (2023) e1103, https://doi.org/10.1002/iid3.1103.

[55] J.L. Mougeot, B.D. Noll, F.K. Bahrani Mougeot, Sjögren's syndrome X-chromosome dose effect: an epigenetic perspective, Oral Dis. 25 (2) (2019) 372–384, https://doi.org/10.1111/odi.12825.

[56] K. Liu, B.T. Kurien, S.L. Zimmerman, et al., X chromosome dose and sex bias in autoimmune diseases: increased prevalence of 47,XXX in systemic lupus erythematosus and Sjögren's syndrome, Arthritis Rheumatol. 68 (5) (2016) 1290–1300, https://doi.org/10.1002/art.39560.

[57] R. Sharma, V.M. Harris, J. Cavett, et al., Rare X chromosome abnormalities in systemic lupus erythematosus and Sjögren's syndrome, Arthritis Rheumatol. 69 (11) (2017) 2187–2192, https://doi.org/10.1002/art.40207.

[58] Z. Liu, A. Chu, Sjögren's syndrome and viral infections, Rheumatology and therapy 8 (3) (2021) 1051–1059, https://doi.org/10.1007/s40744-021-00334-8.

[59] K. Otsuka, M. Sato, T. Tsunematsu, et al., Virus infections play crucial roles in the pathogenesis of Sjögren's syndrome, Viruses 14 (7) (2022) 1474, https://doi.org/10.3390/v14071474.

[60] S.C. Pflugfelder, C. Crouse, I. Pereira, et al., Amplification of Epstein-Barr virus genomic sequences in blood cells, lacrimal glands, and tears from primary Sjögren's syndrome patients, Ophthalmology 97 (8) (1990) 976–984, https://doi.org/10.1016/s0161-6420(90)32476-4.

[61] X. Mariette, J. Gozlan, D. Clerc, et al., Detection of Epstein-Barr virus DNA by in situ hybridization and polymerase chain reaction in salivary gland biopsy specimens from patients with Sjögren's syndrome, Am. J. Med. 90 (3) (1991) 286–294.

[62] S. Whittingham, L.J. McNeilage, I.R. Mackay, Epstein-Barr virus as an etiological agent in primary Sjögren's syndrome, Med. Hypotheses 22 (4) (1987) 373–386, https://doi.org/10.1016/0306-9877(87)90033-8.

[63] M. Maślińska, The role of Epstein-Barr virus infection in primary Sjögren's syndrome, Curr. Opin. Rheumatol. 31 (5) (2019) 475–483, https://doi.org/10.1097/bor.0000000000000622.

[64] H. Nakamura, Y. Horai, A. Tokuyama, et al., HTLV-I virological and histopathological analysis in two cases of anti-centromere-antibody-seropositive Sjögren's syndrome, Mod. Rheumatol. 23 (1) (2013) 133–139, https://doi.org/10.1007/s10165-012-0641-x.

[65] S.J. Lee, J.S. Lee, M.G. Shin, et al., Detection of HTLV-1 in the labial salivary glands of patients with Sjögren's syndrome: a distinct clinical subgroup? J. Rheumatol. 39 (4) (2012) 809–815, https://doi.org/10.3899/jrheum.111075.

[66] C.H. Tung, Y.C. Chen, Y.C. Chen, Association between anti-hepatitis C viral intervention therapy and risk of Sjögren's syndrome: a national retrospective analysis, J. Clin. Med. 11 (15) (2022) 4259, https://doi.org/10.3390/jcm11154259.

[67] J.O. Maldonado, M.E. Beach, Y. Wang, et al., HCV infection alters salivary gland histology and saliva composition, J. Dent. Res. 101 (5) (2022) 534–541, https://doi.org/10.1177/00220345211049395.

[68] O.D. Argyropoulou, V. Pezoulas, L. Chatzis, et al., Cryoglobulinemic vasculitis in primary Sjögren's Syndrome: clinical presentation, association with lymphoma and comparison with Hepatitis C-related disease, Semin. Arthritis Rheum. 50 (5) (2020) 846–853, https://doi.org/10.1016/j.semarthrit.2020.07.013.

[69] C.C. Sorgato, E.S.M. Lins, J.C. Leão, et al., EBV and CMV viral load in rheumatoid arthritis and their role in associated Sjögren's syndrome, J. Oral Pathol. Med. : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 49 (7) (2020) 693–700, https://doi.org/10.1111/jop.13036.

[70] L. García-Montoya, C.N. Sáenz-Tenorio, I. Janta, et al., Hemophagocytic lymphohistiocytosis in a patient with Sjögren's syndrome: case report and review, Rheumatol. Int. 37 (4) (2017) 663–669, https://doi.org/10.1007/s00296-016-3601-5.

[71] E. Greenan, G. Tynan, D. Collins, et al., Beyond dry eye: the greater extent of Sjögren's systemic disease symptoms, the impact of COVID-19 and perceptions towards telemedicine identified through a patient co-designed study, Health Expect. : an international journal of public participation in health care and health policy 26 (6) (2023) 2252–2263, https://doi.org/10.1111/hex.13823.

[72] K. Konishi, H. Kuwahara, Y. Fujimoto, et al., Severe COVID-19 as a possible mediator of autoimmunity and Sjögren's syndrome, Cureus 15 (2) (2023) e35290, https://doi.org/10.7759/cureus.35290.

[73] H. Luo, X. Zhou, Bioinformatics analysis of potential common pathogenic mechanisms for COVID-19 infection and primary Sjogren's syndrome, Front. Immunol. 13 (2022) 938837, https://doi.org/10.3389/fimmu.2022.938837.

[74] S. Kovats, Estrogen receptors regulate innate immune cells and signaling pathways, Cell. Immunol. 294 (2) (2015) 63–69, https://doi.org/10.1016/j.cellimm.2015.01.018.

[75] S.S. McCoy, E. Sampene, A.N. Baer, Association of Sjögren's syndrome with reduced lifetime sex hormone exposure: a case-control study, Arthritis Care Res. 72 (9) (2020) 1315–1322, https://doi.org/10.1002/acr.24014.

[76] Y. Xuan, X. Zhang, H. Wu, Impact of sex differences on the clinical presentation, pathogenesis, treatment and prognosis of Sjögren's syndrome, Immunology 171 (4) (2024) 513–524, https://doi.org/10.1111/imm.13740.

[77] N. Ishimaru, K. Saegusa, K. Yanagi, et al., Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjögren's syndrome through fas-mediated apoptosis, Am. J. Pathol. 155 (1) (1999) 173–181, https://doi.org/10.1016/s0002-9440(10)65111-5.

[78] Y.M. Da, K.Y. Niu, S.Y. Liu, et al., Does Cimicifuga racemosa have the effects like estrogen on the sublingual gland in ovariectomized rats? Biol. Res. 50 (1) (2017) 11, https://doi.org/10.1186/s40659-017-0115-x.

[79] M.N. Manoussakis, M. Tsinti, E.K. Kapsogeorgou, et al., The salivary gland epithelial cells of patients with primary Sjögren's syndrome manifest significantly reduced responsiveness to 17β-estradiol, J. Autoimmun. 39 (1–2) (2012) 64–68, https://doi.org/10.1016/j.jaut.2012.01.005.

[80] D.A. Schaumberg, J.E. Buring, D.A. Sullivan, et al., Hormone replacement therapy and dry eye syndrome, JAMA 286 (17) (2001) 2114–2119, https://doi.org/10.1001/jama.286.17.2114.

[81] E.O. Johnson, M. Kostandi, H.M. Moutsopoulos, Hypothalamic-pituitary-adrenal axis function in Sjögren's syndrome: mechanisms of neuroendocrine and immune system homeostasis, Ann. N. Y. Acad. Sci. 1088 (2006) 41–51, https://doi.org/10.1196/annals.1366.018.

[82] E.O. Johnson, F.N. Skopouli, H.M. Moutsopoulos, Neuroendocrine manifestations in Sjögren's syndrome, Rheum. Dis. Clin. N. Am. 26 (4) (2000) 927–949, https://doi.org/10.1016/s0889-857x(05)70177-0.

[83] L. Yang, W. Wei, X. He, et al., Influence of hormones on Sjögren's syndrome, Curr. Pharmaceut. Des. 24 (35) (2018) 4167–4176, https://doi.org/10.2174/1381612824666181010153536.

[84] C.P. Mavragani, G.E. Fragoulis, H.M. Moutsopoulos, Endocrine alterations in primary Sjogren's syndrome: an overview, J. Autoimmun. 39 (4) (2012) 354–358, https://doi.org/10.1016/j.jaut.2012.05.011.

[85] G.M. Verstappen, S. Pringle, H. Bootsma, et al., Epithelial-immune cell interplay in primary Sjögren syndrome salivary gland pathogenesis, Nat. Rev. Rheumatol. 17 (6) (2021) 333–348, https://doi.org/10.1038/s41584-021-00605-2.

[86] S. Negrini, G. Emmi, M. Greco, et al., Sjögren's syndrome: a systemic autoimmune disease, Clin. Exp. Med. 22 (1) (2022) 9–25, https://doi.org/10.1007/s10238-021-00728-6.

[87] E.K. Kapsogeorgou, A.G. Tzioufas, Interaction of human salivary gland epithelial cells with B lymphocytes: implications in the pathogenesis of Sjögren's syndrome, Mediterranean journal of rheumatology. 31 (4) (2020) 424–426, https://doi.org/10.31138/mjr.31.4.424.

[88] Y.Z. Gong, J. Nititham, K. Taylor, et al., Differentiation of follicular helper T cells by salivary gland epithelial cells in primary Sjögren's syndrome, J. Autoimmun. 51 (2014) 57–66, https://doi.org/10.1016/j.jaut.2013.11.003.

[89] S. Cha, A.B. Peck, M.G. Humphreys-Beher, Progress in understanding autoimmune exocrinopathy using the non-obese diabetic mouse: an update, Crit. Rev. Oral Biol. Med. : an official publication of the American Association of Oral Biologists 13 (1) (2002) 5–16, https://doi.org/10.1177/154411130201300103.

[90] F. Rosignoli, V. Roca, R. Meiss, et al., Defective signalling in salivary glands precedes the autoimmune response in the non-obese diabetic mouse model of sialadenitis, Clin. Exp. Immunol. 142 (3) (2005) 411–418, https://doi.org/10.1111/j.1365-2249.2005.02930.x.

[91] A.M. Pedersen, A. Bardow, B. Nauntofte, Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjogren's syndrome, BMC Clin. Pathol. 5 (1) (2005) 4, https://doi.org/10.1186/1472-6890-5-4.

[92] S.A. Waterman, T.P. Gordon, M. Rischmueller, Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjögren's syndrome, Arthritis Rheum. 43 (7) (2000) 1647–1654, https://doi.org/10.1002/1529-0131(200007)43:7<1647::Aid-anr31>3.0.Co;2-p.

[93] T.B. Enger, M.H. Aure, J.L. Jensen, et al., Calcium signaling and cell volume regulation are altered in Sjögren's Syndrome, Acta Odontol. Scand. 72 (7) (2014) 549–556, https://doi.org/10.3109/00016357.2013.879995.

[94] T. Ichiyama, E. Nakatani, K. Tatsumi, et al., Expression of aquaporin 3 and 5 as a potential marker for distinguishing dry mouth from Sjögren's syndrome, J. Oral Sci. 60 (2) (2018) 212–220, https://doi.org/10.2334/josnusd.17-0150.

[95] M.J. Barrera, M. Sánchez, S. Aguilera, et al., Aberrant localization of fusion receptors involved in regulated exocytosis in salivary glands of Sjögren's syndrome patients is linked to ectopic mucin secretion, J. Autoimmun. 39 (1–2) (2012) 83–92, https://doi.org/10.1016/j.jaut.2012.01.011.

[96] A.M. Wu, G. Csako, A. Herp, Structure, biosynthesis, and function of salivary mucins, Mol. Cell. Biochem. 137 (1) (1994) 39–55, https://doi.org/10.1007/bf00926038.

[97] H.H. Sung, I. Castro, S. González, et al., MUC1/SEC and MUC1/Y overexpression is associated with inflammation in Sjögren's syndrome, Oral Dis. 21 (6) (2015) 730–738, https://doi.org/10.1111/odi.12339.

[98] M.J. Barrera, S. Aguilera, E. Veerman, et al., Salivary mucins induce a Toll-like receptor 4-mediated pro-inflammatory response in human submandibular salivary cells: are mucins involved in Sjögren's syndrome? Rheumatology 54 (8) (2015) 1518–1527, https://doi.org/10.1093/rheumatology/kev026.

[99] P. Sandhya, B.T. Kurien, D. Danda, et al., Update on pathogenesis of sjogren's syndrome, Curr. Rheumatol. Rev. 13 (1) (2017) 5–22, https://doi.org/10.2174/1573397112666160714164149.

[100] M.P. Spachidou, E. Bourazopoulou, C.I. Maratheftis, et al., Expression of functional Toll-like receptors by salivary gland epithelial cells: increased mRNA expression in cells derived from patients with primary Sjögren's syndrome, Clin. Exp. Immunol. 147 (3) (2007) 497–503, https://doi.org/10.1111/j.1365-2249.2006.03311.x.

[101] X. Wang, H. Bootsma, J. Terpstra, et al., Progenitor cell niche senescence reflects pathology of the parotid salivary gland in primary Sjögren's syndrome, Rheumatology 59 (10) (2020) 3003–3013, https://doi.org/10.1093/rheumatology/keaa012.

[102] B. Stolp, F. Thelen, X. Ficht, et al., Salivary gland macrophages and tissue-resident CD8+ T cells cooperate for homeostatic organ surveillance, Sci Immunol 5 (46) (2020) eaaz4371, https://doi.org/10.1126/sciimmunol.aaz4371.

[103] W. Chen, F. Yang, G. Xu, et al., Follicular helper T cells and follicular regulatory T cells in the immunopathology of primary Sjögren's syndrome, J. Leukoc. Biol. 109 (2) (2021) 437–447, https://doi.org/10.1002/jlb.5mr1020-057rr.

[104] A.G. Tzioufas, E.K. Kapsogeorgou, H.M. Moutsopoulos, Pathogenesis of Sjögren's syndrome: what we know and what we should learn, J. Autoimmun. 39 (1–2) (2012) 4–8, https://doi.org/10.1016/j.jaut.2012.01.002.

[105] G.M. Verstappen, P.M. Meiners, O.B.J. Corneth, et al., Attenuation of follicular helper T cell-dependent B cell hyperactivity by abatacept treatment in primary Sjögren's syndrome, Arthritis Rheumatol. 69 (9) (2017) 1850–1861, https://doi.org/10.1002/art.40165.

[106] H. Ueno, Human circulating T follicular helper cell subsets in health and disease, J. Clin. Immunol. 36 (1) (2016) 34–39, https://doi.org/10.1007/s10875-016-0268-3.

[107] M. Akiyama, W. Alshehri, K. Yoshimoto, et al., T follicular helper cells and T peripheral helper cells in rheumatic and musculoskeletal diseases, Ann. Rheum. Dis. 82 (11) (2023) 1371–1381, https://doi.org/10.1136/ard-2023-224225.

[108] V.G. Blinova, V.I. Vasilyev, E.B. Rodionova, et al., The role of regulatory T cells in the onset and progression of primary Sjögren's syndrome, Cells 12 (10) (2023) 1359, https://doi.org/10.3390/cells12101359.

[109] M.I. Christodoulou, E.K. Kapsogeorgou, N.M. Moutsopoulos, et al., Foxp3+ T-regulatory cells in Sjogren's syndrome: correlation with the grade of the autoimmune lesion and certain adverse prognostic factors, Am. J. Pathol. 173 (5) (2008) 1389–1396, https://doi.org/10.2353/ajpath.2008.080246.

[110] C.Y. Gao, Y. Yao, L. Li, et al., Tissue-Resident memory CD8+ T cells acting as mediators of salivary gland damage in a murine model of Sjögren's syndrome, Arthritis Rheumatol. 71 (1) (2019) 121–132, https://doi.org/10.1002/art.40676.

[111] S. Tasaki, K. Suzuki, A. Nishikawa, et al., Multiomic disease signatures converge to cytotoxic CD8 T cells in primary Sjögren's syndrome, Ann. Rheum. Dis. 76 (8) (2017) 1458–1466, https://doi.org/10.1136/annrheumdis-2016-210788.

[112] J.Y. Barr, X. Wang, D.K. Meyerholz, et al., CD8 T cells contribute to lacrimal gland pathology in the nonobese diabetic mouse model of Sjögren syndrome, Immunol. Cell Biol. 95 (8) (2017) 684–694, https://doi.org/10.1038/icb.2017.38.

[113] H. Zhou, J. Yang, J. Tian, et al., CD8(+) T lymphocytes: crucial players in Sjögren's syndrome, Front. Immunol. 11 (2020) 602823, https://doi.org/10.3389/fimmu.2020.602823.

[114] A. Alunno, O. Bistoni, E. Bartoloni, et al., IL-17-producing CD4-CD8- T cells are expanded in the peripheral blood, infiltrate salivary glands and are resistant to corticosteroids in patients with primary Sjogren's syndrome, Ann. Rheum. Dis. 72 (2) (2013) 286–292, https://doi.org/10.1136/annrheumdis-2012-201511.

[115] S. Wang, H. Shen, B. Bai, et al., Increased $CD4^{+}CD8^{+}$ double-positive T cell in patients with primary sjögren's syndrome correlated with disease activity, Journal of immunology research 2021 (2021) 6658324, https://doi.org/10.1155/2021/6658324.

[116] J. Li, M. Zhao, W. Luo, et al., B cell metabolism in autoimmune diseases: signaling pathways and interventions, Front. Immunol. 14 (2023) 1232820, https://doi.org/10.3389/fimmu.2023.1232820.

[117] G. Nocturne, X. Mariette, B cells in the pathogenesis of primary Sjögren syndrome, Nat. Rev. Rheumatol. 14 (3) (2018) 133–145, https://doi.org/10.1038/nrrheum.2018.1.

[118] Y. Zong, Y. Yang, J. Zhao, et al., Characterisation of macrophage infiltration and polarisation based on integrated transcriptomic and histological analyses in Primary Sjögren's syndrome, Front. Immunol. 14 (2023) 1292146, https://doi.org/10.3389/fimmu.2023.1292146.

[119] D. Zhou, N.A. McNamara, Macrophages: important players in primary Sjögren's syndrome? Expet Rev. Clin. Immunol. 10 (4) (2014) 513–520, https://doi.org/10.1586/1744666x.2014.900441.

[120] L. Zhao, W. Xu, Z. Chen, et al., Aberrant distribution of CD3+CD56+ NKT-like cells in patients with primary Sjögren's syndrome, Clin. Exp. Rheumatol. 39 (1) (2021) 98–104, https://doi.org/10.55563/clinexprheumatol/uzzz6d.

[121] X. Zhou, Q. Li, Y. Li, et al., Diminished natural killer T-like cells correlates with aggravated primary Sjögren's syndrome, Clin. Rheumatol. 41 (4) (2022) 1163–1168, https://doi.org/10.1007/s10067-021-06011-z.

[122] M.N. Manoussakis, E.K. Kapsogeorgou, The role of intrinsic epithelial activation in the pathogenesis of Sjögren's syndrome, J. Autoimmun. 35 (3) (2010) 219–224, https://doi.org/10.1016/j.jaut.2010.06.011.

[123] M. Moriyama, J.N. Hayashida, T. Toyoshima, et al., Cytokine/chemokine profiles contribute to understanding the pathogenesis and diagnosis of primary Sjögren's syndrome, Clin. Exp. Immunol. 169 (1) (2012) 17–26, https://doi.org/10.1111/j.1365-2249.2012.04587.x.

[124] E.K. Kapsogeorgou, H.M. Moutsopoulos, M.N. Manoussakis, Functional expression of a costimulatory B7.2 (CD86) protein on human salivary gland epithelial cells that interacts with the CD28 receptor, but has reduced binding to CTLA4, J. Immunol. 166 (5) (2001) 3107–3113, https://doi.org/10.4049/jimmunol.166.5.3107 (Baltimore, Md. : 1950).

[125] S. Katsiougiannis, R. Tenta, F.N. Skopouli, Endoplasmic reticulum stress causes autophagy and apoptosis leading to cellular redistribution of the autoantigens Ro/Sjögren's syndrome-related antigen A (SSA) and La/SSB in salivary gland epithelial cells, Clin. Exp. Immunol. 181 (2) (2015) 244–252, https://doi.org/10.1111/cei.12638.

[126] X. Wang, A. Shaalan, S. Liefers, et al., Dysregulation of NF-kB in glandular epithelial cells results in Sjögren's-like features, PLoS One 13 (8) (2018) e0200212, https://doi.org/10.1371/journal.pone.0200212.

[127] P. Ewert, S. Aguilera, C. Alliende, et al., Disruption of tight junction structure in salivary glands from Sjögren's syndrome patients is linked to proinflammatory cytokine exposure, Arthritis Rheum. 62 (5) (2010) 1280–1289, https://doi.org/10.1002/art.27362.
[128] M.N. Manoussakis, M.P. Spachidou, C.I. Maratheftis, Salivary epithelial cells from Sjogren's syndrome patients are highly sensitive to anoikis induced by TLR-3 ligation, J. Autoimmun. 35 (3) (2010) 212–218, https://doi.org/10.1016/j.jaut.2010.06.010.
[129] T. Duan, Y. Du, C. Xing, et al., Toll-like receptor signaling and its role in cell-mediated immunity, Front. Immunol. 13 (2022) 812774, https://doi.org/10.3389/fimmu.2022.812774.
[130] Y. Horai, H. Nakamura, Y. Nakashima, et al., Analysis of the downstream mediators of toll-like receptor 3-induced apoptosis in labial salivary glands in patients with Sjögren's syndrome, Mod. Rheumatol. 26 (1) (2016) 99–104, https://doi.org/10.3109/14397595.2015.1045256.
[131] K.E. Marks, S. Flaherty, K.M. Patterson, et al., Toll-like receptor 2 induces pathogenicity in Th17 cells and reveals a role for IPCEF in regulating Th17 cell migration, Cell Rep. 35 (13) (2021) 109303, https://doi.org/10.1016/j.celrep.2021.109303.
[132] S.K. Kwok, M.L. Cho, Y.M. Her, et al., TLR2 ligation induces the production of IL-23/IL-17 via IL-6, STAT3 and NF-kB pathway in patients with primary Sjogren's syndrome, Arthritis Res. Ther. 14 (2) (2012) R64, https://doi.org/10.1186/ar3780.
[133] T. Shimizu, H. Nakamura, A. Takatani, et al., Activation of Toll-like receptor 7 signaling in labial salivary glands of primary Sjögren's syndrome patients, Clin. Exp. Immunol. 196 (1) (2019) 39–51, https://doi.org/10.1111/cei.13242.
[134] L. Alexopoulou, Nucleic acid-sensing toll-like receptors: important players in Sjögren's syndrome, Front. Immunol. 13 (2022) 980400, https://doi.org/10.3389/fimmu.2022.980400.
[135] L. Zheng, Z. Zhang, C. Yu, et al., Expression of Toll-like receptors 7, 8, and 9 in primary Sjögren's syndrome, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 109 (6) (2010) 844–850, https://doi.org/10.1016/j.tripleo.2010.01.006.
[136] J. Fu, H. Shi, N. Cao, et al., Toll-like receptor 9 signaling promotes autophagy and apoptosis via divergent functions of the p38/JNK pathway in human salivary gland cells, Exp. Cell Res. 375 (2) (2019) 51–59, https://doi.org/10.1016/j.yexcr.2018.12.027.
[137] H. Shi, C.Q. Yu, L.S. Xie, et al., Activation of TLR9-dependent p38MAPK pathway in the pathogenesis of primary Sjögren's syndrome in NOD/Ltj mouse, J. Oral Pathol. Med. : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 43 (10) (2014) 785–791, https://doi.org/10.1111/jop.12209.
[138] T. Liu, L. Zhang, D. Joo, et al., NF-κB signaling in inflammation, Signal Transduct. Targeted Ther. 2 (2017) 17023, https://doi.org/10.1038/sigtrans.2017.23.
[139] W. Chen, J. Lin, H. Cao, et al., Local and systemic IKKε and NF-κB signaling associated with Sjögren's syndrome immunopathogenesis, Journal of immunology research. 2015 (2015) 534648, https://doi.org/10.1155/2015/534648.
[140] E. Zilahi, T. Tarr, G. Papp, et al., Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjögren's syndrome, Immunol. Lett. 141 (2) (2012) 165–168, https://doi.org/10.1016/j.imlet.2011.09.006.
[141] A. Nezos, E. Gkioka, M. Koutsilieris, et al., TNFAIP3 F127C coding variation in Greek primary sjogren's syndrome patients, Journal of immunology research 2018 (2018) 6923213, https://doi.org/10.1155/2018/6923213.
[142] G. Nocturne, J. Tarn, S. Boudaoud, et al., Germline variation of TNFAIP3 in primary Sjögren's syndrome-associated lymphoma, Ann. Rheum. Dis. 75 (4) (2016) 780–783, https://doi.org/10.1136/annrheumdis-2015-207731.
[143] R. Kong, L. Sun, H. Li, et al., The role of NLRP3 inflammasome in the pathogenesis of rheumatic disease, Autoimmunity 55 (1) (2022) 1–7, https://doi.org/10.1080/08916934.2021.1995860.
[144] T. Liu, L. Zhang, D. Joo, et al., NF-κB signaling in inflammation, Signal Transduct. Targeted Ther. 2 (1) (2017) 17023, https://doi.org/10.1038/sigtrans.2017.23.
[145] S.K. Kim, J.Y. Choe, G.H. Lee, Enhanced expression of NLRP3 inflammasome-related inflammation in peripheral blood mononuclear cells in Sjögren's syndrome, Clinica chimica acta; international journal of clinical chemistry 474 (2017) 147–154, https://doi.org/10.1016/j.cca.2017.09.019.
[146] A.G. Vakrakou, S. Boiu, P.D. Ziakas, et al., Systemic activation of NLRP3 inflammasome in patients with severe primary Sjögren's syndrome fueled by inflammagenic DNA accumulations, J. Autoimmun. 91 (2018) 23–33, https://doi.org/10.1016/j.jaut.2018.02.010.
[147] L. Niu, S. Zhang, J. Wu, et al., Upregulation of NLRP3 inflammasome in the tears and ocular surface of dry eye patients, PLoS One 10 (5) (2015) e0126277, https://doi.org/10.1371/journal.pone.0126277.
[148] R.N. Li, T.T. Ou, C.H. Lin, et al., NLRP3 gene polymorphisms in rheumatoid arthritis and primary sjogren's syndrome patients, Diagnostics 13 (2) (2023) 206, https://doi.org/10.3390/diagnostics13020206.
[149] S.M. Hong, J. Lee, S.G. Jang, et al., Type I interferon increases inflammasomes associated pyroptosis in the salivary glands of patients with primary Sjögren's syndrome, Immune network 20 (5) (2020) e39, https://doi.org/10.4110/in.2020.20.e39.
[150] R. Fernandez-Ruiz, T.B. Niewold, Type I interferons in autoimmunity, J. Invest. Dermatol. 142 (3 Pt B) (2022) 793–803, https://doi.org/10.1016/j.jid.2021.11.031.
[151] I.L.A. Bodewes, A. Björk, M.A. Versnel, et al., Innate immunity and interferons in the pathogenesis of Sjögren's syndrome, Rheumatology 60 (6) (2021) 2561–2573, https://doi.org/10.1093/rheumatology/key360.
[152] S. Pestka, C.D. Krause, M. R. Walter Interferons, interferon-like cytokines, and their receptors, Immunol. Rev. 202 (2004) 8–32, https://doi.org/10.1111/j.0105-2896.2004.00204.x.
[153] M. Colonna, TLR pathways and IFN-regulatory factors: to each its own, Eur. J. Immunol. 37 (2) (2007) 306–309, https://doi.org/10.1002/eji.200637009.
[154] L.A. Aqrawi, J.L. Jensen, G. Øijordsbakken, et al., Signalling pathways identified in salivary glands from primary Sjögren's syndrome patients reveal enhanced adipose tissue development, Autoimmunity 51 (3) (2018) 135–146, https://doi.org/10.1080/08916934.2018.1446525.
[155] J. Lee, J. Lee, S.K. Kwok, et al., JAK-1 inhibition suppresses interferon-induced BAFF production in human salivary gland: potential therapeutic strategy for primary Sjögren's syndrome, Arthritis Rheumatol. 70 (12) (2018) 2057–2066, https://doi.org/10.1002/art.40589.
[156] I.L.A. Bodewes, S. Al-Ali, C.G. van Helden-Meeuwsen, et al., Systemic interferon type I and type II signatures in primary Sjögren's syndrome reveal differences in biological disease activity, Rheumatology 57 (5) (2018) 921–930, https://doi.org/10.1093/rheumatology/kex490.
[157] B.M. Szczerba, P.D. Rybakowska, P. Dey, et al., Type I interferon receptor deficiency prevents murine Sjogren's syndrome, J. Dent. Res. 92 (5) (2013) 444–449, https://doi.org/10.1177/0022034513483315.
[158] H. Nakamura, Y. Horai, T. Shimizu, et al., Modulation of apoptosis by cytotoxic mediators and cell-survival molecules in Sjögren's syndrome, Int. J. Mol. Sci. 19 (8) (2018) 2369, https://doi.org/10.3390/ijms19082369.
[159] J.K. Smith, A.A. Siddiqui, L.A. Modica, et al., Interferon-alpha upregulates gene expression of aquaporin-5 in human parotid glands, J. Interferon Cytokine Res. : the official journal of the International Society for Interferon and Cytokine Research 19 (8) (1999) 929–935, https://doi.org/10.1089/107999099313479.
[160] Z. Brkic, N.I. Maria, C.G. van Helden-Meeuwsen, et al., Prevalence of interferon type I signature in CD14 monocytes of patients with Sjogren's syndrome and association with disease activity and BAFF gene expression, Ann. Rheum. Dis. 72 (5) (2013) 728–735, https://doi.org/10.1136/annrheumdis-2012-201381.
[161] S.W. Jackson, H.M. Jacobs, T. Arkatkar, et al., B cell IFN-γ receptor signaling promotes autoimmune germinal centers via cell-intrinsic induction of BCL-6, J. Exp. Med. 213 (5) (2016) 733–750, https://doi.org/10.1084/jem.20151724.
[162] P.P. Domeier, S.B. Chodisetti, C. Soni, et al., IFN-γ receptor and STAT1 signaling in B cells are central to spontaneous germinal center formation and autoimmunity, J. Exp. Med. 213 (5) (2016) 715–732, https://doi.org/10.1084/jem.20151722.
[163] O. Odusanwo, S. Chinthamani, A. McCall, et al., Resolvin D1 prevents TNF-α-mediated disruption of salivary epithelial formation, Am. J. Physiol. Cell Physiol. 302 (9) (2012) C1331–C1345, https://doi.org/10.1152/ajpcell.00207.2011.
[164] T. Cao, J. Zhou, Q. Liu, et al., Interferon-γ induces salivary gland epithelial cell ferroptosis in Sjogren's syndrome via JAK/STAT1-mediated inhibition of system Xc(.), Free Radic. Biol. Med. 205 (2023) 116–128, https://doi.org/10.1016/j.freeradbiomed.2023.05.027.
[165] A. Charras, P. Arvaniti, C. Le Dantec, et al., JAK inhibitors suppress innate epigenetic reprogramming: a promise for patients with Sjögren's syndrome, Clin. Rev. Allergy Immunol. 58 (2) (2020) 182–193, https://doi.org/10.1007/s12016-019-08743-y.
[166] E. Apostolou, E.K. Kapsogeorgou, O.D. Konsta, et al., Expression of type III interferons (IFNλs) and their receptor in Sjögren's syndrome, Clin. Exp. Immunol. 186 (3) (2016) 304–312, https://doi.org/10.1111/cei.12865.

[167] G. Finotti, N. Tamassia, M.A. Cassatella, Interferon-λs and plasmacytoid dendritic cells: a close relationship, Front. Immunol. 8 (2017) 1015, https://doi.org/10.3389/fimmu.2017.01015.
[168] T. Ersahin, N. Tuncbag, R. Cetin-Atalay, The PI3K/AKT/mTOR interactive pathway, Mol. Biosyst. 11 (7) (2015) 1946–1954, https://doi.org/10.1039/c5mb00101c.
[169] D.A. Fruman, H. Chiu, B.D. Hopkins, et al., The PI3K pathway in human disease, Cell 170 (4) (2017) 605–635, https://doi.org/10.1016/j.cell.2017.07.029.
[170] M. Ojaniemi, V. Glumoff, K. Harju, et al., Phosphatidylinositol 3-kinase is involved in Toll-like receptor 4-mediated cytokine expression in mouse macrophages, Eur. J. Immunol. 33 (3) (2003) 597–605, https://doi.org/10.1002/eji.200323376.
[171] K. Miyazawa, A negative regulator or just an unconcerned passerby: phosphoinositide 3-kinase signalling in IL-12 production, J. Biochem. 152 (6) (2012) 497–499, https://doi.org/10.1093/jb/mvs122.
[172] P. Zeng, Z. Jiang, Z. Huang, et al., PI3K/AKT/mTOR signaling pathway is downregulated by runzaoling (RZL) in Sjögren's syndrome, Mediat. Inflamm. 2022 (2022) 7236118, https://doi.org/10.1155/2022/7236118.
[173] H. Nakamura, Y. Horai, T. Suzuki, et al., TLR3-mediated apoptosis and activation of phosphorylated Akt in the salivary gland epithelial cells of primary Sjögren's syndrome patients, Rheumatol. Int. 33 (2) (2013) 441–450, https://doi.org/10.1007/s00296-012-2381-9.
[174] S. Nayar, J. Campos, C.G. Smith, et al., Phosphatidylinositol 3-kinase delta pathway: a novel therapeutic target for Sjögren's syndrome, Ann. Rheum. Dis. 78 (2) (2019) 249–260, https://doi.org/10.1136/annrheumdis-2017-212619.
[175] I.E. Stergiou, L. Chatzis, A. Papanikolaou, et al., Akt signaling pathway is activated in the minor salivary glands of patients with primary Sjögren's syndrome, Int. J. Mol. Sci. 22 (24) (2021) 13441, https://doi.org/10.3390/ijms222413441.
[176] S.S. Bozorgi, G.B. Proctor, G.H. Carpenter, Rapamycin delays salivary gland atrophy following ductal ligation, Cell Death Dis. 5 (3) (2014) e1146, https://doi.org/10.1038/cddis.2014.108.
[177] D. Heras-Sandoval, J.M. Pérez-Rojas, J. Hernández-Damián, et al., The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration, Cell. Signal. 26 (12) (2014) 2694–2701, https://doi.org/10.1016/j.cellsig.2014.08.019.
[178] N. Silver, G.B. Proctor, M. Arno, et al., Activation of mTOR coincides with autophagy during ligation-induced atrophy in the rat submandibular gland, Cell Death Dis. 1 (1) (2010) e14, https://doi.org/10.1038/cddis.2009.12.
[179] I. Pusceddu, B. Dieplinger, T. Mueller, ST2 and the ST2/IL-33 signalling pathway-biochemistry and pathophysiology in animal models and humans, Clinica chimica acta; international journal of clinical chemistry 495 (2019) 493–500, https://doi.org/10.1016/j.cca.2019.05.023.
[180] S.M. Jung, J. Lee, S.Y. Baek, et al., The Interleukin 33/ST2 axis in patients with primary Sjögren syndrome: expression in serum and salivary glands, and the clinical association, J. Rheumatol. 42 (2) (2015) 264–271, https://doi.org/10.3899/jrheum.140234.
[181] A.M. Miller, Role of IL-33 in inflammation and disease, J. Inflamm. 8 (1) (2011) 22, https://doi.org/10.1186/1476-9255-8-22.
[182] Y.S. Choi, H.J. Choi, J.K. Min, et al., Interleukin-33 induces angiogenesis and vascular permeability through ST2/TRAF6-mediated endothelial nitric oxide production, Blood 114 (14) (2009) 3117–3126, https://doi.org/10.1182/blood-2009-02-203372.
[183] G. Luo, Y. Xin, D. Qin, et al., Correlation of interleukin-33 with Th cytokines and clinical severity of dry eye disease, Indian J. Ophthalmol. 66 (1) (2018) 39–43, https://doi.org/10.4103/ijo.IJO_405_17.
[184] A. Awada, C. Nicaise, S. Ena, et al., Potential involvement of the IL-33-ST2 axis in the pathogenesis of primary Sjogren's syndrome, Ann. Rheum. Dis. 73 (6) (2014) 1259–1263, https://doi.org/10.1136/annrheumdis-2012-203187.
[185] R. Hayat, M. Manzoor, A. Hussain, Wnt signaling pathway: a comprehensive review, Cell Biol. Int. 46 (6) (2022) 863–877, https://doi.org/10.1002/cbin.11797.
[186] A. Martín-Medina, N. Cerón-Pisa, E. Martinez-Font, et al., TLR/WNT: a novel relationship in immunomodulation of lung cancer, Int. J. Mol. Sci. 23 (12) (2022) 6539, https://doi.org/10.3390/ijms23126539.
[187] W.J. Chae, A.L.M. Bothwell, Canonical and non-canonical Wnt signaling in immune cells, Trends Immunol. 39 (10) (2018) 830–847, https://doi.org/10.1016/j.it.2018.08.006.
[188] J. Liu, Q. Xiao, J. Xiao, et al., Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities, Signal Transduct. Targeted Ther. 7 (1) (2022) 3, https://doi.org/10.1038/s41392-021-00762-6.
[189] J. Fernández-Torres, N. Pérez-Hernández, G. Hernández-Molina, et al., Risk of Wnt/β-catenin signalling pathway gene polymorphisms in primary Sjögren's syndrome, Rheumatology 59 (2) (2020) 418–425, https://doi.org/10.1093/rheumatology/kez269.
[190] A. Karataş, Z. Ömercikoğlu, B. Öz, et al., Wnt signaling pathway activities may be altered in primary Sjogren's syndrome, Turk. J. Med. Sci. 51 (4) (2021) 2015–2022, https://doi.org/10.3906/sag-2102-367.
[191] F. Kontos, T. Michelakos, T. Kurokawa, et al., B7-H3: an attractive target for antibody-based immunotherapy, Clin. Cancer Res. : an official journal of the American Association for Cancer Research 27 (5) (2021) 1227–1235, https://doi.org/10.1158/1078-0432.Ccr-20-2584.
[192] P. Li, Y. Yang, Y. Jin, et al., B7-H3 participates in human salivary gland epithelial cells apoptosis through NF-κB pathway in primary Sjögren's syndrome, J. Transl. Med. 17 (1) (2019) 268, https://doi.org/10.1186/s12967-019-2017-x.
[193] D. Wang, M. Zhou, Y. Wang, et al., Suppression of high-mobility group box 1 ameliorates xerostomia in a Sjögren syndrome-triggered mouse model, Can. J. Physiol. Pharmacol. 98 (6) (2020) 351–356, https://doi.org/10.1139/cjpp-2019-0337.
[194] L.T. Woods, J.M. Camden, J.M. Batek, et al., P2X7 receptor activation induces inflammatory responses in salivary gland epithelium, Am. J. Physiol. Cell Physiol. 303 (7) (2012) C790–C801, https://doi.org/10.1152/ajpcell.00072.2012.
[195] S. Eltom, C.S. Stevenson, J. Rastrick, et al., P2X7 receptor and caspase 1 activation are central to airway inflammation observed after exposure to tobacco smoke, PLoS One 6 (9) (2011) e24097, https://doi.org/10.1371/journal.pone.0024097.
[196] T. Nakamoto, D.A. Brown, M.A. Catalán, et al., Purinergic P2X7 receptors mediate ATP-induced saliva secretion by the mouse submandibular gland, J. Biol. Chem. 284 (8) (2009) 4815–4822, https://doi.org/10.1074/jbc.M808597200.
[197] C. Baldini, C. Rossi, F. Ferro, et al., The P2X7 receptor-inflammasome complex has a role in modulating the inflammatory response in primary Sjögren's syndrome, J. Intern. Med. 274 (5) (2013) 480–489, https://doi.org/10.1111/joim.12115.
[198] Y. Shen, X. Yu, Q. Wang, et al., Association between primary Sjögren's syndrome and gut microbiota disruption: a systematic review and meta-analysis, Clin. Rheumatol. 43 (2) (2024) 603–619, https://doi.org/10.1007/s10067-023-06754-x.
[199] Y. Zou, W. Xiao, D. Liu, et al., Human umbilical cord mesenchymal stem cells improve disease characterization of Sjogren's syndrome in NOD mice through regulation of gut microbiota and Treg/Th17 cellular immunity, Immunity, inflammation and disease 12 (1) (2024) e1139, https://doi.org/10.1002/iid3.1139.
[200] B. Wei, A. Wang, W. Liu, et al., Identification of immunological characteristics and cuproptosis-related molecular clusters in primary Sjögren's syndrome, Int. Immunopharm. 126 (2024) 111251, https://doi.org/10.1016/j.intimp.2023.111251.