

SIGNALING PATHWAYS: A KEY TO UNLOCKING NEW TREATMENTS FOR SJÖGREN'S SYNDROME

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Abstract

Sjögren's syndrome (SS) is a multifaceted autoimmune disorder characterized by chronic inflammation of exocrine glands, leading to debilitating dryness of the eyes and mouth, alongside systemic manifestations. This review elucidates the complex interplay of immunological, genetic, and environmental factors underlying SS pathogenesis, highlighting the essential roles of various autoantibodies and cytokines, particularly those within the JAK-STAT signaling pathway. A keen focus is placed on the adaptive immune response, where activated T and B cells drive chronic inflammation and tissue damage. Additionally, the review examines the dysregulation of intrinsic cellular signaling mechanisms, including the Hippo and Akt pathways, emphasizing their contributions to cellular polarity and structural integrity in salivary glands. The current therapeutic landscape is critically assessed, noting the limited efficacy of existing treatments and the emerging potential of JAK inhibitors to simultaneously target multiple inflammatory pathways, thus paving the way for more precise and effective management strategies. By integrating insights from recent research, this paper advocates for a multi-target therapeutic approach in SS, aiming to mitigate the intricate cytokine network and restore glandular function, ultimately improving patient outcomes.

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Introduction

Sjögren's syndrome (SS) is a self-aggressive type of illness because of chronic inflammation of the exocrine glands, leading to formation of glandular affections accompanied by dryness of eyes and mouth and extra-glandular hurts that are transferred to systemic organs. As usual a polyclonal hypergammaglobulinemia appears and several autoantibodies among which are rheumatoid factor and antinuclear, anti-Ro/SS-A, and anti-La/SS-B antibody are emitted [1,2].

Besides there could be other autoantibodies against M3 muscarinic acetylcholine receptors (M3R) produced in salivary gland epithelial cells (SGECs) and those against alpha (α)-fodrin, a type of cytoskeleton protein. In total there are two types of SS: primary SS which doesn't include any autoimmune diseases and secondary SS that is connected with other autoimmune diseases among which are rheumatoid arthritis and systemic lupus erythematosus (SLE) [3,4].

In epidemiological research realized in Japan in 2011 it was shown that almost 68,483 individuals have SS, with a level of occurrence in 0.05%. The medium age of respondents was 60.8 ± 15.2 years. Moreover, the proportion between men and women was 1:17.4 with

predominant age of the beginning of the disease in 40–60 years [5,6].

There is a connection between genetic liability, endocrine disturbances, involving the lack of female hormones, bacterial and viral infections such as Epstein–Barr virus, human T lymphotropic virus 1 and the progress of SS. In addition, the degradation of salivary gland tissues can stimulate inflammation [7–10]. Consequently, after cell destruction, autoantigens such as Ro/SS-A protein, La/SS-B protein, M3R, α -amylase, heat shock 10/60 protein, and α -fodrin are released [11,12]. SGECs and antigen-introducing cells display these autoantigens as antigen peptides to antigen-specific autoreactive T cells, resulting in T cell activation. Activated T cells generate cytokines like interleukin (IL)-2. The continued division of T cells leads to the production of inflammatory cytokines, including interferon gamma (IFN- γ), IL-17, and tumor necrosis factor- α [13–15]. These protein substances influence on acinar and ductal epithelial cells thus increasing the activity of the following costimulatory and adhesion molecules: CD40, CD80, CD86, and ICAM-1 on the cell exteriority, in this way intensifying inflammatory response [16,17]. Moreover, cytotoxic T cells strengthened by these immune responses provoke programmed death of cells in acinar and ductal epithelial cells through Fas

ligand/interactions, perforin, and granzymes, resulting in progressive glandular tissue disruption, tissue disintegration, and chronic sialadenitis [18]. Besides, such cytokines as IL-6, born by energized T cells stimulate the reproduction of polyclonal B cells, leading to an autoantibody generation and uncontrolled reproduction of cells [19,20].

The microstructure of salivary and lacrimal tissues of patients with SS in a such condition that the decay of acinar cells, the enlargement of ductal epithelial cells, spreading and accumulation of mononuclear cells, mostly CD4+ T and B cells encircling these cells are observed. Therefore, adaptive immune disturbances that are the result of energized T and B cells, have a crucial meaning in tissue dysfunctions and chronic inflammation in SS [21-24].

Nevertheless, there are many signal processes that display not only antigens but evoke an evident inflammation and tissue harms as an inborn immune reply to injuries by microbes [25-27]. However, the innate immune response, which is a reaction to tissue destruction triggered by microbes, is also activated by multiple signaling cascades, which do not only present antigens but also cause direct inflammation and tissue damage. It's worth noting that the adaptive immunity additionally stimulates cells taking part in the inborn immunity, increases immune operation and persistent inflammation [28,29]. Accordingly, the inborn immune reply plays a key role both in the primary reply in SS and the growth of persistent inflammation [30-32].

At present SS isn't treated fundamentally. In such difficult cases as interstitial lung disease the use of corticosteroids and immunosuppressive agents is possible. Nevertheless, a significant suitable therapy is mostly applied for other extra-glandular or glandular lesions. After the definition of the root of the disease, taking into consideration the variety of features and affections, a particular treatment should be elaborated [33,34].

Signaling pathways involved in SS pathogenesis

Table 1. Key Moments of Signaling Pathways in Sjögren's Syndrome

Signaling Pathway	Key Aspects	Implications for SS
JAK-STAT	1. Cytokine Binding	Cytokines like IL-6, IL-21 bind to receptors on immune cells.
	2. JAK Activation	JAKs phosphorylate themselves and receptor tails, initiating signaling.

Signaling Pathway	Key Aspects	Implications for SS
Hippo	3. STAT Phosphorylation	Activated JAKs phosphorylate STATs, which then dimerize and translocate to the nucleus.
	4. Gene Expression	STATs influence gene expression related to inflammation and immune response.
	1. Cell Polarity Regulation	TAZ interacts with E-cadherin for maintaining epithelial architecture.
	2. TAZ Activation	Dysregulation leads to loss of cell junction integrity and promotes autoimmunity.
Akt	3. ECM Remodeling	TAZ influences gene expression for extracellular matrix, affecting glandular structure.
	4. Tissue Integrity Loss	Impaired Hippo signaling contributes to structural defects in salivary glands.
	1. Akt Phosphorylation	Triggered by various cytokines, signaling oxidative stress and inflammation.
	2. Downstream Targeting (e.g., PRAS40, FoxO1)	Activates pathways related to survival and proliferation.
	3. EMT Promotion	Linked to changes in epithelial cells, though

Signaling Pathway	Key Aspects	Implications for SS
		not fully evidenced in SS.
	4. Feedback Mechanism	Inflammation acts as a feedback loop for continued Akt activation, sustaining immune response.

JAK-STAT

The JAK-STAT pathway consists of four intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) and seven STAT transcription factors (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6). This pathway plays a pivotal role in transmitting signals from various cytokines that regulate immune responses, inflammation, cell activation, and survival [35-37]. When a cytokine binds to its receptor on the cell surface, JAK enzymes facilitate the transfer of phosphates from ATP to the receptor's intracellular domains, to the JAK proteins themselves, and to other downstream molecules like STAT. Once activated, STAT proteins move into the nucleus to influence the expression of specific gene sets [38,39].

Imbalance of the JAK-STAT pathway has been linked to various immune disorders. As a result, JAK inhibitors (JAK-i), which work by competitively binding to ATP and disrupting this signaling cascade and subsequent gene expression, have emerged as a promising therapeutic approach in the field of rheumatology [40-42].

A few JAK inhibitors (JAK-i) have been developed or are in development, including first-generation pan-JAK inhibitors such as tofacitinib, baricitinib, ruxolitinib, and peficitinib, and second-generation, more preferential JAK inhibitors like filgotinib, upadacitinib, and decernotinib [43,44]. Tofacitinib primarily inhibits JAK1 and JAK3, but also affects JAK2 and TYK2, and it became the first oral JAK inhibitor approved for treating rheumatoid arthritis (RA) and psoriatic arthritis [45,46]. Baricitinib, which inhibits JAK1 and JAK2, is also used in RA treatment, along with filgotinib and upadacitinib, which more preferentially inhibit JAK1. Provided the extensive number of cytokines that signal through the JAK-STAT pathway, the groundbreaking potential of oral small molecule JAK inhibitors lies in their ability to block multiple cytokines and related pathways simultaneously [47-49]. This stands in contrast to biotechnological anti-cytokine drugs, which target individual cytokines. In primary Sjögren's syndrome

(pSS), this versatility translates into the possibility of creating useful therapies that target numerous pathways with a sole drug, while anti-cytokine therapies have largely failed in clinical tests. The cytokine environment in pSS is highly intricate and diverse [50-52]. Among the cytokines signaling through the JAK-STAT pathway, IL-6, IL-7, IL-21, and IL-23 are thought to play roles in pSS pathogenesis. The pro-inflammatory cytokine IL-6 has been found in elevated levels in the serum, saliva, and tears of pSS patients and is linked to disease development [53-55]. Despite IL-6's role in critical immune processes, including B and T cell differentiation and activation, the use of tocilizumab, a monoclonal antibody that antagonizes the IL-6 receptor, did not show improvement in systemic symptoms over 24 weeks in contrast to placebo in a randomized, controlled trial in pSS patients [56-58].

IL-21 plays a pivotal role in type I interferon (IFN) signaling, the development of follicular subtypes, activation of IL-17-producing T-helper (Th) cells, and in the distinction of plasma cells and activation of B cells. Elevated levels of IL-21 have been found in the serum of patients with primary Sjögren's syndrome (pSS), and these levels are linked to a reduction in memory B cells alongside an increase in naïve B cells [59-61]. RNA sequencing of minor salivary glands (MSG) in pSS patients has also shown increased expression of IL-21 and IL-21-inducible genes, such as IL-21R, JAK3, STAT1, HLA-B, CCR7, and CXCL10. These elevated IL-21 gene signatures are connected with higher scores on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), as well as an increase in B cells, memory B cells, CD4+ T cells, and CD8+ T cells [62,63]. Notably, the enlargement of IL-21 T-follicular-helper (Tfh) cells, driven by inducible co-stimulator (ICOS), has been observed in pSS patients with ectopic germinal centers and mucosa-associated lymphoid tissue (MALT) lymphoma [64,65].

IL-23A is a pro-inflammatory cytokine essential for sustaining and developing Th17 cells and innate lymphoid cells (ILC) 3, as well as promoting the creation of type 3 cytokines, such as IL-17 and IL-22. Immunohistochemical staining has revealed high IL-23 expression in the submandibular glands of C57BL/6.NOD-Aec1Aec2 mice and in salivary gland biopsies from primary Sjögren's syndrome (pSS) patients, particularly within lymphocytic foci and on epithelial tissues [66,67]. In pSS salivary glands, elevated IL-23 expression correlates with increased levels of IL-17 and IL-17-producing cells, primarily Th17 and ILC3 cells. Consistent with this upregulation of IL-23, IL-22 and STAT3 are also significantly elevated at both the protein and mRNA levels in the inflamed salivary glands of pSS patients, accompanied by the expansion of IL-22-producing cells [68,69].

In a virus-induced model of autoantibody formation in salivary glands of adult mice, Barone et al. further

validated IL-22's role in pSS pathogenesis. They demonstrated that IL-22 establishes a critical connection between mucosal infection, B-cell recruitment, and humoral autoimmunity [70,71]. Engagement of the IL-22 receptor was found to be both necessary and sufficient for inducing differential expression of CXCL12 and CXCL13 in epithelial and fibroblastic stromal cells, which are crucial for B-cell recruitment and the formation of tertiary lymphoid organs (TLOs). Blocking IL-22 effectively disrupted TLO formation and reduced autoantibody production, highlighting its key role in driving pSS pathology [72,73].

Growing evidence indicates that the IL-7 axis plays a crucial role in primary Sjögren's syndrome (pSS) by driving T-cell responses and promoting B-cell lymphogenesis. Elevated levels of IL-7 and its receptor, IL-7R α , have been observed in the salivary glands of pSS patients, with IL-7R α expression correlating with the severity of sialadenitis and contributing to the formation of ectopic lymphoid structures in the glands [74-76]. Notably, exogenous IL-7 administration accelerated the onset of pSS in a mouse model, while blocking IL-7R α signaling prevented disease development. This suggests that therapeutic targeting of the IL-7 axis, either through direct inhibition of IL-7R α or by blocking downstream pathways like JAK-STAT, could be beneficial in pSS [77].

In addition to IL-7, thymic stromal lymphopoietin (TSLP) also signals through a receptor complex containing the common IL-7R α chain and the TSLPR (Thymic stromal lymphopoietin receptor) chain. TSLP has emerged as a novel biomarker for pSS and related lymphoproliferative disorders. Like IL-7, the TSLP pathway operates through JAK-STAT signaling, and its effects may be moderated by JAK inhibitors [78,79]. Moreover, recent findings show that IL-7, secreted by salivary gland epithelial cells (SGECs) under the influence of interferons (IFNs), can activate T cells in pSS. These T cells, in turn, secrete IFN- γ , perpetuating a vicious cycle that enlarges the IFN-driven pathogenic mechanism, a hallmark of connective tissue diseases like pSS [80].

In the intricate cytokine network of primary Sjögren's syndrome (pSS), increasing evidence highlights the pivotal roles of type I interferons (IFNs) (mainly IFN- α and IFN- β), type II IFN (IFN- γ), and more recently, type III IFN (IFN- λ) in disease pathogenesis [81-83]. Studies have shown the upregulation of IFN-regulated genes (IRGs), creating distinct "IFN signatures" in both peripheral blood and minor salivary gland (MSG) biopsies from pSS patients. IFNs, while primarily involved in host defense against infections, also regulate cell differentiation, proliferation, survival, and death, and they are crucial modulators of immune function [84,85]. In pSS, an overactive IFN system is driven by persistent processes, such as autoantigenic overload and insufficient regulatory mechanisms,

combined with genetic susceptibility and epigenetic changes. Although the signaling pathways of different IFN types vary via specific receptor complexes, many share downstream activation through the JAK-STAT pathway, which is a key regulator [86-88]. Thus, targeting the JAK-STAT pathway offers a way to modulate the biological effects of IFN activation. In pSS, type I IFN plays a central role in initiating and amplifying inflammation within the salivary glands, where it is primarily released by plasmacytoid dendritic cells (pDCs) and salivary gland epithelial cells (SGECs) in response to external (e.g., viral or bacterial) or internal (e.g., autoantigenic) triggers [89,90]. With the expression of over 2,000 genes, type I IFN has broad biological effects, including innate immune responses such as dendritic cell maturation, enhanced antigen presentation, upregulation of chemokines, and stimulation of T and B lymphocytes. Notably, type I IFN promotes key adaptive immune responses, including CD8 $^{+}$ lymphocyte activation, differentiation of Th1 and Th17 cells, suppression of regulatory T cells (Tregs), and B-cell hyperactivation [91,92]. This hyperactivation occurs via increased B-cell activating factor (BAFF) release and a lowered threshold for B-cell receptor (BCR) activation. B-cell dysregulation is a critical factor in pSS pathogenesis, contributing to both autoimmunity and lymphoproliferation, which are linked to many clinical manifestations and the increased risk (5%-10%) of lymphoma development in pSS patients. In pSS, type II IFN (IFN- γ) is primarily produced by T lymphocytes, but also by NK cells, B cells, macrophages, and to a smaller degree, dendritic cells [93-96]. IFN- γ plays a role in antimicrobial defense, apoptosis, inflammation, and tissue damage. Recent data suggest an amplification loop between IL-7—a key cytokine in T-cell responses—and IFN- γ , highlighting the interconnected roles of SGECs, T cells, and B cells in pSS pathogenesis. This feedback loop further underscores the IFN system's central role in bridging key cellular players in pSS. Emerging research has also focused on type III IFN (IFN- λ), with growing evidence suggesting its potential involvement in both autoimmune and malignant disorders, adding another layer of complexity to the IFN system in pSS [97-99].

Historically, primary Sjögren's syndrome (pSS) has been classified as a type I interferon (IFN)-driven disease, but studies have reported discrepancies in IFN signature expression between peripheral blood and minor salivary gland (MSG) biopsies, even within the same patient. Peripheral blood tends to exhibit a predominant type I IFN signature, while MSG biopsies more often show a type II IFN (IFN- γ) signature [100-102]. Notably, elevated IFN- γ transcriptional levels in MSG biopsies have been associated with a higher risk of lymphoma development, suggesting that IFN signatures might serve as potential biomarkers for predicting lymphoma progression in pSS. Furthermore, researchers have identified three distinct IFN expression patterns in MSG biopsies—purely type I, purely type II, and a

mixed type I/type II pattern—each linked to specific clinical manifestations in pSS [103,104]. A recent and innovative study introduced a novel classification system for pSS based on a multi-omic analysis of peripheral blood from both pSS patients and healthy controls. This study emphasized the central role of IFN signatures in defining molecular subtypes of pSS. Among the four identified clusters (C1, C2, C3, and C4), pSS patients in clusters C1, C3, and C4 were distinguished by specific combinations of type I and type II IFN expression levels [105,106]. While future studies are necessary to integrate peripheral blood and tissue-derived data, given that many key events in pSS occur in the salivary glands, this new classification represents an important step toward developing precision medicine approaches. Such advances may help address the heterogeneity in pSS that has contributed to the breakdown of many clinical tests in the past [107,108].

Regarding type III IFN (IFN- λ), higher expression has been observed in MSG biopsies from pSS patients compared to non-pSS sicca control subjects. Moreover, recent research reported a synergistic effect between IL-29, part of the type III IFN system, and IFN- α in inducing BAFF and CXCL10 via prolonged STAT1 phosphorylation in salivary gland epithelium [109,110].

Data on JAK and STAT expression in pSS salivary glands are limited, but Aota et al. demonstrated strong JAK1 and JAK2 expression in ductal and acinar cells of MSG biopsies from pSS patients via immunohistochemical analysis. Increased expression of STAT1 and STAT3 has also been found in pSS MSG biopsies [111-113]. STAT1 upregulation has been linked to IFN- α , IFN- γ , and IL-6 stimulation, while STAT3 overexpression correlates with IL-22 and IL-17 signaling. Recent findings suggest that STAT3 plays a role in epigenetic regulation, specifically in DNA methylation and hydroxymethylation processes in pSS, which predominantly affect IFN- α - and IFN- γ -regulated genes and oxidative stress pathways. Notably, JAK inhibitors (e.g., AG490 and ruxolitinib) were able to reverse global DNA hydroxymethylation induced by IFN- α , IFN- γ , and H₂O₂ in human salivary gland epithelial cells (SGECs) [114-116].

Hippo

As a complicated autoimmune illness, SS (Sjogren's syndrome) has eluded identification of the main factors and processes responsible for its evolution and pathophysiology. While immune system faults have long been considered a cause of SS, recent research has demonstrated the significant role of loss of cell polarity and structural integrity in its etiology [117,118]. The results presented here further support the hypothesis that the loss of salivary cell junctional integrity is critical in SS, suggesting that the Hippo signaling pathway, in particular, is a key factor in this

disease. The authors show an argument that a Hippo effector, TAZ, interacts with two main identifiers of cellular polarity, E-cadherin and α -catenin, and that this interaction is necessary for proper cytodifferentiation and organization of acinar and ductal structures [119-121]. Notably, dysregulation of Hippo signaling is observed in SMGs from NOD mice and labial specimens from human SS patients, supposing that faults in Hippo signaling are connected with this disease [122-124].

Enhanced proof assumes structural defects as an original participant of SS and autoimmunity. In NOD mice, an animal model for SS and type 1 diabetes, regeneration of target organs with exogenous stem cells restores the normal morphology of both SMGs and pancreatic islets, making them resistant to disease [125-127]. Earlier studies suggest that the onset of autoimmunity in NOD mice may result from developmental defects, as normally developed SMGs from NODs evade autoimmune exocrinopathy. Besides, structural faults and hyposalivation in NOD salivary glands can happen regardless lymphocytic infiltration. Recent discoveries in patients with Sjögren's Syndrome (SS) suggest that the immune system might not be the sole cause of salivary gland dysfunction [128,129]. Some affected glands show acinar cell atrophy, disruption of E-cadherin junctions, protein mislocalization, duct dilation, and ECM remodeling. Interestingly, the severity of these pathological changes, including secretory defects, does not always correlate with the level of lymphocytic infiltration. This indicates that in some cases, impaired secretion and autoimmunity may not be directly connected [130,131].

During the embryonic development of the submandibular gland (SMG), the Hippo pathway effector TAZ is found at cell-cell junctions in the polarized acinar progenitor cell layer. In newly forming secondary duct regions, TAZ shifts from a diffuse cytoplasmic distribution to a concentrated organization at intercellular junctions, where it colocalizes with F-actin. This localization is supported by increased TAZ phosphorylation during embryonic branching morphogenesis [132,133]. TAZ's colocalization with F-actin in duct-forming regions corresponds with a growing interaction with E-cadherin and α -catenin, indicating a role for junctional TAZ in establishing polarity in secondary duct cells. Lats2 knockdown alters TAZ localization and results in defects in branching morphogenesis and secondary duct formation. Similarly, NOD embryonic SMGs exhibit features like those of Lats2 siRNA-treated glands, suggesting that Hippo pathway deregulation may cause structural defects in NOD SMGs [134-136]. At embryonic day 15.5, some TAZ is nuclear, supporting its role as a transcriptional coactivator of genes involved in ECM remodeling during SMG cytodifferentiation. Additionally, TAZ is localized in the basal layer and surrounding mesenchymal/myoepithelial regions, hinting at a non-

junctional and non-nuclear role during SMG development. These observations parallel studies showing TAZ's significance in normal lung alveolarization in mice, another tissue that develops through branching morphogenesis. E-cadherin plays a crucial role in establishing cell polarity within epithelial tissues [137-139]. Previous research has shown that cytodifferentiation of the SMG is linked to enhanced interactions between α -catenin and E-cadherin. The cellular localization of YAP, which is a paralog of TAZ, is controlled by its binding to E-cadherin and α -catenin. In this study, we demonstrate that TAZ, similar to YAP, is associated with α -catenin and E-cadherin complexes, suggesting a similar regulatory mechanism for its subcellular localization [140,141]. The interactions between TAZ and E-cadherin complexes in the SMG are likely mediated by α -catenin, although there is a possibility that some α -catenin may associate with TAZ independently of E-cadherin. The increase in interactions between TAZ, E-cadherin, and α -catenin during SMG cytodifferentiation strongly indicates that the Hippo pathway is crucial for maintaining junctional integrity and polarity during SMG-branching morphogenesis. Notably, human labial SS tissues show structural defects in the acini and ducts, associated with the loss of E-cadherin and its junctional partners [142]. This aligns with findings of reduced E-cadherin and altered cell polarity in other SS studies. Defects in cell polarity in SS may influence Hippo signaling, affecting downstream transcriptional events. Alternatively, inhibition of Hippo signaling might lead to improper localization of TAZ to the nucleus, altering transcription and leading to ECM remodeling [143,144]. As TAZ acts as a transcriptional coactivator of CTGF, a key factor in tissue fibrosis, its subcellular localization regulation is likely crucial in SS. In the mature SMG, cells in the intercalated duct regions next to the acini are believed to function in acinar cell replacement during tissue renewal. Therefore, defects in ductal cell polarity might impact adult tissue homeostasis and could be worsened by hormonal conditions or environmental factors, potentially explaining the common late onset of this disease [145,146].

When examining patients with varying levels of inflammation, we observed significant heterogeneity in tissue integrity among the biopsies, with structural defects present in gland regions not adjacent to infiltrates. While the loss of structural integrity has been associated with hyposecretion in some Sjögren's syndrome (SS) cases, its potential role in increasing susceptibility to lymphocytic infiltrations has not been investigated [147-149]. Interestingly, the ablation of the E-cadherin junctional protein, α -catenin, has been shown to induce lymphocytic infiltration both in mouse models and in various cancers. Further research is needed to determine how structural defects and loss of polarity in the submandibular gland (SMG) might lead to increased susceptibility to autoimmune reactions [150,151].

Currently, the etiology of SS is still debated. A common etiopathogenic model suggests that genetic predispositions, triggered by environmental, pathological, and immunological factors, drive the clinical manifestations of the disease. In this model, the loss of secretory function is thought to result from the cytotoxicity caused by progressive lymphocytic infiltration. Here, we propose a molecular explanation for at least a subset of SS cases by demonstrating that the dysregulation of the Hippo pathway and the associated tissue structural integrity might be an underlying cause of the disease [152,153].

Akt

Research increasingly points to the involvement of the Akt/mTOR pathway in the pathogenesis of primary Sjögren's syndrome (pSS). Phosphorylation of Akt at residues T308 and S473, along with downstream targets such as FoxO1 (phosphorylated at S319) and PRAS40 (phosphorylated at T246), has been observed in the epithelial and mononuclear cells of pSS patients' minor salivary glands (MSGs), but not in sicca-controls [154-156]. This suggests a specific activation of the Akt/mTOR pathway in pSS, which is consistent with findings in other autoimmune diseases such as rheumatoid arthritis and scleroderma, where mTOR activation is also observed. Importantly, inhibition of this pathway, particularly via rapamycin, has shown to reduce pro-inflammatory T-cell subsets (Th17) and increase regulatory T cells (Tregs) in lupus and experimental models [157-159].

Although cytokines and growth factors are known to activate the Akt pathway, the exact triggers in pSS remain unidentified. There is a potential link between IFN signaling, highly upregulated in MSGs of pSS patients, and Akt activation. IFN signaling can induce inflammation through Akt activation, and Akt1 has been shown to fully activate IFN-regulated gene expression [160-162]. However, since the staining pattern for phosphorylated Akt was consistent throughout the tissue and not localized near inflammatory lesions, and because it was present in patients with mild inflammation, inflammation likely acts as a positive feedback loop rather than an initiating factor for Akt activation. The role of Akt in epithelial cells warrants further study. Akt signaling has been associated with epithelial-to-mesenchymal transition (EMT) in cancer, but EMT has not been documented in pSS, and solid tumors are rare [163,164]. Nevertheless, *in vitro* studies suggest that IL-17, IL-22, and TGF- β 1 may promote EMT in salivary gland epithelial cells (SGECs), linking epithelial Akt activation in pSS to disease pathogenesis rather than tumor formation. Given the presence of Akt activation in epithelial tissues distant from inflammatory lesions and its detection in patients with mild disease, Akt activation may reflect an intrinsic epithelial response characteristic of pSS. Viral infections and/or epigenetic changes have been proposed as potential triggers of this epithelial

activation. Interestingly, *Helicobacter pylori* has been linked to Akt pathway activation in gastric epithelial cells, associated with MALT lymphoma and adenocarcinoma development. These observations suggest that a microbial or viral infection could similarly activate the Akt pathway in pSS [165-167].

While there was initial speculation that Akt might be involved in pSS-associated non-Hodgkin lymphoma (NHL), particularly given the role of the PI3K/Akt/mTOR pathway in other hematologic malignancies and NHL development in *Helicobacter pylori* infections, this study found no significant association between Akt signaling and NHL development in pSS patients [168,169]. The Akt/mTOR pathway was universally activated in all pSS patients, regardless of lymphoma risk or disease features, indicating it does not distinguish patient subsets. However, its potential involvement in the early stages of lymphomagenesis, combined with other pathways, cannot be excluded [170].

Given the broad activation of the PI3K/Akt/mTOR pathway in pSS, it remains a promising target for therapeutic intervention. Numerous inhibitors targeting this pathway have been tested in malignancies, but their side effects limit their application in benign diseases like pSS. A trial involving seletalisib, a PI3K δ inhibitor, showed a non-significant reduction in disease activity, but was terminated before achieving statistical reliability [171,172].

Conclusion

In conclusion, Sjögren's syndrome represents a complex interplay of immune dysregulation, genetic predisposition, and environmental triggers that culminate in significant glandular and systemic dysfunction. The multifactorial nature of this disease underscores the necessity for a comprehensive understanding of its pathophysiology, particularly the roles of autoantibodies, pro-inflammatory cytokines, and key signaling pathways such as JAK-STAT, Hippo, and Akt. Current therapeutic options remain limited, often yielding suboptimal results, which emphasizes the urgent need for novel, targeted therapies that can more effectively address the underlying immunological disturbances.

Emerging evidence suggests that JAK inhibitors may offer a promising strategy to modulate the intricate cytokine milieu characteristic of primary Sjögren's syndrome, allowing for a more tailored approach to treatment. Moreover, by delving deeper into the roles of structural integrity and cell signaling in glandular health, future research could unveil new avenues for intervention that target not only the symptoms but also the root causes of the disease.

Ultimately, a shift toward precision medicine, guided by a more nuanced understanding of the varied presentations and mechanisms of Sjögren's syndrome, may lead to enhanced therapeutic outcomes and an improved quality of life for affected individuals.

Continued exploration in this field is essential, as it holds the potential to redefine our approach to this challenging autoimmune condition.

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