Evolving mechanisms in the pathogenesis of Sjögren's disease: one year in review 2025

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ABSTRACT

The year 2025 has brought significant progress in understanding the pathogenesis of Sjögren's disease (SjD). By 2025, SjD is no longer conceived as a gland-restricted sicca disorder driven by isolated B-cell hyperactivity or interferon signalling, but as a dynamically organised epithelial-stromal-immune ecosystem. Recent advances in immunogenetics, epigenomics, and single cell/spatial multi-omics have revealed that disease initiation precedes overt lymphocytic infiltration and is rooted in epithelial interferon licensing and metabolic reprogramming. Stromal fibroblasts and vascular mural cells subsequently acquire immunoregulatory states that scaffold tertiary lymphoid structures, sustaining antigen presentation, autoantibody generation, cytotoxic lymphocyte activity, and chronic inflammation. Beyond descriptive mapping, patient-derived organoid models have now provided causal validation, demonstrating that epithelial dysfunction is mechanistically actionable and partially reversible. Collectively, these converging lines of evidence reposition SjD as a mechanistically programmable and endotype-stratifiable disease, explaining clinical heterogeneity and opening the path toward precision medicine. Reflecting this conceptual shift, an international consensus formalised the nomenclature change from 'syndrome' to 'disease', reinforcing its systemic and biologically unified nature.

Introduction: a new conceptual map

By 2025, advances in available technologies have shifted the conceptual framework of Sjögren's disease (SjD) away from viewing epithelial dysfunction, B-cell hyperactivity, and interferon signalling as discrete analytical entry points. These tools now allow us to examine the disease as a cohesive tissue ecosystem, revealing how these processes intersect within a shared biological context. Within this ecosystem, epithelial cells are not passive targets but active players that sense danger and license immune responses. Stromal fibroblasts and vascular mural cells join them as partners in shaping the microenvironment. Together, these elements create niches that sustain tertiary lymphoid structures (TLS), where antigen presentation, cytokine production, and immune cell interactions are continuously reinforced. This environment nurtures interferon-driven epithelial states, cytotoxic lymphocyte activity, and persistent autoantibody production, establishing chronic inflammation and even predisposing to lymphoma (1). The 2024-2025 literature has expanded earlier frameworks by integrating multiomic, genetic, and functional insights, moving from conceptual models to experimentally validated mechanisms. The consequence of this integrated view is a new therapeutic orientation: treatments and biomarkers are increasingly tailored to biological endotypes, with precision medicine emerging as a practical reality. Reflecting this change, an international consensus has now officially adopted the term 'Sjögren's disease' instead of 'syndrome', emphasising its systemic nature and moving away from the outdated primary/secondary dichotomy (2).

Genetics

Numerous susceptibility loci, located both within and outside the major histocompatibility complex (MHC), have been linked to SjD, as demonstrated by multiple case control studies (3). Among these, the human leukocyte antigen (HLA) class II gene alleles, situated in the 6p21.3 region, are the primary genetic contributors to SjD

Table I. Genetic insights into Sjögren's disease.

Concept	Key point	References
HLA class II susceptibility	Strongest genetic signal in SjD	(3-5)
	Modest effect sizes indicate polygenicity	(3-5)
Non-HLA loci and IFN pathways	Risk variants in *IRF5, STAT4, TNFAIP3, IL12A, OAS1*	(5, 6)
	TNFAIP3 variants linked to lymphoma	(7, 8)
	Large-scale GWAS reveal additional risk loci	(6, 10)
Ancestry-specific architecture & PRS	Population-specific loci (Han Chinese, Taiwan Han)	(9, 10)
	PRS improve genetic stratification	(9-11)
	Distinct genetic patterns in Ro/SSA$^+$ vs Ro/SSA$^+$	(11)
Serological endotypes	Ro/SSA$^+$ enriched for *IL12A, IRF5, STAT4*	(11)
	Ro/SSA$^+$ associated with *JAK3*	(11)
	ANA$^+$/SSA$^+$ shows intermediate genetic loading	(11)
X-chromosome contribution	Escape from X-inactivation (*TLR7, CXorf21*)	(12)
	Increased immune gene dosage → heightened IFN responses	(12)
TLR7 signalling	Variants alter nucleic acid sensing and IRF7 activation	(13)
DDX6-CXCR5 locus	Five functional SNPs in DDX6–CXCR5 region	(14)
	Additional genes implicated (*e.g. IL10RA, BCL9L, TRAPPC4*)	(14)
	DDX6 regulates antiviral RNA sensing	(14)
	CXCR5 guides B/T follicular trafficking in GC-like niches	(14)

pathogenesis, although they confer only a modest risk for disease development (maximum odds ratio of approximately 3) (3). Several alleles, including the HLA-DRB1*03:01, DQA1*05:01, and DQB1*02:01, have been shown to confer the strongest and most consistent associations with Sjögren's disease across diverse ancestries; however, their direct clinical implications remain limited (4). Beyond the HLA region, multiple non-HLA genes and single gene polymorphisms (SNPs) have been implicated in disease susceptibility and immune dysregulation. The most of these non-HLA variations involve the interferon (IFN) pathway or IFN-inducible genes, including SNPs in IRF5, STAT4, TNFAIP3, IL12A and OAS1 genes (5). Polymorphisms within the IRF5 locus -such as the 5-bp CGGGG insertion/deletion in the promoter region and the downstream SNP rs10488631- have been associated with elevated risk of developing SjD and increased IRF5 expression in peripheral blood mononuclear cells and salivary gland epithelial cells. Notably, the Ro/SSA-negative subgroup lacks the IRF5 promoter variant, showing genetic similarities to primary biliary cholangitis (PBC), which probably suggests divergent pathogenic pathways among SjD subtypes.

With the advent of genome-wide association studies (GWASs), a powerful and unbiased approach for identifying links between genetic variants and biological traits, and the increasing use of polygenic risk scores, the study of SjD genetics has entered a new era. This was clearly summarised in a large-scale GWAS meta-analysis by Khatri *et al*., including 3,232 patients and 17,481 controls of European descent, identifying ten novel significant susceptibility loci outside the HLA region: CD247, NAB1, PTTG1-MIR146A, PRDM1-ATG5, TNFAIP3, XKR6, MAPT-CRHR1, RPTOR-CHMP6-BAIAP6, TYK2, and SYNGR1 (6). Interestingly, combining polygenic risk scores conferred a 12-fold increased risk of developing SjD, which decreased to 5.5-fold when HLA loci were excluded. Of particular interest, TNFAIP3 and its regulatory partner TNIP1 act to suppress TLR-induced apoptosis and provide negative feedback control of the NF-κB signalling pathway. Single-nucleotide polymorphisms (SNPs) in TNFAIP3, such as rs2230926, have been linked to an increased risk of lymphoma among SjD patients in both Caucasian and Asian populations, though not necessarily to heightened SjD susceptibility overall (7). However, this variant did not show a significant association in an Italian cohort, whereas another SNP, rs6920220, was identified as potentially relevant (8).

Similarly, the largest hospital-based GWAS conducted in a distinct ancestry, the Taiwan Han population, comprising 11,390 SjD patients and 113,900 control subjects, confirmed previously identified HLA associations (such as HLA-DRB1*15:01 and HLA-DQA1*03:01) and uncovered eight novel loci associated with SjD (IQCJ, CTXN3, HLA-DRB9, MTCO3P1, PSMG3-AS1, ATRNL1, SMYD4, and TENM1). In addition, it successfully replicated the well-known in Han Chinese risk variant rs117026326, which is located within the GTF2I gene on chromosome 7 (9). The calculated polygenic risk score based on the GWAS results for pSS patients revealed that SjD shares a similar genetic background with other autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (10).

To date, most genetic investigations have focused primarily on anti-Ro/SSA-positive cases, leaving the Ro/SSA-negative subgroups largely unexplored. Of particular interest, ANA-positive but SSA/SSB-negative individuals -commonly classified within the broader seronegative category- presented with an intermediate polygenic risk scores when HLA variants were considered. Nevertheless, when only non-HLA variants were assessed, their scores were comparable to Ro/SSA-

positive patients (11). These findings imply that the ANA-positive-Ro/SSA-negative subgroup may constitute a distinct genetic entity, meriting separate analysis in future research. Conversely, when comparing Ro/SSA-negative cases to the overall SjD cohort, the JAK3 locus appeared as a unique risk variant in this subgroup, opening new therapeutic avenues involving JAK/STAT pathway inhibitors.

The X chromosome seem to play a pivotal role in the pronounced female predominance of SjD, as it harbours numerous immune-related genes such as CXorf21 and TLR7 (12). These genes can escape X-chromosome inactivation, resulting in overexpression, immune system hyperactivation, and ultimately susceptibility to autoimmunity. Notably, this mechanism has been demonstrated so far in systemic lupus erythematosus (SLE), which shares several immunopathological features with SjD (12). Several studies have highlighted a robust association between splicing variations and SNPs in the TLR7 gene and the onset and progression of SjD (13). Recent data indicate that TLR7 overactivation in plasmacytoid dendritic cells (pDCs) and other immune cells promotes immune dysregulation. TLR7-mediated IFN-α production activates both IRF7 and IRF5/NF-κB signalling pathways, which in turn leads to pro-inflammatory cytokine release.

Given the overlapping genetic and molecular features between SLE and SjD, Wiley *et al*. explored the DDX6-CXCR5 locus (14). Five functional SNPs were identified, including rs57494551, located in an intron of DDX6, as well as rs4938572, rs4936443, rs7117261, and rs4938573 within the promoter/enhancer region. Chromatin mapping across this locus further revealed several additional candidate genes, namely *lnc-PHLDB1-1*, *IL10RA*, *BCL9L*, and *TRAPPC4*. DDX6 (DEAD-box RNA helicase 6) is a central regulator of the viral RNA recognition pathway of the innate immune system and a key modulator of type I interferon responses, whereas CXCR5 (C-X-C chemokine receptor type 5) plays a critical role in adaptive immunity by guiding B cells and T follicular helper cells into germinal centres and germinal-centre-like structures such as those forming in the salivary glands of patients with SjD and the kidneys of patients with SLE (14).

Take home messages

- Strongest single-gene associations in SjD lie within the HLA class II region (*e.g*. HLA-DRB1*03:01, DQA1*05:01, DQB1*02:01), although even these confer only modest risk (odds ratios in the ~2-3 range) (3-6, 10).
- Numerous non-HLA loci (especially genes involved in the interferon pathway and innate immunity, *e.g*. IRF5, STAT4, TNFAIP3) also contribute to SjD susceptibility, highlighting a complex multigene architecture beyond the classical HLA risk (5-10).
- Genetic risk stratification is now more feasible via polygenic risk scores (PRS) and large GWAS, with evidence of ancestry-specific loci and gene dosage effects (for example X-chromosome genes such as TLR7 may help explain female predominance in SjD) (9-13).

Epigenetics

The epigenome has gained increasing attention in elucidating the pathomechanisms of the disease. DNA methylation affects multiple immune and epithelial cell types implicated in disease pathophysiology, including B cells, T cells, monocytes, and SGECs (15-16). Epigenome-wide association studies (EWAS) in SjD patients have revealed widespread hypomethylation at CpG sites, particularly within genes involved in type I IFN signalling, such as STAT1, IFI44L, IFITM1, MX1, IRFs, and USP18 (17). Noteworthy, the number of differentially methylated loci was higher in B cells than in T cells, and many of these sites correlated with disease activity and autoantibody positivity.

Chi *et al*. (18) conducted a cluster analysis of DNA methylation patterns in labial minor salivary gland tissue from 131 participants (64 cases and 67 non-cases) in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry (18). The investigators identified four distinct methylation-based clusters: clusters 1 and 2 were predominantly composed of SjD patients, while clusters 3 and 4 included less than 40% of the total SjD cases and most non-cases. Although self-reported symptoms did not differ significantly among clusters, disease severity correlated with DNA methylation patterns; more severe SjD cases were enriched in clusters 1 and 2, while milder cases were more frequently found in clusters 3 and 4. These findings shed light on the role of epigenetic regulation in the clinical heterogeneity and disease activity of SjD.

Further reanalysis of this dataset (19), coupled with another dataset from the Gene Expression Omnibus repository (GSE110007), showed consistent hypomethylation in genes involved in immune responses to Epstein-Barr virus (EBV) infection, such as SLAM7, RUNX3, Bcl-2, FAS, and CD247. In addition, several X-linked genes (CD40LG, SHROOM2, PLP1, WAS, IL2RG, CXCR3, and SASH3) were significantly hypomethylated, suggesting a possible epigenetic contribution to female predominance of SjD. Notably, hypomethylation of the WAS gene may disrupt cytoskeletal dynamics and lymphocyte signalling.

N6-methyladenosine (m6A) is the most abundant reversible post-transcriptional modification in eukaryotic mRNA, with METTL14 being one of the principal methylases involved. Overexpression of EZH2 and METTL3 in B cells from patients with SjD was recently found to be associated with increased disease activity, as indicated by elevated ESSDAI scores. EZH2 contributes to disease progression by suppressing B-cell apoptosis through the epigenetic modification 'H3K27me3'. Furthermore, METTL3-mediated m6A alteration enhances the stability and expression of EZH2 mRNA, thereby further promoting B cell activation and amplifying autoimmune processes. Collectively, suppression of the EZH2 pathway may alleviate disease manifestations, offering a promising new therapeutic strategy for the management of SjD (20).

Recent epigenomic studies have also drawn attention to the dysregulation of various microRNAs (miRNAs). Despite heterogeneity across 23 studies -likely

Table II. Epigenetic insights into Sjögren's disease.

Concept	Key points	References
IFN-related CpG hypomethylation	Hypomethylation in interferon-stimulated genes (*STAT1, IFI44L, IFITM1, MX1*)	(15-17)
	Epigenetic dysregulation observed in immune and epithelial cells	(15, 16)
	Stronger methylation effects in B cells	(17)
Methylation-based patient clusters	Four distinct epigenetic clusters in salivary glands	(18)
	IFN-dominant clusters correlate with increased disease severity	(18, 19)
	External datasets confirm immune-driven epigenetic divergence	(19)
Pathogenic epigenetic enzymes	EZH2 promotes B-cell survival and dysregulated immunity	(20)
	METTL3 stabilises *EZH2* via m^6A modification	(20)
MicroRNAs as biomarkers and regulators	miR-146a/b involved in IFN-driven inflammatory circuits	(21, 22)
	miR-155 associated with lymphomagenesis	(22)
	miR-92a-3p linked to subclinical atherosclerosis	(23)
	miR-23b-3p exerts protective NF-κB-suppressive effects	(25)

due to differences in sample size, processing and analytical methods- certain miRNAs, including miR-146a/b, miR-155, and miR-188, have been repeatedly implicated (21). Notably, miR-146a and miR-146b were consistently upregulated in PBMCs, salivary glands and, saliva of SjD patients, with their expression levels correlating with disease activity markers such as the ESSPRI score and salivary gland ultrasound findings (19). The role of miR-155 remains controversial, as studies reported increased, decreased, or unchanged expression levels. However, it is functionally linked to T-cell regulation via targeting SOCS, and its expression in $CD4^+$ T lymphocytes has been connected to disease activity. Bruno *et al*. observed miR-155 upregulation in SjD patients who experienced non-Hodgkin's lymphoma (NHL), that was correlated positively with focus score, BAFF-R, and IL-6R levels- biomarkers of aberrant B cell activation and lymphomagenesis (22). Furthermore, Zehrfeld *et al*. identified miR-92a-3p as a potential biomarker for the early molecular detection of subclinical atherosclerosis in SjD, reflecting an association between its expression profiles and increased cardiovascular risk (23). Finally, Carvajal *et al*. aimed to elucidate how IFN-γ influences the expression of hsa-miR-424-5p and hsa-miR-513c-3p, which regulate proteins associated with protein degradation and secretory function -namely ATF6, SEL1L, HERP, XBP-1s, and GRP78 (24). The authors pointed out that IFN-γ downregulates hsa-miR-424-5p, leading to elevated expression of ATF6 and SEL1L transcripts. On the other hand, hsa-miR-513c-3p is shown to be upregulated, resulting in decreased XBP-1s and GRP78 transcript and protein levels.

In addition to their diagnostic and pathogenic significance, recent evidence suggests that specific miRNAs may also hold therapeutic potential by acting as molecular safeguards against autoimmune diseases, including SjD. In this context, Cai *et al*. investigated both an animal model and submandibular gland epithelial cells lines and demonstrated that miR-23b-3p, which is downregulated in NOD mice, can alleviate disease manifestations when overexpressed. Mechanistically, miR-23b-3p exerts its protective effect by targeting SOX6 and inhibiting the NF-κB signalling pathway, thereby attenuating inflammation and tissue damage (25).

Take home messages

- Extensive hypomethylation of CpG sites in immune and epithelial cells-particularly in genes involved in type I interferon (IFN) signalling (*e.g*. STAT1, IFI44L, IFITM1, MX1, IRFs, USP18) is a hallmark epigenetic feature in Sjögren's disease (SjD) (15-17, 19).
- Epigenetic profiles (especially DNA methylation clusters) correlate with clinical heterogeneity in SjD: patients with more severe disease fall into methylation clusters characterised by distinct patterns, suggesting epigenetic modifications may help stratify disease severity (18, 19).
- Epigenetic mechanisms (including DNA methylation changes, histone-modifying enzymes like EZH2/METTL3 and deregulated microRNAs such as miR-146a/b, miR-155) represent both biomarker opportunities and therapeutic targets in SjD (20-25).

Environmental factors and hormonal influences

Among the environmental exposures comprising the exposome, infections – particularly viral – have emerged as notable contributors to the pathogenesis of SjD. The mechanisms by which infections induce a breakdown in immune tolerance include molecular mimicry, epitope spreading, and bystander activation.

EBV has been extensively studied in this context. It has been shown to stimulate lymphocytic activation within ectopic germinal centres, and EBV-infected autoreactive B cells have been identified in these structures within the salivary glands of patients with SjD (24). Several studies have reported increased levels of EBV DNA in biopsy-obtained samples, along with a higher prevalence and elevated titres of antibodies against EBV antigens in SjD compared to controls -findings that have been associated with viral reactivation (26-27). In a recent analysis of previously healthy female individuals experiencing primary EBV infection, Hudson and his group provided compelling evidence that autoantibody production may be driven by acute EBV infection (28). Specifically, anti-Ro52 and anti-Ro60 autoantibodies were detectable as early as seven days post-infection, with undergoing class switching from IgM to IgG.

Although a structural similarity between the viral antigen EBNA-1 and the La/SSB autoantigen has been identified, a study involving a SjD patient with chronic active EBV infection, did not detect any cross-reactivity between the isolated anti-La/SSB autoantibodies and EBNA-1 (29). Therefore, molecular mimicry alone may not fully explain autoantibody production in SjD.

Beyond EBV, a recent nationwide, population-based, case-control study, involving 5,751 SjD patients and 28,755 matched controls, demonstrated a significant association between prior herpes zoster exposure and an increased risk of SjD (30). Importantly, this association was most pronounced when the interval between the last recorded varicella-zoster virus (VZV) infection and the index date was less than three months, highlighting a potential temporal link between viral reactivation and disease onset.

Growing data also points to a possible role of SARS-CoV-2 infection in SjD-like immunopathology. Minor salivary gland biopsies from patients recovering from COVID-19 have revealed focal lymphocytic infiltrates resembling those observed in SjD (31).

Cui *et al*. explored a potential causal relationship between Helicobacter pylori (H.pylori) infection and SjD using a bidirectional Mendelian randomisation (MR) approach (32). Leveraging publicly available databases and a large-scale GWAS, the authors minimised the influence of cofounding factors and reverse causality on correlation effects. Their findings provided genetic evidence that H.pylori infection may elevate the risk of developing SjD, while conversely, SjD itself may predispose individuals to a higher risk of H.pylori infection.

Increasing evidence has also highlighted the dynamic interplay between the gut microbiome and immune-mediated disorders, such as inflammatory bowel diseases, diabetes mellitus, and SLE. Similarly, gut microbiota dysbiosis has been implicated in SjD, with patients exhibiting significantly reduced microbial diversity compared to healthy controls, a pattern that correlates with greater disease severity (33). In this context, Wang *et al*. through a two-sample MR analysis, identified a protective effect of genus Eubacterium coprostanoligenes group, which may mitigate disease progression by down-regulating CXCL6 expression (34).

The exact association between tobacco use and SjD remains ambiguous. A recent meta-analysis of five studies showed a statistically negative correlation between current smoking and disease onset and development (35) , whereas data on former smokers are still inconsistent. When smoking status was categorised as 'never' *versus* 'ever' smokers, the frequency of "ever" smokers was found to be significantly higher among SjD patients (36). Bandeira *et al*. suggested that smoking may influence the clinical expression of an evolving connective tissue disease, potentially modifying its phenotype (37). This complexity reflects divergent patterns seen in other immune-mediated diseases -for instance, the protective role in ulcerative colitis in comparison with the detrimental effect in Crohn's disease. Equally important is the alternative explanation of reverse causality; patients might quit smoking in response to early sicca symptoms prior to diagnosis (37). This possibility emphasises the need for prospective, longitudinal studies to clarify causation. In the interim, the selection of non-SjD sicca individuals as controls may help bypass the question of dryness symptoms being the trigger for smoking cessation.

The immunomodulatory function of vitamin D is essential for maintaining immune homeostasis, primarily by suppressing excessive immune responses. Hence, vitamin D deficiency may exacerbate autoimmune conditions by impairing regulatory mechanisms and promoting pro-inflammatory processes. Several meta-analyses have reported an association between low vitamin D levels and increased SjD severity and activity (38). Nonetheless, conflicting results from other studies underscore the need for further investigation. Of note, a vitamin D-related SNP, VDR rs7975232, has been proposed as a potential risk factor for SjD, although its relevance appears to be population-specific (39). Therefore, additional large-scale, multi-ethnic genetic studies are urgently warranted to unravel the interaction between vitamin D, genetic susceptibility and disease progression.

Given the strong female predominance of SjD and frequent onset around menopause, sex hormones have long been implicated in the pathogenesis of the disease. Turner *et al*. investigated hormonal risk factors and steroidal hormones levels in patients with SjD and non-SjD sicca. They reported that patients with SjD were less likely to report hirsutism and displayed lower androstenedione and testosterone premenopause levels when compared with non-SjD sicca. Furthermore, androstenedione levels were inversely correlated with minor salivary gland focus score, suggesting a protecting role for androgens in modulating salivary gland inflammation (40).

Although precise estimates remain elusive, SjD has been reported as an immune-related adverse event in patients undergoing treatment with immune checkpoint inhibitors (ICIs) (41-42). For instance, blocking the PD-1/PD-L1 pathway has been shown to enhance T cell activation, leading to lymphocytic infiltration of the salivary gland epithelium (43). In a related hypothesis, Pringle *et al*. proposed that ICI-induced sicca manifestations may be driven by dysregulated IFN-γ signalling, suggesting a novel form of type II interferonopathy (44). Additionally, Pellegrino *et al*. described a clinical case of atezolizumab-induced SjD in a patient with triple-negative breast cancer, in which early diagnosis allowed for effective management without interruption of oncologic therapy, resulting in almost complete clinical resolution of the adverse event (45).

Take home messages

- Environmental infectious exposures, including EBV, VZV, SARS-CoV-2, *H. pylori*, and gut microbiota dysbiosis, play a significant role in SjD pathogenesis by promoting loss of immune tolerance through mechanisms such as molecular mimicry, epitope spreading, and bystander activation (24, 26-34).

- Hormonal influences, vitamin D deficiency, smoking behaviour, and iatrogenic immune modulation (*e.g.* immune checkpoint inhibitors) collectively shape susceptibility to, and clinical expression of, SjD underscoring the interplay between immune, endocrine, and environmental factors in disease development (35-45).

Early epithelial sensing and metabolic divergence as drivers of innate-adaptive immune crosstalk in SjD

Recent evidence has repositioned the initiating events of SjD upstream of lymphocytic infiltration, highlighting salivary gland epithelial cells as active innate immune sentinels rather than passive targets. These epithelial cells in salivary glands act as sentinels, sensing nucleic acids and initiating interferon responses before lymphocytic infiltration occurs (46). Metabolic profiling further reinforces the concept of compartment-specific immunopathology. Luo *et al*. (47) profiled immune cell metabolism and found that innate subsets were heavily reliant on respiratory chain activity, whereas adaptive populations such as B and T lymphocytes displayed enriched nucleic acid and amino acid metabolism. These metabolic programs highlight fundamental differences in distinct energetic demands within the glandular microenvironment and how immune cell compartments adapt to the glandular microenvironment reflecting. Extending this immunometabolic and transcriptional convergence across autoimmune phenotypes, Lin *et al*. (48) identified STAT1 and CD8A as shared central nodes linking SjD with Hashimoto thyroiditis, underscoring the existence of conserved adaptive immune activation signatures that transcend individual target organs.

Metabolic rewiring within the Sjögren's salivary gland microenvironment also plays a critical role in modulating immune cell responses, in particular on $CD4^+$ T cells, as recently demonstrated by Certo *et al*. (49). This work showed increased metabolic demand in the presence of tertiary lymphoid structures in the salivary glands accompanied by a switch to increased glycolysis and downstream aberrant lactate production. Interestingly, several lactate transporters on immune cells have been identified and shown to be able to influence immune cell activation and differentiation, alongside their tissue-retention (50). In the context of Sjögren's disease, inflammation leads to increase lactate levels, able to enhance/increase disease-specific release of IL-21 within TLS, a key B cell activator, an effect that could be abrogated by blocking SLC5A12, an inducible lactate transporter restricted to $CD4^+$ T cells and more recently found on B cells where lactate promotes the release of pro-inflammatory cytokines in a SLC5A12-dependent manner (51). Of relevance, pharmacological and genetic impairment of SLC5A12 was able to disrupt tertiary lymphoid structure formation in a mouse model of viral-induce sialoadenitis (49).

Take home messages

- Salivary gland epithelial cells serve as active innate immune sentinels, sensing nucleic acids and initiating type I interferon responses upstream of lymphocytic infiltration, thereby fostering early crosstalk between epithelial and immune compartments (46, 55).
- Distinct metabolic programmes in innate *versus* adaptive immune cells (*e.g.* reliance on mitochondrial respiration in innate subsets vs up-regulation of nucleic-acid and amino-acid metabolism in B/T lymphocytes) highlight how metabolic rewiring in the glandular microenvironment contributes to compartment-specific immunopathology in SjD (47, 48).

Bulk and single-cell transcriptional profiling and spatial dissection of the epithelial-stromal-immune eco-system in SjD

Building on the emerging paradigm that epithelial interferon licensing acts as the initiating checkpoint in SjD, next-generation single-cell and spatial multi-omics have begun to clarify how this early innate activation is translated into structured, tissue-level immunopathology. At the systemic level, McDermott *et al*. showed that even naïve B cells display a primed interferon signature, while $CD4^+$ and $CD8^+$ T cells are skewed toward Th1-polarised effector states, thus indicating that pathogenic programming is already established before tissue infiltration (52). Within the salivary glands, using bulk RNA sequencing linked to cell deconvolution approaches, Pontarini *et al*. demonstrated the coexistence of follicular and extrafollicular B-cell activation able to stratify patients by rheumatoid factor and double anti-Ro/SSA and anti-La/SSB seropositivity. Interestingly this work highlighted a rheumatoid factor-dependent, ectopic germinal centre-independent extrafollicular signature strongly associated with activation of type-1 interferon and viral sensing through the RIG-1 pathway, providing a molecular rationale for the clinical heterogeneity of SjD (53).

In addition to RF-driven salivary gland transcriptomic signatures, Inamo *et al*. recently unravelled key transcriptional differences between classic anti-SSA+ SjD and SjD patients with anti-centromere antibodies (ACA), a subset characterised by distinct clinical characteristics. Using single-cell RNA sequencing, T cell and B cell receptor sequencing and spatial transcriptomics they demonstrated the following key salivary gland signatures able to differentiate the two subsets including enrichment of memory B cells in ACA+ SjD, activated interferon signature in anti-SSA+ compared to TGFβ signalling enhancement in ACA+ SjD (54).

Using imaging mass cytometry, Wu *et al*. further localised cytotoxic $CD8^+$ T cells at the epithelial-immune interface, supporting a model of direct epithelial injury beyond B cell-driven mechanisms (55). Nayar *et al*. (56) added a stromal dimension by uncovering fibroblast and mural cell states with active immunoregulatory properties within tertiary lymphoid structures, implying that the stromal compartment actively instructs, rather than passively accommodates, immune organisation. These paradigm-shifting insights have only become accessible through single-cell

and spatial technologies, which have redefined pSS not as a uniform lymphocytic infiltrate, but as a dynamically organised epithelial-stromal-immune ecosystem-initiated by interferon-licensed epithelium, actively scaffolded by immune-reprogrammed stromal niches, and diversified through coexisting follicular, extrafollicular, and cytotoxic immune programs. Collectively, these findings support a model in which SjD encompasses at least two dominant and a third transitional endotype, IFN-epithelial/CD8$^+$, BAFF-GC-driven B cell, and stromal-immune, each with distinct molecular trajectories and potential therapeutic implications.

Take home messages

- Advanced single-cell and spatial transcriptomic analyses reveal that SjD is not merely a uniform lymphocytic infiltrate but rather a dynamically structured epithelial-stromal-immune ecosystem, initiated by interferon-licensed epithelium and scaffolded by stromal niches (52-56).
- Distinct molecular endotypes appear (*e.g.* IFN-epithelial/CD8$^+$, BAFF/GC-driven B-cell, stromal-immune), each with specific transcriptional signatures and spatial context, offering opportunities for tailored therapeutic stratification (52, 53, 55, 56).

Functional modelling and causal validation through patient-derived organoids

Patient-derived salivary gland organoids have recently enabled true mechanistic experimentation, moving beyond observational profiling to causal testing of epithelial-immune crosstalk. In a landmark study, Meudec *et al*. (57) demonstrated that interferon-driven epithelial dysfunction directly impairs cholinergic-induced secretory responses, a functional lesion that was partially reversible with JAK inhibition, thus providing experimental proof that epithelial interferon licensing is not merely correlative but mechanistically pathogenic and pharmacologically targetable. Complementing this, independent reports have shown that salivary gland stem/progenitor cells undergo premature senescence, resulting in diminished regenerative capacity and suggesting that failure of epithelial repair actively contributes to disease chronicity rather than reflecting bystander exhaustion (58). A third, genetically anchored layer of causality derives from Mendelian randomisation, as demonstrated by Xu *et al*., who implicated CD27 expression on B cells as pathogenic while CD3 expression on naive Tregs appeared protective reinforcing a bidirectional model in which genetic determinants can tune both effector amplification and regulatory insufficiency (59). Together, these converging experimental and genetic approaches demonstrate that pSS is not solely an inflammatory state but a mechanistically programmable and, at least partially, reversible epithelial-immune disease, providing a functional basis for patient-tailored therapeutic intervention.

Take home messages

- Patient-derived salivary-gland organoid models demonstrate that interferon-driven epithelial dysfunction is not merely correlative but mechanistically pathogenic in SjD, and that this dysfunction is, at least partially, reversible via JAK-inhibition (57).
- Salivary-gland stem/progenitor cell senescence and Mendelian-randomisation evidence (*e.g.* CD27 on B cells as risk, CD3 on naive Tregs as protective) support a model of SjD as a mechanistically programmable epithelial-immune disease, opening the way for functionally targeted therapies (58, 59).

Conclusions

Recent advances in multi-omics, functional modelling, and genetic inference have substantially refined the current understanding of SjD. The cumulative literature from 2024-2025 allow us to recognise the disease as a tissue-specific epithelial-stromal-immune network rather than a process driven solely by B-cell hyperactivity or interferon signalling. Epithelial licensing, stromal reprogramming, and immune heterogeneity appear to cooperate in sustaining chronic inflammation, offering a plausible explanation for the marked clinical variability observed among patients. The emergence of patient-derived organoids and Mendelian randomisation provides experimental and genetic support for a mechanistically actionable and potentially reversible disease process. These insights reinforce the need for endotype-based stratification and encourage the development of targeted therapeutic strategies grounded in discrete pathogenic pathways. Future work should prioritise integrating molecular profiling into clinical decision-making, validating biomarkers linked to treatment response, and determining whether early intervention in specific biological endotypes can modify long-term outcomes, including lymphoma risk and extra-glandular progression.

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