Review

Pathogenesis of Sjögren's disease: one year in review 2024

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ABSTRACT

The pathogenesis of Sjögren's disease (SjD) is still elusive; however, the disease is widely recognised as a multistep disorder triggered by the interplay of environmental, hormonal and genetic factors. Innate immune system plays a crucial role in the initiation of the inflammatory process, but the amplification and the perpetuation of the autoimmune process require a continual interaction between the innate and adaptive immune systems. Several important contributions elucidating SjD pathogenesis have been recently published due to emerging technologies. This review provides an overview of the recent literature focusing, in the first part, on new insights into genetic and epigenetics studies. In the second part, we will discuss new findings related to salivary epithelial glandular cells and their interaction with other immune cells, type I interferon signature and innate immunity. Finally, as ectopic germinal centres like structures in the salivary glands of patients with SjD have been critically involved in autoreactive B cell activation and have been associated with progression towards B cell lymphomas, we will focus on new insights into their regulation in SjD and novel insights into the transition to lymphoma. Hopefully, a better comprehension of SjD complexity will pave the way to highly targeted therapeutic strategies.

Introduction

Sjögren's disease (SjD) is a complex systemic autoimmune disease typically characterised by chronic inflammation of the salivary and lachrymal glands and a broad spectrum of extra-glandular manifestations and immunological abnormalities (1). SjD is a recognised model of multifactorial diseases triggered by the interplay of environmental, hormonal and genetic factors (2-7). Genetic and epigenetic alterations, immunological abnormalities and inflammatory pathways participate in SjD pathogenesis resulting in a continual interaction between the innate and adaptive immune systems (8, 9). In this review, following the others of this series (10-12), we will provide an update on our current understanding of SjD pathogenesis focusing on new insights into genetics and epigenetics, innate and adaptive immune system dysfunction and tertiary lymphoid structures. Hopefully, a better comprehension of SjD pathogenesis will open the avenue for new individualised diagnostic and therapeutic approaches to the disease, improving patients' management and long-term outcome.

Novel insights into genetics and epigenetics

Large-scale genetic and epigenetic studies have revealed robust associations between SjD and genetic variants of genome-wide significance in both the HLA locus and more than twenty non-HLA loci (3, 13). These genes are engaged in both innate and adaptive immune response and participate in the dysregulated molecular mechanisms involved in the pathogenesis of SjD (3, 13). Recently, a polygenic risk score (PRS) has been developed based on whole genome data and able to predict SjD disease particularly in Ro/SSA+ subjects: noteworthy, in those patients the SNPs carried on the HLA appeared to be the strongest genetic risk factors for the disease (3). Consistently with these data, Bianchi *et al*. (14) have recently confirmed that independently from the diagnosis of SjD, in patients with systemic autoimmune diseases and positive anti-Ro/SSA and anti-La/SSB, MHC appeared as the key and strongest genetic locus associated with both generalised autoimmune predisposition and

specific autoantibody positivity. The authors derived these findings from a targeted DNA sequencing of coding and regulatory regions from approximately 1,900 immune-related genes in a cohort of 2,292 patients with systemic lupus erythematosus (SLE), SjD, and myositis and 1,252 controls. Similarly, in 2024, known HLA alleles, including HLA-DRB1*15:01 and HLA-DQA1*03:01, were successfully replicated in a consistent effect direction in the Taiwan Han population through a hospital-based genome-wide study (GWAS) thus confirming the relevance of HLA also in a population of Asian origin (15).

To date, however, most of the studies have been performed in Ro/SSA+ patients and the genetic risk of Ro/SSA- subjects have been scarcely explored. Radziszewski *et al*. (16) have recently presented new findings on specific genetic associations in patients with and without anti-Ro/SSA antibodies. The authors confirmed that the Ro/SSA+ subjects had a much stronger HLA association than Ro/SSA- patients. By contrast, when comparing Ro/SSA- to the all-SjD dataset, risk JAK3 locus was unique to the Ro/SSA- GWAS paving the way for the use of novel drugs targeting the JAK-STAT pathways. In both the subsets, two loci were specifically analysed (IRF5-TNPO3 and LOC643529). Noteworthy, the Ro/SSA+ subset has both the IRF5 promoter effect and the extended haplotype through TNPO3 similarly to SLE and systemic sclerosis (SSc) whereas the Ro/SSA- lack the IRF5 promoter effect analogously to primary biliary cholangitis.

Regarding the genetic common risk between SjD and SLE, Wiley *et al*. (17) have recently performed fine mapping across SjD and SLE, to identify potential common functional SNPs in the shared DDX6-CXCR5 risk locus, possibly implied in similar disease mechanisms. DDX6 is involved in viral RNA recognition and in the modulation of type I interferon signalling whereas CXCR5 is implied in the trafficking of B and T follicular cell to peripheral lymphoid organs. The authors identified five common functional SNPs in the DDX6-CXCR5 interval: rs57494551 in an intron of DDX6, and rs4938572, rs4936443, rs7117261, and rs4938573 in the promoter/enhancer region of DDX6 and CXCR5. Electrophoretic mobility shift assays and luciferase expression assays showed cell type-specific differences in protein binding and promoter or enhancer activity, respectively, at each SNP. Extensive bioinformatic analyses also suggest that the SNPs are likely to work within the local chromatin regulatory network to regulate cell type-specific expression of several other genes on the DDX6-CXCR5 interval including Lnc-PHLDB1-1, BCL9L and TRAPPC4.

Besides genetic studies, recent research has also focused on epigenetics changes in SjD and specifically on DNA methylation. Recent studies have clearly demonstrated that DNA methylation affects many cell types implicated in SjD pathophysiology including B and T lymphocytes, monocytes and epithelial cells (18, 19). Chi *et al*. (20) performed a cluster analysis of DNA methylation data from labial salivary gland (LSG) tissue collected from 131 study participants (64 cases and 67 non-cases) in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry. The authors compared serological assays, histopathologic examination, oral and ocular tests and self-reported symptoms in SjD cases that clustered separately. Finally, the authors identified regions of differential methylation between SjD subsets and explored possible relevant biological differences contributing to phenotypic heterogeneity in SiD. The authors identified 4 clusters with distinct levels of DNA methylation: namely, clusters 1 and 2 were SjD dominant and clusters 3 and 4 included less than the 40% of the total SjD cases and most non-cases. No significant differences in self-reported symptoms among the clusters were reported, whereas severe SjD cases belong more often to clusters 1 and 2 and mild SjD cases belong more often to clusters 3 and 4 with disease severity correlating with levels of DNA methylation. This LSG dataset and a second dataset GSE110007, consisting of 13 glands from patients with SS and 15 non-case glands as controls (21) were recently re-analysed to compare differential methylation patterns between SjD cases and non-cases (22). The authors found that genes involved in immune responses to Epstein-Barr virus infection were significantly hypomethylated in SjD including SLAM7, RUNX3, BCL2, FAS, and CD247. Moreover, significantly hypomethylated genes in chromosome X were identified including CD40LG, SHROOM2, PLP1, WAS, IL2RG, CXCR3, and SASH3 possibly contributing to sex bias in disease development. Finally, the study revealed a significant hypomethylation of the WAS gene on chromosome X in LSG tissues of individuals with SjD that encodes the Wasp protein, in turn implied in the rearrangement of the cytoskeleton during signal transduction in platelets and lymphocytes.

mi-RNAs expression is also crucial in SjD pathogenesis. Nonetheless, according to a recent systematic literature review, miRNA studies revealed considerable variations regarding candidate biomarker miRNAs, most likely due to variation in sample size, processing and analytical methods, but also because of the heterogeneity and the complexity of SjD (23). However, a few studies described similar miRNAs to be differentially expressed such as miR-146, miR-155 and miR-188 (23). Intriguingly miRNAs have also been associated with SjD complications and comorbidities. Namely, miR-155 has been shown as upregulated in SjD patients who experienced non-Hodgkin lymphoma (NHL) (24) whereas miR-92a-3p levels correlated positively with subclinical atherosclerosis in SjD (25). One of the most intriguing novel contributions on this topic is the study by Carvajal *et al*. (26). The authors explored the effect of IFN-γ on the expression of hsa-miR-424–5p and hsa-miR-513c-3p, miRNAs that modulate the expression of several proteins involved in protein degradation and secretory dysfunction, including ATF6, SEL1L, HERP, XBP-1s and GRP78. The authors showed that IFN-γ may activate a pathway that decreases hsa-miR-424–5p, which in turn increases ATF6α and SEL1L transcript levels as well as a pathway that increase hsa-miR-513c-3p, which in turn decrease XBP-1s and GRP78 transcript and protein levels. Both pathways may contribute to endoplasmic reticulum (ER) stress and salivary gland dysfunction.

Novel insights into salivary gland epithelial cells, IFNs signature

Salivary gland epithelial cells (SGECs) play an active role in initiating and amplifying the inflammatory response in SjD by expressing on their surface MHC-II and immune-regulatory molecules (CD80, ICAM, CD40), and by attracting CD4 T- and B-cells in the exocrine glands (8, 27). Therefore, investigating epithelial cells specific interactions with lymphocytic cells and other immune cells as well as exploring SGEC metabolisms and secretory functions or identifying mechanisms that regulate SGECs pro-inflammatory signalling are major "hot topics" of the current research in SjD pathophysiology. Several important contributions have been published lately due to emerging technologies including single-cell and spatial transcriptomics as well as proteomics. Moreover, in addition to SGEC cultures, growing interest has recently arisen for organoids self-organising 3-D structures, that recapitulate the spatial organisation of their organ of interest, and have been optimised from the murine and human submandibular and parotid salivary glands (28-30). Organoids will offer a more advanced model system for studying epithelial cells and recently their cell composition has been described in comparison to matched adherent SGEC cultures showing that they contain more epithelial cell types and a higher proportion of ductal cells (29).

On the one hand, recent studies have clearly described morphology changes in SGECs altering salivary gland integrity and function even before direct immune inflammatory infiltration.

Pranzatelli *et al*. (31) utilising unbiased single-cell and spatial transcriptomics intriguingly described a population of PRR4+CST3+WFDC2- seromucous acinar cells in human LSGs that was specifically targeted in SjD representing the most numerous seromucous acinar cells population in non-SjD patients and less than half of the total seromucous acinar cells in patients with SjD. The authors demonstrated that the loss of PRR4+CST3+WFDC2- seromucous acinar cells in SjD was related to autoreactive cytotoxic GZMK+CD8+ T cells that were physically associated with epithelial cells. Notably these findings are in line with the increasing amount of evidence highlighting the presence and functional role of CD8+ T cells in the salivary glands inflammatory infiltrate (32, 33).

Katsiougiannis *et al*. (34) described SGEC metabolic alterations mainly related to mitochondria in SjD patients. The authors investigated the whole cell proteome of cultured SGEC from LSG biopsies of SjD patients and sicca controls to map the functional differences between these cell populations. Subsequently, LSGs of patients and controls were analysed by electron microscopy to explore potential ultrastructural alterations. The authors identified 474 differentially expressed proteins that clustered into two distinct expression patterns: the first cluster characterised by highly abundant proteins in SjD patients and low abundant proteins in controls and the second cluster *vice versa* characterised by low abundant proteins in SjD patients and highly abundant in controls. The first cluster showed enrichment in pathways that have been previously described also in SjD saliva by means of proteomic analysis (35, 36): trafficking, exocytosis, innate immunity and neutrophils degranulation. In contrast, the second cluster was enriched for proteins mainly related to lipid metabolism and valine, leucine and isoleucine degradation, all metabolic pathways associated with mitochondria. Electron microscopy confirmed the decrease and the morphological abnormalities of the total number of mitochondria in SjD-SGEC suggesting that insufficient metabolic performance of mitochondria may ultimately affect the functions of the cells thus fostering a cellular stress condition. The link between immune cell function and cell metabolic reprogramming is still in its infancy. However, hopefully, drugs targeting metabolic pathways aberrantly activated in the inflammatory microenvironment should be looked at with interest in the next future (37, 38).

From the other side, recent literature has strengthened the scientific evidence that SGECs are not just "innocent casualties" in the pathogenesis of SjD but actively contribute to the inflammatory process of the disease (27).

Nakamura *et al*. (39) demonstrated that besides plasmacytoid dendritic cells (pDCs) that are considered the major producer of type I IFN in SjD, SGECs can also actively contribute to type I IFN production. A great amount of evidence has shown over the time that the 'so-called' type I IFN signature, is associated with the development of systemic extra-glandular manifestations, and a substantial production inflammatory cytokines and autoantibodies (8). Noteworthy, Bettacchioli *et al*. (40) has recently showed a gradual increase in the activation of IFN signalling depending on antibody positivity with seronegative patients presenting an IFN score of approximately zero and Ro52+/Ro60 + patients presenting a positive IFN signature that exceeded those of the other groups. Nakamura *et al*. (39) described a pivotal role of SGECs in type I IFN production. The authors investigated by RNA sequencing analysis the ectopic misexpression of lysosome-associated membrane protein 3 (LAMP3) in SGECs of patients with SjD and found that LAMP3 expression in SGECs was induced by type I IFN. In mouse models they demonstrated that LAMP3 expression can induce ectopicTLR-7 expression in SGECs and amplify IFN production. Overall, the authors suggested that in the early steps of SjD pathophysiology an abnormal type I IFN response to viral infection might trigger LAMP3 misexpression in salivary glands of individuals with genetic susceptibility. Subsequently, LAMP3 may induce ectopic TLR-7 expression thus fostering type I IFN production in SGECs, ultimately creating a positive feedback loop that may maintain LAMP3 misexpression.

Considering the crucial role of SGECs in initiating and amplifying the inflammatory response, a better understanding of the mechanisms regulating pro-inflammatory signalling in SGECs able to limit their dysfunction has appeared as pivotal. Recently, post-transcriptional mRNA modifications, specifically N6-methyladenosine (m6A) RNA methylation, have been identified as crucial in gene regulation (41, 42). Truffinet *et al*. (43) has recently explored the involvement of RNA m6 A modifications in SGEC function. The authors high-

lighted the role of RNA m6A pathway as a protector of SGECs in response to pro-inflammatory triggers showing that the writer METTL3 catalytic activity led to the general inhibition of IFN transcriptional responses in SGEC (*i.e.* CXCL10). By contrast, the inhibition of METTL3 resulted in dsRNA accumulation and increased the recruitment of NK, T- and B- cells and B cell activation by SGEC in the framework of an IFN-rich environment. SjD patients exhibited insufficient upregulation of METTL3 in SGEC in response to inflammatory triggers, inadequate for efficiently controlling the inflammatory response.

Novel insights into innate immunity

Innate immune cells and pathways have long been recognised as dysregulated in both the exocrine tissues and the peripheral blood of patients with SjD, particularly during its early stages, with significant downstream effects on the adaptive immune system. Recently, beyond the established interferon-1 producing role of non-conventional plasmacytoid dendritic cells (pDCs) (44), pivotal insights emerged regarding the orchestrating role of type 2 conventional dendritic cells (cDC2s) in SjD. cDC2s recruitment in tissue lesions is dependent on the CX3CL1–CX3CR1 axis and an imbalance in antigen processing is noted, with an upregulated uptake of antigens and a decreased antigen degradation capacity, with type I IFNs playing a regulatory role in these processes (12, 45). Furthermore, inflammatory CD64+ cDC2s expressing high levels of MICa/b (a ligand for the activating receptor NKG2D) have been shown to activate a highly cytotoxic NK cell population located in close proximity within the salivary glands, underscoring a potential role in the interplay between inflammatory cDC2s and NK cells in driving SjD's pathogenesis (46). This process is further supported by a reduction in the absolute numbers of peripheral blood NK cells in patients with SjD and renal tubular acidosis, suggesting increased NK cell homing to affected tissues (47).

Innate lymphoid cell (ILC) subsets have also been investigated in SjD, in the peripheral blood and minor salivary gland (MSG) tissue. While no significant differences were observed in ILC subpopulations between patients and controls in the peripheral blood, a distinct pattern emerged in the salivary gland tissue. Specifically, the number of ILC3 cells was higher in lymphocytic-infiltrated tissue compared to non-infiltrated tissue. These ILC3 cells were predominantly located at the periphery of T and B cell infiltrates and were associated with smaller infiltrates and more recent diagnoses. This finding suggests that ILC3 cells may play a role in the initial phase of lymphocytic infiltrate formation and organisation in SjD (48).

Publicly available single-cell transcriptomics data on peripheral blood mononuclear cells (PBMCs) from SjD patients, as well as bulk RNA sequencing of SjD MSG biopsies were combined to study the implication of monocytes and macrophages in SjD pathogenesis. The analysis revealed that macrophages are the most abundant innate immune cells, significantly expanded in both peripheral blood and the periphery of damaged MSG tissue compared to controls, and cluster into 5 distinct sub-phenotypes. Notably, the M1-like macrophage cluster, characterised by the expression of IL-1β, TNF-α, CCL3, and NLRP3, was associated with an increased infiltration of immune cells, a senescence-associated secretory phenotype, and marked metabolic reprogramming (49). In parallel, the decreased expression of the T-cell immunoglobulin and ITIM domain (TIGIT), an immune checkpoint coinhibitory molecule, in CD14+ monocytes from SjD patients correlated with greater disease activity, severity, and elevated production of autoantibodies and IgG (50). Similar associations were observed with CD226+ CD14+ monocytes, which are elevated in SjD patients, suggesting that both inhibitory and activation markers on monocytes contribute to the immunopathology of the disease (51). Even though these cells highly co-express Fas and IL-2Rα the rate of apoptosis does not seem to be increased (52).

The neutrophil population, though less studied in SjD, has recently been implicated in disease mechanisms. A preliminary study identified both non-lytic and lytic NETosis occurring in neutrophils from SjD patients, potentially linked to IL-40, a cytokine associated with B cell homeostasis. IL-40, which is found at elevated levels in MSG tissue, was shown to induce NETosis, suggesting a distinct and persistent form of neutrophil activation in SjD (53). However, these observations require further research to identify the role of NETs in the peripheral blood and tissue lesions of SjD patients.

Interferons have long been implicated in the pathogenesis of SjD, though findings in the field have sometimes been conflicting. This year, significant advancements were made, led by Blake Warner and his team. Using an integrative "omics" platform, they provided evidence that the interferons-Janus kinases-signal transducer and activator of transcription (IFN-JAK- STAT) pathway is unequivocally activated in the salivary glands and PBMCs of patients with SjD. This bulk signature is highly cell-specific, driven predominantly by salivary epithelial cells and infiltrating immune cells, highlighting the potential of JAK inhibitors as a targeted therapeutic approach in SjD (54). Furthermore, another study identified the JAK/STAT1 pathway, triggered by interferon-γ, as a key inducer of salivary gland epithelial cell (SGEC) death via ferroptosis. This process is mediated through the inhibition of the Xc-/GSH/GPX4 axis, offering additional insight into the molecular mechanisms driving tissue damage in SjD (55). Additionally, a protective role against apoptosis was attributed to mesencephalic astrocyte-derived neurotrophic factor (MANF), which has the ability to reverse endoplasmic reticulum stress (ERS)-induced autophagy downregulation. MANF was shown to reduce apoptosis and Ro52/SSA antigen expression through regulation of the AKT/mTOR/LC3B signalling pathway in human submandibular gland tissue cells and an experimental Sjögren's syndrome (ESS) mouse model (56).

Abnormal cellular metabolism has also been at the centre of attention lately. A proteomic analysis of SGECs from 9 patients and 6 controls revealed a striking transformation of SGECs into an innate immune-like phenotype. This shift

was marked by enrichment in pathways associated with neutrophil degranulation, membrane trafficking, exosome-mediated transport, and exocytosis. In addition to these functional changes, notable mitochondrial abnormalities were observed. Mitochondria in SGECs appeared elongated and swollen while exhibiting fewer and structurally abnormal cristae (34). Similar mitochondrial disturbances were observed in some infiltrating lymphocytes, as reported by another research group. Further RNA sequencing data focusing on mitochondria-related metabolic pathways revealed that mitochondrial electron transport and respiratory chain complexes in the glandular microenvironment were positively correlated with the presence of innate immune cells (57). Moreover, elevated lactate levels may contribute to mitochondrial DNA damage and leakage, which can be recognised by the cGAS-STING pathway. This activation promotes NF-κB and type I IFN-mediated inflammation in epithelial cells, further enhancing their innate immune-like properties and suggesting a close link between mitochondrial dysregulation and immune cell activity in SjD pathogenesis (58).

Novel insights into the regulation of ectopic germinal centres (GCs)

Ectopic GCs forming in the SG of patients with SjD are critically involved in autoreactive B cell activation and have been associated with progression towards B cell lymphomas, hence understanding their regulation in SjD is of critical importance. While most studies on ectopic GCs have been reported on labial SG biopsies in adult patients, recent work from the Groningen group demonstrated that in a comparative analysis of parotid vs labial glands, parotid glands contained significantly higher B cell infiltration, increased numbers of ectopic GCs per glandular area and more severe pre-lymphomatous lympho-epithelial lesions (59) which is in agreement with the clinical observation that B cell lymphomagenesis more frequently arises from parotid glands in SjD patients, The same group also reported the interesting findings that patients with paediatric-onset SjD display higher numbers of B and T lymphocytes density, a higher B/T lymphocyte ratio, and a higher numbers of ectopic GCs defined either as CD21+ follicular dendritic cell networks or displaying BCL6+ GC B cells, suggesting that the paediatric-onset subset of SjD is characterised by enhanced B cell proliferation and ectopic GC responses compared to adult-onset SjD (60). Ectopic GCs formation and function is regulated by highly specialised CD4+ Th cells, such as Tfh (T follicular helper) cells and Th17 cells, which positively regulate GCs and T follicular regulatory (Tfr) cells, which controls the magnitude of the GC response. In particular, Tfh cells have been previously shown to play a pivotal role in the pathogenesis of SjD by promoting ectopic GC formation and supporting B cell activation and antibody production. Luo *et al*. (61) recently conducted labial SG RNA-sequencing with biopsies stratified for the presence of high *versus* low Tfh infiltration, defined as CD4+CXCR5+ICOS+ cells. Tfh high SG were characterised by transcriptomic signatures of virus-mediated IFN response as well as metabolic reprogramming with hypoxia and elevated glycolysis and oxidative phosphorylation levels. As expected, SjD patients in the Tfh-high group demonstrated a higher positive rate of ANA, rheumatoid factor (RF) serum IgG levels.

In physiological conditions, pathogen-induced memory Tfh cells play an important role in maintaining high-affinity protective antibody responses. Symonds *et al*. (62) recently reported in murine models a novel subset of memory-like Tfh cells which develop in the absence of active infection, express FR4 and Egr2 and support B cell-mediated IgG production and GC formation. Remarkably, these cells displayed close resemblance to circulating Tfh cells that are increased in the bloods of SjD patients suggesting their involvement in SjD pathogenesis.

In addition to Tfh, Th17 cells have been implicated in the initiation of ectopic GC responses in several experimental models of autoimmunity and in patients with autoimmune diseases, although their pathogenic role in SjD remains unclear. Recently, Gan *et al*. (63) unravelled a positive feedback loop between the glucocorticoid-induced tumour necrosis factor receptor ligand (GITRL) and Th17 cells in experimental SjD (NOD mice) and in SjD patients. In this study GITRL was able to directly induce the expansion of granulocyte-macrophage colony-stimulating factor positive (GM-CSF+) CD4+ T cells and Th17 cells via increased STAT3 phosphorylation mediated by mammalian target of rapamycin complexes 1 (mTORC1). Interestingly, the administration of an rAAV vector expressing short hairpin RNA targeting GITRL was able to ameliorate SG disease in NOD mice, suggesting that this pathway may be implicated in the pathogenesis.

Therapeutic targeting of ectopic GC, either directly via B cell depletion/inhibition or via modulation of Tfh and/or Th17 responses is an attractive approach in SjD. Lee *et al*. (64) recently showed that syndecan-1 (SDC-1), a major transmembrane heparan sulfate proteoglycan (HSPG) that binds to and regulates heparan sulfate (HS)-binding molecules, including chemokines such as CXCL13, is involved in experimental SjD and ectopic GC formation via binding to CXCL13 through the HS chain. Accordingly, SDC-1 and CXCL13 co-colocalised in the inflamed SG of NOD/ShiLtJ mice and treatment with 5 mg/kg HS intraperitoneally thrice per week was able to attenuate SG B-cell infiltration and ectopic GCs formation.

In a recent *post-hoc* analysis of the TRACTISS trial of Rituximab in SjD, aimed at identifying biomarkers for predicting response or resistance to B cell depletion therapy using the new Composite of Relevant Endpoints for Sjögren Syndrome (cCRESS) and Sjögren Tool for Assessing Response (STAR) composite endpoints, Pontarini *et al*. (65) reported a comprehensive longitudinal data analysis of SG biopsies and peripheral blood before and after rituximab treatment, incorporating flow cytometry, serum cytokines, and SG RNA sequencing. This work showed that in SjD patients responders to treatment, rituximab prevented SG inflammation by inhibiting class-switched memory B cell accumulation and progression of ectopic

GC responses via downregulating genes related to immune-cell recruitment, lymphoid organisation, and T cell activation. Interestingly, key chemokines and T cell cytokines involved in regulating ectopic GC responses such as CXCL13, IL-21, IL-22, IL-17A, IL-17F displayed higher baselines serum levels in responders according to STAR criteria, with longitudinal analysis revealing a selective reduction of T cell-related cytokines in clinical responders. In contrast, cCRESS responders primarily showed decreased SG B cell infiltration and lower expression of genes related to T cell co-stimulation, complement activation, and Fcγ-receptor engagement. Both cCRESS and STAR responders showed significant improvements in SG exocrine function, linked to transcriptional restoration of glandular epithelial and metabolic processes. Overall, this study demonstrated that, although ectopic GC in SjD is regulated by highly specialised CD4 T cells, a bidirectional T/B cell cross-talk, which can be altered upon prolonged and repeated B cell depletion, is critical for reciprocal T/B cell activation and sustained autoreactive adaptive immune responses in the SG of SjD patients.

Novel insights into the transition to lymphoma

One of the most fascinating and scientifically intriguing aspects of SjD is its association with the development of lymphoproliferative disorders, particularly non-Hodgkin's lymphoma. Each year, numerous scientific investigations aim to identify specific predictors of lymphoma development and unravel the sequence of events leading to this transformation. A highlight of this year's research was the work of Duret *et al*. leveraging data from the French nationwide ASSESS (Assessment of Systemic Signs and Evolution in Sjögren's Syndrome) cohort. This study compared the transcriptome of eight patients who developed primary lymphoma (6 marginal zone lymphoma, 2 DLBCL, 1 follicular) with 324 primary SjD controls. The findings revealed that Bruton's tyrosine kinase (BTK), a crucial mediator of B-cell receptor (BCR) signalling, and a proliferation-inducing ligand (APRIL), a cytokine involved in B cell activation and growth, were overexpressed in patients before the onset of lymphoma (66). When focusing specifically on DLBCL, another study reinforced the critical role of the BCR signaling pathway, identifying it as the only enriched pathway in these cases. This was further linked to SjD peripheral naive B cells and salivary gland-infiltrating cells, with CD79A, CD79B, and LAMTOR4 emerging as particularly noteworthy gene loci (67).

Immunogenetic sequencing has emerged as a crucial tool for investigating the progression from antigen-naïve B cell clones to malignant lymphoproliferative disorders in SjD. A recent breakthrough in this field involved the use of immunoglobulin (IG) gene repertoire sequencing to study both tissue and blood samples during pre-lymphoma stages. The study demonstrated that extra-nodal marginal zone lymphoma (eMZL) clonotypes can be detected in both minor salivary gland tissue biopsies and peripheral blood prior to the clinical diagnosis of overt eMZL or before lymphoma relapse (68). In parallel, exome-wide somatic mutation analyses of autoreactive rheumatoid factor (RF)-expressing memory B cells from six SjD patients further emphasised the malignant potential of these cells. The study found that RF+ B cells carry an elevated number of mutations, including genes commonly mutated in MALT lymphomas and ABC-type DLBCLs. Remarkably, one patient developed a DLBCL 26 months after a RF clone had been identified in a salivary gland biopsy two years earlier and in peripheral blood 11 months prior to lymphoma diagnosis. The malignant RF clone showed significant expansion and ongoing somatic hypermutation of the IGHV, indicative of active immune selection and transformation into a cancerous phenotype (69). These findings raise compelling questions about the role of RF+ B cells in SjD, with the authors proposing that these cells might be considered as (pre)neoplastic. For clinical practice, detecting B-cell clonality in the MSG by an easy to perform standardised multiplex PCR assay combined with heteroduplex analysis by microcapillary electrophoresis offers a valuable prognostic tool. This method has been shown to correlate strongly with the presence of lymphoma or other known lymphoma risk factors in SjD, enabling closer monitoring and timely intervention (70).

In conclusion, the emergence of modern technology has rapidly fostered significant progresses in our understanding of the main pathogenic mechanisms of SjD leading to design specific and individualised therapeutic strategies. Hopefully, in the next future new insights into the pathogenesis of the disease will provide a basis for precision medicine in SjD.

Take home messages

- GWAS studies have demonstrated a divergent genetic architecture in Ro/SSA positive and in Ro/SSA negative patients (16).
- Levels of DNA methylation in labial salivary glands correlate with disease severity (20).
- Organoids will offer a more advanced model system for studying epithelial cells (29).
- Unbiased single-cell and spatial transcriptomics have shown the loss of PRR4+CST3+WFDC2- seromucous acinar cells in SjD due to the autoreactive cytotoxic attack of GZMK+CD8+ T cells (31).
- SGECs actively contribute to type I IFN production through misexpression of LAMP3 (39).
- m6 A RNA methylation pathway in SGEC of SjD is inadequate to regulate the inflammatory response (43).
- An interplay between type 2 conventional dendritic cells and natural killer cells might contribute to the tissue lesion formation in SjD (45, 46).
- Type 3 innate lymphoid cells may play a role in the initial phases of SjD pathogenesis (48).
- Tfh cells have been previously shown to play a pivotal role in the pathogenesis of SjD by promoting ectopic GC formation and supporting B cell activation and antibody production (61).
- GITRL may exacerbate disease activity and promote pathogenic Th17 response in SjD through a GITRL-mTORC1-GM-CSF loop (63).

- A bidirectional T/B cell cross-talk, which can be altered upon prolonged and repeated B cell depletion, is critical for reciprocal T/B cell activation and sustained autoreactive adaptive immune responses in the SG of SjD patients (65).
- Extra-nodal marginal zone lymphoma (eMZL) clonotypes can be detected in both minor salivary gland tissue biopsies and peripheral blood prior to lymphoma diagnosis (68).

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