Review

Pathogenic Mechanisms and Treatment Advancements of Sjogren's Syndrome

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Abstract: Sjogren's syndrome (SS) is one of the most common chronic autoimmune diseases primarily affecting the salivary and lacrimal glands, leading to dry mouth and dry eyes, with systemic involvement in severe cases. This article provides an overview of the pathogenic mechanisms underlying SS, including genetic predisposition, immune dysregulation, cytokine imbalances, autoantibody production, and metabolic alterations. Additionally, advancements in treatment strategies are discussed, ranging from symptomatic relief to targeted biological therapies, such as B-cell depletion and cytokine modulation. While significant progress has been made in understanding the pathological mechanisms of SS, challenges persist in disease classification, biomarker identification, and therapeutic development. Future research is needed to focus on refining diagnostic criteria and exploring novel therapeutic interventions to improve disease management and patient outcomes.

Keywords: Sjogren's syndrome; biomarkers; immunopathogenesis; B-cell activation; cytokine imbalance, autoantibodies; DNA methylation; immunotherapy

1. Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disorder characterized by lymphocytic infiltration of the exocrine's salivary and lacrimal glands, leading to dry eyes and mouth symptoms [1]. SS is the broader term encompassing both primary and secondary Sjogren's syndrome [2]. Primary Sjogren's syndrome (pSS) occurs independently, meaning that it is not associated with another autoimmune disease. Secondary Sjogren's syndrome, on the other hand, occurs in conjunction with another autoimmune disease, such as lupus, scleroderma, or rheumatoid arthritis, which often complicates the clinical landscape as patients may experience symptoms of both SS and the accompanying autoimmune disorder [3]. Thus, this review will mainly address pSS as it specifically refers to Sjogren's syndrome occurring as a standalone condition and is often referred to interchangeably with SS.

The urgency in understanding Sjogren's syndrome becomes apparent when considering its varying prevalence across populations, ranging from 0.1% to 4.8%, making it a highly common autoimmune condition [4]. This broad variability in prevalence underscores the need to scrutinize the geographical and demographic determinants shaping the incidence of SS. Moreover, the annual incidence of SS averages 3.9 cases per 100,000 individuals per year, with a higher incidence in women compared to men. With a striking gender ratio between 9:1 to 14:1 (female to male), SS further warrants comprehensive investigation into genetic predispositions, environmental triggers, and age-related aspects that contribute to its intricate epidemiological profile [5].

Beyond its prevalence and incidence rates, SS affects patients' quality of life and health outcomes. The persistent dryness of eyes and mouth significantly impairs daily functioning, causing discomfort, difficulty in swallowing, speaking, and performing routine tasks. It also often extends beyond glandular dysfunction, leading to systemic manifestations affecting various organs, including the lungs, kidneys, and nervous system [6].

A comprehensive understanding of the pathogenic mechanisms, risk factors, and effective treatment strategies for SS is essential to mitigate the multifaceted challenges posed by this complex autoimmune disease, thereby improving the quality of life and health outcomes for individuals living with SS. However, the challenges in managing SS lie in its molecular intricacies, including the variability of disease phenotypes and the long indolent course of the disease. Overall, this article aims to provide a comprehensive review of the current understanding and management of SS, including the classification criteria, potential biomarkers to improve diagnosis and

treatment, and the potential role of metabolism in immune cell function and its implications for personalized therapeutic interventions.

2. Immunopathogenesis of SS

The immunopathogenesis of SS involves a complex interplay of various immune cells, cytokines, chemokines, and autoantibodies. Understanding each of these pathways may allow for the identification of potential therapeutic targets. A representative illustration of these pathways and the main cell groups involved is presented in Figure 1.

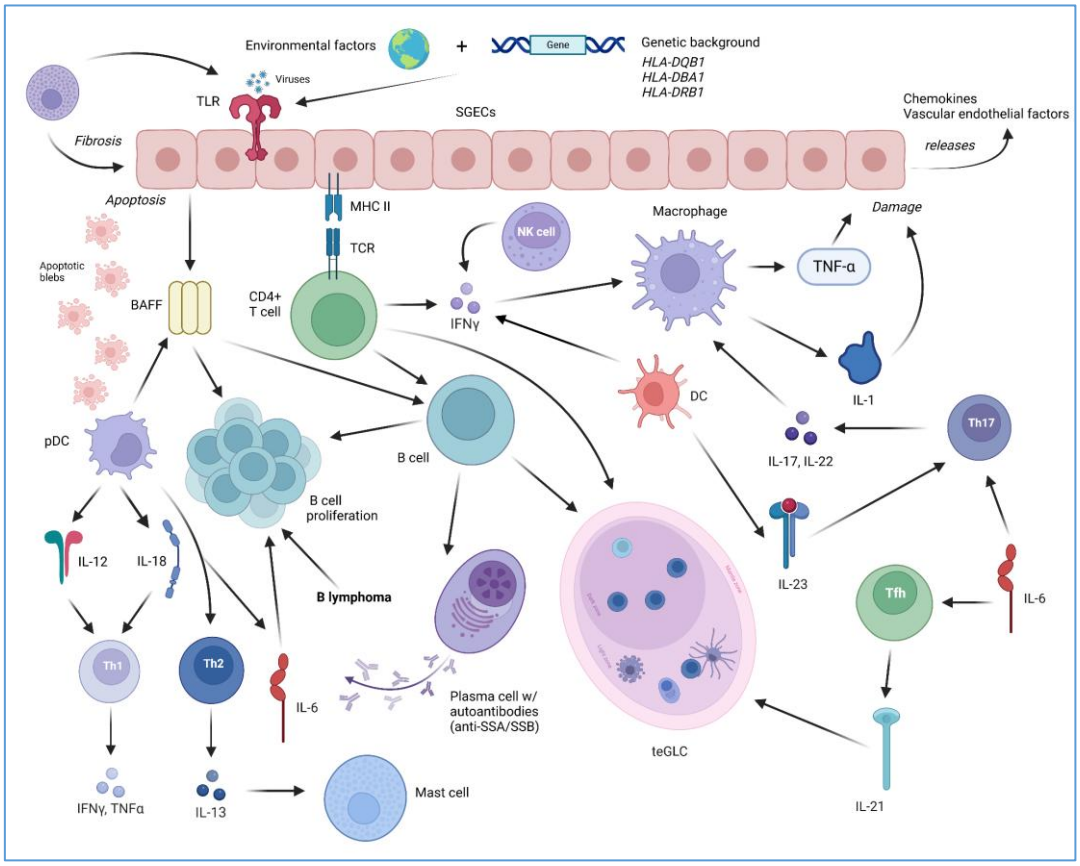

Figure 1. Pathologic mechanisms of pSS and the cells/molecules involved in salivary gland damage [7–9]. APC: antigen-presenting cells; BAFF: B cell activating factor; DC: dendritic cell; IFN: interferon; IL: interleukin; MHC: major histocompatibility complex molecule; pDC: plasmacytoid dendritic cell; SGECs: salivary glands epithelial cells; TCR: T cell receptor; teGLC: tertiary ectopic germinal-like center; Th: T helper cell; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-alpha.

2.1. Genetic Polymorphisms in the Major Histocompatibility Complex (MHC)

The major histocompatibility complex (MHC), also known as the human leukocyte antigen (HLA) complex, has been extensively studied in the context of pSS. This complex plays a crucial role in orchestrating immune responses and antigen presentation via encoding proteins that are involved in presenting T cells, which deal with foreign antigens, hinting at its importance in MHC polymorphisms in the pathogenesis of the disease [10].

The MHC region has been found to harbor genetic associations with SS in both European and Asian populations, highlighting the genetic heterogeneity of SS according to ancestry. Genome-wide association study (GWAS) identified several significant associations in Europeans, including the MHC, IRF5, and STAT4 regions, while associations were observed in the KLRG1 and SH2D2A regions in Asians [5]. These differences in genetic association indicate high levels of heterogeneity in the MHC region, with highly significant differences in allele frequencies between the study populations.

GWAS has also identified alleles belonging to MHC, specifically HLA-DR and HLA-DQ isotypes. The presence of these alleles has been suggested to contribute to the genetic predisposition of autoimmune conditions, including SS. These alleles interact with other factors, such as environmental triggers or viral infections, to activate pathogenic pathways. Polymorphisms in the HLA-DQB1 gene, which encodes a MHC II molecule, affect antigen

presentation and immune responses, contributing to the development of autoimmunity by influencing their binding affinity of self-antigens, which leads to the activation of autoreactive T cells and the production of autoantibodies [7]. Inherently, this makes patients genetically susceptible to autoimmune conditions, such as SS.

Additionally, disease-associated variants in the HLA locus have been found to affect the expression of HLA-DRB5 on B cells based on the genotype and sex of the carrier, indicating the influence of biological sex on disease development. Specifically, CD74 (TNIP1 locus), PXK and CTSB (FAM167A-BLK locus) are involved in B cell signaling and have genotype-dependent effects on gene expression in B cells, which are differentially expressed based on the carrier's genotype and sex [11].

2.2. Dysregulation of Cytokines

Cytokines are small proteins secreted by immune cells that serve as messengers in intercellular communication, mobilizing different immune responses [12]. In pSS, the dysregulation of cytokines disrupts the delicate balance between pro-inflammatory and anti-inflammatory signals, causing persistent inflammation and tissue damage to the salivary and lacrimal glands [13]. These biomarkers are often noted by elevated levels of the specific cytokine.

Exposure to pro-inflammatory cytokines has been shown to display a dual effect on the activation of salivary gland stem cells (SGSCs) through toll-like receptor (TLR) activation. Initially, there is a significant increase in organoid formation efficiency in response to a cytokine cocktail, which is a blend of different cytokines to simulate a specific immune response in order to study disease pathogenesis, such as for pSS. This is followed by a decrease in organoid formation efficiency to levels significantly below those observed in healthy control cells. This drastic change in organic formation efficiency suggests that while proinflammatory cytokines initially simulate the proliferation of SGSCs, prolonged exposure to these cytokines may lead to the exhaustion and dysfunction of SGSCs in pSS. Additionally, exposure to pro-inflammatory cytokines may lead to the proliferation and differentiation of healthy SGSCs. These cytokines within the glandular tissue could provide mitotic signals, driving SGSC exhaustion in pSS, leading to a senescent, aging-like phenotype and hyposalivation. Ultimately, these findings suggest that targeting the inflammatory process alone may not be sufficient to restore salivary production. There must also be interventions aimed at replenishing SGSC levels in conjunction with resolving inflammation [14].

One key factor in the pathogenesis of pSS is the activation of interferon (IFN) pathways. IFNs are a type of cytokines released in response to viral infections, tumors, and other immune stimuli, thereby playing a role in regulating immune responses and inflammation [15]. In a multi-omic study on pSS patients, who were clustered into four distinct groups based on pSS-related gene expression and immune dysregulation patterns, it was found that both type 1 and 2 IFN pathways are involved in the pathogenesis of pSS [16]. These IFN pathways promote the activation of various effector T cells and B cells, enhancing the effector function and cytotoxic activity of CD4+ T cells, as well as regulating the expression of costimulatory molecules [17].

Dysregulation inflammation against an inert and relatively low-virulence mycobacterium may also be correlated with dysregulated, non-resolving, and host-detrimental inflammation in mycobacterial infection. More specifically, increased circulating type 1 IFN levels and unregulated type 1 IFN-inducible genes have been observed in peripheral blood mononuclear cells (PBMCs) and salivary gland tissues in patients with pSS, which also have been implicated in patients with dysregulated inflammation of mycobacterial infection. This means that there may be a shared immunological pathway between nontuberculous mycobacterial (NTM) infection and SS [18].

The dysregulation of the production of B-cell activating factor (BAFF) is another key factor in the pathogenesis of pSS. BAFF overexpression sustains autoreactive B cells by enhancing survival signals, particularly in the presence of co-stimulatory cytokines like IL-6 and IL-21. When environmental triggers promote the activation of the innate immune system and the production of IFNs in the first stages of pSS, BAFF, which is induced by type 1 and 2 IFNs, activates autoreactive B cells. Similar to IFNs, when BAFF is overexpressed in pSS patients, the excessive activation and survival of B cells causes the production of autoantibodies and the formation of lymphocytic infiltrates in the salivary glands. This leads to continuous B cell activation and subtle deficiencies in the control of the nuclear factor-kB activation, which might underlie the increased lymphomagenesis associated with SS [11]. Furthermore, studies have found that other innate immune cells can produce cytokines that stimulate B cells, including the Epstein-Barr virus (EBV), which produces APRIL (a proliferation-inducing ligand), and human T cell lymphotropic virus type 1 (HTLV1), of which the infection can lead to the increased concentration of tumor necrosis factor (TNF) [19].

Various interleukins, which are cytokines produced by different immune cells that regulate communication between immune cells, are dysregulated in pSS. IL-21 promotes the expansion and activation of T follicular helper (TFH) cells, which perpetuates the pathogenic immune response by B cells, inherently increasing aberrant antibody production [20]. IL-12 promotes the activation of type 2 IFN pathways via both innate and adaptive immune systems [21]. Th17 cells produce IL-17 and IL-23, which stimulate inflammatory mediators, causing local inflammation within the glands and the destruction of glandular tissues [22]. IL-6 is a pro-inflammatory cytokine that contributes to B-cell hyperactivity and autoantibody production, tissue damage within affected glands via matrix metalloproteinase (MMPs) secretion, and potentially systemic complications including arthralgia, fatigue, and systemic inflammation [23].

The aberrant alterations of various molecules in the immune system leads to a dysregulated cytokine network, for instance, an imbalance between pro-inflammatory and anti-inflammatory cytokines. Specifically, Sjögren's is characterized by an overproduction of pro-inflammatory cytokines such as IFN-γ, IL-12, IL-18, IL-6, and BAFF, while anti-inflammatory cytokines like IL-4 and TGF-β are under-expressed. A summary of the cytokines involved and their functions in SS is presented in Table 1.

Table 1. A partial list of cytokines involved in SS and their functions.

Cytokine	Source of cells	Function in SS
IL-6	Macrophages, SGECs	Promotes B cell hyperactivity, autoantibody production, systemic inflammation
IL-17	Th17 cells	Induces local inflammation and tissue destruction in glands
IL-21	T follicular helper (Tfh) cells	Stimulates B cells, enhances germinal center activity
IL-22	Th17, NK cells	Promotes immunofibroblast proliferation during the formation of tertiary lymphoid structures (TLS)
IL-13	Th2 cells	Drives stromal cell differentiation during TLS formation
IL-12	Dendritic cells, macrophages	Activates IFN-γ pathway, enhances T cell cytotoxicity
IFN-α/β	Plasmacytoid dendritic cells (pDCs)	Induces BAFF, promotes antiviral and autoimmune response pathways
BAFF	Monocytes, epithelial cells	Supports B cell survival, contributes to autoantibody production and lymphomas
TNF-α	Macrophages, infected cells	Promotes inflammation, contributes to TLS maintenance
CXCL13	Immunofibroblasts, dendritic cells	Attracts B cells to TLS

2.3. Formation of Tertiary Lymphoid Structures (TLS)

TLS resembles lymphoid structures seen in lymph nodes and act as sites for immune cell aggregation, activation, and local immune responses [24]. In pSS, these structures form in salivary and lacrimal glands, which interact with immune cells and perpetuate chronic inflammation, which inherently contributes to tissue damage [25].

Cytokines are also responsible for driving the differentiation of stromal cells into immunofibroblasts during TLS formation [26]. IL-13 controls early signal engagement on immunofibroblast progenitors, which upregulates SS markers such as podoplanin (PDPN), ICAM-1, and VCAM-1. IL-22, on the other hand, induces cell proliferation of immunofibroblasts. These two cytokines work with TNF-alpha and LT-alpha-beta-2 to promote the acquisition of immune-pathogenic phenotype during TLS assembly.

Once the TLS is assembled, chemokines recruit and activate immune cells, which triggers the inflammatory processes in pSS. The production of chemokines in SGECs and adhesion molecules creates a local inflammatory microenvironment that supports the recruitment and retention of cells within the TLS and the activation of immunofibroblasts. These immunofibroblasts express chemokines, including CXCL13, CCL19, and CCL21, which act as chemoattractants by attracting and guiding B cells, T cells, and dendritic cells to the TLS. The

immunofibroblasts also express ICAM-1 and VCAM-1, which are adhesion molecules, that facilitate the interaction between immune and stromal cells as they organize immune cell clusters for immune responses. Thus, interfering with signals responsible for the establishment of the immunofibroblast-rich microenvironment within TLS could have therapeutic implications for TLS-associated diseases [26].

2.4. Presence of Autoantibodies

Autoantibodies contribute to immune-mediated damage of salivary and lacrimal glands by perpetuating the inflammatory response and the formation of lymphoepithelial lesions in the salivary glands [27]. The most common autoantibodies characterized in SS are anti-SSA (Ro) and anti-SSB (La) antibodies, which specifically target self-antigens present in the nuclei of cells within the salivary and lacrimal glands [28]. The immune system erroneously recognizes self-antigens as foreign, leading to the production of autoantibodies by B-cells. In time, anti-SSA and anti-SSB antibodies may lead to cell injury, apoptosis, and inflammatory responses within the affected glands, which manifest into the dysfunction and destruction of the targeted exocrine glands in SS patients [29]. As covered in previous sections, there are various ways that autoantibodies could be generated, including via genetic polymorphisms in the MHC, dysregulation of the production of BAFF, and dysregulation of IFNs.

A newly identified autoantibody, anti-calponin 3, has been discovered in 11% of SS patients, with a higher frequency in those with neuropathies, suggesting that anti-calponin 3 antibodies may play a role in the development of neuropathic symptoms in SS. The expression of this antibody in non-neural satellite cells in the dorsal root ganglia (DRG) of the test rats also suggests that these cells may be a target in SS [30]. This is notable as these cells are in the peripheral nervous system, rather than the salivary and lacrimal glands where most of the other targets are located.

2.5. Dysregulation of Metabolism

The complexities of the immune system are reflected in the numerous metabolic pathways and molecules that are involved may serve as potential therapeutic targets for SS. These include: glycolysis, which increases its activity in immune cells to support inflammatory response and antibody production [31]; fatty acid oxidation (FAO), which generates energy for homeostatic proliferation and survival of quiescent lymphocytes [32]; tricarboxylic acid (TCA) cycle, which allows extracellular glucose to be used to also generate energy for homeostatic proliferation of quiescent lymphocytes [33]; oxidative phosphorylation, which is increased in T cells when more energy is required [34]; citrate export and fatty acid synthesis; which converts citrate into acetyl-CoA to provide carbons for fatty acid synthesis for immune cell function [35]; glutamine metabolism, which supports immune cell function in order to increase UDP-N-acetylglucosamine accumulation and protein glycosylation and function [36]; one-carbon metabolism, which generates S-adenosylmethionine that is involved in DNA and histone methylation [37]; and alpha-ketoglutarate, which is the key intermediate in multiple metabolic pathways [38].

More importantly, the dysregulation of metabolism via disrupting any of these pathways impacts immune cell function and dysfunction. One method to study this is through impairing energy production, which is essential for immune cell activation, proliferation, and effector functions. For example, defects in glycolysis or oxidative phosphorylation can impair T-cell activation and cytokine production, which are essential in pSS. Another method is directly altering the biosynthesis of essential molecules required for immune cell function. An example would be impairing fatty acid synthesis, which would affect the production of lipid mediators involved in immune cell signaling and inflammation. Disrupting redox balance, which is the balance of reactive oxygen species (ROS) production and antioxidant defense mechanisms, may lead to oxidative stress that disrupts metabolism. Excessive ROS can damage immune cells and impair their function, while inadequate antioxidant defenses can compromise immune cell viability and function. The differentiation of immune cells is also important in metabolism, and any alterations may cause the generation of dysfunctional or exhausted immune cell subsets. For instance, dysregulated metabolism can lead to the development of exhausted T cells in chronic infections or cancer, may also contribute to the development of SS. Last, but not least, dysfunctional immunometabolism, which refers to the reciprocal relationship between metabolism and immune cell function, may disrupt the balance between immune cell activation and regulation, which would lead to excessive inflammation in salivary glands or overall immune suppression. Dysregulated metabolism in regulatory T cells impairs their suppressive function and contributes to the formation of autoimmune diseases, such as pSS or the accompanying disease in secondary SS [13].

2.6. DNA Methylation

DNA methylation is an epigenetic change that plays a crucial role in the pathogenesis of pSS by influencing gene expression and contributing to the dysregulation of immune and inflammatory processes. Hypomethylation

of various genes involved in pSS is associated with increased gene expression levels that affect stress response, immune response, and immune transduction, suggesting a potential role in the dysregulated immune response in pSS [39]. Notably, genes such as CD40, CXCR5, and IFI44L show hypomethylated promoters in SS patients, correlating with increased expression and enhanced B and T cell activation. With this in mind, studies have identified transcription factor binding motifs within the hypomethylated promoter regions and pSS-associated differentially methylated CpG islands (DMCs). The motifs include antioxidant response elements (ARE), interferon-stimulated response elements (IRE), and PU.1 binding motifs [40]. Furthermore, methylation quantitative trait loci (meQTLs) have been identified in regions encompassing HLA-DQA1, HLA-DQB1, and HLA-DQA2 loci, suggesting the potential role of DNA methylation in modulating HLA gene expression and immune dysregulation in pSS [23].

Since DNA methylation is an epigenetic change, it could also interact with genetic risk factors and influence disease susceptibility and progression of pSS. A study found that differentially methylated DNA regions in B-cell lymphocytes overlap with genetic risk loci associated with pSS, which is evidence that genetic and epigenetic factors can work together to contribute to the pathogenesis of pSS [41]. Similarly, another study identified epigenetic dysregulation in salivary gland epithelial cells associated with the expression of the SSB gene, detection of anti-SSB/LA antibodies, and lymphocyte infiltration, which also provides evidence of epigenetic modifications interacting with genetic factors to affect the immune response and inflammatory tissue damage in pSS patients [40].

Understanding the role of DNA methylation in pSS pathogenesis provides insight on potential therapeutic targets, including via directly modulating DNA methylation or finding drugs to reverse the epigenetic changes associated with DNA methylation pathways in pSS. A detailed illustration of DNA methylation and its mechanism is presented in Figure 2.

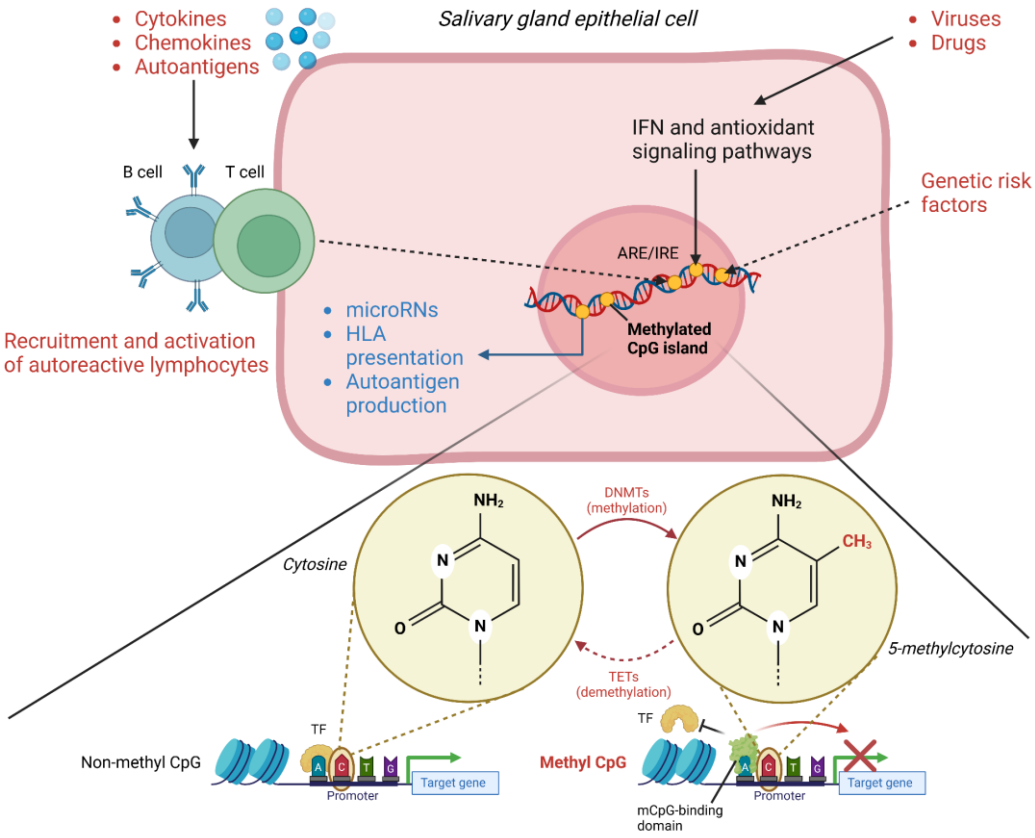

Figure 2. DNA methylation and its role in gene regulation, mediated by methyltransferases (DNMTs) and Ten Eleven Translocation (TET) proteins. DNA methylation can modulate cellular processes by restricting transcription factor (TF) binding, while demethylation facilitates gene expression. In pSS, DNA methylation of antioxidant response elements (ARE) and interferon response elements (IRE) may contribute to disease pathophysiology by influencing epithelial cell activation and lymphocytic recruitment. These processes, driven by environmental factors, stress responses, and genetic predisposition, highlight the complex interplay of epigenetics in pSS [40,42].

2.7. CD-40/CD154

In a study on a mouse model of pSS, researchers found that chronic CD40-CD154 expression and pathway activation were present in their salivary glands, indicating their involvement in the disease pathway. CD40-CD154 is active in various processes in pSS, including germinal center (GC) formation, ectopic lymphoid structure (ELS) formation, B-cell diversification, and antibody-secreting cell differentiation [43].

Therapeutic blockade with an anti-CD154 monoclonal antibody has been shown to inhibit cellular and molecular outcomes downstream of this costimulatory pathway, which led to several potential therapeutic implications of blockage. For one, it has been shown to suppress sialadenitis, which is the inflammation of the salivary glands and a major symptom of pSS. Additionally, it inhibited the formation of ELS, which are abnormal lymphoid structures that contribute to the pathogenesis of pSS, in affected tissues. Last, but not least, it was found that anti-CD154 antibodies decreased the production of circulating anti-Ro autoantibodies, as well as the number of infiltrating lymphocytes and macrophages [43].

Similarly, clinical studies have suggested the safety and efficacy of CD40 blockade with another drug called iscalimab, which is a CD40-blocking antibody for pSS. Results have shown that iscalimab was well-tolerated and led to a reduction in disease activity compared to a placebo. It has been shown to also inhibit sialadenitis by targeting CD40-expressing non-B cell types involved in the pathogenesis of pSS, such as macrophages and dendritic cells. Additionally, iscalimab suppresses ELS formation and function by inhibiting CD40-CD154 interactions in salivary glands. One distinguishing factor of iscalimab from anti-CD154 antibody is its ability to reduce B-cell hyperactivity, which is evidenced by the observed reductions in germinal center-associated chemokine CXCL 13 levels, which is elevated in the serum of pSS patients [44].

3. Clinical Manifestations of SS

3.1. Ocular Manifestations

Dryness of the eyes, known as xeropthalmia, are caused by reduced tear production and poor quality of tears, and patients experience a gritty or sandy feeling in the eyes, itching, burning, and redness. They may also experience photophobia, which is increased sensitivity to light, as a result of inadequate lubrication. Inflammation of the eyes, known as conjunctivitis, results from inflammation of the conjunctiva, which is the thin membrane covering the white part of the eye. It manifests as redness, irritations, and a sensation of a foreign body present in the eye. Xeropthalmia and conjunctivitis often appear together, known as keratoconjunctivitis sicca, which is one of the hallmark features of SS. This condition results from the inflammation and dysfunction of the lacrimal glands, leading to reduced tear production and subsequent ocular discomfort [45].

3.2. Oral Manifestations

Dryness of the mouth, known as xerostomia, results from the destruction of glandular tissue and impaired saliva production from various infiltrations of the salivary glands by immune cells, including lymphocytes and plasma cells. This dryness causes discomfort, difficulty in speaking, chewing, swallowing, and altered taste perception [45].

As a result of SS, there is a decrease in saliva function, which disrupts the maintenance of pH in the oral cavity, whose stability is important to oral demineralization. SS patients exhibit notably lower pH and buffer capacity in their parotid saliva than individuals without SS. Even the slightest changes in pH may lead to dental caries, which are usually root and incisal caries but are not evidenced to contribute to periodontitis.

Dental plaque, composed of numerous bacterial species forming a biofilm on tooth surfaces, plays a pivotal role in providing a space for oral microbial pathogens to grow and develop into dental caries. In individuals without SS, normal saliva flow dislodges and expels these bacteria from the tooth surfaces and oral cavity. Thus, the lack of saliva flow in SS patients increases the chances of contracting opportunistic infections and the proliferation of cariogenic microorganisms, which cause dental caries.

Similarly, the reduced saliva flow and altered oral environment may also create favorable conditions for fungal infections, specifically oral candidiasis. This leads to white patches or plaques on the tongue, palate, and inner cheeks, causing discomfort and altered taste perception. The oral mucosal tissue may also weaken, resulting in ulcerations, erythematous patches, and petechiae. Inter-oral manifestations range from subtle to evident, such as a desiccated, sticky, and furrowed tongue, alongside decreased or absent saliva pooling at the floor of the mouth. These symptoms are often also associated with inflammation, which may also externally manifest itself in swollen major salivary glands, specifically near the parotid glands [46].

3.3. Systemic Manifestations

In addition to direct ocular and oral manifestations, SS can also present various systemic manifestations that extend beyond the primary involvement of the exocrine glands and affect multiple organ systems throughout the body. These further complicate the management of the disease because it requires a comprehensive approach to address the diverse symptoms and organ involvement [7]. This includes articular and musculoskeletal symptoms, such as joint and muscle pain, stiffness, arthritis-resembling symptoms, and fatigue [45]. It can also include neurological symptoms, specifically peripheral neuropathy, which leads to tingling sensations, numbness, and weakness in the limbs [30]. Some individuals may also experience complications in the pulmonary system, developing interstitial lung disease and respiratory issues [23]. Manifestations can also involve the renal system, which refers to kidney complications, such as tubulointerstitial nephritis [7]. These systemic manifestations can vary significantly among individuals with SS, and not all patients experience all these symptoms. The presence and severity of systemic involvement may differ, impacting the overall disease course and prognosis for affected individuals.

4. Current Treatment Strategies

4.1. Classification Criteria

Given the heterogeneity of pSS, the development of the classification criteria, such as those proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), play a notable role in improving the diagnosis and treatment of pSS as the criteria provide standardized guidelines for identifying and classifying patients. These criteria utilize a weighted sum of diagnostic items, including focus score in minor salivary gland biopsy, presence of anti-SSA/Ro antibodies, ocular staining score, unstimulated whole saliva flow rate, and Schirmer's test results, to classify patients with pSS. By using numerical-based standardized criteria, healthcare providers can ensure that patients will receive appropriate and timely treatment based on their specific classification. Additionally, the criteria aid in enrolling consistent patient populations in clinical trials, which is crucial for evaluating the efficacy of treatments and developing targeted therapies [7].

The classification criteria are imperfect. In pursuit of improving it, a study found that ultrasound scoring systems showed good sensitivity and specificity for diagnosing SS and fulfilling the classification criteria. Its result on the 2016 ACR/EULAR criteria suggests that ultrasound findings correlate well with the results of labial biopsy, which is considered the gold standard for diagnosing pSS. Further tests found that the use of ultrasound reduced the need for patients to get a labial biopsy, which is invasive. Ultrasound not only provides a non-invasive method to assess changes in the salivary glands but to evaluate the response to therapeutic interventions and treatment effects as well [47].

4.2. Biological Therapies

Biological treatments target specific immune pathways and cellular components that modulate the dysregulated immune response characteristics of pSS. One of the most extensively investigated biological drugs for pSS is an immunotherapeutic agent called rituximab, which targets B cells by depleting them and has shown promising results in reducing symptoms like fatigue and improving salivary flow in over 80% of pSS patients [45]. These patients have also shown a reduction in the mean daily corticosteroid dose, which is used in pSS patients to manage extra-glandular symptoms [48]. However, clinical trials have reported inconsistent efficacy, with some patients experiencing minimal symptom relief. Additionally, adverse events such as infusion reactions or hypogammaglobulinemia, and increased susceptibility to infections highlight the limitations of rituximab as a universal treatment for pSS.

Compared to rituximab, iscalimab offers a more targeted blockade of CD40-mediated signaling, which not only impacts B cell hyperactivity but also affects non-B cell components such as dendritic cells and macrophages. While both therapies reduce lymphocytic infiltration and ELS formation, iscalimab appears to modulate immune activation more broadly, which could contribute to its favorable safety profile observed in early trials. However, direct head-to-head comparative trials are currently lacking [44].

Other forms of immunotherapy that are currently in use include belimumab, which is a monoclonal antibody that targets B lymphocyte stimulators, and abatacept, which is a T-cell co-stimulation inhibitor. Another type of biological treatment is cell therapy, specifically using induced pluripotent stem cells (iPSCs) that are derived from patient-matched cells to generate functional salivary gland cells for transplantation [29], as well as bone marrow cells/cell lysates [49,50]. A representative summary of the various treatment targets and their respective potential therapies is presented in Figure 3.

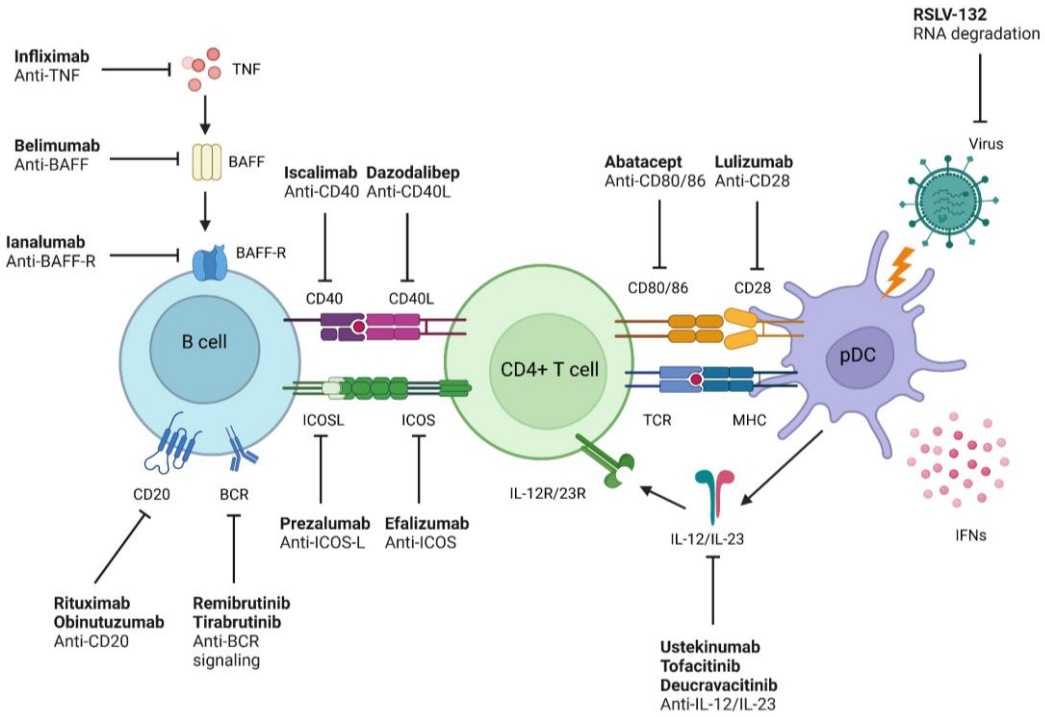

Figure 3. Therapeutic targets and corresponding treatments in pSS. Studies in pSS have identified key processes involved in the disease, such as lymphocyte regulation, antigen presentation, TLR and IFN signaling, and tissue homeostasis. Among these, lymphocyte regulation and TLR/IFN signaling pathways are major targets for current and developing treatments, offering potential therapeutic strategies for pSS [23,51]. APC: antigen-presenting cells; BAFF: B cell activating factor; BCR: B cell receptor; ICOS: inducible T-cell costimulator; IFN: interferon; IL: interleukin; MHC: major histocompatibility complex molecule; pDC: plasmacytoid dendritic cell; TCR: T cell receptor; TNF: tumor necrosis factor.

4.3. Non-Biological Therapies

Non-biological therapies encompass a range of treatment options aimed at managing systemic manifestations and improving overall disease control. Corticosteroids, such as prednisone, are commonly employed to manage symptoms like arthritis and cutaneous manifestations of SS. Hydroxychloroquine, an antimalarial drug, is used to address various systemic symptoms as well in SS [4]. In cases of severe and acute systemic manifestations of SS, treatment with glucocorticoids and immunosuppressant drugs are used to control active systemic disease and prevent disease progression. These systemic therapies are tailored based on the severity of organ-specific involvement, with a focus on using glucocorticoids at the minimum effective dose and duration [52]. Because non-biological therapies are less direct than biological therapies, more extensive research is required.

4.4. Symptomatic Relief

Because many of the targeted therapies are still under development, the main treatment approach for pSS involves various effective symptomatic relief strategies. Topical medications, such as artificial tears and saliva substitutes, are used to manage sicca manifestations by alleviating dryness in the eyes and mouth, respectively. For patients with moderate or severe oral dryness and residual salivary gland function, oral muscarinic agonists are recommended as the treatment of choice to stimulate salivary flow. In cases of severe or refractory keratoconjunctivitis sicca, the addition of topical cyclosporine A may be considered to suppress underlying inflammation. Furthermore, the use of secretagogues, such as pilocarpine and cevimeline, are both cholinergic agonists that have been shown to increase saliva production and improve dry mouth symptoms [6]. For individuals experiencing joint symptoms, nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics may be prescribed to alleviate discomfort in affected areas. However, it is important to note that these treatments cannot be relied on in the long term because they do not target the root of the problem.

5. Challenges

Despite the extensive research that has been done in the field, there are several limitations and challenges in conducting clinical trials for pSS treatments. For one, although pSS is a quite prevalent autoimmune disease, a limited number of patients are often available for enrollment in clinical trials. This makes it difficult to achieve statistically significant results and generalize the findings to a larger population. Additionally, there is a lack of standardized diagnostic criteria, as it has evolved. This shortfall can lead to variability in patient populations enrolled in clinical trials that may affect the interpretation of study results. Similarly, this deficiency can be seen in the lack of validated outcome measures specific to pSS. This makes it challenging to assess treatment efficacy and compare results across different studies. Currently, the most commonly used outcome measures are subjective symptoms and surrogate markers of disease activity [48].

These limitations arise from the limited understanding of the disease pathogenesis, which makes it challenging to identify specific therapeutic targets and develop targeted therapies. The heterogeneity of the disease is the core of the problem. SS is a heterogeneous disease with varying clinical manifestations and disease severity, which makes it challenging to identify appropriate patient populations for clinical trials to assess treatment responses. Inherently, this results in a limited availability of treatment options. There are currently no approved disease-modifying targeted therapies specific to SS [52].

6. Conclusions

SS is a complex autoimmune disorder with a multifaceted pathogenesis involving genetic predisposition, immune dysregulation, and environmental triggers. The disease primarily targets exocrine glands, leading to significant glandular dysfunction, but it also extends to systemic manifestations affecting multiple organ systems. Recent advancements in understanding SS have highlighted key pathogenic mechanisms, including cytokine dysregulation, autoantibody production, and metabolic alterations, offering potential therapeutic targets.

The identification of various distinct molecular biomarkers of SS has opened avenues for personalized treatment approaches tailored to the immune dysregulation patterns observed in patients with varying symptoms. The experimental strategies associated with each approach highlight the evolving landscape of precision medicine in SS, with a focus on targeting specific immune pathways and tailoring treatments to individual patients. Current treatment strategies primarily focus on symptom management, with emerging biological and immunomodulatory therapies showing promise for disease modification. However, challenges remain in developing standardized diagnostic criteria and targeted treatments due to the heterogeneity of the disease. In the next a few years, the identification of robust biomarkers, such as IFN signatures, SGEC-derived cytokine panels, and DNA methylation profiles, could enable earlier diagnosis and stratification of SS patients. Paired with emerging biologics and metabolic modulators, this biomarker-driven approach may facilitate more precise and effective therapeutic interventions tailored to disease subtype and activity level. Future research is warranted to prioritize identifying reliable biomarkers, refining classification criteria, and exploring novel therapeutic approaches to improve patient outcomes and quality of life.

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