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REVIEW

Updating on the Dual Role of Salivary Gland Epithelial Cell (SGEC) in Sjögren's Disease

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Abstract: Sjögren's disease, an autoimmune inflammatory disease, currently lacks effective treatment options. The salivary gland, a crucial exocrine organ responsible for saliva production and local immune responses on mucous membranes, is frequently impaired in individuals with Sjögren's disease. Restoring salivary gland function poses a significant challenge for researchers. Salivary epithelial cells, recognized as pivotal components of the salivary gland, have been increasingly implicated as key initiators of inflammation and exhibit innate immune cell-like properties. On the whole, SGEC plays a protective role in the physiological state, and can also participate in the persistence of inflammation as an initiating factor in the pathological state. In the review, we explore the interplay between Ca+, endoplasmic reticulum (ER), and mitochondrial homeostasis imbalance in salivary epithelial cells. Additionally, we provide an overview of current literature on research advancements related to Pattern Recognition Receptors (PRRs), programmed cell death, posttranslational modification (PTM), and oral microecology, etc. specifically focusing on their implications in salivary epithelial cells. Given the crucial role of salivary gland epithelial cells in the onset of Sjögren's disease, a treatment based on salivary gland epithelial cells may have the potential to alleviate the condition by addressing the inflammatory response in the salivary glands.
Keywords: Sjögren's disease, pattern recognition receptor, salivary gland epithelial cell, immune homeostasis, innate immune

Introduction

Sjögren's disease (SjD) is a systemic autoimmune disease that mainly involves secretory glands, especially lacrimal and salivary glands, and can involve multiple organs.[1] It is often accompanied by fatigue, musculoskeletal pain and other symptoms, which seriously affects the quality of life of patients. The existing epidemiological survey data in various regions show that the incidence and prevalence of SjD vary greatly worldwide.[2,3] It is currently believed that among all chronic autoimmune rheumatism, SjD is still one of the diseases with high incidence.[4] Current diagnosis and treatment strategies for Sjögren's disease are not enough to address the current status of lymphocyte infiltration and salivary gland dysfunction.[5] According to the complex role of salivary gland epithelial cells in the development of SjD, further research is needed to successfully rescue the salivary gland function of SjD.[6] Most of therapy methods can effectively improve the subjective symptoms of patients, but there is less afford to the imbalance of immune system.

Both innate and adaptive immune cells are key pathogenic factors of Sjögren's disease.[7,8] However, Sjögren's disease has a significant Interferon (IFN)-I characteristic, and the activation of innate immune signals is a key factor in inducing the IFN-I characteristic.[9] At present, the role of various innate immune signaling pathways, including TLR, cGAS-STING and NLR, in the pathogenesis of Sjögren's disease has been clarified.[10–12] Given the current status that the etiology of Sjögren's disease has not been elucidated, in-depth research is crucial to understand its potential pathogenesis and find new therapeutic targets.[13] The important role of SGEC in this disease was proposed about forty years ago, but it was ignored for more than 30 years. However, the role of SGEC in this disease are less well understood. As the most important cellular component of the salivary glands, SGEC plays a dual role in this disease.[14] Firstly, salivary gland epithelial cells (SGEC) are the victim during the autoimmune injury in Sjögren's disease.[15] Then, as the main cell component of SG, SGEC also plays an important role in

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secreting saliva, aquaporins and so on.[16] In the past decade, the biological function of SGEC has been extensively studied.[17] SGEC injury or inappropriate activation can show similar functions to innate immune cells, which can activate innate immune signals, recruit inflammatory cells and aggravate local inflammatory responses.[18] Therefore, it is imperative to explore strategies for mitigating pathological injury in SGEC and preserving cellular homeostasis, which warrants significant attention.

The immune system needs to be kept in balance, and the goal of treatment for autoimmune diseases such as SjD is to suppress excessive immune responses and restore stability.[19] In general, in SjD, many pathways and processes in the salivary glands may be disrupted, including epithelial cell activation,[20] innate immune signaling,[21] and adaptive immune activation.[22] These studies have been summarized in several excellent researches.[23–25] However, most of the emphasis has been on how to protect SGEC from injury. As our understanding of the cellular biology of salivary gland epithelial cells (SGEC) continues to advance, researchers have increasingly focused on the role of SGEC in triggering inflammatory signals and exploring therapeutic strategies aimed at regulating SGEC cell homeostasis.[26] These efforts aim to enhance salivary gland (SG) injury recovery and restore immune balance in Sjögren's disease, thus garnering attention within the scientific community. Recently conducted studies on locally specific gene over-expression in SGEC have provided further evidence supporting the role of SGEC as an inflammatory inducer.[27] However, the mechanisms of regulating SGEC cell homeostasis to protect SG function are still unclear.

In this review, we first review the physiological function and the innate immune defense role of SGEC. Second, we explore the immunogenicity of SGEC in pathological conditions. Finally, we summarize the evidence and regulatory mechanisms of proinflammatory signal activation induced by SGEC dyshomeostasis.

The Physiological Functions and Defensive Roles of SGEC

The function and composition of salivary glands provide valuable insights into the overall health status of the body, and numerous studies have been conducted to identify saliva biomarkers for disease diagnosis.[28,29] Salivary glands primarily consist of epithelial cells and connective tissue,[30] with epithelial cells being the main cell type responsible for saliva secretion within these glands.[31] Specifically, salivary gland epithelial cells can be categorized as acini cells, duct cells, myoepithelial cells, among others.[32] The function of salivary glands is predominantly manifested through saliva as a carrier. Acini cells produce and secrete mucus-rich saliva while the contraction of surrounding muscle epithelial cells facilitates its release into the oral cavity via ducts.[33] Extracellular hormones or neurotransmitters (such as acetylcholine or cholecystokinin) can bind to G protein-coupled receptors on the basal membrane,[34,35] serving as initiating signals for various biological processes that trigger Ca2+ release from the endoplasmic reticulum[36] and subsequently stimulate extensive primary saliva production. Saliva, serving as a cleansing fluid in the oral cavity, plays a pivotal role in maintaining oral hygiene and safeguarding teeth and oral mucosa against physical and chemical harm.[37] Moreover, it harbors numerous proteins that are indispensable for the host's defense mechanism against pathogens[38] Being constantly exposed to foreign pathogens, saliva acts as the primary line of defense for both human and animal oral mucosa. It shields tooth surfaces from acid-induced damage caused by dietary intake and oral bacteria. Patients with insufficient saliva secretion face an elevated risk of tooth demineralization, dental caries, oral mucositis, and fungal infections.[32] Additionally, saliva encompasses a plethora of signaling molecules including nerve growth factor (NGF),[39] epidermal growth factor (EGF),[40] fibroblast growth factor (FGF),[41] and vascular endothelial growth factor (VEGF)[42] which play crucial roles in promoting healing processes of both oral mucosal and esophageal wounds as well as facilitating skin wound repair. Furthermore, secretory immunoglobulin IgA assumes a vital function in orchestrating immune responses within the oral mucosa.[43] The concised function of Salivary Gland Epithelial Cells under physiological conditions can be seen in Figure 1.

Immunogenicity in SGEC Pathological State

The function of SGEC in physiological state is as described above. In pathological state, SGEC can also act as a disease inducing factor and participate in the progression of the disease.[17] Currently, the factors that have been found to cause damage to SGEC include calcium homeostasis imbalance, mitochondrial dysfunction, endoplasmic reticulum stress, activation of the PRR signaling pathway, programmed cell death and so on.

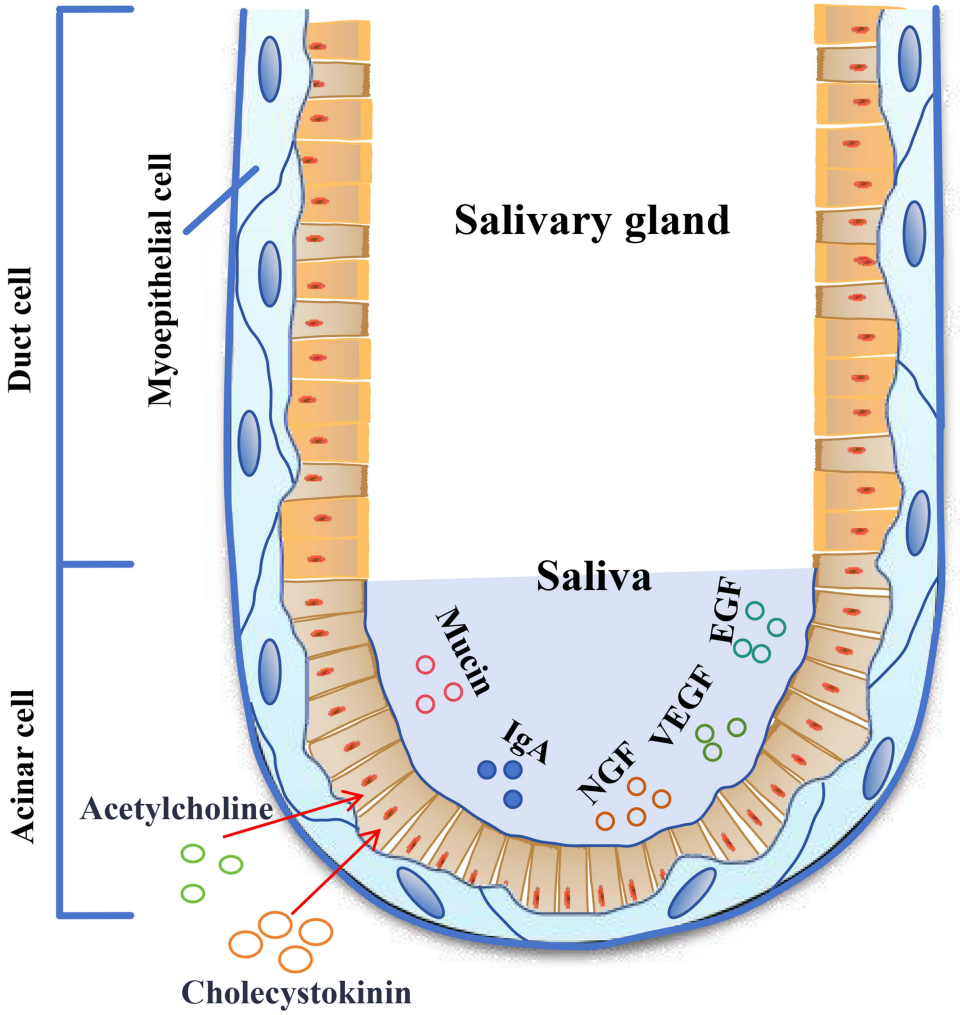

Figure 1 The function of Salivary Gland Epithelial Cells under physiological conditions.

Calcium Homeostasis Imbalance

Saliva secretion is a two-stage process in which glandular cells produce an isotonic saliva initially, which is then modified by the duct system into a hypotonic fluid.[44] Ca^{2+} is a key factor in controlling salivary gland function. Studies have found that in physiological conditions, salivary mucous cells enhance PKC activity by inducing the release of intracellular Ca^{2+} pools through VIP, thereby mediating the co-secretion of mucin proteins with muscarinic.[45] In pathological conditions, defects in Ca^{2+} signaling have been observed in radiation-induced loss of salivary gland function[46] and salivary gland dysfunction associated with Sjögren's disease.[47] Defects in epithelial cell calcium signaling in Sjögren's disease are associated with a decline in salivary gland secretion.[48] Recent studies have found that IL-17 causes salivary gland dysfunction in Sjögren's disease by inhibiting TRPC1-mediated calcium transport.[49] Inducing Ca^{2+} signaling can promote saliva secretion and prevent immune cells from infiltrating the salivary gland in a Sjögren's disease mouse model.[50] However, the cause of calcium homeostasis imbalance in the salivary gland of Sjögren's disease patients still needs further research.

Mitochondrial Dysfunction

Oxidative-Reduction Homeostasis Imbalance

In almost all subcellular organelles, including the cytoplasm, endoplasmic reticulum (ER), mitochondria, and peroxisomes, reactive oxygen species (ROS) can be generated as byproducts of their fundamental metabolic functions.[51] Physiological ROS plays a pivotal role in regulating cellular function disorders under normal conditions. However, it can

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also contribute to the pathogenesis of various diseases such as infectious diseases,[52] autoimmune diseases,[53] tumors,[54] and metabolic disorders.[55] The functions of immune cells are intricately linked to diverse metabolic pathways, with immune cell metabolism being inseparable from redox reactions.[56] Studies have revealed that patients with Sjögren's disease exhibit downregulation of glutathione peroxidase 4 (GPX4) expression in salivary glands. This downregulation induces an increase in lipid ROS levels within SjD SGECs, subsequently promoting STAT4 phosphorylation and nuclear translocation. Consequently, STAT4 binds to the AQP5 promoter region leading to inhibition of AQP5 expression and saliva secretion.[57] Experimental studies have further demonstrated significantly elevated ROS fluorescence levels accompanied by reduced mitochondrial membrane potential in NOD mice SGEC compared to the ICR group.[58] Collectively, these findings suggest that ROS accumulation is a critical factor contributing to mitochondrial damage and hypofunction in SGEC during Sjögren's disease.

Mitochondrial Metabolic Dysfunction

Inflammatory epithelial diseases are caused by a co-disorder of immune cells and epithelial cells.[59] Sjögren's disease was previously known as autoimmune epithelitis, characterized by abnormal activation of epithelial cells and extensive infiltration of lymphocytes in the salivary gland. From an immune-metabolic perspective, it is evident that any metabolic alterations in target epithelial cells in Sjögren's disease (SjD), regardless of the underlying cause, can induce an immunogenic phenotype.[60] Thus, salivary gland epithelial cells (SGEC) have the potential to directly modulate the susceptibility and/or severity of autoimmune responses. In comparison to normal SGEC, SjD-SGEC exhibit reduced mitochondrial content, swollen and elongated mitochondria, as well as fewer and aberrant cristae.[61] These metabolic changes primarily involve mitochondria and are accompanied by pronounced morphological alterations in situ. Transcriptome sequencing offers insights into the transformation process of SGEC from SjD patients into innate immune cells while uncovering translational modifications associated with metabolic remodeling.[14] RNA sequencing-based investigations have revealed distinct distribution patterns of innate and adaptive immune cells within salivary gland tissue from primary Sjögren's disease (SjD) patients, which are linked to diverse mitochondrial metabolic pathways thereby influencing disease progression.[62,63] Further research is warranted to elucidate the role of mitochondrial metabolism in SGEC during Sjögren's disease.

Maladaptive Mitochondrial Autophagy

Autophagy is a crucial regulatory pathway for cellular self-protection in various immune cells, including neutrophils, eosinophils, mast cells, and NK cells, enabling the maintenance of cellular homeostasis.[64] Recently, researchers have also started to focus on autophagy in salivary gland epithelial cells. Current studies have demonstrated that modulating autophagy can exert a protective effect on the parotid gland pathology in Sjögren's disease. Conversely, inhibiting autophagy can worsen the parotid gland pathology.[58,65] Interestingly, some studies indicate a significant correlation between the level of autophagy in small salivary gland lymphocytes of Sjögren's disease patients and the extent of lymphocyte infiltration within these glands.[66] The m6A methylation process may participate in immune infiltration and autophagy regulation in primary Sjögren's disease (SjD), thereby contributing to its pathogenesis.[67] Furthermore, certain researchers propose that inflammation-induced autophagy and survival mechanisms promote activation of SGECs in primary SjD SGECs and reflect histopathological severity. They consider autophagy as a central factor underlying primary SjD pathogenesis and suggest it as a potential therapeutic target.[68] However, further research is needed to confirm the role of autophagy in salivary gland epithelial cells of Sjögren's disease patients.

Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is the largest organelle in the cell and plays a crucial role in protein synthesis, lipid metabolism, and other essential cellular processes. When triggered by internal and external stimuli such as ischemia,[69] oxidative stress,[70] infection,[71] drug toxicity,[72] and calcium homeostasis imbalance,[73] disturbances in ER homeostasis lead to the unfolded protein response (UPR), resulting in the accumulation of misfolded proteins within the ER and initiating the endoplasmic reticulum stress (ERS) response to restore ER homeostasis. In pathological conditions, ERS can also modulate immune cell functions, contributing to immune system dysregulation.[74] Chronic inflammation can

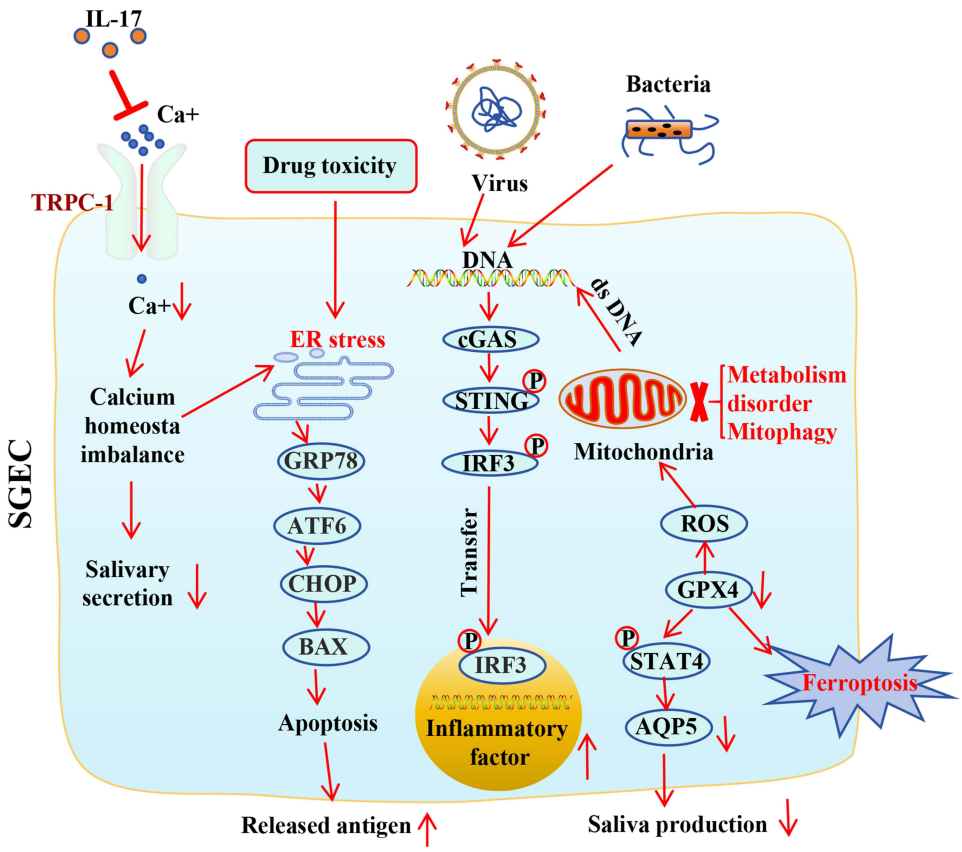

Figure 2 Diagram illustrating the pathogenic mechanism of SGEC involving dysregulation of mitochondrial and endoplasmic reticulum homeostasis.

disrupt MUC1 secretion and induce ER stress, impacting saliva quality in Sjögren's disease patients.[75] Furthermore, it has been demonstrated that the GRP78-ATF6-CHOP signaling pathway associated with ER stress is overactivated in primary Sjögren's disease.[76] Sjögren's disease is characterized by the excessive expression of type I interferon,[77] which can induce ERS in SGECs, leading to the massive production of Ro52/SSA antigen and downregulation of autophagy, thereby increasing cell apoptosis.[78] Interestingly, studies have also found that merc in SGEC mediates the transfer of calcium from the endoplasmic reticulum to the mitochondria, promoting ATP production and playing a crucial role in calcium homeostasis.[79] In contrast, the inflammatory cascade signal triggered by endoplasmic reticulum stress in pathological conditions is an important factor causing dysfunction of salivary gland epithelial cells in Sjögren's disease. Calcium homeostasis imbalance and mitochondrial damage in salivary gland epithelial cells can be seen in Figure 2.

Activation of the PRR Signaling Pathway

Innate immunity distinguishes various pathogen-associated molecular patterns (PAMPs) as the first line of defense against pathogen infection.[80] Common PRRs include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nod-like receptors (NLRs), and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs).[81] Recently, salivary gland epithelial cells have been considered a special innate immune cell,[14,60] and they also express a variety of PRRs on their surfaces. The specific summary is as follows.

Activation of Inflammasome

Several types of inflammasomes, such as NLRP1 inflammasome, NLRP3 inflammasome, NLRC4 inflammasome, IPAF inflammasome, and AIM2 inflammasome,[82] have been identified. Among these, the NLRP3 inflammasomes have been extensively studied in the context of Sjögren's disease. The NLRP3 inflammasome is known to play a pivotal role in the

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pathogenesis and progression of various autoimmune diseases.[83] Recent research has demonstrated activation of the NLRP3 inflammasome in the salivary glands of Sjögren's disease patients,[84] with a potential mechanism involving SGEC pyroptosis induced by type I IFN in SjD patients.[85] Although there have been studies investigating the involvement of the AIM2 inflammasome in Sjogren's syndrome pathogenesis, most of them have primarily focused on peripheral blood mononuclear cells and lacrimal epithelial cells. Therefore, further investigations are warranted to elucidate the role of AIM2 and other inflammasomes in salivary epithelial cell dysfunction.

Activation of TLR Signaling Pathway

Toll-like receptors (TLRs) are a distinct subset of PRRs, playing a pivotal role in pathogen recognition and inflammation induction.[86] Currently, 11 TLR family members have been identified, with TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11 located on the cell surface and TLR3, TLR7, TLR8, and TLR9 situated in the endosome/lysosome compartment.[87] In the context of Sjögren syndrome (SjD), particular attention has been given to the study of TLR2, TLR3, TLR4, and TLR7. Interleukin-15 (IL-15), an inflammatory cytokine implicated in SjD pathogenesis, is induced by SGEC through activation of TLR2, resulting in NF-kB-mediated inflammatory responses.[88] Additionally, TLR3 is involved in apoptosis mediation and phosphorylated Akt activation within salivary gland epithelial cells from SjD patients.[89] TLR-7 is predominantly expressed in monocytes and ducts of minor salivary glands in patients with Sjögren's disease, and is associated with downstream signaling pathways related to type I interferon, suggesting that TLR-7-mediated innate immunity plays a role in the development of glandular inflammation in SjD.[90] Additionally, TLR7 activation of SGEC cells in SjD patients promotes the presentation of the TRIM21/Ro52-SS-A antigen via the MHC class I pathway.[91] Conversely, lysosomal-associated membrane protein 3 induces ectopic TLR7 expression on salivary gland epithelial cells, amplifying the type I interferon response in Sjögren's disease.[92] A notable characteristic of SjD patients is the presence of mucin proteins outside their normal location within the extracellular matrix of salivary glands. These ectopic salivary mucin proteins can be recognized by TLR4 expressed on epithelial cells, initiating an inflammatory response and attracting inflammatory cells to proliferate and prolonging inflammation, thereby promoting the chronic features of SjD.[93]

Activation of the cGAS-STING Signaling Pathway

cGAS plays a crucial role as a sensing protein in the innate immune response, in recognizing microbial DNA and endogenous DNA (including mitochondrial DNA (mtDNA) and genomic DNA).[94] Recent findings suggest that activation of the cGAS-STING pathway can promote the expression of type I interferon (IFN) and pro-inflammatory cytokines, which play an important role in the pathogenesis of Sjögren's disease.[12,79,95] Studies have found that patients with SjD have a high lactate environment in their labial glands, and lactate can damage mitochondrial DNA (mtDNA) and cause its leakage, thereby activating the cGAS-STING pathway.[96] Our previous studies have found that the cGAS-STING signaling pathway is significantly activated in salivary glands of Sjögren's disease patients. The cGAS-STING signaling pathway is significantly related to the pathogenesis of Sjögren's disease, and regulating autophagy is a key brake that limits the activation of the cGAS-STING signaling pathway.[58] However, the specific regulatory mechanisms remain to be further elucidated.

Other Pattern Recognition Receptor-Related Signaling Pathways

AIM2 (Absent in melanoma 2) is a cytoplasmic DNA-recognition protein capable of identifying double-stranded DNA, and forms the AIM2 inflammasome, a protein platform that triggers the innate immune response. Studies have demonstrated that genomic DNA activation of the AIM2 inflammasome and STING leads to an inflammatory reaction in meibomian gland MECs, potentially contributing to the development of SjD.[97] However, there is currently limited research on how C-type lectin receptors and RIG-I-like receptor-related signaling pathways impact salivary gland epithelial cells in Sjögren's disease patients. Figure 3 shows activation of pattern recognition receptor-associated signaling pathways in salivary gland epithelial cells.

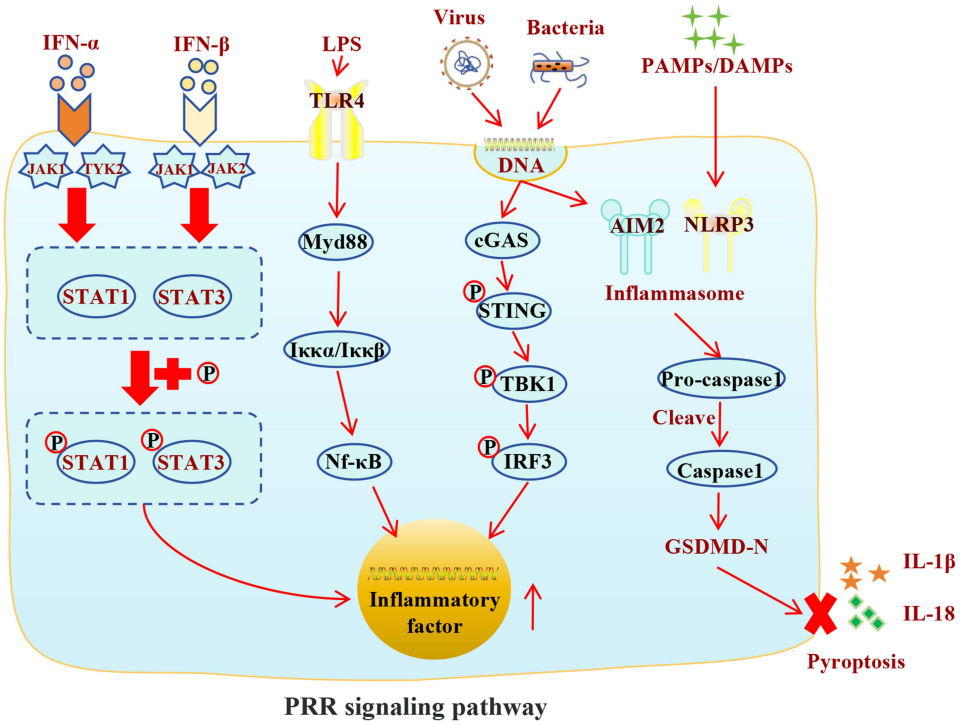

Figure 3 PRR signaling pathway are involved in the activation of inflammatory signaling pathways in SGEC.

Programmed Cell Death

Programmed cell death (PCD) refers to the elimination of unwanted cells through multiple distinct pathways in order to maintain cellular homeostasis. The main types of programmed cell death include apoptosis, autophagy, ferroptosis, and pyroptosis, among others.[98] Increased apoptosis of epithelial cells is the main cause of exocrine gland dysfunction and epithelial gland structural damage in patients with SjD.[99] Therefore, lymphocyte-induced epithelial cell apoptosis is considered a key factor in decreased exocrine function. Subsequently, the release of antigens into the apoptotic bodies from the apoptotic cells is the main route for presenting self-antigens to the immune system.[10] In vitro studies have shown that epithelial cell apoptosis can trigger the release of apoptotic bodies containing nuclear material, including Ro/SSA and La/SSB antigens.[23] Among these, autophagy and pyroptosis have already been reviewed earlier, so they are not discussed again.

Ferroptosis is a novel form of regulated cell death (RCD) caused by fatal accumulation of iron-dependent and lipid peroxidation products, ultimately leading to membrane damage and cell death.[100] It is currently believed that epidermal cell-derived proteins involved in ferroptosis are present in plasma exosomes from SjD patients. Complement C5 and C9 may be new molecules involved in ferroptosis that play an important role in the pathology of SjD epithelial cells. Plasma exosomes from SjD patients, rather than those from non-autoimmune sicca syndrome (nSS) patients, contain ferroptosis-related proteins. The content of apoptosis-related proteins in exosomes reflects the state of epithelial cell lesions more than that in plasma.[101] Interferon-γ induces ferroptosis in salivary gland epithelial cells of Sjögren's disease (SjD) through JAK/stat1 mediated inhibition of system Xc. JAK or STAT1 inhibition in SGEC reverses the downregulation of SLC3A2 and GPX4 induced by IFN-γ, as well as IFN-γ-induced cell death.[15] GPX4 is a key molecule in the ferroptosis process. Downregulation of GPX4 expression in salivary gland epithelial cells can cause salivary secretion dysfunction in Sjögren's disease through lipid ROS/pSTAT4/AQP5 axis.[57]

Crosstalk Between SGECs and Lymphocytes

SGECs play a pivotal role in the pathological changes of lymphocyte infiltration within the salivary gland of patients with Sjögren's disease (SjD). Current research primarily focuses on elucidating the interactions between epithelial cells

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and B cells, as well as T cells. SGECs possess the ability to regulate recruitment, activation, and differentiation of immune cells in SjD. Phenotypic flow cytometry analysis and cytokine studies have confirmed that SGECs secrete B cell activating factor (BAFF) while also modulating the activation and differentiation processes of B cells.[102] Gene expression profiling in SGECs has revealed upregulation of genes associated with interferon signaling pathway and immune response (HLA-DRA, IL-7, and B cell activation factor receptor) in primary Sjögren's disease (SjD). Additionally, activated genes CD40 and CD48 exhibited upregulation specifically in salivary gland-derived B lymphocytes from SjD patients. Furthermore, SGECs can enhance survival of B lymphocytes; notably, those derived from SjD patients exhibit higher pro-B lymphocyte survival activity compared to controls.[103] Moreover, LAMP3 expression can induce apoptosis in SGECs leading to reduced expression of proteins involved in saliva secretion along with impaired lysosomal function. Consequently, damage-associated molecular patterns (DAMPs) are released via Toll-like receptors to activate immune cells.[18] However, further investigations are warranted to ascertain whether these interactions hold true universally.

Abnormal Epigenetic Modifications

The key mechanisms of epigenetics encompass various processes, including methylation modification, histone modification, and non-coding RNA regulation.[104] During the progression of Sjögren's disease, significant alterations in epigenetic modifications are frequently observed in immune cells and salivary gland epithelial cells, indicating a robust association with autoimmune responses.[105] Currently, more and more research is focusing on the role of epigenetic changes in the onset of Sjögren's disease. Methylation modification encompasses DNA methylation and RNA methylation, which play pivotal roles in regulating gene expression and cellular functions by modulating the accessibility of DNA to transcription factors and other regulatory proteins.[106] The present study investigated the association between DNA methylation and the European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI) score, revealing a significantly higher number of differential methylation regions in patients with high ESSDAI scores compared to those with low ESSDAI scores.[107] The study revealed an increased proportion of B cells in the LSG tissue of SjD patients compared to non-SjD controls, accompanied by upregulated gene expression associated with B cell function and reduced methylation of genes involved in immune response and immune tolerance.[108] An epigenetic analysis of LSGs in SjD patients revealed distinct methylation patterns at CpG sites with differential methylation between SjD subgroups, providing evidence for the involvement of epigenetic factors in the heterogeneity of SjD.[109] The dysfunction of the IRE1alpha/XBP-1 pathway, which is associated with DNA methylation, may result in impaired salivary gland function in patients diagnosed with Sjögren's disease.[110] The aforementioned findings further underscore the significance of methylation modifications in the pathogenesis of SjD and have the potential to inform the development of novel diagnostic and therapeutic strategies.[111]

The RNA modification methyladenosine N6 (m6A) is widely recognized as the most prevalent form of RNA methylation. Extensive research has demonstrated its significant involvement in immune infiltration and autophagy processes associated with SjD.[67] The presence of M6A methylation and the upregulation of METTL3 protein exhibit associations with blood serological markers and dry eye symptoms in patients diagnosed with primary Sjögren's disease.[112] When exposed to inflammatory stimuli, the impairment of m6A modification in SGEC facilitates the generation of double-stranded RNA (dsRNA), thereby potentially amplifying the interferon cycle and contributing to the pathogenesis of Sjögren's disease.[113] However, METTL3-mediated m6A modifications impeded the formation of dsRNA and activation of IFN signaling. Additionally, the m6A methylation detector can aid in subtyping patients with Sjögren's disease into diagnostic subgroups through consensus clustering, thereby categorizing SjD patients into distinct m6A patterns. The m6A score of Group B patients surpasses that of Group A patients.[114] However, further investigation is required to elucidate the immunoregulatory role of methylation modification in this disease.

Post-translational modifications (PTMs) are implicated in a diverse array of biological processes and play a crucial role in modulating protein structure, activity, and function.[115] Numerous studies have demonstrated the widespread involvement of protein post-translational modifications in the regulation of inflammatory processes.[116] However, there remains a paucity of research on PTMs in the pathogenesis of Sjögren's disease. A recent comparative proteomic analysis of serum samples identified and validated ITIH3 as a potential biomarker, while also pinpointing hexosamine and arginine modification sites on ITIH3. Furthermore, analysis of autoantibody subtypes against arginine-modified ITIH3

peptides allowed for further differentiation between patients with rheumatoid arthritis (RA), primary Sjögren's disease, RA-secondary SjD, and healthy controls.[117] Additionally, some studies have characterized the newly discovered Kmal (lysine acetylation form) in SjD and provided proteomic data for SjD patients. Notably, several key differentially modified proteins were found to be associated with the cell adhesion pathway, which is implicated in the development of SjD.[118] In terms of PTMS, it is also a research direction that needs to be paid attention to in the future to recognize and regulate the immune homeostasis of salivary epithelial cells in response to imbalance immune responses.

Oral Microecology Disorder

There is increasing evidence that the diversity of the microbiome is associated with high disease activity in Sjögren's disease.[119] Changes in the microbiome have a negative impact on the pathogenesis of Sjögren's disease. However, the causal relationship, especially the impact of oral microecology on salivary gland epithelial cells, is not yet clear.[120] Researchers have detected exogenous (microbial) or endogenous (endogenous retrovirus) genomes in salivary gland epithelial cells of Sjögren's disease patients, which may help clarify the mechanism by which microorganisms participate in the activation of salivary gland epithelial cells in Sjögren's disease.[121] In addition, bioinformatics analysis based on the transcriptome of salivary glands can also reveal the existence of multiple innate immune signaling pathways and signal activation related to pathogen infection in salivary glands of Sjögren's disease patients, indicating that disruption of oral microecology participates in the pathogenesis of the disease.[58] However, diagnostic indicators related to this need to be further validated by large-sample clinical studies, and the effects of oral microecology on SGEC epithelial cells need to be further elucidated through experimental studies.

Future Outlook

The presence of unknown trigger factors in salivary gland epithelial cells may activate the innate immune response and subsequently lead to an adaptive immune response against self-antigens, thereby positioning the epithelial cells as both the medium and target of the response.[122] In recent years, advancements in transcriptomics, proteomics, and metabolomics technologies have provided a deeper understanding of the physiological and pathological mechanisms underlying Sjögren's disease. The altered oral microbiome in Sjögren's disease patients has been a focal point for researchers for numerous years.[123] Investigations into SjD-like microbial dysbiosis in individuals with pre-SjD or non-SjD related diseases suggest that changes in the microbial community may precede the onset of primary Sjögren's disease. Furthermore, it has been observed that SjD patients treated with HCQ experience partial alleviation of microbial dysbiosis. However, there remains disordered composition within the microbial community.[124] A reduction in saliva flow seems to be unrelated to simple microbial dysbiosis but rather affects host-related risk factors.[125] A bioinformatics analysis of the composition of salivary microbiota revealed significant differences in oral microbial composition between the anti-SSA antibody positive and negative groups. The microbial diversity of patients with SjD was lower than that of non-SjD patients. And several potential genetic markers of SjD at the level of microbiota were identified, such as a decrease in the abundance of Lactobacillus or an increase in the abundance of Streptococcus.[126] There are significant differences in microbial dysbiosis between SjD patients and non-SjD patients, and it is unrelated to oral candidiasis and DMFT.[127] The mechanism by which oral microecology participates in the physiological and pathological process of this disease still needs further in-depth research.

In addition, while research on single-cell sequencing in Sjögren's disease is gradually increasing, the focus has primarily been on mononuclear cells[128] and CD4 T cells.[129] However, there remains a significant gap in genomic sequencing that specifically targets the single-cell transcriptome and spatial transcriptome of salivary gland epithelial cells. Although single-cell RNA sequencing (scRNA-seq) can identify cell subpopulations within tissues, it does not capture their spatial distribution or reveal the local network of cell-to-cell communication for in situ action. On the other hand, spatial transcriptomics can elucidate RNA localization within tissues but lacks complete transcriptomic information.[130] Therefore, there is an urgent need to integrate the results of single-cell and spatial transcriptome sequencing to map out the trajectory of cell differentiation and gene regulatory networks, as well as to characterize cell-to-cell communication and regulatory networks within tissues.[131] This integration will further illuminate the role played

by salivary gland epithelial cells in shaping the immune microenvironment of salivary glands in patients with Sjögren's disease.

Restoring the function of the salivary gland is the primary objective in treating Sjögren's disease,[132] as it relies on the functional integrity of epithelial tissue. However, there remains a limited understanding of SGEC in this disease. Consequently, researchers primarily focus on comprehending secretory physiology and exploring potential regenerative strategies to repair SGs and restore saliva production.[133] It is imperative to adopt a comprehensive perspective that encompasses the interplay between innate immunity and adaptive immunity while elucidating the role of salivary gland epithelial cells in this process.[134] Nevertheless, current research predominantly concentrates on individual cell interactions,[135] necessitating an urgent need for holistic comprehension of local immune physiology and pathology within submental gland tissue. As immunologists, we can consider utilizing organoid research or clinically-based investigations as pivotal approaches to unraveling Sjögren's disease pathogenesis in future studies.

Conclusion

SGEC plays a protective role in the physiological state, and can also participate in the persistence of inflammation as an initiating factor in the pathological state. Given the crucial role of salivary gland epithelial cells in the onset of Sjögren's disease, a treatment based on salivary gland epithelial cells may have the potential to alleviate the condition by addressing the inflammatory response in the salivary glands. How to restore the immune function of hyperactive salivary gland epithelial cells to a state of calmness is a worthy subject for future research.

Data Sharing Statement

This is review paper and no data has been produced.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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