Review Article

JOMP Journal of Oral Medicine and Pain

eISSN 2383-8493
J Oral Med Pain 2023;48(2):39-44
https://doi.org/10.14476/jomp.2023.48.2.39

Role of Homeostatic Changes in Salivary Gland Acinar Cells in Primary Sjögren's Syndrome: A Review

Jin-Seok Byun

Department of Oral Medicine, School of Dentistry, Kyungpook National University, Daegu, Korea

Received June 7, 2023
Revised June 13, 2023
Accepted June 14, 2023

Correspondence to:
Jin-Seok Byun
Department of Oral Medicine, School of Dentistry, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, Korea
E-mail: jsbyun@knu.ac.kr
https://orcid.org/0000-0002-6182-1238

Primary Sjögren's syndrome (pSS) is an autoimmune progressive disease characterized by dysfunction and inflammation of the salivary glands. The underlying mechanisms of salivary gland involvement in pSS remain unclear, and researchers have primarily focused on immunological phenomena, making it difficult to distinguish between the cause and effect of the disease. Consequently, our research aims to directly investigate changes in homeostasis occurring in acinar cells, specifically in the context of muscarinic signaling, mucins, aquaporins, and forkhead box protein O1, to elucidate the initial step of pSS. We compare the disease-related phenomena observed in salivary gland acinar cells in pSS with the overall process of salivary secretion.

Keywords: Aquaporins; Forkhead box protein O1; Mucins; Muscarinic signaling; Primary Sjögren's syndrome; Salivary gland acinar cells

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by dysfunction and inflammation of the exocrine glands, particularly the salivary and lacrimal glands [1]. This condition can result in reduced production of saliva and tears, leading to symptoms such as dry mouth and eyes. During the progression of Sjögren's syndrome, the immune system mistakenly attacks the moisture-producing glands, causing inflammation, and damage to the glandular tissue. Among the various signs and symptoms, oral dryness is one of representative symptom observed in patients with pSS. In this context, a particularly important diagnostic indicator is the positive infiltrating lymphocyte score in salivary gland biopsy [2,3].

The salivary glands are a major target organ in the progression of pSS [4]. To gain a comprehensive understanding of salivary gland dysfunctions in pSS, it is crucial to investigate the role of the main saliva producers, known as the salivary epithelia. The salivary gland epithelium is the layer of cells that lines the salivary glands. It consists of various epithelial cell types, which perform specific functions in the production, modification, and secretion of saliva. The cell types in the salivary gland epithelium include acinar, ductal, and myoepithelial cells. Of these, acinar cells are found in the acini of the salivary glands and are responsible for synthesizing and secreting primary saliva. Acinar cells produce saliva by actively transporting ions, such as sodium, and potassium, across their cell membranes. They also secrete enzymes, proteins, and other substances that contribute to the composition of saliva. Ductal cells receive primary saliva from the acinar cells, modifying its composition before its secretion into the oral cavity. Myoepithelial cells function as machinery for the contraction of acini.

Salivary gland epithelial cells have been considered not only as passive bystanders in excessive immune-mediated

organ failures but also as key cells associated with disease progression [5,6]. Among the salivary epithelial components, acinar cells have been studied extensively in the context of disease progression. Compared with normal salivary gland acinar cells (SGACs), dysfunctional SGACs in pSS exhibit several structural and functional abnormalities, including reduced neurotransmission, abnormal intracellular metabolic procedures, distorted secretion of salivary components, and even the production of proinflammatory cytokines [6,7]. Although the cause and effect of these changes are still under debate, elucidating the underlying mechanism will help researchers understand and overcome the disease. In this review, we discuss the changes in SGACs in Sjögren's syndrome and their importance in relation to decreased salivary production and proinflammatory consequences.

ABNORMALITY OF SALIVARY GLAND ACINAR CELLS

SGACs are the primary functional parenchymal cells responsible for producing primary saliva in the salivary glands. These cells constitute the majority of the glandular tissue and play a crucial role in saliva production. SGACs can be classified as serous or mucous based on the type of saliva they produce. They possess specialized structures and functions that optimize saliva production. A series of processes within the acinar tissue are essential for optimal salivary secretion, including 1) maintaining a normal morphological structure, 2) responding to parasympathetic salivation signaling, 3) producing secretory granules, and 4) facilitating saliva production and transport to the lumen. In this section, we will explore the pathological phenomena observed in Sjögren's syndrome acinar cells in relation to these processes. The graphical abstract associated with this section is presented in Fig. 1.

1. Morphological Distortion

The glands of patients with pSS exhibit a disorganized basal membrane and atrophy in SGACs. Research has indicated that the observed distortion of the basement membrane in acinar cells with pSS is primarily associated with laminin and type IV collagen [8]. Changes in laminin distribution in the basement membrane of acinar cells can serve as an indicator of the progression of Sjögren's syndrome, as changes in laminin expression levels can be observed prior to excessive lymphocyte infiltration [9]. In terms of glandular acinar atrophy, the absence of laminin α chains and alpha 1 may impair the ability of progenitor cells to differentiate into acinar cells, resulting in acini atrophy and ductal cell hyperplasia [10]. Researchers have also focused on the activity of matrix metalloproteinases, which may be linked to remarkable changes in the structural organization of the basal lamina and apical surface of acini in patients with Sjögren's syndrome [11].

Morphological changes observed in the acinar cells of

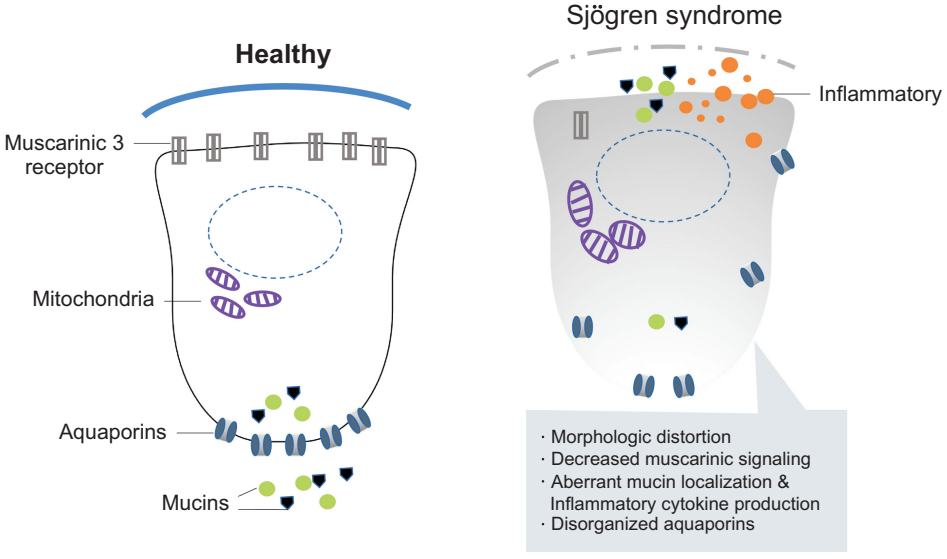

Fig. 1. Abnormalities in salivary gland acinar cells.

individuals with pSS include cytoplasmic accumulation of lipid droplets and swollen mitochondria [12]. Mitochondria play a crucial role in cellular physiology, multiple signaling pathways, and cell metabolism. Moreover, their morphological changes can be contributing factors to various pathological symptoms observed in pSS, such as epithelial autophagy, and autoantibody expression.

2. Reduced Muscarinic Salivation Signaling

Muscarinic signaling plays a vital role in the functioning of acinar cells in the salivary glands, and alterations in this signaling pathway have been implicated in pSS. Muscarinic receptors are G protein–coupled receptors found in various tissues. They are primarily activated by the neurotransmitter acetylcholine and are involved in mediating the effects of the parasympathetic nervous system. When acetylcholine binds to muscarinic receptors, it initiates a series of intracellular signaling events that can have diverse physiological effects depending on the tissue and receptor subtype. There are five subtypes of muscarinic receptors, namely M1-M5, which are distributed in different tissues and cell types. Among these subtypes, the M3 receptor is primarily expressed in salivary glands and plays a crucial role in primary salivation. Activation of the acetylcholine–M3 receptor interaction induces phospholipase C activation, leading to the degradation of phosphatidylinositol 4,5-bisphosphate into inositol trisphosphate and diacylglycerol, which in turn results in an increased intracellular Ca^{2+} concentration. The increased cytosolic Ca^{2+} concentration opens apical chloride channels and basolateral potassium channels, facilitating primary saliva production [13]. Additionally, activation of the M3 receptor triggers the trafficking of aquaporin (AQP) 5 from the cytoplasm to the apical membrane, enabling rapid water transport across the cell membrane [14].

Studies have demonstrated a decrease in the expression levels of M3 receptors in the salivary glands of patients with pSS compared with healthy individuals. This reduction in M3 receptor expression can contribute to impaired glandular function and decreased saliva production, as observed in patients with pSS [15]. Furthermore, pSS is characterized by the presence of autoantibodies targeting M3 receptors, potentially affecting their function and exacerbating glandular dysfunction [14,16]. Moreover, intracellular signaling pathways downstream of muscarinic receptors in pSS can be dysregulated, leading to impaired secretion of fluid, electrolytes, and other components of saliva by acinar cells.

3. Aberrant Mucin Localization and Proinflammatory Cytokine Secretion

For normal saliva functioning, the composition of salivary proteins is important, in addition to water volume. Salivary proteins, including mucins, enzymes, antibodies, and immunoglobulins, as well as proline-rich proteins and statherin, serve different functions, and properties. Mucins, belonging to the mucin family are large, heavily glycosylated proteins. Salivary mucins are secreted from the apical pole of acinar cells and contribute to the viscoelastic properties of saliva, providing oral cavity lubrication, moistening, and protection. Changes in salivary mucins can affect oral health, as alterations in mucin composition and/or function may contribute to dry mouth (xerostomia), which leads to difficulties in chewing, swallowing, and increased susceptibility to dental caries and oral infections.

Changes in salivary mucins have been observed in Sjögren's syndrome, contributing to the characteristic dry mouth and other symptoms experienced by patients with the condition. Changes in salivary mucins in patients with Sjögren's syndrome are multifactorial and can be influenced by various underlying factors. including decreased mucin production, altered mucin composition, and abnormal mucin distribution, and clearance. Several studies have hypothesized changes in the amount or composition of mucins in the saliva of patients with pSS. However, most of these studies did not confirm significant differences compared with healthy individuals [17,18]. Instead, researchers found that the distribution of mucins, such as mucin-5B (MUC5B), MUC7, and MUC1, in the salivary gland acinar cells of patients with Sjögren's syndrome was altered compared with that in normal populations. In Sjögren's syndrome, the salivary mucin components MUC5B and MUC7 are localized adjacent to the apical pole [19,20]. Mislocalized mucins are partially transported outside the membrane, where they can activate toll-like receptor 4, resulting in autocrine production of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 [19]. Interestingly, an overload of MUC1 in the acinar

cells of patients with Sjögren's syndrome may induce an apoptosis-like phenotype [19,21]. Collectively, these findings suggest that mislocalized mucins can create an inflammatory environment in the salivary glands of patients with Sjögren's syndrome, leading to cellular stress, and even cell death.

4. Disorganized AQPs

AQPs, a family of membrane proteins that play a critical role in facilitating the movement of water and other small molecules across cell membranes, play a crucial role in SGACs by facilitating water transport across their membranes. Thirteen different isoforms of AQPs are known to exist [22]. In human salivary glands, AQP1 is expressed on myoepithelial cells, AQP3 is present within the basal membrane of acinar cells, and AQP5 is located in the apical membrane of acinar cells [23]. Reduced levels or altered distribution of AQPs can impair water transport and contribute to decreased saliva production, resulting in the characteristic dry mouth observed in pSS. Several studies have emphasized the importance of AQPs in Sjögren's syndrome. For example, decreased AQP1 expression and the presence of anti-AQP1 autoantibodies have been reported in the salivary glands of patients with Sjögren's syndrome [24,25]. However, AQP1 deficiency was found to have no observable effect on saliva production [26], and anti-AQP1 autoantibodies have not been associated with a reduced salivary flow rate [25]. Regarding AQP3, although its expression was found to increase and decrease in the apical and basolateral sides, respectively, of salivary gland acini in a Sjögren's syndrome group compared with a normal control group [27], it remains unclear whether this phenotype is a result or a cause of Sjögren's syndrome. Therefore, further studies are necessary to better understand the precise roles of AQP1 and AQP3 in salivary hypofunction occurring in patients with Sjögren's syndrome.

The role of AQP5 in SGACs under pSS is relatively well-defined. The presence of autoantibodies to AQP5 in the serum of patients with Sjögren's syndrome has been confirmed [28], and systematic studies have revealed the abnormal intracellular localization of AQP5 [29-31], including a study incorporating AQP5-targeted gene therapy in a Sjögren's syndrome animal model [32]. Typically, AQP5 is localized to the apical or luminal membranes of acinar cells in the salivary glands, where it facilitates the movement of water across these membranes. However, in Sjögren's syndrome, AQP5 can exhibit abnormal distribution patterns within the affected glands. In the acinar cells of patients with Sjögren's syndrome, the normal apical distribution of AQP5 is reduced and shifted toward the periphery, basal membrane, or into the cytoplasm [27,33]. This abnormal localization may be a consequence of the inflammatory process and immune cell infiltration in the glands. The mechanisms underlying the mislocalization of AQP5 in Sjögren's syndrome are not fully understood, but they are believed to involve various factors, including autoantibodies, and pro-inflammatory cytokines. Animal experiments have revealed that altered AQP5 protein levels may be related to the degree of inflammatory response [34]. Patients diagnosed with pSS exhibit the presence of major inflammatory cytokines, including type 1 interferons, IL-1β, interleukin-17, TNF-α, and B-cell activating factor [35-37]. Given that the activation of muscarinic and adrenergic receptors plays a primary role in the translocation of AQP5, the aberrant localization of AQP5 might be part of defective muscarinic M3 receptor signaling or altered intracellular protein interactions associated with AQP5.

FORKHEAD BOX O1 (FoxO1) AS a DIRECT REGULATOR OF AQP5

In our previous study entitled "Function of FoxO1 as a key regulating factor for AQP5", the authors provided insights into the decreased expression of AQP5 in the salivary gland of patients with Sjögren's syndrome [38]. FoxO1 is an abbreviation of Forkhead box protein O1, a protein that is well-known for its various physiological regulatory functions, including vascular growth, oxidative stress, and metabolism [39-41]. In the aforementioned study, the authors initially established a correlation between FoxO1 expression and decreased AQP5 gene and protein expression in the minor salivary glands of patients with Sjögren's syndrome. Subsequently, they confirmed these findings using rat submandibular gland cell line C6 in loss- and gain-of-function experiments. The authors found that FoxO1 can bind directly to the promoter region of AQP5, providing a clear

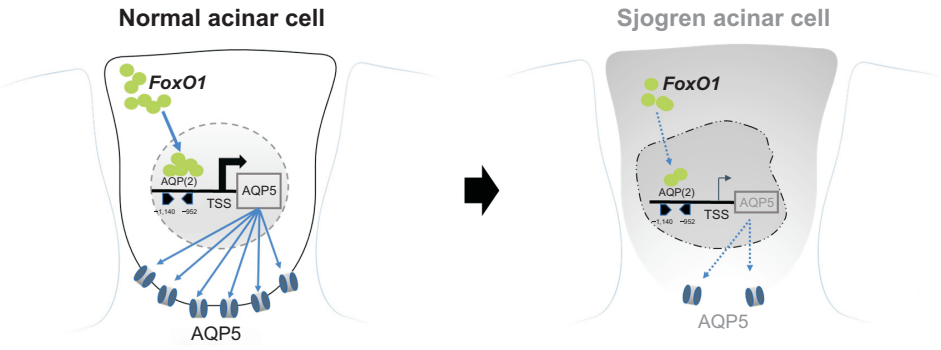

Fig. 2. Decreased FoxO1 expression directly affects the downregulation of AQP5 expression. AQP, aquaporin; FoxO1, forkhead box O1; TSS, transcription start site.

explanation for the reduced salivation observed in patients with Sjögren's syndrome independent of autoimmune inflammatory consequences. Their study is significant because it not only reconfirms the reduced expression of AQP5 in the salivary gland under Sjögren's syndrome but also reveals the novel role of FoxO1 as a direct upstream regulator associated with AQP5-mediated reduction in salivary secretion. The graphical abstract of this study is shown in Fig. 2.

CONCLUSION

Salivary gland dysfunction is a prevalent clinical manifestation of Sjögren's syndrome. While genetic factors predominantly influence susceptibility to the syndrome, it is crucial to acknowledge the involvement of various signaling pathways, systems, and processes in its disease progression. Although the relative significance of these factors during disease onset and progression remains unclear, dysregulation of acinar cell functional machinery is a key contributor to the homeostatic imbalance observed in pSS. This review emphasizes the pivotal role of SGACs, providing insights into their involvement not only as passive bystanders in immune-mediated organ failure but also as key mediators associated with disease initiation and progression.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets used in the current study are available from the corresponding author upon reasonable request.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) RS-2023-00208416.

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