Japanese Dental Science Review 60 (2024) 232–238

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Associations between metabolic disorders and Sjögren's disease

Chihiro Iwaya [a,b,1], Junichi Iwata [a,b,c,*,1]

[a] Department of Diagnostic & Biomedical Sciences, The University of Texas Health Science Center at Houston (UTHealth), School of Dentistry, Houston, Texas 77054, USA
[b] Center for Craniofacial Research, The University of Texas Health Science Center at Houston, School of Dentistry, Houston, TX 77054, USA
[c] MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX 77030, USA

ARTICLE INFO

Keywords:
Sjögren's disease
Cholesterol metabolism
Metabolic disorders
Autoimmune disorders

ABSTRACT

Sjögren's disease (SjD) is a systemic autoimmune disorder characterized by dry eyes and mouth caused by chronic inflammation and is often accompanied by various extra-glandular manifestations, including fatigue and diffuse pain. Although the pathogenesis of the disease remains elusive, several factors (e.g. environmental, genetic and hormonal factors, abnormal metabolic status) are associated with this condition. Accumulating evidence suggests a potential role of cholesterol metabolism in immune and non-immune modulation in various diseases. In this review, we summarize the current findings on the associations between cholesterol metabolism and SjD.

1. Introduction

A dysregulated cholesterol/lipid metabolism has been associated with various autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and SjD. For example, presence of atherosclerosis and an increased risk of cardiovascular mortality lead to a higher risk of RA [1]. Several other clinical findings suggest a link between autoimmune diseases and atherosclerosis/dyslipidemia [2–5]. In addition, increased serum triglycerides, as well as increased levels of very low-density lipoprotein (VLDL) cholesterol, have been reported in patients with SLE, while decreased high-density lipoprotein (HDL) cholesterol (known as 'good cholesterol') has been observed [6]. Interestingly, reduced serum cholesterol levels due to either diet-restricted cholesterol intake or treatment with statins, which suppress cholesterol synthesis but also elicit immunosuppressive effects, can improve the symptoms of autoimmune diseases [7–11]. These evidences clearly show that cholesterol metabolic issues are related to autoimmune diseases, and not just a coincidence. These findings obtained through human cohort studies are also supported by experiments in mice; hyperlipidemia and atherogenic dyslipidemia induce proinflammatory cytokine secretion by dendritic cells in mice, which is a key step of inflammatory responses in autoimmune diseases [12–14]. However, it remains largely unknown whether and how cholesterol metabolism plays a role in SjD.

Conversely, patients with autoimmune diseases often develop atherosclerosis [15]. Interestingly, metabolomics data in RA and primary SjD show apparent differences between these diseases [16], indicating that certain metabolites can become potential diagnostic markers for each autoimmune disease. Currently, there is a research gap in the contribution of abnormal metabolism(s) to the cause, activity, and progression of autoimmune diseases. In this review, we summarize the evidence showing the link between abnormal cholesterol metabolic status and SjD.

2. SjD characteristics

SjD is one of the most common autoimmune disorders, with a prevalence of 0.1—0.6 % in adults [17]. SjD has been known in the past as Sjögren's syndrome; however, since the symptoms are now well characterized, it was renamed to SjD [18]. Another complication in the classification and terminology of this disease is the definition of primary versus secondary SjD. It should be noted that primary SjD is distinct from secondary SjD given the absence of other autoimmune rheumatic diseases and predominance in peri- and post-menopausal women (average of 50 years of age at diagnosis). As defined by the American-European Consensus Group, primary SjD has been used for describing patients without any potentially associated diseases, and secondary SjD has been used for describing patients with potentially associated disease(s), such

* Correspondence to: 1941 East Road, BBS 4208, Houston, TX 77054, USA.
E-mail addresses: Junichi.Iwata@uth.tmc.edu, juniwata@umich.edu (J. Iwata).
[1] Current affliation: Department of Orthodontics and Pediatric Dentistry, University of Michigan School of Dentistry, Ann Arbor, MI 48109, USA.

https://doi.org/10.1016/j.jdsr.2024.06.002
Received 17 April 2024; Received in revised form 24 June 2024; Accepted 27 June 2024

as other well-defined connective diseases and/or autoimmune diseases, and presenting SjD-like symptoms (e.g. dry mouth and dry eyes) in the exocrine glands [19]. SjD is characterized by lymphocytic infiltrations, which are abundant in $CD4^+$ T cells, in the exocrine glands, mainly the salivary glands (SGs) and lacrimal glands (LGs). These lymphocytic infiltrations cause acinar cell death or changes in glandular epithelial cell morphology and characteristics or exocrine mechanisms, resulting in reduced saliva and tear production and oral and ocular dryness [17, 20, 21]. Some patients develop extra-glandular manifestations in multiple organs/tissues, such as the lung (e.g. pulmonary arterial hypertension, interstitial lung disease), joints (arthralgia), skin (e.g. xerosis cutis, pruritus, primary localized cutaneous nodular amyloidosis, annular erythema), nervous system (neurological symptoms), and kidney (e.g. interstitial nephritis, renal tubular acidosis) [22–24].

The diagnosis is based on a combination of symptoms (e.g. dryness of mouth/eye), physical examination (e.g. saliva flow test, biopsy of minor salivary glands on the lip), and serologic tests (e.g. detection of anti-Ro/SSA and anti-La/SSB antibodies) [17]. To date, due to lack of definite diagnostic marker(s) as well as progress marker(s) for SjD (there is no single test for SjD), the diagnosis takes an average of 2.8 years. In addition, some patients with other autoimmune diseases, such as SLE and RA, frequently develop SjD-like symptoms, called secondary SjD [25–29]. These conditions make it more complex to reach a diagnosis because there is no clear boundary between such diseases and each patient develops a wide variety of clinical symptoms at different degrees (Table 1). For example, one of the most widely used diagnostic markers, the anti-Ro/SSA and anti-La/SSB antibodies, are detectable only in approximately 40—70 % and 20—40 % of SjD patients, respectively [30–33]. Interestingly, the presence of anti-Ro/SSA autoantibody anti-correlates with serum total cholesterol levels, whereas the presence of anti-La/SSB autoantibody is strongly associated with lower serum HDL levels [34]. Early-onset SjD has unique clinical manifestations, such as elevated immunoglobulin levels, higher anti-Ro/SSA and anti-La/SSB positivity, and severe $CD4^+$ T cell lymphopenia [35]. On the other hand, SjD that is negative for both anti-Ro/SSA and anti-La/SSB antibodies is more frequent in men or patients with aggressive disease progression and presents a higher risk for interstitial lung disease [36]. SjD patients presenting anti-centromere antibody (ACA) show distinct characteristics [37–39]. For example, patients positive for ACA are less frequently positive for either anti-Ro/SSA antibody, anti-La/SSB antibody, rheumatoid factor (RF), or immunoglobulin levels than the ones negative for ACA. In addition, it is known that ACA-positive patients show lower disease activity, longer disease duration (more than 5 years), and less active humoral immune system [37–39]. Thus, there is an urgent need to identify novel biomarkers for diagnosis at the pre- or early stage of clinical onset, as well as novel therapeutic strategies for SjD. Currently, several autoantibodies (e.g. AQP5, M3R, ENO1, HMGB1) are being considered as new candidate biomarkers for the diagnosis of SjD [40, 41].

Table 1
Clinical features of SjD.

Clinical characteristics	Frequency (%) in SjD patients (Number of Patients)	References
Lymphocytic infiltration in the lacrimal and salivary glands	78 % (n = 229) and 79 % (n = 1010)	[42,43]
Keratoconjunctivitis sicca and xerostomia	38 % (n = 318), 89 % (n = 1343), and 53.8 % (n = 312)	[37, 44, 45]
Vaginal dryness	53 % (n = 33) and 56 % (n = 33)	[46,47]
Non-productive cough	41-50 % (n = 33)	[48–50]
Salivary gland swelling	30 % (n = 1343)	[44]
Systemic symptoms	Fatigue: 70 % (n = 120)	[51]
	Arthralgia: 48 % (n = 1010) and 94 % (n = 120)	[43,51]
Anti-nuclear antibodies	85 % (n = 1010), 68 % (n = 1343), and 72.4 % (n = 312)	[43–45]
Anti-Ro/SSA antibodies	52 % (n = 1010), 68 % (n = 1343), and 53.2 % (n = 312)	[43,44]
Anti-La/SSB antibodies	34 % (n = 1010), 36 % (n = 1343), and 18.9 % (n = 312)	[43–45]
Rheumatoid factor	48 % (n = 1010), 51 % (n = 1343), and 29.2 % (n = 312)	[43–45]
Anti-centromere antibody	14 % (n = 318) and 16 % (n = 62)	[38,39]

2.1. Cholesterol/lipid metabolism aberrations in SjD

Although the prevalence of abnormal metabolic conditions in patients with SjD varies between cohort studies, an accumulating number of studies support that there is a clear link between SjD and metabolic diseases, such as diabetes and cardiovascular disease [44, 52–54] (Table 2). For instance, a cohort study in the United Kingdom showed that hypertension (28–50 % vs 15.5–25.6 %, $P < 0.0001$) and hypertriglyceridemia (21 % vs 9.5 %, $P = 0.002$) are more prevalent in women with primary SjD (n = 538) compared to age-matched healthy women (n = 410) [55]. A cohort study in Germany showed that hypertension (73.8 % vs 38.2 %, $P < 0.001$) and hypercholesterinemia (55.7 % vs 23.9 %, $P < 0.001$) are significantly more prevalent in patients with primary SjD (n = 61) compared to sex- and age-matched control individuals (n = 251) [45]. A cohort study in Spain showed that there is a higher prevalence of hypertriglyceridemia (22 % vs 15 %, $P = 0.023$) in individuals with primary SjD (n = 312 including both sexes) than in controls (n = 312 including both sexes) [54]. Another cohort study in the European population revealed that hypercholesterolemia (30 % vs 23 %, $P < 0.001$) is more prevalent in women with primary SjD (n = 788) compared to healthy women (n = 4774), whereas the prevalence of hypertension was less associated with primary SjD (32 % vs 28 %, $P = 0.021$) [44]. In addition, there is a higher prevalence of dyslipidemia (abnormal amounts of lipids such as triglycerides, cholesterol, and/or phospholipids) in primary SjD (cohort study of women in Brazil, with 71 patients and 71 healthy control individuals) [56]. The prevalence of metabolic syndrome and diabetes is also higher in primary SjD (39 % vs 17 % in a cohort study involving women in Brazil and 27 % vs 13 % in a cohort study including both sexes in Spain, respectively) [54,56]. Thus, several cohort studies show significant associations between SjD and

Table 2
Metabolic disorders in SjD.

Laboratory measurements	Frequency (%) in SjD patients	Frequency (%) in healthy individuals	*P*-value	References
Obesity	11 % (n = 788)	21 % (n = 4774)	$P < 0.001$	[44]
	19.5 % (n = 200)	18.6 % (n = 200)	$P = 0.899$	[55]
Diabetes mellitus	4 % (n = 788)	7 % (n = 4774)	$P = 0.001$	[44]
	3 % (n = 200)	2 % (n = 200)	$P = 0.543$	[55]
	28 % (n = 254)	18 % (n = 254)	$P = 0.006$	[55]
Hypertension (WHO definition)	28 % (n = 200)	15.5 % (n = 200)	$P = 0.003$	[55]
Hypertension (NCEP definition)	50 % (n = 200)	25.6 % (n = 200)	$P < 0.0001$	[55]
Hypercholesterolemia	19 % (n = 200)	17.5 % (n = 200)	$P = 0.796$	[55] [44]
	30 % (n = 788)	23 % (n = 4774)	$P < 0.001$	
Hypercholesterinemia	55.7 % (n = 61)	23.9 % (n = 251)	$P < 0.001$	[52]
Hypertriglyceridemia	21 % (n = 200)	9.5 % (n = 200)	$P = 0.002$	[55]

NCEP, National Cholesterol Education Program; SjD, Sjogren's disease; WHO, World Health Organization.

abnormal metabolic conditions. A differentiated lipid serum profile has been reported in primary SjD (cohort study in women at the National Institute of Dental and Craniofacial Research (NIDCR) Sjogren's Syndrome Clinic in the US, with 46 patients and 12 healthy control individuals) [34], and a higher rate of subclinical atherosclerosis is significantly associated with primary SjD (cohort study including White Italian women, with 37 patients and 35 healthy control individuals) [57].

Interestingly, some clinical studies suggested that metabolic status may affect SjD activity and progression. For instance, patients with primary SjD showed higher frequency of hypertriglyceridemia (P = 0.002, 200 patients and 200 age-matched healthy control individuals) in the United Kingdom [55]. Among primary SjD, patients with hypertriglyceridemia (n = 42) showed a higher frequency of abnormal salivary flow ($P = 0.030$) and antinuclear antibody positivity ($P = 0.021$), a marker for immune system hyperactivity, compared to patients without hypertriglyceridemia (n = 158) [55]. In addition, in a cohort study in Brazil, patients with SjD and dyslipidemia (n = 56) showed higher levels of erythrocyte sedimentation rate ($P = 0.03$), which reflects a chronic inflammatory state, compared to patients with SjD but without abnormal lipid profiles (n = 17) [58]. However, as debated on various metabolic conditions, causative effects of high levels of serum cholesterol/lipid on SjD should be further studied with large-scale multi--populations cohort studies.

Aberrations in metabolic enzymes, not only in exocrine tissues but also in immune cells, are involved in SjD pathogenesis. For instance, *HUWE1*, an E3 ubiquitin ligase, is highly expressed in $CD4^+$ T cells in patients with SjD (the NCBI GEO database, 18 patients and 18 healthy control individuals) [59]. The inhibition of *Huwe1* reduced serum cholesterol levels and suppressed $CD4^+$ T cell activity in *NOD/ShiLtj* mice, a SjD model [59]. *CYP51A1/Cyp51*, a mitochondrial enzyme that catalyzes demethylation of lanosterol and dihydrolanosterol at the beginning of the Bloch and Kandutsch-Russell pathway in cholesterol biosynthesis, is specifically upregulated in $CD4^+$ T cells isolated from patients compared with middle-aged female controls, and in activated $CD4^+$ T cells isolated from mouse spleens compared with non-activated controls [60].

An altered lipid and cholesterol metabolism in SjD animal models suggests a relationship between inflammation and excessive cholesterol. Epithelial cells in the LGs of *NOD.H2*^{b} mice, a SjD model, show altered lipid metabolism, production of inflammasomes, and downregulated expression of genes related to cholesterol metabolism, suggesting that impairment of lipid metabolism and inflammasome formation are key factors for the pathogenesis and progression of the SjD-like phenotype in *NOD.H2*^{b} mice [61]. Treatment with ketoconazole of *NOD/ShiLti* mice, another SjD model, ameliorated SjD-like phenotypes, namely lymphoid infiltration into the SGs and reduced saliva flow rate, suggesting that excessive cholesterol is linked to SjD [60]. Interestingly, in *ApoE* deficient mice, a SLE model, simvastatin (a drug that suppresses cholesterol production) was able to reduce autoantibody production, lymphocyte proliferation, and atherosclerotic lesion formation at a dose lower than that needed to normalize serum cholesterol levels [62].

Patients with primary SjD and hypertriglyceridemia were more likely to show reduced salivary flow (95.2 % vs 81.3 %, $P = 0.003$) and positive antinuclear antibodies (90.6 % vs 70.6 %, $P = 0.02$) compared to sex- and age-matched healthy control individuals in a cohort study of women in United Kingdom (538 patients and 410 healthy control individuals) [55]. Consistent with these findings, the prevalence of primary SjD is higher in patients with hypercholesterolemia than in individuals with normal cholesterol levels [44, 63–65]. A population-based multicenter cohort study in Italy showed that individuals with hypercholesterolemia had a higher risk of SjD than the healthy control group ($P < 0.001$, 788 patients and 4774 healthy control subjects) [44]. Moreover, patients with primary SjD and metabolic syndrome showed higher scores in body mass index, as well as higher levels of serum cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, proinflammatory cytokine interleukin (IL) 6 production, and cooccurrence of hypertension or type II diabetes, in contrast to lower levels of B-cell activating factor (BAFF) expression, compared to primary SjD without metabolic diseases (cohort study including women in Brazil, 82 % White patients and 86 % White healthy control individuals, 28 patients with metabolic syndrome, and 43 patients without metabolic syndrome) [56]. Therefore, high fat/cholesterol diets and metabolic diseases are considered to be associated with SjD and hyposalivation [56, 63, 66, 67]; however, the precise role of cholesterol metabolism in the SGs, under physiological and pathological conditions, remains largely unknown.

Interestingly, some clinical reports suggest that statins, which are drugs that normalize cholesterol levels, may be beneficial for autoimmune diseases including SjD [68,69]. For example, statin use is associated with a lower risk of blepharitis [70] and inhibition of inflammatory response caused by anti-M_3 peptide IgG in SjD [71]. Since no prospective randomized trials have been conducted yet, there is a considerable debate about beneficial effects of statins on autoimmune diseases. Future studies will address this important question about the onset and potential therapeutic target for SjD.

2.2. Correlation between cholesterol metabolism aberrations and exocytosis defects in the salivary glands in SjD

An altered saliva content is a sign of major oral health issues [72,73]. For instance, saliva content is altered in individuals with metabolic diseases such as type II diabetes and obesity, who present oral health issues at higher frequency, including xerostomia [74,75]. Acinar cells in the SGs (submandibular, sublingual, and parotid glands and minor SGs) are responsible for the production and secretion of salivary protein components such as amylase (crucial for digestion), mucins (crucial for lubrication), and immunoglobulins (crucial for immunity) [76]. This secretion process can be stimulated by both sympathetic and parasympathetic nerves, although it is constitutively active at low levels in the absence of stimulation [77,78]. The secretion process called exocytosis includes secretory vesicle (SV) trafficking, docking, priming, and membrane fusion [78]. A failure in any step of exocytosis results in altered secretion of salivary proteins, leading to a failure in the digestion of foods, lubrication, prevention of infection (dental caries and periodontal diseases), and halitosis (bad breath) [74,75]. In addition, exosomes, which contain cytosolic and endosomal proteins, microRNAs, and autoantigens are released from acinar cells into the mucosal lumen [79–81]. Recent studies indicate that salivary protein secretion is altered in individuals with metabolic syndromes, type II diabetes, and obesity [82–84], suggesting a potential link and/or association between salivary protein secretion (including exocytosis and exosomal secretion) and an abnormal metabolism. Indeed, exocytosis defects and aberrant salivary protein secretion, as well as altered exosome contents, have been identified in acinar cells of the SGs in SjD patients and mouse models [85, 86].

Proteomics analysis and subsequent bioinformatic analyses using SG epithelial cells showed that cholesterol metabolism, as well as several basic metabolic pathways, is significantly upregulated in primary SjD. Interestingly, the bioinformatic analysis showed that proteins related to membrane trafficking, exosome-mediated transport, and exocytosis were significantly abundant, whereas proteins related to vesicle transport were significantly fewer in patients with SjD compared to patients who have xerostomia without matching the criteria for SjD [21]. These findings are supported by pathohistological investigations; for example, SNARE proteins (STX3, STX4, SNAP23, and VAMP8) are dislocated from the apical side to the basal side of SGs, and mucins are abnormally deposited in the extracellular matrix (ECM) in SjD [87].

The release of the vesicle contents from acinar cells is a Ca^{2+}-dependent process. Synaptotagmin-1 (SYT1), a transmembrane SV protein, acts as a Ca^{2+} sensor and initiates membrane fusion to open a pore. The expression of SYT1 at both mRNA and protein levels is

upregulated in labial SGs, and SYT1 colocalizes with STX4 at the basolateral membrane of acinar cells in primary SjD [88]. Three-dimensional (3D) cultures with acinar cells from human submandibular glands (SMGs) confirmed that *SYT1* overexpression can accelerate exocytosis, and TNFα stimulation alters cellular polarity so that SV secretion dislocates from the apical side to the basolateral side. In addition, serous acinar cells in patients with primary SjD accumulated MUC7-containing SVs throughout the cytoplasm and showed abnormal distribution of RAB3D from the apical side to the entire cytoplasm [89]. Other studies also showed that acinar cells in patients with SjD contain enlarged, accumulated SVs prior to the onset of overt SjD symptoms [85,90]. These dislocations are also observed in the LGs in male NOD mice, a SjD model [91]. Thus, defects in salivary protein secretion might be a dysfunction related to the onset of SjD.

There are some evidences that membrane cholesterol amount plays a crucial role in exocytosis. In primary rat lactotroph cultures, depletion of membrane cholesterol by methyl-β-cyclodextrin (MβCD) increases fusion pore conductance and pore radius, whereas high cholesterol level decreases them, suggesting that cholesterol amount affects exocytosis through the regulation of fusion pore size [92]. On the other hand, cholesterol can stabilize a fusion pore, which is formed by *v*-SNARE synaptobrevin/VAMP2, syntaxin-1A, and SNAP25, at the opening stage of exocytosis by altering membrane bending rigidity [93,94]. Moreover, in pancreatic beta cells, excessive cholesterol suppresses glucose-stimulated SV fusion via incomplete compound fusion (kiss-and-run fusion), which results in a decrease in insulin exocytosis [95]. Taken together, these findings suggest that excessive cholesterol may lead to abnormal SV fusion and exocytosis, which can trigger SjD (Fig. 1).

2.3. Mouse models for SjD

Since most patients with SjD are diagnosed at the late stages of the disease, the pathological changes occurring prior to clinical manifestations remain unclear. Therefore, animal models are essential to identify the pathogenic mechanism, especially at early stages of the disease (Fig. 2). Although substantial advancements have been made through the analysis of various mouse models [96], one of the current limitations is that the majority of mouse models for SjD develop SjD-like phenotypes due to mutation(s) in genes expressed in immune cells and alterations in the immune system [96,97]. Therefore, it is critical to develop new models for SjD without defects in immune cells.

We have recently reported that ectoderm-derived cell-specific conditional knockout mice for the *Atg7* and *Atg3* genes ($Atg7^{F/F}$;*K14-Cre* mice [hereafter *Atg7* cKO mice], and $Atg3^{F/F}$;*K14-Cre* mice [hereafter *Atg3* cKO mice]) show phenotypes that recapitulate primary SjD (e.g. immune cell infiltration, acinar cell death, hyposalivation, and presence of anti-Ro/SSA and anti-La/SSB antibodies) [98]. Interestingly, pro-inflammatory cytokines such as IL6, IL12, and granulocyte-macrophage colony-stimulating factor are significantly upregulated in the SMGs in these mutant mice, which is observed as early as inflammatory cell infiltration occurs. Mice with a deficiency in the exocytosis process [*Noc2* [99,100], *Rab3d* [101,102], *Rab27a* [102, 103], *Rab27b* [102,103], and *Vamp8* [104]] exhibit enlarged and accumulated SVs in the SGs and LGs and decreased total amount protein amount in saliva and tears. In agreement with these findings in mouse models, data from patients [85, 87, 89, 105] showed alterations in exocytosis in acinar cells (e.g. ectopic exocytosis, accumulation of SV contents in the ECM), which trigger inflammation and autoimmunity.

3. Conclusions

The secretion of salivary proteins is important for the maintenance of oral health. Individuals with metabolic syndromes show altered salivary protein content and have a higher risk of developing oral diseases [82–84]. The number of individuals with obesity and hypercholesterolemia, which contribute to the development of oral diseases, is increasing in the US; therefore, there is an urgent need to take measures against oral diseases caused by these metabolic syndromes. In this review, we summarized the current knowledge on the associations between cholesterol metabolism aberrations and SjD, as well as potential cellular mechanisms in SjD. The identification of the underlying mechanism(s) will provide new insights into the role of cholesterol metabolism in SjD pathogenesis.

Ethic approval and consent to participate

Not applicable.

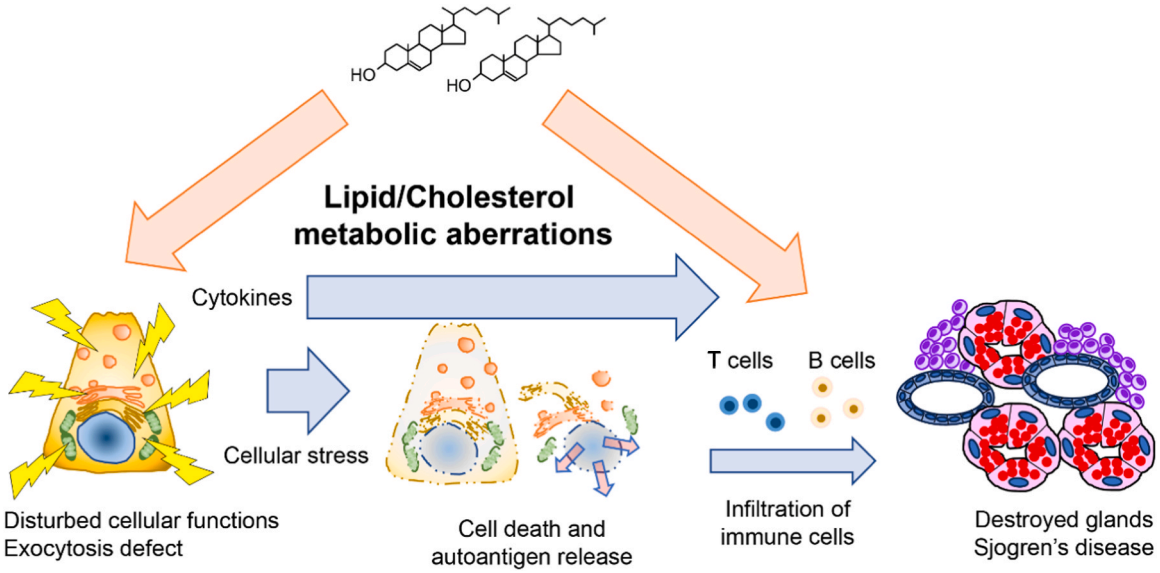

Fig. 1. Potential mechanism for SjD related to lipid/cholesterol metabolic aberrations. Cholesterol overload induces both cellular disfunctions and immune cell activation. The cellular disfunctions result in cell death, leading to autoantigen release. Inflammation in the glands will destroy acinar and duct cells as often seen in the late/severe stage of Sjogren's disease.

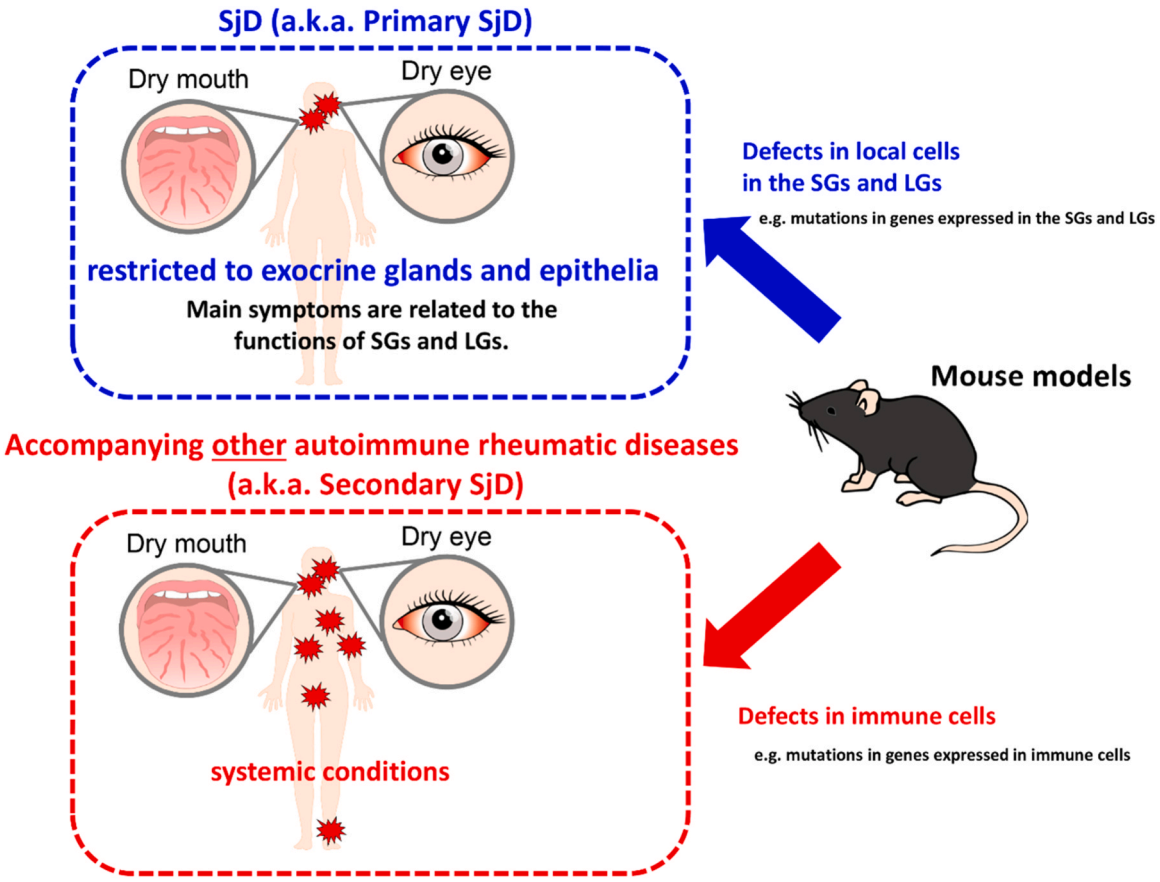

Fig. 2. Classification of SjD and representative mouse models for primary and secondary SjD. Clinical symptoms of SjD are restricted to exocrine glands and epithelium; main symptoms are related to the dysfunctions of SGs and LGs. Mouse models with SG/LG tissue-specific mutations in genes or with mutations in genes related to immune responses are useful to study SjD (a.k.a. primary SjD). Clinically, SjD often accompanies with other autoimmune diseases; these conditions used to be stated as secondary SjD. Since systemic symptoms exist, it may be mainly caused by abnormal immune responses. Mouse models with mutations in genes related to immune system are useful to study these conditions.

Authors' contributions

Prepared the manuscript: CI and JI. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Funding

This study was supported by a faculty fund from UTHealth School of Dentistry to JI. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interests

All the authors hereby certify that there is no conflict of interest of financial nature.

Data Availability

Not applicable.

References

[1] McGrath CM, Young SP. Lipid and metabolic changes in rheumatoid arthritis. Curr Rheuma Rep 2015;17:57.
[2] Ryu H, Kim J, Kim D, Lee JE, Chung Y. Cellular and molecular links between autoimmunity and lipid metabolism. Mol Cells 2019;42:747–54.
[3] Dhawan UK, Margraf A, Lech M, Subramanian M. Hypercholesterolemia promotes autoantibody production and a lupus-like pathology via decreased DNase-mediated clearance of DNA. J Cell Mol Med 2022;26:5267–76.
[4] Huang S, et al. Dyslipidemia is associated with inflammation and organ involvement in systemic lupus erythematosus. Clin Rheuma 2023;42:1565–72.
[5] Robinson G, Pineda-Torra I, Ciurtin C, Jury EC. Lipid metabolism in autoimmune rheumatic disease: implications for modern and conventional therapies. J Clin Invest 2022;132.
[6] Hodis HN, Quismorio Jr FP, Wickham E, Blankenhorn DH. The lipid, lipoprotein, and apolipoprotein effects of hydroxychloroquine in patients with systemic lupus erythematosus. J Rheuma 1993;20:661–5.
[7] Aktas O, et al. Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin. J Exp Med 2003;197:725–33.
[8] Youssef S, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 2002;420:78–84.
[9] Ghazizadeh R, Tosa M, Ghazizadeh M. Clinical improvement in psoriasis with treatment of associated hyperlipidemia. Am J Med Sci 2011;341:394–8.
[10] Roman MJ, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2399–406.
[11] Yu HH, et al. Statin reduces mortality and morbidity in systemic lupus erythematosus patients with hyperlipidemia: A nationwide population-based cohort study. Atherosclerosis 2015;243:11–8.
[12] Reynolds CM, et al. Dietary saturated fatty acids prime the NLRP3 inflammasome via TLR4 in dendritic cells-implications for diet-induced insulin resistance. Mol Nutr Food Res 2012;56:1212–22.
[13] Westerterp M, et al. Cholesterol Accumulation in Dendritic Cells Links the Inflammasome to Acquired Immunity. e1296 Cell Metab 2017;25:1294–304. e1296.
[14] Ryu H, et al. Atherogenic dyslipidemia promotes autoimmune follicular helper T cell responses via IL-27. Nat Immunol 2018;19:583–93.
[15] Sanjadi M, et al. Atherosclerosis and autoimmunity: a growing relationship. Int J Rheum Dis 2018;21:908–21.

[16] Li J, et al. LC-MS-based serum metabolomics reveals a distinctive signature in patients with rheumatoid arthritis. Clin Rheuma 2018;37:1493–502.
[17] Mariette X, Criswell LA. Primary Sjogren's Syndrome. N Engl J Med 2018;378:931–9.
[18] Baer AN, Hammitt KM. Sjogren's Disease, Not Syndrome. Arthritis Rheumatol 2021;73:1347–8.
[19] Vitali C, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
[20] Cortes-Troncoso J, et al. T cell exosome-derived miR-142-3p impairs glandular cell function in Sjogren's syndrome. JCI Insight 2020;5.
[21] Katsiougiannis S, et al. Salivary gland epithelial cell in Sjogren's syndrome: Metabolic shift and altered mitochondrial morphology toward an innate immune cell function. J Autoimmun 2023;136:103014.
[22] Fox RI. Sjogren's syndrome. Lancet 2005;366:321–31.
[23] Carvajal Alegria G, et al. Epidemiology of neurological manifestations in Sjogren's syndrome: data from the French ASSESS Cohort. RMD Open 2016;2:e000179.
[24] Llamas-Molina JM, Velasco-Amador JP, De la Torre-Gomar FJ, Carrero-Castano A, Ruiz-Villaverde R. Localized Cutaneous Nodular Amyloidosis: A Specific Cutaneous Manifestation of Sjogren's Syndrome. Int J Mol Sci 2023;24.
[25] Rasmussen A, et al. Previous diagnosis of Sjogren's Syndrome as rheumatoid arthritis or systemic lupus erythematosus. Rheumatology 2016;55:1195–201.
[26] Qin B, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:1983–9.
[27] Pasoto SG, Adriano de Oliveira Martins V, Bonfa E. Sjogren's syndrome and systemic lupus erythematosus: links and risks. Open Access Rheuma: Res Rev 2019;11:33–45.
[28] Ibanez-Cabellos JS, Seco-Cervera M, Osca-Verdegal R, Pallardo FV, Garcia-Gimenez JL. Epigenetic Regulation in the Pathogenesis of Sjogren Syndrome and Rheumatoid Arthritis. Front Genet 2019;10:1104.
[29] Oliveira HF, et al. Serologic profile and clinical markers of Sjogren syndrome in patients with rheumatoid arthritis. Oral Surg, Oral Med, Oral Pathol Oral Radiol 2015;119:628–35.
[30] Toda I. Autoantigens and Sjogren syndrome. Cornea 2002;21:S13–6.
[31] Chen W, Cao H, Lin J, Olsen N, Zheng SG. Biomarkers for primary Sjogren's syndrome. Genom, Proteom Bioinforma 2015;13:219–23.
[32] Fayyaz A, Kurien BT, Scofield RH. Autoantibodies in Sjogren's syndrome. Rheum Dis Clin North Am 2016;42:419–34.
[33] Baer AN, Walitt B. Sjogren syndrome and other causes of sicca in older adults. Clin Geriatr Med 2017;33:87–103.
[34] Lodde BM, et al. Serum lipid levels in Sjogren's syndrome. Rheumatology 2006;45:481–4.
[35] Wei L, et al. Patients with early-onset primary Sjogren's syndrome have distinctive clinical manifestations and circulating lymphocyte profiles. Rheumatology 2022;61:597–605.
[36] Chen J, et al. Anti-SSA/SSB-negative primary Sjogren's syndrome showing different clinical phenotypes: a retrospective study of 934 cases. Adv Rheuma 2023;63:21.
[37] Liu Y, et al. Anticentromere antibody positive patients with primary Sjogren's syndrome have distinctive clinical and immunological characteristics. Clin Exp Rheuma 2023. https://doi.org/10.55563/clinexprheumatol/o3pxq0.
[38] Park Y, et al. Clinical influences of anticentromere antibody on primary Sjogren's syndrome in a prospective Korean cohort. Korean J Intern Med 2021;36:1492–503.
[39] Nakamura H, et al. Anti-centromere antibody-seropositive Sjogren's syndrome differs from conventional subgroup in clinical and pathological study. BMC Musculoskelet Disord 2010;11:140.
[40] Chen M, et al. Anti-HMGB1 antibody is a potential characteristic autoantibody for Sjogren's syndrome. Sci Rep 2022;12:6020.
[41] He J, Jiang J, Baumgart K. Candidate autoantibodies for primary Sjogren's syndrome: where are they now? Clin Exp Rheuma 2022;40:2387–94.
[42] Sharma R, et al. Sjogren Syndrome without Focal Lymphocytic Infiltration of the Salivary Glands. J Rheuma 2020;47:394–9.
[43] Ramos-Casals M, et al. Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine 2008;87:210–9.
[44] Bartoloni E, et al. Cardiovascular disease risk burden in primary Sjogren's syndrome: results of a population-based multicentre cohort study. J Intern Med 2015;278:185–92.
[45] Zippel CL, et al. Premature stroke and cardiovascular risk in primary Sjogren's syndrome. Front Cardiovasc Med 2022;9:1048684.
[46] Maddali Bongi S, Del Rosso A, Orlandi M, Matucci-Cerinic M. Gynaecological symptoms and sexual disability in women with primary Sjogren's syndrome and sicca syndrome. Clin Exp Rheuma 2013;31:683–90.
[47] Haga HJ, Gjesdal CG, Irgens LM, Ostensen M. Reproduction and gynaecological manifestations in women with primary Sjogren's syndrome: a case-control study. Scand J Rheuma 2005;34:45–8.
[48] Papiris SA, et al. Lung involvement in primary Sjogren's syndrome is mainly related to the small airway disease. Ann Rheum Dis 1999;58:61–4.
[49] Mialon P, et al. A longitudinal study of lung impairment in patients with primary Sjogren's syndrome. Clin Exp Rheuma 1997;15:349–54.
[50] Bellido-Casado J, et al. Bronchial inflammation, respiratory symptoms and lung function in Primary Sjogren's syndrome. Arch Bronc– 2011;47:330–4.
[51] Aksoy A, et al. Increased Frequency of Hand Osteoarthritis in Patients with Primary Sjogren Syndrome Compared with Systemic Lupus Erythematosus. J Rheuma 2016;43:1068–71.
[52] Robinson CP, et al. Elevated levels of cysteine protease activity in saliva and salivary glands of the nonobese diabetic (NOD) mouse model for Sjogren syndrome. Proc Natl Acad Sci USA 1997;94:5767–71.
[53] Binder A, Maddison PJ, Skinner P, Kurtz A, Isenberg DA. Sjogren's syndrome: association with type-1 diabetes mellitus. *British journal of*. rheumatology 1989;28:518–20.
[54] Perez-De-Lis M, et al. Cardiovascular risk factors in primary Sjogren's syndrome: a case-control study in 624 patients. Lupus 2010;19:941–8.
[55] Juarez M, et al. Cardiovascular risk factors in women with primary Sjogren's syndrome: United Kingdom primary Sjogren's syndrome registry results. Arthritis care Res 2014;66:757–64.
[56] Augusto KL, et al. Metabolic syndrome in Sjogren's syndrome patients: a relevant concern for clinical monitoring. Clin Rheuma 2016;35:639–47.
[57] Vaudo G, et al. Precocious intima-media thickening in patients with primary Sjogren's syndrome. Arthritis Rheum 2005;52:3890–7.
[58] Cruz W, et al. Is there a link between inflammation and abnormal lipoprotein profile in Sjogren's syndrome? Jt Bone Spine 2010;77:229–31.
[59] Yin J, et al. HECT, UBA and WWE domain containing 1 represses cholesterol efflux during CD4(+) T cell activation in Sjogren's syndrome. Front Pharm 2023;14:1191692.
[60] Yin J, et al. CYP51-mediated cholesterol biosynthesis is required for the proliferation of CD4(+) T cells in Sjogren's syndrome. Clin Exp Med 2022. https://doi.org/10.1007/s10238-022-00939-5.
[61] Delcroix V, et al. Lacrimal Gland Epithelial Cells Shape Immune Responses through the Modulation of Inflammasomes and Lipid Metabolism. Int J Mol Sci 2023;24.
[62] Aprahamian T, et al. Simvastatin treatment ameliorates autoimmune disease associated with accelerated atherosclerosis in a murine lupus model. J Immunol 2006;177:3028–34.
[63] Ramos-Casals M, et al. High prevalence of serum metabolic alterations in primary Sjogren's syndrome: influence on clinical and immunological expression. J Rheuma 2007;34:754–61.
[64] Kaltreider HB, Talal N. Bilateral parotid gland enlargement and hyperlipoproteinemia. Jama 1969;210:2067–70.
[65] Goldman JA, Julian EH. Pseudo-Sjogren syndrome with hyperlipoproteinemia. Jama 1977;237:1582–4.
[66] Carramolino-Cuellar E, et al. Salivary flow and xerostomia in patients with type 2 diabetes. J Oral Pathol Med: Publ Int Assoc Oral Pathol Am Acad Oral Pathol 2018;47:526–30.
[67] Shikama Y, Kudo Y, Ishimaru N, Funaki M. Potential role of free fatty acids in the pathogenesis of periodontitis and primary Sjogren's Syndrome. Int J Mol Sci 2017;18.
[68] Gurevich VS, Shovman O, Slutzky L, Meroni PL, Shoenfeld Y. Statins and autoimmune diseases. Autoimmun Rev 2005;4:123–9.
[69] Riboldi P, Gerosa M, Meroni PL. Statins and autoimmune diseases. Lupus 2005;14:765–8.
[70] Feng KM, Chung CH, Chen YH, Chien WC, Chien KH. Statin Use Is Associated With a Lower Risk of Blepharitis: A Population-Based Study. Front Med (Lausanne) 2022;9:820119.
[71] Reina S, Passafaro D, Sterin-Borda L, Borda E. Atorvastatin inhibits the inflammatory response caused by anti-M(3) peptide IgG in patients with primary Sjogren's syndrome. Inflammopharmacology 2012;20:267–75.
[72] Piombino P, et al. Saliva from obese individuals suppresses the release of aroma compounds from wine. PloS One 2014;9:e85611.
[73] Vors C, et al. Salivary composition in obese vs normal-weight subjects: towards a role in postprandial lipid metabolism? Int J Obes 2015;39:1425–8.
[74] Javaid MA, Ahmed AS, Durand R, Tran SD. Saliva as a diagnostic tool for oral and systemic diseases. J Oral Biol Craniofacial Res 2016;6:66–75.
[75] Liu J, Duan Y. Saliva: a potential media for disease diagnostics and monitoring. Oral Oncol 2012;48:569–77.
[76] Wilmarth PA, et al. Two-dimensional liquid chromatography study of the human whole saliva proteome. J Proteome Res 2004;3:1017–23.
[77] Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. Auton Neurosci 2007;133:3–18.
[78] Ishikawa Y, et al. Water channels and zymogen granules in salivary glands. J Pharm Sci 2006;100:495–512.
[79] Hayashi T, Hoffman MP. Exosomal microRNA communication between tissues during organogenesis. RNA Biol 2017;14:1683–9.
[80] Gonzalez-Begne M, et al. Proteomic analysis of human parotid gland exosomes by multidimensional protein identification technology (MudPIT). J Proteome Res 2009;8:1304–14.
[81] Kapsogeorgou EK, Abu-Helu RF, Moutsopoulos HM, Manoussakis MN. Salivary gland epithelial cell exosomes: a source of autoantigenic ribonucleoproteins. Arthritis Rheum 2005;52:1517–21.
[82] Bencharit S, et al. Salivary proteins associated with hyperglycemia in diabetes: a proteomic analysis. Mol Biosyst 2013;9:2785–97.
[83] Rao PV, et al. Proteomic identification of salivary biomarkers of type-2 diabetes. J Proteome Res 2009;8:239–45.
[84] Panchbhai AS, Degwekar SS, Bhowte RR. Estimation of salivary glucose, salivary amylase, salivary total protein and salivary flow rate in diabetics in India. J Oral Sci 2010;52:359–68.
[85] Barrera MJ, et al. Sjogren's syndrome and the epithelial target: a comprehensive review. J Autoimmun 2013;42:7–18.
[86] Castro I, et al. Aberrant MUC1 accumulation in salivary glands of Sjogren's syndrome patients is reversed by TUDCA in vitro. Rheumatology 2019. https://doi.org/10.1093/rheumatology/kez316.

[87] Barrera MJ, et al. Aberrant localization of fusion receptors involved in regulated exocytosis in salivary glands of Sjogren's syndrome patients is linked to ectopic mucin secretion. J Autoimmun 2012;39:83–92.
[88] Cortes J, et al. Synaptotagmin-1 overexpression under inflammatory conditions affects secretion in salivary glands from Sjogren's syndrome patients. J Autoimmun 2019;97:88–99.
[89] Bahamondes V, et al. Changes in Rab3D expression and distribution in the acini of Sjogren's syndrome patients are associated with loss of cell polarity and secretory dysfunction. Arthritis Rheum 2011;63:3126–35.
[90] Castro I, et al. Oral dryness in Sjogren's syndrome patients. Not just a question of water. Autoimmun Rev 2013;12:567–74.
[91] da Costa SR, et al. Male NOD mouse external lacrimal glands exhibit profound changes in the exocytotic pathway early in postnatal development. Exp Eye Res 2006;82:33–45.
[92] Rituper B, et al. Vesicle cholesterol controls exocytotic fusion pore. Cell Calcium 2022;101:102503.
[93] Wu L, Courtney KC, Chapman ER. Cholesterol stabilizes recombinant exocytic fusion pores by altering membrane bending rigidity. Biophys J 2021;120: 1367–77.
[94] Stratton BS, et al. Cholesterol Increases the Openness of SNARE-Mediated Flickering Fusion Pores. Biophys J 2016;110:1538–50.
[95] Xu Y, Toomre DK, Bogan JS, Hao M. Excess cholesterol inhibits glucose-stimulated fusion pore dynamics in insulin exocytosis. J Cell Mol Med 2017;21: 2950–62.
[96] Park YS, Gauna AE, Cha S. Mouse Models of Primary Sjogren's Syndrome. Curr Pharm Des 2015;21:2350–64.
[97] Tanaka Y, et al. Increased Indoleamine 2,3-dioxygenase levels at the onset of Sjogren's syndrome in SATB1-conditional knockout mice. Int J Mol Sci 2021;22.
[98] Suzuki A, et al. Impaired GATE16-mediated exocytosis in exocrine tissues causes Sjogren's syndrome-like exocrinopathy. Cell Mol life Sci: CMLS 2022;79:307.
[99] Cheviet S, Waselle L, Regazzi R. Noc-king out exocrine and endocrine secretion. Trends Cell Biol 2004;14:525–8.
[100] Matsumoto M, et al. Noc2 is essential in normal regulation of exocytosis in endocrine and exocrine cells. Proc Natl Acad Sci USA 2004;101:8313–8.
[101] Riedel D, et al. Rab3D is not required for exocrine exocytosis but for maintenance of normally sized secretory granules. Mol Cell Biol 2002;22:6487–97.
[102] Meng Z, et al. Imbalanced Rab3D versus Rab27 increases cathepsin S secretion from lacrimal acini in a mouse model of Sjogren's Syndrome. Am J Physiol Cell Physiol 2016;310:C942–54.
[103] Chiang L, et al. Rab27b regulates exocytosis of secretory vesicles in acinar epithelial cells from the lacrimal gland. Am J Physiol Cell Physiol 2011;301: C507–21.
[104] Wang CC, et al. VAMP8/endobrevin as a general vesicular SNARE for regulated exocytosis of the exocrine system. Mol Biol Cell 2007;18:1056–63.
[105] Sreebny L, Zhu WX. Whole saliva and the diagnosis of Sjogren's syndrome: an evaluation of patients who complain of dry mouth and dry eyes. Part 1: Screening tests. Gerodontology 1996;13:35–43.