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REVIEW

Lipid Metabolism: An Emerging Player in Sjögren's Syndrome

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Abstract

Sjögren's syndrome (SS) is a chronic autoimmune disorder that primarily affects the exocrine glands. Due to the intricate nature of the disease progression, the exact mechanisms underlying SS are not completely understood. Recent research has highlighted the complex interplay between immune dysregulation and metabolic abnormalities in inflammatory diseases. Notably, lipid metabolism has emerged as a crucial factor in the modulation of immune function and the progression of autoimmune diseases, including SS. This review explores the prevalence of dyslipidemia in SS, emphasizing its role in the onset, progression, and prognosis of the disease. We specifically described the impact of altered lipid metabolism in exocrine glands and its association with disease-specific features, including inflammation and glandular dysfunction. Additionally, we discussed the potential clinical implications of lipid metabolism regulation, including the role of polyunsaturated fatty acids (PUFAs) and their deficits in SS pathogenesis. By identifying lipid metabolism as a promising therapeutic target, this review highlights the need for further research into lipid-based interventions for the management of SS.

Keywords Sjögren's syndrome · Lipid metabolism · Dyslipidemia · Metabolomics · Inflammation

Introduction

Sjögren's syndrome (SS) is the second most prevalent autoimmune disorder [1], exhibiting a significant female predominance, mainly among perimenopausal women [2, 3]. It is characterized by persistent chronic inflammation and an elevated immune response that damages the exocrine glands, especially the salivary and lacrimal glands, resulting in symptoms such as dry mouth and dry eyes [4, 5]. Clinically, SS is classified as primary Sjögren's syndrome (pSS) when it occurs in isolation. Conversely, when SS is associated with other autoimmune disorders, it is referred to as secondary Sjögren's syndrome (sSS) [6]. In addition to the involvement of the exocrine gland, SS can also present with metabolic syndrome (MetS) and systemic manifestations, including cardiovascular dysfunction, neuropathy, and pulmonary complications [7, 8].

MetS, which consists of multiple cardiovascular risk factors [9], including hypertension, diabetes, obesity, and dyslipidemia, is more common in patients with pSS [10]. Notably, pSS patients with MetS exhibit higher body mass index (BMI), body fat mass, and waist circumference, reflecting central obesity. These patients also showed elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides [11], indicating the link between lipid metabolism dysregulation and increased cardiovascular risk in pSS patients. Besides, obesity has also been identified as a major environmental factor contributing to the development and progression of autoimmune diseases, including SS [11]. Studies show that higher BMI is associated

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with increased Routine Assessment of Patient Index Data 3 (RAPID3) scores, suggesting that obesity may exacerbate disease severity in SS patients [12].

Lipids are essential metabolic cues, which, under normal physiological conditions, serve as vital energy sources, structural components of cell membranes, and signaling molecules that regulate various physiological processes [13]. For instance, cholesterol in the cytoplasmic membrane is a fundamental constituent of the lipid raft [14, 15]. However, under pathological conditions, lipids and their metabolites are necessary for activation, function, and differentiation, thereby playing a critical role in the inflammatory processes [16, 17]. They influence the immune system stability through various mechanisms, including Toll-like receptor (TLR) stimulation, oxidative stress promotion, endothelial cell damage, and modulation of hormone and growth factor secretion. These mechanisms ultimately regulate the pathogenesis of autoimmune diseases [18–21]. Although the precise etiology of SS remains unclear, recent technological advancements have highlighted the critical role of lipid metabolism and dyslipidemia in the development of SS, offering new insights into its pathogenesis [22].

Current research on lipid metabolism in autoimmune conditions, particularly SS, has primarily focused on the roles of circulating lipoproteins, fatty acids (FAs), and lipid mediators in disease progression. Dyslipidemia, a very common metabolic disorder associated with SS, appears to correlate with clinical symptoms and disease activity. Case studies from various regions consistently demonstrated a decrease in high-density lipoprotein (HDL) cholesterol, which correlates with elevated serum markers that reflect disease activity, such as immunoglobulin G (IgG) and anti-SSA/SSB antibodies. Additionally, increased levels of total cholesterol (TC), LDL-C, and triglycerides (TGs) are frequently observed in SS patients, further supporting the association of lipid metabolism and dyslipidemia with SS pathogenesis [23–26]. Additionally, research on lipid mediators in SS has indicated that serum levels of pro-inflammatory adipokines, including adiponectin and resistin, were elevated in pSS patients [10]. Changes in the local lipid metabolism of exocrine glands are associated with inflammatory damage and are likely to serve as initial risk factors for autoimmune-mediated destruction [27]. Meanwhile, drugs targeting lipid metabolism and lipid mediators, such as polyunsaturated fatty acids (PUFAs), fibrate, agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ), or liver X receptors (LXRs), are considered to have potential therapeutic effects in managing autoimmune conditions like SS [28].

Given the growing body of research on lipid metabolism in SS, it is clear that lipid metabolic disorders play a critical role in the pathogenesis of SS. This review aims to explore the involvement of lipid metabolism disorders in the pathogenesis and progression of SS, with a particular focus on the advancements related to serum lipid profiles and lipid metabolism within salivary and lacrimal gland tissues, along with their underlying mechanisms. Furthermore, we discuss the potential clinical benefits of regulating lipid metabolism as a therapeutic approach for SS. Overall, this seeks to enhance our understanding of SS from the perspective of lipid metabolism and facilitate the development of new therapeutic strategies.

The Pathogenesis of Sjogren's Syndrome

The pathogenesis of SS is intricate and involves genetic predispositions, environmental influences, and immune system activation. Although research continues to explore the exact triggers and mechanisms involved in SS pathogenesis, advances in genetic studies have provided significant insights into its development. Though the number of genome-wide genetic variations identified in SS remains relatively low, a genome-wide association study (GWAS) has identified some of the genetic factors associated with SS [29]. These genetic variants are primarily associated with genes involved in TLR signaling, interferon response pathways, lymphocyte homeostasis, and antigen presentation processes, which are crucial in the pathogenesis of SS [30].

The environmental risk factors also play a key role in the onset and progression of pSS. These include infection, especially Epstein-Barr (EB) virus infection, vitamin D deficiency, stress, smoking, and silicone breast implants [31]. In women, pSS is most commonly diagnosed postmenopause, possibly due to reduced estrogen levels. Viruses affect the immune system through various mechanisms, including molecular mimicry, bystander activation, production of superantigen proteins, or programming to produce viral cytokines similar to host cytokines [32]. Although the causal relationship between EB virus infection and SS is not yet clear in current research, most studies support that the EB virus may be involved in the first stage of immune tolerance failure [33].

The prevailing hypothesis regarding the pathogenesis of SS posits that environmental risk factors, such as viral infections, initiate the activation of exocrine gland epithelial cells in genetically predisposed individuals. This activation triggers a cascade that engages the innate immune system, ultimately leading to a robust interaction between innate and adaptive immune cells [34]. In women with estrogen deficiency, a reduction in dihydrotestosterone (DHT) levels, which normally protect acinar cells in the exocrine glands, can further exacerbate the autoimmune inflammatory response [35]. Under the influence of genetic and environmental risk factors, dysfunctional exocrine glandular epithelial cells release pro-inflammatory cytokines, resulting in immune cell infiltration. Type I interferon (IFN-α) is

believed to play a critical role in SS pathogenesis, with plasmacytoid dendritic cells (pDCs) being the main producers of IFN-α. These cells, in turn, promote T lymphocyte differentiation and function as antigen-presenting cells in the early stages of the disease [36]. Necrotic or apoptotic exocrine glandular cells, alongside autoantibodies targeting RNA-binding proteins, activate specific TLRs on pDCs, leading to increased IFN-α production. Early in SS, $CD4^+$ T cells are the primary contributors to lymphocyte infiltration in the exocrine glands [37]. Additionally, an imbalance between Th17 cells (which are excessively active) and regulatory T (Treg) cells (which are insufficient) significantly contributes to disease progression [38]. B cells, overactivated in SS, produce autoantibodies against SSA and SSB, driving the formation of lymphocytic sialadenitis and ectopic germinal centers [39].

Dyslipidemia and Autoimmune Diseases

Dyslipidemia, characterized by elevated TC, TGs, and low-density lipoproteins (LDLs), or decreased HDL, has been frequently observed in individuals with autoimmune diseases [40, 41]. Research suggests that lipid metabolism disorders significantly influence the onset and progression of autoimmune conditions through various mechanisms [42–44]. Dyslipidemia affects immune cell activation, particularly T and B cells, and systemic metabolic factors such as leptin and adiponectin can either promote or inhibit inflammatory processes. Furthermore, lipid accumulation induces tissue damage, triggering immune responses that exacerbate autoimmune disease activity. A meta-analysis has shown that low HDL cholesterol levels and hypercholesterolemia are associated with an increased risk of rheumatoid arthritis (RA) [45]. In models of systemic lupus erythematosus (SLE), hyperlipidemia promotes IL-27 production, which, in turn, drives disease progression [46]. In animal models of psoriasis, hyperlipidemia increases interleukin-6 (IL-6) production by $CD1b^+$ dendritic cells, which stimulates autoreactive T cells to produce IL-17A, further aggravating the condition [47]. Additionally, dyslipidemia is often linked with elevated levels of systemic inflammatory markers such as tumor necrosis factor-β (TNF-β), IL-6, and high-sensitivity C-reactive protein (hs-CRP), reinforcing its association with inflammatory processes [48]. PUFA supplementation has been proposed as a potential therapeutic approach for various inflammatory autoimmune diseases, including RA [49], SLE [50], and psoriasis. Notably, excessive lipid intake can increase mitochondrial β-oxidation in B cells, promoting their maturation and accelerating the production of autoantibodies, particularly in SLE [51]. Given that SS shares numerous clinical and pathophysiological features with other autoimmune diseases, particularly SLE and RA, the role of lipid metabolism in SS pathogenesis warrants further investigation [52]. Evidence suggests that abnormal lipid metabolism is frequently observed in autoimmune diseases, underscoring its potential involvement in disease development.

Abnormalities of Lipid Metabolism in SS

Dyslipidemia in SS

The relationship between dyslipidemia and pSS was first explored in 2005 by Lodde et al. [23], who conducted a serum lipid profiling study of pSS patients. Subsequent research consistently demonstrates that pSS patients exhibit a higher incidence of dyslipidemia compared to the general population [23–26, 53–59] (Table 1). However, variations in the serum lipid profiles of SS patients across studies are likely influenced by factors such as racial differences, socioeconomic status, sample diversity, and study size. Furthermore, dyslipidemia in pSS has been associated with several demographic factors, including gender, age, smoking status, and disease activity, with more pronounced lipid abnormalities observed in patients with heightened autoimmune responses and elevated inflammation levels [60]. Interestingly, despite corticosteroid use being a known risk factor for dyslipidemia, no significant influence on hypertriglyceridemia was noted among steroid-treated pSS patients [61]. Though recent genetic studies, including GWAS, have begun unraveling lipid-related genes' involvement in SS, the number of identified variations remains relatively low [62]. A particularly relevant finding utilized the two-sample Mendelian randomization analysis, which investigated the role of cholesteryl ester transfer protein (CETP), a drug used for cholesterol reduction, in SS. The study identified genetic proxies for CETP inhibition through large population-level GWAS data. The results indicated that genetically reduced CETP activity was associated with a significantly lower risk of SS. CETP is involved in the transfer of cholesteryl esters from HDLs to triglyceride-rich lipoproteins, influencing cholesterol metabolism. The study found that CETP inhibition, rather than a general reduction in LDL cholesterol, appeared to specifically reduce SS risk, suggesting that lipid metabolism abnormalities could play an important role in the development of SS [62]. However, accumulative evidence suggests a potential link between lipid metabolism and SS, although the causal relationship remains elucidated.

Lipid Deposition in Exocrine Glands Might Be the Start of Inflammation of SS

While fat deposition in the salivary glands generally increases with age in the general population, patients with

Table 1 Serum lipid profiling of pSS patients across various studies

Year	Author	Country	Dyslipidemia	References
2005	Vaudo, G	Italy	HDL cholesterol significantly decreased	[53]
2006	Lodde, B. M	USA	HDL cholesterol significantly decreased, and TC significantly increased	[23]
2006	Gerli, R	Italy	Patients with anti-SSA/SSB had lower HDL cholesterol level	[54]
2007	Ramos-Casals, M	Spain	A higher frequency of dyslipidemia	[55]
2010	Kang, J. H	Taiwan	A higher prevalence of hyperlipidemia	[24]
2010	Cruz, W	Brazil	A significant tendency towards dyslipidemia	[56]
2010	Pérez-De-Lis. M	Spain	A higher frequency of hypertriglyceridemia	[57]
2015	Bartoloni, E	Italy	Hypercholesterolemia was more prevalent	[25]
2019	Cai, X	China	TC and LDL cholesterol significantly increased, and HDL cholesterol significantly decreased	[26]
2023	Quevedo Mayorga, P. A	Italy	Higher rates of disease activity in patients with low levels of HDL cholesterol	[58]
2023	Santos, C. S	Spain	A higher prevalence of higher LDL cholesterol levels. Increased TC and TG have been associated with reduced HDL cholesterol levels	[59]
2023	Quevedo Mayorga, P. A	Colombia	Low levels of HDL cholesterol showed higher rates of disease activity	[63]
2024	Yang, L	China	Increased TG level was correlated with heightened disease activity	[64]

HDL high-density lipoproteins, *TC* total cholesterol, *LDL* low-density lipoproteins, *TG* triglyceride

pSS exhibit significantly higher levels of fat accumulation in these glands compared to healthy individuals. Premature and extensive fat deposition in the salivary glands is a distinctive feature of pSS patients [65]. Additionally, magnetic resonance (MR) imaging has shown accelerated fat accumulation in the lacrimal glands of pSS patients, further suggesting the involvement of lipid metabolism in the disease process [66]. Notably, the extent of fat deposition in exocrine glands correlates with the severity of glandular dysfunction, implying that abnormal lipid metabolism may contribute to the progression of pSS.

Animal model studies provide further support for the role of lipid deposition in exocrine glands. For example, lipid droplets were detected in the lacrimal glands of 4-month-old male non-obese diabetic (NOD) mice before the clinical onset of SS symptoms [67]. Another study found lipid deposition in the lacrimal glands of model animals prior to lymphocyte infiltration, with the accumulation primarily consisting of cholesterol esters (CEs). Moreover, in 12-week-old male NOD/SCID mice, lipid droplet aggregation was observed in the lacrimal glands, similar to age- and gender-matched NOD mice, but without any accompanying lymphocyte infiltration [27]. This finding strongly suggests that lipid deposition is not merely a consequence of dacryoadenitis but rather an early event that may act as an initiating factor for subsequent inflammation [27]. Rapid lipid deposition in the lacrimal gland was also observed after just 1 month on a high-fat diet [68], underscoring the sensitivity of lacrimal gland cells to hyperlipidemia (Fig. 1).

Profiling of Metabolomics of Saliva and Tears in SS

In recent years, metabolic profiling of saliva and tears has emerged as a promising approach to identifying dysregulated metabolites in pSS. A recent lipidomic analysis revealed significant differences in the lipid profiles of saliva and tears from pSS patients, notably characterized by an overall increase in total lipid concentration [69]. Additionally, principal component analysis (PCA) of the saliva from pSS patients, compared to healthy controls, demonstrated a reduction in metabolite diversity, with lower levels of glycine, tyrosine, uric acid, and fucose in pSS patients' saliva [70]. These alterations in salivary metabolites are thought to correlate with the degree of inflammation present in the disease [71, 72]. Specific changes in lipid metabolites in both saliva and tears are summarized in Table 2. The role of metabolomics in the pathophysiology of pSS warrants further investigation, as these metabolic alterations may provide valuable insights into disease progression and treatment responses. Future studies should focus on determining whether metabolic profiling can serve as a reliable tool for predicting the progression of pSS or monitoring the effects of therapeutic interventions [71].

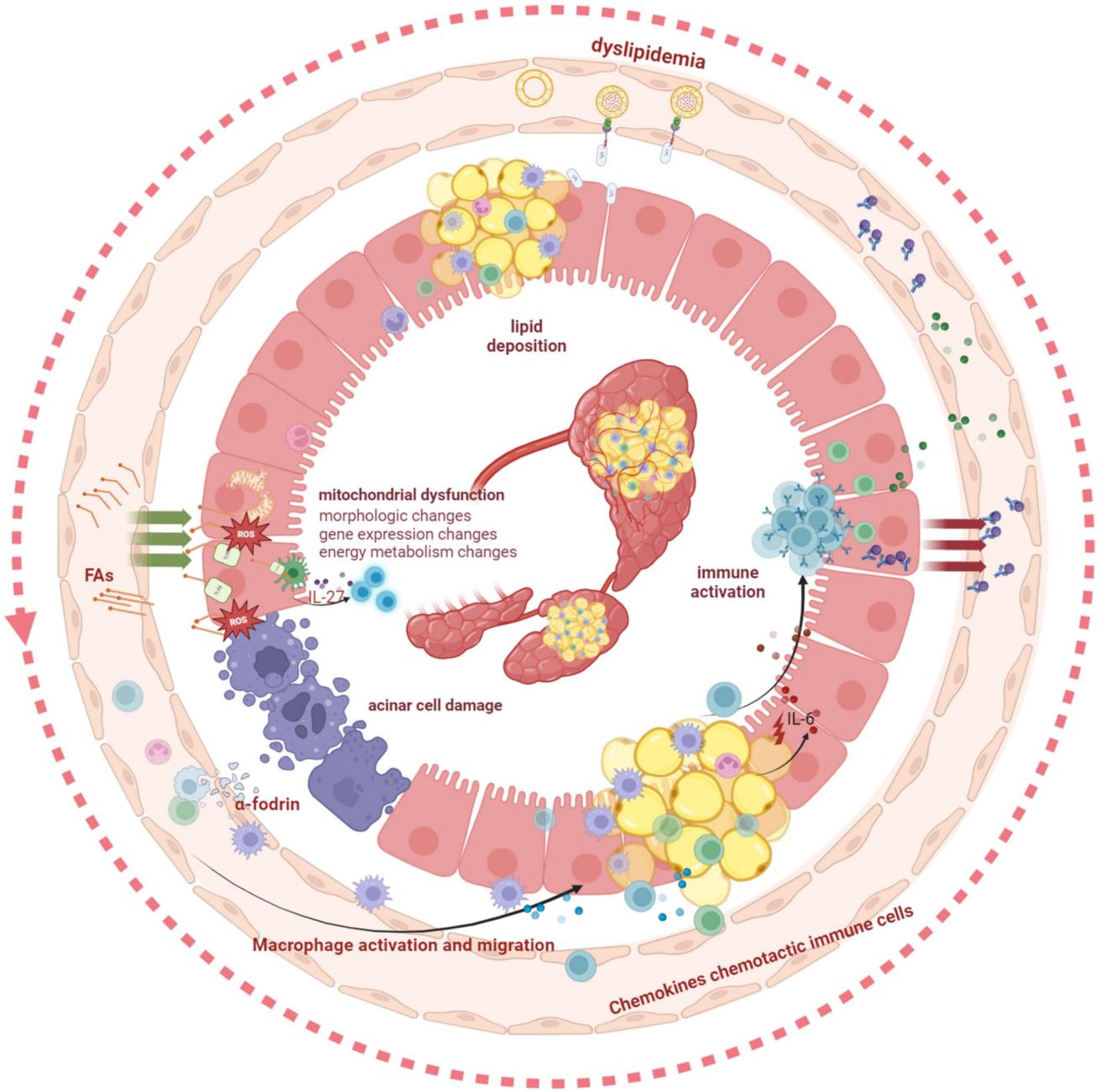

Fig. 1 Effects of lipid metabolism on exocrine gland inflammation in SS. Compared to healthy individuals, SS patients exhibit marked dyslipidemia, characterized by significantly reduced levels of HDL cholesterol and elevated levels of TC, LDL cholesterol, and TGs. Dyslipidemia induces lipoprotein lipase (LPL) activity, which breaks down TGs into fatty acids, leading to lipid deposition in target glands. Abnormal metabolism of unsaturated or saturated fatty acids results in mitochondrial dysfunction, endoplasmic reticulum stress, and increased production of reactive oxygen species (ROS), which can trigger apoptosis in salivary and lacrimal gland cells. This process leads to the breakdown of α-fodrin, with mononuclear macrophages recognizing and migrating toward the affected glands. Additionally, hyperlipidemia activates dendritic cells through the TLR-4 pathway, stimulating IL-27 production and promoting further immune cell recruitment to the affected glands. Lipid deposition in the salivary glands induces IL-6 production by salivary epithelial cells, driving B cell maturation and promoting the survival of plasma cells. This, in turn, exacerbates the inflammatory environment, amplifying both the autoimmune response and dyslipidemia in SS

Table 2 Changes in lipid metabolism in saliva and tears

Year	Author	Country	Abnormal lipid metabolism in saliva and tears	References
2021	Ewurum, A	USA	Notable elevated ratio of cholesteryl ester/wax ester and more straight chains in meibum	[73]
2021	Herrala, M	Finland	Significant differences of FA 16:0, FA 16:1, CE 16:0, LPC 18:0, and LPE 18:0 in the saliva	[71]
2021	Fineide, F	Norway	Significant differences of SPM, PC, DAG, CE, WE, and DAG in the saliva and tear fluid lipidome	[69]
2021	Urbanski, G	France	Six lipids in tears: LPC C16:1, C18:1, and C18:2; sphingomyelin C16:0 and C22:3; and PCaa C42:4, which can predict the pSS status	[74]
2024	Piacenza Florezi, G	Brazil	An increased concentration of lactate, alanine, malate, arginine, leucine, valine, and isoleucine in pSS	[75]

FA fatty acid, *CE* cholesteryl palmitic acid, *LPC* lysophosphatidylcholine, *LPE* lysophosphatidylethanolamine, *SPM* sphingomyelins, *PC* diacylglycerophosphocholine, *DAG* diacylglycerols, *CE* cholesterol esters, *WE* wax esters, *PCaa* phosphatidylcholine diacyl

Mechanisms of Lipid Metabolism Disorders Involved in SS

Effects of Lipid Metabolism Disorder on Immune Cells in SS

Lipids and their metabolites play a crucial role in the regulation of immune cells [76], contributing to both pro-inflammatory and anti-inflammatory responses. These lipids fulfill energy requirements, regulate membrane fluidity, and act as inflammatory mediators during immune responses [15, 77]. Furthermore, lipid metabolites not only indirectly regulate antigen presentation but also directly influence immune cells by acting as cytokines [78] (Fig. 2).

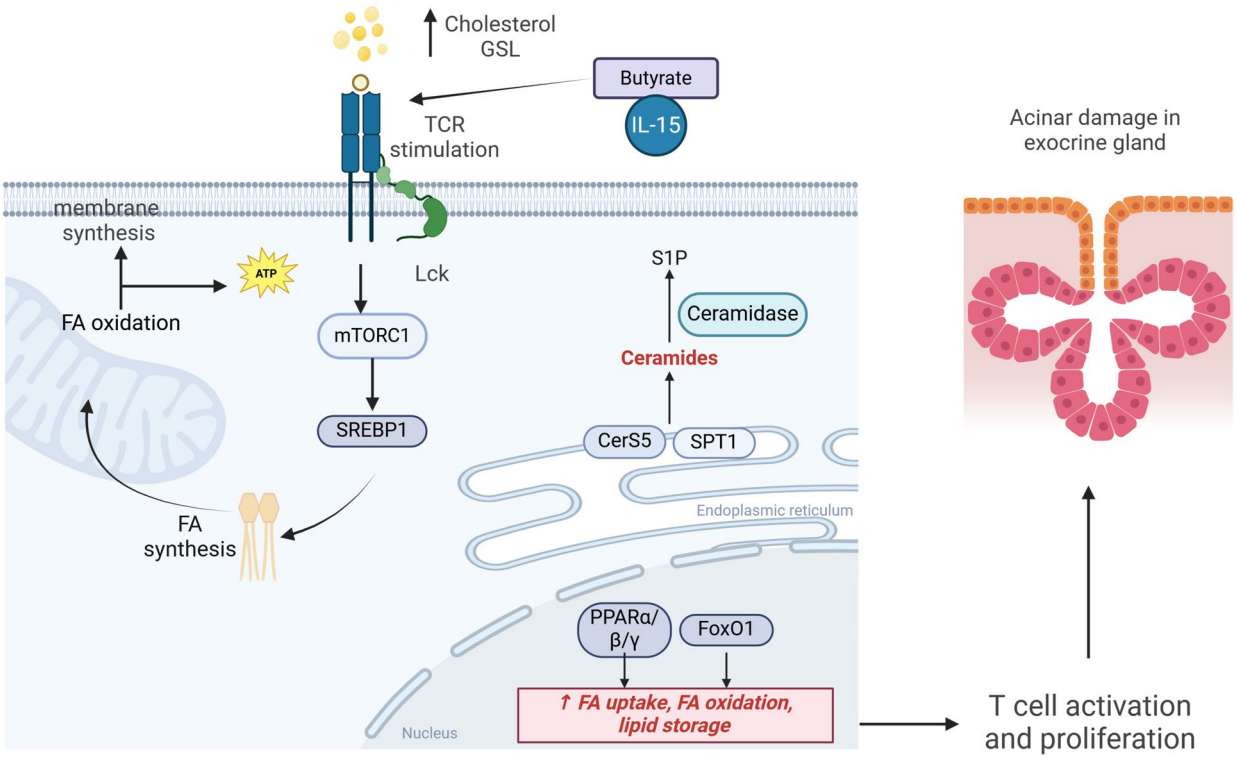

Fig. 2 Effects of lipid metabolism disorders on T cells in SS. In T cells, fatty acids and cholesterol are essential for their proliferation, differentiation, and morphogenesis, supporting critical processes such as membrane synthesis, energy production, and TCR signal transduction. The proliferation, maturation, and activation of T cells contribute to acinar damage in the exocrine glands. Notably, the synthesis and accumulation of FAs promote the differentiation of proinflammatory Th17 cells, which play a pivotal role in the pathogenesis of SS development

Effects of Lipid Metabolism Disorders on T Cells in SS

Dyslipidemia contributes significantly to the activation of T cells and inflammatory mediators in SS. The proliferation, differentiation, and morphogenesis of T cells rely on the availability of FAs and cholesterol, which are essential for cell membrane synthesis, energy production, and T cell receptor (TCR) signaling [79]. Lipid rafts, specialized membrane microdomains, play a vital role in the segregation and integration of key signaling molecules during immune cell activation [80, 81]. HDL cholesterol and apolipoprotein A-I (apo A-I) mediate cholesterol efflux in antigen-presenting cells (APCs), thereby altering lipid raft structure and reducing T cell activation [82]. When lipid metabolism is dysregulated, the accumulation of free FAs and cholesterol further enhances the immune activity of T cells [83, 84]. Upon activation of the TCR, T cells stimulate FA synthesis and mevalonate metabolism through key signaling pathways involving PI3K, Akt, and mTOR [85]. $CD4^+$ T cells are the predominant lymphocytes infiltrating the exocrine glands in SS, and they persistently stimulate local immune responses, exacerbating inflammation and tissue destruction [86, 87]. Inhibition of fatty acid synthesis in memory $CD4^+$ T cells results in decreased production of interferon-gamma (IFN-γ), a key inflammatory cytokine [88]. In activated $CD4^+$ T cells, fatty acid and phospholipid synthesis is upregulated, which is consistent with the activation of the sterol regulatory element-binding protein 1 (SREBP-1) [89]. Additionally, cholesterol biosynthesis, facilitated by the enzyme CYP51, is crucial for the proliferation of $CD4^+$ T cells in NOD/LtJ mice, a model for SS [90]. Furthermore, IL-17-positive T cells have been identified surrounding adipocytes in SS, indicating a potential link between lipid metabolism and T cell activation in the pathogenesis of the disease [91]. Blocking de novo fatty acid synthesis inhibits Th17 cell proliferation and promotes the generation of Treg cells [92]. The epidermal fatty acid-binding protein (E-FABP) has also been shown to promote Th17 cell differentiation by regulating Foxp3 expression, a key marker of Treg cells [93].

$CD8^+$ T cells contribute to acinar damage in the exocrine glands [94, 95] and may persist within glandular tissue, exerting immune effects during the advanced stages of SS [96]. During the production of $CD8^+$ memory T cells, metabolism is reprogrammed to enhance mitochondrial fatty acid oxidation (FAO) [97]. Notably, studies have shown that upon stimulation with butyrate, $CD8^+$ T cells exhibit increased sensitivity to IL-15, leading to the expression of higher levels of the transcription factor FoxO1 [98] (Fig. 2).

Effects of Lipid Metabolism Disorders on B Cells of SS

A prominent feature of SS is the heightened activity of B cells, which is evidenced by the production of autoantibodies and the formation of ectopic lymphoid structures within glandular tissues. Furthermore, SS patients are at an increased risk of developing B-cell lymphoma [99]. In B cells, lipid rafts—specialized microdomains within the plasma membrane—aggregate at the binding sites of B cell antigen receptors (BCRs), acting as platforms for receptor signaling and transport [76]. Mechanistically, upon activation of B cells, the BCR moves into lipid rafts to enhance signaling. However, in SS patients, especially in the presence of less mature B cells (CD45RA low), the BCR and CD19 (a co-receptor) remain in the rafts for much longer, amplifying signals. This prolonged signaling could contribute to the autoimmune activation of B cells in SS. However, the BCR is excluded from lipid rafts much faster in normal controls, suggesting a more controlled response [100]. Disruption of these lipid rafts using cholesterol-chelating agents impairs BCR redistribution, highlighting the critical role of lipid rafts in B cell activation and signaling [101].

Activated B cells show a marked increase in de novo fatty acid synthesis. Disrupting intracellular lipid metabolism can severely affect B cell function and their ability to engage in immune responses [102, 103]. Moreover, extracellular lipids serve as critical energy sources and nutritional substrates for B cells while also acting as important signaling molecules that modulate adaptive immune responses. Statins, which inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, have been shown to regulate B cell activity and may offer potential therapeutic benefits for managing autoimmune diseases, including SS [104–107]. Despite these insights, there is a lack of comprehensive research focusing on the precise role of lipid metabolism in B cells within pSS patients. In the salivary glands of pSS patients, B cells and plasma cells are notably abundant in areas with significant fat accumulation [108].

Ferroptosis is a type of planned cell death that involves the formation of significant numbers of lipid peroxides in the cell, which then catalyze unsaturated fatty acids on the cell membrane, resulting in membrane rupture and cell death [109]. Glutathione peroxidase 4 (GPX4) is a natural ferroptosis inhibitor that uses glutathione (GSH) to convert lipid peroxides to non-toxic lipid alcohols, sparing cells from toxic damage caused by lipid peroxides [110]. In SS, downregulation of GPX4 in salivary gland epithelial cells (SGECs) impairs their ability to clear lipid reactive oxygen species (ROS), leading to lipid peroxidation. The accumulation of lipid ROS activates STAT4, which becomes phosphorylated (pSTAT4) and translocates to the nucleus. There, pSTAT4 binds to the promoter region of aquaporin 5 (AQP5), inhibiting its expression. Reduced AQP5 levels impair water transport in SGECs, resulting in ferroptosis of SGECs [111]. Meanwhile, epithelial cells are more susceptible to damage due to increased PUFA [112]. Conversely, saturated fatty acids (SFAs), such as palmitate, triggers IL-6

production in the SGECs through the activation of NF-κB and p38 MAPK pathways [113]. Additionally, palmitate tempts α-fodrin degradation via caspase-3 activation and leads to the apoptosis in these cells [113].

Adipocytes, particularly those located in IL-6-rich regions, can trigger IL-6 production by salivary gland epithelial cells. This, in turn, promotes the differentiation of B cells into antibody-secreting cells, thereby enhancing local inflammatory responses [11]. Additionally, levels of TC and HDL cholesterol are correlated with elevated serum concentrations of IgG, an indirect marker of B cell activation [23]. The ABCA7 transporter, which mediates the release of cytosolic cholesterol and phospholipids to form HDL cholesterol, may serve as an autoantigen to activate autoantibody production. This suggests that ABCA7 might play a role in maintaining lipid homeostasis in pSS patients [114, 115]. Despite these preliminary findings, the role of lipid metabolism in B cells remains an underexplored area in SS research, representing a significant gap in current understanding (Fig. 3).

Effects of Lipid Metabolism Disorders on Innate Immune Cells of SS

In addition to adaptive immune cells, innate immune cells, such as macrophages and dendritic cells (DCs), play a significant role in the development of SS [99, 116]. Macrophages are frequently observed in various stages of pSS, and their increased presence is linked to more severe tissue damage and higher biopsy lesion scores [116]. The sterol regulatory element-binding protein (SREBP), a key regulator of fatty acid and cholesterol synthesis, is abundantly expressed in macrophages and enhances their inflammatory responses [117]. Moreover, fatty acid synthase (FAS), a crucial enzyme in fatty acid biosynthesis, has been shown to be essential for the induction of pro-inflammatory (M1) macrophages, which contribute to the inflammatory process in SS [118, 119]. The accumulation of fatty acids and dysfunctional lipid metabolism may induce the generation of ROS and trigger metabolic reprogramming in macrophages, leading to further inflammatory responses [120] (Fig. 4). LXRs, which regulate cholesterol homeostasis and cholesterol efflux, are important in controlling lipid metabolism in macrophages [121]. LXR target genes, such as ABCA1, ABCG1, and SREBP-1c, are involved in cholesterol and fatty acid metabolism. Activation of LXRs, through the inhibition of NF-κB signaling, has been used to suppress inflammation [122–124]. Recent studies have shown that constitutively active LXR in macrophages can stimulate cholesterol efflux and inhibit inflammation triggered by lipopolysaccharide (LPS) [125]. Furthermore, PPAR-γ, which is essential for adipocyte growth and glucose balance, exerts broad anti-inflammatory effects in macrophages and other cell types [126, 127]. PPAR-γ mediates important anti-inflammatory activities in epithelial cells, including those in the salivary glands. In patients with SS, the expression of PPAR-γ in the salivary epithelium of patients with Sjogren's syndrome is significantly reduced [128]. Fenofibrate, a PPAR-α agonist,

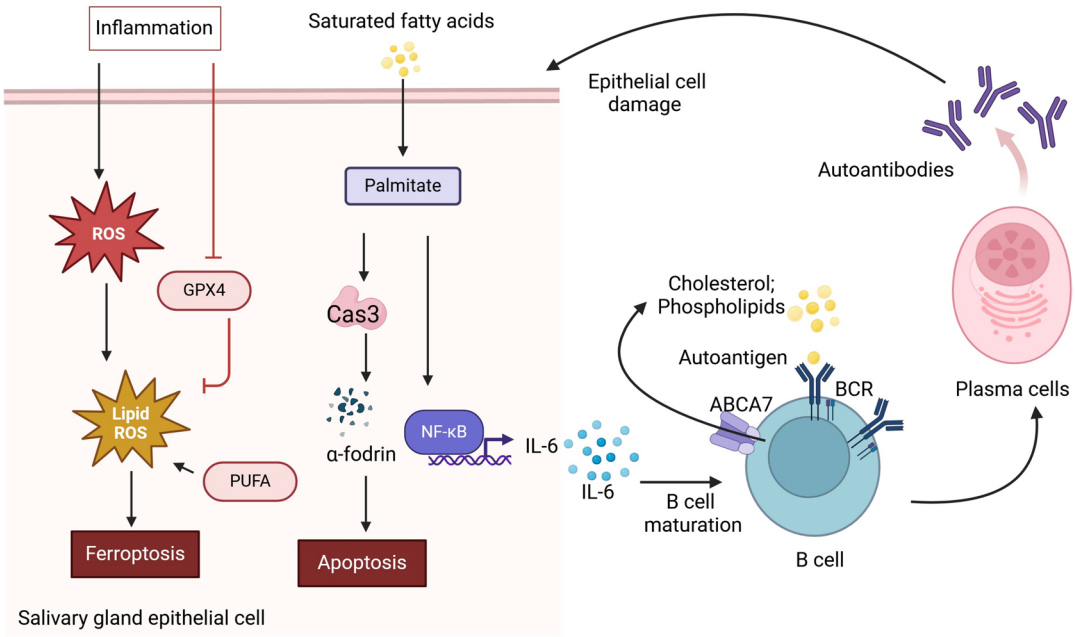

Fig. 3 Effects of lipid metabolism disorders on B cells in SS. In B cells, lipids stimulate the production of IL-6 by salivary gland epithelial cells, which, in turn, promotes the maturation of B cells into antibody-secreting cells and supports the survival and maintenance of plasma cells in SS

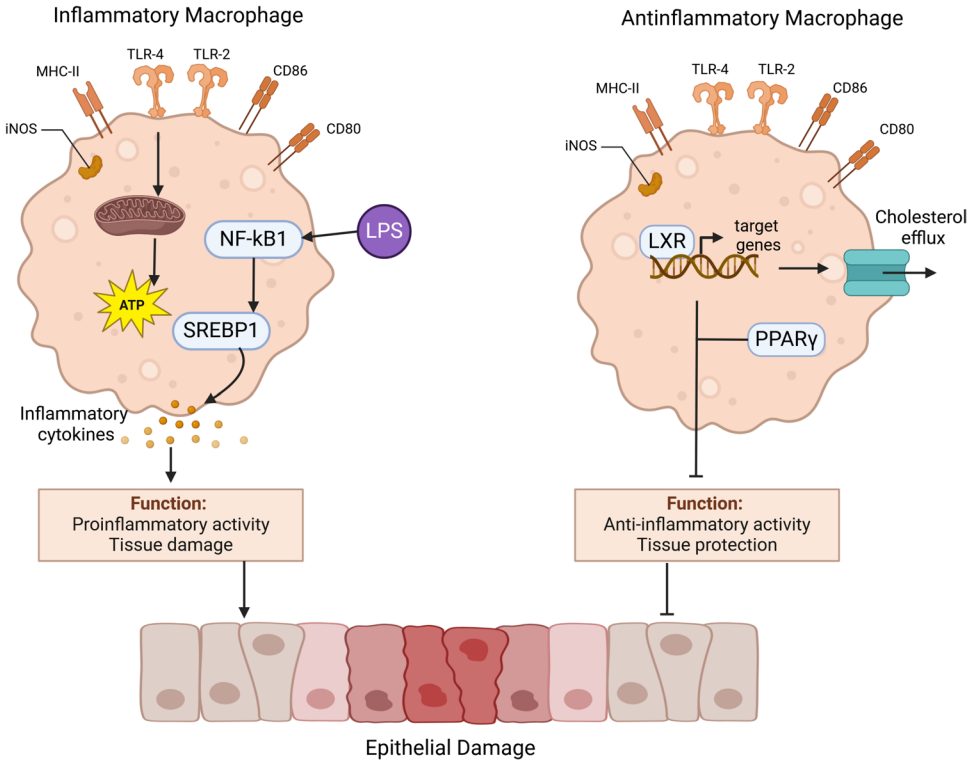

Fig. 4 Effects of lipid metabolism disorders on macrophages in SS. In macrophages, lipids are recognized by TLRs as pathogen-associated molecular patterns and play a crucial role in the initiation and perpetuation of chronic inflammation in SS. Dyslipidemia induces metabolic reprogramming in macrophages, which can lead to the generation of ROS, further amplifying the inflammatory process

has shown potential in improving SS-like symptoms, such as dacryoadenitis in NOD mice, by modulating Th1/Th17 and Treg cell responses, partly through upregulation of the PPAR-α/LXR-β signaling pathway [129]. These findings highlight the potential molecular strategies involving nuclear receptors that modulate lipid metabolism and inflammation in SS.

In DCs, lipids act as second messengers and effectors, playing a critical role in cell differentiation and the regulation of important immune functions [130]. The de novo synthesis of fatty acids enhances DC activation, supporting the proliferation of cellular structures like the Golgi apparatus and endoplasmic reticulum [131]. TLRs, present on both DCs and macrophages, mediate immune responses by recognizing pathogen-associated molecular patterns (PAMPs), such as oxidized LDL cholesterol, lipoproteins, and other endogenous ligands released during stress or inflammation [132, 133]. TLRs, present on both DCs and macrophages, mediate immune responses by recognizing PAMPs, such as oxidized LDL cholesterol, lipoproteins, and other endogenous ligands released during stress or inflammation. These PAMPs are released in response to stress or chronic inflammation and are derived from microbes to act as endogenous ligands to be recognized by TLRs, leading to prolonged inflammatory conditions [120, 134]. Inhibition of acetyl-CoA carboxylase (ACC) reduces TLR expression and cytokine production, impairing the immune functions of DCs [135]. Despite significant research into lipid metabolism in innate immune cells, the relationship between lipid metabolism disorders and immune dysregulation in SS remains underexplored (Fig. 5).

Effects of Dyslipidemia on Inflammation in SS

Effects of Lipid Metabolism Disorders on Inflammation in Exocrine Glands of SS

Biochemical studies and animal models suggest that dysregulation of essential fatty acid and arachidonic acid metabolism may contribute to atrophy in salivary and lacrimal glands in pSS [136]. One model has proposed a mechanism wherein palmitic acid induces pSS by promoting apoptosis in SGECs and the degradation of α-fodrin through caspase-3 activation [11, 113, 137]. APCs recognize α-fodrin as an autoantigen after its release during cell lysis, triggering monocyte-macrophage infiltration and glandular cell damage. Furthermore, serum-free fatty acids activate the IL-1 signaling pathway in monocytes, leading to the upregulation of adhesion molecules in vascular endothelial cells. This enhances monocyte migration to inflammatory sites in the salivary glands of pSS patients [138]. In SS model mice fed on a high-fat diet, a significant increase in IL-1β and TNF-α was observed in the lacrimal glands, along with substantial lipid deposition after 1 month [68]. This lipid accumulation induces

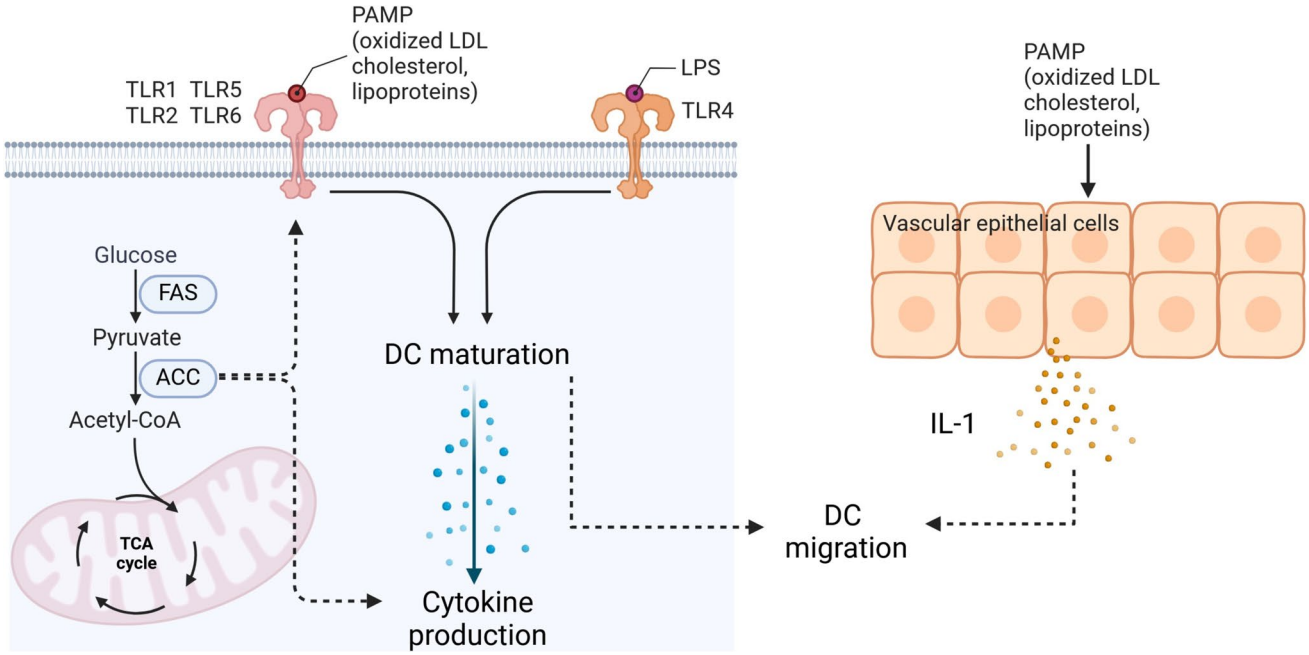

Fig. 5 Effects of lipid metabolism disorders on DC cells in SS. Lipids act as second messengers and effectors during DC differentiation and regulate their necessary migration by inducing IL-1 production from vascular endothelial cells for the progression of SS

oxidative stress in lacrimal gland acinar cells and their microenvironment [139], which triggers an inflammatory response and acinar cell death (Fig. 2).

Effects of Lipid Metabolism Disorders on Systemic Inflammation of SS

Current research is increasingly focusing on the relationship between plasma lipid changes and inflammatory markers in SS patients. Inflammatory biomarkers such as serum anti-SSA/SSB antibodies, IgG levels, and erythrocyte sedimentation rate (ESR) reflect disease activity in pSS [140, 141]. Compared to normolipidemic pSS patients, those with dyslipidemia tend to exhibit higher levels of antinuclear antibodies and ESR [25, 54, 56]. Additionally, low HDL cholesterol levels are correlated with higher EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) scores [58]. Blood lipid profiles hold potential as indicators of disease activity, although further clinical studies are needed to fully establish their value. Our recent study identified a correlation between osteoarthritis in pSS patients and elevated TG and TC levels in serum [142]. However, variations in clinical results, likely due to differences in testing populations and methodologies, highlight the need for broader studies linking lipid levels to disease markers or associated complications (e.g., cardiovascular disease and interstitial lung disease). Such studies would improve the clinical diagnosis and treatment of SS.

Role of Aberrant Lipid Metabolism in Mitochondrial Dysfunctions in SS

Mitochondrial alterations are observed in the salivary gland epithelium of pSS patients, including mitochondrial matrix swelling, membrane disorganization, rupture, and increased interaction with the endoplasmic reticulum [143, 144]. Transmission electron microscopy reveals progressive mitochondrial swelling and lipid droplet accumulation in salivary epithelial cells as the disease advances. Notably, significant adipose tissue development in the salivary glands is associated with the downregulation of genes involved in mitochondrial fatty acid β-oxidation [91]. Bioinformatics analysis has shown altered expression of genes related to the mitochondrial respiratory chain in pSS, which affects gluconeogenesis, the tricarboxylic acid (TCA) cycle, and the metabolism of pyruvate, lipids, ketones, and amino acid [145]. Both pyruvate and FAs serve as primary fuel sources in the TCA cycle [146], but β-oxidation of FAs generates energy and ROS through the production of acetyl-CoA [147]. The reduced expression of enzymes involved in the terminal phase of mitochondrial β-oxidation [148] suggests a significant inhibition of acetyl-CoA supply to the TCA cycle, pointing to mitochondrial dysfunction as a potential mechanism underlying the metabolic alterations in pSS.

Regulating Lipid Metabolism Could Be a Therapeutic Strategy for SS

Dietary Control

Recent studies indicate a link between high-fat diets and the exacerbation of autoimmune diseases [140–142]. Nutritional interventions are believed to alleviate the severity of autoimmune disease–related pathological changes [149]. A study involving (NZB × NZW)F1(B/W) mice found that calorie restriction maintained lower levels of IFN-γ, IL-10, and IL-12 mRNA, akin to those observed in younger animals, regardless of dietary fat content. This suggests that caloric restriction may alleviate pSS by reducing immune activity in glandular tissues [150]. Given the potential role of PUFAs in slowing the progression of SS, there has been growing interest in whether PUFAs could serve as an effective treatment for pSS patients (Table 3). In pSS patients, the levels of different types of PUFAs correlate with immunopathological markers and clinical disease status, such as IgM rheumatoid factors and anti-SSA/Ro antibodies [151]. One clinical trial found that omega-6 administration reduced ocular surface inflammation and improved symptom scores in pSS patients [28]. Furthermore, higher dietary intake of omega-3 fatty acids was associated with a reduced incidence of dry eye symptoms in a large cohort of participants in the American Women's Health Study [152]. Despite the lack of long-term studies, recent evidence suggests that pSS patients tend to have inadequate intake of PUFAs [153]. Higher omega-3 levels correlate with fewer ocular symptoms, lower ESSDAI scores, and reduced salivary chemokine (C–C motif) ligand 2 (CCL2) levels, while omega-6 levels are negatively correlated with IL-21, suggesting that omega-3 and omega-6 may both contribute to reducing chronic inflammation in SS patients [154]. However, the clinical benefits of oral PUFA supplements are limited, and it remains unclear whether PUFAs can be used as a standardized treatment for SS. Further research is necessary to determine the optimal composition, dosage, and indications for these nutrients and to better understand how they could improve symptoms in SS patients.

Therapeutic Strategies Targeting Dyslipidemia

Ongoing research into how dyslipidemia influences the onset and progression of SS underscores the clinical importance of correcting these lipid disorders. Researchers have highlighted the potential benefits of addressing dyslipidemia in managing SS, with various therapeutic approaches showing promise.

Statins

Statins, which inhibit HMG-CoA reductase, are widely recognized lipid-modulating agents. These drugs significantly reduce TC and LDL cholesterol levels, lower TGs to some extent, and increase HDL cholesterol levels [134, 156]. In animal models of SS, oral atorvastatin was found to decrease levels of IL-1β, PGE-2, and matrix metalloproteinase-3 (MMP−3) in the submandibular glands. This effect appears to be mediated by cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), suggesting a potential anti-inflammatory role for atorvastatin in SS treatment [157].

Table 3 The therapeutic effect and relationship of PUFAs on SS

Year	Study model	Country	PUFAs	Findings	References
2002	Double-blind placebo-controlled randomized trial	Sweden	High-dose GLA	GLA treatment for fatigue in pSS is ineffective	[155]
2005	Randomized, double-masked, controlled clinical trial	Italy	LA and GLA	PGE1 levels increased in the tears of SS patients. Ocular surface signs and symptoms improved	[28]
2005	Cross-sectional	USA	ω−3 and ω−6 FAs	A higher dietary intake of *n*−3 FAs is associated with a decreased incidence of dry eye symptoms in women	[152]
2009	Animal model	France	GLA, DHA, EPA	The lipid homeostasis of extra orbital LG was affected, and the course of dry eye was partially prevented	[154]
2020	Cross-sectional	Mexico	ω−3 and ω−6 FAs	PSS patients had deficient omega intake. Lower ocular symptoms, ESSDAI scores, and salivary CCL2 correlated with higher ω−3 levels	[153]

GLA gamma-linolenic acid, *LA* linoleic acid, *PGE1* prostaglandin E1, *FAs* fatty acids, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *CCL2* chemokine (C–C motif) ligand 2

Fibrate

Fibrates, another class of lipid-lowering drugs, are particularly effective at lowering serum triglyceride levels [158]. In animal studies, fenofibrate was shown to reverse pathological changes in the lacrimal glands induced by a long-term high-fat diet [68]. Specifically, fenofibrate upregulates the expression of the *Pparα* gene, thereby reducing lipid deposition in lacrimal gland acinar cells [68]. Additionally, fenofibrate reduces the infiltration of inflammatory cells, including Ly6g-positive neutrophils, $CD4^+$ T lymphocytes, and F4/80-positive macrophages. This leads to a reduction in the expression of inflammatory cytokines such as TNF-α, MMP-2, and MMP-9, while restoring lacrimal secretion function in the lacrimal glands [68].

Hydroxychloroquine

Hydroxychloroquine (HCQ) is a widely used antirheumatic drug for various autoimmune diseases, including SS. HCQ has been shown to provide benefits across several disease aspects, including reducing somatic symptoms (e.g., fatigue), improving joint and glandular involvement, enhancing saliva flow, and normalizing laboratory abnormalities [159, 160]. A study by Migkos et al. [161] found that HCQ treatment significantly decreased TC and the AS index while increasing HDL cholesterol levels in pSS patients. The exact mechanism by which HCQ exerts hypolipidemic effects remains unclear, though chloroquine, a structurally similar drug, may enhance lipid clearance and upregulate LDL receptors in the liver [162]. Additionally, chloroquine may inhibit lysosomal function and cholesterol synthesis in the liver, further influencing lipid metabolism [163].

Targeting Cholesterol Metabolism in T Cells

Interfering with cholesterol metabolism in $CD4^+$ T cells has emerged as a potential therapeutic approach for SS. Cholesterol metabolism plays a crucial role in TCR signaling, which regulates T cell activation and proliferation. Ubiquitin ligase HUWE1 is positively correlated with $CD4^+$ T cell activation and the pathogenesis of SS. Inhibition of HUWE1 enhances cholesterol efflux from $CD4^+$ T cells mediated by apoAI and HDL, reducing intracellular cholesterol levels and inhibiting T cell activation [164]. In mice, HUWE1 inhibition led to reduced TNF-α levels in peripheral blood and decreased lymphocyte infiltration in the submandibular glands, highlighting its therapeutic potential [164]. Additionally, the cholesterol synthesis inhibitor ketoconazole, which blocks the CYP51 enzyme, significantly reduced $CD4^+$ T cell infiltration in the submandibular glands of NOD/ShiLtJ mice [90]. However, the long-term use of ketoconazole may lead to liver toxicity and hypogonadism [165], presenting challenges for clinical application in SS treatment.

Therapeutic Potential of Drugs Targeting Lipid Metabolism or Signaling in SS

The development of Th17 cells, which play a pivotal role in the pathogenesis of pSS, is heavily dependent on acetyl-CoA carboxylase 1 (ACC1)-mediated de novo fatty acid synthesis and the glycolytic-lipogenic metabolic pathway. Berod et al. [92] demonstrated that inhibition of ACC1 disrupts fatty acid synthesis, subsequently inhibiting the glycolysis-lipogenesis pathway. This inhibition prevents Th17 cell formation while promoting the differentiation of anti-inflammatory $Foxp3^+$ regulatory T (Treg) cells. Given this, ACC1 has emerged as a promising target for immune regulation in pSS treatment.

Several bioactive lipids implicated in inflammation are now being explored as potential therapeutic targets for autoimmune diseases like pSS. Ceramides, which are formed by the binding of long-chain sphingosine to fatty acids through amide bonds, play a crucial role in inflammatory signaling and may serve as key targets for intervention in pSS [166]. Treatment with myriocin, an anti-ceramide agent, has been shown to reduce the frequency of IFN-γ and Th1 cells in the salivary glands of SS model mice. Additionally, it enhances the expression of aquaporin 5 and sodium–potassium-chloride co-transporter 1 (NKCC1), leading to reduced inflammation and improved saliva flow rate [167].

Similarly, advances in lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) research have revealed new avenues for treating autoimmune diseases [168]. LPA receptor (LPAR) signaling induces IL-17 production via the ROCK and p38 MAPK pathways, which promotes SS progression. Inhibitors of LPAR have been shown to restore tear and saliva production in recipient mice, significantly reducing IL-17 levels in both serum and lacrimal glands, suggesting that LPAR inhibition could offer a novel therapeutic approach for pSS [169]. S1P signaling, which promotes $CD4^+$ T cell proliferation and IFN-γ production in pSS patients, also enhances Fas expression and Fas-mediated apoptosis in SGECs while increasing IL-6 secretion in ductal epithelial cells [170]. Regulating the S1P signaling pathway may, therefore, provide another potential strategy for pSS treatment.

Adipokines, such as leptin and adiponectin, are secreted by adipose tissue and play critical roles in both energy homeostasis and inflammation. Leptin, for instance, promotes apoptosis of SGECs in SS by upregulating IL-4 secretion in B lymphocytes and activating the Jak2/Stat3 signaling pathway [171]. In the NOD model of pSS, leptin levels and its receptor (OB-R) increase as the disease progresses. Notably,

downregulation of OB-R through recombinant adeno-associated virus (rAAV)-mediated gene delivery can reduce glandular inflammation in NOD models [172], suggesting that targeting OB-R expression could provide a promising therapeutic approach for pSS. Leptin also enhances T-cell differentiation, contributing to inflammation, whereas adiponectin has anti-inflammatory effects [173]. Adiponectin induces IL-10 production and reduces TNF-α levels, potentially offering therapeutic benefits by dampening inflammation in pSS [174]. Therefore, strategies aimed at reducing leptin levels or promoting adiponectin synthesis may prove effective in managing SS.

PPAR-γ, a ligand-activated transcription factor, plays a crucial role in regulating immune responses and inflammation in autoimmune diseases [126]. PPAR-γ is involved in eicosanoid signaling downstream of arachidonic acid and controls lipid homeostasis while inhibiting pro-inflammatory cytokine-dependent activation [175]. Agonists of PPAR-γ have shown potential in treating SS by rescuing lacrimal gland secretion that is inhibited by IL-1β [176] and attenuating the activation of NF-κB and apoptosis of SGECs induced by pro-inflammatory agents [128]. In animal studies, PPAR-γ agonists reduced IL-6 and TNF-α expression in salivary glands while enhancing IL-4 production in serum, indicating a role in modulating the Th1/Th2 immune response balance [177]. Furthermore, PPAR-γ agonists may regulate the energy metabolism of SGECs by upregulating adiponectin, suggesting a multifaceted role for PPAR-γ in managing SS [178].

LXRs, members of the nuclear receptor superfamily, are key regulators of cholesterol metabolism and have profound effects on immune cell function and inflammatory responses. As such, LXRs are promising targets for autoimmune disease therapies [179]. The anti-inflammatory mechanisms of LXRs include transrepression of pro-inflammatory gene promoters, modification of macrophage phenotype, and increased cholesterol efflux. Additionally, LXRs regulate membrane lipid composition, which influences the plasma membrane signaling system and increases the synthesis of anti-inflammatory fatty acids [180]. Although the therapeutic potential of LXRs in pSS treatment is recognized, studies targeting LXRs in this context are still limited and require further exploration to understand their full therapeutic efficacy.

Resolvin D1 Treatment

Specialized pro-resolving mediators (SPMs) belong to class of lipid mediators, derived from *n*−3 and *n*−6 PUFAs, that play crucial roles in terminating inflammation and promoting tissue repair [181]. Among these, resolvins—particularly those derived from eicosapentaenoic acid (EPA) as the E-series (RvE) and from docosahexaenoic acid (DHA) as the D-series (RvD)—are well known for their potent anti-inflammatory properties [182]. Resolvin D1 (RvD1), a member of the D-series, has gained attention for its potential therapeutic application in SS.

RvD1 has been extensively studied for its effects on reducing inflammation in autoimmune diseases, including SS. Research has shown that RvD1 can reduce the secretion of several inflammatory mediators, such as TNF-α, IL-17, IL-13, IL-12, IL-9, and granulocyte colony-stimulating factor, all of which are critical in the pathogenesis of SS [118, 119]. By enhancing the phagocytic capacity of macrophages, RvD1 facilitates the clearance of apoptotic cells, preventing their lysis and necrosis, a process that contributes to controlling inflammation. Additionally, RvD1 has been found to decrease conjunctival goblet cell secretion stimulated by leukotrienes. This is clinically significant for treating ocular immune responses and mitigating the symptoms of dry eye, a common manifestation in SS patients [183]. More detailed studies indicate that RvD1 also inhibits TNF-α-mediated inflammatory responses and helps restore the organization of parotid gland cells. This is attributed to its ability to enhance cell migratory ability and polarity through the PI3K/Akt signaling pathway, which aids tissue repair and inflammation resolution in the rat parotid Par-C10 cell line [184].

Aspirin-triggered resolvin D1 (AT-RvD1), a modified form of RvD1, also exhibits strong anti-inflammatory activity. In animal models, AT-RvD1 has been shown to prevent inflammation in the submandibular gland of mice by blocking TNF-α-mediated caspase-3 activation, a key pathway in apoptosis and inflammation [185]. Another study demonstrated that treatment of NOD/ShiLtJ mice with AT-RvD1 improved glandular secretory function, reduced glandular lymphocyte infiltration, and promoted tissue healing, especially when combined with dexamethasone [186]. Moreover, AT-RvD1 treatment led to a reduction in the number of Th17 cells in the submandibular glands of an SS-like mouse model, reinforcing its anti-inflammatory mechanisms and suggesting the potential for regulating key immune cells involved in SS pathogenesis [187]. At the same time, other studies show that the pharmacokinetic models of RvD1 are being improved [188, 189] (Fig. 6).

While RvD1 and AT-RvD1 have demonstrated promising results in preclinical models, further investigation is needed to fully understand their therapeutic potential for human patients. Pharmacokinetic models of RvD1 are currently being refined to optimize its delivery and efficacy in clinical settings [182, 183]. Although much of the current research focuses on the role of RvD1 and AT-RvD1 in salivary gland inflammation, other SPMs with similar pro-resolving and anti-inflammatory properties should also be explored for their potential to alleviate SS disease progression. Given the compelling data, SPMs represent an exciting avenue for future treatment strategies targeting the

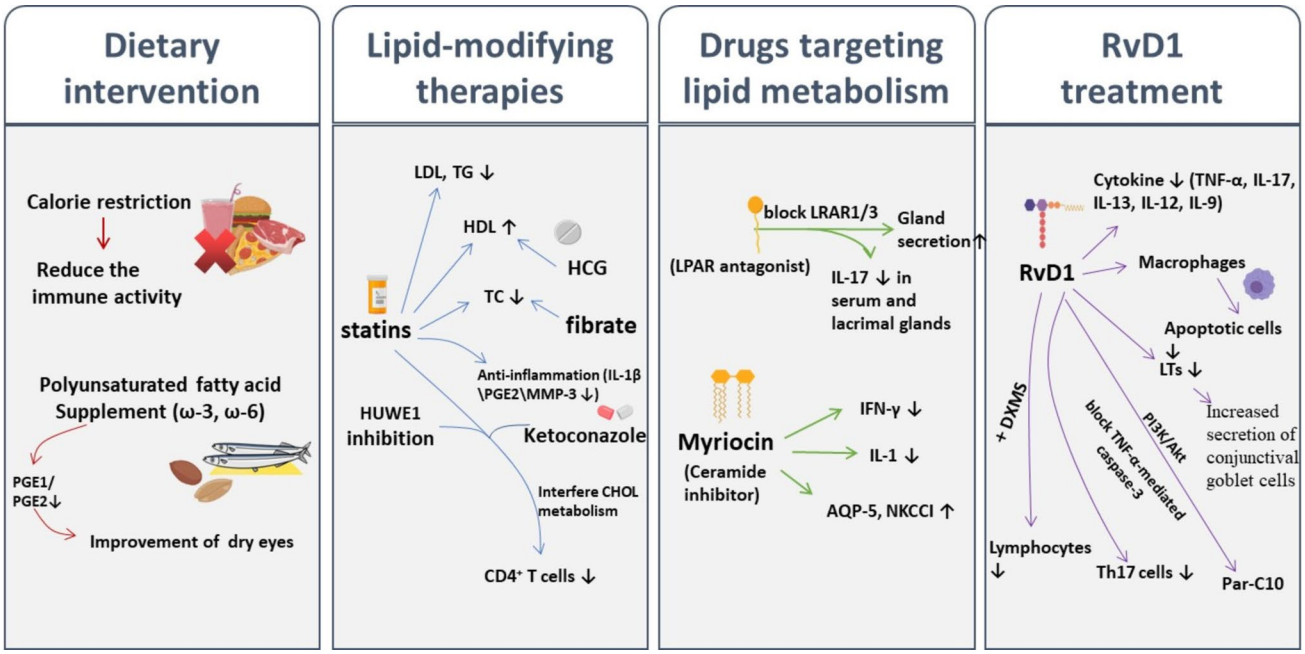

Fig. 6 Regulating lipid metabolism could be a therapeutic strategy for treating SS. The following strategies can potentially target the lipid metabolism to effectively treat SS: (1) dietary control: calorie restriction can improve pSS status by reducing immune activity in glandular tissues. Oral supplementation with ω−6 and ω−3 fatty acids can improve dry eye symptoms; (2) lipid-modifying therapies: statins, fibrate, and HCQ can improve blood lipid abnormalities in SS patients and exert anti-inflammatory effects. Statins, HUWE1 inhibitors, and ketoconazole can inhibit the proliferation and activation of $CD4^+$T cells by affecting cholesterol metabolism; (3) drugs targeting lipid metabolism: LPAR1/LPAR3 antagonist Ki16425 restores tear and saliva secretion, reducing IL-17 levels in serum and lacrimal glands. Myriocin reduces IFN-γ and Th1 cells and increases the expression of AQP5 and NKCC1, promoting water movement and salivary gland function recovery; (4) RvD1 treatment: RvD1 reduces the secretion of various inflammatory factors, enhances macrophage phagocytosis of apoptotic cells, reduces conjunctival goblet cell secretion stimulated by leukotriene, blocks TNF-α-mediated caspase-3 activation, and promotes Par-C10 cell line recovery through PI3K/Akt signaling. RvD1 also reduces Th17 cell numbers and, when combined with dexamethasone, reduces glandular lymphocyte infiltration and promotes tissue healing

inflammation-resolution balance in autoimmune diseases like pSS. However, further research, especially in human pharmacology and clinical trials, will be essential to determine the therapeutic feasibility and long-term safety of these lipid mediators in treating SS.

Discussion and Conclusion

Dyslipidemia is prevalent in autoimmune diseases, including SS, and is closely linked to disease activity. Metabolomics provides direct insights into an individual's current physiological state, making it a valuable tool for understanding disease etiology and identifying biomarkers. Although the pathogenesis of SS remains unclear, the relationship between lipid metabolism and SS progression is relatively well established. Furthermore, the therapeutic potential of regulating lipid metabolism has garnered significant attention in the clinical management of SS.

However, several limitations in the available literature warrant consideration. A notable limitation is the variation in lipid profile changes observed in SS patients across different studies. Factors such as population diversity, socioeconomic status, racial differences, and sample size may contribute to these inconsistencies. Additionally, the use of varying diagnostic criteria and methodologies for lipid profiling may explain the conflicting findings regarding the prevalence and nature of dyslipidemia in SS. For example, while several studies link dyslipidemia to heightened disease activity, others report no significant correlation. These discrepancies may stem from differences in disease severity or the presence of comorbid conditions among study populations.

Abnormal lipid profiles have also been identified in the saliva and tears of SS patients. Dyslipidemia is believed to contribute to SS progression primarily by impacting immune cell function and promoting inflammation. However, therapeutic strategies discussed in the available literature and reviewed here predominantly focus on managing dyslipidemia, with limited attention given to alternative approaches targeting immune dysfunction and inflammation directly. While dietary interventions and pharmacological treatments for dyslipidemia, such as statins, fibrates, and PUFAs, have demonstrated protective effects

by reducing inflammation and managing lipid levels, their clinical efficacy in addressing the broader immune dysregulation observed in SS remains underexplored.

This narrow focus on lipid metabolism overlooks other critical aspects of SS treatment, such as immunomodulatory therapies (e.g., biologics targeting B cells and T cells) and anti-inflammatory drugs commonly used to manage SS-related symptoms. There is also a need to critically evaluate the limitations of existing therapies. For instance, while statins have shown anti-inflammatory properties in some autoimmune conditions, their long-term safety and efficacy in SS, particularly in patients with pre-existing liver conditions or muscle-related side effects, require further investigation. Statins are associated with risks of liver dysfunction and muscle injuries [190, 191]. Similarly, although PUFAs have demonstrated benefits in reducing ocular inflammation, improvements in SS symptoms have been inconsistent across studies. Further exploration is needed to determine the specific components, dosages, and indications for PUFA-based interventions in SS treatment.

Beyond managing dyslipidemia, emerging therapeutic approaches targeting lipid metabolism show promising potential. SPMs, such as RvD1, are potent anti-inflammatory agents that could help modulate immune responses and restore glandular function in SS. However, targeting lipid metabolism and signaling pathways in SS treatment requires additional clinical evidence. Moreover, further investigation is necessary to explore the potential of other SPMs in reducing inflammation in exocrine glands. Similarly, the use of PPAR-γ agonists, which regulate lipid homeostasis and exhibit broad anti-inflammatory effects [192], represents another promising area of research. LXRs, which modulate cholesterol metabolism and immune cell function [193], also show potential as therapeutic targets for SS. Despite their promise, these treatments remain largely experimental, and further research is needed to validate their efficacy in reducing systemic inflammation and immune-mediated glandular damage in clinical settings.

Overall, understanding the mechanisms of SS from the perspective of lipid metabolism, developing effective treatments and interventions, and providing molecular explanations for disease processes remain to be challenging but critical areas for future research.

Author Contribution Keni Chang, Peiming Luo and Zizhen Guo contributed equally to this work. They participated in the conception of the study, performed the literature review, and were major contributors to writing the manuscript. Lufei Yang, Jincheng Pu, Fang Han and Feiyang Cai assisted in the literature review and drafting of the manuscript. Jianping Tang and Xuan Wang provided oversight and guidance throughout the project, critically revised the manuscript for important intellectual content, and provided final approval for publication.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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