mTOR signaling pathway in primary Sjögren's syndrome: Pathogenesis and potential therapeutic targets (Review)

RONGXIU HUO*, YANTING YANG*, CHENGCHENG WEI*, YANG YANG, DANLI MENG, JINYING LIN and XINXIANG HUANG

Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi 530016, P.R. China

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Abstract. Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder that can progress from asymptomatic glandular involvement to systemic manifestations affecting multiple organs, thereby imposing a notable economic burden on both patients and society. The pathogenesis of pSS is complex and involves multifactorial interactions between genetic, environmental and immune components. Although pSS is a common rheumatic disease, current therapeutic approaches primarily focus on symptom management and no curative treatment is available. Therefore, it is key to identify novel and effective therapeutic strategies for affected individuals. The mTOR signaling pathway is a key regulatory pathway in numerous types of cell, playing a crucial role in immune regulation, inflammation and autophagy. Activation of this pathway can promote inflammation by inducing immune dysregulation, thereby contributing to the pathogenesis of pSS. Conversely, inhibition of the mTOR signaling pathway mitigates these pathological processes and may help alleviate disease severity. Thus, the mTOR signaling pathway represents a promising therapeutic target for pSS. The present review aimed to elucidate the role and underlying mechanisms of the mTOR signaling pathway in pSS and provide a theoretical foundation for developing targeted therapeutic interventions.

Correspondence to: Professor Xinxiang Huang, Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Qingxiu, Nanning, Guangxi 530016, P.R. China
E-mail: nnhxx_china@163.com

*Contributed equally

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1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by lymphocyte infiltration of exocrine glands, resulting in glandular dysfunction and irreversible tissue damage, which may manifest as dry mouth and eyes (1). If extraductal involvement occurs, manifestations involving the lungs, joints, skin, muscles, kidneys and nervous system may appear (1-3). The pathogenesis of pSS is unclear at present. Scholars have proposed various pathogenic mechanisms for this disease, including genetic susceptibility (4), infection (5), the role of salivary gland (SG) epithelial cells (6), immune cells [B, T and dendritic cells (DCs)] (7-9) and the combined action of cytokines (10). These factors causing immune disorders jointly lead to pro-inflammatory consequences, resulting in damage to glands and extraglandular organs. Although understanding of the pathogenesis of this disease is advancing, there is currently no specific treatment for pSS. The treatment is limited to symptom relief. Certain targeted drugs, such as belimumab and rituximab that target B cells, have been used in the treatment of pSS, but they are only used for severe and refractory systemic disease (11). However, certain patients have poor response to drugs and the occurrence of adverse reactions, so it is necessary to find targeted drugs that can be applied to a range of patients with pSS.

The mTOR signaling pathway serves a crucial role in cellular metabolism, proliferation and survival. Studies in mouse psoriasis models have shown that excessive activation

of mTOR is associated with autoimmune diseases, such as psoriasis (12,13). In 2013, the role of mTOR signaling pathway activation in SS was first described (14), but the mechanism of its specific occurrence and development in pSS has not yet been fully elucidated. The excessive activation of mTOR is associated with immune disorders (15), namely the activation of immune cells and the secretion of pro-inflammatory factors, which disrupts the balance of the immune system. This may be associated with the occurrence and development of pSS. PSS has a notable impact on patient health and quality of life, as well as causing a social and economic burden. Therefore, by reviewing the potential role of the mTOR signaling pathway in pSS, the present study aimed to identify the potential pathogenesis of pSS and therapeutic targets.

2. Methodology

A comprehensive literature search was performed using PubMed (ncbi.nlm.nih.gov/pubmed/), Web of Science (webofscience.com/wos/woscc/basic-search) and Google Scholar (https://scholar.google.com) databases. The search terms were as follows: 'Sjögren's syndrome', 'mammalian target of rapamycin', 'mTOR signaling pathway and composition', 'mTOR and immune cells', 'mTOR and B cells', 'mTOR and T cells', 'mTOR and monocytes/macrophages', 'mTOR and dendritic cells', 'Sjögren's syndrome and epidemiology', 'Sjögren's syndrome', 'Sjögren's syndrome and mTOR and pathogenesis', 'Sjögren's syndrome and molecular pathways', 'Sjögren's syndrome and pathogenesis', 'Sjögren's syndrome and treatment', 'Sjögren's syndrome and mTOR signaling pathway inhibitors', 'Sjögren's syndrome and rapamycin. 'Sjögren's syndrome and metformin', 'Sjögren's syndrome and PI3K inhibitors', 'Sjögren's syndrome and sirolimus', 'Sjögren's syndrome and berimumab', 'systemic lupus erythematosus and PI3K inhibitors' and 'systemic lupus erythematosus and sirolimus'. After reading the abstracts of the literature, duplicate and irrelevant studies were excluded. Exclusion criteria were as follows: i) Not related to the topic of the article; ii) Repetitive literature; iii) correspondence or letter. For the repetitive studies, articles with higher impact factors were selected for the review. A total of 123 relevant papers were included, including original research and review articles.

3. mTOR signaling pathway

In 1991, TOR was identified during the screening of rapamycin-resistant yeast mutants (16). Rapamycin, used as an immunosuppressant and anticancer drug, interacts with TOR to regulate cell proliferation and metabolism (16). In 1994, its mammalian homolog, mTOR, was discovered (17). mTOR is a serine/threonine kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase family (18). It is a highly conserved protein composed of 2,549 amino acids, with a molecular weight of ~289 kDa (19). mTOR forms two distinct complexes, mTOR complex (mTORC)1 and 2 (Fig. 1) (20). mTORC1 contains three core components: mTOR, the mammalian lethal Sec13 protein 8 and the mTOR regulatory-associated protein (Raptor), along with DEP domain-containing mTOR-interacting protein (Deptor). By contrast, mTORC2 lacks Raptor but contains Rictor (20). These two complexes differ in composition and function. mTORC1 regulates protein and lipid synthesis, suppresses catabolic processes such as lysosomal biogenesis and autophagy, promotes cell proliferation and survival and responds to environmental cues such as nutrients, stress, oxygen levels and growth factors (21). By contrast, mTORC2 primarily influences cell survival, metabolism and cytoskeletal organization and is involved in regulating cell chemotaxis and migration (22).

Upstream of mTOR, various growth factors and signaling molecules, including PI3K and the tuberous sclerosis complex (TSC1/2), regulate its activation (Fig. 1) (23). The downstream targets of the PI3K pathway include serine/threonine kinases such as Akt, which participate in metabolic regulation, cell survival and proliferation (24). Thus, mTOR serves as a central hub connecting multiple signaling pathways and regulating key cellular functions. Among these, the PI3K/Akt/mTOR signaling pathway plays a critical role in controlling metabolism and determining cell fate processes, including proliferation, differentiation and apoptosis (25,26).

Downstream of mTOR, the primary effectors include ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein (20). Once mTORC activates S6K, it transmits upstream signals to multiple effectors, regulating mRNA translation, promoting protein and lipid synthesis and inhibiting autophagy. These processes collectively enhance cell proliferation (Fig. 1) (27,28). Several regulatory molecules also modulate the mTOR signaling pathway, including TSC1/2 and PTEN, which serve as negative regulators of mTOR activity, preventing excessive activation and uncontrolled cell proliferation (Fig. 1) (29). Decreased mTOR activation impairs lymphocyte development, proliferation and migration, leading to immune deficiency. Conversely, hyperactivation of mTOR is associated with autoimmune disease (30,31).

4. mTOR signaling pathway in immune cells

The mTOR signaling pathway serves a pivotal role in regulating the activation, proliferation and differentiation of immune cells, thereby influencing their functional properties. Dysregulation of this pathway can lead to immune imbalance (32-66) (Fig. 2). Due to its critical role in immune cell development and function, mTOR signaling has garnered increasing research attention.

mTOR signaling pathway and DCs. DCs are specialized immune cells responsible for initiating innate immune responses by capturing, processing and presenting antigens to naïve T cells. They serve a vital role in bridging innate and adaptive immunity by promoting T cell activation (32). Studies have demonstrated that the mTOR signaling pathway is key for regulating the development and differentiation of DCs (33,34). In both NOD/B6.SJL mice and humans, inhibition of mTORC impairs DC expansion induced by growth factors (34,35). Conversely, loss of PTEN activates the PI3K/Akt/mTOR signaling pathway, thereby promoting DC proliferation and expansion (34). Under the regulation of transcription factors IFN regulatory factors 5 and 7, mTORC1 activation enhances the expression of type I IFN in DCs (36).

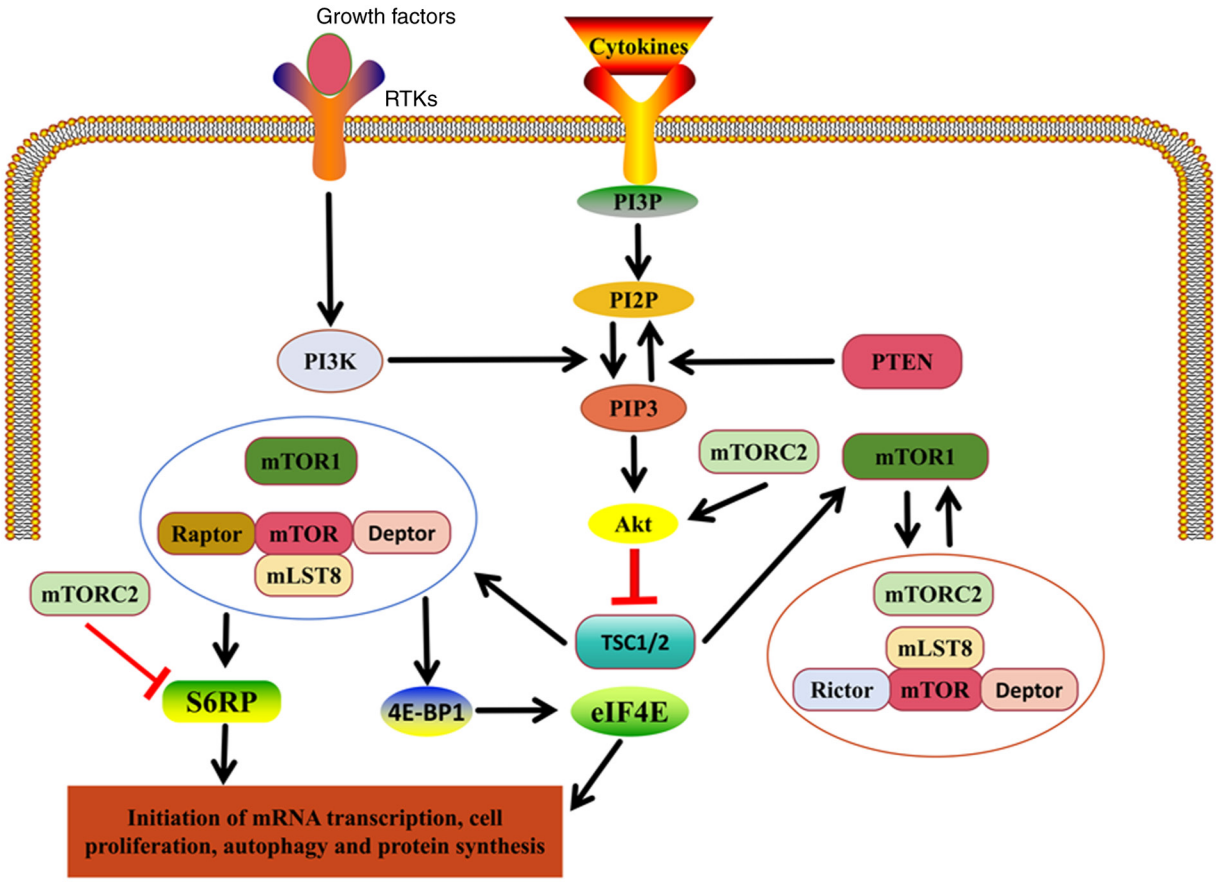

Figure 1. mTOR signaling pathway components and related functions. Growth factors, cytokines and mitogen-activated RTKs attach to the plasma membrane by recruiting PI3K, which catalyzes PIP2 to PIP3 conversion. PTEN can inhibit this process. PIP3 promotes AKT activation via the activity of mTORC1 and mTORC2. AKT activation induces the phosphorylation of the downstream substrate TSC2 and inhibits its activity, promotes the activation of mTORC1, activates the downstream S6RP and initiates eukaryotic protein translation. Activation of 4E-BP1 enhances the release of eIF4E. mTOR signaling promotes cell cycle progression, cell proliferation, survival and protein synthesis. RTK, receptor tyrosine kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; TSC, tuberous sclerosis; 4E-BP, eIF4E-binding protein; mLST8, mammalian lethal with SEC thirteen 8; Rictor, rapamycin-insensitive companion of mTOR; S6KP, ribosomal S6 kinase polypeptide; Raptor, regulatory-associated protein of mTOR.

IL-4 activates mTORC1 in monocytes, inducing their differentiation into DCs, whereas inhibition of mTOR promotes DC apoptosis (37,38).

mTOR signaling pathway and monocytes/macrophages. Monocytes and macrophages are phagocytic immune cells that initiate and regulate inflammation through diverse signaling mechanisms. They migrate to inflammatory sites, where they differentiate into macrophages with distinct functional phenotypes (39,40). The mTOR signaling pathway plays a central role in monocyte activation and differentiation into heterogeneous macrophage subsets, thereby maintaining immune homeostasis. Dysregulation of this pathway disturbs immune balance and has been implicated in various inflammatory diseases, such as gout and sepsis (42,43). Deletion of the TSC2 gene in monocytes results in mTORC1 activation, which enhances IL-10 production while suppressing pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α following lipopolysaccharide stimulation (44). Additionally, activation of the PI3K/Akt/mTOR signaling pathway promotes polarization of monocytes toward the M2 macrophage phenotype (45). Conversely, inhibition of this pathway favors polarization toward the M1 phenotype (45,46). Persistent mTORC1 activation in macrophages induces hypertrophy and proliferation, contributes to immune pathology and is associated with granuloma formation (47).

mTOR signaling pathway and T cells. T cells are key components of the adaptive immune system. Upon antigen recognition by the T cell receptor and the presence of co-stimulatory molecules and cytokines, CD28-mediated co-stimulation activates the PI3K/Akt/mTOR signaling pathway. This activation supports metabolic activity and initiates the activation, proliferation, and differentiation of $CD4^+$ and $CD8^+$ T cells (48). When mTOR activity is low, immature T cells remain in a quiescent state (49). Conversely, hyperactivation of mTOR enhances IL-12-mediated signal transducer and activator of transcription 4 signaling, leading to increased expression of IFN-γ and T-box transcription factor TBX21, which promotes $CD4^+$ T cell differentiation into the T helper (Th)1 phenotype (50). Overactivation of mTORC2 in T cells induces high expression of the transcription factor GATA3 and promotes differentiation into Th2 cells, accompanied by the production of IL-4, IL-5 and IL-13 (51). In the presence of transforming growth factor (TGF)-β and IL-6, excessive activation of mTORC1 upregulates the transcription factor retinoic acid-related

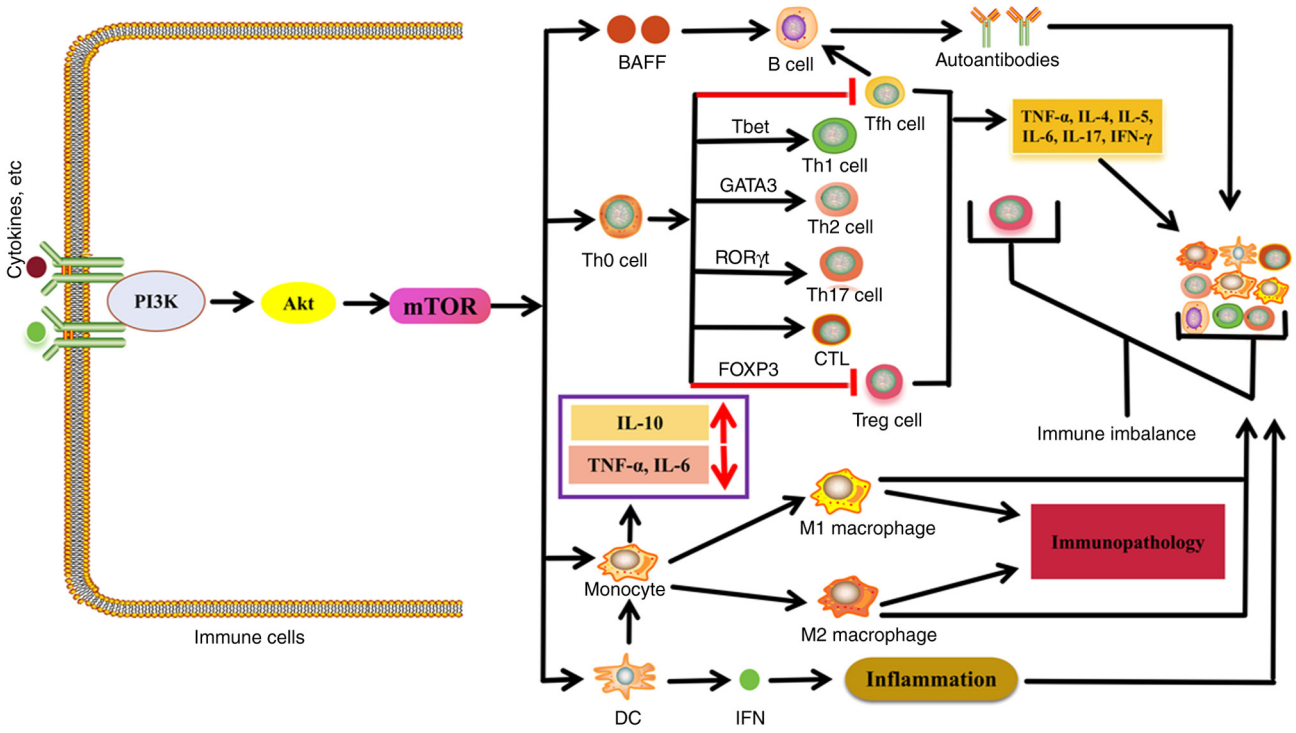

Figure 2. Effects of mTOR signaling pathway activation on immune cells. mTOR signaling is activated in immune cells under the action of cytokines and growth factors. DCs secrete type I IFN and differentiate into monocytes. Monocytes primarily differentiate into M1 cells, leading to an imbalance between M1 and M2 macrophages and the release of cytokines, which causes immunopathology. The activation of the mTOR signaling pathway in T cells increases the expression of Tbet, GATA3 and RORγt and decreases the expression of FOXP3, promoting the differentiation of primordial T cells into Th1, Th2, Th17 cells and CTL, inhibiting the differentiation into Treg and Tfh cells and causing an imbalance between Th17 and Treg cells. Th17 cells secrete pro-inflammatory cytokines, such as TNF-α, IL-6, IL-17 and IFN-γ. The activation of the mTOR signaling pathway enhances BAFF stimulation, thereby leading to the uncontrolled proliferation of B cells and the production of excessive autoantibodies. This immune imbalance is associated with autoimmune diseases. DC, dendritic cell; Tbet, T-box transcription factor TBX21; GATA3, GATA binding protein 3; RORγt, retinoic acid receptor-related orphan receptor γt; FOXP3, forkhead box P3; Th, thelper; CTL, cytotoxic T lymphocyte; Treg, regulatory T; Tfh, T follicular helper; TNF, tumor necrosis factor; BAFF, B cell activating factor.

orphan receptor (ROR)γt, driving $CD4^+$ T cell differentiation into Th17 cells (51-52). Conversely, inhibition of mTOR favors the differentiation of regulatory T (Treg) cells and T follicular helper (Tfh) cells (48,53). Experimental evidence shows that knockout of the mTOR gene in mice increases the population of forkhead box P3 $(FOXP3)^+$ Treg cells (54-55). By contrast, increased mTORC1 activity disrupts Treg stability, resulting in elevated production of IL-17 and IL-1β and enhancing inflammatory responses (54-55). Moreover, loss of TSC2 leads to increased generation of effector $CD8^+$ T cells, indicating that mTORC activity is essential for effector $CD8^+$ T cell differentiation, whereas memory $CD8^+$ T cell formation is markedly reduced (56,57). In summary, the mTOR signaling pathway serves as a central regulatory hub that coordinates multiple aspects of T cell biology, including development, activation, differentiation, survival and memory formation.

mTOR signaling pathway and B cells. B cells are essential components of the immune system. The differentiation fate of immature B cells depends on the integration of signals from B cell receptors (BCRs), co-stimulatory molecules and cytokines (58). Following BCR activation, AKT is recruited and phosphorylated, leading to activation of the PI3K/Akt/mTOR signaling pathway. This activation promotes protein synthesis, proliferation and differentiation in B cells and amplifies BCR and CD40 signaling, enabling naïve B cells to rapidly differentiate into antibody-secreting cells via the extrafollicular (EF) pathway and migrate to germinal centers (59). Decreased mTORC1 activation in B cells impairs early development and decreases the formation of antibody-secreting plasma cells (60,61). Conversely, hyperactivation of mTORC1 accelerates EF plasma cell differentiation (62). Disruption of mTOR transcription hinders B cell development and proliferation at multiple stages (63). For example, the survival, proliferation and metabolic activity, both oxidative and glycolytic, of pre-B cells are diminished, while peripheral B cell populations are depleted. This results in plasma cell dysfunction and a failure to complete the preparatory processes required for antibody production (54-65). Furthermore, mTOR activation enhances the stimulatory effects of B cell activation factor (BAFF), promoting uncontrolled B cell proliferation and contributing to pathological autoimmunity (66). These findings indicate that excessive mTOR signaling promotes dysregulated B cell proliferation, potentially leading to autoimmune disease.

5. Epidemiology of pSS

According to a global epidemiological study based on PubMed and Embase data, the overall incidence of pSS was 6.92 cases/100,000 person-years, and the overall prevalence was 60.82 cases/100,000 people in 2013 (67). pSS is more common in middle-aged female patients, with a male-to-female incidence ratio of ~9:1 (68). The diagnostic age of pSS is generally ~50 years, with an average diagnostic age ranging from

51.6±13.8 to 62.0±13.0 years old (69,70). The initial symptoms typically appear before diagnosis, because patients often ignore dry mouth and eyes (69,70). In addition, the incidence of pSS increases with age. The incidence rate peaks in female patients aged between 55 and 64 years and in male patients aged between 65 and 74 years (71). The prevalence of pSS varies in different regions. Research has found that the prevalence of pSS among patients with a European background is twice as high as that among non-European patients (72). There are also differences between ethnicities. Black patients are diagnosed with SS at an earlier age, and the male-to-female ratio of Asian patients is 27:1 (73). In a systematic review and meta-analysis, it was found that the standardized mortality rate of patients with pSS is 1.38 (74). The primary causes of death are cardiovascular diseases, solid organ and lymphoid malignancy and infections (74). In addition, multiple risk factors [such as male sex, older age at diagnosis, extraductal involvement, vasculitis, anti-Sjögren syndrome B antibody (SSB) positivity, hypocomplementemia and cryoglobulinemia] are associated with an increased mortality rate (74).

6. Potential mechanisms of mTOR signaling in the pathogenesis of pSS

The pathogenesis of pSS is highly complex (75). Similar to other autoimmune diseases, its development is influenced by genetic predisposition, viral infection and environmental factors (75). These pathogenic factors contribute to pSS primarily by inducing abnormal immune responses, leading to dysregulated activation of immune cells, inflammatory mediators, signaling pathways and the IFN system. This immune dysregulation promotes extensive lymphocytic infiltration of the submandibular glands, resulting in structural damage, impaired glandular function and ultimately the onset of pSS (76). Treatment of submandibular gland epithelial cells with bleomycin activates the Akt/mTOR signaling pathway, accelerates apoptosis and disrupts glandular architecture, indicating that aberrant mTOR activation may contribute to pSS pathogenesis (77). In a study of 58 patients with pSS, mTOR and PTEN protein expression was significantly elevated in SG biopsy samples, suggesting that both molecules may serve roles in disease development (78). Co-elevation of these proteins has also been reported in tumors (79), potentially reflecting a compensatory increase in PTEN to counteract excessive mTOR activity. However, additional research is required to elucidate the influence of PTEN in pSS pathogenesis.

In Th17 cells from patients with pSS, the mRNA levels of PI3K, Akt, mTOR and IL-17 are significantly higher than those in healthy controls (80,81). This suggests activation of the PI3K/Akt/mTOR signaling pathway contributes to the proliferation and differentiation of $CD4^+$ T cells into Th17 cells and promotes IL-17 secretion (80,81). Activation of the mTOR pathway facilitates the nuclear translocation of RORγt, promotes Th17 differentiation and inhibits expansion of the Treg population, resulting in immune dysregulation and an imbalance between Th17 and Treg cells (82,83). IL-17 produced by Th17 cells induces the secretion of pro-inflammatory cytokines such as TNF-α and IL-1β. It also attracts immune cells to the SG by stimulating IL-8 and chemokine release, thereby amplifying glandular inflammation (84). In addition, Th17 cells secrete IL-22, which recruits B cells and enhances autoantibody production via cytokine-mediated stimulation (85). Inhibition of mTOR decreases RORγt protein expression and Th17 polarization, while increasing FOXP3 expression and Treg cell numbers, thereby restoring the Treg/Th17 balance (86). These observations indicate that the Th17/Treg imbalance driven by mTOR pathway activation serves a key role in initiating and promoting pSS progression.

As aforementioned, activation of the mTORC signaling pathway also induces the proliferation and differentiation of $CD4^+$ T cells into Th1 and Th2 subsets. The immune response in the SG of patients with pSS is predominantly mediated by Th1 cells, and Th1-associated cytokines such as IFN-γ and TNF-α are significantly elevated in SG tissue (87,88). These cytokines disrupt the integrity of tight junctions in SG epithelial cells and decrease the number of vesicle cells, thereby impairing glandular secretory function (88,89). Th2 cells contribute to B cell activation through cytokines such as IL-4 (90). The mTORC signaling pathway also activates macrophages, monocytes and DCs, which produce large quantities of type I IFN and IFN-γ, amplifying the inflammatory response and inducing elevated expression of BAFF. Elevated BAFF levels are observed in the SG of patients with pSS (91). The interaction between BAFF and its receptor promotes B cell activation, maturation and proliferation, leading to aberrant antibody production, including anti-Sjögren's-syndrome-related antigen (SS)A and anti-SSB autoantibodies. These autoantibodies bind glandular epithelial cells and transmit activating signals to T cells, driving their differentiation into $CD8^+$ cytotoxic T lymphocytes (CTLs) (88). CTLs accumulate within the SG, where they secrete high levels of IFN-γ and TNF-α, sustaining glandular inflammation and contributing to the pathogenesis of pSS (88). Additionally, type I IFN stimulates macrophages to produce the chemokine C-X-C motif ligand 13 (CXCL13), which promotes B cell aggregation within the SG, thereby intensifying the inflammatory response (92). In this proinflammatory milieu, the mTOR signaling pathway activates macrophages to polarize toward the M1 phenotype, leading to the release of proinflammatory cytokines such as TNF-α, IL-6 and IL-12 (93,94). These cytokines accelerate extracellular matrix degradation and cell apoptosis, promote T cell differentiation into Th1 cells and exacerbate glandular inflammation, resulting in tissue destruction (93,94). As pSS progresses, this chronic inflammation gradually subsides, and M1 macrophages polarize toward the M2 phenotype under the influence of TGF-β1 signaling (88,95). M2 macrophages secrete anti-inflammatory mediators, including IL-10 and TGF-β, which further reinforce M2 polarization and signaling, thereby promoting glandular fibrosis (88,95). Under this sustained inflammatory state, vascular endothelial cells in the SG become damaged. Intercellular adhesion molecule-1 facilitates the adhesion of immune cells to endothelial surfaces, promoting endothelial cell activation. Consequently, vascular inflammatory responses increase vascular permeability, creating a favorable environment for the migration of immune cells, such as DCs, macrophages and lymphocytes, from the periphery into the SG, thereby enhancing immune cell infiltration (75,96,97). Therefore, in pSS, activation of the mTOR signaling pathway primarily influences immune cell proliferation and differentiation, contributes to immune imbalance,

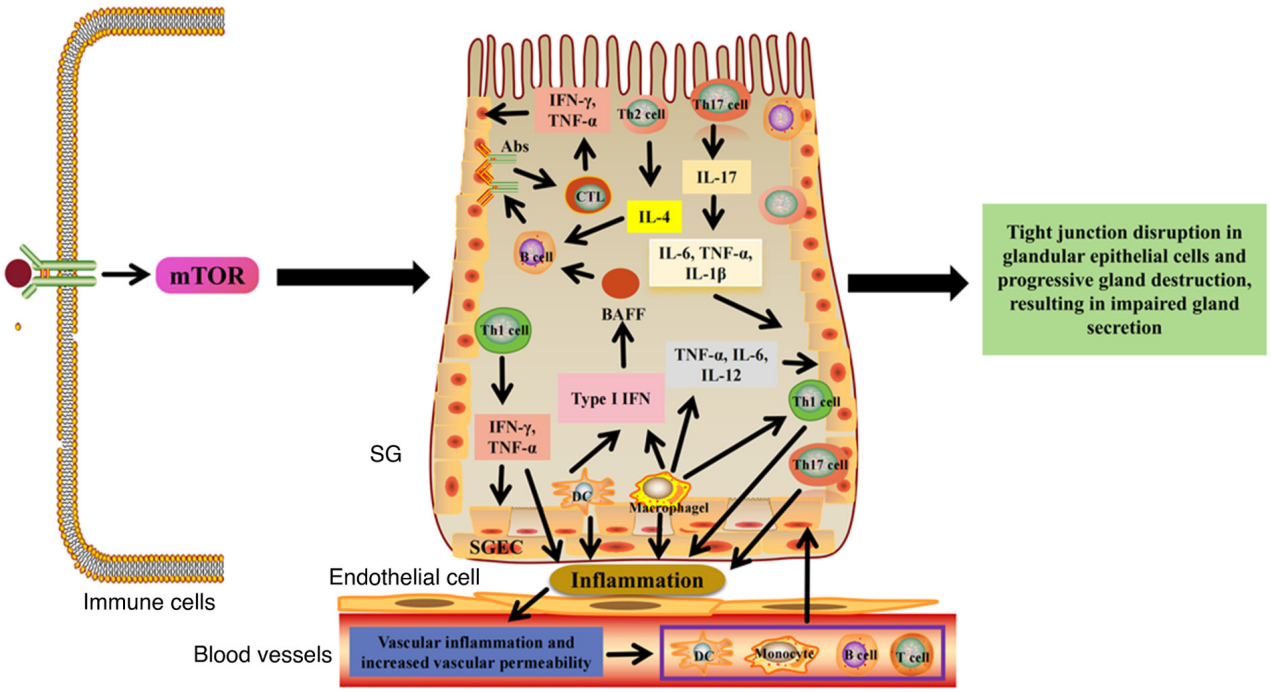

Figure 3. Potential mechanisms of mTOR signaling in the pathogenesis of pSS. In pSS, the levels of inflammatory cytokines and growth factors increase. After binding receptors on the surface of immune cells, These inflammatory cytokines and growth factors activate the mTOR signaling pathway of these cells, promoting the proliferation and differentiation of immune cells and their infiltration into the glands. For example, DCs secrete a large amount of type I IFN. In addition to secreting a large amount of type I IFN, the infiltration of M1 macrophages can also produce inflammatory cytokines (TNF-α, IL-6, IL-12) and induce T cells to differentiate into Th1 cells. When T cells are activated by the mTOR signaling pathway, they differentiate into Th1, Th2 and Th17 cells and CTL, and infiltrate glandular epithelial cells. Th1 cells secrete pro-inflammatory cytokines such as IFN-γ and TNF-α, while Th17 cells secrete IL-17 and induce the production of IL-6, TNF-α and IL-1β. Th2 cells secrete IL-4, promoting the activation of B cells. Under the action of type I IFN, BAFF is activated, which leads to the activation of B cells and the production of excessive autoantibodies. These antibodies bind glandular epithelial cells, activating CTL and secreting IFN-γ and TNF-α. Under the influence of immune cells and inflammatory cytokines, inflammation of the glands and blood vessels occurs, leading to an increase in vascular permeability. Under the action of chemokines, DCs, B and T cells and monocytes in peripheral blood migrate to the glands. In this state of immune imbalance, the tight junction structure of glandular epithelial cells is disrupted, leading to progressive damage to the glandular structure and secretory dysfunction, which develops into pSS. DC, dendritic cell; Th, thelper; CTL, cytotoxic T lymphocyte; Treg, regulatory T; TNF, tumor necrosis factor; BAFF, B cell activating factor; Ab, autoantibody; SGEC, salivary gland epithelial cell; pSS, primary Sjögren's syndrome; SG, salivary gland.

such as Th17/Treg disequilibrium and M1/M2 polarization imbalance, promotes the production of inflammatory cytokines and chemokines and facilitates immune cell infiltration into the SG. The resulting inflammatory response disrupts the tight junctions of glandular epithelial cells, progressively destroying glandular architecture via atrophy, ductal dilation and narrowing, leading to glandular damage and secretory dysfunction (Fig. 3).

Activation of the Akt/mTOR signaling pathway may improve pSS progression (98). This occurs because mTOR activation induces the expression of membrane-associated microtubule-associated protein light chain 3, which promotes autophagy and exerts a protective effect against glandular atrophy (98).

7. Current treatments for pSS

At present, the specific treatment plan for pSS is unclear, and there is no radical cure. Symptomatic treatment is the primary approach, with the aim of alleviating the symptoms of exocrine diseases and controlling extraductal manifestations. The first-line treatment drugs for SS-associated dry eye syndrome include artificial tear drops and lubricating ointments (99). Topical cyclosporine, when used alone or in combination with topical steroids, as well as oral muscarinic receptor agonists such as rutin, serve as lacrimal gland secretants and help alleviate dry eye symptoms (100). For dry mouth symptoms, patients drink water frequently during the day and chew sugar-free gum to increase saliva flow and maintain oral lubrication (99,100). At the same time, it is recommended that patients maintain oral hygiene and have regular dental check-ups due to the risk of tooth decay. If necessary, muscarinic agonists should be used to promote SG secretion (101). There are also challenges in the treatment of pSS outside the gland. Typically, the management strategies of closely related systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are used. These drugs include non-steroidal anti-inflammatory drugs, glucocorticoids, immunosuppressants (such as methotrexate, leflunomide, sulfasalazine or cyclosporine) and biological agents (such as belimumab and rituximab) (101). When pSS involves some organ complications, such as lung diseases, decreased blood cell (such as white blood cells and platelets) levels, vasculitis, kidney disease and central nervous system and musculoskeletal disorder, these drugs (such as methotrexate, leflunomide, sulfasalazine or cyclosporine) need to be used in combination (99,102). Depending on the overall organ involvement, it may be necessary to consult specialists and adopt a comprehensive multidisciplinary approach. Although these drugs have achieved certain therapeutic effects, they

cannot cure the disease and there are some adverse reactions, such as infections, osteoporosis, gastrointestinal and cardiovascular complications, gonadal toxicity, bone marrow suppression, fetal malformation and miscarriages (103). This also highlights the need for potential therapies.

8. Potential of targeting mTOR signaling in the treatment of pSS

As aforementioned, the immune dysregulation resulting from excessive activation of multiple immune cell types by the mTOR signaling pathway in patients with pSS contributes to disease onset and progression. Beyond SG involvement, this dysregulation may also affect extraglandular organs, leading to complications that impair organ function and, in severe cases, threaten patient survival (74). Therefore, targeting the mTOR signaling pathway represents a key therapeutic strategy for improving clinical outcomes in patients with pSS.

Immunohistochemical analysis of SGs from patients with pSS has shown increased expression of phosphorylated Akt and mTOR in infiltrating lymphocytes, suggesting that activation of the Akt/mTOR signaling pathway may be associated with pSS pathogenesis (104). *In vitro,* treatment with fangchinoline, an mTOR pathway inhibitor, suppresses Akt/mTOR signaling in B cells, leading to decreased cell proliferation, cell cycle arrest and enhanced apoptosis (104). Mesencephalic astrocyte-derived neurotrophic factor (MANF), an evolutionarily conserved protein secreted by brain astrocytes, is upregulated during inflammation and is implicated in the pathogenesis of inflammatory disease (105). When MANF is co-cultured with lymphocytes from patients with *pSS in vitro* study, it downregulates Akt and mTOR phosphorylation and promotes autophagy in $CD4^+$ T cells (106). Moreover, MANF decreases lymphocytic infiltration in the SG and tripartite motif-containing 21/SSA expression (106). Similarly, co-culture of rapamycin (100 nM) with Th and B cells from patients with pSS *in vitro* inhibits mTOR activity, thereby reducing the activation and proliferation of these cells and suppressing IFN-γ and immunoglobulin G production (80). Another *in vitro* study using iguratimod to treat $CD4^+$ T cells from patients with pSS showed that the drug targets pyruvate dehydrogenase kinase 1, inhibiting the Akt/mTOR signaling pathway (107). This inhibition suppresses the activation, proliferation and differentiation of Tfh cells, further impairing B cell activation and differentiation (107). Collectively, these *in vitro* studies support the therapeutic potential of targeting the mTOR signaling pathway in the treatment of pSS.

In a mouse model of pSS, treatment with a rapamycin nanoparticle formulation (250 μM) downregulates mTOR gene expression and significantly decreases lymphocyte infiltration in the lacrimal glands (LGs), while simultaneously minimizing systemic toxicity (14). Compared with intraglandular delivery, the residence time of rapamycin within the LGs is prolonged. Consequently, a lower total drug dose is sufficient to suppress LG inflammation and improve tear secretion, with no evidence of necrosis or fibrosis in the glands (108). These findings suggest that rapamycin represents a promising therapeutic candidate for pSS-associated lacrimal gland inflammation, achieving efficacy through localized delivery that allows dose reduction and minimizes systemic side effects. Runzaoling (RZL), a traditional Chinese medicine clinical prescription with immunomodulatory properties, administered via continuous gavage to non-obese diabetic (NOD) mice for 10 weeks inhibits the mTOR signaling pathway, downregulates IL-17 expression in Th17 cells of the submandibular gland and decreases $CD4^+$ T cell differentiation into Th17 cells (81). In addition, metformin has demonstrated immunoregulatory and anti-inflammatory effects (109). In a pSS mouse model, oral administration of metformin for 9 weeks enhances Treg cell populations through activation of the AMPK/mTOR signaling pathway (110). It also suppresses Th1, Th17 and Tfh cell differentiation and decreases B cell activation, thereby lowering the levels of IL-6, TNF-α and IL-17 (110). In a *in vivo* study, the combined use of artemisinin salts and metformin demonstrated a greater improvement in salivary secretion compared with artemisinin salts alone (111). This combination primarily regulates the PI3K/Akt pathway, inhibiting apoptosis and autophagy in SGs of patients with type 2 diabetes-associated xerostomia, thereby alleviating SG damage (111). These findings highlight the potential of metformin to target the mTOR signaling pathway for the treatment of pSS. Another compound with antirheumatic properties, fangchinoline, a biologically active dibenzylisoquinoline alkaloid, activates the Akt/mTOR signaling pathway in NOD mice (104). Fangchinoline effectively inhibits B lymphocyte proliferation, decreases lymphocytic lesions in the submandibular gland and increases salivary secretion in mice (104). Seletalisib, a potent and selective oral PI3K inhibitor that modulates the Akt/mTOR signaling pathway, significantly decreases phosphorylation of ribosomal protein S6 in pSS mice (112). Treatment with seletalisib also decreases the numbers of B and T lymphocytes and plasma cells in the SG, leading to reduced autoantibody titers and improved salivary secretion (112). Similarly, oral administration of parsaclisib in pSS mice ameliorates SG inflammation, decreases BAFF expression in saliva and lowers levels of autoreactive B cells and autoantibodies (113). PI3Kδ inhibitor AS2819899 suppresses T cell-dependent antibody production, markedly reduced anti-double-stranded DNA antibody titers and improves renal dysfunction in spontaneous systemic lupus erythematosus (SLE) mice (114). Similarly, alpelisib, a PI3Kα inhibitor, modulates B and T cells in a murine model of SLE nephritis by inhibiting PI3Kα activity, which decreases proinflammatory cytokine and autoantibody production, diminishes glomerular complement deposition and improves renal histopathology and function (115).

Regarding clinical studies, available data remain limited. In a two-stage randomized, double-blind clinical study, treatment of patients with pSS using seletalisib led to decreased B and T cell numbers within the SG and shrinkage of glandular lesions, demonstrating the therapeutic potential of targeting the PI3K/mTOR signaling pathway in pSS management (116). However, adverse events were reported, including diarrhea, abnormal hepatic and renal function and allergic dermatitis (116). In a single-center, single-arm phase II clinical study involving patients with connective tissue disease-associated immune thrombocytopenia (ITP), oral administration of the mTOR inhibitor sirolimus (6-15 ng/ml) for 6 months produced no therapeutic response in pSS-associated ITP (pSS-ITP) cases and no significant changes were observed in lymphocyte subsets; no serious adverse effects were detected during the study period (117). Conversely, another clinical study reported that 75% of patients with pSS-ITP who receive sirolimus

Table I. Summary of the potential of drugs targeting mTOR signaling pathway in primary Sjögren's syndrome.

Drug	Study type	Target	Potential therapeutic effect	(Refs.)
Fangchinoline	*In vitro*	Akt/mTOR	Inhibits B cell proliferation; induces B cell cycle arrest and promotes their apoptosis	(104)
MANF	*In vitro*	AKT and mTOR	Activates autophagy; decreases infiltration of salivary gland lymphocytes, proportion of $CD4^+$ T cell subsets and levels of autoantibodies	(106)
Rapamycin	*In vitro*	mTOR	Inhibits the activation, proliferation and differentiation of Th and B cells; decreases the production of IFN-γ and immunoglobulin G	(80)
Iguratimod	*In vitro*	PDK1	Attenuates downstream Akt phosphorylation; inhibits the activity of mTORC1 and activation, proliferation and differentiation of Tfh and B cells	(107)
Rapamycin	NOD mouse model	mTOR	Decreases the infiltration of LG lymphocytes while lowering toxicity; inhibits LG inflammation and improves tear production	(14,108)
Runzaoling	NOD mouse model	PI3K/AKT/ mTOR	Downregulates STAT3 and IL-17 expression in the submandibular gland and Th17 cells; decreases activation of $CD4^+$ T lymphocyte differentiation to Th17 cells	(81)
Metformin	NOD/ShiLtJ mouse model	PI3K/Akt, AMPK/ mTOR	Decreases the Th17 and Th1 cell population and increases the regulatory T cell population in the peripheral blood and spleen; modulates the balance between Tfh and follicular regulatory T cells; decreases B cell differentiation into germinal center B cells; decreases the serum immunoglobulin G levels; maintains the balance between IL-10- and IL-17-producing B cells; inhibits apoptosis and autophagy; decreases salivary gland inflammation and restores the salivary flow rate	(110,111)
Fangchinoline	NOD/Ltj mouse model	AKT/mTOR	Significantly improves salivary secretion and decreases the number of lymphocytic foci in the submandibular gland	(104)
Seletalisib	Mouse model	PI3Kδ	Decreases accumulation of lymphocytes and plasma cells within the SG; decreases the titer of autoantibodies; improves saliva secretion	(112)
Parsaclisib	Mouse model	PI3Kδ	Decreases BAFF in saliva; ameliorates the severity of salivary gland inflammation; decreases circulating levels of autoantibodies	(113)
AS2819899	NZB/W F1 mouse model	PI3Kδ	Significantly decreases anti-dsDNA antibody titers and improves kidney dysfunction	(114)
Alpelisib	NZBWF1/ OlaHsd and MRL-lpr mice model	PI3Kδ	Decreases production of proinflammatory cytokines, autoantibodies and glomerular complement deposition; improves glomerular lesions and kidney function	(115)
Seletalisib	Clinical trial	PI3Kδ	Decreases serum IgM and IgG concentrations and size and organisation of salivary gland inflammatory foci; no significant changes in saliva and tear flow	(116)
Sirolimus	Clinical trial	mTOR	Increases ratio of Treg cells, while decreasing levels of IL-8 and IL-17A; improves complement levels; elevates platelet levels but some patients do not respond.	(117-121)
Belimumab	Clinical trial	BAFF	Decreases total B cells in peripheral blood short-term; memory B cells decrease below baseline with the progress of treatment; decreases CXCL13 concentration; no notable improvement in xerostomia	(122,123)

MANF, mesencephalic astrocyte-derived neurotrophic factor; Th, T helper; PDK, pyruvate dehydrogenase kinase; mTORC, mTOR complex; Tfh, T follicular helper; LG, lacrimal gland; NOD, non-obese diabetic; BAFF, B cell activating factor; ds, double-stranded; Treg, regulatory T.

achieve overall remission (118). Of two patients with SS and SLE, one attained complete remission after 6 months and no severe drug-related toxicity was observed, and the other patient had no significant response (118). Similarly, in a clinical study of seven patients with pSS-ITP treated with sirolimus for 6 months, the complete, partial and non-response rates were 42.9, 42.9 and 14.3%, respectively (119). Treatment with sirolimus increased the proportion of Treg cells while significantly decreasing IL-8 and IL-17A levels (119). These findings suggest the therapeutic potential of sirolimus in pSS, however, larger studies are required to confirm its efficacy and safety. Notably, numerous patients experience adverse effects during treatment, including oral ulcers, hypercholesterolemia, gastrointestinal reactions and fungal infections (119). In other autoimmune diseases, sirolimus has also demonstrated favorable therapeutic efficacy: In a real-world clinical study involving 52 patients with SLE treated with sirolimus, complement levels improved more markedly at 3 and 6 months compared with those in the tacrolimus group (120). Moreover, a higher proportion of patients in the sirolimus group maintained prednisone doses ≤7.5 mg/day (120). In the treatment of lupus nephritis, sirolimus produces greater improvements in complement levels at 3, 6 and 12 months compared with mycophenolate mofetil therapy (121). The aforementioned studies reported mild adverse effects, including infection, leukopenia, gastrointestinal discomfort, rash and mild renal dysfunction. However, no serious adverse events or discontinuations of sirolimus therapy were observed (120,121). A clinical study found that belamcainide treatment of patients with pSS causes a transient decrease in total B cell counts in peripheral blood, whereas memory B cell levels remain elevated for a prolonged period before declining below baseline with continued therapy (122). The concentration of CXCL13, an alternative biomarker (B lymphocyte stimulator) reflecting SG immune activity, is decreased, however, no significant improvement in xerostomia symptoms is observed compared with controls (122). A preliminary clinical study reported upregulation of the PI3K/Akt/mTOR signaling pathway, which may be associated with inadequate clinical response to belamcainide (123).

The aforementioned *in vitro* studies, animal experiments and clinical investigations demonstrate that targeting the mTOR signaling pathway offers promising therapeutic potential in pSS (Table I). However, several limitations remain concerning the current evidence for its efficacy in patients with pSS. First, existing research has predominantly focused on preclinical investigations, including *in vitro* and animal studies, while clinical data are limited, with small sample sizes and inconsistent outcomes between studies (104-123). Second, the translational gap between preclinical models and human physiology introduces potential discrepancies in efficacy and safety. To address these issues, large-scale, prospective clinical trials are warranted to evaluate the therapeutic effects of mTOR pathway inhibition in pSS. Such studies will also clarify its safety profile and strengthen the generalizability and robustness of conclusions.

9. Conclusion

pSS is an autoimmune disease that not only affects the quality of life of patients but also increases economic burden. The immune disorder caused by mTOR activation is a potentially important factor in the pathogenesis of SS. Targeting the mTOR signaling pathway regulates the balance between immune cells. Therefore, mTOR signaling pathway inhibitors are promising and beneficial drugs in the treatment of pSS, but associated adverse reactions are noted. At present, there is still a lack of research on the activation of the mTOR signaling pathway and its targeting in pSS. The specific mechanisms involved in this signaling pathway and at the molecular level have not yet been clarified. Large-scale prospective studies are required to confirm the efficacy in reducing inflammation or raising platelets) and mechanisms. Optimal drug dosage and safety of mTOR inhibitors in pSS should be explored to provide novel therapeutic windows for pSS.

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Authors' contributions

RXH, CCW and YTY wrote the manuscript. DLM, YY and JYL performed the literature review and constructed figures. XXH conceptualized and designed the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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