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Mechanisms Underlying BAFF-Mediated Salivary Gland Damage in Sjögren's Disease and Advances in Targeted Intervention

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Abstract: ***Sjögren's disease (SjD) is a systemic autoimmune disease characterized by lymphocytic infiltration and persistent damage to exocrine glands. Clinical symptoms vary widely among individuals, and the insidious onset of the disease makes it prone to missed or misdiagnosis. B-cell activating factor (BAFF) participates in the regulation of multiple immune signaling pathways by binding to three types of receptors: BAFF-R, TACI, and BCMA. Existing studies have confirmed that BAFF expression levels are significantly elevated in the peripheral blood and salivary gland tissues of SjD patients and are closely associated with disease activity; By activating the NF-κB, PI3K/Akt/mTOR, and JAK-STAT signaling pathways, BAFF disrupts B-cell immune tolerance, promotes the proliferation and activation of autoreactive lymphocytes, and stimulates the massive secretion of autoantibodies, thereby inducing chronic inflammation and functional damage in the glands, while simultaneously increasing the risk of secondary non-Hodgkin lymphoma in SjD patients. This article systematically reviews the naming consensus and pathological characteristics of Sjögren's disease, elucidates the structural features of BAFF and the molecular pathways through which it mediates the pathogenesis of Sjögren's disease, and summarizes the key role of BAFF in disease progression, thereby providing a theoretical foundation for investigating the pathogenesis of Sjögren's disease and developing new targeted drugs.***

Keywords: Sjögren's disease, BAFF, Autoimmune diseases, Signaling pathways, Lymphocytes**.**

1. Introduction

Sjögren's disease (SjD) is a systemic autoimmune disease characterized by lymphocytic infiltration and proliferation, as well as progressive damage to exocrine glands—primarily the lacrimal and salivary glands. Impaired salivary function leads to a series of symptoms, such as dry mouth, which significantly reduces patients' quality of life [1]. SjD predominantly affects middle-aged and elderly women, presenting with diverse clinical manifestations and significant variability in symptoms among patients [2]. Studies have shown that traditional Chinese medicine can effectively improve clinical symptoms in SjD patients by regulating the expression of B-cell activating factor (BAFF), with a good safety profile. BAFF is a member of the tumor necrosis factor superfamily. By binding to three different receptors, it participates in multiple signaling pathways and regulates autoimmunity through the modulation of B-cell and T-cell development, survival, differentiation, and cytokine production. This article provides a systematic review of the latest research progress on the use of TCM to regulate BAFF for the treatment of SjD, with the aim of offering guidance for clinical diagnosis and treatment.

2. Clinical Background of Sjögren's Disease

2.1 Nomenclature of Sjögren's Disease

In the past, we typically referred to this disease as "Sjögren's Syndrome," which was classified into primary and secondary forms [1]. The 2023 International Rome Consensus on the Nomenclature of Sjögren's Disease strongly recommends that the term "Sjögren's disease" replace "Sjögren's Syndrome," with "Sjögren disease" serving as the official academic designation. The acronym "SjD" should be used as the abbreviation for "Sjögren's disease." It is recommended to use "associated" rather than "secondary" to better reflect its definition as a distinct systemic autoimmune disease [3,4].

2.2 Pathological Characteristics of Sjögren's Disease (SjD)

SjD predominantly affects women between the ages of 30 and 50. Clinical manifestations are diverse and include dry mouth, dry eyes, dry skin, fatigue, chronic joint pain, and involvement of multiple major organs. The disease has an insidious onset, and clinical symptoms vary widely, often leading to delayed or misdiagnosis [5]. Its pathogenesis is not yet fully understood; current research indicates that T/B lymphocyte hyperactivity plays a significant role in SjD [6], BAFF mediates immune dysregulation by regulating the differentiation and survival of T and B lymphocytes. Studies have confirmed significantly elevated BAFF levels in the serum and salivary glands (SG) of SjD patients [6], and other research indicates that single-nucleotide polymorphisms (SNPs) in the BAFF gene are associated with the pathogenesis of SjD [7]. Anti-BAFF therapy significantly reduced lymphocyte infiltration in the salivary glands, decreased the proportion of CD4 T cells in the salivary glands, reduced the number of B cells in the blood, spleen, and lymph nodes, and increased salivary flow [8].

3. BAFF Structure and Its Ligand

B-cell activating factor (BAFF/BLYS) belongs to the TNF ligand superfamily and is highly homologous to APRIL. It is also known as the tumor necrosis factor superfamily member 13b (TNFSF13B) gene, located on chromosome 13, which encodes the BAFF protein [9]. The BAFF protein exists in two forms: as a type II membrane protein (mBAFF/BLyS) or as a soluble protein (sBAFF/BLyS). The membrane-bound form

of BAFF is processed into the soluble form through proteolytic cleavage, typically forming a trimeric complex; the BAFF trimer can further assemble into a 60-mer, thereby enhancing its interaction with receptors [10,11]. BAFF is primarily expressed by certain T cells, as well as B cells, monocytes, dendritic cells, neutrophils, macrophages, salivary gland cells, and conjunctival epithelial cells. BAFF exerts its effects by binding to three distinct receptors: the T-cell-specific receptor transmembrane activator and CAML-interacting factor (TACI), the B-cell maturation antigen (BCMA), and the BAFF receptor (BAFF-R/BR3) [12]. BAFF modulates autoimmunity by regulating the development, survival, differentiation, and cytokine production of B and T cells.

4. Mechanisms of Action of BAFF and Its Receptors in SjD

4.1 NF-κB Signaling Pathway

SjD is primarily driven by B-cell activation. Activation of BAFF stimulates B-cell and T-cell function and regulates humoral immunity through calmodulin-dependent NF-AT, as well as NF-κB and AP-1 activation. BAFFR is the most important receptor for BAFF and exerts positive feedback regulation with the B-cell receptor (BCR) [13]. Surface expression of BAFFR is significantly reduced in both the naive and memory B-cell populations of patients with Sjögren's disease, upon binding of BAFF to BAFF-R, the non-classical NF-κB pathway—centered on NIK-IKKα—is activated, leading to the phosphorylation of the NF-κB2 precursor p100 and its proteolytic cleavage into the active form p52. This complex then translocates to the nucleus to regulate the transcription of target genes, thereby maintaining the survival and proliferation of autoreactive B cells [14]. In SjD, the abnormal upregulation of BAFF disrupts B-cell immune tolerance, causing autoreactive B cells to evade apoptosis and differentiate into plasma cells. These plasma cells continuously produce autoantibodies, which, upon deposition in target organs such as the salivary glands, trigger glandular inflammation and functional damage. Furthermore, activation of the BAFF-NF-κB pathway promotes the differentiation of B cells into lymphoid follicle-like structures, exacerbating local lymphocyte infiltration in the salivary glands and further aggravating the destruction of glandular tissue [15]. One study demonstrated that in a SjD mouse model treated with BAFF inhibition, lymphocyte infiltration into the salivary glands (SGs) was significantly reduced, and salivary flow was significantly improved. Treatment with anti-BAFF antibodies increased the proportion of CD3- and CD4-positive double-negative (DN) T cells in the SGs, leading to an increase in the proportion of Foxp3-regulated T cells within the SGs [14].

BAFF-R is present intracellularly in both normal and neoplastic B lymphocytes and can activate signaling through the classical NF-κB1 and non-classical NF-κB2 pathways. Nuclear BAFF-R is also associated with NF-κB/c-Rel; it activates the NF-κB signaling pathway via BAFF, CD154, Bcl-xL, IL-8, and Bfl-1/A1, and forms a functional transcriptional complex with c-Rel to regulate the expression of c-Rel target genes. The NF-κB inhibitor (IκB) kinase (IKK) protein complex is essential for the activation of the NF-κB pathway; both IKKα and IKKβ participate in histone H3 phosphorylation. BAFF-R can bind to IKKβ and enhance its kinase activity, further promoting histone H3 phosphorylation. Within the nucleus, BAFF-R forms a functional protein complex with c-Rel and IKKβ, promoting chromatin remodeling and transcription factor binding, thereby regulating the survival and proliferation of both normal and neoplastic B lymphocytes [15]. Studies have shown that Sjögren's disease (SjD) is highly associated with the risk of non-Hodgkin lymphoma (NHL); individuals with SjD have a 13. 7-fold higher risk of developing NHL than the general population [16,17].

4.2 PI3K/Akt/mTOR Signaling Pathway

BAFF expression levels are significantly elevated in the serum, salivary gland tissue, and peripheral blood of SjD patients, and are positively correlated with disease activity. High-concentration BAFF (hsBAFF) can enhance the phosphorylation of UNC-51-like kinase 1 (ULK1) and downregulate the expression of microtubule-associated protein 1 light chain 3 (LC3-II) by activating the Ca^{2+}-calmodulin-dependent kinase II (CaMKII)-Akt/mTOR signaling pathway, thereby inhibiting B-lymphocyte autophagy and promoting cell proliferation and survival [18]. BAFF can directly trigger the activation of PI3K; sustained PI3K activation is positively correlated with the titer of anti-La/SjDB antibodies [19]. After binding to the BCR on the surface of B cells, these antigens can activate PI3K via the BCR signaling pathway, creating a synergistic effect with BAFF-mediated signaling. This keeps the PI3K-Akt-mTOR pathway continuously activated, leading to the polarization of activated $CD4^+$ T cells into Th17 cells, which secrete pro-inflammatory cytokines such as IL-17, thereby exacerbating the local inflammatory response in the salivary glands [20]. BAFF-induced B-cell survival is independent of ERK1/2 activation but requires ERK5 activation. During BAFF-induced B-cell survival, the absence of ERK5 did not alter BAFF-mediated activation of the PI3K-Akt pathway, indicating that the PI3K-Akt pathway and the ERK5 pathway are independent, parallel signaling axes. and the two work synergistically from different dimensions (anti-apoptosis and autophagy inhibition) to mediate BAFF's regulation of B-cell survival [21].

4.3 JAK-STAT Signaling Pathway

The JAK-STAT pathway plays a key role in autoimmune and systemic inflammatory responses and serves as the signaling pathway for many cytokines [22,23]. The JAK-STAT signaling pathway can be activated by cytokines such as IFN-α, IFN-γ, IL-6, and long non-coding RNAs, and STAT dimers translocate to the cell nucleus to regulate the transcription of target genes. Among the cytokines that transmit signals via the JAK-STAT pathway, IL-6, IL-7, IL-21, IL-23, IFN-α, IFN-β, IFN-γ, and IFN-λ have been shown to potentially be involved in the pathogenesis of SjD [24,25]. BAFF levels in the serum of patients with Sjögren's disease (SjD) are significantly elevated and positively correlated with serum IgG, anti-Ro/SjDA, and anti-La/SjDB. At the same time, the expression of the BAFF receptors BR3 and TACI on peripheral blood mononuclear cells is higher than that in healthy controls (HC), with the BR3+/CD14+ ratio being approximately 2. 5 times

that of HCs and significantly higher than the TACI+/CD14+ ratio; furthermore, the BR3+/CD14+ ratio is positively correlated with serum IgG and IgM levels as well as the ESSDAI disease activity score in patients [26]. In vitro experiments showed that soluble BAFF (sBAFF) can significantly promote the secretion of IL-6 by monocytes in SjD by specifically binding to BR3 (rather than TACI) on monocytes; IL-6 production was positively correlated with the BR3+/CD14+ ratio. Furthermore, soluble factors such as IL-6 secreted by monocytes can further activate B cells, driving their excessive production of IgG, contributing to the disease progression of pSjD [27].

Type I IFNs (primarily IFN-α and IFN-β), Type II (IFN-γ), and Type III (IFN-λ) play important roles in the pathogenesis of SjD. Studies have shown that BAFF expression in the neutrophils of SjD patients is closely associated with the intensity of interferon profiles. Bioinformatics analyses have demonstrated elevated levels of IFN-γ and BAFF in SjD samples. In this model, the number of CD20+ B cells and cells expressing IFN-γ and BAFF was increased. IFN-γ induces BAFF protein expression; reducing IFN-γ levels significantly decreases BAFF expression and inhibits lymphocyte infiltration in mouse exocrine gland tissues, whereas BAFF overexpression reverses the inhibitory effect of IFN-γ. Studies have found that rs2069705 enhances IFNγ transcription by promoting the interaction between its promoter and STAT4. The SNP rs2069705 in the IFNγ gene enhances IFNγ transcription, activates the JAK/STAT1 pathway, and increases transcription in the BAFF promoter region, thereby leading to B-lymphocyte infiltration in exocrine glands [28,29]. Type I interferon directly induces BAFF expression via IRF1 and IRF2, while IRF4 and IRF8 act as negative regulators of BAFF expression. In patients with SjD, blocking type I interferon leads to downregulation of BAFF, accompanied by a reduction in autoreactive B-cell clones and autoantibodies [30]. IL-21 is a key cytokine in the type I interferon (IFN) signaling pathway, IL-17-producing T helper cells, and plasma cell differentiation and B-cell activation. IL-23 is a pro-inflammatory cytokine that is essential for the maintenance and expansion of Th17 and innate lymphoid cells (ILC) 3, as well as for the production of type 3 cytokines such as IL-17 and IL-22. Immunohistochemical staining has demonstrated strong IL-23 expression in the submandibular glands of C57BL/6. NOD-Aec1Aec2 mice, as well as in lymphocytes and epithelial tissues from SjD salivary gland biopsies [31]. Upon binding to the IL-21 receptor on submandibular gland epithelial cells, IL-21 activates JAK1 and JAK3, induces STAT1 and STAT3 phosphorylation, and regulates the expression of target genes (CCR7, CXCR5, CXCL10, and IL-21), thereby promoting the proliferation of B lymphocytes and Th17 cells as well as immunoglobulin production [32]. Increased expression of IL-23 in the salivary glands of SjD patients is associated with increased expression of IL-17 and IL-17-secreting cells (primarily Th17 and ILC3). Following the release of type I IFN, adaptive immune responses may occur, such as stimulation of CD8+ lymphocytes, differentiation of Th1 and Th17 lymphocytes, suppression of regulatory T (Treg) cell activity, enhanced BAFF release, and a reduction in the B-cell receptor (BCR) threshold, leading to excessive B-cell activation [33]. In Sjögren's disease (SjD), both single-cell RNA sequencing (scRNA-seq) of submandibular glands (MSGs) and transcriptomic analysis of peripheral blood mononuclear cells (PBMCs) revealed cell-type-specific upregulation of the JAK-STAT pathway and interferon-stimulated genes (ISGs). In vitro experiments showed that JAK inhibitors significantly reduced STAT levels in SGECs and PBMC monocytes.

5. Summary

Sjögren's Disease (SjD) has now been standardized under the international Rome Consensus, distinguishing it from the traditional Sjögren's disease; it is a systemic autoimmune disease with distinct pathological characteristics, and the excessive activation of T and B lymphocytes is its core pathological basis. BAFF, a key cytokine regulating lymphocyte homeostasis, is abnormally overexpressed in patients with SjD. By binding to specific receptors on the surface of target cells, it simultaneously activates the NF-κB, PI3K/Akt/mTOR, and JAK-STAT—three core signaling pathways. By promoting B-cell survival and proliferation, inhibiting lymphocyte autophagy, and amplifying the release of interferons and pro-inflammatory factors, BAFF disrupts immune tolerance at multiple levels, leading to lymphocyte infiltration and tissue damage in exocrine glands such as the salivary and lacrimal glands. Furthermore, single-nucleotide polymorphisms in the BAFF gene, as well as inflammatory mediators such as interferon family molecules, IL-6, IL-21, and IL-23, can interact with BAFF to create a cascading amplification effect, further exacerbating autoimmune dysregulation. Moreover, high BAFF expression is strongly associated with disease activity in Sjögren's disease and the risk of secondary lymphoma. Targeted interventions focused on BAFF and its downstream signaling pathways can effectively suppress glandular inflammation and restore glandular secretory function, representing a key research direction for innovative treatments of Sjögren's disease. This article comprehensively summarizes the molecular network through which BAFF regulates immune imbalance in Sjögren's disease, providing a theoretical framework for further exploration of disease mechanisms, the development of specific targeted drugs, and clinical disease assessment.

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