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**Review**

# Pathophysiologic role of Interleukin-33/ST2 in Sjögren's syndrome

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## Declaration of interest

The authors have no conflict of interest to state.

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This work has not been submitted or published elsewhere.

**Abbreviations**

| | |
|---|---|
| BAFF: | B cell activating factor |
| CXCL: | Chemokine ligand |
| DAMPs: | Damage-associated molecular patterns |
| ESSDAI: | Eular (European league against rheumatism) Sjogren's syndrome activity index |
| FS: | Focus score |
| HMGB-1: | High mobility group box -1 |
| HLA: | Human leukocyte antigen |
| ICAM-1: | Intercellular adhesion molecule-1 |
| ICOS: | Inducible costimulatory molecule |
| Ig: | Immunoglobulin |
| IFN: | Interferon |
| IL: | Interleukin |
| IL-1RAcP: | Interleukin 1 receptor accessory protein |
| KCS: | Keratoconjunctivitis sicca |
| MAPK: | Mitogen activated protein kinase |
| NFkb: | Nuclear factor kappa beta |
| NMO: | Neuromyelitis optica |
| pSS: | Primary Sjögren's syndrome |
| RA: | Rheumatoid arthritis |
| SG: | Salivary gland |
| SS: | Sjögren's syndrome |

| | |
|---|---|
| sSS: | Secondary Sjögren's syndrome |
| ST2: | Suppression of tumorigenicity 2 receptor |
| sST2: | Soluble form of ST2 |
| ST2L: | Longer membrane found form of ST2 |
| TLR: | Toll-like receptor |

**Highlights**

* in pSS, IL-33 is released from damaged epithelial salivary cells

* in pSS, IL-33 exhibits a dual role as alarmin as well as a pro-inflammatory cytokine

* IL-33 might work as a central actor in initiating a vicious auto-inflammatory loop

**Abstract**

Interleukin-33 (IL-33) is a member of the IL-1 family and has dual functions as a nuclear factor as well as a cytokine. The pivotal role of IL-33 as an active player contributing to aberrant local and systemic damage has been highlighted in several inflammatory and autoimmune diseases. Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by dry eyes and mouth syndrome due to local dysfunctions of exocrine glands, but also accompanied with systemic manifestations. The pathophysiology of pSS has been advocated as a conjecture of activated B and T cells as well as the production of inflammatory cytokines and autoantibodies, driving epithelial tissue damage and disease progression. In pSS, IL-33 is released in the extracellular space from damaged salivary cells upon pro-inflammatory stimuli and/or dysfunction of epithelial barrier. Counter-regulatory mechanisms are initiated to limit the pro-inflammatory actions of IL-33 as portrayed by an increase in the decoy receptor for IL-33, the soluble form of ST2 (sST2). In pSS and associated diseases, the levels of IL-33 are significantly elevated in the serum or tears of patients. Mechanistically, IL-33 acts in synergy with IL-12 and IL-23 on NK and NKT cells to boost the production of IFN-γ contributing to inflammation. TNF-α, IL-1β and IFN-γ in turn further increase the activation of IL-33/ST2 pathway, thereby constituting a vicious inflammatory loop leading to disease exacerbation. IL-33/ST2 axis is involved in Sjögren's syndrome and opens new perspectives as therapeutic target of one of the culprits in the inflammatory perpetuation.

## Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease with the peculiar hallmark of lympho-plasmocytic infiltration of salivary and lacrimal glands leading to xerostomia (dry mouth) and keratoconjunctivitis sicca (KCS) (1, 2). The prevalence of SS is variable (depending on the geographical localization) but recent studies have estimated it to be between 0.1-0.6% in 2 Norwegian cohorts but an estimated global prevalence of 0.3 to 1/1000 persons has been established (3, 4). SS occurs in middle-aged patients with a high female predominance of 9 to 1 (4). It is classified either as primary (pSS) when occurring alone or secondary (sSS) to other autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (1, 5). Besides the involvement of exocrine glands defining the classical sicca syndrome, systemic manifestations resulting from the lymphocytic infiltration of organs can be present in up to 40% of cases (1). Of note, the sicca syndrome is characterized by symptoms of ocular and oral dryness without the presence of autoantibodies and the absence of lymphocytic infiltration in the salivary glands. There are actually no specific diagnostic criteria for SS. However, for clinical studies and teaching purposes, SS is classified according to the American-European classification criteria, which include subjective and objective criteria of xerostomia and KCS as well as the presence of autoantibodies (anti-Sjögren's syndrome related antigen A (SSA) and/or B (SSB) antibodies and histopathological salivary gland involvement (6, 7). Noteworthy, novel circulating autoantibodies are continuously discovered in the serum of in pSS patients (e.g. anti-SP-1, anti-CA6, anti-PSP) and open new perspectives as biomarkers of clinical subentities or as predictors of disease progression or response to treatments (8). The actual criteria for the classification of pSS have been recently revised and include the presence of anti-SSA autoantibodies, a reduced unstimulated whole salivary flow (<0.1ml/min), a reduced tear production as measured by the Shirmer's test (which consists in placing a filter paper in the lower eyelid and measuring the moisture of the

paper band; the test is positive if <5mm/5min on at least one eye), presence of abnormal ocular staining scores and the presence of focal lymphocytic infiltration in the labial salivary glands as defined by a focus score (FS) of at least one. The FS is defined as the number of mononuclear cells infiltrates containing at least 50 inflammatory cells per $4mm^2$ of glandular tissue. The Chisholm score is another grading score of the inflammatory infiltrates in the salivary glands with grade 1 defined as a slight infiltrate, grade 2 as a moderate infiltrate of less than 50 lymphocytes, grade 3 equivalent to FS=1 and grade 4 with a FS >1) (2, 9, 10). Because of the lack of a gold standard for the diagnostic of SS, the reference standard being actually used relies on the use of American-European classification criteria by experienced clinicians (6). The lack of specific diagnostic tests combined with the high prevalence of sicca symptoms in the general population makes the diagnosis of SS even more complicated. This holds true especially in early disease where the symptoms and signs are usually mild and might explain the time delay before a diagnosis of SS. The importance of making the diagnosis of pSS is cardinal because of the high risk of developing lymphoma and serious systemic complications (11, 12). The morbidity of patients suffering from SS is debilitating, ranging from severe fatigue to organ impairment. Besides pSS-specific autoantibodies, free light chains, released during the production of immunoglobulins by activated B cells, might complete in a near-future the arsenal of biomarkers available to the clinician for establishing the diagnosis and the disease activity index (13).

The pathophysiology of SS is complex. Despite the quantum leaps made to unearth the different mechanistic processes underlying the autoimmune abnormality, the aetiology of the disease still remains to be discovered (14). It is believed that the combination of several factors might trigger immunological abnormalities leading to overt disease (15). Recently, a new concept involving the pathophysiology of SS has been forwarded whereby the conjuncture of genetic predisposal, environmental insults and hormonal disequilibrium can

lead to the activation of the resting epithelium with the enhanced expression of Toll-like receptors (TLR)-2, 3, 4, 7, 8, 9 (16-19), leading to the liberation of damage-associated molecular pattern molecules (DAMPs) and the release of pro-inflammatory cytokines (IFN, TNF-α, IL-6, IL-7, IL-17), themselves fostering inflammation (14, 18). The main pro-inflammatory cytokines in pSS are IFN-α, IFN-γ, IL-17, IL-7, Tumor necrosis factor α (TNF-α), IL-1β and B-cell activating factor (BAFF) (20-23). Type I interferons (IFNs) also play a pivotal role in the pathogenesis of SS (24). Type-1 IFN activation and secretion result in the activation of immature dendritic cells, in BAFF secretion, increased T cell proliferation and survival, induction of several chemokines (CXCL9, CXCL10, CXCL11) and the promotion of Th1 responses (24). B cell activating factor (BAFF) favors B cell proliferation, maturation and survival and is primarily induced by type I and type II interferons (25, 26). Animal models for SS have been pivotal in clarifying the role of pro-inflammatory cytokines in disease pathogenesis (27-30).

The role of epithelial cells in initiating and promoting the pathophysiological events underlying SS is paramount (31, 32). Even if the triggering and orchestrating of the first stages of the disease are still not well known, there is no shadow of doubt that there is an impairment in the function and structure of the epithelial cells of the salivary glands (SG). The epithelial cells of the SG, once activated, act as antigen presenting cells, at the forefront of the disease processes. In essence, the expression of CD40 as well as adhesion molecules, Intercellular adhesion molecule-1 (ICAM-1) and co stimulation molecules such as B7 and inducible costimulatory molecule (ICOS) are significantly up regulated which in turn trigger the activation of CD4+ T cells as well as Human Leukocyte antigen (HLA) type II molecules (18, 32-35). Moreover, following the activation of the epithelial cells, there is also an enhanced local liberation of chemokines and pro-inflammatory cytokines and B cell activating factors (36). The overall resultant effect of the activation of the epithelial cells and

unabated production of pro-inflammatory cytokines promote B and T cells homing and antigen cell presentation in a vicious loop fashion thereby amplifying the interactions between epithelial cells and immune cells**.** Furthermore, following interferon type 1 secretion, there is also the secretion of B-cell activating factor by the activated epithelial cells thereby promoting B cells activation and proliferation (26, 37-40). These detailed orchestrated sequences of immune activation resulting in aberrant lymphocyte homing, in unrestrained pro inflammatory cytokine released and overt SG destruction clearly define the prominent role of the epithelial cells as seminal to the development of SS (41). Thus, SS has also been termed as autoimmune epithelitis (31, 35, 42-44).

**Interleukin-33: biology and functions**

Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines displaying protean features and functions pertaining to health and disease (45, 46). IL-33 as a cytokine exerts its downstream effects by binding to a heterodimer constituted by its primary receptor ST2 and its co receptor, IL-1 receptor accessory protein (IL-1RAcP). IL-33 is expressed in several tissues and is highly abundant in endothelial cells. Other major sources of IL-33 are epithelial cells in barrier tissues that are in contact with the external environment. Furthermore, the expression of IL-33 can be induced during inflammatory states. In patients with chronic pulmonary obstructive disease or patients with atopic dermatitis, the levels of nuclear IL-33 are significantly increased (47, 48). One of the particular hallmarks of IL-33 is that of a dual function cytokine exerting intracellular and extracellular characteristics. Under normal conditions of tissue homeostasis, constitutively expressed, intracellular IL-33 plays a role as a guardian maintaining the integrity of barrier cells through the regulation of gene expressions (49). In parallel, IL-33 exerts its function as an alarmin or damage associated molecular pattern (50). Following a breach in an intact epithelial barrier and cells destruction, IL-33 is passively released in the extracellular milieu. The release or passive secretion of IL-33 in the

extracellular domains is possible ensuing cell death by necrosis and/or active necroptosis. IL-33 lacks the classical non-canonical processing and export pathways as well as the traditional signal sequence (51). Because of this unclassical pathway of liberation, IL-33 has been termed as an alarmin (52). When released during cell injury, IL-33 binds to its receptor ST2 and to its co-receptor IL-1RacP (53, 54). The binding of IL-33 to ST2 induces a conformational change enabling the interaction with IL-1RacP enabling downstream activation of Nuclear factor kappa beta (NfκB) and Mitogen activated protein kinase (MAPK) pathways leading to the proliferation, cell survival, cytokine secretion (IL-4, IL-5, IL-13) and amphiregulin expression by ST2 positive cells. There are several counter regulatory mechanisms that limit the pro-inflammatory effects of the IL-33/ST2 axis. The IL-33 receptor is produced in 2 isoforms namely, a short soluble form (sST2) and a longer membrane-bound form designated as ST2L. The soluble form, sST2 is present in human serum, where it acts as a decoy receptor by binding to IL-33 thereby abrogating its systemic effects (55, 56). Besides, the IL-33/ST2 axis is also blocked by the single immunoglobulin domain IL-1R-related molecule (SIGGIR) which dismembers the heterodimer ST2/IL-1RacP and by the ubiquitin-proteasome system which breaks down ST2 (53).

On the other hand, the main biological effects of IL-33 are mediated by ST2L expression. Recombinant IL-33 reportedly has ST2L-dependent effects on many different, mostly hematopoietic, target cells in human and mice, including mast cells, different subsets of CD4+ T cells, basophils, eosinophils, monocytes, macrophages, natural killer cells, invariant natural killer T cells and activate neutrophils, in which IL-33 induces the production of various cytokines and chemokines (57-60). As the ST2L is expressed on many cells involved in the Th2 response, the principal role and the most studied of IL-33 is its involvement in models of allergy and parasitic infections (61). But IL-33 also displays pro-inflammatory effects in disease models that are independent of Th2-type immunity, and induces a Th1 or a

Th17 profile (46, 62).

**The role of IL-33/ST2 axis in inflammatory diseases**

The IL-33/ST2 axis has been shown to be involved in several inflammatory and autoimmune diseases (46). IL-33 stimulated by infectious agents is released following cell death or enhanced stress can entail significant and unabated inflammatory responses thereby wreaking damage to local and systemic tissues. Another possible role for IL-33 as a potential culprit in inflammatory diseases might stem from unbridled IL-33 driven regulatory responses to dampen the pro-inflammatory properties of IL-33. Several studies have linked IL-33 to asthma, cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease, uveitis, systemic sclerosis and systemic lupus erythematosus (63-69). In RA, for example, one of the most characteristic inflammatory rheumatic disease, IL-33 and ST2 are significantly increased not only in the serum of patients but also in their synovium, with higher levels correlating with high disease activity (70). In mice models for RA, administration of IL-33 aggravated disease pattern whilst blocking IL-33 signalling significantly decreased disease activity (71, 72). The main downstream effects resulting from overt and unrestrained IL-33/ST2 axis signalling are mainly due to the excessive production of pro-inflammatory cytokines (such as IFN-$\gamma$, TNF-$\alpha$ and IL-17), activation of B1 cells, and the recruitment of neutrophils and mast cells into the joints (73, 74).

**Expression of IL-33 and ST2 in Sjogren's syndrome**

There are several compelling lines of evidence delineating the pathogenic role of IL-33/ST2 axis in primary SS patients (75-80). The serum levels of IL-33 and ST2 were significantly increased in pSS patients relative to controls. No association was found between IL-33 levels and disease activity (measured by ESSDAI) (75). Significant associations were found between sST2 and ESSDAI and between ST2 and disease duration for pSS. In one study,

sST2 were significantly increased in pSS patients with haematological abnormalities with sST2 being correlated with low platelet counts (77). No clinical variables or particular disease pattern were found to be associated with IL-33 although one study found increased sera levels of both IL33 and ST2 in pSS patients with interstitial lung involvement (80). There was no significant association of IL-33 and ST2 serum levels following the levels of lymphocytic infiltration (focus scores) in the salivary glands of pSS patients.

The expression of IL-33, ST2 and IL-1RacP was depicted in the salivary glands (SG) of both pSS patients and controls (75). The expression of IL-33 in SG of patients with SS displayed a particular fashion in that expression was significantly increased in moderately high grades of inflammatory infiltrates (grade 2 and 3 Chisholm scores) whereas in the patients with very low or very high grades of inflammation had comparable levels of IL-33 expression. ST2 expression in the SG was predominantly observed in the cytoplasmic compartment of the ducts. The expression of ST2 in the acinar cells was significantly reduced relative to that observed in the ductal cells of SG (75). In pSS patients, we observed a downregulation of the expression of ST2 in the ducts of SG. This downregulation of the ST2 expression in the ducts of pSS patients was observed with Chisholm scores of 3 and 4. IL-1RacP expression in SG was observed in the basolateral membrane and cytoplasmic compartment of ducts and acini. In pSS patients, a downregulation of the expression of IL-1RacP was observed compared to the sicca patients. In a similar fashion as that observed for ST2 expression, the diminished immunostaining of IL-1RacP was predominantly observed in pSS patients with Chisholm scores of 3 and 4.

Moreover, the involvement of IL-33 in the ocular severity of pSS patients was recently shown. The IL-33 levels in the tears of patients with pSS were significantly increased relative to non-SS dry eye patients and controls and correlated with IL-4 and IL-5 levels in the tears as well. The levels of IL-33 in the tears of pSS patients were strongly associated with the

severity of ocular involvement (dryness of the eyes and ocular surface staining). This study suggests the potential role of IL-33 in the ocular involvement defining pSS (78).

Neuromyelitis optica (NMO), also known as Devic's syndrome, is a rare autoimmune disease affecting the central nervous system that is found in association with pSS (81). The serum levels of IL-33 were recently shown to be significantly increased in patients with NMO. Patients with NMO and typical characteristic brain lesions had significantly higher serum IL-33 levels than those without brain lesions. Besides, an initially enhanced serum IL-33 level during acute phases were associated with higher disease activity and higher relapse rates (82).

IgG4-related disease, also known as Mikulicz's disease, was originally classified as a subtype of pSS because of the clinical and biochemical similarities and overlapping of clinical signs and symptoms (83). The defining histological features of IgG4 related disease encompass significant plasma cell infiltration as well as germinal center formation with positive IgG4 plasma cells staining. In a recent study by Furukuwa and colleagues, the expression of serum levels of IL-33 were significantly increased in both pSS and IgG4 disease related patients relative to controls (76). Moreover, the serum levels of IL-33 in IgG4 related patients significantly decreased after corticosteroid treatment thereby delineating the potential role of serum IL-33 as a marker not only of disease activity but also as biomarker predictor of response to therapy (76). Furthermore, the mRNA expressions of IL-33, ST2 as well as Th2 cytokines (IL-4 and IL-13) from SG of pSS and IgG4-related patients were significantly increased. In IgG4-related salivary glands, M2 macrophages were identified as the main producers of IL-33. Therefore, in IgG4 related patients, it has therefore been postulated that IL-33 could contribute to the pathogenesis of disease through overt and exuberant Th2 immune activation responses (76, 84).

**Pathophysiologic role of IL-33 in Sjogren's syndrome**

One of the key functions of IL-33 is to act as an alarmin. These alarmins also known as DAMPs include defensins, HMGB1, IL-18, S100A8/A9 amongst others, are secreted by dying cells following necrosis (85). Once released in the extracellular milieu, they can activate downstream cytokine receptors as well as TLRs triggering inflammatory responses. Other alarmins such as HMGB1 and S100A8/A9 have been described to play an active role in pSS (86, 87). Similarly to other alarmins described in pSS, IL-33 acts as an alarmin triggering downstream inflammatory responses. Under inflammatory conditions, there is an upregulation of IL-33 expression in the SG (75). This increase of IL-33 was most potent under the action of IFN-γ. The differential expression of IL-33 in SG with significantly increased immunostaining in moderate grades of inflammatory infiltrates and a fainted staining in higher inflammatory focus scores supports the role of IL-33 as an endogenous alarmin, which is increased locally in the SG to alert the immune system of impending threat. Intra-nuclear IL-33 is mobilized and accumulates in the epithelial tissues in early pathogenic and less advanced disease stages (depicted by Chisholm scores of 2 and 3) and is secondarily released in the extra-cellular medium following severe important epithelial alterations. IL-33 all alone does not trigger pro-inflammatory cytokine release in pSS. The downstream inflammatory responses of IL-33 are mediated through the combined action with other inflammatory cytokines namely IL-12 and IL-23, triggering a more than ten-fold increase in the secretion of IFN-γ. Intracellular cytokine detection by flow cytometry demonstrated that IFN-γ secreting cells were mainly NK and NKT cells that have cardinal roles in the pathogenesis of pSS (75, 88). The NKT cell/IL-33 signalling axis is a well-defined and documented axis. There are compelling lines of evidence supporting the fact that IL-33 cannot by itself activate NKT cells (89). IL-33 acting as an alarmin triggers and amplify the activation of NKT cells through innate as well as adaptative immune responses. Similar to NK cell, NKT cells constitutively express on their surface the ST2 chain that is specific to the IL-33 receptor thereby

contributing as a co-stimulatory agent to Th1 (IFN-γ) , Th2 (IL-4) and Th17 (IL-17A) NK and NKT cell cytokine production (90, 91). In our study, we could not depict Th17 responses following either IL-12 or IL-23 stimulation of NK and NKT cells. Taken together, similarly to other conditions, IL-33 mediates the production of IFN-γ in pSS in an IL-12 and IL-23 dependent fashion.

In summary, IL-33/ST2 axis as a new pathogenic pathway in pSS could be recapitulated as follows: In the setting of genetic predisposal, hormonal disequilibrium or environmental stress, there is an upregulation of TLRS and ensuing activation of the epithelium. In early disease stages, the damaged epithelium in a botched attempt to restrain the autoimmune dysregulation, enhances the expression of IL-33. With disease progression and in advanced stages, upon pro-inflammatory stimuli and further epithelial damage, IL-33 is released in the extracellular space. Counter-regulatory mechanisms are initiated to limit the pro-inflammatory actions of IL-33 as portrayed by an increase in the decoy receptor for IL-33, sST2. Moreover, IL-33 acts synergistically with IL-12 and IL-23 on NK and NKT cells to increase the production of IFN-γ further contributing to inflammation. TNF-α, IL-1β and IFN-γ in turn further increase the activation of IL-33/ST2 pathway, thereby constituting a vicious inflammatory loop leading to disease progression and perpetuation (Figure 1).

**Conclusion**

In this review, the fundamental role of the IL-33/ST2 axis in the pathogenesis of pSS was delineated. As such, IL-33 is a pleiotropic molecule but mainly displaying dual like properties of an alarmin and that of a pro-inflammatory cytokine. In pSS, IL-33 exhibits both properties functioning as alarmin as well as a pro-inflammatory cytokine. Targeting the IL-33/ST2 axis in primary Sjogren's syndrome could be potential therapeutic option in the future.

**Figures (in color)**

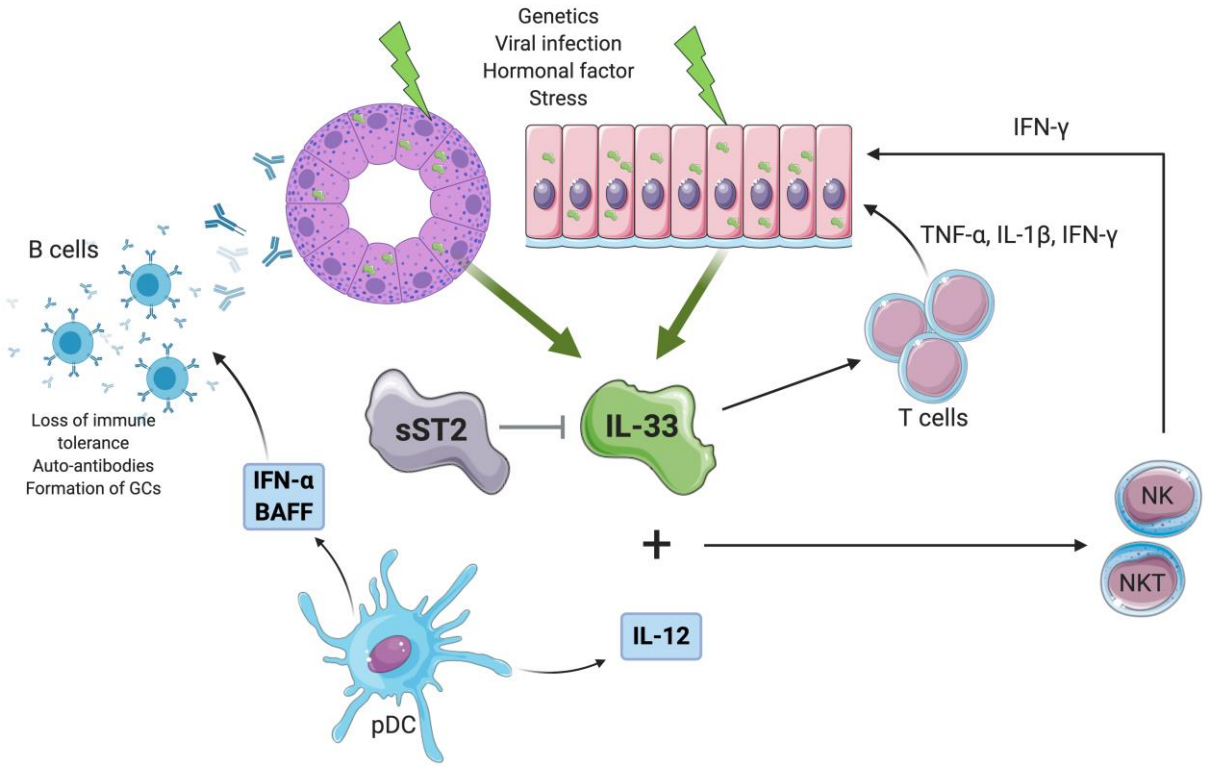


**Figure 1.** Hypothesis of the involvement of IL-33/ST2 axis in the pathogenesis of primary Sjögren's syndrome. In the setting of genetic predisposition, hormonal imbalance and psycholological stress, there is an activation of the (salivary) epithelium, an increase in the expression of toll-like receptors (TLRs -3, -4 and -7) leading to the release of pro-inflammatory cytokines such as TNF-α. Counter regulatory mechanisms to dampen the inflammatory response are activated. Alarmins such as IL-33 are released. Activation of plasmacytoid dendritic cells (pDC) triggers the release of IFN-α response with the release of B cell activating factor (BAFF) that in turn favours the proliferation of B cells inside of germinal centers (GCs). There is also the secretion by dendritic cells of IL-12 working in a concerted fashion with IL-33 to activate NK and NKT cells thus promoting the release of IFN-γ. IFN-γ in turn acts on the epithelial cells to further release IL-33 in the extracellular milieu thereby constituting a vicious auto-inflammatory loop entertaining local and systemic

damage contributing to disease perpetuation. This cartoon has been drawn using the free BioRender app (https://biorender.com/).

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