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Review

Type I interferons in Sjögren's syndrome

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ABSTRACT

Sjögren's syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration of the salivary and lachrymal glands resulting in dry eyes and mouth. Genetic predisposition, pathogenic infections and hormones have been implicated in the pathogenesis of the disease. Studies in the last several years have revealed marked over-expression of the type I interferon (IFN)-inducible genes in the peripheral blood and salivary glands of patients with Sjögren's syndrome. The expression of the type I IFN-inducible genes in Sjögren's syndrome also positively correlates to titers of anti-Ro and anti-La autoantibodies, which are typical for this disease. Plasmacytoid dendritic cells (pDC) are the major source of type I IFN production and activated pDC are detected in minor salivary gland biopsies from patients with primary Sjögren's syndrome. In addition, polymorphisms in genes important both for the production and response to type I IFN are associated to increased risk for Sjögren's syndrome. Because type I IFN bears a variety of biological functions, such as defense against viral infections and activation of the immune system, these results suggest that the type I IFN system has an important role in the pathogenesis of Sjögren's syndrome. A variety of mechanisms causing an activation of the type I IFN system are discussed in this review. Given the pivotal role of type I IFN in the disease process, therapeutic interventions targeting the type I IFN signaling pathway have the potential to benefit the patients with elevated type I IFN status and such hypothesis needs to be carefully evaluated in clinical development.

Contents

1. Introduction

Sjögren's syndrome is named after Henrik Sjögren who reported detailed clinical and histological findings in 19 women with xerostomia and keratoconjunctivitis sicca in his dissertation in 1933 [1]. Sjögren's syndrome is a chronic autoimmune disease characterized by mononuclear cell infiltration of exocrine glands, particularly, salivary and

Abbreviations: type I IFN, type I interferons; pSjS, primary Sjögren's Syndrome; SLE, systemic lupus erythematosus; pDC, plasmacytoid dendritic cell; iDC, interdigitating dendritic cells; fDC, follicular dendritic cells; NK, natural killer cells; Treg, regulatory T cells; MSG, minor salivary gland; SGEC, salivary gland epithelial cell; PBMC, peripheral blood mononuclear cells; AGS, Aicardi–Goutieres Syndrome.

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lacrimal glands, which finally results in glandular atrophy and deficient function. The clinical consequences of Sjögren's syndrome are typically dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Besides these, Sjögren's syndrome also exhibited systemic features of autoimmune diseases as it progress in multiple organs such as lung, liver, kidney, vascular, gastrointestinal and nervous systems [2–6]. Many patients may also experience fatigue and pain in joints and muscle. A variety of studies have shown that a portion of Sjögren's syndrome patients exhibited an ongoing B-cell hyperactivity which may be associated with an increased incidence of lymphoid malignancies [7–9]. Sjögren's syndrome can occur alone, defined as primary Sjögren's syndrome (pSjS), or together with almost any other autoimmune disease, but most frequently with rheumatoid arthritis (RA) or SLE, thus defined as secondary Sjögren syndrome. Such overlap connective tissue diseases have recently been reviewed by Iaccarino et al. [10]. pSjS affected approximately 0.1–0.4% of the general population with large female preponderance with ratio of female:male about 9:1 [11–14].

In this review, we mainly focus on pSjS.

2. Pathogenesis of Sjögren's syndrome

The common feature of affected organs in Sjögren's syndrome is periepithelial lymphocytic infiltration which eventually leads to dysfunction of the affected organs. The salivary glands are the most studied organs as they are affected in almost all the patients and easily accessible for clinical and experimental tests. The hallmark of histopathological findings is generally the progressive focal infiltration of mononuclear cells, replacing glandular epithelium (lymphoepithelial lesion) [15]. In a recent report, Christodoulou et al provided a comprehensive survey regarding the composition of infiltrated cell types and its association with the lesion severity. Their results showed that the distribution of infiltrating mononuclear cells at the lesions of Sjögren's patients varied according to lesion severity and correlated with disease manifestations by staining of minor salivary gland (MSG) biopsies [16]. The percentage of different immune cell populations among the total infiltrated mononuclear cells were significantly different among MSG tissues with mild, intermediate or severe inflammatory lesions; total T cell, CD4+ T cell, T/B cell ratio and iDC incidences were negatively, whereas B cell and macrophage incidences were positively correlated with infiltration grade and biopsy focus scores [16]. Tregs were found to be predominant in intermediate lesions and were also observed to be correlated with the grade of the autoimmune lesion and certain adverse prognostic factors such as the presence of C4 hypocomplementemia and salivary gland enlargement [20,21]. Increased macrophages and dendritic cells were also observed in MSGs from patients with Sjögren's syndrome but not from non-Sjögren's syndrome disease control subjects, particularly in B cell rich areas and in germinal center-like structures in patients. They may correlate with adverse predictors of lymphoma development [22]. A recent study by Theander et al. indicated that the germinal center-like lesions in labial salivary gland biopsies taken at pSjS diagnosis was highly predictive of the risk of non-Hodgkin's lymphoma (NHL) development [23]. Both of the infiltrated T and B lymphocytes at salivary gland are activated as surface markers for activation, MHC class II molecules, IL-2 receptors, were observed to be expressed [17]. In addition, the infiltrated and activated plasma cells in MSG secreted immunoglobulins with isotypes mainly of IgG and IgM, whereas in normal salivary glands, IgA is the dominant isotype [18]. In a recent report, Varin et al. showed that in Sjögren's syndrome, B lymphocytes were associated with direct tissue damage by inducing epithelial cells of salivary glands into apoptosis through protein kinase C delta activation [19]. In fact, the principal characteristic feature of Sjögren's syndrome is the presence of a variety of autoantibodies directed against organ or systemic non-organ autoantigens. Antinuclear antibodies are present in the sera of 80% of patients. Among them, two antibodies targeting ribonucleoproteins, Sjögren's syndrome antigen A (Ro) and Sjögren's syndrome antigen B (La) are included in the official criteria for diagnosis of Sjögren's syndrome [20–22]. These two autoantibodies, however, also exist in other autoimmune diseases, such as systemic lupus erythematosus (SLE). Other autoantibodies such as anti-annexin autoantibodies have been found with the potential as biomarkers for autoimmune diseases [23]. Among anti-annexin autoantibodies, anti-annexin XI antibody was observed in Sjögren's syndrome. Antibodies to SSA antigen (Ro52/Ro60), are now known to consist of two different proteins coded by distinct cDNAs and isolated anti-Ro52 antibodies showed high prevalence in autoimmune diseases including Sjögren syndrome [24]. Autoantibodies possess important diagnostic and prognostic value in assessing disease activity in autoimmune diseases. In a recent report, Racanelli et al. reviewed the different lines of research which are presently being conducted to understand how these autoantibodies are generated (e.g. through apoptotic body formation, molecular mimicry and other mechanisms) and cellular locations where they target self antigens to cause an autoimmune disease [25].

Several studies have also suggested that glandular or acinar epithelial cells play an important role in the pathogenesis of Sjögren's syndrome as they may actively participate in the induction and perpetuation of the inflammatory process at disease sites [26]. Epithelial cells at disease sites of Sjögren's syndrome showed elevated expression of stimulatory molecules, such as CD40, B7 and adhesion molecules, as well as lymphoid chemokines and BAFF, suggesting the potential role of epithelial cells in attracting and activating DCs, T cells and B cells in the inflammatory glandular tissues [26–30].

Interestingly, most human autoimmune diseases including Sjögren's syndrome have increased incidence and prevalence in females. Sex hormones may preset the susceptible environment for subjects and influence humoral and cell-mediated immune responses. Experiments in animal models suggested a role for estrogen deficiency in Sjögren's syndrome and may indicate that estrogen deficiency stimulates salivary epithelial cells to present autoantigen to the CD4+ T cells to induce lesions in the salivary glands, which resemble those of human Sjögren's syndrome [31,32]. Data from both human and autoimmune animal studies were recently reviewed to determine reasons for sex differences in autoimmune disease [33]. Another sex hormone, Prolactin (PRL) was reported to regulate immune response and be able to stimulate autoimmunity and to be associated with a variety of autoimmune diseases including pSjS [34].

Although the accumulating evidences confirmed the infiltration and activation of inflammatory cells at biopsies of affected glandular organs, the mechanisms that generate, attract and activate these autoreactive cells at disease sites still remain unclear. It has been hypothesized that in genetically susceptible subjects, environmental stimuli, viral infection or hormonal aberration all could result in generating autoreactive lymphocytes and induce autoimmune attack on glandular organs. See Section 5 for a more comprehensive discussion.

3. Type I IFN in Sjogren's syndrome

3.1. Activated type I IFN in autoimmune diseases

The type I interferon (IFN) family consists of multiple members including IFN-α, -β, -ε, -κ, -ω, -δ, and -τ [35,36]. They bear a variety of biological functions, such as defending against viral or bacterial infection, immuno-modulation, and anti-proliferation. Due to their pluripotent function, type I IFNs, more specifically IFN-α/β have been intensively studied for decades for their important roles in immunity/autoimmunity and cancers. Although IFN-α/β can be produced by many types of cells when exposed to environmental threats such as viral or bacterial infections, the most potent source of IFN-α/β production is plasmacytoid dendritic cells (pDCs), which produce more than 1000-fold IFN-α/β than any other cell type [37–39]. Activated type I IFN signaling pathway will induce the