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Editorial

Sjögren's syndrome: pathogenesis

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ABSTRACT: Sjögren's syndrome is a chronic inflammatory disease of the lacrimal and salivary gland with subsequent keratoconjunctivitis sicca and xerostomia. Histopathologic findings include damaged acini of the lacrimal and salivary glands with mononuclear cell infiltrates of lymphocytic and plasma cell type. The cause of the damage is cell-mediated cytotoxicity. The pathogenesis of Sjögren's syndrome is still unknown. The role of viral infections failed to show a causative effect. On the other hand, tissue destruction was shown to be mediated by activated T cells of CD4⁺ type that home into the lacrimal gland. This process is signal-mediated through the T-cell receptor that interacts with class II antigen on the epithelial cells of exocrine glands. This, in turn, induces the expression of Fas/APO-1 and Fas-mediated apoptosis of acinar cells. Granzyme A and perforin are cytolytic enzymes secreted by activated T lymphocytes that seem to participate in acinar cell destruction. (Eur J Ophthalmol 1999; 9: 1-7)

KEY WORDS: Sjögren's syndrome, T-cells CD4⁺, TCR receptors, Fas/APO-1, Apoptosis, Ganzyme A

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INTRODUCTION

Sjögren's syndrome(SS) is a chronic inflammatory disease of unknown etiology. It is characterized by mononuclear cell infiltration, and subsequent destruction of the lacrimal and salivary glands. Mikulicz was the first to describe this entity in 1892. He described a farmer who suffered from dry eyes and mouth, and died of appendicitis. Mikulicz performed an autopsy because of swelling of the lacrimal submandibular, and parotid glands. He saw what he described as mononuclear infiltration of the lacrimal and salivary glands. This was the first description of what we now refer to as Sjögren's syndrome (1). Although the term "Mikulicz" is used to describe the clinical picture of swelling of the lacrimal and parotid glands, it is a misnomer, because Mikulicz was describing Sjögren's syndrome. Therefore, Mikulicz syndrome, Mikulicz's disease and Sjögren's syndrome are all synonyms. In 1933 Henrick Sjögren from Stockholm gave the most accurate description of this entity, and in 1936 Duke Elder honored Sjögren by calling the disease Sjögren's syndrome (2).

Clinical presentation and diagnostic tests

The disease occurs more commonly in females than in males. The clinical picture is that of keratoconjunctivitis sicca and xerostomia with or without other systemic findings. Subjective ocular symptoms include dryness of the eyes and the sensation of a foreign body. These two symptoms showed the highest discriminating power between SS patients and normal controls (3). Ocular signs consist of the absence of the tear meniscus. The tear film may show filamentous debris, with mucus and epithelial filaments on the corneal surface. Punctate keratitis with loss of the corneal luster are common findings in cases such as these. In some patients with severe keratoconjunctivitis, sicca keratinization of the conjunctiva may occur. Corneal epithelial defects and corneal perforation may occur specifically in those patients who receive topical steroids. The pathogenesis of ocular surface lesions is due to an underlying deficiency of various constituents, including aqueous layer, lysozyme, β lysin, lactoferrin and immunoglobulins. In addition, tears contain amylase, per-

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oxidase and hexosaminidase, which are important in breaking down the mucus. It has been demonstrated that normal lacrimal duct epithelium produces epidermal growth factor (4). This implies that a corneal epithelial defect is likely to be persistent in the absence of adequate tears, not only due to dryness, but rather due to a deficiency of the epidermal growth factor, which is essential for the normal growth of ocular surface epithelium. The most characteristic finding in patients with Sjögren's syndrome is the mononuclear cell (predominantly, CD4+ T cells) infiltration of the exocrine glands, including salivary and lacrimal glands. A biopsy of the labial accessory salivary glands is one of the main diagnostic criteria for the diagnosis of SS. It is a simple procedure, whereby 5 lobules are obtained and sent for hematoxylin-eosin staining. The specimen is graded by a focus score according to the severity of infiltration. In fact, the European community multi-center study on the diagnostic criteria for SS evaluated the accuracy of the most commonly used tests of oral and ocular involvement in SS (3). It showed that minor salivary gland biopsy (MSGB) has a good balance between sensitivity and specificity when a focus score>1 was considered indicative of the diagnosis. It is certainly the test most widely used, and given its high specificity, it has been suggested as a potential single diagnostic criterion for SS. However, Schirmer's test without anesthesia and rose bengal staining remain reliable clinical tests for the diagnosis of SS (3).

Classification

Sjögren's syndrome can be divided into two main groups. The first is primary Sjögren's syndrome or the sicca complex, where keratoconjunctivitis sicca and xerostomia are present. The secondary form of the disease is called the sicca with a systemic autoimmune disease. These patients usually have a different type of disease than patients with primary SS. Associated systemic autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosis, periarteritis nodosa and scleroderma, among many other conditions. There are clinical and laboratory differences between primary and secondary Sjögren's syndrome. Symptoms of keratoconjunctivitis sicca with salivary glands and parotid gland swelling are all seen in primary Sjögren, but less frequently so in secondary Sjögren. Anti-SS antibodies are more frequent in primary Sjögren. Similarly, antinuclear antibodies and the association with HLA-DR3 are more commonly seen with the primary type of the disease. An animal model for Sjögren's syndrome is the F1 hybrid New Zealand mouse (NZB/NZW F1) (5). The F1 hybrid mouse has a hyperactive T cell, anti-erythrocytes antibodies, anti-DNA antibodies, anti-natural thymocytes antibodies, immune complex nephritis, lymphoid proliferation and neoplasia of the lymphoid tissue. The lacrimal gland of this animal model shows foci of mononuclear cell infiltration, mostly lymphocytes and some plasma cells surrounding the lacrimal ductules. This is one of the early findings in Sjögren's syndrome. These mice have keratoconjunctivitis sicca and deficiency of salivary gland secretions. If we consider the fact that rodents do not have lysozyme, the absence of tear lysozyme is not an indicator of the disease. Histopathologic findings are reminiscent of findings observed in humans. They may have swelling of the lacrimal glands. In the early stages acini can still be seen, but in later stages the acini are damaged and infiltrated with mononuclear cells of the lymphocytic and plasma cell type. The cause of damage to the lacrimal gland is cell-mediated cytotoxicity or auto-antibodies to the lacrimal gland cells (6).

Pathogenesis

Although the etiology of SS is still elusive, data regarding the pathogenesis of tissue destruction and cellular activation mechanisms are accumulating rapidly. In the early forties, it was suggested that vitamin A deficiency or vitamin deficiency in general may contribute to autoimmune diseases and SS. Hormonal factors were thought to be involved in the pathogenesis of SS because the disease was more common in females than in males. The advent of molecular biology has recently contributed significantly to an understanding of the pathogenesis of Sjögren's syndrome.

Role of viral infections

Investigators have explored the role of viral infection in the initiation of the autoimmune process. Early work suggested persistent cytomegalovirus (CMV) and herpes simplex virus infection in SS (7). Other studies suggested a role played by Epstein-Barr virus (EBV) in the pathogenesis of SS. Elevated levels of

EBV DNA and antibody responses to EBV-encoded proteins have been found in groups of patients with SS in the United States, Europe and Japan (8-10). Mariette and colleagues identified EBV genes in salivary glands of patients with SS (9). Similarly, Pflugfelder and coworkers detected EBV genes in the lacrimal glands of patients with SS using polymerase chain reaction (11). These patients were seropositive for EBV antigen. EBV genomic sequence, however, is frequently found in the lacrimal tissues of normal subjects, as well (12). This is ascribed to the latency of this virus in the salivary and lacrimal glands, normally, after primary infection. Fox and Kang suggested the possibility of EBV reactivation being secondary to immunoproliferation in the lacrimal and salivary glands rather than causative of this process (13). In fact, the long latent period between initial EBV infection, before the age of 10 years, and the onset of SS makes it difficult to attribute a primary causative role for this virus in the initiation of the disease. It could be that immunologic disregulation causes immunosuppression, leading to EBV proliferation. This association, therefore, may be incidental. Nevertheless, mechanisms by which EBV may participate in the pathogenesis of SS should be studied further.

Retroviruses attracted the attention of researchers as a potential participant in the pathogenesis of SS. Retroviral particles of antigenicity similar to that of the human immunodeficiency virus (HIV) have been identified in the salivary glands of patients with SS (14). It is well documented that patients with AIDS may have xerostomia and dry eye symptoms. AIDS patients may show a lymphocytic focus score of two or more in their salivary glands biopsy specimens. The predominant T-cell population was found to be the suppressor (CD8+) T cells type in contrast to the helper T cell subset (CD4+) subset that usually characterizes SS (15). Furthermore, Norman Talal observed that 41% of patients with SS react to P24 core protein of HIV (16).

The role of T-cells

The impairment of salivary and lacrimal gland function in SS is due to tissue destruction of acinar and ductal cells accompanied by lymphocytic infiltration. This is believed to be immunologically mediated (17). The major type of cells infiltrating the exocrine glands in SS patients are T cells of CD4+ and CD45Ro+ and a small number of B cells. These are activated T lymphocytes that are homing into the lacrimal and salivary glands. At this stage two questions emerge, the first one being what makes these cells home into the lacrimal gland, and how do they induce acinar and ductal cell destruction? It was uniformly observed that class II MHC molecules are expressed on antigen presenting cells in autoimmune diseases and are presented to reactive T lymphocytes (18). In normal body defense mechanisms macrophages present antigens to helper (CD4+) T lymphocytes using class II molecules. Numerous observations pointed to the fact that the targets of autoimmune responses express class II molecules (19). These examples include corneal transplant rejection, uveitis and proliferative vitreoretinopathy. T-cell activation depends on a signal mediated through the T-cell receptor (TCR) that will interact with class II antigen on the epithelial cells of exocrine glands. This, in turn, will activate Fas antigen or CD95/APO-1 and trigger a chain of reactions that will lead to the destruction of the acini (Fig. 1).

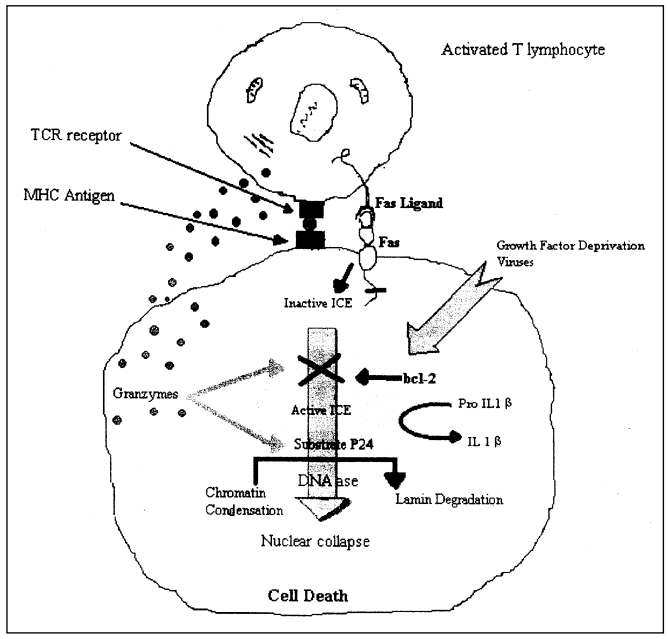

Fig. 1 - *Fas induced programmed cell death signals. Activated T lymphocyte expresses FasL which binds to epithelial cell Fas antigen. This activates Interleukin converting enzyme (ICE) that in turn converts pro-IL to IL-1 (the active form). A chain reaction is induced resulting in chromatin condensation and nuclear collapse or apoptosis. Growth factors deprivation (TGF-β) may activate ICE cascade. The bcl-2 inhibit the activation of ICE and hence apoptosis.*

The majority of immune repsonses depend on the

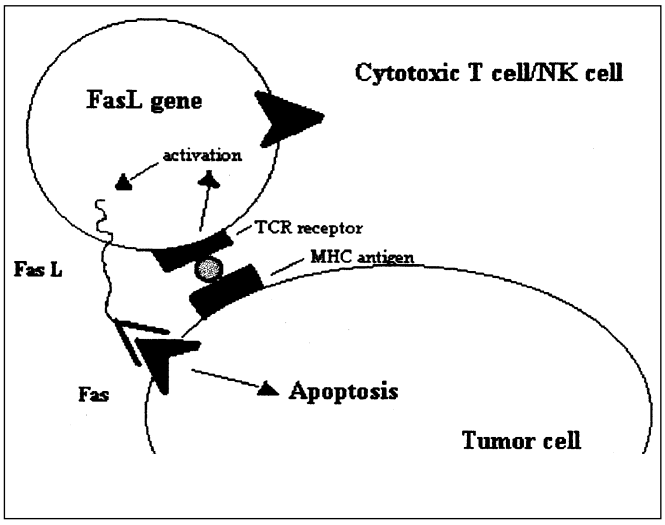

Fig. 2a - *Mechanisms of the immune system combat against tumor cells.*
Cytotoxic T cells or natural killer cells express FasL. They bind to Fas antigen of tumor cells and induce their death by apoptosis. Cytotoxic T cells commit suicide after completion of their mission by activation of their Fas antigen.

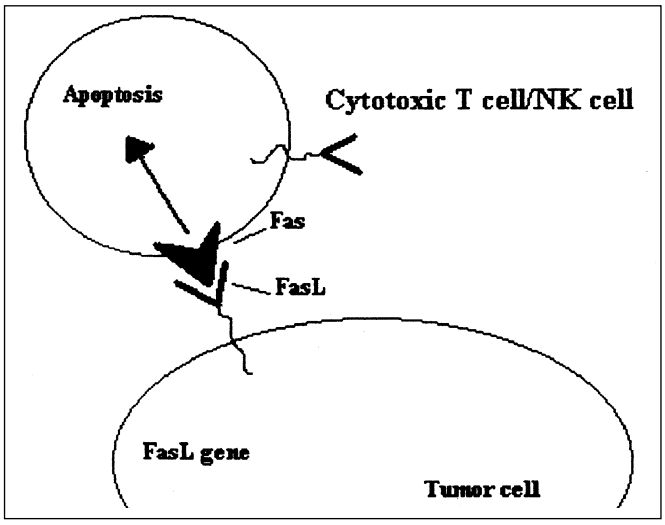

Fig. 2b - *Tumor cells counterattack.*
Tumor cells may become resistant to Fas mediated death or apoptosis by expressing FasL themselves and downregulating their Fas antigen. They kill their attackers by binding to the Fas antigen of the cytotoxic T cells which die then by apoptosis before executing their mission.

activation of T lymphocytes of helper (CD4) and cytotoxic T (CD8) cell types that recognize antigens through TCR. The stimulation of T-cell-antigen receptor is mandatory, but not sufficient to induce complete T-cell activation (20). Complete T-cell activation requires a second signal which is costimulatory via different pathways, the most important of which is the B7:CD28/CTLA-4 pathway. For instance, "naïve" T cells may ignore MHC-TCR signals in the absence of costimulators (20). On one hand, there are two types of CD4 helper T cells. Type 1 cells are induced by interleukin-12 produced by macrophages. Type 2 helper cells depend on the interaction of CD28 with B7-2 of the costimulator pathways and are induced by interleukin-4 (21). The pathogenesis of different immune diseases is apparently strongly influenced by the type of helper T cells involved. Polarization towards type 1 CD4 helper cells was found to be a key mechanism in autoimmune and granuloma-forming diseases, and in this context the costimulator molecules B7 induce and sustain the generation of pathogenic type 1 helper T cells. In contrast, polarization towards type 2 helper cells can impair cell-mediated immunity, resulting in anergy, and, hence, they may be detrimental in infectious diseases such as leprosy. Understanding the role of the costimulor pathway may lead to novel immunosuppressive modalities that involve antibodies or antagonists to these molecules. The exact role of this pathway is yet to be explored in Sjögren's syndrome.

Fas and Fas ligand expression in Sjögren's syndrome

The Fas antigen (CD95 or APO-1) is a type I membrane protein on cell surface that belongs to the tumor necrosis factor/nerve growth factor receptor family (TNF). It has a cytoplasmic domain designated as the death domain and is necessary and sufficient for transduction of apoptotic signals (22-24). The Fas antigen induces programmed cell death when cross-linked with its physiologic ligand, FasL. FasL, a type II transmembrane protein, is also a member of the TNF receptor family. It is expressed on activated lymphocytes and in nonlymphoid sites or immune privileged sites such as the sertoli cells of the testis, the retina and the anterior chamber in the eye (25). It was also found that it is expressed by tumor cells that evade the immune system (Fig. 2 a and b) to preserve their existence and induce apoptosis of their attacker, the cytotoxic T cell/NK cells (26).

Antigen presenting cells express on their surface an autoreactive antigen as a complex with major histo-

compatibility complex (MHC). The antigen-MHC complex interacts with the T cell receptor on activated T cells. This, in turn, induces the expression of Fas/APO-1 and FasL (Fig. 1).

The role of Fas-mediated apoptosis was assessed in patients with SS and it was shown that Fas and FasL are abnormally expressed in the acinar and ductal epithelial cells (27). This is in contrast with normal controls that did not express Fas/FasL. Acinar cells died by apoptosis as was proved by using in situ DNA fragmentation or TUNEL procedures (immunohistochemical staining procedure indicative of apoptosis) (27). The lymphoid inflammatory infiltrates around these cells have an upregulated expression of FasL and are, in addition, blocked in their ability to commit to apoptosis. The Fas antigen of the epithelial cells interact with T cells FasL. This induces further intracellular signals for the cells to commit to programmed cell death (PCD) and undergo apoptosis. One of those signals is the activation of Interleukin converting enzymes (ICE), a key player in the apoptotic cascade. ICE has multiple substrates of the protease type. For instance, it converts protease II-1β to its active form. Activation of ICE is controlled by DNA damage, growth factor deprivation and granzymes, which are cytolytic enzymes produced by activated T lymphocytes. The FasL+ T cells, on the other hand, escape the immune surveillance system and do not undergo apoptosis resulting in the perpetuation of chronic inflammation (28). Moreover, some studies showed an increased expresion of the suppressor oncogene bcl-2, in the periductal lymphocytic infiltrates, which might be involved in inhibiting PCD of these lymphocytes (27). The bcl-2 is a protooncogene that encodes a protein localized on the mitochondrial membrane. Its major function is to inhibit apoptosis caused by physiologic or pathologic stimuli (29). It is noteworthy to mention that bcl-2 is deregulated or over expressed in tumor cells like B cell follicular lymphoma. Further studies on the FasL and the role of bcl-2 are needed to clarify the picture. The discussed role of Fas/FasL and T lymphocytes in the apoptosis mechanism in Sjögren's syndrome displays some contrast to that of other autoimmune diseases. For instance, the programmed cell death of the thyrocytes in Hashimotos's Thyroiditis is independent of infiltrating T lymphocytes (30). FasL is constitutively expressed both in normal and Hashimoto's (HT) thyrocytes and insignificantly expressed on infiltrating T lymphocytes; however, Fas is upregulated in HT thyrocytes. This process is induced by IL-1β, probably released by macrophages. The end result is an apoptotic fratricide of the thyrocytes without the contribution of other cells (30).

Granzyme A and perforin

The cardinal feature in Sjögren's syndrome is tissue destruction accompanied by lymphocytic infiltration. However, the actual tissue destruction mechanisms have not been fully elucidated. Attention has recently been directed to granzyme A and perforin A, two cytolytic enzymes that are present in activated CD4+ T cells (31). It is suggested that activated CD4+ T cells are induced to exhibit killer function which is believed to be generally exhibited by CD8+ T cells or the cytotoxic T cells. Tsubota and Saito (32) demonstrated lymphocytes containing granzyme A in SS biopsy specimen raising the possibility that activated CD4+ T cells containing this enzyme may destroy epithelial cells with antigens presented by class II molecules on their surface (Fig. 1). In fact, cyclosporin A is commonly known to suppress T cells which may in part explain granzyme A and perforin suppressive action.

Cytokines and adhesion molecules

Leukocyte adhesion is a crucial step in the process of lymphocytes homing into the exocrine glands of Sjögren's syndrome patients. It is actually a crucial step in both normal immune responses and inflammatory processes; adhesion molecules include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E selectin (endothelial-leukocyte adhesion molecule-1 ELAM-1). ICAM-1 was found in epithelial cells of acini and ductular structures and VCAM-1 in postcapillary venules and mononuclear cells in SS (33). These adhesion molecules are usually expressed in reaction to inflammatory cytokines like interferons (IFN) and interleukins (IL).

Transforming growth factor beta (TGF-β) is another cytokine that seems important in regulating mucosal immunity. Down regulation of TGF-β may lead to dysfunction of the immune and inflammatory responses of SS (34). TGF-β downregulates IFN induced class II antigen expression and is an inhibitor of INFγ. Consequently, decreased TGF-β expression could lead to

the presentation of self antigens. Moreover, TGF-β inhibits cell binding of lymphocytes to high endothelial venules in the mucosal immune system. A decrease in TGF-β may, therefore lead, to aberrant lymphocytic infiltration of salivary glands. Saito and coworkers (34) found TGF-β to be strongly expressed in ductal epithelial cells of normal salivary glands, whereas it was not detectable in those with SS. If TGF-β can inhibit the induction of T cell activation and cytokine production and modulate the presentation of self antigens by inappropriate cells, would the local administration of TGF-β or TGF-β gene modulate mucosal immunity and, hence, offer a new mode of treatment for Sjögren's syndrome?

Interferon α (IFN α) is another regulatory protein of multifunctional biological effects. It is an active intercellular mediator that induces resistance to viral infections. In contrast, interferon γ is one candidate factor that induces expression of class II molecules during local inflammation. Infection by EBV or other viruses may promote class II molecules independent of the effect of interferon γ. On the other hand, interferon α has an inhibitory effect on EBV induced transformation of human B lymphocytes. This may suggest a possible role for IFNα in the treatment of the lymphoproliferation in Sjögren's syndrome.

CONCLUSIONS

Advances in molecular biology have influenced our thinking and contributed to our understanding of the pathogenesis of Sjögren's syndrome. These findings may suggest new modalities in the treatment of autoimmune diseases. It is becoming obvious that the pillars for future therapy rest on understanding the causative trigger, identifying the selective immunologic target, and considering gene therapy. In other words, we will be transiting from the age of non selective immunosuppressive treatment modalities to an era of normal immunologic reconstitution.

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