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Primary Sjögren's Syndrome: Current Pathophysiological, Diagnostic and Therapeutic Advances

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1. Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disease characterized by the lymphocytic infiltration of exocrine glands, mainly the salivary and lachrymal glands entailing the classical sicca syndrome of xerostomia (Sjögren, 1933) and xeropthalmia. Lymphocytic infiltration of other organs results in systemic manifestations. SS is classified as either primary (pSS), when occurring alone, or secondary (sSS), when occurring in addition to other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or myositis. As one of the most frequent autoimmune disease, affecting approximately 0.5% of the world population, SS is often associated with other diseases such as Hashimoto thyroiditis, coeliac disease, Biermer's disease or systemic sclerosis. SS evolves as a slow, insidious disease affecting predominantly middle-aged women (female to male ratio of 9:1), SS lies at the cross roads of autoimmune diseases characterized by both cellular and humoral abnormalities. The disease typically affects middle-aged women around their fourth and fifth decades with extremes ranging from to 2 to 83 years. The morbidity of patients suffering from SS is incapacitating ranging from severe fatigue to evolving arthralgia. Even if the patients suffering from SS have a mortality rate comparable to the general population, they present an increased risk of developing lymphoma. The diagnosis of SS is based upon defined criteria according to the American-European consensus encompassing subjective and objective clinical signs and symptoms as well as immunological alterations. The pathogenesis of SS is complex and involves many components taking part in the autoimmune destruction of exocrine glands: pro-inflammatory cytokines secretion, apoptosis, matrix metalloproteases upregulation, autoantibody formation, as well as T and B cell proliferation. In SS, the classical histological findings in exocrine glands comprise focal inflammatory infiltrates, cell destruction and fibrosis in later stages of the disease. So far, SS treatment has been mainly symptomatic, consisting in relieving the clinical signs. However, recent pathophysiological findings have led to the development of new treatments.

2. Diagnostic criteria

The diagnosis of SS is currently essentially based on the American-European criteria. These criteria, 6 in total, include 2 subjective and 4 objective criteria. The subjective criteria are

ocular and oral symptoms, while the objective criteria are ocular signs, histopathology, salivary gland involvement, and autoantibodies. Experts have recommended making the diagnosis of SS when 4 of the 6 criteria are present, as long as histopathology or serology is positive, or when 3 of any of the 4 objective criteria are present (Vitali et al., 2002).

It necessary to bear in mind that the most frequent symptoms of SS include the triad of fatigue, polyarthralgia and sicca symptoms, which are often commonly found in the general population and aging population. Many drugs have anti-cholinergic properties, which complicate the diagnostic process of SS. Exclusion criteria for the diagnosis of SS include the presence of hepatitis C and HIV viruses, sarcoidosis, prior cervical radiation, lymphoma, graft versus host disease and the use of anti-cholinergic drugs (Vitali et al., 2002).

2.1 Ocular symptoms

Ocular symptoms are taken into consideration when patients complain about troublesome dry eyes, recurrent sensation of sand or gravel in the eye, or the use of tear substituent.

2.2 Oral symptoms

Oral symptoms are considered pertinent when patients experience daily feeling of dry mouth, recurrent or persistent swollen salivary glands, or frequent drinking to facilitate dry food swallowing.

2.3 Ocular signs

Evidence of ocular involvement relies on positive Schirmer's test (<5mm/min) or positive ocular dye score (score > 4 according to the van Bijsterveld score; Van Bijsterveld, 1969).

2.4 Histopathology

A histological sign is considered positive when minor salivary gland biopsy show a focus score >1 (more than 50 lymphocytes per 4 mm^2 of tissue).

2.5 Salivary gland involvement

Objective evidence of salivary gland involvement relies on low unstimulated saliva flow (< 1.5ml/15 min), abnormal sialography, or altered salivary scintigraphy.

2.6 Autoantibodies

Serological signs are considered positive when the presence of antibodies to either Ro (SSA) or La (SSB) or both are detected in the serum.

2.7 New diagnostic tools

To prevent excessive prescriptions of exams for establishing diagnosis of SS, newer diagnostic tools have been validated. However, these tools have not yet been included in the American-European diagnosis criteria of SS. For example, ultrasonography of salivary glands might prove to be useful to detect anatomical changes in parotid and submandibular glands, with similar diagnostic ability to sialography. Detection of hypoechoic areas, echogenic streaks, cysts and irregular gland margins are highly suggestive of SS (Tagaki et al., 2010). Parotid MRI can also prove to be an adjunct diagnostic tool to detect heterogeneity in salivary glands and specific cystic lesions (Roberts et al., 2008).

3. Pathophysiology of SS

The pathophysiology of SS is highly complex. Despite tremendous progress made to unearth the different mechanistic processes underlying the autoimmune abnormality, the etiology of the disease still remains to be discovered. It is actually held that in patients with predisposed genetic background, the combination of viral infections and/or environmental stress leads to epithelial cell activation and upregulation of toll-like receptors(TLR). Initiation of disease is favored by alterations of glandular architecture such as modification of extracellular matrix and cell-cell interactions (that may lead to gene expression reprogramming by epigenetic gene modifications triggered by mecanotransduction). Activation of innate immunity through TLR, leads to T cell activation and secretion of pro-inflammatory cytokines. Moreover, following epithelial cell activation, there is an upregulation of pro-apoptotic molecules and autoantigen processing resulting in the formation of exosomes, activation of dendritic cells (secretion of IFNα) and further activation of T cells. In advanced stages of the disease, following BAFF activation, B-cell proliferation, and aberrant lymphocyte homing favoring diseased gland destruction and the formation of germinal centers and ensuing lymphoma (Figure 1).
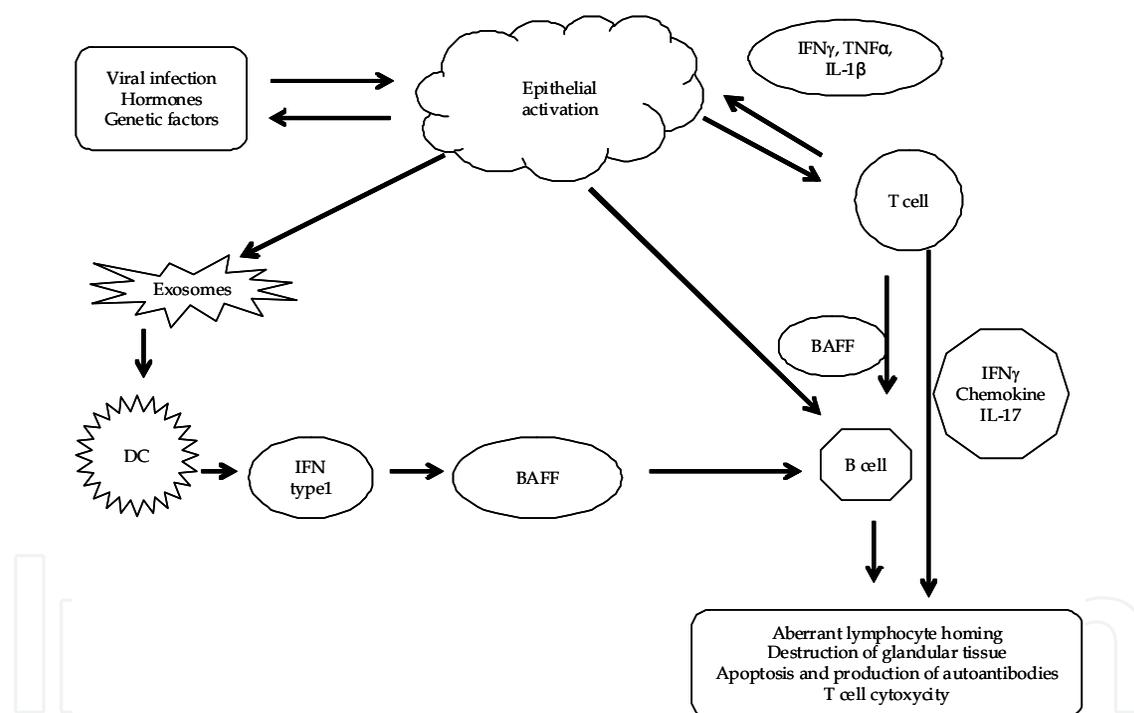

Fig. 1. Mechanisms underlying the pathogenesis of SS. Hormones, viral infections and environmental factors in appropriate genetic background are believed to trigger initial events in SS. Epithelial cells are activated resulting in T and B cell activation. T cells produce pro-inflammatory cytokines, which in turn perpetuates activation of epithelial cells, and stimulates B cell activation and proliferation resulting in aberrant lymphocyte homing, autoantibodies production, germinal ectopic centers and tissue destruction. Following epithelial cell activation, production of exosomes activates dendritic cells to produce type 1 IFN and thus BAFF secretion. BAFF stimulates aberrant B-cell maturation resulting in the production of self-reactive B cells synthesising autoantibodies. BAFF: B-cell activating factor; DC: dendritic cells; IFN: interferon; Il-1β: interleukin-1 β; TNF-α: tumor necrosis factor α.

3.1 Environmental factors
3.1.1 Viral infections

Ebstein-barr, Human T Lymphotropic Virus-1 and hepatitis C have been proposed to be associated with SS. However, the link between these viral infections and SS remains weak (Pflugfelder et al., 1993; Green et al., 1989, Haddad et al., 1992; Iwakiri et al., 2009). Coxsackie virus was found to be increased in SS salivary glands, but these findings have been the subject of some controversies (Triantafyllopoulou et al., 2004, Gottenberg et al., 2006a). Innate immunity is classically stimulated by infectious agents, which results in type I interferon production. Upon viral infection, the activation of the interferon pathway can be perpetuated by the formation of immune complexes containing viral RNA, thereby leading to plasmacytoid dendritic cell activation and production of interferon-α.

3.1.2 Stress

Stress has been advocated as being a forerunner of SS, since pSS patients experienced a high degree of stress prior to the onset of disease (Karaiskos et al., 2009).

3.2 Endocrine factors
3.2.1 Sexual hormones

The high female to male predominance of SS clearly delineates the role of hormones in the pathogenesis of SS. Estrogenic action is largely imputed in the high female predominance in several autoimmune diseases, including SS (Whitacre, 2001). Estrogens and androgens are thought to respectively contribute or protect to autoimmunity. Onset of SS generally occurs around menopause, when modification of the androgen-estrogen ratio occurs. Patients with SS have been shown to possess lower systemic concentrations of dehydroepiandrosterone (DHEA) than matched aged-controls (Valtysdottir et al., 2001). Furthermore, decreased salivary DHEA levels, reduced cystein-rich secretory protein (CRISP-3, a protein upregulated by DHEA) expression, alteration of CRISP-3 polarized expression in acini, altered and decreased conversion of DHEA, and abnormal expression of steroidogenesis enzymes were detected in SS patients (Laine et al., 2007, Porola et al., 2008; Spaan et al., 2009). Women's local salivary gland dihydrotestosterone production is totally dependent on DHEA conversion, rendering them highly vulnerable to local androgen deficiency.

Estrogens play a cardinal role in targeting salivary epithelial cell and stimulating apoptosis through a Fas-mediated mechanism (Ishimaru et al., 1999). Retinoblastoma-associated protein 48 (RbAp48) induces tissue specific apoptosis in salivary glands depending on the level of estrogen deficiency (Ishimaru et al., 2008). More recently, the presence of functional estrogen receptors has been observed in salivary epithelial cells (Tsinti et al., 2009). In the latter study, estrogen was shown to block expression of ICAM-1, an adhesion molecule displaying increased expression in salivary glands of SS patients. It may therefore be speculate that estrogen deficiency might lead to increased innate immunity.

Prolactin, a pro-inflammatory hormone, stimulates estrogen activity and inhibits estrogen production, high level T cell proliferation, IL2 receptor expression, IFN-γ production and stimulation of antibody production (Taiym et al., 2004). Higher levels of prolactin are detected in SS patients, and may be involved with the production of autoantibodies involved in SS (Taiym et al., 2004).

3.3 Genetic factors
3.3.1 Genetic variation

Genetic predisposition is widely accepted as being an important etiological factor in many autoimmune diseases (Hewagama & Richardson, 2009). Several studies support the existence of predisposition to SS (Jonsson et al., 2007). Alleles within the major histocompatibility complex class II gene region, predominantly the HLA-DR and HLA-DQ (Loiseau et al., 2001), are implicated in the pathogenesis of SS. Susceptibility alleles in SS patients may also vary according to ethnic origin (Bolstad and Jonsson, 2005).

An increasing body of evidence for the implication of other gene variants outside the HLA locus association is being put forth recently. Gene polymorphisms of IRF-5 and STAT-4 genes, two transcription factors of pivotal importance in interferon pathway, have been associated with various autoimmune diseases (Martinez et al., 2008), as well as with SS (Miceli-Richard et al., 2007; Korman et al., 2008; Miceli-Richard et al., 2009; Nordmark et al., 2009, Gestermann et al., 2010). The most significantly associated single nucleotide polymorphism (SNP) of the IRF5 gene was a 4 fold repetition, instead of three, of a sequence within the promoter region (Nordmark et al., 2009). An association between this polymorphism and high levels of IRF5 mRNA was demonstrated in PBMCs and in cultured salivary epithelial cells after viral infection (Miceli-Richard et al., 2009). STAT4 polymorphism was also associated with SS (Nordmark et al., 2009; Korman et al., 2008; Gestermann et al., 2010; Palomino-Morales et al., 2010).

MECP2 and IL2-IL21 polymorphisms have also been associated with SS (Cobb et al., 2010; Maiti et al., 2010). Gene polymorphisms in IL-10, IL-6, IL-1 receptor antagonist, IL-4 receptor α, TNF-α, IFN-γ and TGF-β1 have also been associated with pSS (Cobb et al., 2008).

PTPN22 (protein tyrosine phosphatase nonreceptor 22), primarily expressed in lymphoid tissues, has been suggested to have prominent roles in T-cell signaling. The 1858 T allele of PTPN22 has been shown to be a risk factor for SS in one Columbian study whilst other studies did not find any significant association with SS (Gomez et al., 2005; Ittah et al., 2005).

PTEN, a tumour suppressor gene, displayed a rare mutations shown to be associated concomitantly with SS and Cowden disease (Raizis et al., 1998) and may be associated, in diseases, with the latter occurrence of non-Hodgkin lymphoma.

Very recently, a large Swedish-Norwegian study has associated potentially muscarinic receptor-3 gene variant with SS (Appel et al., 2011). In this study, focus scores, abnormal Schimer's test and autoantibody presence were associated with muscarinic receptor-3 SNPs.

Recent data have suggested an increased association between immune system genes and the pathogenesis of primary SS. Indeed, an increase in the copy number of 2 genes linked to immune regulation-FCGR3B and CCL3L1-that can confer susceptibility to SS (Mamtani et al., 2010). A similar study revealed, besides confirming association of STAT4 and IRF5/TNPO3, three new loci as being associated as well with SS. However, the SNPs studied were not associated with the presence of anti-SSA/anti-SSB antibodies; though they are all involved in B-cell differentiation and activation (Nordmark et al., 2011).

Finally, in contrast one polymorphic variant, 168His of the minor histocompatibilty antigen HA-1, has been described as protective, lowering the risk of pSS (Harangi et al., 2005).

3.3.2 Epigenetic control

Epigenetic mechanisms are currently and increasingly being associated in disease processes, including autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus,

systemic sclerosis and SS (Pan and Sawalha., 2009; Richardson, 2007; Hewagama & Richardson, 2009; Brooks et al., 2010). In salivary glands from SS patients undergoing extracellular matrix remodelling, mechanotransduction may convey organ structural modifications that will inturn affect epigenetic control of gene expression (Gonzalez et al., 2011a). Indeed, the global DNA methylation of salivary glands from SS patients appears to be decreased, while specific genes appear to be hypermethylated (Gonzalez et al., 2011b).

MicroRNAs (miRNA) are an emerging field of epigenetic gene expression control, with potential involvement in autoimmune diseases (Dai & Ahmed, 2011; Alevizos & Illei, 2010a). miRNAs are small (20-22 nucleotides RNAs), resulting from a complex cellular processing, leading to RNA sequestration or destruction. miRNAs 17 & 92 have been shown to be associated with SS (Alevizoz et al., 2011a). Another study showed that over-expression of 2 miRNAs (miR-574 and miR-768-3p) participates to the epigenetic control of gene expression in salivary glands from SS patients (Alevizos et al., 2011b). These two micro-RNAs were associated with a high degree of inflammation and correlated with the histological focus score. As such, they could represent future biomarkers of inflammation in SS patients (Alevizos & Illei, 2010b, 2011). In animal model of SS, upregulation of miRNA 150 and 146 in PBMC and target tissue was observed (Lu et al., 2010). Furthermore, miR23A is highly expressed in salivary glands from SS patients and may regulate CUL3 expression (Gonzalez et al., 2011a).

3.4 Immune system alterations

The innate immune system plays a fundamental role in the pathogenesis of SS. Following viral infection, an increase in the expression of Toll-like receptors (TLR) has been shown in the salivary glands of SS patients. The functional TLR 2, 3, 4 as well as myeloid differentiation factor 88 (MYD88) are expressed in the labial salivary glands of SS patients (Kawakami et al., 2007). Following TLR activation in salivary glands, an increase in CD54 (ICAM-1) expression and IL-6 production, as well as upregulation of CD54, MHC class I and CD40 have been observed (Spachidou et al., 2007). Upregulation of TLR3 in salivary glands of female new Zealand/WF1 female mice, in response to polyinosinic:polycytidylic acid (a TLR3 ligand) resulted in activation of cytokine pathways and severe loss of glandular function (Deshmukh et al., 2009). These data underline increased TLR signaling pathways in salivary glands of SS patients leading to production of proinflammatory cytokines, T cell activation and a T helper type 1 driven immune response.

Upregulated expression of human leukocyte antigen (HLA) molecules occurs in epithelial cells of salivary glands from SS patients and may be involved in antigen presentation, leading to destruction of the tissue by CD4+ T cells as well as cytokine production and stimulation of B cells proliferation and differentiation (Jonsson et al., 2002).

Several cytokines have been implicated in the pathogenesis of SS. Increased expression of IFN-regulated genes has been shown in salivary glands from SS patients (Gottenberg et al., 2006; Hjelmervik et al., 2005), as well as in PBMC and whole blood (Emamian et al., 2009). Increased serum levels of IFN-α and β have been observed in pSS patients. Circulating PDC express high levels of CD40 (a marker of cellular activation), which correlate with the expression level of several type 1 IFN-induced genes in monocytes (Wildenberg et al., 2008). Type-1 IFN activation and secretion result in activation of immature dendritic cells, BAFF secretion, stimulation of Fas ligand expression and increased apoptosis, increased T cell proliferation and survival, induction of several chemokines and favoring Th1 responses

(Mavragani and Crow., 2010). Increased expression of TNF-α, IL-1, IL-12, IL-18, and IFN-α has also been shown in SS patients (Vougarelis and Tzioufas, 2010, Becker et al., 2010). Recently, the role of IL-17 producing cells (Th17) has been underlined in the pathogenesis of SS (Nguyen et al., 2008; Espinosa et al., 2009). The IL-23/Th17 pathway triggers autoimmune exocrinopathy and systemic autoimmunity. Mice lacking Ro 52 antigen are characterized by increased proinflammatory cytokines, tissue inflammation and systemic inflammation. Loss of IL-23 and IL-17 in Ro52 null mice, results in protection from systemic autoimmunity (Espinosa et al., 2009). Elevated serum levels of IL-17 and Th17 cells in patients with SS and related cytokines are predominant in salivary glands and strongly correlate with histological focus score (Katsifis et al., 2009).

Once T-cell infiltration of epithelial cells is established, CD4+ T cells and PDC produce B-cell targeted cytokines and other survival factors such as B-cell-activating factor of the tumor necrosis factor family (BAFF, also known as BLYS) and APRIL (Lavie et al., 2004). Ectopic germinal centre-like structures are a hallmark of B cell activation and proliferation and occur in about 20% of patients with pSS (Garcia-Carrasco et al., 2002). B cell hyperactivity has been found in SS patients (Kassan and Moutsopoulos, 2004). BAFF promotes B-cell survival and antibody secretion. BAFF-transgenic mice develop clinical features of SS, polyarthritis and lupus (Mackay and Schneider, 2009). SS patients display increased BAFF serum levels correlating with decreased BAFF-R expression on B-cells and disease activity (Sellam et al., 2007). BAFF secretion is induced by type 1-IFN in monocytes and dendritic cells, type 1 IFN in monocytes and salivary epithelial cells (Ittah et al., 2006), virus or double stranded DNA in salivary epithelial cells (Ittah et al., 2008). BAFF can be released by the epithelial salivary cells and B cells. B cell dysregulation plays a crucial role in perpetuating inflammation and tissue damage (Pers et al., 2007). Decreased levels of apoptosis among BAFF-expressing cells in salivary epithelial cells result in increased levels of BAFF expression, which in turn amplifies B cell signaling and proliferation and increased production of antibody-producing plasma cells (Mariette et al., 2003; Groom et al., 2002; Jonsson et al., 2005).

3.5 Autonomic system

Autonomic system dysfunction is also considered as a central feature in the pathogenesis of SS (Fox and Stern, 2002; Dawson et al., 2001). It might be responsible for glandular dysfunction and diminished salivary and lachrymal production (Waterman et al., 2000; Humphreys-Beher et al., 1999). The role of autonomic dysfunction in SS pathogenesis is supported by the presence of anti muscarinic M3 receptors (M3R) autoantibodies in SS patients (Naito et al., 2005; Nakamura et al., 2008). In the salivary glands of SS patients, there is an upregulation of M3R, which might be the corollary of antagonistic M3R autoantibodies or impaired release of acetylcholine (Beroukas et al., 2002a) or yet modified epigenetic control on M3R (Appel et al., 2010). Furthermore, M3R Tcells play a fundamental role in autoimmune sialoadenitis (Iizuka et al., 2010). An additional mechanism that could contribute to autonomic dysfunction is elevated levels of acetylcholinesterase in the salivary glands of patients with SS (Dawson et al., 2000). Decreased levels of acetylcholine due to increased cholinesterase levels result in glandular dysfunction and diminished production of saliva (Dawson et al., 2001).

3.6 Autoantibodies

Autoantibodies against Ro (SSA) and La (SSB) are found in the serum of pSS and sSS patients (Garcia-Carrascos et al., 2002). They are linked to the onset, severity, duration and

extraglandular manifestations of SS (Jonsson et al., 2002; Skopouli et al., 2005). It is still undetermined if these antibodies play a direct pathogenic role in the glandular damage. Nonetheless, there is evidence supporting a role of anti Ro and anti La antibodies in the local autoimmune response. Indeed, autoantibodies to Ro and La have been found in saliva and infiltrating cells of salivary glands in patients with SS. Increased mRNA production of La in acinar epithelial cells and translocation of La protein, resulting in membrane localization, in the conjunctival epithelial cells have been observed in SS patients (Hammi et al., 2005; Tzioufas et al., 1999).

Autoantibodies against α–fodrin, a major constituent of the cytoskeleton, have also been detected in sera from patients with SS. Abnormal location of α-fodrin on the surface of apoptotic-induced cells suggests the role of α-fodrin in SS through apoptotic pathways. Aberrant proteolysis of α-fodrin results in its expression at the surface of apoptotic epithelial cells entailing the autoimmune process (Locht et al., 2008; Willeke et al., 2007).

Autoantibodies to muscarinic M3 receptors, found in the serum of SS patients, induce the inhibition of the synapse between the efferent nerves and the salivary glands, leading to decreased saliva production (Fox and Stern, 2002; Sumida et al., 2010).

More recently, antibodies against carbonic anhydrase II, VI and XIII have been described in relation to renal manifestations of SS (Pertovaara et al., 2011).

3.7 Epithelial cells activation

Impaired function and/or architectural destruction of epithelial cells occur in salivary glands from SS patients. Epithelial cells are now considered as playing active roles in immune defenses (Manoussakis and Kapsogeorgou, 2010). Epithelial salivary glands cells, even if not proven to act as antigen-presenting cells possess all the features to do so (Manoussakis et al., 1999; Matsumura et al., 2001). Epithelial cells might act as non-professional antigen-presenting cells, and thereby participate in autoimmune responses leading to the development of SS (Tsunawaki et al., 2002; Xanthou et al., 2001; Dimitriou et al., 2002; Lavie et al., 2004). Proinflammatory cytokines and other factors can induce activation of surrounding epithelial cells (Abu-Helu et al., 2001). Furthermore, as a result of apoptosis and formation of exosomes, epithelial cells present intracellular autoantigens such as the Ro and La autoantigens, further contributing to the autoimmune process. Besides, following type 1 IFN stimulation and viral infection of epithelial cells, the latter releases BAFF thereby activating B cells (Kapsogeorgou et al., 2005; Ittah et al., 2009).

3.8 Apoptosis

A pivotal role for apoptosis as a pathogenic mechanism in SS-related glandular damage has been demonstrated. Increased apoptosis of the ductal and acinar epithelia occurs in pSS patients. Upregulation of the expression of several apoptotic-related molecules has been described in lymphocytes and epithelial cells from salivary glands of patients with SS. Epithelial cell apoptosis contributes to the glandular destructive lesions through the upregulation of molecules leading to the proteolysis of exocrine autoantigens and ensuing glandular damage. Disequilibrium between pro-apoptotic signals and anti-apoptotic mechanisms might act as the basis of epithelial cell destruction of exocrine glands in pSS.

Apoptotic cell death might also function in a specific fashion favoring abnormal exposure of nuclear and cytoplasmic autoantigens thereby providing mechanism of antigen presentation to autoreactive T cells. Furthermore, anti-Ro and anti-La autoantibodies can activate

caspase-3 and cleave PARP and trigger apoptosis. Furthermore, these autoantibodies have been shown to also activate extrinsic apoptotic pathways by transcriptional upregulation and activation of caspase-8. Anti-Ro and anti-La autoantibodies could trigger apoptosis resulting into tissue destruction (Ramos-Casals and Font, 2005).

3.9 Alterations of proteins involved in glandular function

Aquaporins (AQP) are small transmembrane proteins involved in water flow across cell membranes. Several AQPs are expressed in salivary glands and lachrymal glands (Delporte, 2009). AQP5, expressed on salivary acinar cells, contributes to salivary flow (Ma et al., 1999). A modified distribution of AQP5 expression has been documented in both human salivary and lachrymal glands from pSS patients (Steinfeld et al., 2001; Tsubota et al., 2001) and in SS animal models (Konttinen et al., 2005; Soyfoo et al., 2007, Sasaki et al., 2007; Ohashi et al., 2008). Treatment by rituximab restored apical localization of AQP5 (Ring et al., 2006). A decreased expression of AQP1 in salivary glands of SS patients was observed (Beroukas et al., 2001; Beroukas et al., 2002). Both AQP5 and AQP1 could participate to the pathogenesis of SS, although they can not account for salivary and lachrymal secretory defects.

An active remodelling of the basal lamina is taking place in acinar and ductal cells from SS patients. In normal salivary glands, laminin 5 bridges the basal lamina with epithelial cells by forming adhesion complexes through specific integrin α6β4 (Velozo et al., 2009). Modified expression of basal laminins, laminins 1 and 5, occurs during different stages of SS (Kwon et al., 2006; Laine et al., 2004). In salivary acinar cells from SS patients, altered distribution of α6β4 integrin results in the destruction epithelial cell complexes with laminins (Velozo et al., 2009). Tight junction protein levels and distribution of ZO-1, occluding, claudin-1 and claudin-4 were modified in patients with SS (Ewert et al., 2010). Therefore, maintenance of equilibrium between cell-cell and cell-basal lamina attachment is necessary to ensure gland cell survival.

4. Clinical manifestations

4.1 Xeropthalmia

Xerophtalmia is often less prominent than xerostomia. It is therefore necessary to follow a detailed anamnestic investigation to detect symptoms of ocular dryness. The main complaint of xeropthalmia is foreign-body sensation, but other symptoms such as grittiness, thick rope like secretions at the inner canthus, photosensitivity, burns, and sensation of having a veil before the eyes, absence of tears after irritation or emotion are all frequent features of xerophtalmia. Xerophtalmia is due to the lymphocytic infiltration of lachrymal glands leading to reduced lachrymal flow and tear composition, thereby altering corneal and conjunctival epithelia, characterizing the known condition of keratoconjunctivitis sicca (KCS). In severe disease, functional disability with visual impairment may occur (Fox, 2005).

4.2 Xerostomia

More than 90% of patients with SS complain of symptoms resulting from functional alteration of salivary glands. The symptoms range from dry mouth and lips, the need to drink more water when eating, to difficulties in the mastication process. In the early phase

of the disease, xerostomia is less obvious for the patients but with disease progression and severe alteration of salivary glands, xerostomia manifests as a painful syndrome with the sensation of permanent mouth burns, taste alteration, fissuring of the tongue, angular cheleitis and ulcers. Further progression of xerostomia leads to multiple complications such as teeth decay, atrophy of lingual papillae, increased incidence of mucosal infections (primarily candidiasis) loss of teeth and ultimately dentition (Fox, 2005).

4.3 Systemic manifestations
4.3.1 Musculoskeletal manifestations
More than 70% of patients complain of articular manifestations. Symmetric, non-erosive, polyarthritis affecting the small joints can also be observed and precede the sicca syndrome. Myalgias are also a frequent feature, accompanied with asthenia, fatigue and muscle tenderness, reminiscent of a fibromyalgia-like syndrome (Mavragani and Moutsopoulos, 2010).

4.3.2 Respiratory manifestations
Reduced secretion from nasal epithelial cells results in nasal crusting, epistaxis and recurrent sinusitis. Tracheal dryness results in a dry non-productive cough and dyspnoea. In > 50% of SS patients, dry irritating cough was present without any radiographic abnormalities. Bronchial hyperreactivity might lead to small airways obstruction. Due to lymphocytic hyperplasia, severe airway obstruction can also occur (Parke, 2008).
Interstitial lung disease (ILD) is a classic manifestation of SS. These patients present cough, dyspnea on exertion, bilateral pulmonary infiltrates on plain radiographs and several other abnormalities on computer tomography scanner. Later stages of the disease are characterized by its evolution to fibrosis and neutrophilic alveolitis (Parambil et al., 2006).
Lymphocytic interstitial pneumonia (LIP), previously considered as a hallmark of lung involvement in SS, forms part of the spectrum of ILD. It is a consequence of bronchus associated lymphoid tissue proliferation (BALT) (Parambil et al., 2006).
Patients with SS are at increased risk of developing lymphoma, usually low grade MALT lymphoma and primary pulmonary lymphoma. These patients present few clinical symptoms contrasting with severe radiographic changes (Parke, 2008).
Pulmonary hypertension is a very rare finding in patients with SS. Only 17 cases have been documented in the literature. Prolonged vasospasm and vasculature remodeling have been assigned to contribute to the development of this pathology (Launay et al., 2007).

4.3.3 Renal manifestations
Tubular renal acidosis and glomerulonephritis are two main features of kidney involvement in SS. Distal tubular acidosis is the most frequent renal manifestation of SS occurring in up to 20% of cases. Very often, it is asymptomatic without any clinical or biological impact. Glomerulonephritis is rare in SS, and often due to cryoglobulinemia (Aasarod et al., 2000).

4.3.4 Cutaneous features
Besides the classical features of dry skin, other skin manifestations are present. Purpura is presents as petechia, which are localized in the lower limbs. Histological analysis shows leucocytoclastic vasculitis. The symptoms usually resolve with corticosteroids. Other skin manifestations include erythema nodosa, vitiligo, and digital ulcers (Kittridge et al., 2011).

4.3.5 Neurological manifestations

The spectrum of neurological disorders associated with SS is broad ranging from peripheral neuropathy to central nervous involvement. The frequency of neurological involvement in SS is relatively low and might precede the diagnosis of SS (Segal et al., 2008).

The cardinal features of CNS involvement in SS are very much identical to that of systemic lupus erythematosus. As such, the clinical profile includes hemiparesis, cranial neuropathy and more often optic nerve neuropathy, brainstem and cerebellar disorders, movement disorders, epilepsia. Spinal cord syndromes include transverse myelitis, Brown-Sequard syndrome and progressive myelitis. Because of the occurrence of optic neuropathy and myelitis, a diagnosis of multiple sclerosis is often evoked. Furthermore, MRI imaging shows hyperintense lesions in the white matter. Neuromyelitis optica (Devic's disease) is often associated with SS and is characterized by episodes of myelitis and optic neuropathy. The clinical features of neuropsychiatric syndrome include often cognition, anxiety, mood changes, and depression and sleep disorders (Lafitte et al., 2001).

Peripheral neuropathy is much more frequent than CNS involvement and precedes the diagnosis of SS. Sensory neuronopathy is considered to be distinctive of SS but sensorimotor neuropathy, sensory neuropathy, autonomic neuropathy, moneuritis multiplex are amongst other features of peripheral nervous system involvement. Trigeminal neuropathy is one of the most frequent manifestations of neurological invovement in SS (Lafitte et al., 2001). In most of the cases, sensory ataxia, painful sensory neuropathies, and trigeminal neuropathy are related to sensory ganglionitis, whereas mononeuritis multiplex and multiple cranial neuropathies are more closely associated with peripheral nerve vasculitis (Segal et al., 2008).

4.3.6 Gastrointestinal features

The manifestations of gastrointestinal tract are not very specific and include oesphageal dysmotility and gastro intestinal reflux. There are no specific liver abnormalities, which can be attributed to SS, but autoimmune hepatitis and primary biliary cirrhosis can be associated diseases (Mavragani and Moutsopoulos, 2010; Fox, 2005).

4.3.7 Serological manifestations

Several hematological features such as anemia, leucopenia and thrombopenia can be present. Anemia is a rare feature and when it exists, it is rarely due to inflammation but results from hemodilution due to polyclonal hypergammaglobulinemia. Leucopenia < 4000/mm3 is present in 30% of cases. In certain cases of major hypergammaglobulinemia, a hyperviscosity syndrome can be present. Typical symptoms include headaches, visual impairement and hemorrhages (Fox, 2005).

4.4 Lymphoma

Patients with SS have a 20 to 40-fold risk of developing non-hodgkin lymphoma (NHL) as compared to the general population. NHL has a prevalence of about 4% in SS and occurs classically following a median of 7.5 years after its initial diagnosis. The most frequent histological type of NHL is the MALT lymphoma. The histopathological features of MALT lymphoma include reactive lymphoid follicles, small plasma cells, lymphoepithelial lesions and MZ and/or monocytoid B cells. The clinical course of NHL lymphoma is indolent and the clinical characteristics include small tumor burden and good performance status. The most frequent anatomical localizations are the salivary glands but extra nodal sites can be

involved, such as stomach or kidneys.The clinical and biological factors heralding imminent are low C4 levels, palpable purpura, high β2-microglobulin levels, CD4 lymphocytopenia, parotid gland swelling and persistent enlargement and hypocaptation on salivary scintigraphy, mixed monoclonal cryoglobulinemia, leg ulcers, splenomegaly and the presence of serum or urine monoclonal bands (Voulgarelis and Moutsopoulos, 2008).

5. Therapeutic approaches

Conventional therapy of SS is symptomatic and consists in alleviating of sicca features. As such, treatment consists in the use of artificial saliva and tears, surgical removal of plugs in the lachrymal ducts, the use of topical cyclosporine for ocular symptoms. Cholinergic drugs such as pilocarpine and civemeline are available to increase glandular secretion. Hydroxychloroquine is prescribed for arthralgia and myalgia, but recent studies have shown that it also has slight anticholinesterase properties in improving glandular function (Rihl et al., 2009). The efficacy of steroids is limited and restricted to patients with arthritis and severe extraglandular manifestations. Immunosuppressive treatments such as cyclophosphamide and azathioprine are used for systemic features of SS. More recently, newer immunosuppressive drugs, such as mizoribine and mycophenolate mofetil, have shown promising results. These drugs inhibit inosine monophosphate dehydrogenase, the rate-limiting enzyme for purine synthesis, and have an antiproliferative effect on activated lymphocytes (Becker et al., 2010). An intraoral electrostimulation device showed promising results in alleviating xerostomia and increasing salivary output (Strietzel et al., 2011).

5.1 B-cell targeted therapies

Rituximab, a chimeric monoclonal mouse antibody that targets CD20 at the surface of B-cells, is the most studied biologic therapy in SS. Several pilot studies have shown efficacy of rituximab in terms of improvement of fatigue, quality of life and glandular function. A randomized-controlled trial has confirmed these results (Meijer et al., 2010). Epratuzumab is a humanized antibody directed against the B cell antigen CD22. An open labeled trial has shown improvement of sicca symptoms and fatigue scores (Steinfeld et al., 2006).

5.2 Inhibition of IFN release

Interferon-α (IFN) plays a pivotal role in the pathogenesis of several autoimmune diseases including SS. Besides antiviral effects, IFN-α has immunomodulating properties. Four pilot studies have shown beneficial effects of oromucosal IFN-α, whereby salivary flow was increased and salivary gland histology after treatment demonstrated reduced lymphocytic infiltrâtes (Cummins et al., 2003; Tobon et al., 2010). A phase III trial performed later, showed an increase in unstimulated salivary flow but the main clinical endpoint, which was improvement of stimulated salivary flow, was not met.

5.3 Transplantation of bone-marrow-derived stem cells

Stem cells from the spleen, when harvested and transplanted in NOD mice, an animal model for SS, have been shown to regenerate salivary epithelial cells (Faustman et al., 2010). Current undergoing trials are investigating whether the transplanted adult hematopoietic cells can restore glandular function in patients suffering from SS.

5.4 Gene therapy

Gene therapy consists in the introduction of new genetic material in an individual for therapeutic purposes. Several targets for gene therapy include aquaporins, inflammatory mediators, apoptotic molecules and intracellular molecules.

Initial gene therapy studies, using serotype 5 adenoviral vector (Ad5), showed extremely efficient *in vivo* gene transfer to rodent salivary glands (Mastrangeli et al., 1994). Further studies using Ad5 encoding human aquaporin 1 (Ad5hAQP1), a water channel, showed the function and potential utility of this vector to restore impaired saliva flow in rats with irradiated-induced salivary hypofunction (Delporte et al., 1997). The efficacy and scaling studies of this particular gene therapy were then performed in large animal models: rhesus macaques (O'Connell et al., 1999) and miniature pigs (Li et al., 2004). A NIH clinical trial using Ad5hAQP5 has been undertaken to test the safety and efficacy in individuals with irradiation-induced parotid salivary hypofunction.

Gene transfer therapies based on the anti-inflammatory properties of IL-10 and vasoactive intestinal peptide (VIP) have also been proposed as future treatment of SS. Indeed, administration of adenovirus vectors encoding either human IL-10 or VIP to salivary glands from NOD mice, a mouse model for SS, led to significant salivary flow improvement (Kok et al., 2003; Lodde et al., 2006).

Gene transfer has also been used to treat chronic sialadenitis and modulate apoptosis in a murine model of SS: B6-gld/gld mice deficient in Fas ligand. When infected with murine cytomegalovirus, these mice presented chronic sialadenitis similar to SS. Delivery of a recombinant adenovirus vector coding for Fas ligand to the salivary glands of these mice, induced a significant reduction in infiltrating lymphocytes (Fleck et al., 2001).

As IL17A administration to mice salivary glands, using recombinant adenoviral vector, leads to SS-like disease (Nguyen et al., 2011), localized anti-IL-17 might be effective in preventing glandular dysfunction.

5.5 Other therapeutic perspectives

BAFF is a cytokine that prevents apoptosis of B-cells and thereby contributes to the hyperreactivity of B cells and their survival. Increased BAFF secretion might explain in part the partial response of rituximab in SS patients. Targeting BAFF might therefore prove to be a future therapeutical approach (Mariette, 2008). In systemic lupus erythematous, an autoimmune disease that shares similar pathogenetic features with SS, in that both diseases are characterized by an interferon signature, Belimumab, an anti-BAFF monoclonal agent, has shown beneficial effects in a randomized controlled trial (Navarra et al., 2011). Atacicept, a fusion protein inhibiting B cell stimulation, could be a promising therapeutic drug in SS (Dorner et al., 2009).

Other therapeutic perspectives for SS also include the restoration of salivary glands function using bone marrow-derived cells (BMDCs) (Tran et al., 2011) and tissue engineering of salivary glands (Kagami et al., 2011). BMDCs transplantation by intravenous injection rescues salivary gland function in mice with head and neck irradiation by preventing apoptosis, increasing tissue vascularization, increasing the number of proliferating cells, and maintaining the putative salivary stem cells (Sumita et al., 2011; Lombaert et al., 2008). Furthermore, BMDCs transplantation into NOD mice treated as well with complete Freund's adjuvant (CFA), led to both qualitative and quantitative saliva restoration, and normoglycemia (Khalili et al., 2010). Tissue engineering of salivary glands utilizes cells, biodegradable scaffold, and signals to regenerate tissues. Since the pioneer work reporting

the culture of salivary epithelial cell culture (Brown 1974), several culture procedures have been described (Horie et al., 1996; Aframian et al., 2004; Joraku et al., 2005; Tran et al., 2006). A multipotent stem cell population has been discovered in human adult salivary glands (Okumura et al., 2003; Hisatomi et al., 2004; Kishi et al., 2006), but their potential for engineering salivary glands has not been proven. Developping appropriate scaffold materials will be essential for salivary gland tissue engineering (Kagami et al., 2011).

6. Conclusions

SS is one of the most frequent autoimmune diseases, characterized by the dysregulation of cellular and humoral mechanisms, thereby portraying the prototype of autoimmune disorders. Although, the pathogenesis of SS still remains to be discovered, tremendous progress has been made in deciphering the intrinsic abnormalities behind initiation and perpetuation of inflammation and tissue destruction. The herald of new pathophysiological mechanisms such as epigenetic control may prove cardinal in tailoring new treatments providing improved relief to patients with SS.

7. Acknowledgements

8. References

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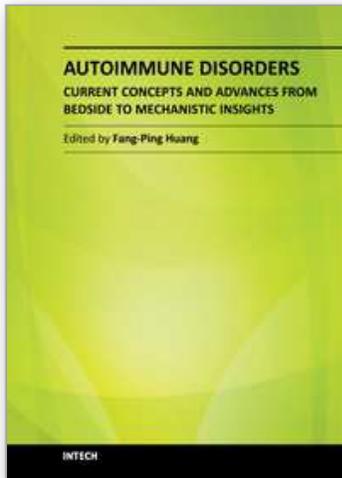
Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights
Edited by Dr. Fang-Ping Huang

Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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