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Cytokines in Sjögren's syndrome

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Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic chronic inflammatory autoimmune disorder that affects secretory organs like the salivary and lachrymal glands. Patients complain of dry eyes and dry mouth (sicca symptoms) and often have systemic manifestations, such as Raynaud's phenomenon, arthritis, fatigue and vasculitis. Its estimated prevalence is 0.5% with a female to male ratio of 9:1 (Fox, 2005). The pathogenesis of the disease is largely unknown and to date, no universally effective therapy is available. The histological hallmark of SS is the presence of focal infiltration of T and, to a lesser degree, B lymphocytes in the salivary glands indicating a chronic inflammatory process (Daniels and Fox, 1992; Vitali et al., 2002). This chronic inflammation is reflected by an imbalance in cytokines both locally in the glands and systemically in the blood. The scope of this review is to summarize the current data on cytokine abnormalities described in patients with SS.

Cytokines

Cytokines are powerful regulators of the innate and adaptive immune system. They play a central role in controlling the direction, amplitude, and duration of the inflammatory response. Aberrations in their expression may lead to immune deficiency, allergy or autoimmunity. Cytokines are pleiotropic and can be secreted by hematopoietic cells and numerous other cell types. Most cytokines have a predominantly pro- or anti-inflammatory effect, but many can exert both functions, depending on their environment.

Immune responses have been traditionally divided into two groups, Th1 and Th2, although it has recently become clear that many immune responses have features of both. A Th1 response is characterized by activation of effector T cells and the production of interferon γ (IFN γ). A Th1 response clears intracellular organisms, but is also involved in many autoimmune diseases. The main feature of Th2 responses is a humoral immune response through the activation of B cells and the production of antibodies. The main cytokine involved in Th2 responses is interleukin (IL) 4. An imbalanced Th2 response results in allergies but is also linked to autoimmunity (reviewed in (Crane and Forrester, 2005)). SS is thought to be a Th1 dominated disease primarily because IFN γ and its related cytokines are consistently found to be highly expressed in SS patients. Moreover, salivary gland derived T cells from patients produce the Th1 cytokines IFN γ and IL2 *ex vivo*, but no or low levels of the Th2 cytokine IL4 (Brookes et al., 1996). However, the significant hypergammaglobulinemia and high levels of autoantibodies together with high expression of IL10, another Th2 cytokine, demonstrate a simultaneous activation of the Th2 response.

These data reflect that although the Th1/Th2 concept is useful in understanding cytokine networks and responses, its direct applicability in systemic human autoimmune diseases, such as SS, is limited.

Cytokines and salivary gland dysfunction in Sjögren's syndrome

Cytokines may contribute to the pathogenesis of SS in various ways. They play a central role in the initiation and perpetuation of inflammation in the secretory glands. The imbalance of pro-over anti-inflammatory cytokines results in cumulative damage in the glands leading to decreased secretory function. Although infiltration of the gland by lymphocytes is a hallmark of SS, some patients suffer from significant secretory dysfunction without major glandular destruction (Fox and Speight, 1996; Humphreys-Beher et al., 1999). Since some cytokines are upregulated even in the absence of lymphocytic infiltrates they may have a direct effect on epithelial cells independent from damage caused by inflammation. Since cytokines are key molecules in systemic inflammation, they may contribute to systemic complications of SS as well. Many cytokines that are overexpressed in the glands and serum have been related to episodes of vasculitis or other systemic features. SS patients are also at a higher risk than the normal population for developing non-Hodgkin's lymphoma in the exocrine glands (Tzioufas and Voulgarelis, 2007; Voulgarelis et al., 1999). Although, the mechanisms responsible for lymphomagenesis is not well understood it most likely includes cytokine-driven processes, such as chronic stimulation of B and/or T cells and formation of ectopic germinal centers (Mariette, 1999). (See table 1.)

Major pro-inflammatory cytokines in Sjögren's syndrome

The major pro-inflammatory cytokines found to be important in SS are the interferons, IL12, IL18, TNF α , IL1 β , IL6 and B-cell activating factor (BAFF). Whether the recently discovered IL17, IL23 and the related T cell subset (Th17 cells) play an important role in SS is still unknown.

Interferons

Interferons were the first cytokines discovered. They play a crucial role in the innate immune response against viruses (Isaacs and Lindenmann, 1957) but over the past decades it was shown that they have a much broader spectrum of function. They activate T cells and macrophages, affect class switching of B cells, enhance antigen presentation and upregulation of inter cellular adhesion molecules, all leading to an activated immune state ready to fight off pathogens. IFNs also play a crucial role in auto-immunity (Baccala et al., 2005; Bave et al., 2005; Gota and Calabrese, 2003) (Tak, 2004). There are two groups of interferons; Type I interferon (IFN α and IFN β) is secreted by virus-infected cells and plasmacytoid dendritic cells (pDC) while type II, or IFN γ is mainly secreted by T cells, natural killer (NK) cells and macrophages (Le Page et al., 2000).

IFNs play a central role in the pathogenesis of SS. They are aberrantly expressed in patients and many cytokines and transcription factors that are overexpressed in patients are IFN inducible (Bave et al., 2005; Gottenberg et al., 2006; Hjelmervik et al., 2005; Hu et al., 2007; Wildenberg et al., 2008). Moreover, pathways that are related to IFN signaling are significantly upregulated in SS patients (Gottenberg et al., 2006). This profile has been referred to as 'the interferon signature' (Bave et al., 2005).

IFN α

Low levels of IFN α are constitutively present in a variety of cells and are found circulating in the blood, whereas high titers are rapidly produced in the presence of danger signals such

as a viral infection (Taniguchi and Takaoka, 2001). IFN α is also upregulated in autoimmune diseases like systemic lupus erythematosus (SLE) (Ronnblom and Alm, 2001).

In salivary gland biopsies from SS patients IFN α is detected at higher levels in acini and endothelial cells compared to controls (Oxholm et al., 1992) but, IFN α is mainly secreted by pDCs, which are found in the salivary glands of SS patients but not in healthy controls (Gottenberg et al., 2006). Serum levels of IFN α were found to be high in SS patients compared to normal individuals by some groups (Anaya et al., 2005; Szodoray et al., 2005), but not by others (Bave et al., 2005). On the contrary, some groups observed low circulating levels of IFN α and argued that this could lead to reduced beneficial NK cell activity and reduced anti-viral defense mechanisms in patients (Shiozawa et al., 1990).

IFN γ

IFN γ is the major cytokine involved in a Th1 response, a response designed to clear intracellular pathogens. However, overexpression of IFN γ and an exaggerated Th1 response are also involved in many autoimmune diseases, like RA and multiple sclerosis (MS) (Hemmer et al., 2006; Schulze-Koops and Kalden, 2001). The production of IFN γ is directly stimulated amongst other cytokines by IFN α and IFN β (Baccala et al., 2005). The presence of IFN γ creates a pro-inflammatory environment in the salivary gland as illustrated by the observation that treatment of human salivary gland (HSG) cells with IFN γ , in the presence or absence of TNF α , results in increased levels of adhesion molecules and upregulation of antigen presenting molecules on the cell surface (Wu et al., 1994).

IFN γ mRNA is overexpressed by infiltrating cells in the salivary gland of patients with primary SS, but has normal systemic levels in the same patients (Oxholm et al., 1992; van Woerkom et al., 2005). Contradicting results have been published on whether healthy individuals express IFN γ in the salivary gland at constitutive levels (Fox et al., 1994; Kontinen et al., 1999; Oxholm et al., 1992; Wakamatsu et al., 2007). IFN γ inducible proteins, however, were clearly found in salivary gland of SS patients but not in healthy controls (Wakamatsu et al., 2006; Wakamatsu et al., 2007), supporting the notion of increased IFN γ expression in SS.

Interestingly, IFN γ is also highly expressed in individuals with sicca symptoms who do not have any histological signs of inflammation in the gland (van Woerkom et al., 2005). It is possible that, in addition to maintaining an inflammatory response with recruitment of T and B cells, IFN γ also has a direct effect on the secretory function of the gland. *In vitro* data support this: prolonged treatment of HSG with IFN γ in the presence or absence of TNF α leads to a persistent depletion of intracellular Ca²⁺ stores and thus to an exhausted response system (Wu et al., 1996). Moreover, IFN γ reduces the growth of HSG in a concentration dependent way (Daniels et al., 2000; Wu et al., 1994), suggesting that IFN γ may impair damage repair in the salivary gland.

IL12 and IL18

IL12 and IL18 are pro-inflammatory cytokines, closely related to IFN γ , which work synergistically to drive a Th1 response. They are both predominantly secreted by monocytes and macrophages and promote IFN γ secretion (Dinarello, 2007).

IL12 and IL18 were found to be overexpressed in SS. Expression of IL12 was primarily observed in the infiltrating cells (Bombardieri et al., 2004; Eriksson et al., 2004; Sakai et al., 2008), whereas IL18 was detected in acinar cells, ductal cells and macrophages in salivary glands of SS patients, but not in healthy subjects, patients with chronic graft-versus-host disease or chronic non-SS sialoadenitis. Some groups, but not all, found that IL18 is particularly high in those patients with anti-Ro and anti-La autoantibodies (Bombardieri et

al., 2004; Kolkowski et al., 1999; Manoussakis et al., 2007). IL18 may be involved in the lymphomagenesis of SS patients, since high levels of IL18 correlated with low levels of circulating complement, salivary gland enlargement and germinal center formation, all of which are thought to be risk factors for lymphoma development (Bombardieri et al., 2004; Manoussakis et al., 2007).

TNF α

TNF α is produced by monocytes, CD4+ T cells and epithelial cells. It upregulates the apoptotic receptor Fas on many cells including HSG (Matsumura et al., 2002) and in combination with IFN γ sensitizes cells to apoptosis (Kamachi et al., 2002; Kulkarni et al., 2006). Moreover, it also plays a role in the presentation of autoantigens since the nuclear antigens Ro, La and alpha fodrin, recognized by autoantibodies in many SS patients, are only transported to the membrane surface of salivary gland cells which undergo apoptosis in the presence of TNF α (McArthur et al., 2002).

High levels of TNF α and TNF α secreting cells have been found in peripheral blood and in lymphocytic infiltrates in salivary gland biopsies from patients with SS (Koski et al., 2001; Oxholm et al., 1992; Willeke et al., 2003). TNF α , and its two receptors; TNFR-p55 and TNFR-p75 are present in biopsies of healthy controls but are expressed at higher levels in SS patients (Koski et al., 2001). The expression level of TNF α did not correlate with the focus score (Moutsopoulos et al., 2008), but serum levels are especially high in patients positive for rheumatoid factor (RF) (Garcic-Carrasco et al., 2001) suggesting a correlation of TNF α expression and severity of systemic involvement.

IL1 β

IL1 β activates vascular endothelium and lymphocytes. Together with TNF α it is considered to be the key inflammatory cytokine in chronic inflammation, however, surprisingly little is known about its role in SS. IL1 β secreting circulating lymphocytes are significantly upregulated in SS patients compared to healthy controls and non-SS sicca patients, and its level correlates with disease duration and RF levels (Ek et al., 2006; Willeke et al., 2003). Immunohistochemical staining of salivary glands of SS patients showed expression of IL1 β whereas biopsies from controls did not (Oxholm et al., 1992).

IL6

IL6 is important for B cell growth and differentiation. It is thought to induce the production of autoreactive antibodies by infiltrating B cells via upregulation of specific cytokines and through its effect on the terminal differentiation of the immunoglobulin producing plasma B cell (Ishihara and Hirano, 2002). IL6 has a role in T cell stimulation and recruitment since it promotes the transition of naïve T cells to cytotoxic T cells. It also upregulates intercellular adhesion molecule 1 (ICAM 1) which functions as a receptor for activated T cells and on many cells as a co-stimulatory molecule for B cells (Chen et al., 2006).

IL6 was found highly expressed in serum and in peripheral circulating lymphocytes of SS patients, and was absent in most of the healthy controls. High levels of IL6 correlated with the degree of infiltration in the gland and the number of extraglandular symptoms (Boras et al., 2004; Garcic-Carrasco et al., 2001; Hulkkonen et al., 2001b; Nguyen et al., 2008; Szodoray et al., 2004a; Vucicevic Boras et al., 2006). IL6 was found consistently at high levels in saliva of SS patients. Moreover, it was found in labial gland biopsies of SS, but was not detected or was detected at lower levels in healthy controls (Boras et al., 2004; Grisius et al., 1997; Nguyen et al., 2008; Oxholm et al., 1992; Tishler et al., 1999). IL6 together with TNF α seems to be directly associated with inflammation of the gland since these two

cytokines are overexpressed in saliva of SS patients but not in patients with drug-induced xerostomia (Vucicevic Boras et al., 2006).

BAFF

One of the most recently described cytokines implicated in SS is BAFF which belongs to the superfamily of TNF related cytokines and promotes B cell survival (Mackay and Browning, 2002). BAFF exists in a membrane bound and a secreted form. BAFF induces major lymphoproliferative disorders in transgenic mice with B cell hyperplasia and hyperglobulinemia resembling the autoimmune phenotype of SLE (Gross et al., 2000). At a later age these mice develop a SS like disease with infiltrates in the salivary gland and a reduced salivary flow (Mackay et al., 1999).

BAFF is equally expressed in *ex vivo* cultured epithelial cells of the salivary gland of healthy individuals and SS patients, however patients also express BAFF at low levels in infiltrating T cells in the salivary gland whereas healthy people do not (Ittah et al., 2006). SS patients also have high serum and salivary levels compared to healthy individuals whereas the expression levels of membrane bound BAFF does not differ between patients' and healthy controls' epithelial cells (Daridon et al., 2007; Pers et al., 2007). Plasma and salivary secreted BAFF levels are especially higher in patients with hypergammaglobulinaemia, higher focus scores and in patients positive for anti-Ro and anti-La antibodies (Gottenberg et al., 2005; Jonsson et al., 2005; Mariette et al., 2003). BAFF induces a significant anti-apoptotic effect in peripheral B cells of SS patients; this effect is even more evident in B cells from SS patients with hypergammaglobulinemia (Szodoray et al., 2004b). This may indicate that BAFF is important in germinal center formation and may contribute to lymphomagenesis, but data on this are still inconclusive (Gottenberg et al., 2005; Jonsson et al., 2005; Mariette et al., 2003).

IL17 and IL23

A recently discovered subset of T lymphocytes involved in inflammation and autoimmunity, the so called Th17 cells, was originally discovered in mice and is characterized by the secretion of the powerful pro-inflammatory cytokines IL17 and IL23 (Cua et al., 2003; Park et al., 2005) and IFN γ when cells are stimulated with IL12 (Annunziato et al., 2007). In humans, Th17 cells are derived from memory T cells under the influence of IL1 β , IL6 and/or IL23. IL4 inhibits the development of Th17 (Acosta-Rodriguez et al., 2007; Chen et al., 2007; van Beelen et al., 2007; Wilson et al., 2007). Th17 cells are very effective in clearing extracellular pathogens. They are also believed to have a pivotal role in the initiation and perpetuation of autoimmunity. IL17 induces the expression of a variety of pro-inflammatory cytokines like IL6, TNF, and intercellular adhesion molecules in a variety of cells (Steinman, 2007).

IL17 may be an important player in the pathogenesis of SS, but data are lacking to support this to date. IL17 could be detected in serum and saliva of about fifty percent of a small group of SS patients, but also in a similar percentage in healthy control subjects. In biopsies of patients, the lymphocytic foci stained positive for both IL17 and IL23, especially in the CD4 $^{+}$ T cells, and showed diffuse staining on epithelial cells. Healthy individuals and sicca patients also showed low expression of IL17 but this was confined to ductal epithelium (Nguyen et al., 2008; Sakai et al., 2008).

Anti-inflammatory cytokines

In contrast to the overexpression of pro-inflammatory cytokines, anti-inflammatory cytokines are undetectable or are expressed at relatively low levels in SS. Interestingly, IL10, which is considered an anti-inflammatory cytokine, is overexpressed in SS.

TGF β

Transforming growth factor β (TGF β) is a bipolar cytokine crucial to the development of immunity. It is often associated with exaggerated immune excitability and overexpression is associated with increased fibrosis. Conversely, TGF β is key in limiting innate and adaptive immune responses, particularly self-reactive T cells, to restore immune homeostasis and to prevent autoimmunity (reviewed in (Prud'homme and Piccirillo, 2000; Wahl, 2007)).

TGF β mRNA is found in normal and SS salivary glands (Kolkowski et al., 1999), but is reduced in SS patients with a high focus score (Ogawa et al., 1995). TGF β is immunohistochemically detected in the ductal epithelial cells of normal and inflamed salivary gland tissues but is absent in ductal epithelial cells surrounded by infiltrated activated T cells in the diseased gland (Kizu et al., 1996).

IL4

IL4 is another classical anti-inflammatory cytokine and the main cytokine in a Th2 type immune response. This cytokine is absent or low in mucosal biopsies of SS patients (Kolkowski et al., 1999). Moreover, the ratio of the pro-inflammatory cytokine IFN γ to IL4 is higher in the salivary gland and lower in the peripheral blood of patients (van Woerkom et al., 2005) reflecting a skewed immune pattern towards a Th1 response locally in the gland.

IL10

IL10 is an anti-inflammatory cytokine involved in Th2 type responses. IL10 produced by regulatory T cells suppresses the effector immune responses. However, in the presence of IFN γ it can exert a pro-inflammatory effect (Sharif et al., 2004). IL10 is an important B cell activating factor and prolonged stimulation of naive B cells with IL10 leads to plasma cell formation (Rousset et al., 1992; Rousset et al., 1995).

High plasma levels of IL10 correlate with a higher susceptibility for SS (Anaya et al., 2005; Hulkkonen et al., 2001a). High serum levels of IL10 in SS patients are associated with higher titers of IgA rheumatoid factor, anti-Ro, and anti-La antibodies, and with the severity of lymphocytic infiltration in the salivary gland. Moreover, patients who have high levels of IL10 had significantly more episodes of cutaneous vasculitis (Anaya et al., 2005). T cells isolated from salivary gland from SS patients produce significantly higher levels of IL10 in contrast to the circulating T cells of the same patients (Brookes et al., 1996). A significant elevation of IL10 was found in saliva of SS patients compared with healthy controls. In patients, these elevated IL10 levels significantly correlated with the severity of dryness of the mouth and eyes and with the erythrocyte sedimentation rate (Bertorello et al., 2004). These data indicate that higher levels of circulating IL10 are associated with more systemic involvement and also play a role in the local inflammatory process. Since high IL10 levels are related to more severe disease, it is possible that the increased secretion of IL10 represents an anti-inflammatory control mechanism while it contributes at the same time to B cell activation.

Summary

Cytokines play a central role in the regulation of immunity and dysregulation of the cytokine network contributes to both systemic and exocrine manifestations of SS. The cytokine imbalance in SS is characterized by the overexpression of pro-inflammatory cytokines, such as IFN γ , IL12 and IL18. Two other cytokines, IL6 and BAFF, which are important in T and B cell activation and autoantibody production, are also upregulated. Concomitantly, IL4 and TGF β , two important anti-inflammatory cytokines are downregulated, possibly indicating loss of protection from autoimmunity. In contrast, the anti-inflammatory Th2 cytokine IL10

is highly expressed in SS patients and albeit ineffective in controlling inflammation, it may contribute to B cell activation and autoantibody production. (See figure 1.) Although the expression levels of many cytokines are known in SS, less is known about the mechanisms by which they contribute to exocrine gland dysfunction. Future research will need to be expanded to other cytokines important in chronic inflammation, such as IL1 β , IL17 and IL23 as well as the effects of these cytokines on both local and systemic inflammation and secretory functions. A better understanding of the abnormalities in the cytokine network and their role in the pathogenesis of SS will likely lead to the identification of the best therapeutic targets for this disease.

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Figure 1.

The cytokine profile found in Sjögren's Syndrome (SS) is imbalanced with the overexpression of numerous pro-inflammatory cytokines (on the left) versus low or undetectable levels of anti-inflammatory cytokines (on the right). The bipolar interleukin 10 (IL10) is highly expressed and may exert both anti- and pro-inflammatory effects in SS. The expression levels of the pro-inflammatory cytokines IL17 and IL23 are still unknown. (TGF= transforming growth factor, IFN= interferon, BAFF= B cell activating factor).

Table 1

Effects of cytokines in Sjögren's Syndrome

Cytokines in Sjögren's syndrome have been shown to play a role in:

- **Inflammation**; initiation and progression of inflammatory damage in the secretory organs
 - Direct effect on saliva and tear producing cells leading to **impaired fluid secretion**
 - Chronic stimulation of B and T cells leading to **lymphomagenesis**
 - **Systemic complications**
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