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SPECIAL ARTICLE

The Role of T Lymphocytes in Sjögren's Syndrome

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SUMMARY **The exact role of T cells in the immunopathogenesis of Sjögren's syndrome (SS) is not well understood and is discussed herein. It seems plausible that this autoimmune disorder is associated strongly with the functions of autoantigen-specific CD4 cells. T cell receptor Vβ gene usage appears to be unrestricted. Furthermore, elevated gene expression of T cell-derived cytokines such as IFN-γ, IL-1, IL-6, IL-10 and IL-13 seen in salivary glands of SS patients and the animal models of this disorder suggests that the course of SS may be mediated by Th1 and Th2 cells. Defining the precise role of these CD4 cells subsets in SS would certainly provide insights into the establishment of immunotherapeutic bimodal.**

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease characterized by oral and ocular dryness. The clinical spectrum of this pathological entity are not discussed herein and readers may refer to extensive reviews elsewhere.[1-3]

The precise mechanism by which immunopathogenesis of SS occurs is poorly understood. For example, the autoantigen(s) responsible for the induction of autoimmune response in this disease has not yet been well defined. In this respect, several salivary gland-derived autoantigens, nuclear autoantigens and a recently identified 120 kDa α-fodrin have been believed to trigger, by as yet unidentified mechanism(s), the autoimmune response in SS.[4,5] Furthermore, increased T cell infiltration in the salivary glands of SS suggests that this disease may be a T cell-mediated autoimmune disorder.[6,7] Recent studies in both humans and animal models seem to support this hypothesis, but the precise roles of the activated autoreactive T cells in the development of this disease remain however to be clarified further and briefly discussed herein.

CD4 (helper T cells) cells in SS

Immunohistochemical studies have revealed that T cells are predominant among the infiltrating immunocompetent cells in the salivary glands of patients with SS.[6-11] Phenotypically, most of this cell population was $CD4^+$ and, to a lesser extent, $CD8^+$ cells. In these studies, the infiltrating T cells expressed CD45 molecules, IL-2 receptor (IL-2R), αβT cell receptors (αβTcR), and both LFA-1 (leucocyte function-associated molecule-1) and MHC class II molecules, suggesting that this cell population is in the activated stage. Of interest, almost 2.8% of these infiltrating T cells expressed γδTcR molecules.[7] In the peripheral blood of SS patients, increased number of $CD45RO^+$ γδTcR cells, especially those having HLA alleles

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DRB1*030, DQA1*0501, and DQB1*0201, were also observed.[12] As yet, the role of this putative T cell subpopulation in SS is unknown, but may function as a secondary line defence, perhaps via its cytotoxic effects.[13] Alternatively, early antigen recognition during the development of SS may be carried out by this cell population, since the action of these cells is much earlier that that of T cells expressing αβTcR.[14] Another unique feature of γδT cells is that antigen presenting cells for nonpeptidic antigens are not required for the activation of this T cell subpopulation,[14] suggesting that tissue damage-derived autoantigens in SS may be recognized directly by these cells without the need of antigen presenting cells. These contentions remain speculative and need to be investigated further. Furthermore, immunohistological findings of the salivary glands obtained from SS patients have been supported by studies using animal models. Female C3H/He and CRJ:CD-1 mice which had been thymectomized 3 days after birth and subsequently immunized with Freund's complete adjuvant-emulsified submandibular salivary gland homogenate developed autoallergic sialadenitis resembling to human SS.[15,16] In these studies, the cellular infiltrates observed in the salivary glands were predominantly CD4 cells. Likewise, salivary glands of NSF/*sld* mutant, aged C57BL/6 and immunodeficient alymphoplasia mice which spontaneously develop SS-like lesions were yet again infiltrated mainly by this cell population.[17-19] Predominant CD4 cell infiltration could also be seen in lacrimal glands of a murine model of primary SS.[20]

Although immunohistological analysis has revealed predominantly a T cell infiltrate in the salivary glands of SS, the exact pathogenic role of this cell subpopulation is still far from clear. The difficulty in determining the function of this cell subset has also been hampered by the fact that the exact autoantigen(s) responsible for the induction of autoimmune response in SS has not yet been well defined. Thus, functional assays of salivary gland-derived autoantigen-specific T cells at a clonal level remain to be carried out. The work of Fox and his colleagues has, in this respect, provided some insights into the possible immunoregulatory roles of this cell population in SS (see ref. 21, for review). Based upon their studies, it seems plausible that the production of autoantibodies is dependent upon CD4 cell activity, since depletion of this T cell subset from mitogen-stimulated salivary gland lymphocyte cultures abolished the production of antibodies *in vitro*. The results of this study have most recently been supported indirectly by the fact that mitogen-stimulated CD4 cell clones established from SS-derived salivary gland mononuclear cells released high levels of IL-10.[22] Thus, B cell hyperactivation leading to the development of B cell lymphoma and the production of autoantibodies as seen in SS may be associated with the biological function of this cell subset. Furthermore, in an animal model, transfer of mononuclear cells isolated from inflamed submandibular glands of MRL/lpr mice to severe combined immunodeficiency (SCID) mice resulted in the development of lesions in both salivary and lacrimal glands of the recipients and the production of autoantibodies directed to the former glands.[23] This study also revealed that if the donor cells were treated with anti-CD4 and anti-Vβ8 antibodies prior to cell transfer, the lesion could be suppressed, suggesting that the induction of SS-like lesions in SCID mice is a CD4 cell-mediated phenomenon and that the lesional development is associated with TcR Vβ gene expression (see also below).

Dependent upon their distinct cytokine profiles, murine CD4 cells can be divided into two cell subsets.[24-26] CD4 cells which preferentially release IL-2 and IFN-gamma in absence of IL-4, IL-5, IL-6, IL-10 and IL-13 are termed CD4 cells type 1 (Th1 cells), whereas type 2 cells (Th2 cells) only produce the latter, but not the former, group of cytokines. Th0 cells are referred to CD4 cells which produce both groups of cytokines. Th1 and Th2 cells are also known to regulate reciprocally and help the induction of delayed type hypersensitivity (DTH) and antibody production, respectively. Thus in some cases, the induction of DTH responsiveness is commonly parallel with suppressed antibody production, and vice versa. The division of CD4 cell subsets seems also to exist in humans,[27] but unlike in the murine immune system, human IL-10 is produced by both types of CD4 cell subsets.[28]

Recent evidences have indicated that CD4 cell subsets may play an important role in the development of autoimmune diseases. In experimental allergic encephalomyelitis (EAE), an animal model for human multiple sclerosis (MS), myelin basic protein (MBP)-speci-

fic murine CD4 cells isolated from the central nervous system and lymph nodes preferentially produced IL-2 and IFN-gamma, but not IL-4, suggesting that EAE is mediated by Th1 cells.[29] A Th1 cell-mediated autoimmune disease has also been postulated to occur in the development of insulin-dependent diabetes mellitus.[30] In patients with SS, salivary gland-derived CD4 cell expressed IL-2, IFN-gamma, IL-10 and IL-13, but not IL-4 and IL-5, mRNA.[31,32] Two possible explanations of these findings have been proposed.[30] Firstly, the induction of salivary gland inflammation in SS is indeed mediated by autoantigen-specific Th1 cells whilst non-T cells may be cellular sources of IL-10.[33] However, it may be unlikely to occur, since CD4 cell clones derived from salivary glands of SS patients produce high levels of IL-10, in fact much higher than those of peripheral blood mononuclear cells of the same patients.[22] Secondly, IL-2, IFN-gamma and IL-10-producing CD4 cells in SS are believed to represent a distinct type of CD4 cell subset, other than Th1 and Th2 cells. As yet, one should take this conclusion cautiously, since both human CD4 cell subsets release IL-10 which inhibits the activation of each of these cell subsets reciprocally.[28] That SS-derived salivary gland CD4 cells produce these types of cytokines is not unexpected and they may still be considered as Th1 type cells. It has been shown recently that Th1-derived IL-2 and IFN-gamma mRNA expression as well as IL-10 gene expression are consistently detected in labial gland biopsies of SS patients, whereas Th2 cell-associated IL-4 and IL-5 mRNA expression is detected in some SS patients characterized by B cell accumulation,[34] indicating that Th1 cells may play a crucial role during the course of SS, whilst Th2 cells may promote B cell activation.

Alpert and co-workers have revealed recently that elevated levels of CD4 cell-derived granzyme A mRNA expression are significantly correlated with the number of cellular infiltrates in the salivary gland biopsies of SS patients.[35] Granzymes (A and B in humans; A, B, C, D, E, F, and G in mice) produced by cytotoxic cell effectors such as natural killer (NK) cells and cytotoxic T cells are one of the effector molecules for the induction of target cell death.[36] The results of the above study[35] have, therefore, raised speculation that one of the mechanisms by which CD4 cells play a role in SS may be via the production of granzyme A which in turn induces glandular epithelial cell damage. In addition, the work of Matmura and colleagues has shown that an increased expression of surface molecule Fas antigen is seen on the ductal epithelial cells of SS patients as compared to the healthy persons,[37] suggesting that the action of cytotoxic T cells on epithelial cell damage may be via Fas-Fas ligand (FasL) interaction. No evidence for a cytolitic mechanism in the tissue damage during the course of SS has been reported. It is now known that the induction of target cell death due to cytotoxic T cells can be generated by two distinct, but not necessarily mutually exclusive, pathways. Firstly, upon activated cytotoxic T cell-target cell interaction, granzyme and perforin-containing cytoplasmic granules accumulate at the site of interaction and subsequently release these products into the target cells. Pore formation on the target cells due to these molecules lead to cell death.[36,38] The second mechanism involves the interaction of surface molecule Fas-FasL interaction.[39] In this respect, activated cytotoxic T cells express FasL molecules and upon interaction with Fas-bearing target cells, death of the latter cells occurs. Despite continuing debate on the primary mechanism of T cell-mediated cytotoxicity, it has been documented that $CD8^+$ cytotoxic cells kill the target cells via both mechanisms, whereas $CD4^+$ cytotoxic cells act preferentially via Fas-FasL interaction.[40] The extrapolation of this finding in SS await further evidence.

The immunoregulatory role of antigen presenting cells (APC) in determining the activation of autoreactive CD4 T cells during the progression of SS is unknown. A significantly elevated expression of major histocompatibility complex (MHC) class II molecules on salivary gland epithelial cells of patients with SS suggests that this cell population may function as APC during the course of SS.[41-43] In humans, an increased expression of MHC class II molecules on epithelial cells promoted the antigen presentation functions of these cells to activate T cell clones.[44] Likewise, the ability of self-peptide-bearing thyroid epithelial cells to activate T cells in both MHC class I and II restricted fashion during the development of autoimmune thyroiditis[45] highlights the possibility of an antigen presentation function of epithelial cells in the salivary gland T cell activation. It should be borne in mind that epi-

thelial cells require the presence of IFN-gamma, since MHC class II molecules are not normally expressed on these cells.[46] This cytokine not only induces the expression of these molecules, but also creates a new cryptic antigenic epitope due to its ability to generate a distinct protein cleavage during antigen processing by non-professional APC (e.g., epithelial cells).[47] The presentation of these cryptic epitopes by APC would subsequently activate previously ignored autoreactive T cells. The extrapolation of these findings in the immunopathogenesis of SS is as yet to be determined. Possible cryptic autoantigens in SS have recently been put forward, since alternative splicing creates at least 4 distinct SS-B/La isoforms; one of them is suspected to increase the immunogenicity of SS-B/La.[48] It is worth determining whether an increased expression of CD4 T cell-derived IFN-gamma on salivary glands of SS patients[31,49] is associated with increased MHC class II expression on salivary gland epithelial cells promoting their antigen presentation function and/or is parallel with the development of new antigenic epitopes in SS.

CD8 (suppressor/cytotoxic T cells) cells in SS

The role of CD8 T cells in SS is perhaps one of the most intriguing questions. Immunohistologically, a paucity of infiltrating CD8 T cells in the salivary glands of both human SS and animal models has been detected, suggesting that the development of SS is associated with a failure of CD8 cell activity.[6-9,16-18] This contention has been supported by observation that transfer of CD8 cell-depleted salivary gland mononuclear cells of MRL/lpr mice into SCID mice did not prevent the development of SS-like lesion in the recipients.[23] The work of Brookes and colleagues has revealed that salivary gland-isolated CD8 cell clones established from SS patients produced IFN-gamma,[22] implying that these cell clones may act to regulate partly the initiation of Th1 cell activation. As with EAE and EAU (experimental autoimmune uveitis), transfer of orally activated CD8 donor cells resulted in suppressed clinical symptoms of these autoimmune diseases in the recipients, suggesting that the development of these diseases is associated with failure of CD8 cell functions.[50,51] Transfer of salivary CD8 cells isolated from SS-induced donor animals would certainly provide further informations on the role of this cell population in SS.

T cell receptor usage in SS

The interaction of TcR molecules, such as αβ or γδTcR, on T cells and antigen fragment-bearing MHC molecules on APC is a crucial step in antigen recognition by T cells, thereby inducing T cell activation. The rearrangement and expression of genes encoding these TcR molecules are similar to those of immunoglobulin, which involve the joining of individual variable (V), diversity (D) and joining (j) region gene segments. However, details of these molecular events are not discussed herein and have been reviewed elsewhere.[52]

The TcR gene usage has been associated with the development of certain autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS) in which certain TcR Vβ chains may be used to recognize respective immunodominant autoantigens.[53,54] The TcR repertoir seen in the animal studies of SS[18,23] raises a question as to the precise site of TcR molecules interacting with both autoantigen fragments and MHC molecules during the antigen recognizing process in this disease (Table 1). Infiltrating CD4 cells in the salivary glands of both NSF/*sld* mutant and MRL/lpr mice expressed predominantly Vβ8 and, to lesser extent, Vβ6 mRNA, suggesting that although Vβ gene usage is unrestricted, salivary gland CD4 cells may use certain TcR Vβ genes in recognizing autoantigen fragments presented by APC. Likewise, an immunohistological study of spontaneously inflamed salivary glands of NOD mice also demonstrated that the most frequent Vβ gene expression is Vβ8.1,2.[55] Reverse transcript-polymerase chain reaction analysis of lacrimal glands of the murine model of SS seemed to support the Vβ8 gene usage in this autoimmune disorder.[20] Indeed, T cells of lip specimens obtained from SS patients expressed mainly Vβ2 and Vβ13 genes, implying that the course SS may be associated with this TcR rearrangement.[56] In addition, Kay and colleagues have revealed that reduced number of peripheral blood TcR Vβ6.7$^+$ lymphocytes could be observed in SS patients.[57] Vβ TcR gene usage in SS has also been supported by an observation that transfer of Vβ$^+$ cell-depleted salivary gland mononuclear cells of MRL/lpr mice into SCID mice did prevent the development of SS like-lesion in the recipients.[23]

Table 1 The predominant T cell receptor (TcR) usage in Sjögren's syndrome

Species	Specimens	TcR usage	Ref.
Humans	Labial glands	Vα8, Vα12, and Vβ8	11
	*PBL	Vβ13.1	11
	Lips	Vβ2 and Vβ13	56
	PBL	Vβ6.7	57
NSF/*sld* and MRL/*lpr* mice	Salivary glands	Vβ8 and Vβ6	18, 23
	Lacrimal glands	Vβ8	20
NOD mice	Salivary glands	Vβ1,2	55

*PBL= peripheral blood lymphocytes

It should, however, be kept in mind that in both animal and human studies of MS and RA, TcR Vα gene usage has also been found, suggesting that both TcR Vα and Vβ genes, dependent partly upon the genetic background, may play a role in the development of these autoimmune disease.[53,54] Of interest, an elevated expression of both TcR Vα and Vβ gene could be detected in the labial gland biopsies of the same patients.[11] In this study, labial gland-derived Vα8, Vα12, and Vβ8 gene expression seemed to be predominant in SS. The extrapolation of both TcR Vα and Vβ gene usage in the immunopathogenesis of SS is to be further determined; yet, it has been suggested that expression of these genes may reflect distinct stages of the disease.[11]

A preferential use of Vβ-bearing CD4 cells during antigen recognition in SS also raises an open question as to whether superantigens are involved in the activation of this cell subset. The term superantigens refers to bacteria or virus-derived molecules that activate polyclonally T cells via direct cross linking Vβ elements of TcR and MHC class II molecules of APC. *Staphylococcus* enterotoxins B, group A streptococcal antigens and mouse mammary tumor viruses (MMTV) are few examples of these molecules.[58-60] In the development of autoimmune diseases such as RA, an increased number of Vβ element-bearing T cells in RA patients[53] and high levels of superantigen-stimulated peripheral blood T cell proliferation co-cultured with RA-derived synoviocytes[61] lead to the suggestion of the involvement of superantigens in this autoimmune disorder. No direct evidences to indicate that superantigens play a role in the course of SS have yet been reported. In this respect, the works of Huber and colleagues have shown that strong human T cell proliferation could be observed when fetal T cells were cultured with Epstein-Barr virus (EBV)-transformed B cells (see ref. 62, for review). The cell proliferation was Vβ TcR and MHC class II restricted, indicating that EBV may be belong to the superantigen family. Because of several findings showing a strong association between EBV and the course of SS,[63-66] it is possible that in SS, EBV may act as a superantigen which involves in glandular B cell lymphoma and excessive glandular T cell proliferation already recognizing SS-associated low affinity autoantigens. Thus, this herpes virus may partly play a pivotal role in SS by accelerating the abolishment of peripheral self-T cell tolerance. This contention awaits further experimental support.

Cytokines in T cell regulation of SS

Cytokines providing signals necessary for cell to cell communication as well as cell activation are prerequisites. Indeed, that these biologically active polypeptides mediate many pathological conditions such as autoimmune and infectious diseases is also well known.[67,68] For example, in MS, cytokines such as IL-1 and Il-6

have been implicated in accelerated myelin damage.[69] IFN-gamma and IL-4 may also play an important role in the immunopathogenesis of myasthenia gravis, an autoimmune disease characterized by lack of acetylcholine receptors at the neuromuscular junction.[70] Of note, each cytokine does not function independently from other cytokines and exclusively to one particular cell type or soluble polypeptide. This article focuses, merely on the possible role of cytokines in T cell activities during the course of SS, unless otherwise stated.

Diminished IL-2 production of culture supernatants from SS-derived peripheral blood lymphocytes (PBL) stimulated *in vitro* with mitogens has been observed.[71] In this study, an increased production of this cytokine was, in contrast, detected in the culture supernatants of salivary gland-isolated lymphocytes taken from the same patients. IL-2 mRNA expression of salivary gland CD4 cells from these patients was also upregulated, when compared to that of PBL-isolated CD4 cells.[31] The reason of this distinct cytokine profile in SS as seen from PBL and salivary gland lymphocytes is not well understood. Presumably, increased levels of IL-2 in salivary glands of SS patients reflect a locally increased autoreactive T cell activation. Support can be drawn from the fact that high levels of IL-2Rs on the salivary gland T cells of these patients have been revealed.[6-10] As previously suggested, lack of IL-2 levels seen from the PBL of SS patients might be due to increased activities of CD8 cells as judged by a reduced peripheral blood CD4:CD8 cell ratio.[71] It may be, however, unlikely to occur in SS, since CD8 cells also release this cytokine.[72,73] Hence, the levels of peripheral IL-2 as a marker for systemic CD8 cell activities which inhibit the ongoing immune response in SS remain uncertain.

In both human and animal models, an increased IL-1 mRNA expression in the salivary glands of SS compared to the controls has been reported.[20,31,75] Salivary gland epithelial cells appear to be the main source of this cytokine.[31] Of interest, the expression of IL-1β mRNA in the salivary glands of MLR/lpr mice could already be detected in 1 month old mice and was continously expressed throughout the onset of sialadenitis.[74] These results suggested therefore that IL-1 may function as a proinflammatory cytokine in SS; yet, the exact role of this cytokine in T cell regulation during the course of SS is questionable. This cytokine is capable augmenting the production of T cell-derived IL-2 in the presence of mitogens or antigens,[75] suggesting that T cell activation can be upregulated by IL-1. The extrapolation of this contention in SS remains to be elucidated.

As with IL-1 mRNA expression, TNF-α gene expression could also be detected in the salivary gland biopsies of SS patients and MLR/lpr mice.[31,75] In these mice, this cytokine seems to be expressed before the onset of sialadenitis,[75] suggesting that along with IL-1, TNF-α may be one of the inflammatory cytokines in SS. Both TNF-α and IL-1, but not by the former cytokine alone, are able to effectively activate T cells.[75] Thus, that TNF-α functions as a complimentary cytokine in the T cell activation during the progression of SS can not be ruled out and needs to be further determined. Of interest, this cytokine is also produced by salivary gland CD8 cells isolated from SS patients.[31] The extrapolation of this finding in the immunopathogenesis of SS is speculative. It is possible that in this autoimmune disorder, TNF-α produced by this cell subpopulation may participate in salivary gland epithelial cell damage via the induction of apoptosis.

The expression of IL-4 and IL-5 mRNA in salivary glands of SS patients only with characteristic of abundant B cell infiltration could be detected.[35] The exact role of these cytokines during the course of SS is however unclear. It may be that excessive B cell activation leading to B cell lymphoma in this salivary gland disorder is partly associated with increased levels of these cytokines. If so the progressive stage of SS may be regulated by Th2 cells.

It has been shown that epithelial cells of salivary glands of patients with SS express IL-6 mRNA.[31] Of note, the gene expression of this cytokine could be observed from 3 months of age in MRL/lpr mice and was closely associated with the onset of autoimmune sialadenitis,[74] suggesting that this cytokine participates in the acceleration of this autoimmune disease. This cytokine not only functions on B cell terminal differentiation, but also on T cell proliferation and differentiation.[76,77] In this respect, IL-6 alone is able to act as an inducer of IL-2 responsiveness. In synergy with IL-1, this

cytokine is required for optimal T cell-derived IL-2 production. That increased autoreactive T cell activation and high levels of IL-2 occuring in the salivary glands of patients with SS are mediated by IL-6, along with IL-1 and TNF-α, would therefore be obvious. In addition, IL-6 in SS may also contribute considerably in B cell hyperactivation, one of the immunological characteristics of SS, in the salivary glands.

In patients with SS, salivary gland CD4 cells express IFN-gamma, but not IL-4 and IL-5 mRNA.[31] This cytokine is known to have direct effects on the activation of Th1 cells.[24,25,27] Of interest, the development of Th1 cells apparently requires the presence of IL-12. In this respect, it has been revealed that professional APC such as antigen-activated macrophages release IL-12 which in turn stimulates natural killer (NK) cell activation to release IFN-gamma.[25,78] This extrapolation of this pathway on the immunopathogenesis of SS is unclear, since IL-12 gene expression in SS is only occasionally detected.[34] Likewise, in the early stage of the murine model of SS, upregulation of IL-12 gene expression could be detected in the lacrimal glands.[20] Lack of IL-4 and IL-5-producing Th2 cells in SS[31] may partly be mediated by this cytokine as shown by the fact that the development of Th2 cells can be downregulated by this cytokine.[78] Moreover, along with its ability to promote Th1 cells, IFN-gamma may also exert antiviral activities in this disease, since the expression of certain viruses such as EBV and human T lymphotropic virus type I (HTLV-I) could be observed in salivary gland biopsies of SS.[63-66,79,80]

Salivary gland IL-10 mRNA expression has been shown in patients with SS.[22,31,34] The biological functions of this cytokine in the course of SS are only speculative. Perhaps, proliferation of αβ and γδT cells and expression of IL-2R on T cells as seen in the salivary glands of SS may be upregulated by this cytokine in an autocrine fashion.[81,82] Moreover, the possibility that this cytokine, in synergy with IL-2, is involved in salivary gland B cell hyperactivation of SS patients needs to be further investigated.[83] Of note, both human and mouse IL-10 amino acid sequences share homology of an open reading frame, BCRF1, in the EBV genome and a product of this viral gene is known as virus IL-10 (vIL-10).[84,85] Because of this similarity, it would also be worth determining whether or not IL-10 plays a role in persistent EBV survival in the salivary gland epithelial cells of SS.[63-66]

Whilst IL-10 at both transcriptional and protein levels may be detected from mononuclear cells of SS-derived salivary glands and peripheral blood, IL-13 gene expression has only been seen in these cells isolated from SS salivary glands, suggesting that IL-13 may produce and act locally to induce B cell hyperactivation seen in SS.[32] There is evidence that IL-13 produced by T cells shares its biological activities like IL-4 and acts preferentially on monocytes and B cells.[86] The work of Bansal and colleagues in this respect has demonstrated that there was significantly elevated serum levels of soluble CD23 (sCD23) in SS patients, suggesting that B cell hyperactivation in this autoimmune disorder may be associated with high levels of this molecule.[87] Because IL-13 is able to enhance CD23 expression in B cells,[88,89] one may speculate therefore that increased levels of sCD23 in SS may be due to high levels of IL-13. Alternatively, this cytokine may involve in enhanced expression of CD72 on B cells and increased production of IgG and IgM autoantibodies in SS.[89-91]

Of interest, during pathological examination of TGF-β1-deficient mice, salivary gland inflammation resembling to SS lesion was observed,[92] indicating that TGF-β1 may be protective in the development of SS in this animal model. The gene expression of this cytokine labial biopsies was also detected in a SS patient.[34] Despite the fact that the exact role of this cytokine in the immunopathogenesis of this organ specific autoimmune disease remains to be elucidated, it is possible that it may be protective by suppression of autoreactve T cell and B cell activation.[93]

Conclusion

Attempts to elucidate the role of CD4 cell subsets in the immunopathology of SS have been made. Accumulating evidence seems to suggest that the development of this disorder is dependent upon the functions of this cell population in the glandular sites, via its ability to help the production of autoantibodies and release the cytotoxic effector molecules, such as granzyme A' directed to glandular tissues. The role of TcR molecules is not clear, since no

restriction of TcR gene usage has been observed. Thus, immunotherapy based upon the expression of TcR molecules remains uncertain. Increased levels of cytokines such as IL-1, IL-6 IFN-gamma IL-10, IL-13, and TGF-β suggest that these cytokines, by an as yet defined mechanism, play a crucial role in the activation of glandular autoreactive-CD4 cells and/or B cell hyperactivation during the course of SS; however, the regulation of these cytokines *in vivo* remains unclear. In this respect, animal models which develop glandular lesions resembling to human SS have been developed to delineate the exact functions of these cytokine on the regulation of autoantigen-specific CD4 cell subsets *in vivo* in SS. These models would provide a suitable tool to elucidate the immunopathogenesis on this organ specific autoimmune disease and construct its immunotherapeutic models.

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