MINI-REVIEW

Salivary gland and autoimmunity

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Abstract : Recent evidences suggest that the apoptotic pathway plays a central role in tolerazing T cells to tissue-specific self antigen, and may drive the autoimmune phenomenon in the salivary glands. We found that retinoblastoma-associated protein RbAp48 overexpression induces p53-mediated apoptosis in the salivary glands caused by estrogen deficiency. We demonstrated that transgenic (Tg) expression of RbAp48 resulted in the development of autoimmune exocrinopathy resembling Sjögren's syndrome (SS). $CD4^+$T cell-mediated autoimmune lesions in the salivary glands were aggravated with age, in association with autoantibody productions. We obtained evidences that salivary epithelial cells can produce interferon-γ (IFN-γ) besides interleukin (IL)-18, which activates interferon regulatory factor-1 (IRF-1), and class II transactivator (CIITA). Indeed, the autoimmune lesions into *Rag2*$^{-/-}$ mice were induced by the adoptive transfer of lymph node cells from *RbAp48*-Tg mice. These results indicate a novel immunocompetent role of epithelial cells that can produce IFN-γ, resulting in loss of local tolerance prior to developing gender-based autoimmunity. The studies reviewed the molecular mechanisms on the development of salivary gland autoimmunity, and gender-related differences in SS. J. Med. Invest. 56 Suppl. : 185-191, December, 2009

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PATHOGENIC ASPECTS OF THE SALIVARY GLANDS

Primary Sjögren's syndrome (SS) is generally considered to be a T cell-mediated autoimmune disorder characterized by lymphocytic infiltrates and destruction of the salivary glands, and systemic production of autoantibodies to the ribonucleoprotein (RNP) particles SS-A/Ro and SS-B/La (1-3). It is assumed that autoreactive T cells bearing CD4 molecule may recognize unknown autoantigen triggering autoimmunity in the salivary glands, leading to clinical symptoms of dryness of the mouth and eyes (sicca syndrome) (4) Despite extensive study of the underlying cause of SS, the pathogenesis remains obscure. A combination of immunologic, genetic, and environmental factors may play a key role on development of autoimmune lesions in the salivary glands (4). Moreover, the histopathology of human SS is not fully understood. Lymphocytes first surround the salivary ducts and then extend into the acinar epithelium, leading to diminished glandular secretion as a result of apoptosis. Id3 is an early response gene involved in T cell receptor-mediated cell selection, and it is reported that Id3 knockout mice develop autoimmune lesions similar to SS and adoptive transfer of Id3 knockout T cells caused SS in non-susceptible mice (5). Indeed, epithelial cell activation has been proposed to be the major pathological process in SS with increased expression of class II antigens, and Fas on epithelial cells in this disease (6). It is reported that B

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cell activation leads to the production of autoantibodies and polyclonal hyper-gammaglobulinaemia characteristic of SS, and the B cell activation may account for the increased propensity of these patients to developing lymphomas (7). BAFF is a member of the TNF superfamily, and is involved in B cell maturation and survival. It was found at increased levels in serum, and salivary tissues of the patients with SS, and is expressed by T cells (8). Moreover, BAFF transgenic mice display a phenotype similar to SS or SLE (9). These data imply an important role for T and B cell interaction in the pathogenesis of salivary gland autoimmunity.

ROLE OF APOPTOSIS

Apoptosis plays an important role in maintaining T cell repertoire and deletion of autoreactive T cells (10, 11), and is regulated by a number of gene products that promote cell death or extend cell survival (12, 13). Fas ligand (FasL) mediates cell death by cross-linking Fas receptor in apoptosis-sensitive Fas^+ cells (14, 15). It is now evident that the interaction of Fas with FasL regulates a large number of pathophysiological processes of apoptosis including autoimmune diseases (16-19). Recent studies have confirmed the observation that apoptotic cells in various cell types implicated as the sourse of autoantigen when stimulated with different proapoptotic stimuli (20-22). Much evidence shows that β-cell apoptosis is a fundamental process involved in the pathogenesis of type 1 diabetes (23, 24). In addition to apoptosis being the main mechanism by which β cells are destroyed, β-cell apoptosis has been implicated in the initiation of type 1 diabetes mellitus. These studies support that exaggerated β-cell damage can induce activation of β-cell-specific T cells. Therefore, the apoptotic cells may be a critical determinant contributing to the initiation of autoimmunity by having the capacity to instruct antigen-presenting cells (APCs) to modulate immune responses so that the outcome is T cell activation. Our previous reports identified a 120 kDa α-fodrin as an important autoantigen in murine and human SS (25, 26). It has demonstrated definitively the intracellular pathway of Ro, La and α-fodrin autoantigens as a result of apoptosis, suggesting a possible mechanism by which antigens may be exposed at the cell surface to APCs such as macrophages or dendritic cells (DC). Although cleavage of certain autoantigens during apoptosis may reveal immunocryptic epitopes that could potentially induce autoimmune responses in systemic autoimmune diseases (19, 27), accumulated evidences suggest an important role of apoptosis in the disease pathogenesis of SS (28, 29). We found that a significant increase of $TUNEL^+$-apoptotic epithelial duct cells in the salivary glands was detected in NFS/sld SS model, compared with those in control mice at all ages (30). Moreover, we confirmed that tissue-infiltrating $CD4^+$ T cells are responsible for tissue destruction as judged by *in vitro* ^{51}Cr release cytotoxic assay against MSG cells (30). Although it has been reported that Fas-induced apoptosis seems to be the major killing pathway of the $CD4^+$ cytotoxic T cells (31), our data suggest that one mechanism by which activated $CD4^+$ T cells induce cytotoxicity towards salivary gland cells in murine SS model is Fas-based (30). Our recent immunofluorescence analysis from SS patients demonstrated that a cleavage product of α-fodrin was present in epithelial duct cells of the labial salivary gland biopsies from SS patients, but not in control glands (26). These data suggest that increased activity of caspase cascade is involved in the progression of α-fodrin proteolysis during the initial stages on the development of primary SS.

SALIVARY GLAND AUTOIMMUNITY DEVELOPS IN RbAp48-TG MICE

We have generated *RbAp48*-Tg mice where the RbAp48 gene is expressed in the salivary and lacrimal glands using the gland-specific promoter (32, 33). When the histopathology of all organs from those mice were analyzed, we found that autoimmune exocrinopathy resembling SS developed in almost all *RbAp48*-Tg mice at 24-wks-old or more, but not in the wild-type (WT) mice. Lymphocyte infiltration in salivary glands of *RbAp48*-Tg mice becomes more frequent at around 30- to 50-wks of age, and a significantly higher incidence of inflammatory lesions was found in female Tg mice at all ages. Many infiltrating lymphocytes were observed in periductal areas with varying degrees, and shown in focal appearance. A majority of infiltrating cells in salivary and lacrimal glands was $Thy1.2^+$ $CD4^+$ T cells, while a minor proportion of $B220^+$B cells, $CD8^+$ T cells and $CD11b^+$ cells were observed. When the function of salivary glands in *RbAp48*-Tg mice was analyzed, the average volume of tear and saliva secretion from *RbAp48*-Tg mice was significantly lower

than that from the WT group at 30-wks of age or more. Regarding the peripheral T cell phenotype of *RbAp48*-Tg mice, T cell activation markers ($CD44^{high}$, $CD62L^{low}$, $CD45RB^{low}$) were up-regulated on $CD4^+$ T cells in cervical lymph nodes (cLNs) from *RbAp48*-Tg mice, compared with those from WT mice. As for the phenotype of $CD4^+CD25^+Foxp3^+$ Treg cells, no difference was detected in thymus, spleen, and cLNs between *RbAp48*-Tg and WT mice. Moreover, culture supernatants from anti-TCRβ and -CD28 mAb-stimulated cLN T cells obtained from *RbAp48*-Tg mice contained higher levels of interleukin (IL)-2, and interferon-γ (IFN-γ), while no difference in IL-4, and IL-10 levels between *RbAp48*-Tg and WT mice was observed by ELISA. Of particular interest is that a higher titer of serum autoantibodies against SS-A (Ro), SS-B (La) and 120 kDa α-fodrin was detected in *RbAp48*-Tg mice, compared with that in WT mice by ELISA (33). This result is consistent with the characteristic flow cytometric finding that showed a significant $CD5^+B220^+$ fraction capable of autoantibody production (34) which appeared in spleen cells from *RbAp48*-Tg mice compared to WT mice. In addition, significantly increased $CD21^{high}IgM^{high}B220^+$ marginal zone B cells were observed in both cervical lymph nodes and spleen from *RbAp48*-Tg mice compared with those from WT mice. These results may provide a new animal model for autoimmune exocrinopathy resembling SS (33), which should help us to further understand how autoreactive T cells are developed, and subsequently influence the development of autoimmunity.

SALIVARY GLAND EPITHELIAL CELLS AS ANTIGEN-PRESENTING CELLS

It has been well known that nonlymphoid cells that express MHC class II molecules provoke autoimmune responses (35, 36). However, it is undetermined whether MHC class II-expressing epithelial cells can function as antigen-presenting cells. We frequently observed MHC class II molecule expression on the salivary gland cells in *RbAp48*-Tg mice, not in WT mice. The salivary epithelial cells play a pivotal role in the induction and regulation of immune responses by virtue of their ability to present self-peptides to $CD4^+$ T cells (37). To examine whether salivary epithelial cells could act as antigen-presenting cells, mouse salivary gland (MSG) cells, splenocytes, and splenic $CD11c^+$ dendritic cells (DCs) from *RbAp48*-Tg mice and WT mice were compared in terms of their capacity to express MHC class II, and costimulatory molecules including CD86, CD80, and ICAM-1 by flow cytometric analysis. Among them, a considerably large proportion of MHC class II^+, $CD86^+$ cells, $CD80^+$ cells, and ICAM-1^+ cells was observed on MSG cells from Tg mice, compared with those from WT mice (Fig. 1). MSG cells were enriched by enzymatic treatment, several antibodies against immune cells and epithelial cells, and magnetic beads. On the other hand, although the expressions of MHC Class II and CD86 on the splenocytes and $CD11c^+$ DCs were higher than those on both MSG cells, the expressions of CD80 and ICAM-1 on the professional APCs were similar or lower than those on the MSG

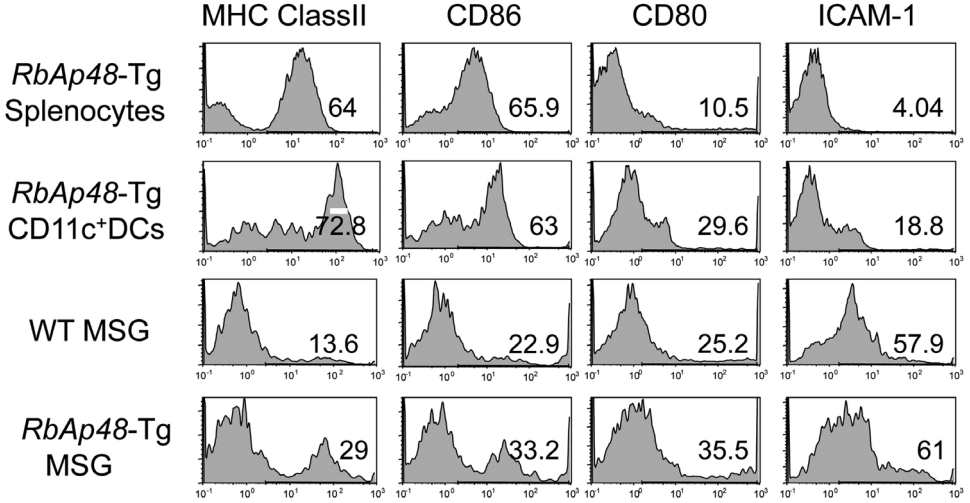

Fig. 1. Expression of antigen-presenting cell markers in salivary epithelial cells from RbAp48-Tg mice (Ref. #33). Antigen-Presenting cell (APC) markers of splenocytes, splenic DCs, and mouse salivary gland (MSG) cells from WT and *RbAp48*-Tg mice were analyzed by flow cytometer using anti-MHC class II, anti-CD86, anti-CD80, and anti-ICAM-1 mAbs..

cells. These expressions (MHC class II$^+$, CD86$^+$, CD80$^+$, and ICAM-1$^+$) on salivary epithelial cells from *RbAp48*-Tg mice were also confirmed by confocal analysis. Moreover, to examine whether the peripheral T cells from *RbAp48*-Tg mice can respond to the MSG cells that show phenotypes for the APCs, CFSE-labeled purified CD4$^+$ (1×10^5) T cells from *RbAp48*-Tg mice were co-cultured with the MSG cells (1, 2×10^5) from those mice or WT mice. Although CD4$^+$ T cells from B6 mice could not respond to both B6 and *RbAp48*-Tg MSG cells, CD4$^+$ T cells from *RbAp48*-Tg mice were capable of responding to MSG cells from *RbAp48*-Tg mice, but not with those from WT mice, while anti-MHC class II antibody inhibits these responses. Furthermore, proliferation assay using [^{3}H]-thymidine incorporation demonstrated that purified CD4$^+$ T cells of cLNs from *RbAp48*-Tg mice were more proliferative to the MSG cells from *RbAp*48-Tg mice relative to those from WT mice (33).

CRUCIAL ROLE OF EPITHELIAL IFN-γ PRODUCTION

The expression of MHC class II molecules is generally regulated at the transcriptional levels including the transcription factor interferon regulatory factor (IRF)-1 (38, 39) and the class II transactivator (CIITA), the master regulator for MHC class II gene expression (40, 41). It has been shown that IRF-1 is a primary responsible gene of the IFN-γ response (42). In *in vitro* studies using human salivary gland (HSG) cells (43), IFN-γ-induced mRNAs of IRF-1 and CIITA were significantly enhanced by the treatment of Tamoxifen (Tam), which is an antagonist of estrogen and can induce RbAp48 (44), or transfection of pCMV-*RbAp48* plasmid in the dose-dependent manner, not in MCF-7 cells (human mammary gland cell line). In addition, we analyzed the IRF-1 promoter activity using *RbAp48*-transfected HSG cells with and without IFN-γ by luciferase assay. We observed significantly enhanced IRF-1 promoter activity in *RbAp48*-transfected HSG cells with IFN-γ, not in MCF-7 cells. To our surprise, in *RbAp48*-Tg mice, a prominent expression of IFN-γ was detected in salivary epithelial cells besides sporadically positive infiltrating cells of *RbAp48*-Tg mice, not WT mice. These findings were observed mainly in the MHC class II$^+$ ductal epithelium adjacent to lymphoid infiltrates. Epithelial IFN-γ expression in the exocrine glands of *RbAp48*-Tg mice was up-regulated during the course of autoimmune exocrinopathy (33). Induction of IFN-γ expression may occur through many different types of stimulation, including cross-linking of cell-surface receptors and stimulation with cytokines, including IL-2, IL-12, and IL-18 (44) (34). It has been demonstrated that IFN-γ synthesis is predominantly induced by stimulation with IL-18 (45). Consistent with a previous report (46), IL-18 expression was observed in salivary epithelial cells in *RbAp48*-Tg mice, not in WT mice. Confocal analysis revealed that differential expression of IL-18 and IFN-γ was clearly observed, *i.e.* IL-18 mainly in the acinar cells and IFN-γ in the duct cells, within salivary epithelial cells from *RbAp48*-Tg mice, not from WT mice (Fig. 2). Epithelial IFN-γ and IL-18 productions were confirmed by flow cytometry using MSG cells without immune cells from *RbAp48*-Tg, not from WT mice, while there was no difference in both IFN-γ and IL-18 expressions of cLN cells between WT and *RbAp48*-Tg

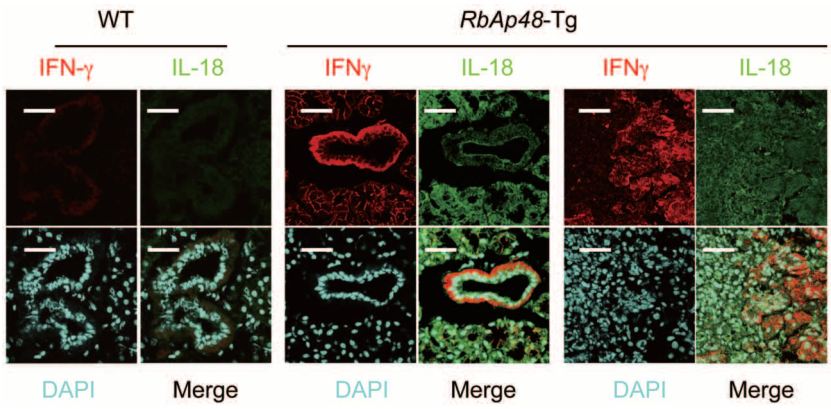

Fig. 2. IFN-γ and IL-18 production in salivary epithelial cells from RbAp48-Tg mice (Ref. #33). Confocal analysis of IFN-γ, IL-18 or DAPI of salivary gland tissues from WT and *RbAp48*-TG mice at 32 weeks of age. Alexa-488- or Alexa-568-conjugated anti-rat IgG as the second antibodies were used. Photos are representative of three to five mice.

mice. Although the production of IL-18 in salivary gland cells has been detected in a previous report (46), there has been no proof for IFN-γ production of salivary gland cells in any report. Therefore, to confirm IFN-γ production of salivary glands, detection of IFN-γ using tissue homogenates was performed. High concentration of IFN-γ was detected in the tissue homogenates of salivary glands from *RbAp48*-Tg mice by ELISA. Furthermore, the detection of IFN-γ mRNA of MSG cells was performed by *in situ* hybridization using the RNA probe of mouse IFN-γ gene. More intensive signal for IFN-γ mRNA in duct cells of salivary glands from *RbAp48*-Tg mice was observed compared with that from WT mice. *In vitro* studies using HSG cells demonstrated that the expressions of IL-18, IFN-γ and MHC class II (HLA-DR) were observed when treated with Tam or transfected with pCMV-*RbAp48*, while they were inhibited when treated with 17β-estradiol (E2), caspase 1 inhibitor (Ac-YVAD-CHO) (Ci), and siRNA of *RbAp48* (si). Confocal analysis confirmed the expressions of IL-18, and IFN-γ in HSG cells treated with Tam or transfected with pCMV-*RbAp48*. It is important to note that IL-18 is secreted earlier (by 6 hours) than IFN-γ production and HLA-DR expression (by 12 hours) in Tam-stimulated and *RbAp48*-transfected HSG cells.

CONCLUDING REMARKS

We demonstrated that autoimmune exocrinopathy resembling SS developed in almost all *RbAp48*-Tg mice, and that a high titer of serum autoantibodies against SS-A (Ro), SS-B (La) and 120 kDa α-fodrin was detected in these Tg mice. We found frequently MHC class II molecule expression on the exocrine gland cells with autoimmune lesions in *RbAp48*-Tg mice. Although it has been undetermined whether MHC class II-expressing epithelial cells can function as antigen-presenting cells, our data strongly suggest that the epithelial cells may function as antigen-presenting cells during development of autoimmunity. In *RbAp48*-Tg mice, a prominent expression of epithelial IFN-γ was detected besides sporadically positive infiltrating cells. These findings were observed mainly in the MHC class II$^+$ ductal epithelium. Epithelial IFN-γ expression in the salivary glands was up-regulated during the course of autoimmune exocrinopathy. These data demonstrate a direct molecular mechanism by which estrogen deficiency induces tissue-specific overexpression of RbAp48, subsequently developing CD4$^+$ T cell-mediated autoimmunity through epithelial IFN-γ production. Thus, reducing the RbAp48 overexpression is a possible effective therapy for gender-based autoimmunity in the salivary glands.

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