FEATURED NEW INVESTIGATORS

Thymic stromal lymphopoietin in tonsillar follicular dendritic cells correlates with elevated serum immunoglobulin A titer by promoting tonsillar immunoglobulin A class switching in immunoglobulin A nephropathy

HONGXUE MENG[1], HUINING LI[1], RINTARO OHE, YE AUNG NAING, SURAN YANG, TAKANOBU KABASAWA, TOMOYA KATO, MITSUMASA OSAKABE, HIROYA OHTAKE, AKIHIRO ISHIDA, JUNLI LU, LEI ZHANG, NOBUO OHTA, SEIJI KAKEHATA, KENSUKE JOH, QINGTAO SHI, XIAOMING JIN, JINGSHU GENG, and MITSUNORI YAMAKAWA

HARBIN, CHINA; AND YAMAGATA AND SENDAI, JAPAN

Immunoglobulin A (IgA) nephropathy (IgAN) is characterized by high serum IgA levels and IgA deposition in the renal mesangium. Previous studies suggest that elevated serum IgA partly originates from the tonsils. Here, we investigated the mechanisms of IgA production in the tonsils of patients with IgAN. Immunohistochemistry revealed that the number and relative percentage of IgA-bearing cells were significantly increased in the tonsils of IgAN patients. Compared with non-IgAN patients, enhanced IgA class switching and overexpression of thymic stromal lymphopoietin (TSLP), TSLP receptor (TSLPR), activation-induced cytidine deaminase (AID), transforming growth factor-β1 (TGF-β1), B cell-activating factor of the tumor necrosis factor family (BAFF), and a proliferation-inducing ligand (APRIL) were detected in follicular dendritic cells (FDCs) of tonsillar germinal centers from IgAN patients. Importantly, TSLP correlated with IgA production in isolated FDC-associated clusters. Serum TSLP levels were increased and correlated with IgA overexpression in the tonsils and serum of IgAN patients. These data indicated that TSLP overexpression in tonsillar FDCs may promote IgA class switching in IgAN patients through the cooperative roles of AID, TGF-β1, BAFF, and APRIL. Therefore, interactions between TSLP in FDCs and IgA production in tonsils may be an important mechanism contributing to the pathogenesis of IgAN. (Translational Research 2016;176:1–17)

[1] H.M. and H.L. contributed equally to this study.

From the Department of Pathology, Harbin Medical University Cancer Hospital, Harbin, China; Department of Pathological Diagnostics, Yamagata University Faculty of Medicine, Yamagata, Japan; Department of Pathology, Harbin Medical University, Harbin, China; Department of Pathology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, China; Department of Otolaryngology, Head and Neck Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan; Department of Pathology, Sendai Shakaihoken Hospital, Sendai, Japan.

H.M. is a lecturer in the Department of Pathology, Harbin Medical University Cancer Hospital, Harbin, China; and the Department of Pathological Diagnostics, Yamagata University Faculty of Medicine, Yamagata, Japan.

Submitted for publication January 1, 2016; revision submitted April 10, 2016; accepted for publication April 22, 2016.

Reprint requests: Mitsunori Yamakawa, Department of Pathological Diagnostics, Yamagata University Faculty of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan; e-mail: k-moh@med.id.yamagata-u.ac.jp or Hongxue Meng, Department of Pathology, Harbin Medical University Cancer Hospital, 150 Haping Road, Harbin, China; e-mail: menghongxue15@163.com.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.04.008

Abbreviations: AID = activation-induced cytidine deaminase; APRIL = a proliferation-inducing ligand; BAFF = B cell-activating factor of the TNF family; BSA = bovine serum albumin; cDNA = complementary DNA; CSR = class switch recombination; DCs = dendritic cells; FBS = fetal bovine serum; FDCs = follicular dendritic cells; GC = germinal center; GLTs = germline transcripts; IgAN = IgA nephropathy; IHC = immunohistochemistry; IL-7Rα = IL-7 receptor α chain; ISH = in situ hybridization; LCM = laser capture microdissection; PBS = phosphate-buffered saline; RT-PCR = reverse transcription polymerase chain reaction; TGF-β1 = transforming growth factor-β1; TNF = tumor necrosis factor; TSLP = thymic stromal lymphopoietin; TSLPR = TSLP receptor

AT A GLANCE COMMENTARY

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Background

Pathogenic immunoglobulin A (IgA), partly from tonsillar origin, has been suggested to be a key factor in the pathogenesis of IgA nephropathy (IgAN), and tonsillar germinal center B cells may acquire IgA expression by undergoing class switch recombination.

Translational Significance

Our study provides the first evidence that thymic stromal lymphopoietin and TSLPR were expressed in tonsillar follicular dendritic cells and may promote IgA class switching in the tonsils of IgAN patients through interactions with activation-induced cytidine deaminase- and IgA-inducing cytokines. These results explain the favorable outcome of tonsillectomy in IgAN patients; thus, TSLP-TSLPR autocrine/paracrine loop is an attractive immunomodulator candidate and may highlight a promising strategy for therapeutic intervention in IgAN.

INTRODUCTION

Immunoglobulin A (IgA) nephropathy (IgAN), the most common form of primary glomerulonephritis, is characterized by qualitative abnormalities in circulating IgA and IgA deposition in the renal mesangium.[1,2] Although the origin of elevated IgA remains unclear, recent studies have suggested that mesangial IgA deposits could be derived from mucosal primed plasma cells.[3] Chronic and recurrent tonsillitis are thought to play an important role in new onset and progression of IgAN.[4] Moreover, the benefits of tonsillectomy in patients with IgAN suggest that tonsillar focal infection may be closely related to IgA deposition in the glomerular mesangium of IgAN patients and elevated serum IgA may partly originate from affected tonsils.[5]

Palatine tonsils are lymphoepithelial tissues that provide a first line of defense against inhaled foreign pathogens. They act as important inductive sites for mucosal B-cell responses.[6] The germinal center (GC) is the main site of B cell proliferation and IgA class switching supported by follicular dendritic cells (FDCs).[7] On activation by antigen and accessory signals, tonsillar GC naive IgM^+ IgD^- B cells may acquire IgA expression by undergoing class switch recombination (CSR).[8] IgA class switching is initiated by production of Iα-Cα germline transcripts (GLTs) and mediated by activation-induced cytidine deaminase (AID), yielding a chimeric Iα-Cμ switch circle transcript.[9,10] Details of CSR are shown in Supplementary Fig S1. Currently, the molecular and cellular mechanisms underlying the generation of IgA and CSR in tonsillar GCs of IgAN patients remain largely unknown.

FDCs are unique accessory cells that trap immune complexes and serve as a source of antigen for GC B cells.[11] Therefore, immune complexes on FDCs can promote AID production and class switching. Furthermore, IgA switching may rely on proliferation- and survival-inducing cytokines of the tumor necrosis factor (TNF) family, such as B cell-activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) secreted by activated dendritic cells (DCs) and FDCs.[8,12] Transforming growth factor (TGF)-β1 is also involved in IgA switching by promoting GLT. By releasing IgA-inducing cytokines (TGF-β1, BAFF, and APRIL), FDCs enhance IgA production in Peyer's patches.[13] However, it is unknown whether FDCs contribute to IgA production in tonsillar GCs in the context of IgAN. Furthermore, the stimuli recognized by tonsillar FDCs and their correlation with AID- and IgA-inducing cytokines are still uncertain.

Human palatine tonsils have deep, branched, antigen-retaining crypts with a reticular epithelium.[14] Tonsillar crypt epithelium is activated to secrete the innate switch factor BAFF and the thymic stromal lymphopoietin (TSLP), which further promotes CSR.[15] TSLP is an interleukin (IL)-7-like type 1 cytokine, which exerts its biologic activities by binding to a heterodimeric receptor that consists of the IL-7 receptor α chain (IL-7Rα) and the TSLP receptor (TSLPR) chain.[16,17] TSLP can be induced by exogenous stimuli, including trauma, infection with microbes, toll-like receptor ligation, and host-derived pro-inflammatory and Th2