

Activating mechanism of innate immunity via toll-like receptors in IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS)

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Background:

IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS) is a unique inflammatory disorder characterized by the elevation of serum IgG4 and infiltration of IgG4-positive plasma cells in lacrimal and salivary glands (SGs). Regarding the immunological aspects of this disease, it is well known that IgG4 is induced by T helper type 2 (Th2) cytokines such as IL-4 and IL-13. We previously reported that these Th2 cytokines contributed to IgG4 production in IgG4-DS. In addition, recent studies indicated that the activation of innate immunity also plays a key role in the IgG4 production upon stimulation with toll-like receptor (TLR) ligands. In this study, we thus examined the expression of innate immune molecules, especially TLRs in SGs from patients with IgG4-DS.

Methods:

Gene expression was analyzed by DNA microarray in submandibular glands (SMGs) from patients with IgG4-DS (n=6), chronic sialoadenitis (CS) (n=3), and controls (n=3). Differentially expressed genes of TLR family were validated by real-time polymerase chain reaction (PCR) and immunohistochemical staining in SGs from patient with IgG4-DS (n=15), SS (n=15), CS (n=9), and controls (n=9). Finally, we assessed the phenotype (lymphocytic infiltration, fibrosis, and weight of affected organs) of human TLR7 (huTLR7)-transgenic mice compared with wild-type C57BL/6 mice.

Results:

In IgG4-DS, Five genes of TLR family (TLR4, TLR7-10) were overexpressed by DNA microarray. PCR validated significantly higher expression of TLR7 in IgG4-DS compared with the other groups. Immunohistochemical analysis confirmed that the expression pattern of TLR7 was similar to that of the M2 macrophage marker CD163. Recent study demonstrated that TLR7 agonist stimulates macrophages to production of IL-33, which is identified as a cytokine that activates Th2 immune responses. Therefore, we focused on the relationship between TLR7 and IL-33 in IgG4-DS. The result showed that the mRNA expression of TLR7 was positively correlated with that of IL-33 in only IgG4-DS.

In huTLR7-transgenic C57BL/6 mice, the number of infiltrating lymphocytes and fibrosis score in the SMGs and pancreas were significantly higher than those in wild-type mice, while there was no significant difference in the weight of any organs between the two groups of mice.

Conclusions:

IgG4-DS patients showed overexpression of TLR7 in M2 macrophages in SGs. Moreover, huTLR7-transgenic mice partly showed lymphocytic infiltration and fibrosis in the SMGs and pancreas. Our current data suggest that TLR7-expressing M2 macrophages might promote the activation of Th2 immune responses via the local inflammation with IL-33 secretion in IgG4-DS.