Interleukin-33 produced by M2 macrophages and other immune cells contributes to Th2 immune reaction of IgG4-related disease

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Objective:

IgG4-related disease (IgG4-RD) is characterized by elevated serum IgG4 and marked infiltration of IgG4-positive cells in multiple organs. Since it is well known that IgG4 is induced by helper T type 2 (Th2) cytokines such as IL-4 and IL-13, IgG4-RD is speculated to be a Th2-dominant disease. IL-33 is a recently described cytokine that is secreted by damaged epithelial cells, macrophages, and dendritic cells (DCs), and potently activates Th2 immune responses. Therefore, to clarify the contribution of IL-33 to the pathogenesis of IgG4-RD, we examined infiltrating cells expressing IL-33 in salivary glands (SGs) from patients with IgG4-RD.

Methods:

SG samples were collected from patients referred to the Department of Oral and Maxillofacial Surgery, Kyushu University Hospital between 2010 and 2014. Seven patients with IgG4-RD, 10 with primary Sjögren's syndrome (SS), and 10 with oral squamous cell carcinoma as a control group participated in this study. We assessed the expression of IL-33 and related molecules in the SGs of patients with IgG4-RD versus that in patients with SS and controls.

Results:

Expression of IL-33 and its receptor (ST2) was strongly detected around ectopic germinal centers (GCs) in the SGs from patients with IgG4-RD, whereas IL-33 was expressed only in epithelial cells in patients with SS and controls. Serum IL-33 levels in patients with pSS were higher than that in controls, and IgG4-RD showed the decrease in serum IL33 after steroid therapy. Moreover, IL-33 and $CD68^{+}/CD163^{+}$ macrophages were mainly distributed around ectopic GCs in patients with IgG4-RD. Double immunofluorescence staining showed that IL-33 expression co-localized with $CD68^{+}/CD163^{+}$ macrophages. Finally, mRNA expression levels of IL-33 showed a positive correlation to those of Th2 cytokines (IL-4 and IL-13) in patients with IgG4-RD.

Conclusions:

We confirmed IL-33 overexpression in M2 macrophages clustered around ectopic GCs in SGs from patients with IgG4-RD. Our current data suggest that IL-33 produced by M2 macrophages might contribute to the pathogenesis of IgG4-RD via aberrant activation of Th2 immune responses.