

Possible involvement of innate immunity in the pathogenesis of IgG4-RD

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Objective:

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), and thus distinguishable from Sjögren's syndrome (SS). Our previous studies have reported that IgG4-DS is a helper T type 2 (Th2)-dominant disease and that aberrant activation of the Th2 immune response plays a key role in the pathogenesis. In addition, recent studies demonstrated that innate immune cells, including monocytes and macrophages, might promote IgG4 production upon stimulation with toll-like receptor (TLR) ligands. In this study, we thus examined whether innate immunity is primarily involved in the pathogenesis of IgG4-DS.

Methods:

We re-evaluated the histological slides from cases of possible IgG4-GID with a resection or excisional biopsy, which we collected from members of the Research Committee of IgG4-RD sponsored by a Health and Labour Sciences Research Grant (Intractable diseases) from the Japanese Ministry of Health, Labour and Welfare; the Committee for Autoimmune Pancreatitis of the Japan Pancreas Society; and the authors of the previous reports.

Results:

Immunohistochemical analysis confirmed that the number of CD163-positive M2 macrophages in the SGs from patients with IgG4-DS were significantly higher than those from the other groups. Real-time PCR examined the expression of TLR family (TLR1-TLR10) in the SGs and then validated the expression of TLR7 in the SGs from patients with IgG4-DS was significantly higher than that from the other groups. Double immunofluorescence staining showed that the expression of TLR7 co-localized with that of CD163 in the SGs from patients with IgG4-DS. As recent studies demonstrated that TLR7 agonist stimulates macrophages to produce IL-33, we examined the relationship between the expression of TLR7 and IL-33 in the SGs. The results showed that the expression of TLR7 was positively correlated with that of IL-33 only in the SGs from patients with IgG4-DS. In huTLR7-transgenic C57BL/6 mice, the number of infiltrating lymphocytes and fibrosis score in the SGs and pancreas were significantly higher than those in wild-type mice, although there was no significant difference in the weight of any organs between the two groups of mice.

Conclusions:

These results suggest that TLR7-expressing M2 macrophages possibly play a key role in the activation of Th2 immune responses via local inflammation with IL-33 secretion.