

DNA microarray analysis of submandibular glands in IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS) indicates a role for macrophage receptor with collagenous structure (MARCO)

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Objectives:

IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS) is a novel clinical disease entity characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells with severe fibrosis in glandular tissues. Although recent studies demonstrated that abnormal innate immune responses might promote IgG4 production, the pathological mechanism of IgG4-DS is still unclear. In this study, we thus addressed to identify the disease-associated genes, especially innate immune molecules, by using exhaustive analysis.

Method:

Gene expression was analyzed by using DNA microarray in submandibular gland (SMG) from patients with IgG4-DS (n=6), chronic sialoadenitis (CS) (n=3), and controls (n=3). DNA microarray analysis was performed in three groups to screen for differentially expressed genes (DEGs). DEGs were validated by real-time PCR and immunohistochemical staining in IgG4-DS (n=18), CS (n=4), Sjögren's syndrome (n=11), and controls (n=10).

Results:

Gene expression patterns in the 3 groups were quite different from each other by the pvclust method and principal components analysis. In IgG4-DS, 1028 up-regulated genes and 692 down-regulated genes were identified as DEGs ($P<0.05$). Gene Ontology (GO) term analysis indicated that the up-regulated DEGs in IgG4-RD encoded proteins involved in T/B cell activation and chemotaxis. PCR validated significantly higher expression of macrophage receptor with collagenous structure (MARCO), a pattern-recognition receptor, in IgG4-RD compared with the other groups ($P<0.01$). MARCO is considered to play an important role in the innate immune response, especially phagocytosis, by binding the ligands, including environmental particles and nanomaterials. Double immunohistochemical analysis confirmed that the expression of MARCO almost merged with that of the M2 macrophage marker CD163. Interestingly, our clinical data showed that the number of onset in a season was similar to the air concentration of PM2.5, a kind of nanomaterials (Fukuoka city, Japan).

Conclusions:

MARCO was identified as a disease-associated molecule in IgG4-DS by DNA microarray. Moreover, M2 macrophages might contribute to the initiation of IgG4-DS via MARCO.