Press release

Title

Sialylation converts arthritogenic IgG into inhibitors of collagen-induced arthritis

Point

- ○Carbohydrate structures on autoantibodies, IgG found in rheumatoid arthritis (RA) have been verified to be involved in the regulation of pathological features of RA.
- ○Sialylation of carbohydrates on the auto-antibodies, IgG resulted in the alleviation of the disease intensity in RA.
- ○These results will provide insights into the construction of novel therapeutic approaches for not only RA, but also various autoimmune diseases.

Abstract

Dr. Yuhsuke Ohmi, a Designated Assistant Professor at the Department of Biochemistry II, Nagoya University Graduate School of Medicine (Dean, Prof. Masahide Takahashi) together with Dr. Koichi Furukawa, a Professor at Chubu University College of Life and Health Sciences, Dr. Yoshimasa Takahashi at the Department of Immunology, National Institute of Infectious Diseases, Dr. Tomohiro Kurosaki at Osaka University, Dr. Nana Kawasaki at Yokohama City University, Dr. Kazuhiko Yamamoto at Department of Orthopedics, Tokyo University, Dr. Atsushi Kumanogo at Osaka University, and Dr. Yoshimasa Takahashi at Nagoya University Hospital have verified that remodeling of carbohydrate structures on the auto-antibodies found in the sera of RA resulted in the suppression of clinical and pathological features of RA.

RA is an autoimmune disease, incidence of which is reaching to 1%, and chronic bone destruction is brought about. In turn, IgG has single N-glycosylation site at the Fc region, and presenting various glycosylation patterns. In particular, it has been well known that sialic acid and/or galactose in the N-glycan on IgG are often deleted in the serum of RA patients. However, its implication has remained to be unclear. In this study, it has been demonstrated that mice genetically lacking sialic acid in IgG due to deficient ST6Gal1 gene in the activated B cells undergo more serious RA disease compared to the wild type mice when experimental arthritis was induced. In other words, it has been suggested that reduced sialylation in IgG induces exacerbation of RA. Furthermore, it has been shown that administration of sialylated auto-antibodies in vitro into RA model mice results in rather alleviation of clinical features of RA.

This novel finding would not only contribute to clarification of RA pathogenesis, but also indicate the possibility that RA disease state is controlled by appropriate modification of the carbohydrate structures on the auto-antibodies. More over, this result will also contribute in the understanding of various autoimmune diseases and in the development of optimal antibody therapy for its property and way of administration, leading to the solution of current health problems under super-aging society.

These results have been published in English Scientific Journal “Nature Communications” (Apr. 5).

1. Background

RA is an autoimmune disease with incidence of ca 1%, showing chronic destructive arthritis. In the patients’ sera of RA, auto-antibodies are found. Above all, levels of antibodies towards citrullinated proteins well correlate with the intensity of the disease, it has been used, therefore, as a diagnostic marker of RA. However, this anti-citrullinated protein antibody (ACPA) has not been well investigated about its nature and implication in the pathogenesis of RA. Generally, IgG has a N-glycosylation site in the Fc region, showing various glyco-forms. Recently, there have been some reports that N-glycans in Fc is involved in the regulation of antibody functions. Particularly, it has been known that massive addition of sialic acid on the N-glycans in IgG, which is administrated into patients to suppress inflammation as IVIG ((intravenous immunoglobulin), results in the increased therapeutic effects (Anthory RM et al: *Science*. 2008). More over, it was also reported that IgG generated by B cells in a T-cell independent manner has an increased sialylation in Fc-N-glycans (Fc-Sia), and suppresses subsequent immunoreaction to the same antigen (Hess C et al: *J Clin Invest*. 2013). These results suggest that presence of sialic acids in IgG Fc-N glycans induces anti-inflammatory reaction and absence of sialic acids enhances inflammation, although precise mechanisms by which glycosylation play roles in regulation of IgG functions have remained to be unclear. In this study, regulatory functions of sialic acids on N-glycans attached on antigen-specific IgG in the regulation of RA disease has been investigated by *in vitro* and *in vivo* experimental systems in order to clarify the novel possibility of antibody therapy.

2. Obtained results

ACPA in RA patients and antigen-specific IgG generated in RA model mice exhibited reduced levels of sialylation in N-glycans on Fc compared with those from healthy donors and normal mice. Then, pretreatment of mice with ACPA containing high levels of sialic acids by genetic modification of ACPA-producing hybridoma cells resulted in the suppression of collagen-induced arthritis (CIA). Furthermore, we established sialic acid-deficient mouse lines in activated B cells based on the genetic deletion of ST6Gal1 (ST6Gal1 $^{flox/flox}$ x AID-Cre mouse), and tried to induce CIA in them. Consequently, ST6Gal1 $^{flox/flox}$ x AID-Cre mice showed increased incidence of RA compared to the AID-Cre mice (control). These results suggested that lack of sialic acids in IgG results in the exacerbation of RA disease.

3. Future scope

All these results suggest a possibility that modification of glycosylation in autoantibodies can be applied for the controlling of disease features, i.e. not only for the analysis of pathogenesis of RA, but also for the development of novel antigen-specific antibody therapy. Furthermore, they might give insights into the investigation of various other autoimmune diseases than RA on their pathogenesis and

improved antibody therapy, thereby contributing in the solution of current health problems under super-aging society.

4. Explanation for words

CIA, collagen-induced arthritis; CAIA, collagen antibody-induced arthritis; RA, rheumatoid arthritis; Fc region, a part of antibody not directly bind to antigens; Fc receptor, receptors mainly expressed on leukocytes, performing various biological functions; ACPA, anti-citrullinated protein antibody, being used as a diagnostic marker of RA, and probably involved in the pathogenesis of RA; sialic acid, one of monosaccharides having negative charge, being expressed abundantly in nervous tissues and cancer cells.

5. Published Journal

Ohmi Y, Ise W, Harazono A, Takakura D, Fukuyama H, Baba Y, Narazaki M, Shoda H, Takahashi N, Ohkawa Y, Ji S, Sugiyama F, Fujio K, Kumanogoh A, Yamamoto K, Kawasaki N, Kurosaki T, Takahashi Y, Furukawa K. Sialylation converts arthritogenic IgG into inhibitors of collagen-induced arthritis. *Nature Communications*. 2016; DOI 10.1038/NCOMMS11205 (To be published on Apr. 5, 2016).

Japanese ver.

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