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Contents

Introduction	1298
Glycosylation Abnormalities of Immunoglobulin in RA	1298
Potential Role of Agalactosyl IgG in the Pathogenesis of RA	1299
Future Perspectives	1300
References	1300

Abstract

Rheumatoid arthritis (RA) is a representative autoimmune disease, although the etiology of which remains unclear. A marked increase in the percentage of sugar chains lacking in galactose in serum IgG molecule (G0) of RA patients was first reported in 1985. This phenomenon occurs even from a fairly early stage of the disease, potentially contributing to the development of RA. G0 is a useful biomarker with values of both diagnosis and evaluation of disease severity for RA. Moreover, accumulating evidences have revealed the potential role of agalactosyl IgG in the pathogenesis of RA. It is expected that clarification at the molecular level of the mechanisms underlying the glycosylation abnormalities leads to the curative treatment of RA.

Keywords

Agalactosyl immunoglobulin G • Rheumatoid arthritis • Biomarker • β -1,4-Galactosyltransferase(GaLT) • Rheumatoid factor

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Introduction

Rheumatoid arthritis (RA) is a representative autoimmune inflammatory disease. Although the etiology of which still remains unclear, deposition of immune complexes with rheumatoid factor (RF), an autoantibody to autologous immunoglobulin G (IgG), at such sites as the synovial membrane, bones, cartilages, and vascular wall, might give rise to the inflammation. Previous studies have demonstrated the abnormal glycosylation in the serum IgG of RA patients, which eventually may affect the immunogenicity of the IgG and production of autoantibodies, including RF. It has become clear now that these sugar-chain abnormalities have a bearing on their physiologic functions and inflammatory reactions and play important roles in the pathogenesis of RA.

Glycosylation Abnormalities of Immunoglobulin in RA

In 1985, the level of serum IgG lacking the galactose (agalactosyl IgG) was found to be markedly increased in RA patients (Parekh et al. 1985). The human IgG molecule has two oligosaccharides (*N*-glycan) linked to the asparagine at position 297 in the CH2 domain (Fig. 1). Detailed analyses of the oligosaccharides of serum IgG were carried out in RA patients using the high-performance liquid chromatography (HPLC) developed by Kondo et al. 1994 (Fig. 2). The structure of *N*-glycan is a biantennary and may involve a lack of fucose or bisecting *N*-acetylglucosamine, besides the lack of galactose; 11 variations have been identified. This analysis confirmed that the proportion of agalactosyl IgG (G0, for example, *N*-glycan VI in Fig. 2) is extremely higher in RA patients as compared to healthy controls.

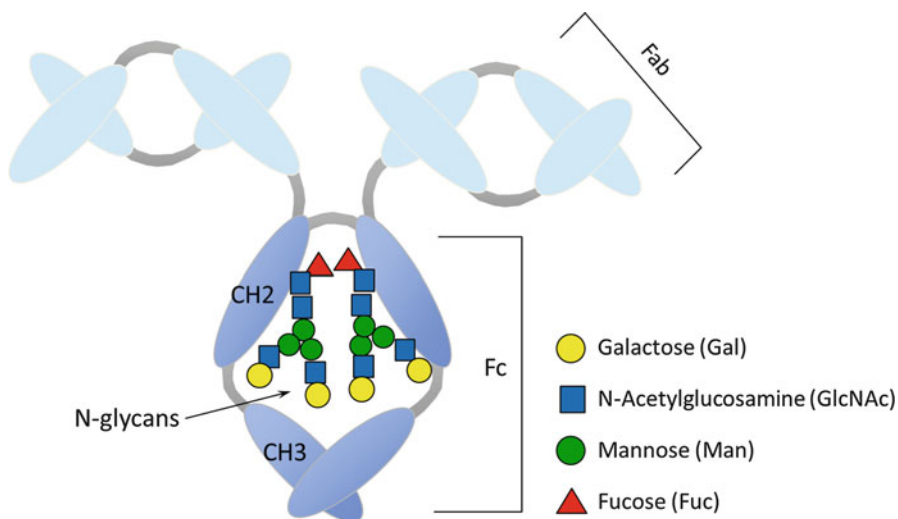


Fig. 1 Structure of *N*-glycan of human IgG

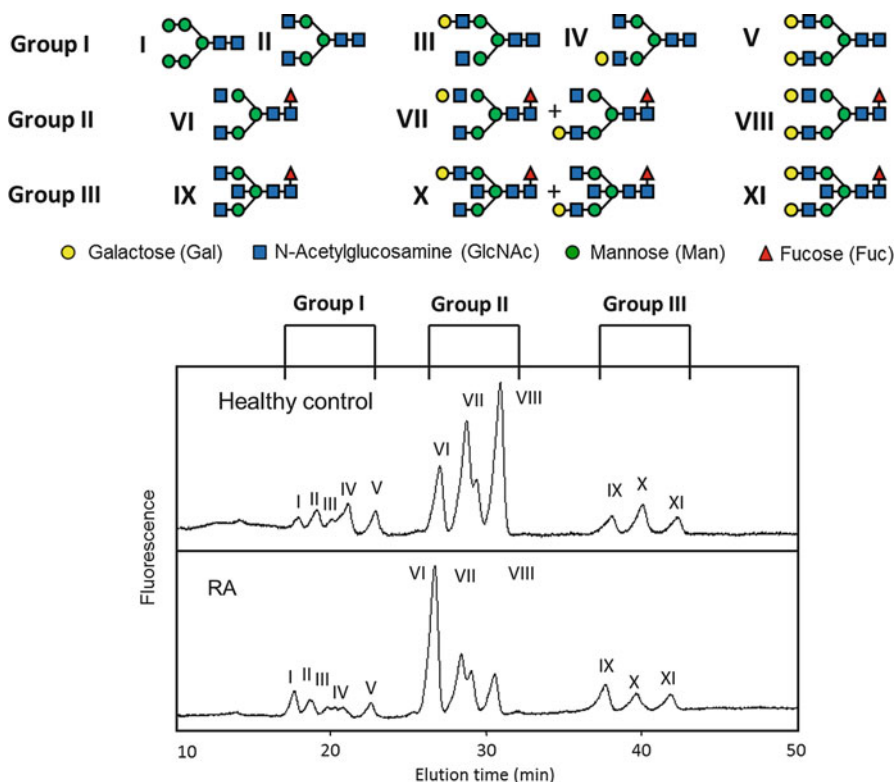


Fig. 2 Principal variations of sugar chains in IgG

On the other hand, our previous paper was the first to reveal not only the hypogalactosylation of IgG *N*-glycans but also a significant decrease in the *N*-acetylgalactosamine content of IgA1 *O*-glycans, by the mass spectrometry of glycopeptides analysis method developed by Wada 2010, indicating glycosylation abnormality is not limited in IgG *N*-glycans.

Potential Role of Agalactosyl IgG in the Pathogenesis of RA

The elevation of G0 occurs even from a fairly early stage of the disease, potentially contributing to the development of RA. Moreover, Tsuchiya et al. reported that G0 correlates with the severity of disease. In conclusion, G0 is a useful biomarker with values of both diagnosis and evaluation of disease severity for RA.

Sugar chains in glycoproteins are known to have a bearing upon the three-dimensional structure of the glycoproteins and to play a role in maintaining their stability, besides having roles in the physiological function. Alterations in the three-dimensional structure consequent upon glycosylation abnormality may

affect the immunogenicity of the molecule, suggesting that such changes may have a bearing on the production the galactose-lacking anti-IgG antibody including RF.

Matsumoto et al. 2000 demonstrated that autoantibody activity of IgG-RF increases with decreasing levels of galactosylation. This phenomenon could explain the mechanism of immune complex formation and the pathogenicity of immune complexes in RA.

In collagen-induced arthritis (CIA), a mouse autoimmune arthritis model, the transfer of agalactosyl IgG antibody to type II collagen caused worsening of the disease state, indicating the involvement of abnormal glycosylation in the pathogenesis of CIA (Rademacher et al. 1994). It has also been demonstrated that the lack of galactose substantially impairs such important physiological functions of IgG as complement activation and Fc receptor-binding capacity (Tsuchiya et al. 1989).

This oligosaccharide modification of IgG in patients with RA seems likely to be regulated by expression of glyco-genes, β -1,4-galactosyltransferase (GalT), in the B cells. There have been demonstrated that β -1,4-GalT activity in the B cells of RA patients is 30–70 % lower as compared with that in healthy controls. It has been shown in recent years that β -1,4-GalT constitutes a family (Furukawa and Sato 1999), and further research to ascertain whether enzyme family has responsible functions for the galactosylation of IgG is anticipated.

Future Perspectives

It is expected that examination of the relationship between the glycosylation abnormalities of the serum immunoglobulins and clinical characteristics in RA patients will enable early diagnosis and yield a better prognosis. In the diagnosis of RA, a novel lectin-enzyme immunoassay (LEIA) (Tsuchiya et al. 1993) which can detect all isotypes of the immunoglobulins (Ig) was developed and is already in use in the clinical practice setting in Japan. This assay has the advantage in terms of sensitivity better than conventional measurement of IgM-RF. However, it is of greater importance, needless to mention, to analyze agalactosyl IgG itself, rather than to analyze the presence of antibodies to agalactosyl IgG. Clarification at the molecular level of the mechanisms underlying the abnormal glycosylation might provide a promising way to the pathogenesis of RA.

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