in disease pathogenesis. We have recently shown that IgG1 ACPA of RA patients harbour different glycan moieties on their Fc-tail, as compared to total sera IgG1. Given the crucial roles of Fc-linked N-glycans for the structure and biological activity of IgG, Fc-glycosylation of antibodies and especially ACPA is receiving considerable interest. However, little is known about the signals and factors that could influence the composition of these carbohydrate structures on secreted IgG produced by B lymphocytes.

Here, we investigated modification of Fc-glycosylation by treatment of B cells with different immune modulatory stimulants. CD19 B cells were isolated from peripheral blood mononuclear cells obtained from blood of healthy donors, and cultured with specific supplements for 7–9 days. Subsequently, IgG was purified by protein A beads from the cell culture supernatants and digested with trypsin. Finally, the Fc-glycans were analysed by mass spectrometry.

We show that both factors belonging to the innate immune system including the toll-like receptor 9 ligand CpG, as well as factors of the adaptive immune system, like the T cell derived cytokine interleukin 21 (IL-21), can modulate IgG Fc-glycosylation. In addition, also 'environmental' factors, such as retinoic acid, a natural metabolite of vitamin A, modulated the glycosylation of IgG Fc. These factors affect Fc-glycan profiles in different ways; CpG and IL-21 increase Fc-linked galactosylation and reduce bisecting N-acetylglucosamine levels, while retinoic acid significantly decreases galactosylation and sialylation levels. Moreover, these effects appeared to be specific for immunoglobulins as no significant changes in the overall glycoforms of cellular proteins were observed. Interestingly, several other cytokines and molecules known to affect B cell biology and antibody production did not have an impact on IgG Fc-coupled glycan profiles.

Together, these results indicate that different stimuli received by B cells during their activation and differentiation can modulate the Fc-linked glycosylation of secreted IgG, without affecting the general cellular glycosylation machinery. These data implicate that modification of Fc-glycans of ACPA secreted by B cells of RA patients could be a promising therapeutic tool to reduce the pathogenicity of ACPA in ACPA-positive RA patients.

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Anticitrullinated protein antibodies (ACPA) are highly specific for rheumatoid arthritis (RA) and have been implicated