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Commentary

Antibody Glycosylation Predicts Relapse in Autoimmune Vasculitis

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In *EBioMedicine*, Kemna et al. hypothesized that glycosylation status of IgG antibodies can predict relapse in PR3-ANCA associated vasculitis (AAV) (Kemna et al., 2017). AAV constitute a group of inflammatory diseases affecting small and medium sized vessels and are characterized by anti-neutrophil cytoplasmic antibodies (ANCA) directed towards proteinase 3 (PR3) and myeloperoxidase (MPO) (Wilde et al., 2011). AAV are severe diseases that can cause kidney failure due to necrotizing glomerulonephritis (NCGN), but can quite often be successfully treated with aggressive immunosuppressive therapy. ANCAs of IgG isotype are most likely involved in driving the disease (Little et al., 2012), and sometimes rise in ANCA titers precede relapses. However, the titers alone seem to be a poor predictor of relapse, and therefore Kemna et al. hypothesized that glycosylation status of the ANCAs could more accurately predict relapse. The rationale for this is that the glycosylation status in the Fc-portion of IgG has proven to influence qualitative aspects of effector functions such as Fc-receptor biding and complement activation (Anthony et al., 2012; Subedi & Barb, 2016). It has also been shown in animal models of AAV that deglycosylation of MPO-ANCA attenuates disease (van Timmeren et al., 2010), and in patients with severe AAV total IgG Fc glycans have lower levels of galactosylation, sialylation, and bisecting *N*-acetylglucosamine (GlcNAc) (Wuhrer et al., 2015). However, glycosylation status of antigen specific IgG has not previously been investigated in AAV patients. In this study, a cohort of 75 patients in remission with a subtype of AAV, called granulomatosis with polyangiitis (GPA) was studied. They all had rising PR3-ANCA titers and 43 patients relapsed within 2–16 months. Affinity purified antibodies from these patients at the time of ANCA rise and relapse were analyzed using an advanced mass spectrometry based methodology that can identify and quantitate specific glycopeptides that represent specific IgG glycoforms in total IgG and PR3-ANCA. This revealed that patients with low galactosylation or sialylation of total IgG1 were highly prone to relapse after an ANCA rise. In relapsing patients, there was a significant decrease of total IgG1 sialylation, galactosylation and bisection and increase of fucosylation from the time of ANCA rise to relapse, while in non-relapsing patients the glycosylation profiles did not change. Somewhat surprising, PR3-ANCA galactosylation, sialylation, and fucosylation decreased in both relapsing and non-relapsing patients.

It has been known for some 30 years now that manifest autoimmune disease is correlated with changes in the glycosylation of antibodies (Parekh et al., 1985), and the list of autoimmune diseases with alteration in IgG glycosylation is rapidly growing with increasingly detailed analysis of glycoforms (for a review see (Goulabchand et al., 2014)). However, the study by Kemna et al. represents the first attempt to by IgG glycan analysis predict relapse in a defined cohort of autoimmune patients under remission. The results are very encouraging, and it will be highly interesting to see a follow up treatment study using ANCA rise in combination with IgG glycan analysis to identify patients that might benefit from early interventions that can potentially prevent relapse of this severe disease.

Disclosure

I declare no competing interests.

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