IgE sialylation: unravelling a key anaphylactic mediator

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Abbreviations: Ig, Immunoglobulin; Fab, antigen-binding fragments; Fc, fragment crystallizable region; FcεRI, Fc epsilon receptor I; MC, mast cells.

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Main text

Immunoglobulin (Ig) E antibodies are heterotetrameric glycoproteins. They are formed by two antigen-binding fragments (Fab) and a fragment crystallizable region (Fc) (1) with seven N-linked glycosylation sites distributed across the heavy chains.(2, 3) Allergen cross-linking of IgE bound to high affinity IgE-receptors (i.e., FcεRI) on mast cells (MCs) and basophils induces the release of mediators that cause allergic symptoms.(4) However, it is largely unknown why patients present a broad spectrum of clinical manifestations and, paradoxically, why many individuals produce allergen-specific IgE without developing allergic symptoms. This indicates that relevant information is still missing about IgE functionality.

Glycosylation is required for proper antibody maturation and determines the specific biological properties of each antibody class (e.g., antigen affinity, Fc receptor binding, downstream immunological activity).(1) Data in cancer and autoimmunity show that glycosylation affects the interaction between Igs and its receptors, thus modulating the pro- or anti-inflammatory properties of Igs in disease-specific patterns.(1) Significantly less is
known about the role of IgE glycosylation in allergy. Niki et al. found that Galectin-9, a lectin expressed by several MCs, suppressed effector cell degranulation by binding to IgE glycans. Furthermore, Shade et al. identified a single glycan in the IgE C3 domain that was essential for triggering anaphylaxis in mice and LAD2 cells (a MC line that derived from a mastocytosis patient). However, the precise mechanisms of this interaction were not fully understood. Recent data by Shade et al. provide novel insights on how IgE glycosylation determines disease-specific allergic responses.

Shade et al. recently studied the IgE glycosylation pattern of peanut-allergic individuals and non-atopic donors (Figure 1). Human LAD2 MCs were sensitized with serum IgE from these two cohorts and activated by anti-IgE crosslinking. MCs sensitized with IgE from non-atopic individuals degranulated less as compared to MCs sensitized with IgE from peanut-allergic patients. Using glycopeptide mass spectrometry, they determined that certain IgE glycosylation sites (N140- and N265-linked complex glycans terminating in galactose) were enriched in IgE from non-atopic subjects while terminal sialic acids were enriched at the N168 and N265 IgE glycosylation sites in peanut-allergic subjects. By analysing the glycan content of IgE from non-atopic and peanut-allergic subjects, they demonstrated that the galactose and sialic acid contents of IgE constituted strong predictors of allergic disease.

In addition to studying glycosylation patterns of total IgE, Shade et al. sought to explore the effects of sialic acid removal from IgE. They observed an attenuation of effector cell degranulation using in vivo and in vitro models (Figure 1). Interestingly, they showed that allergen bound to asialylated IgE did not activate MCs. These results suggest that the removal of sialic acid from IgE may expose an inhibitory glycan that reduces signalling downstream the FcεRI receptor. Using in vivo models, they assessed the therapeutic potential of modulating sialic acid content. By fusing a neuraminidase enzyme towards the N terminus of IgE Fc Cε2–4 domains to remove sialic acid from IgE-bearing cells, they showed an attenuation of allergen-induced anaphylaxis. These findings provide evidence for the possibility of new therapeutic strategies targeting IgE sialylation to regulate acute allergic responses. Moreover, the role of glycosylation in allergic reactions appears to extend beyond IgE. A recent study by Petry et al. assessed the impact of IgG glycosylation in anaphylaxis. Their data suggests that enriched blood IgG Fc N-sialylation may regulate the expression of the inhibitory receptor FcγRIIB and protect from IgG-mediated and IgG-FcγRIIB-controlled-IgE-mediated allergic reactions.

In summary, Shade et al. provide new compelling insights into the glycobiology of IgE and its effect on allergic responses. Modification of IgE glycosylation patterns could potentially lead to a reduction in the severity of allergic reactions, including anaphylaxis. Sialylation and desialylation may well present a promising diagnostic and treatment strategy for peanut allergy and other IgE-mediated allergic diseases but also to empower the protective inflammatory function of IgE in other pathologies.

Figure 1. Increased terminal sialylation is detected on allergic IgE and galactose on non-atopic IgE. Compared to sialylated-human-IgE-sensitized MCs, asialylated-human-IgE-sensitized MCs showed a reduced degranulation following allergen challenge. Sensitization to asialylated-mouse-IgE produced a reduced temperature loss following a challenge. In vitro, sensitized MCs with OVA-specific sialylated-human-IgE were incubated with NEUFcε, or an IgE isotype control, and challenged with OVA. NEUFcε reduced OVA-induced degranulation. In vivo, NEUFcε treatment of mice sensitized with asialylated-mouse-IgE showed a reduced temperature drop after a challenge, compared to those with sialylated-mouse-IgE. Ig, Immunoglobulin; MC, mast cells; NEUFcε, neuraminidase enzyme towards the N terminus of IgE Fc; OVA, ovalbumin.
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