ANTIBODIES

Unmasking IgG responses

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How is it that steady-state serum IgG has anti-inflammatory effects but antigen-specific IgG promotes a pro-inflammatory response following antigen challenge? New research shows that the presence or absence of sialic acid at the terminus of the core glycan in the Fc region of IgG might be the determining factor in mediating these different immune responses.

IgG is recognized by its receptors (FcγRs) through the Fc region, which consists of the constant domains of both heavy chains. The core glycan that is linked to the asparagine residue at position 297 in the Fc region is essential for the binding of IgG to all FcγRs and mediates the induction of immune responses *in vivo*. It has been proposed that different forms of glycan might have a role in modulating the effector function of IgG *in vivo*, but the exact details had not been determined until now.

The authors found that the presence of sialic acid at the terminus of the core glycan might have a role for the activity of IgG. Intravenous immunoglobulin (IVIG) is a purified IgG product with anti-inflammatory effects that is used at high doses for the treatment of several inflammatory disorders. Kaneko *et al*. showed that desialylation of IVIG, by treatment with neuraminidase to remove the terminal sialic-acid residues, abrogated the anti-inflammatory effects of IVIG in a mouse model of rheumatoid arthritis. They then isolated the sialic-acid-enriched fraction of IVIG and compared the effectiveness of this fraction with that of the unfractionated product, in terms of induction of protection in the rheumatoid-arthritis model. They found that the fraction that had been enriched for sialic acid was tenfold more effective at protecting against disease than the unfractionated product.

By contrast, using an active model of inflammation (the mouse nephrotoxic nephritis model), the authors observed that antigen-specific IgG, which is associated with the pro-inflammatory response, was less sialylated than IgG from pre-immune sera. Therefore, a reduction in sialylation of the core glycan in the Fc region of IgG might unmask the pro-inflammatory effects of IgG, functioning as a switch that shifts IgG from having anti-inflammatory effects in the steady state to having pro-inflammatory effects after antigen challenge.

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ORIGINAL RESEARCH PAPER Kaneko, Y., Nimmerjahn, F. & Ravetch, J. V. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* **313**, 670–673 (2006)