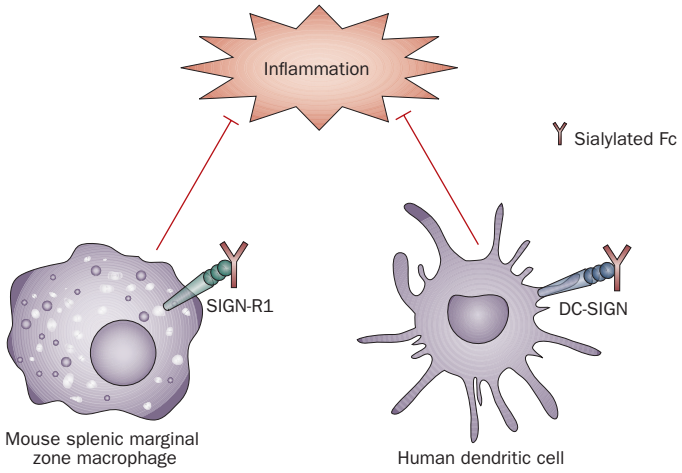
INFLAMMATION

SIGN here for anti-inflammatory activity!

Despite the therapeutic success of intravenous administration of high doses of pooled IgG (intravenous IgG, termed IVIG) in patients with autoimmune and rheumatic diseases, the mechanisms behind the anti-inflammatory effect of this approach are incompletely understood. Jeffrey Ravetch and colleagues from The Rockefeller University in New York report the identification of a population of cells in the spleen, and a receptor, SIGN-R1 (specific ICAM-3 grabbing non-integrin-related 1), which are both required for this activity.

The high doses of IVIG needed for a therapeutic effect led these researchers, in previous studies, to investigate whether only a small fraction of the pooled IgG was responsible for the anti-inflammatory activity of this therapy. Through this work, Ravetch and colleagues showed that IgG molecules with terminal α2,6-sialic acid linkages on their Fc-linked glycans confer the anti-inflammatory activity of IVIG, an activity that is also possessed by recombinant preparations of the sialyated IgG Fc fragments alone.

In their current study, to investigate the cells and pathways involved further, they tested the response to IVIG in mouse strains known to lack specific populations of immune cells: mice without organized follicular structures or spleens failed to respond to IVIG, which suggested that splenic marginal zone macrophages are required for this response. Next, they investigated whether receptors on these cells that can bind to glycopeptides might also be involved. They found that SIGN-R1 binds to sialyated IgG Fc, and is required for the anti-inflammatory activity of IVIG *in vivo* in mice. The human ortholog of SIGN-R1, DC-SIGN—which is expressed by dendritic cells rather than splenic marginal zone macrophages—also binds to sialyated IgG Fc, the researchers found.



What are the possible therapeutic applications of this study? "The work in my laboratory is currently focused on characterizing the signaling pathways that are induced upon sialylated Fc binding to SIGN-R1 on marginal zone macrophages and DC-SIGN on dendritic cells", says Ravetch. "We ... believe we will identify potentially novel cytokines that can be exploited for the development of therapeutics that mimic the effect of IVIG as pure compounds."

Jenny Buckland

Original article Anthony, R. M. *et al.* Identification of a receptor required for the anti-inflammatory activity of IVIG. *Proc. Natl Acad. Sci. USA* **105**, 19571–19578 (2008).

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