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Novel Fc receptors mediating the anti-inflammatory properties of IgG

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The anti-inflammatory activity of intravenous immunoglobulin (IVIG) results from a minor population of the pooled immunoglobulin G molecules that contains terminal α 2,6 sialic acid linkages on their Fc-linked glycans. These anti-inflammatory properties can be recapitulated with a fully recombinant preparation of appropriately sialylated IgG Fc fragments. It has now been demonstrated that these sialylated Fc's require a specific C-type lectin, SIGN-R1, (specific ICAM-3 grabbing non-integrin-related 1) be expressed on macrophages in the splenic marginal zone. Splenectomy, loss of SIGN-R1⁺ cells in the splenic marginal zone, blockade of the carbohydrate recognition domain (CRD) of SIGN-R1, or genetic deletion of SIGN-R1 abrogated the anti-inflammatory activity of IVIG or sialylated Fc fragments. Although SIGN-R1 has not previously been shown to bind to sialylated glycans, it has been demonstrated that SIGN-R1 preferentially binds to 2,6 sialylated Fc as compared to similarly sialylated, biantennary glycoproteins, thus suggesting that a specific binding site is created by the sialylation of IgG Fc. A human orthologue of SIGN-R1, DC-SIGN, displays a similar binding specificity to SIGN-R1 but differs in its cellular distribution, potentially accounting for the some of the species differences observed in IVIG protection. A novel antibody receptor specific for sialylated Fc has been identified as well as the initial step that is triggered by IVIG to suppress inflammation.

References

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