Siglec-8 and Siglec-F: inhibitory receptors on eosinophils and mast cells with pulmonary glycan ligands
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Siglecs (sialic acid binding immunoglobulin-like lectins) are members of the immunoglobulin gene family that contain sialoside binding N-terminal domains. They are cell surface proteins found predominantly on cells of the immune system. Among them, Siglec-8 is uniquely expressed by human eosinophils and mast cells, as well as basophils. Engaging this structure with antibodies or glycan ligands results in apoptosis in human eosinophils and inhibition of release of preformed and newly generated mediators from human mast cells without affecting their survival. Pro-apoptotic effects are also seen when its closest functional paralog, Siglec-F, on mouse eosinophils is similarly engaged in vitro, and beneficial effects are observed after administration of Siglec-F antibody using models of eosinophilic pulmonary and gastrointestinal inflammation in vivo. Siglec-8 targeting may provide a means to specifically inhibit or deplete these cell types.

Both Siglec-8 and Siglec-F recognize the same glycan structure, namely 6′-sulfated sialyl Lewis X and 6′-sulfated sialyl LacNAc, as determined using glycan array technologies. Studies have identified 2,3-linked sialylated glycoprotein structures localized to mouse airway epithelium in tissue sections, where their constitutive expression requires the specific sialyltransferase ST3Gal3. Expression of these ligands in lung is enhanced during allergic inflammation and by cytokines such as IL-13, and is maintained in primary air–liquid interface cultures of mouse lung epithelium. Further characterization suggests that they are high molecular weight sialylated proteins, putatively mucins. By combining analytic glycomics, glycoproteomic mapping, and further in-vitro eosinophil experimentation including the ability of candidate structures to enhance eosinophil apoptosis, a finely detailed appreciation of the structural requirements for productive Siglec-8 and Siglec-F engagement should soon emerge. Cell-directed therapies are increasingly sought after by the pharmaceutical industry for their potential to reduce side effects and increase safety. The challenge is to identify suitable targets on the cell type of interest, and selectively deliver a therapeutic agent. By targeting Siglec-8, monoclonal antibodies and glycan ligand-conjugated nanoparticles may be well suited for treatment of eosinophil and mast cell-related diseases.

References
CD300a is an inhibitory receptor on mast cells, eosinophils, and basophils

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