Siglec-8 complex structures with a therapeutic antibody and a high-affinity sialoside analog

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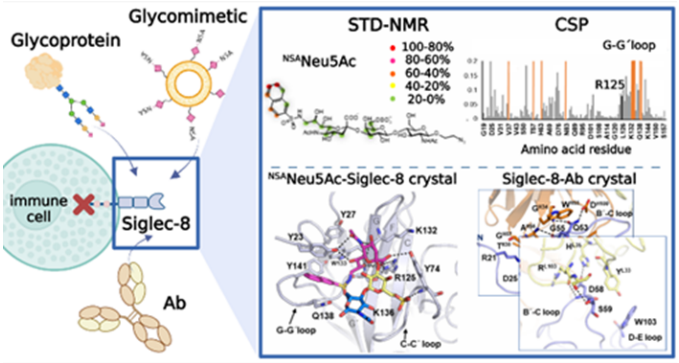
Siglec-8 is an inhibitory receptor that induces eosinophil apoptosis and inhibits mast cell degranulation when bound by monoclonal antibodies (mAbs) or sialylated ligands. Consequently, Siglec-8 has emerged as a crucial negative regulator of inflammatory responses in various diseases, including allergic airway inflammation [1]. Herein, the molecular recognition features of the interaction of Siglec-8 with the monoclonal antibody (mAb) lirentelimab (2C4) and a sialoside mimic with the potential to reduce mast cell degranulation have been deciphered [2]. The X-ray crystallographic solution of the structure of Siglec-8 and the fragment antigen-binding (Fab) component of 2C4 shows that the mAb binds close to the carbohydrate recognition domain on Siglec-8. Additionally, the STD-NMR experiment demonstrates the inhibition of the binding between Siglec-8 and natural ligand in the presence of 2C4. Moreover, using a combination of NMR spectroscopy and X-ray crystallography, we have also deduced the binding mechanism of a high-affinity analog of its sialic acid ligand (9-N-napthylsufonimide-Neu5Ac, ^{NSA}NeuAc). Our data demonstrate that ^{NSA}NeuAc's sialoside ring binds to the classic sialyl binding pocket of the Siglec receptor family, with the high affinity resulting from the accommodation of the NSA aromatic group in a contiguous hydrophobic patch provided by the N-terminal tail and the unique G-G' loop (Figure 1). These results provide pointers for the rational design of the next generation of Siglec-8 inhibitors and explain the foundation for this ligand's observed high affinity [2].



The binding of a sialic acid mimetic with a 9-N aromatic substituent, and antibody with therapeutic potential to Siglec-8 are revealed by a synergic c

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