Hitting the sweet spot: Sialic acid sugars for the treatment of immune diseases and other disorders?

In addition to DNA, proteins and lipids, sugar molecules are essential building blocks for every living cell. There are many different types of sugar molecules in a cell which are linked to one another forming chain or tree-like sugar structures called glycans. Glycans can mainly be found on the cell surface where they are attached to proteins (glycoproteins) or lipids (glycolipids). Cell surface glycans vary enormously in size and composition and show a dazzling diversity and complexity. In humans and other mammals, many glycans have in common that they are capped with one particular type of sugar - sialic acid (Fig. 1).

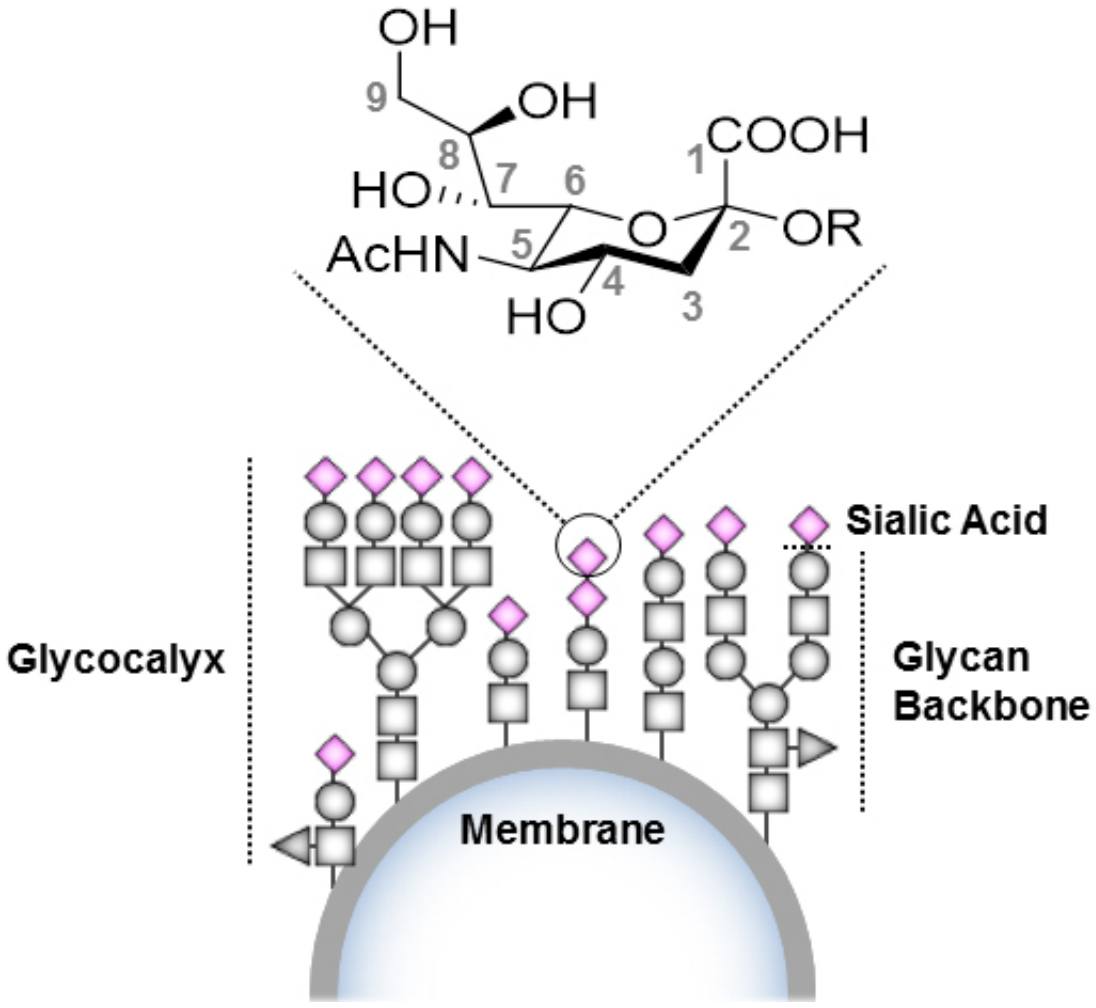

Fig. 1. A cell in which representative glycan structures on its cell surface are depicted as chains of squares and circles. The total collection of all glycans on the cell surface is called the glycocalyx. Sialic acids are depicted as purple diamonds and can be found on the outer end of glycans. The underlying sugars that form the glycan backbone for sialic acids are shown in gray. In the figure,

the chemical structure of a sialic acid is shown. Sialic acids are sugar molecules with nine carbon atoms. By adding other atoms or small molecules to the carbons of a sialic acid, the binding to a Siglec receptor can be modulated.

At the cell surface, sialic acids fulfill many important biological functions. One of them is the regulation of the immune system, a collection of specialized cells that protect us against pathogens and cancer. To properly full fill its task, the immune system has to be turned *on* and *off* at exactly the right time. Sialic acids contribute to this process by interacting with a family of sialic acid-binding receptors on immune cells called Siglecs. In general, the interaction of sialic acids with Siglecs - the sialic acid-Siglec axis – determines the threshold for immune activation and helps the immune system to return to an *off* state (Fig. 2). If this interaction is disturbed, for instance because of a defect in sialic acid expression, regulation of the immune system is out of balance. As result the immune system can start to attack our own body cells leading to autoimmune diseases. On the other hand, cancer cells make use of the sialic acid-Siglec axis to escape from recognition by the immune system and to become resistant against cancer immunotherapy. Cancer cells express high levels of sialic acids that enable them to interact with Siglecs on immune cells. This interaction appears to turn *off* immune cells that otherwise would destroy the cancer cells.

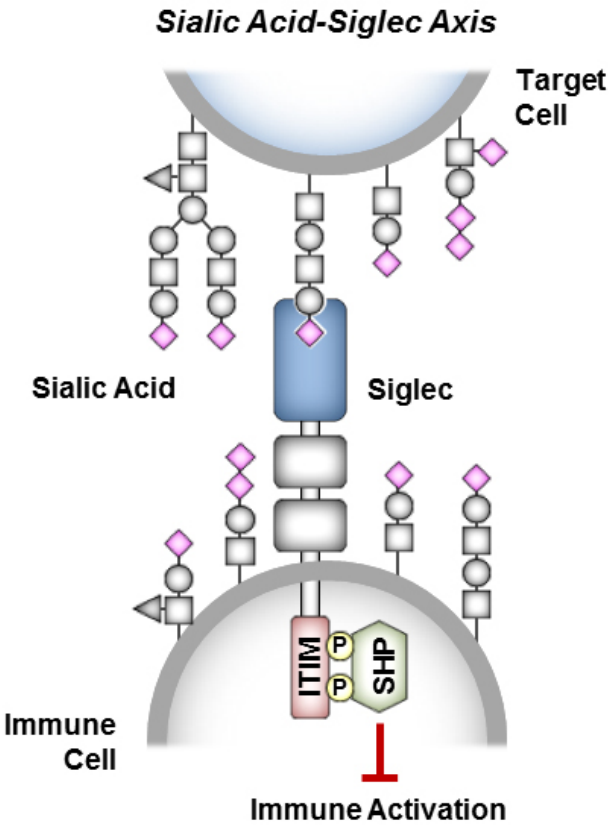

Fig. 2. Interaction between two cells via the sialic acid-Siglec axis is schematically represented. The upper cell represents a target cell (e.g. host cell, cancer cell) and the lower cell one an immune cell. The upper cell presents sialic acids (purple diamonds) that are recognized by Siglecs on an immune cell. When this happens, the intracellular part of the Siglec receptor containing an ITIM (immunoreceptor tyrosine-based inhibition motif) becomes phosphorylated (P) and recruits SHP proteins that inhibit immune cell activation. In other words, sialic acid recognition by the Siglec receptor gives negative signals to the immune cell. Thereby, the sialic acid-Siglec axis dampens immune cells and the immune system.

Siglecs are not exclusively expressed on immune cells, they can also be found on bone cells (osteoclasts) or neural cells (microglia cells) which are involved in bone or brain maintenance, respectively. Failures in sialic acid-Siglec interactions have been linked to bone disease (osteoporosis) and neurological diseases like Alzheimer's disease. As many aspects regarding sialic acids and Siglecs are still poorly understood, it may be extremely rewarding to study the sialic acid-Siglec axis in health and disease in greater detail and to develop novel therapies that can modulate it.

Interestingly, sialic acid sugars can be chemically modified in a way that alters their binding to Siglec receptors. Different research groups have shown that alterations of the sialic acid sugar exist that enhance Siglec binding. For such modified sialic acid to be functional and effectively interact with Siglecs on immune cells, they are best presented in a way that resembles their natural expression in glycans at the cell surface.

Chemically modified sialic acids can be presented to Siglecs in different ways. For instance, they can be attached to nanoparticles that are much smaller than a cell or protein-like structures that integrate into the surface of living cells. Moreover, using a chemical trick, sialic acids on the cell surface can directly be modified to enhance their Siglec binding. In cell culture and mouse experiments, it has already been shown that autoimmunity and inflammation could be reduced by targeting Siglecs on immune cells with the chemically modified sialic acids. Further studies are needed to fully exploit the therapeutic potential of these chemically modified sialic acids.

In conclusion, the sialic acid-Siglec axis regulates important processes in our body and an imbalance herein can contribute to the onset of different diseases. In the future, chemically modified sialic acid sugars with altered Siglec binding characteristics could be applied to control the sialic acid-Siglec axis for the treatment of autoimmunity, cancer and other diseases.

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