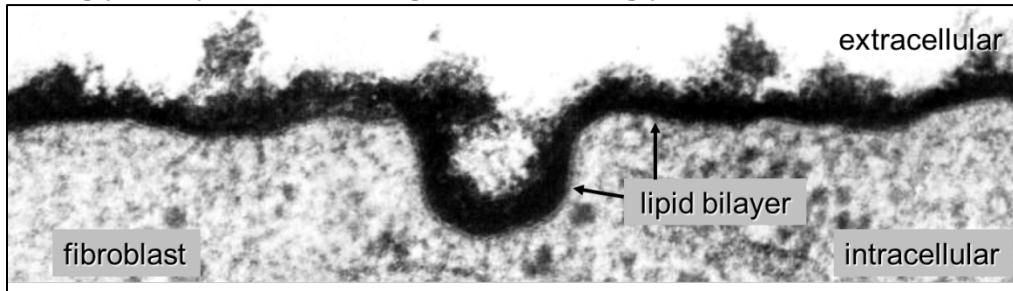


Cell Surface Sialic Acids: The “Dark Matter” of Immune Regulation

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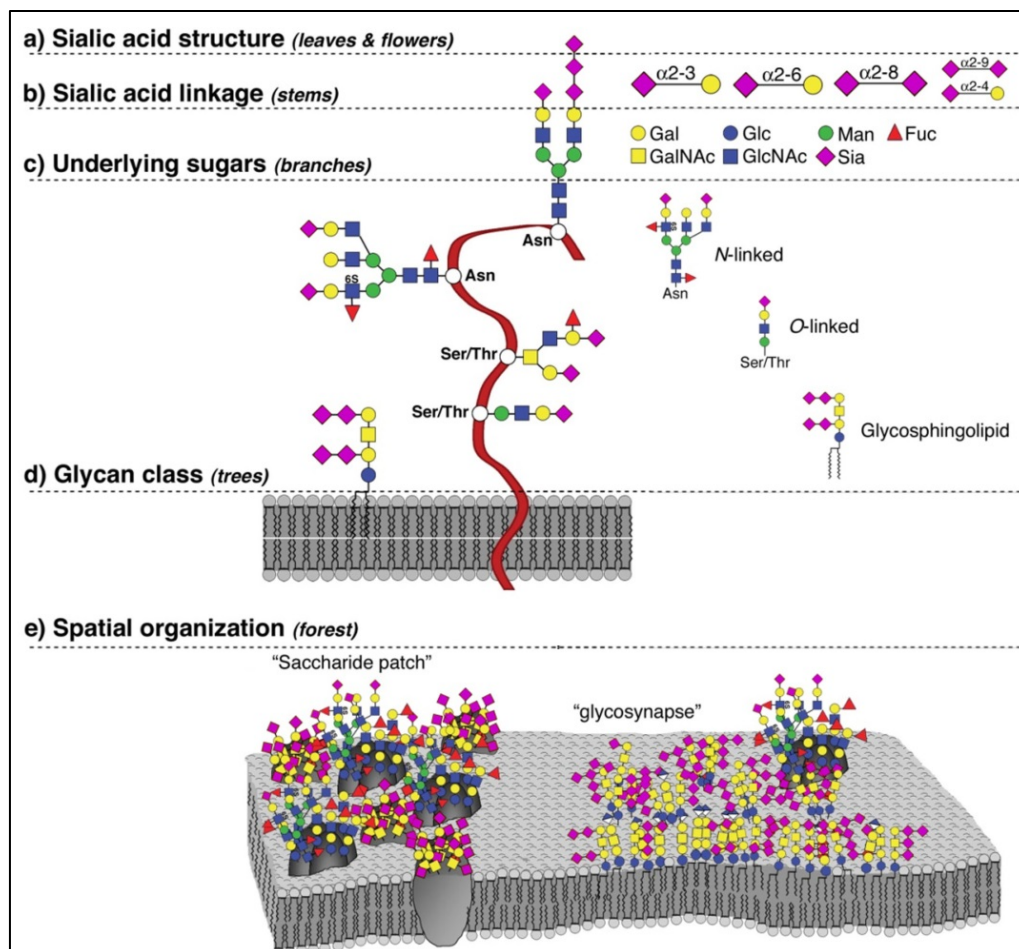
- ✓ Every cell is covered with a dense and complex array of glycans (sugars) – its “glycocalyx”.

The “glycocalyx” surrounding a fibroblast – glycans stained black



Martinez-Palomo, A., et al. Cancer Res. 29, 925-937, 1969

- ✓ The glycocalyx, invisible by many microscopic techniques, is like a forest canopy covering every cell. Composed of glycoproteins and glycolipids, the glycocalyx is organized in levels, from the outermost “leaves and flowers” to the branches and trunks to the forest itself.



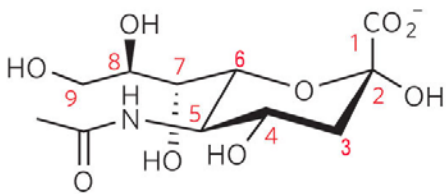
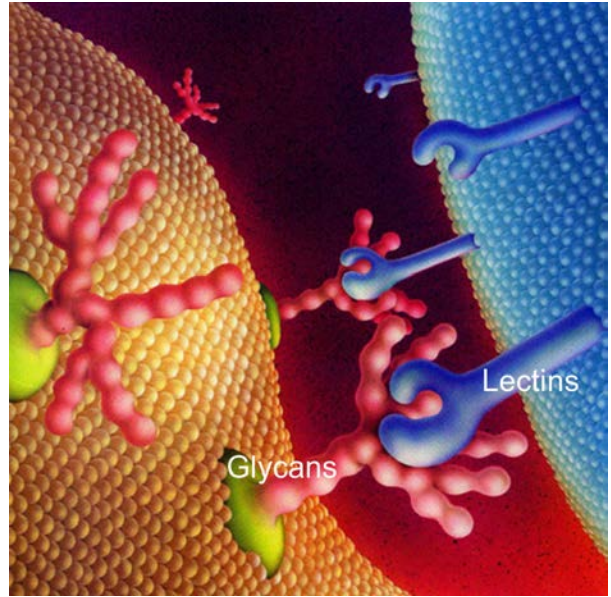
Cohen & Varki (2010) OMICS 4:455

Cell Surface Sialic Acids

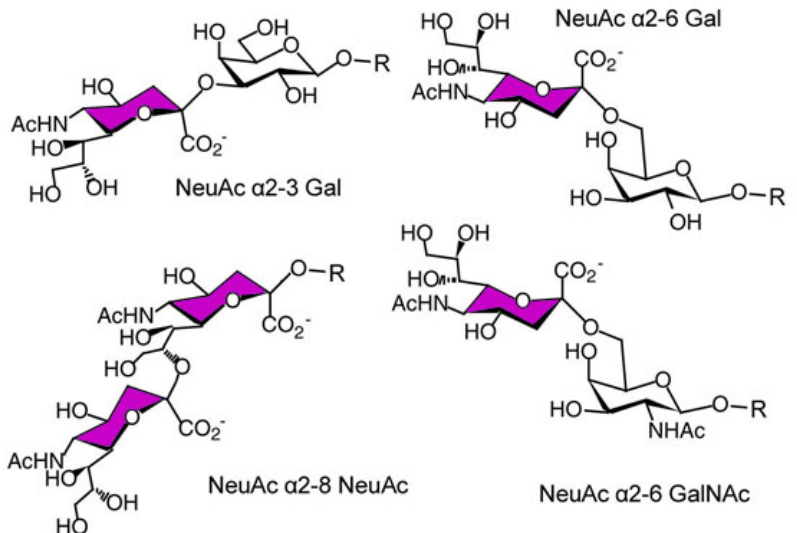
- ✓ Among their functions at the cell surface, glycans code for cell-cell recognition via complementary glycan binding proteins, “lectins”, on apposing cells (trans) or their own surface (cis). These interactions are highly specific, with terminal saccharides typically providing the key binding determinants.

Modified from Sharon and Lis (1993) Scientific American

- ✓ The most abundant and diverse terminal saccharide on mammalian glycans is *sialic acid* (Sia, also called N-acetylneuraminic acid, NeuAc), a nine-carbon backbone sugar with key constituents – a carboxylic acid [1], an N-acetyl group [5] and a glycerol side chain [7,8,9] – that provide great potential for recognition by complementary lectins.



Sialic acid's diversity includes four basic ways in which it can be linked to underlying sugars at the terminus of glycan chains. Twenty sialyltransferase genes are devoted to making these linkages in humans and other mammals.



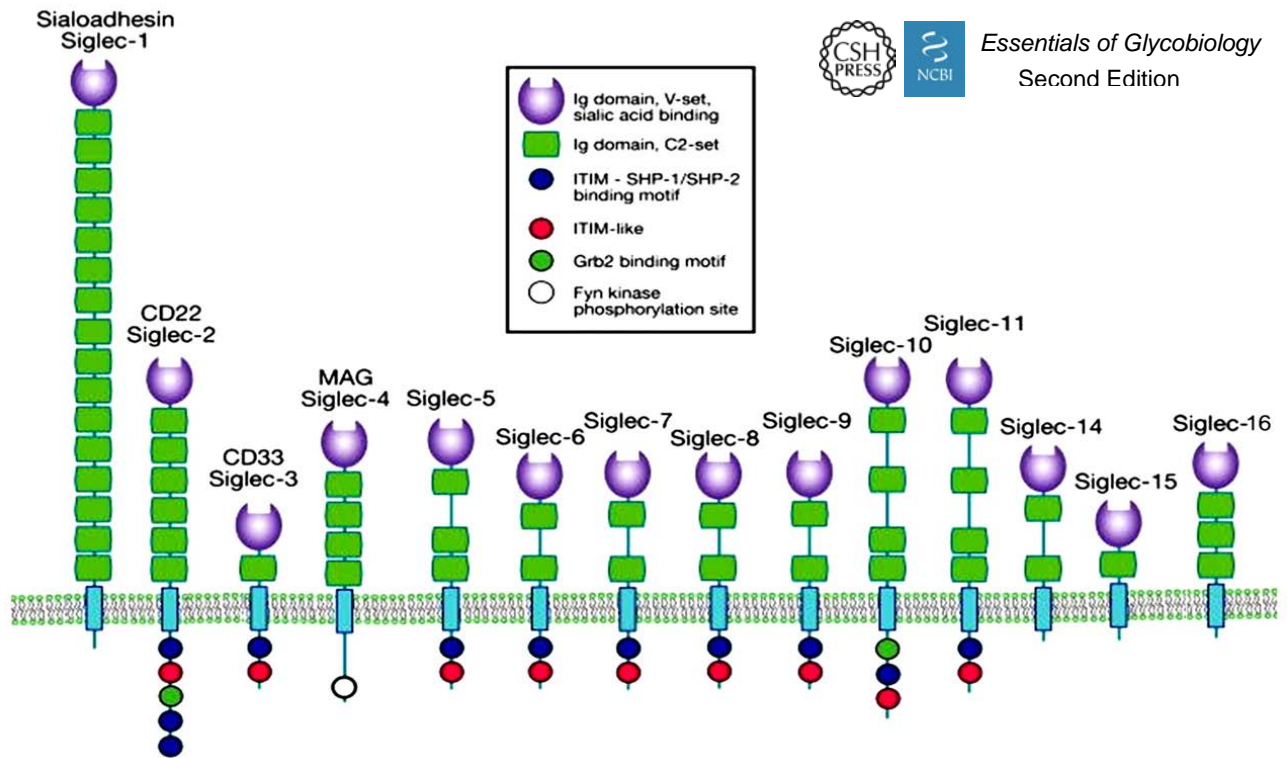
- ✓ Sialic acid recognition is especially important in human immune regulation. Two major families of human lectins recognize sialic acid-bearing glycans: *Selectins* (E, L and P) and *Siglecs* (sialoadhesin, CD22, MAG, CD33, and Siglecs 5-11 & 14-16).

Selectins mediate migration of leukocytes across the endothelium, and recognize an α 2-3-linked sialic acid on glycans that also have a properly spaced fucose (sugar) residue. For this reason, children with a congenital defect in fucose utilization suffer from Leukocyte Adhesion Deficiency type II.

Siglecs, sialic-acid-binding immunoglobulin-like lectins are more diverse in their functions, and evolution has designed them to take advantage of the many ways in which sialic acids can be displayed on the cell surface. Many Siglecs have tyrosine-based signaling motifs, especially immunoreceptor tyrosine-based inhibitory motifs

(ITIMs) implicated in immune regulation. Siglec CD22 is a well-characterized inhibitory receptor of B cells and its interactions sialoglycans on its own surface are important for regulating B-cell signaling. Siglecs 8 and 9 are primarily expressed on different granulocytes, where they can down-regulate inflammation. The functions of these immune regulatory molecules and the sialoglycans they recognize are the focus of this session.

The human Siglec family of sialic acid binding lectins



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