Sulfation on glycans is an important determinant in functional glycomics

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Sulfate modification on specific positions of glycosyl residues would significantly alter its physicochemical property by virtue of conferring a negative charge. In many instances, it simply modulates the binding affinity of the underlying glycan ligand to its cognate glycan binding proteins while in a number of well-known cases, it becomes an integral part of the recognition code itself. For the sialic acid binding immunoglobulin-like lectin (Siglec) family, the binding affinity of human CD22 (Siglec-2), an inhibitory receptor on B cells, to its ligand, 6-sialyl LacNAc (NeuAcα2-6Galβ1-4GlcNAc-), is significantly enhanced by the presence of sulfate on the C6-position of the internal GlcNAc residue. On the other hand, both Siglec-8 and hCD33 expressed on microglia are now known to absolutely require the presence of sulfate on the C6-position of the Gal that is also α2-3-sialylated, which may cap an extended LacNAc or keratan sulfate chains. Overexpression of CHST1 and CHST2, the carbohydrate sulfotransferases responsible for 6-O-sulfation of Gal and GlcNAc on N- and O-glycans, respectively, significantly enhance the binding of several siglecs, with CHST1 shown to drive sialoglycan binding of Siglec-3/8/7/15. To date, defining the variably sulfated glycotopes representing a different permutation of Gal3S, Gal6S, and GlcNAc6S carried on (poly)LacNAc of N- and O-glycans, with and without additional fucose and sialic acids, remains a daunting analytical task not readily performed at sufficiently high sensitivity. Over the years, we have been able to identify myriad sulfo-sialylated Gal and LacNAc glycotopes in different structural settings on a range of glycan carriers by our pioneering mass spectrometry-based sulfoglycomics. Cumulative discovery mode data now opens up new vistas urging for more purposeful systematic approaches that would elucidate their functional relevance in a wide range of biological processes involving glycan recognition.