Poster Presentation

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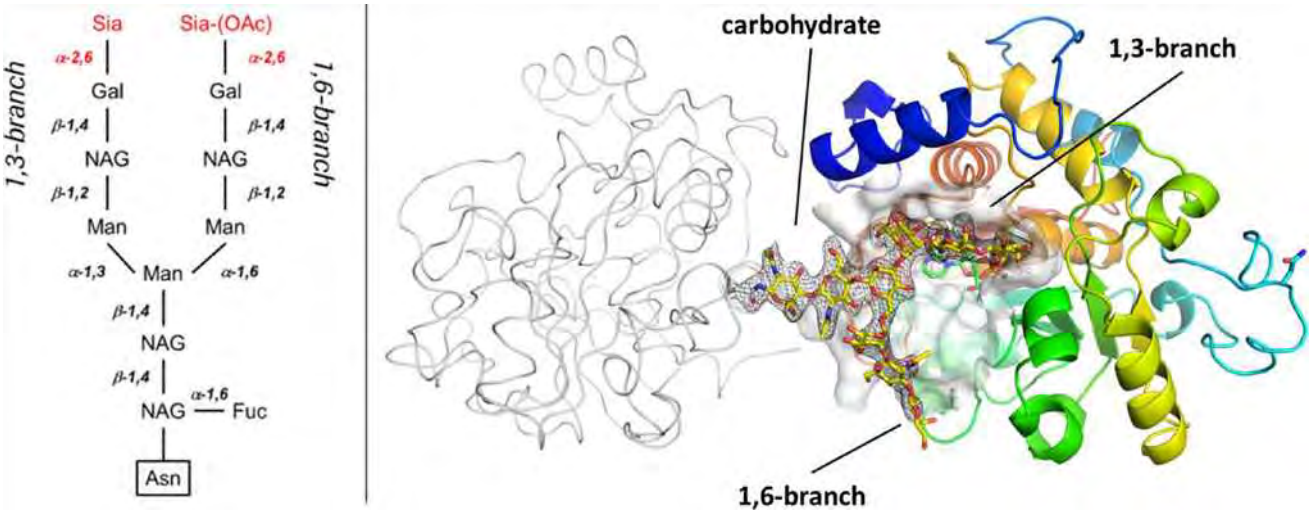
Crystal Structure of Human α-2,6 Sialyltransferase

B. Kuhn[1], J. Benz[1], M. Greif[2], A. Engel[2], H. Sobek[2], M. Rudolph[1]

[1]F. Hoffmann-La Roche, pRED, Basel, Switzerland, [2]Roche Diagnostics, Penzberg, Germany

Human β-galactoside α-2,6 sialyltransferase I (ST6Gal-I) establishes the final glycosylation pattern of many glycoproteins by transferring a sialyl moiety to a terminal galactose. Complete sialylation of therapeutic immunoglobulins is essential for their anti-inflammatory activity and for protein stability. However, a complete glycan tree is difficult to achieve in vitro due to limited activity of ST6Gal-I for some galactose acceptors. No structural information on ST6Gal-I that could help to improve the enzymatic properties of ST6Gal-I for biotechnological purposes was previously available. We describe the crystal structure of human ST6Gal-I, which allows rationalizing the inhibitory activity of cytosine-based nucleotides. ST6Gal-I differs from related sialyltransferases by several large insertions and deletions that determine its regio- and substrate specificity. Excitingly, a large glycan binds to the active site in a catalytically competent orientation, representing the general binding mode of any substrate glycoprotein. This binding mode also rationalizes why some galactose acceptors are incompletely sialylated. Comparison with a bacterial sialyltransferase lends first insight into the Michaelis complex. The results support an SN2 mechanism with inversion of configuration at the sialyl residue and suggest substrate-assisted catalysis with a charge relay mechanism that bears conceptual similarity to serine proteases.

[1] *B. Kuhn, J. Benz, M. Greif, A.M. Engel, H. Sobek, M.G. Rudolph, Acta Cryst. D, 2013, 69, 1826-1838*



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