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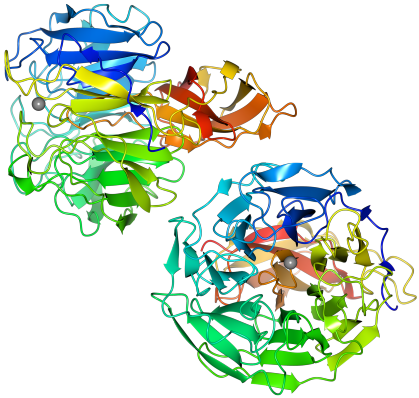

Figure 1. Lateral and rear view of the *Fgr*AlcOx structure in complex with copper (pdb 5C92). The N terminus (blue to yellow) consists of seven Kelch motifs arranged in a β-propeller, enclosing the copper-binding site. The C terminus (orange to red) displays a nine-stranded β-barrel.

Keywords: Copper, EPR, eukaryotic expression, deglycosylation

MS7-O5 Structure of the factor H-sialic acid complex links sialic acid recognition to atypical hemolytic uremic syndrome and reveals a novel conformation of the GM1 glycan

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Complement factor H (FH) ensures down-regulation of the complement alternative pathway upon interaction with specific glycans on host cells, protecting the latter from attack by the host's complement system. There is long-standing evidence that the ubiquitous mammalian glycan cap sialic acid acts as such a self marker to FH, but the low affinity of the interaction and the structural diversity of sialylated glycans have hampered structural and functional investigations. Using ligand-based NMR spectroscopy we defined the FH sialoligosaccharide specificity and found that FH binds to glycans that spot Neu5Acα(2-3)Gal caps. A previously reported crystal form of the two FH C-terminal domains 19 and 20 (1), which contain the sialic acid binding site, were refractory to glycan soaking. Co-crystallization attempts with the GM3 glycan yielded another unliganded crystal form of FH 19-20. Inspection of the protein packing in these two crystals forms prompted us to co- crystallize FH 19-20 with another FH ligand, the thioester domain (TED) of C3b, yielding FH19-20/C3b-TED crystals (2) that were successfully soaked with the GM3 and GM1 glycans. The atomic (2.2 Å resolution) structures of the ternary complexes suggest that sialic acid and the C3b TED together recruit FH to self-cells to which C3b attaches covalently by virtue of its reactive thioester bond - initiating local degradation of C3b on host cells that are covered with sialic acid (3). The structures revealed that numerous FH residues linked to atypical hemolytic uremic syndrome (aHUS), a rare hereditary disease that can lead to kidney failure, cluster in the sialic acid binding site, and their functional impairment with respect to sialic acid binding has since been confirmed (4). Our structures lend an etiological model to aHUS and also bear implications for complement evasion strategies by bacterial pathogens that cover themselves in host-derived sialic acid or recruit FH directly via its sialic acid binding site. Additionally, the complex structure with the GM1 glycan revealed a previously unreported GM1 conformation that escaped NMR-restrained modeling in the past but that is evident in the electron density and was confirmed by molecular dynamics simulations in the 10 μs time scale (5). (1) Jokiranta T.S. et al, EMBO J. 2006. (2) Morgan H.P. et al, Nat Struct. Mol.Biol, 2011. (3) Blaum B.S. et al, Nat. Chem. Biol. 2015. (4) Hyvärinen S. et al, Blood 2016. (5) Blaum B.S. et al., Glycobiology 2016.

Keywords: crystallography, glycobiology, ganglioside, NMR spectroscopy, innate immunity, molecular dynamics