Engineering Immune System Glycoproteins to form Uniform Crystalline Lattices

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Interactions of antibodies and Fc receptors (FcR) play a fundamental role in immunity. However, antibodies and FcR are heavily glycosylated, making it difficult to obtain strongly diffracting crystals. Consequently, most structures for these proteins have been determined at low to medium resolutions (<3.0-2.6 Å). Without modifying the carbohydrates, we are developing procedures for generating crystals of immune system glycoproteins that diffract to high resolutions.

A 2.0 Å structure was previously determined for FcγRIIa with a point mutation of Ser to Phe at position 88[1]. The Phe88 side chain is involved in a key lattice contact by completing a hydrophobic pocket that traps a proline "guest ligand" from a symmetry related receptor monomer. As a result the crystals are robust, allowing a variety of receptor glycoforms to be resolved and the structural analysis extended to 1.5 Å. The role of Phe88 in promoting uniform crystalline lattices has been shown by determining the 2.3 Å resolution structure of the "wild-type" (Ser88) FcγRIIa glycoprotein. The Ser88 receptor crystals were fragile with receptors arranged in a different and more loosely packed crystalline lattice compared to Phe88 receptor crystals.

The improved properties of FcγRIIa crystals containing the lattice forming Phe88 mutation may have profound implications for the field of macromolecular crystal engineering.

[1] Maxwell K.F., et al., *Nat. Struct. Biol.*, 1999. **6**, 437-442.

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