Crystal Structure of a Human Immune Receptor in Complex with the Fc Region of the IgG Antibody

Receptors of the Fc region of immunoglobulin-G (IgG) are key mediators of the immune response. In particular, human Fcγ receptor I (hFcγRI) is the immune receptor with the highest affinity for IgG. To understand the molecular basis of interaction with antibodies, we determined the crystal structure of the complex between hFcγRI and human IgG-Fc at high resolution (1.80 Å). The structure reveals a deep and hydrophobic pocket explaining the strong affinity for IgG antibodies. We propose a general model for binding of IgG to Fc receptors on the cell surface. Our findings have implications for the development of novel therapeutic approaches involving hFcγRI.

Fcγ receptors are a major family of IgG receptors modulating the immune response. In particular, hFcγRI is a high-affinity receptor expressed on the surface of macrophages, monocytes, neutrophils, eosinophils, and dendritic cells. Numerous studies have revealed the key roles of hFcγRI for the immune response, and its connection to autoimmune diseases [1]. Specifically, hFcγRI (also termed CD64) is a transmembrane glycoprotein of 72 kDa binding with high affinity to IgG1, IgG3 and IgG4 (but not IgG2), and the only receptor of the Fcγ family displaying three immunoglobulin-like domains. No crystal structure of the complex between the Fc region of IgG and hFcγRI was reported until recently [2-4], limiting our understanding of this major immune complex, and potentially preventing the development of innovative therapies against autoimmune diseases.

Single crystals of the complex between the extracellular region of hFcγRI and IgG1-Fc were obtained in a solution containing 0.1 M sodium acetate, 0.1 M zinc acetate, 4% (v:v) 1,4-butanediol, and 12% PEG 4,000 (pH 4.6). Data collection was carried out at BL-5A under cryogenic conditions at a resolution of 1.8 Å. Coordinates and structure factors are deposited in the PDB under accession code 4W4O.

In the complex, one dimer of Fc binds asymmetrically to one molecule of receptor (Fig. 1a). We termed the interaction surfaces *subsite 1* and *subsite 2* (Fig. 1b, c). *Subsite 1* occupies 654 Å^2 of contact interface with high shape complementarity (*Sc* = 0.86), and is hydrophobic. *Subsite 2* displays a smaller contact footprint with IgG1-Fc (494 Å^2) and presents lower shape complementarity (*Sc* = 0.78). The glycans attached to Fc and hFcγRI make little contribution to the interaction, an observation that was corroborated in a second study [4].

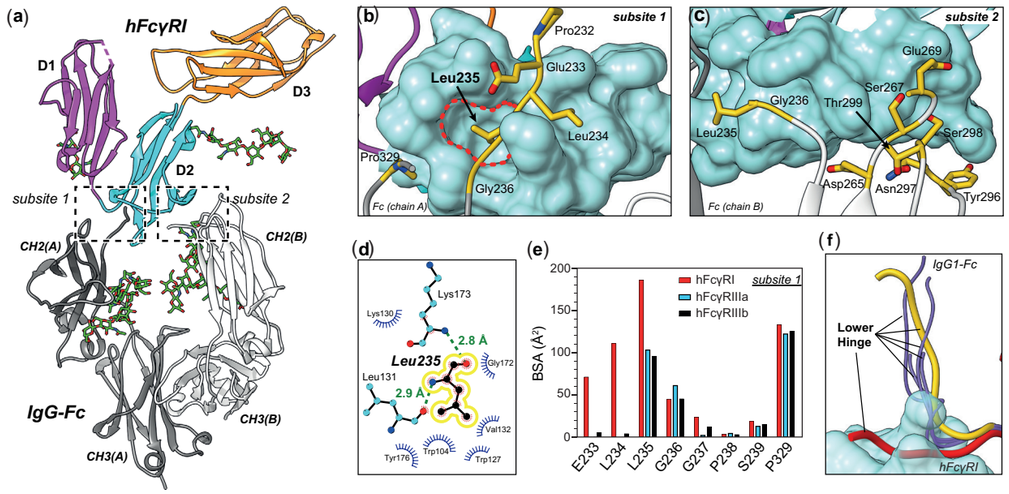

Figure 1: High-resolution crystal structure of the complex between hFcγRI and IgG1-Fc. (a) Overall structure of the complex. (b) Close-up view of *subsite 1*. The surface of hFcγRI is shown in cyan. Residues of IgG1-Fc interacting with the receptor are depicted with sticks. The red line highlights the novel hydrophobic pocket for Leu235. (c) Close-up view of *subsite 2*. (d) Schematic representation of the novel hydrophobic pocket. (e) Interaction surface in *subsite 1* for various Fcγ receptors. (f) Orientation of the hinge. The red ribbon corresponds to IgG1-Fc bound to hFcγRI. Violet or yellow ribbons correspond to the same region of IgG1-Fc bound to other types of Fcγ receptors. The surface of hFcγRI is shown in cyan. The figure was adapted from Kiyoshi *et al.* [2].

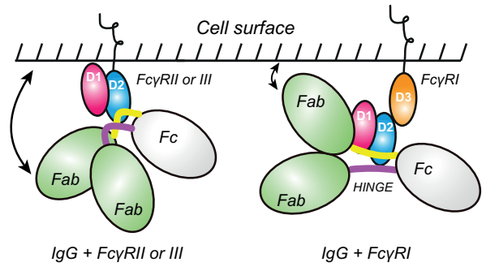

Figure 2: Models of recognition of IgG by Fcγ receptors on the cell surface. The orientation of the Fab region of IgG is different in hFcγRI with respect to other receptors (adapted from Kiyoshi *et al.* [2]).

Detailed examination reveals important differences with other human Fcγ receptors [5]. First, residue Leu235 of one chain of IgG1-Fc is buried in a deep hydrophobic pocket of the receptor (Fig. 1b, d). This cavity is not observed in other Fcγ receptors. Why is this pocket only present in hFcγRI? The reason is because hFcγRI has a unique deletion of one residue in its primary sequence precisely where the pocket exists, generating an empty space on the surface of the receptor suitable for the insertion of Leu235 of IgG1-Fc [2, 4]. In other Fcγ receptors, the additional residue in its primary sequence (Ile or Val) fills up this pocket, hindering the insertion of Leu235 of IgG1-Fc. The existence of this hydrophobic pocket in the complex IgG-1-hFcγRI increases the total buried surface area (BSA) with respect to other Fcγ receptors, explaining its high affinity (Fig. 1e).

The second major difference with other Fcγ receptors is related to the conformation of the lower hinge which connects IgG1-Fc and Fab. Because of the unique hydrophobic pocket described above, the orientation of the lower hinge of IgG1-Fc bound to hFcγRI changes with respect to all other receptors (Fig. 1f). The unique orientation of the lower hinge may influence how IgG is presented on the surface of immune cells, especially that of the Fab region responsible for recognizing antigens (Fig. 2). We propose that the geometry of the IgG-Fcγ receptor complex governs the engagement of antibodies with antigens and/or facilitates the clustering of receptors on the cell surface, thereby modulating the immune response.

In summary, we have determined the recognition mechanism between human IgG1 and the major immune receptor hFcγRI. This discovery of a high-affinity and potentially druggable pocket in hFcγRI not present in other Fcγ receptors may lead to novel therapeutic approaches to combat autoimmune diseases.

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