Insights from Fc receptor biology
A route to improved antibody reagents

Jenny M. Woof
Medical Research Institute; University of Dundee Medical School; Ninewells Hospital; Dundee, UK

Fc receptors and their interaction with antibodies will be a major theme at the forthcoming FASEB Science Research Conference on Immunoreceptors to be held in Snowmass this July (details available at www.faseb.org/src/home.aspx, follow the tabs for Immunoreceptors). Since its inception in the mid 1980s, this meeting series has maintained a focus on Fc receptors, and this year’s meeting will be no exception.

From a therapeutic viewpoint, there is much to be gained from a detailed understanding of the biology of effector molecules such as Fc receptors and complement. Indeed, knowledge of the interaction of IgG with such molecules has been central to the development of improved mAbs with altered functions and transformed half-lives, tailored for particular therapeutic applications. Examples include mAbs designed to maximize complement recruitment or to enhance Fc receptor engagement and triggering of ADCC, or conversely, variants engineered to be unable to engage complement or Fc receptors. Glycoengineering of IgG Fc offers an alternative means to modify effector function capabilities, while development of IgG mutants that display extended or altered serum half-lives has been driven through exhaustive analysis of the interaction with FcRn.

Remarkably, new receptors that have previously eluded characterization are now being described. These include the IgM receptor, which evidence indicates is a molecule also known as TOPO/Fas apoptotic inhibitory molecule 3 whose gene lies close to other known immunoglobulin receptors on chromosome 1, and a receptor for IgD recently documented on basophils. Moreover, we are seeing an appreciation of new roles for existing Fc receptors. An example is the demonstration in a transgenic study that human FcyRIIa can trigger active and passive anaphylaxis and airway inflammation. Moreover, human mast cells, monocytes and neutrophils were shown to produce anaphylactogenic mediators when FcyRIIA was engaged. Hence IgG may contribute to allergic and anaphylactic reactions in humans by engaging FcyRIIa.

Exciting new structural information on Fc receptors and their ligands is emerging. An important example is the solving of the X-ray crystal structure for human FcyRI. While the structural information supports a ligand binding mode similar to those of FcyRII or FcyRIII, the FG-loop in domain 2 of FcyRI with its conserved one-residue deletion appears critical for high affinity IgG binding. A second example concerns the high responder/low responder (HR/LR) polymorphisms of FcyRIIa, which are linked to susceptibility to infections, autoimmune diseases, and the efficacy of therapeutic Abs. New insights into these differences have been provided by the recent solving of the structure for the complex of the HR allele with IgG Fc. Third, understanding of the human IgE-FceRI interaction has moved forward significantly through the solving of the X-ray crystal structure of the complex of FceRI and the entire Fc region of IgE (comprising domains Ce2, Ce3 and Ce4). In a final example, the structural basis for the improved efficacy of nonfucosylated mAbs has been investigated. The X-ray crystal structure of the complex between nonfucosylated IgG Fc and a soluble form of FcyRIIIa carrying two N-linked glycans showed that one of two receptor glycans interacts with nonfucosylated Fc to stabilize the complex. It is proposed that when the Fc glycan is fucosylated this interaction is inhibited due to steric hindrance and, together with the negative effects of Fc fucosylation on the dynamics of the receptor binding site, this provides a rationale for the improved ADCC displayed by nonfucosylated IgG.

A question of interest is precisely how Fc receptors bound to antibody ligands organize themselves within signaling complexes in the cell membrane. Some intriguing clues to this conundrum of molecular architecture are now surfacing. In mast cells, FceRI molecules loaded with IgE form a synapse when presented with antigen that is mobile within a lipid bilayer, via coalescence into large cholesterol-rich

Correspondence to: Jenny M. Woof; Email: j.m.woof@dundee.ac.uk
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Interest in Fc receptors continues unabated, and the contribution that the field can make to mAb development and optimisation is unquestionable. The FASEB SRC on Immunoreceptors will serve as a forum for discourse on the above issues and much more, providing invaluable information and networking opportunities for all those interested in ways to maximize the efficacy of mAbs and mAb-based reagents. Registration is open until 24 June 2012.

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