Poster Presentations

[MS5-P38] Human IgE flips between two acutely bent structures *via* an ensemble of extended conformations Nyssa Drinkwater[1], Ben Cossins[2], Anthony H. Keeble[1], Michael Wright[2], James M. McDonnell[1], Andrew J. Beavil[1], Alistair J. Henry[2], Brian J. Sutton[1].

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Immunoglobulin E (IgE) antibodies mediate allergic reactions, and their binding to FcåRI is responsible for long-term sensitisation of mast cells and basophils [1]. Disruption of this interaction is a validated strategy for therapeutic intervention in allergic diseases including asthma [2]. IgE is known to display an acutely and asymmetrically bent conformation in the Fc region through which it binds to FcåRI; this bend becomes even more acute upon receptor engagement, as shown both crystallographically and in solution [3-7].

We report the crystal structure of a complex formed between IgE-Fc and two bound Fab fragments of a inhibitory anti-IgE antibody, and show that IgE-Fc can also adopt a totally extended conformation. The IgE-Fc has adopted a completely symmetrical conformation that requires an "unbending" of approximately 120° from the previously characterised structure. Molecular dynamics simulation reveals a series of stable conformations for free IgE-Fc that suggest a pathway from the acutely bent crystal structure through stable, extended conformations close to that seen in the Fab complex. We show by ITC, stopped-flow kinetic and FRET analyses that IgE-Fc adopts extended conformations in solution, and that these are an intrinsic property of IgE-Fc, not induced by Fab binding. We propose that IgE-Fc passes through these extended conformations as it flips between two bent conformations in which the CΣ2 domains fold back on opposite faces of the CΣ3-CΣ4 domains.

The ability of IgE to exist in both bent and extended conformations may be essential for allergen recognition by IgE-Fc when bound to FcΣRI on the surface of mast cells, and as the B cell receptor respectively. Understanding the full range of conformations accessible to the free IgE molecule is also key to developing IgE-targeted therapies for allergic disease.

Keywords: X-ray crystallography of immunoglobulins; Fab complex crystallization; conformational flexibility

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