Research on the IgE B cell receptor to suggest new strategies for intervention in asthma

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The risk of developing asthma is associated with the serum concentrations of IgE. IgE concentrations in human serum fall within the range of 10-1000 ng/ml, compared to 10 mg/ml for IgG. The mechanisms of regulation of the IgE B cell receptor (BCR) expression and signalling are unknown. Knowledge of these mechanisms would provide insight into the pathogenesis of asthma and suggest new strategies for therapy.

Our hypothesis is that the organization and behaviour of the IgE BCR (the membrane form of IgE) is vital in the regulation of IgE antibody production. As for the antibodies of other antibody classes (IgM, IgG, IgA), antigen/allergen binding to the IgE BCR stimulates allergen-specific B cells to proliferate and differentiate into plasma cells, which synthesize the secreted form of IgE. The secreted IgE is required for the sensitization of mast cells to allergen-induced activation and the symptoms of asthma. The membrane and secreted forms of IgE (mlgE and slgE) differ in the presence of a membrane anchor in mlgE, of which there are two types, designated mlgE “long” (mlgE_L) and mlgE “short” (mlgE_S). mlgE_L and mlgE_S differ in the length of the extra-membrane-proximal domain (EMPD). mlgE_L is unique to human IgE, while other antibody classes express only the homologous mlgE_S. The EMPD length, the unusual (bent) conformation of IgE, and sequence differences in the cytoplasmic tail from other antibody classes are undoubtedly important in signal transduction and antibody production.

While much is known about the IgM BCR, little is known about that of the IgE BCR. This has been difficult to study in vivo due to the low abundance of IgE-expressing B cells in vivo1,2. The supervisors’ combined expertise will facilitate the proposed research on the organization and behaviour of the IgE BCR upon allergen antigen stimulation making use of state of the art imaging techniques3. The tools would be B cells expressing recombinant mlgE_L and mlgE_S and for comparison mlgG and mlgA specific for the same grass pollen allergens engineered at KCL4,5. Recombinant grass pollen allergens will be inserted into planar lipid membranes in which they can freely diffuse and bind to the BCRs on the B cells. This will enable the imaging of single labelled antibody molecules by powerful new microscopic techniques, including fluorescence resonance energy transfer (FRET), photo-activated localization microscopy (PALM) and stochastic optical reconstruction microscopy (STORM), providing measurements of their motility and reorganization of single mlgE molecules in microclusters as a function of time after contact with allergen at nm resolution6.

We will also image directly IgE expressing human cells. We have the ability to quantify synaptic patterns, signalling and endocytosis in rare cells after we capture them on the bilayers, e.g. with anti-IgE or the allergen with the B cells from allergic individuals. We will compare IgE to IgG antibody expressing B cells. We can expect the BCRs of different antibody class to exhibit dramatically different behaviour reflecting how IgE expression is controlled in health and allergic disease.

Relevant references:
5. Inhibition of allergen-dependent IgE activity by antibodies of the same specificity9 but different class Dodev T, Bowen H, Shamji M, Bax H, Beavil A, McDonnell J, Durham S, Sutton B, Gould H, James L. Allergy, Feb 2015

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