

Editorial

Basophils and mast cells at the centre of the immunological response

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Basophils and mast cells are fascinating, multifunctional, tissue-dwelling cells that have been traditionally associated with the allergic response (1, 2). The aggregation of high-affinity IgE receptors (FcεRI) on mast cells and basophils has long been known as the critical event that initiates allergic reactions (3). Basophils and mast cells can be seen as the central players of the allergic response. The release of a wide collection of mediators (including histamine, tryptase, and chymase) after allergen-specific cross-linking of the FcεRI receptors on these cells initiates the cascade of exposure-related clinical symptoms we have come to associate with allergic disease. However, recent studies suggest these cells may be capable of regulating inflammation, host defense and innate immunity (4), contributing to the initiation, development, expression, and regulation of acquired immune responses, both those associated with IgE and those that are independent of this class of Ig (5).

Basophils have often stood in the shadow of their tissue-fixed mast cell counterparts which share some common features, such as high-affinity IgE receptor expression and the ability to release histamine. In addition to their role in allergic responses, basophils can be activated in non-sensitised individuals by parasitic antigens, plant lectins and viral superantigens (6).

Allergy has recently published interesting papers on mast cells and basophils (7–23), but in this month's issue of *Allergy* we have again placed the focus on basophils and mast cells.

Given that there is such a direct relationship between allergen exposure and release of mediators, it is perhaps not surprising that this aspect alone already has received particular attention in this research field. On one hand, this direct relationship opens a way for *in vitro* approaches to determine existing sensitisations safely. On the other hand understanding how this release is regulated may not only shed new light on the observation that in some sensitised individuals exposure to the allergen does not lead to clinical symptoms, but may ultimately also lead to the identification of new treatment options.

Two prime examples of the *in vitro* approach in aiding the diagnosis of disease are the articles of Kvedariene and Nopp in this issue. The results described by Kvedariene and co-workers show the application of the Basotest™ (Orpegen Pharma, Heidelberg, Germany) in assessing hypersensitivity reactions to neuromuscular blocking agents. The overall sensitivity of just 36% would not allow application of this method in screenings procedures. However, subgroup analysis shows that in those individuals with recent (< 3 years) episodes of anaesthesia-related hypersensitive reactions, this sensitivity increases to 86%. With a specificity of 93%, this would aid the identification of the inducing agent of the hypersensitivity reaction in situations where the patient is receiving several drugs simultaneously. Validation in the identified subgroup would help to establish this method as a safe procedure in a field where it has proven to be hard to find a reliable tool to determine hapten-related hypersensitivity reactions. The experiments of Nopp and co-workers have focused on potential relationships between levels of up-regulated CD63 on CD203c basophils and clinical signs. Interestingly, they were able to show a high level of correspondence between the concentration of allergen able to induce up-regulation of CD63 and the titre of allergen required for a nasal provocation. Moreover, the basophil sensitivity assay was far superior to the assay where the allergen concentration for maximal CD63 up-regulation is determined, although the reason for this discrepancy is unclear.

The manuscripts of Dahl and Wong try to understand the cell types at the transcriptional level. Dahl and co-workers used a micro-array approach to study changes to the transcriptomics of mast cells derived after prolonged culture of purified blood CD133+ cells in the presence of SCF, IL-6, and IL-3. They were able to show that these cells initially express tryptase with relative low levels of chymase, but that the chymase levels increase steadily over the course of the experiment. This suggests that previous observations of tryptase positive tissue mast cells occurring side by side with tryptase and chymase positive mast cells probably points to two differentiation stages of

the same cell type. Two clusters of transcripts that follow the expression profile of tryptase or chymase, support the concept of two differentiation stages. Wong and co-workers have focussed on the signalling cascades that are required for activation of mast cell line HMC-1 by SCF or TNF- α . As measure for activation they investigated the release of several mediators (IL-8, MCP1, RANTES, I309, MIP-1 β , IP10) in the presence or absence of specific inhibitors for the ERK, p38 MAPK, or NF- κ B pathway. A complex picture emerges. The ERK pathway is required for SCF-induced IL-8, MCP1, and I309, whereas these same mediators depend on p38 MAPK after TNF α induction. The ERK pathway is also required for the SCF-specific induction of MIP-1 β , whereas the TNF α -specific induction of IP10 depend both on p38 MAPK and NF- κ B. This understanding of the signalling cascade leading to mast cell activation will prove useful for the application of MAPK and NF- κ B-specific inhibitors in suppressing allergic inflammation.

Krauth et al. in the present issue have taken the role of inhibitors that target mast cells one step further. They investigated the role of statins in human mast cell activation and showed that two of these, cerivastatin and atorvastatin, not only inhibited the anti-IgE-induced release of histamine, but that they were also able to inhibit the SCF-induced differentiation of mast cells from precursors. Given their role in the inhibition of isoprenoids, the authors speculate that statins may affect lipid rafts that are known to be important for assembly of signalling complexes at the plasma membrane.

The manuscript by Jensen and co-workers has evaluated the possible involvement of the Fc ϵ RI receptor in the observation that some individuals with allergen-specific IgE do not show any symptoms after allergen exposure. They compared three groups: non-atopics, individuals allergic for grass or birch pollen, and a group that, although they are mono-sensitized for grass or birch, do not have any clinical symptoms. In partly purified basophils, cell surface levels of Fc ϵ RI and IgE, the sub-chain composition of the receptor complex, and the degree of anti-IgE mediated histamine release were determined. No overall differences were observed in receptor makeup, however receptor cross-linking in the asymptomatic group does reveal a lower propensity for histamine release.

The central role of basophils and mast cells in the allergic response has been well established. Within the recently launched and EU-funded Network of Excellence called GA²LEN (Global Allergy and Asthma European Network) (24) research will also include these cell types. The workpackage on 'early manifestations of IgE sensitisation' aims to understand why not all individuals with IgE directed against an allergen express symptoms related to exposure of the allergen. Special attention will be given to how basophils differ between groups with and without symptoms. This understanding may help us to 'convert' those with complaints to those without complaints. Not curing allergic disease, but by the suppression of symptoms, and vastly improving quality of life in those currently affect by allergic disease.

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