

EDITORIAL

Basophils unlimited

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Basophils are the rarest granulocytes, representing less than 1% of peripheral blood leukocytes. During the 130 years that has passed since they were first described by Paul Ehrlich, they have been one of the most enigmatic inflammatory cells and their precise biological roles are still unclear. With their expression of the high-affinity IgE receptor (FcεRI) and ability to release histamine upon IgE-mediated activation, basophils were long considered to be a distant, and possibly redundant, relative to tissue resident mast cells regarding promotion of allergic inflammation. During the last decade, however, new data have emerged, mainly from animal studies, pointing to previously unrecognized functions of basophils in health and diseases beyond allergy, such as autoimmunity and host defense [reviewed recently by Karasuyama et al. (1)]. These advances have been fostered by newly developed tools for *in vivo* functions of basophils in animal models using basophil-depleting antibodies and genetically engineered mice deficient only in basophils.

One difficulty in basophil research has been, because of their rarity, to obtain sufficient numbers of basophils to perform cell-based studies, for example, to investigate signaling pathways and functional responses, and for models to screen for drug targets. In contrast to *in vitro* differentiation of mast cells, which gives a good yield with high cell purities, there are no protocols that provide corresponding pure cultures of basophils derived from stem cells, especially from mice. One human basophilic-like cell line, KU812 (2), has been used for some studies, but it has several limitations including a variable cell surface expression of FcεRI and low degree of granulation (3). Because of this, *in vitro* studies on basophils have been largely limited to the costly and cumbersome isolation and purification of primary human basophils from whole blood or buffy coats. However, despite the value of data obtained from primary human basophils, given the recent advances in ascertaining the biological role of basophils in mice using *in vivo* models, there is a vital need for a technique that enables the generation of functional mouse basophils with a normal phenotype.

In the current issue of Allergy, Gurzeler et al. (4) describe the generation of 'near-unlimited' numbers of mouse basophils using a genetic approach where myeloid progenitors are immortalized with the transcription factor Hoxb8 in the presence of IL-3 and tamoxifen (4-OHT). The expression of Hoxb8 is under the control of 4-OHT, which means that Hoxb8 is expressed when 4-OHT is present and the progenitor cells expand. To differentiate the magnified progenitors into basophils, 4-OHT was omitted from the cultures, and basophils were differentiated in the presence of IL-3 only. These basophils displayed the currently accepted characteristics of

mouse basophils in that they expressed FcεRI, CD123, CD88, and CD11b but not Kit, CCR3, or Gr-1. More importantly, however, Gurzeler et al. comprehensively studied, for the first time, the ability of these cells to release histamine and leukotriene C4, as well as the archetypal Th2-type cytokines IL-4 and IL-13, to IgE-dependent and IgE-independent stimulation. These observations suggest that basic mediator release characteristics of these mouse basophils broadly resemble those of their human basophil counterparts (Fig. 1).

This technique now permits vital studies into the signal transduction and functional attributes of murine basophils, albeit under the caveat that genetic manipulation and *in vitro* culture may not fully represent the behavior of primary mouse basophils. However, given the impracticality of isolating sufficient numbers of these cells from mouse blood Gurzeler et al. have presented a highly useful tool in which to build on the findings obtained using *in vivo* models. Moreover, it will now be possible to study the functional properties of these cells side by side with primary human basophils which is vital in order to determine to what extent mouse basophils can truly be employed as a surrogate for primary human basophils in, for example, discovering new therapeutic targets for treating allergy and autoimmune diseases.

Although obtaining large number of mouse basophils is now possible, it is important to stress the potential heterogeneity that exists between these cells and their human counterparts (Fig. 1). Despite their apparent similarities in being able to release a number of pro-allergic mediators to IgE-dependent stimuli, there are some fundamental differences between mouse and human basophils which should not be overlooked (5). These include the effects of Fcγ receptors, which are stimulatory in mouse but inhibitory in human basophils. In agreement with Gurzeler et al. (4), mouse

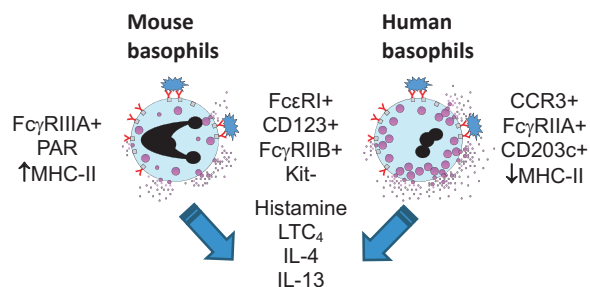


Figure 1 Overview of some of the similarities and differences in mouse and human basophils in terms of cell surface receptor expressions and function.

basophils have previously been reported as being CCR3 negative (6) which is in contrast to human basophils, where the high expression of this chemokine receptor has been demonstrated as a major human basophil marker (7). More importantly, however, are differences in the apparent role of basophils to act as antigen-presenting cells and initiators of Th2 immune responses. Here, mouse basophils have been shown to crucially affect early immunological events associated with antigen/allergen sensitization (8), but these have largely not been reciprocated in human basophils (9, 10). Whereas there is evidence to suggest that mouse basophils express protease-activated receptors, and subsequently respond to protease allergens, this is not the case in human basophils (11). Similarly, mouse basophils take up and process antigens more readily than human basophils, and recent reports indicate that human basophils are not likely to process antigens for presentation on MHC class II molecules (which are only weakly expressed in human basophils) (12). Overall, the current evidence points to potential differences in the ability of basophils to orchestrate early Th2 immune responses, but these cells from both mice and humans do appear to play an important role in exacerbating existing allergy (13).

Finally, Fc γ receptor expressions and functions may differ between mouse and human basophils, where stimulatory actions have been reported in the mouse (14) contrasting with the domination of inhibitory, mainly Fc γ RIIB receptors, in human basophils (15). However, in a rare case of direct comparison between mouse and human basophils, Cassard

and coworkers showed that both cell types actually express inhibitory Fc γ RIIB (16). These authors showed that the differences in cellular responses to IgG receptor triggering are due to the more robust responses of Fc γ RIIA, present on mouse basophils, than Fc γ RIIA on human basophils.

The above caveats should not detract from the possibility of now being able to obtain large numbers of mouse basophils, which is not only a valuable tool in itself but, in certain settings, may also even replace the need for obtaining primary human basophils. However, there is now a crucial need to continue to thoroughly characterize and contrast the biological functions of mouse and human basophils; studies which, in our opinion, are long overdue.

Authors' contributions

BG and GN both wrote this editorial.

Conflict of interest

The authors have no conflicts of interest regarding the publication of this article.

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