

EDITORIAL

Basophils and antigen presentation: of mice and not men?

DOI:10.1111/j.1398-9995.2012.02816.x

It is generally accepted that dendritic cells (DC) are the most potent antigen-presenting cells (APC) in our body in terms of their ability to stimulate naïve T cells. Moreover, in the process of antigen presentation, DCs not only present antigens to T cells (signal 1), with the help of costimulatory molecules (signal 2), but they also provide additional signals to T cells that facilitate their polarization (signal 3) and/or direct them to specific tissue sites by inducing homing molecules (signal 4) (1). In contrast to DCs, other APC, such as B cells and macrophages, are unable to stimulate naïve T cells. To be a functional APC, a specific cell should fulfil several capacities: antigen binding and uptake, antigen processing, loading the antigen onto MHC-II molecules and finally expressing the loaded MHC-II molecule on the plasma membrane together with costimulatory molecules. This implicates that the expression of MHC-II on the plasma membrane of a cell *per se* does not designate antigen-presenting properties. This is, for instance, an important point of debate on the IFN- γ -induced MHC-II expression on mast cells or keratinocytes.

Basophils are increasingly being recognized as immunologically active cells, in addition to their well-established role as inflammatory cells *via* IgE-induced degranulation. Basophils are a major source of pro-allergic cytokines, such as IL-4, and have been shown to be responsible for 72% of IL-4 protein-positive cells in the bronchial mucosa during allergen-induced asthmatic reactions (2). These cells also comprise the dominant IL-4-producing cell in bronchoalveolar lavage fluid following segmental lung challenge (3). Recently, it was shown that, in mouse models, basophils are not only important sources of IL-4 in the induction of an immune response, but they also appear to be able to present antigens (4). In this context, it was speculated that basophils could be vital inducers of any Th2 immune response. Whereas T cells need first to be stimulated by IL-4 to be able to develop into Th2 cells, basophils appear to be well placed to provide this early source of IL-4. The concept of basophils acting as IL-4-releasing APC has been under much discussion lately, both at the level of technical pitfalls, but also at the level of relevance of specific animal models (5). One of the possibilities is in mice that basophils and DCs co-operate in inducing Th2 responses, where basophils produce the necessary IL-4 and DCs present antigen (5, 6).

Translating these interesting basophil properties to humans has been of great interest. However, it is important to appreciate differences in the behaviour of mouse basophils to their human counterparts. Human basophils lack protease-activated receptor expression (PAR), and PAR ligands failed to induce activation of these cells (7). It is therefore question-

able whether PAR activators, such as papain, that have been used in many of the mouse models, are able to elicit basophil-mediated innate triggering that initiates a Th2 response. Another crucial difference is that human basophils cannot be activated through IgG receptors (8) (their functions are inhibited by IgG-mediated triggering *via* Fc γ RIIb receptors). Moreover, circulating basophils in mice has been characterized by their Fc ϵ RI and IL-4 expressions despite substantial differences in morphology to their human counterparts. Classical indicators of basophil function, such as histamine synthesis, granule storage and release, have not been addressed. These differences and lack of characterization have led to concerns regarding the identity of the mouse 'basophil' and highlight major pitfalls in extrapolating these animal models to human allergy (9).

Taking the above into account, there is an urgent need to obtain insights regarding potential antigen-presenting functions of human basophils. In this issue of allergy, Eckl-Dorna and colleagues compare the antigen-presenting properties of different human cell types including basophils (10). Here, basophils were not able to present the birch pollen allergen Bet v 1 to T lymphocytes, whereas a mixture of APC depleted of basophils did. This was observed for both healthy control basophils and basophils obtained from birch pollen allergic individuals. In addition, even IL-3-activated basophils remained unable to present antigen. Very recently, a group in the same institute demonstrated that basophils lacked the machinery to uptake, process and present Bet v 1, although a small increase of HLA-DR was seen after incubating the basophils with both IFN- γ and IL-3 (11). These two papers indicate that it is unlikely that human basophils can act as major APC. However, this is in contrast to recent data presented at the latest EAACI annual meeting where two groups showed that human basophils could present allergens or express MHC-II (12, 13). In addition, Charles and colleagues showed in their work on the role of basophils in antibody production in systemic lupus erythematosus (SLE) that basophils of patients with SLE expressed HLA-DR (14). This group makes a strong statement that blood basophils are not representative for tissue-dwelling basophils. It might be that technical details underlie these differences in human basophils, just as has been the case in the experimental procedures of mouse studies. Importantly, whereas the percentage and number of basophils in blood and tissue is low, there are also issues in the isolation and purification of basophils. This includes the selective loss of basophil subsets during purification, such as the selective loss of HLA-DR carrying basophils in the MACS system.

It is of great interest to further examine the properties of basophils to present antigen in different diseases in the context of their proven potent IL-4-releasing role. However, one should take into account that even in the case that basophils are found to present antigen to T cells, it is highly likely that their role will be a minor one when compared with professional antigen-presenting DCs.

Author's contribution

EK and BG both wrote this manuscript.

Conflict of interest

EK and BG declare no conflict of interest.

Edward F. Knol¹ and Bernhard F. Gibbs²

¹Department of Dermatology/Allergology,
University Medical Center Utrecht,
Utrecht, The Netherlands

²Medway School of Pharmacy,
University of Kent,
Chatham Maritime,
Kent, UK

E-mail: e.f.knol@umcutrecht.nl

References

1. Kalinski P. Dendritic cells in immunotherapy of established cancer: roles of signals 1, 2, 3 and 4. *Curr Opin Investig Drugs* 2009;**10**:526–535.
2. Nouri-Aria KT, Irani AM, Jacobson MR, O'Brien F, Varga EM, Till SJ et al. Basophil recruitment and IL-4 production during human allergen-induced late asthma. *J Allergy Clin Immunol* 2001;**108**:205–211.
3. Schroeder JT, Lichtenstein LM, Roche EM, Xiao H, Liu MC. IL-4 production by human basophils found in the lung following segmental allergen challenge. *J Allergy Clin Immunol* 2001;**107**:265–271.
4. Wynn TA. Basophils trump dendritic cells as APCs for T(H)2 responses. *Nat Immunol* 2009;**10**:679–681.
5. Hammad H, Plantinga M, Deswarte K, Pouliot P, Willart MA, Kool M et al. Inflammatory dendritic cells—not basophils—are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J Exp Med* 2010;**207**:2097–2111.
6. Tang H, Cao W, Kasturi SP, Ravindran R, Nakaya HI, Kundu K et al. The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. *Nat Immunol* 2010;**11**:608–617.
7. Falcone FH, Morroll S, Gibbs BF. Lack of protease activated receptor (PAR) expression in purified human basophils. *Inflamm Res* 2005;**54**(Suppl 1):S13–S14.
8. Bruhns P, Fremont S, Daeron M. Regulation of allergy by Fc receptors. *Curr Opin Immunol* 2005;**17**:662–669.
9. Lee JJ, McGarry MP. When is a mouse basophil not a basophil? *Blood* 2007;**109**:859–861.
10. Eckl-Dorna J, Ellinger A, Blatt K, Ghanim V, Steiner I, Pavelka M et al. Basophils are not the key antigen-presenting cells in allergic patients. *Allergy* 2012;**67**:601–608.
11. Kitzmuller C, Nagl B, Deifl S, Walterskirchen C, Jahn-Schmid B, Zlabinger GJ, Bohle B. Human blood basophils do not act as antigen-presenting cells for the major birch pollen allergen Bet v 1. *Allergy* 2012;**67**:593–600.
12. Lund G, Grauert G, Koed G, Skovsgaard J, Lund K, Wurtzen PA. Investigation of human basophils as antigen-presenting cells for established T-cell lines. *Allergy* 2011;**66**(S94):68.
13. Poulsen B, Blom L, Jensen B, Poulsen L. Human basophils do express major histocompatibility complex class II, but their role as antigen presenting cells is questionable. *Allergy* 2011;**66**(S94):120.
14. Charles N, Hardwick D, Daugas E, Illei GG, Rivera J. Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nat Med* 2010;**16**:701–707.