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Basophils trump dendritic cells as APCs for T_H2 responses

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Abstract

Dendritic cells are best known as antigen-presenting cells that initiate adaptive immune responses. Three new papers suggest that basophils initiate allergen- and helminth-driven $CD4^+$ T helper type 2 responses by functioning as antigen-presenting cells in draining lymph nodes.

Although the cellular and molecular mechanisms that regulate the development of T helper type 1 cell (T_H1 cell), interleukin 17 (IL-17)-producing T helper cell (T_H-17 cell) and regulatory T cell responses are fairly well understood, the specific cellular mediators and factors that control the initiation of T_H2 responses are still highly debated. Although it is certain that dendritic cells (DCs), pattern-recognition receptors and cytokines secreted by DCs are key in the initiation and expansion of most effector and regulatory T cell classes, the relative importance of activated DCs and Toll-like receptor signaling in the development of T_H2 effector responses is less clear. In this issue of *Nature Immunology*, three papers demonstrate that DCs are not required for the generation of $CD4^+$ T_H2 responses to protease allergens[1], helminthic parasites[2] or antigen-immunoglobulin E (IgE) complexes *in vivo*[3]. Instead, all three groups identify the major histocompatibility complex (MHC) class II-positive IL-4-producing basophil as the 'professional' antigen-presenting cell (APC) that is both necessary and sufficient for the generation of type 2 immunity.

Studies have suggested that DCs adopt a fairly limited activation profile when exposed to T_H2-inducing allergens and helminths[4]. They also fail to produce IL-4, the key driver of $CD4^+$ T_H2 cell responses. Therefore, attention has focused on identifying the accessory cells that provide the early innate source of IL-4 and soluble mediators that 'instruct' DC-mediated T_H2 differentiation. Proposed sources of IL-4 have included eosinophils, mast cells, basophils and natural killer T cells, as well as autocrine IL-4 from $CD4^+$ T cells[5-8]. Additional cytokine cofactors have also been identified, including IL-21, IL-25, IL-33 and thymic stromal lymphopoietin, which invariably augment development of T_H2 responses by modulating the activation status of DCs and other APCs[9-12]. The long-standing view of T_H2 differentiation has revolved around this basic theory, which suggests $CD4^+$ T_H2 cell development is driven by DCs that present antigen in the context of MHC class II and by extrinsic cellular and secreted factors that modify DC maturation and provide an early source of IL-4 (refs. [13,14]).

Sokol and colleagues investigate the mechanisms that regulate the development of T_H2 responses after exposure to papain, a cysteine protease hydrolase enzyme from papaya that breaks down complex proteins and thus mimics the activity of proteases secreted by many T_H2-promoting helminth parasites. Although basophils are found mainly in the blood and peripheral tissues, they are rapidly recruited to the lymph nodes during a primary response to papain and in response to the soluble antigens of *Schistosoma mansoni* eggs[15]. Once in the

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lymph nodes, the basophils secrete IL-4 and thymic stromal lymphopoietin, and depletion studies suggest that basophils are critically involved in the generation of antigen-specific T_H2 responses. The conclusion reached was that basophils function as accessory cells for DC-mediated T_H2 differentiation because DCs are also rapidly recruited to the lymph nodes. Nevertheless, the specific identify of the APC population was unclear in those studies[15]. In the manuscript presented here, Sokol and colleagues show that, unexpectedly, DCs are in fact not required for the development of papain-induced T_H2 responses[1]. Although papain-primed DCs initiate the development of T_H2 responses *in vivo*, they are not able to induce $CD4^+$ T_H2 cells *in vitro* unless basophils are included in the culture. Surprisingly, these authors discover that DCs are not even necessary, as basophils alone support the robust proliferation of naive T cells. Thus, unlike the *in vitro* generation of T_H1 and T_H-17 responses, for which DCs, antigen and Toll-like receptor signals are sufficient, T_H2 responses exploit a distinct basophil-dependent but DC-independent mechanism. These findings are unexpected, as basophils have been thought to be MHC class II negative; however, these authors show very convincingly that some activated basophils express MHC class II. Basophils also have the molecular 'machinery' required to function as APCs, as shown by *in vitro* MHC class II-blocking studies. The T_H2 cells generated are also papain specific. These findings collectively provide evidence that basophils can function as professional APCs, at least for the generation of T_H2 responses *in vitro*.

During the *in vivo* generation of T_H1 or T_H-17 responses, DCs encounter pathogens in peripheral tissues, where they sample foreign antigens, become activated and then migrate to the lymph nodes, where they present antigen in the context of MHC class II to naive T cells (Fig. 1). Sokol *et al.* seek to determine whether basophils use a similar mechanism to initiate T_H2 responses or require DCs to escort papain into the draining lymph node, where antigen encounter occurs[1]. To answer these questions, they design a clever set of experiments in which they inject papain into the ear pinna of mice and then excise the ear at either 2 h or 24 h after injection. If DCs are needed to capture and deliver antigen to lymph nodes, rapid excision of the injection site would ablate the development of the T_H2 response in the draining lymph node. Interestingly, they find no difference in T_H2 development at 2 h and 24 h, which suggests that migratory DCs are not involved and that soluble proteins such as papain are being delivered directly to the lymph node. They also show that basophils can endocytose, process and present soluble antigens, but unlike DCs, they are not good at processing particulate antigens. They hypothesize that because most T_H2-inducing antigens from helminth parasites are excretory or secretory proteins, this mechanism would be ideally suited for the generation of T_H2 responses to large extracellular eukaryotic pathogens. In support of that hypothesis, Perrigoue *et al.* show that MHC class II-positive DCs are not required for the generation of protective $CD4^+$ T_H2 cell-dependent immunity to the gastrointestinal nematode parasite *Trichuris muris*[2]. Similar to the studies by Sokol and colleagues[1], the results of Perrigoue *et al.* show that IL-4-producing basophils are MHC class II positive and can promote the MHC class II-dependent differentiation of antigen-specific $CD4^+$ T_H2 cells *in vitro*[2]. More importantly, depletion of basophils *in vivo* with a monoclonal antibody (Mar-1) specific for the receptor FcεRI considerably impairs immunity to *T. muris*, which suggests that basophils facilitate the development of protective T_H2 immunity, thus extending the findings of Sokol *et al.* regarding papain to a complex T_H2-promoting pathogen.

Basophils isolated from the spleens of mice infected with the intestinal nematode *Strongyloides venezuelensis* are also MHC class II positive, as shown by Yoshimoto *et al.*[3]. Splenic basophils from infected mice also secrete IL-4 and, in agreement with the other two studies[1,2], these cells are able to induce the development of antigen-specific T_H2 cells *in vitro* in the absence of DCs[3]. Yoshimoto *et al.*[3] show that IL-4-deficient basophils are not functional, demonstrating that the production of IL-4 by MHC class II-positive basophils is critical for T_H2 differentiation. Interestingly, basophils from naive mice have the same T_H2-inducing ability, so IgE-primed

basophils do not seem to be important. Nevertheless, enhanced T_H2 responses result when antigen-IgE complexes are included in the culture, which suggests that antigen-specific IgE augments the development of antigen-specific T_H2 responses, perhaps by facilitating antigen uptake. Yoshimoto *et al.*[3] also discover that basophils express the lymph node-homing receptor CD62L, which indicates that basophils have the necessary 'machinery' to enter secondary lymphoid tissues where T_H2 responses are initiated. Perhaps most importantly, however, they determine that IL-3 can induce HLA-DR expression on a subset of human basophils. Thus, these important findings may not be restricted to the mouse.

Although all three groups show that MHC class II-positive basophils can initiate T_H2 differentiation *in vitro* in the absence of other professional APCs, it is important to confirm this mechanism *in vivo*. To do this, all three groups use similar and complimentary approaches to rule out the possibility that DCs are involved. Sokol *et al.*[1] and Perrigoue *et al.*[2] both use the CD11c-diphtheria toxin receptor mouse model in which delivery of diphtheria toxin effectively depletes the mice of all CD11c-expressing cells[16]. Sokol *et al.* show that although depletion of DCs blocks T_H1 differentiation, it has no effect on papain induced T_H2 responses[1]. Similarly, Perrigoue *et al.* find that these mice do not have diminished development of protective T_H2 immunity after *T. muris* infection[2]. Both groups also take the opposite approach by restricting MHC class II expression to DCs[17]. Here again, although MHC class II-positive DCs are adequate for the development of T_H1 responses, they are not sufficient for the development of T_H2 responses *in vivo*. Although IL-4 producing basophils are recruited to the lymph nodes in these studies, expression of MHC class II on basophils seems to be critical for the development of the T_H2 response. Notably, however, when the mice in which MHC class II expression is restricted to DCs are infected with *T. muris* and treated with a neutralizing monoclonal antibody to interferon-γ, the production of T_H2 cytokines is restored, which suggests that MHC class II-positive DCs can induce protective T_H2 responses if the counter-regulatory T_H1 response is blocked[2]. Thus, it seems that basophils are not strictly required for the initiation of T_H2 responses. Instead, they promote T_H2 differentiation by blocking DC-induced T_H1 responses, at least during the development of *T. muris*-induced T_H2 responses. Finally, basophil adoptive-transfer studies presented by both Sokol *et al.*[1] and Yoshimoto *et al.*[3] confirm that MHC class II-positive basophils are sufficient for the initiation of T_H2 immunity *in vivo*.

Although the combined results from all three papers convincingly show that basophils can function as professional APCs and trigger T_H2 differentiation both *in vitro* and *in vivo*, studies over the past 15-20 years suggest that a variety of mediators, cell types and mechanisms are involved in the development of polarized $CD4^+$ T_H2 cell responses. Consequently, it will be necessary to determine whether all antigen-specific T_H2 responses are initiated by this basophil-dependent mechanism or whether specific DC subsets or other APC populations trump basophils in some circumstances. In the studies presented here, basophils trump DCs because in addition to functioning as professional APCs, they also produce the key T_H2-differentiating cytokine IL-4. Future studies will need to determine whether IL-4-producing, MHC class II-positive basophils are required simply for the initiation of T_H2 responses or whether they are also critical in the maintenance of chronic T_H2 responses. This information will be particularly useful because it might indicate whether targeting basophils would be beneficial in the treatment of persistent T_H2-mediated diseases such as allergy and asthma. It would also be helpful to understand how basophils recognize specific allergens, proteases and parasite products and how these mediators trigger IL-4 production. Intravital imaging of basophil-T cell interactions in the lymph node in real time, as has been done with DCs, may also show how and when basophils are recruited to the draining lymph node during the initiation of an antigen-specific immune response. In conclusion, although the enigmatic basophil has been widely ignored by immunologists, the discovery that they can function as professional

APCs will probably create a flurry of interest and lead to new and exciting findings about their function in the regulation of disease.

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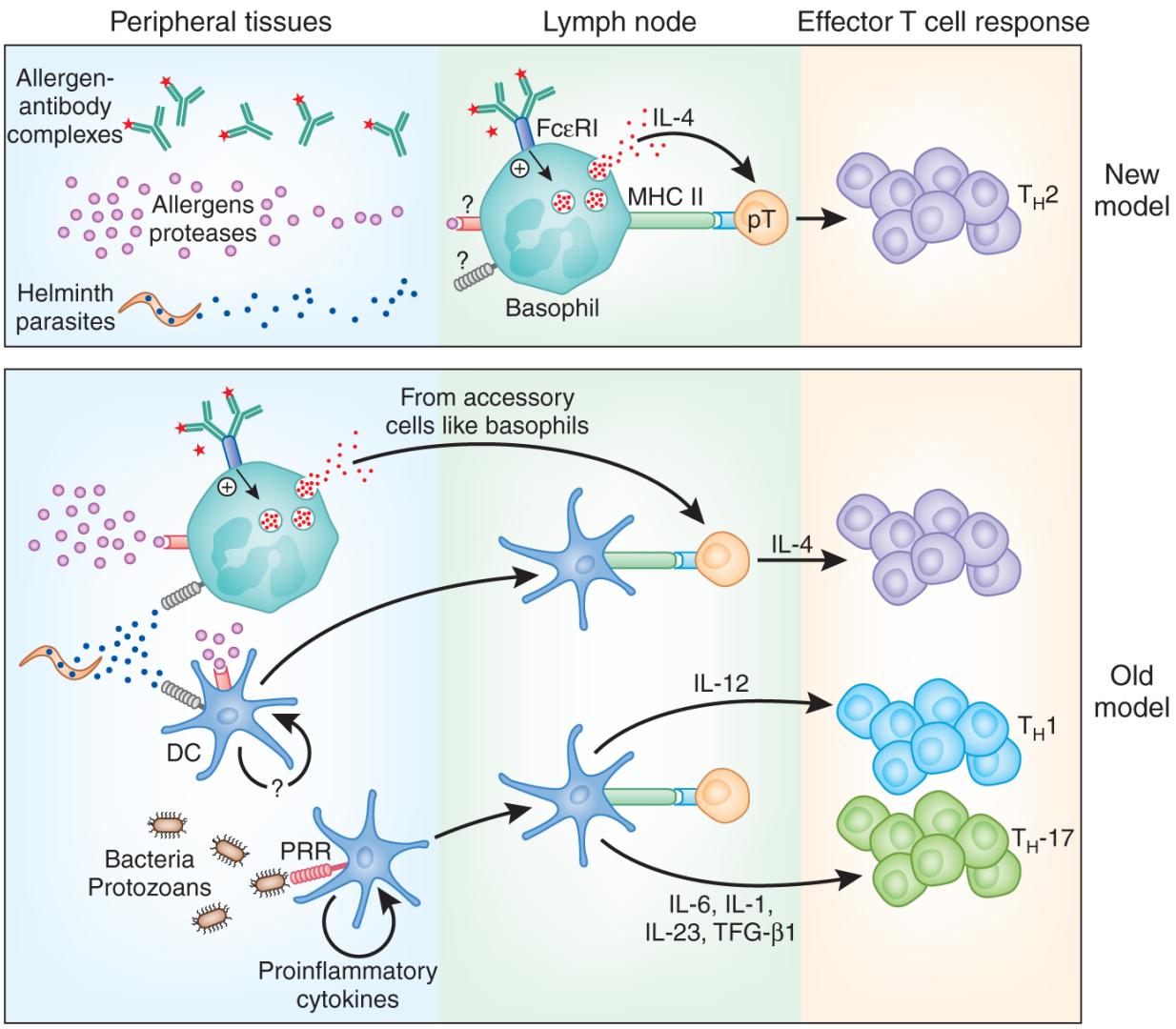

Figure 1.

A new paradigm for the initiation of type 2 immunity. In the present model (bottom), DCs serve as the main professional APCs for the development of antigen-specific $CD4^+$ T cell responses. During the development of T_H1 and T_H-17 responses, DCs are activated in the periphery by various pattern-recognition receptors (PRR) and migrate to the draining lymph nodes, where they present antigen to naive T cells in the context of MHC class II (MHC II). This 'DC_1' population secretes specific cytokines, such as IL-12, that 'instruct' $CD4^+$ T_H1 responses or cytokines such as IL-1, IL-6 and IL-23, which participate in the differentiation of T_H-17 cells. In contrast to T_H1- and T_H-17-promoting antigens, T_H2-inducing allergens, antigen-IgE immune complexes and helminth-derived secreted proteins activate an alternative APC-designated 'DC_2' that requires an exogenous source of IL-4 to direct T_H2 development. In the revised model (top), DCs are not required for the development of antigen-specific T_H2 cell responses, because basophils can function as professional APCs. In contrast to the 'DC_2' population, basophils also produce IL-4 when stimulated by T_H2-inducing antigens in the draining lymph nodes. Consequently, accessory cells are no longer required for the initiation of T_H2 responses in this model. TGF, transforming growth factor.