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REVIEW ARTICLE

Basophils: A Potential Liaison between Innate and Adaptive Immunity

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ABSTRACT

Activation of innate immunity is closely associated to development of protective adaptive immune response. Significant advances have been made to reveal such links between innate immunity and Th1 type adaptive immune responses. By contrast, the role of innate immunity in the development of Th2 type adaptive immune responses is still not well understood. Production of IL-4, a key cytokine in the induction of Th2 immunity, by innate type cells represents an attractive mechanism for such an innate link to Th2 immunity. We have recently reported that in the course of infection with the intestinal nematode, *Nippostrongylus brasiliensis*, a robust basophil accumulation in the liver/spleen occurs and that these basophils display enhanced IL-4 production. Thus, the basophils is an attractive candidate to mediate the innate-adaptive link for Th2 responses and understanding the control of the tissue homing patterns and cytokine responses of basophils in the course of infections may shed important light on the *in vivo* induction of Th2 adaptive immunity.

KEY WORDS

adaptive immunity, basophils, IL-4, innate immunity, parasites

INTRODUCTION

There are increasing evidences that the components of innate immune system play important roles in guiding the development of adaptive immunity. Bacterial and viral infections activate innate immune components via interaction with series of receptors, such as the Toll-like receptors (TLRs) and members of the NOD family.[1] Interactions with TLRs may result in dendritic cell activation/maturation and the subsequent production of modulatory cytokines such as IL-12 and IFNα, which then appear to favor the development of Th1-type immune responses. Importantly, mice deficient in key TLRs or key components of the TLR signaling pathways have a severe defect in mounting adaptive Th1 type immune responses.[2] By contrast, the nature of the link between innate immunity and Th2 type immune responses is much less clear.[3] An attractive candidate to mediate such a link is IL-4, a key cytokine responsible for the *in vitro* generation of Th2 type effector cells. *In vivo*, IL-4 can be produced by several types of cells that participate in the innate immune response, including NKT cells, basophils, eosinophils, and mast cells. Recent observations on the dynamics of basophils and on their enhanced IL-4-production during helminth infections suggests that should be given serious consideration as innate regulators of Th2 induction.[4]

Basophils are the least common of the blood granulocytes; they are generated and mature in the bone marrow, and circulate in the periphery as fully differentiated forms. They have been implicated as major effector cells during parasitic infection and allergic inflammation.[5-7] Until recently, the lack of clear phenotypic markers and the absence of proper animal models have been practical obstacles to further understand their *in vivo* roles in the immunity. Recently, we have reported that basophils are a major source of IL-4 during *Nippostrongylus brasiliensis* infection, confirming earlier work from our group. In this review, we discuss the activation of basophils and their potential role in the development of adaptive immune responses.

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ACTIVATION OF BASOPHILS: REQUIREMENTS OF INNATE AND ADAPTIVE COMPONENTS

We have previously reported that splenic non-B non-T (NBNT) cells produce IL-4 in response to FcR cross-linkage.[8,9] Following infection by *N. brasiliensis* or treatment with goat anti-IgD antibody, both of which induce a strong Th2/IgE response, there are increased numbers of splenic NBNT cells and enhanced IL-4 producing capacity by these cells.[10] Subsequently, these IL-4-producing splenic NBNT cells were identified as basophils by electron microscopic analysis.[11] Coculture or *in vivo* treatment with IL-3 enhanced IL-4 production by basophils in response to FcR cross-linkage.[9] It was further shown that IL-3 primarily produced by activated CD4 T cells induced production of IL-4 by splenic NBNT cells during *Schistosoma mansoni* infection,[12] presumably amplifying the vigorous Th2 type immune response that occurs in the course of this infection. Treatment with IL-3 resulted in enhanced IL-4 production by splenic T cells from mice that had been infected with *Trichinella spiralis*,[13] implying that IL-3-mediated basophil activation might be an important mechanism through which Th2 dominance is established in immune responses to helminths. Indeed, we have recently reported that IL-4 producing cells accumulated in the liver in the course of *N. brasiliensis* infection.[4] Electron microscopic analysis has confirmed their identity as basophils, supporting earlier observations on cells classified as splenic NBNT cells. The accumulation of basophils during *N. brasiliensis* infection is also associated with the enhanced IL-4 production by basophils (on a per cell basis). An important issue that requires resolution is the nature of the stimuli that result in basophil IL-4 production during *N. brasiliensis* infection.

IMMUNE COMPLEXES

Basophils express high levels of FcεRI and cross-linkage of FcεRI or of FcγRII/RIII induces both mediator release from, and IL-4 production by, basophils. The probable importance of antigen-antibody complex-mediated basophil activation is further implied by the strong association of immune responses in which basophil activation occurs with the development of robust IgE responses. The molecular mechanisms underlying IgE/FcεRI mediated activation have been extensively studied in mast cells. Cross-linkage of FcεRI leads to the activation of multiple signaling molecules, including PLCγ, PI3K, MAPK, and PKC, all of which regulate cytokine/chemokine production and mediator release.[14,15] Whether the pathway that operates within the basophils is different from that of mast cells needs further investigation. Addition of IL-3 enhances production of IL-4 and mediator release by basophils, suggesting synergy between the FcεRI-mediated pathway and the IL-3 mediated pathway.[9] However, in certain circumstances, basophil activation occurs in the absence of immunoglobulins, such as in mice that lack B cells and antibodies, indicating that immunoglobulin-independent activation of basophils is also operative *in vivo*.

INTERLEUKIN-3

IL-3 and GM-CSF play essential roles in the differentiation and survival of several myeloid lineages, including basophils, eosinophils, and mast cells. Culture of bone marrow cells with IL-3 promotes the differentiation of bone marrow progenitors into basophils as well as mast cells.[16] Paradoxically, the development of basophils is not impaired in mice deficient in IL-3, although the enhanced production of basophils that occurs upon parasitic infection appeared to be compromised in the absence of IL-3.[17] IL-3 is well known for its capacity to prime basophils for increased production of cytokines and mediators in response to both immune complex-dependent and immune complex-independent activation. IL-3 synergizes with IL-18 in immune complex-independent induction IL-4 production from bone marrow-derived basophils.[16] IL-3 also enhanced immune complex-independent mediator release from basophils stimulated with C5a.[18] The underlying molecular mechanism of IL-3-mediated basophil priming is not well understood. Recent studies have shown that IL-3 enhances MEK/ERK activation in anti-IgE stimulated basophils.[14] IL-3 treatment also induces the activation of JAK2, STAT5 and PLA2 in these cells.[15]

In addition to modulating signaling activities that lead to cytokine production, IL-3 also enhances transendothelial migration of basophils.[19]

CD4 T CELLS

CD4 T cells play a major role in basophil responses in helminthic infections. Infection of immunodeficient Rag2−/− mice with *N. brasiliensis* fails to result in enhanced numbers of basophils or in their enhanced capacity to produce IL-4.[4] Transfer of CD4 T cells into Rag2−/− recipients at the time of infection restored both accumulation of basophils and the increase in their capacity to secrete IL-4 upon stimulation. Furthermore, the transferred T cells need to be capable of mounting an immune response; CD4 T cells from mice transgenic for TCRα and β chains coding for a receptor for a cytochrome C peptide failed to equip Rag2−/− recipients with the capacity to develop helminth-stimulated basophil activation and IL-4 production.[4] This process does not depend on IL-4 production by the CD4 T cells, since CD4 T cells from IL-4−/− donors are fully effective in restoring basophil accumulation and secretion of IL-4 by basophils.[4] As previously reported, IL-3 derived from activated T cells may be the important factor for the IL-4 production from splenic NBNT cells during *Schistosoma*

mansoni infection.[12] These results suggest that antigen-mediated activation of CD4 T cells during helminthic infection leads to the production of the IL-3 that might be necessary for the basophil activation. Nevertheless, *in vivo* neutralization of IL-3 in the course of *N. brasiliensis* infection only partially inhibited the accumulation of basophils in the liver and their subsequent IL-4 production.[4] Among other cytokines that need study *in vivo* are IL-18, which, through its synergy with IL-3, could allow low concentrations for IL-3 to be effective. In addition, IL-9 is known to have important effects in mast cell development and should be studied as a possible T cell derived factor important in basophil responses.[20]

Interestingly, it does appear that Th2 type immunity is needed for the CD4 T cell effect. Infection with *Toxoplasma gondii*, which induces a potent Th1 response, fails to lead to accumulation of basophils or enhanced IL-4-production by these cells.[4] In general, Th1 cells do produce IL-3, although in most cases less that produced by Th2 cells. Further efforts should be made to identify T cell derived factors critical for the basophil activation.

OTHER INNATE TYPE STIMULI

Basophils obtained from peripheral blood express TLR2 and TLR4, as determined both by PCR and flow cytometry.[21] Human basophils secrete IL-4 and IL-13 in response to peptidoglycan, a TLR2 ligand but not to LPS, a TLR4 ligand.[21,22] Similarly, TLR ligands enhance the production of cytokines and mediators when basophils are stimulated through IgE-dependent or independent pathway.[22] Basophils were also shown to produce IL-4 following stimulation with *Schistosoma* egg antigens.[23] Antigens derived from *Helicobacter pylori* and urokinase were shown to activate basophils through N-formyl-peptide receptor-like (FPRL) 1 & 2 and induce chemotaxis of basophils.[24,25] The HIV glycoprotein gp120 binds to H chain of surface IgE, resulting in induction of cytokine production from basophils.[26] Complement 5a (C5a) is another IgE-independent stimulus capable of activating human basophils to produce cytokines and mediators.[27,28] Taken together, basophils may well be activated by parasitic, bacterial or viral-associated products through activation of innate type machinery.

ACTIVATION MECHANISM OF BASOPHILS DURING *N. BRASILIENSIS* INFECTION

Which of these mechanisms are responsible for basophil activation during *N. brasiliensis* infection? Apparently, CD4 T cells play an important role in activating basophils in part via production of IL-3 as neutralization of IL-3 partially diminished both accumulation and IL-4 production by basophils.[4] While basophil responses seem to be restricted to Th2 type immunity, IL-3 is produced by most activated T cells. Therefore, production of IL-3 by itself is inadequate for basophil activation or inhibitors are induced during Th1 responses. It is possible that "innate-type" signals derived from *N. brasililensis* are needed to induce basophil activation. However, whether they operate through TLRs or other receptors described above needs to be determined. It was previously demonstrated that an extract of *N. brasiliensis* stimulates IgE and IgG1 production by inducing *de novo* isotype switching and the production of IL-4/IL-13.[29] Moreover, injection of *N. brasiliensis* extract together with protein antigens was shown to act as adjuvant and to induce development of antigen specific Th2 immune response.[30-32] Although it is not well understood how such immune differentiation by *N. brasiliensis* extract is achieved, it is possible that the activation of TLRs or other innate type receptors expressed on the basophils might be involved in this process.

MIGRATION OF BASOPHILS IN VIVO

Another interesting feature of *N. brasiliensis*-mediated basophil responses is their pattern of accumulation. Basophils are found primarly in the liver, lung, and spleen in this infection. They also can be found in the circulating blood. Interestingly, basophils are completely excluded from the lymph nodes, including draining, non-draining lymph nodes and the Peyer's patches.[4] These results suggest that their migration and/or accumulation during *N. brasiliensis* infection might be driven by chemokine/chemokine receptor interaction.

Chemokine receptors expressed on the basophils include CCR1, CCR2, CCR3, CXCR1, CXCR3, and CXCR4.[33] Microarray analysis of basophils isolated from lung of *N. brasiliensis*-infected mice showed that CCR2 is the major chemokine receptor that is highly expressed on the basophils but not on other granulocytes.[34] Is CCR2 responsible for the basophil recruitment into the lung and liver? CCL2 (also known as Monocyte Chemotactic Protein-1, MCP-1), a ligand for CCR2, has been implicated as a chemoattractant for leukocytes, including macrophages, during inflammatory disorders of the lung and in liver injury.[35,36] The level of CCL2 expression seems correlated with the progress of inflammation or injury within these organs. Further study should address the role of chemokines in the recruitment of basophils during parasite infection.

In addition, chemokines could modulate functions of certain cell types. CCL2 has been reported to enhance Th2 polarization. Mice deficient in CCL2 were unable to mount Th2 type immune response.[37] CCL2 also can stimulate mediator release from the basophils.[38] Similarly, eotaxin enhances immunoglobulin-dependent IL-4 production from the basophils.[39] It is not yet clear whether there are separate mechanisms that are responsible for the *in vivo* accumulation of the basophils and for the activation of cytokine production. It is possible that the chemokine expression

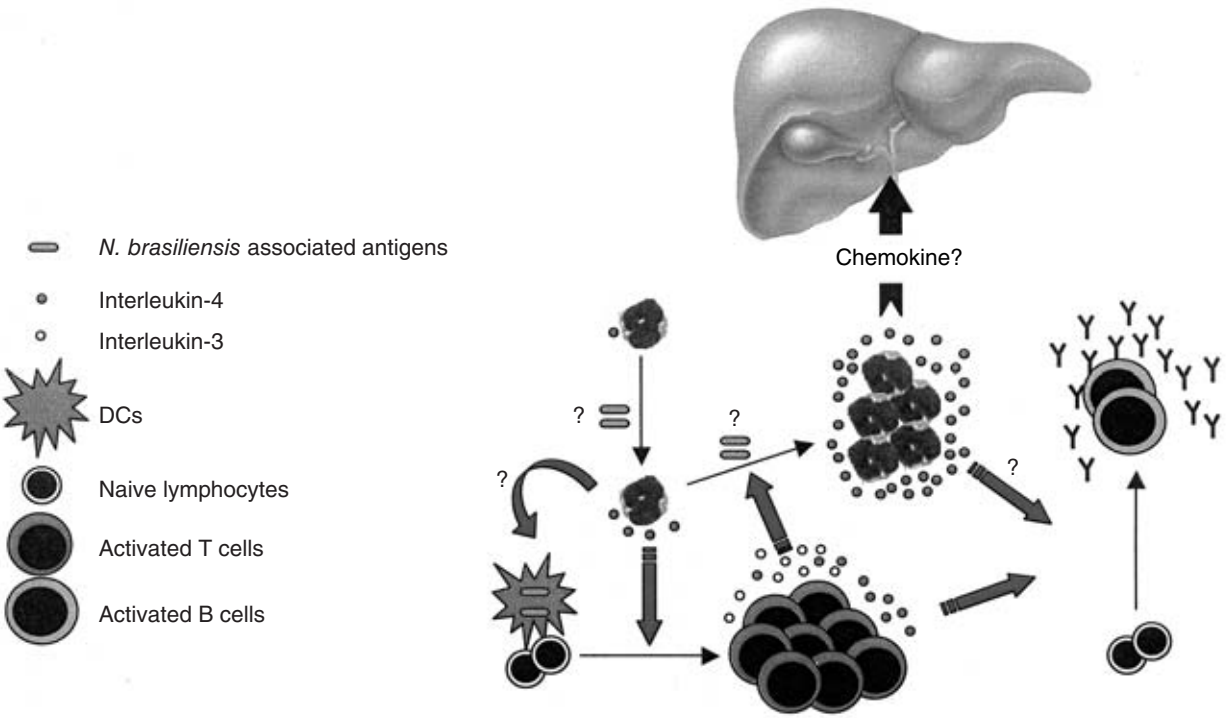

Fig. 1 Proposed model of basophil response during *N. brasiliensis* infection

during the course of infection might recruit basophils into the organs, where they might encounter second signals that induce cytokine and mediator release.

IMMUNOREGULATORY ROLE OF BASOPHILS

Activated basophils produce multiple factors, including mediators and cytokines in addition to IL-4 and IL-13. Studies using mature basophils obtained from bone marrow culture have shown that the basophils spontaneously express transcripts for IL-4, and produce functional IL-4 protein upon stimulation.[40] Activation-induced IL-4 production by basophils is a rapid process so that some IL-4 production can be detected within a few minutes after stimulation.[41] It was recently reported that 20–30% of IL-4 production was observed after transcription inhibitor treatment, and low level of IL-4 production was still found after treatment of cycloheximide, implying that a portion of the IL-4 producing capacity of basophils may represent translation of preformed mRNA.[40] It was shown that the level of IL-4 production by basophils per cell basis appears to be enhanced following *N. brasiliensis* infection. It remains to be determined whether such augmentation of IL-4 production is mediated by direct recognition of parasite-associated antigens or by T cell derived factors.

Several lines of evidences suggest that the basophils exert immunoregulatory functions.[42] It has been reported that basophils are the major IL-4 producing cells during filarial infection,[43] *N. brasiliensis* infection,[4] anti-IgD-induced memory T cell response[44] and even in secondary antibody responses.[45] The total amount of IL-4 produced by basophils may exceed that produced by Th2 CD4 T cells. Such rapid and abundant IL-4 production by basophils strongly suggests the possibility that the basophils might be the critical immune components that may influence the development of Th2 type adaptive immune response. Consistent with this idea, it has been shown that basophils from healthy individuals produce IL-4 upon stimulation with *Schistosoma* egg antigen, indicating that basophils may represent an early source of IL-4 that may subsequently promote Th2 immune response following *Schistosoma* infection. Basophils have been reported to induce B cell isotype switching *in vitro*. It was demonstrated that human basophils but not mast cells induce IgE synthesis by B cells *in vitro*.[46,47] Importantly, basophil-mediated IgE production was abrogated by anti-IL-4 antibody or by blocking CD40L-CD40 interaction, indicating that basophils could activate B cells and induce IgE isotype switching via an IL-4 and CD40L-dependent mechanism.[47]

It was recently demonstrated that the spontaneous development of Th2 type immune response found in IRF2-deficient mice may be due to the increase in basophils found in these mice.[48] Indeed, when transgenic T cells were stimulated with antigen plus T-depleted splenocytes from IRF2-deficient mice, the

transgenic T cells produced IL-4, while same T cells stimulated with wild type splenocytes preferentially produced IFNγ. Therefore, a situation in which basophil number is increased may favor Th2 type immune responses.

PROPOSED MODEL FOR BASOPHIL ACTIVATION AND SUBSEQUENT IMMUNE MODULATION

Will such basophil-mediated immune modulation occur *in vivo*? If so, is induction of basophil response a key component for the parasite-mediated Th2 type immunity? As illustrated in Figure 1, we propose a key regulatory pathway operating between basophils and CD4 T cells. Following infection with *N. brasiliensis*, parasite-associated antigens may directly bind to the receptors expressed on the basophils to trigger cytokine production. It is also possible that the generation of basophils from the bone marrow progenitors may be enhanced by such parasite-associated antigens. Activated basophils may then provide an early source of IL-4 (or of other Th2-promoting factor(s)) so that the activation of parasite antigen specific CD4 T cells occurs in an environment which favors the generation of Th2 phenotype cells. Basophils may also migrate to the spleen (but not lymph nodes) where T cell priming might occur and promote Th2 differentiation. It remains to be defined whether basophils modulate the function of antigen presenting cells during this process, or alternatively, whether parasite derived products may directly modulate dendritic cell function.[49] The resulting Th2 CD4 T cells may then provide help for the basophil activation in part via IL-3. The nature of T cell-derived help needs further investigation. However, it is possible that T cell-derived signal may promote the generation of basophils from the bone marrow. The induction of Th2 CD4 T cell responses and basophil activation might then directly affect B cell isotype switching by providing the proper cytokines and cell-to-cell interaction through CD40-CD40L interaction. The relative contribution of CD4 T cells and basophils for IgE response remains to be tested. If basophils do contribute to B cell isotype switching *in vivo*, then it will be interesting to test the underlying cellular mechanism by which this is achieved. It is likely that basophils may directly migrate to the area where B cell activation occurs. We are currently investigating this issue.

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