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How are T_H2-type immune responses initiated and amplified?

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Abstract

CD4$^+$ T helper (T_H) cells have crucial roles in orchestrating adaptive immune responses. T_H2 cells control immunity to extracellular parasites and all forms of allergic inflammatory responses. Although we understand the initiation of the T_H2-type response in tissue culture in great detail, much less is known about T_H2 cell induction *in vivo*. Here we discuss the involvement of allergen- and parasite product-mediated activation of epithelial cells, basophils and dendritic cells and the functions of the cytokines interleukin-4 (IL-4), IL-25, IL-33 and thymic stromal lymphopoietin in the initiation and amplification of T_H2-type immune responses *in vivo*.

CD4$^+$ T cells are crucially involved in adaptive immune responses. Naive CD4$^+$ T cells differentiate into at least four types of T helper (T_H) cells[1]— T_H1, T_H2, T_H17 and inducible regulatory T cells — in response to different infectious agents, commensal microorganisms or self antigens. T_H2 cells are indispensable for host immunity to extracellular parasites, such as helminths. They are also responsible for the development of asthma and other allergic inflammatory diseases.

T_H2 cells function both through their production of various T_H2 cell-associated cytokines, including interleukin-4 (IL-4), IL-5, IL-9, IL-13 and IL-25 (also known as IL-17E), and through their homing to specific tissue compartments. T_H2 cells regulate B cell class switching to IgE through their production of IL-4. IgE immune complexes activate innate immune cells (including basophils and mast cells, resulting in their degranulation) by cross-linking high-affinity Fc receptors for IgE (FcεRI) on the surface of these cells. Activated basophils and mast cells secrete various products, including cytokines, chemokines, histamine, heparin, serotonin and proteases, which result in smooth muscle constriction, vascular permeability and inflammatory cell recruitment. The expression of FcεRI by these cells is further enhanced by IgE cross-linking, providing a powerful amplification mechanism of IgE-mediated T_H2-type effector responses. T_H2 cells also migrate to the lung or intestinal tissues where they recruit eosinophils (through IL-5) and mast cells (through IL-9) leading to tissue eosinophilia and mast cell hyperplasia. By directly acting on epithelial cells (through IL-4, IL-9 and IL-13) and smooth muscle cells (through IL-4 and IL-13), T_H2 cells induce mucus production, goblet cell metaplasia and airway

Competing interests statement
The authors declare no competing financial interests.

DATABASES
UniProtKB: http://www.uniprot.org
amphiregulin | GATA3 | GFI1 | IL-3 | IL-4 | IL-5| IL-9 | IL-13 | IL-24 | IL-25 | IL-33 | ST2 | STAT5A | STAT6 | TSLP

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hyperresponsiveness (AHR). T_H2-type cytokines also act on T cells (through IL-4, IL-9 and IL-25), macrophages (through IL-4 and IL-13) and IL-5- and/or IL-13-producing non-B non-T cells (NBNT cells) (through IL-25). T_H2 cells may have effects on many other cell types, as IL-4 receptor (IL-4R) and IL-13R are widely expressed throughout the body and, in most instances in which they have been studied, are functional (based on their ability to induce signal transducer and activator of transcription 6 (STAT6) phosphorylation following ligation). T_H2 cells also produce amphiregulin[1] (an epidermal growth factor family member) and IL-24, which has antitumour effects[2]. The production of many other cytokines, including IL-2 (REF. 3), IL-10 (REFS 2,4) and IL-21 (REF. 5), is not unique to T_H2 cells but these cytokines may participate in mediating and/or regulating the functions of T_H2 cells; however, they will not be discussed in detail in this Review.

In addition to being an important T_H2-type effector cytokine, IL-4 has a crucial role in the differentiation of T_H2 cells *in vitro*[6,7]. Through its action on STAT6, IL-4 upregulates the expression of GATA-binding protein 3 (GATA3), the master regulator for T_H2 cell differentiation[8,9], and STAT6 activation is necessary and sufficient for IL-4-mediated GATA3 upregulation[10,11]. T cell receptor (TCR) signalling can also induce GATA3 expression[12]. Other signalling pathways, such as that initiated by Notch activation[13] and by activation of the WNT signalling pathway through β-catenin and T cell factor 1 (TCF1)[14], have been reported to promote GATA3 expression and to lead to the induction of T_H2 cell responses *in vivo* either by allowing IL-4-independent T_H2 cell differentiation or by inducing TCR-driven IL-4 production by naive $CD4^+$ T cells. However, whether the Notch and WNT pathways directly control GATA3 transcription or indirectly elevate GATA3 function through their effects on other key factors requires more detailed study.

STAT5 activation induced by IL-2 is also crucial for T_H2 cell differentiation *in vitro* [15,16]. Neutralization of IL-2 results in the developmental failure of IL-4-producing cells even when IL-4 is exogenously provided and normal cell proliferation is observed[15]. Introduction of constitutively active STAT5A bypasses the requirement of IL-2 for T_H2 cell differentiation. *In vivo,* activation of STAT5 can be promoted by IL-2, IL-7 and/or thymic stromal lymphopoietin (TSLP)[3]. Strong STAT5 activation may lower the concentration of GATA3 needed for inducing T_H2 cell responses. Introduction of constitutively active STAT5A into naive $CD4^+$ T cells *in vitro* allows T_H2 cell differentiation even when the cells are cultured in the absence of IL-4 and in the presence of the T_H1 cell-inducing cytokine IL-12 (REF. 16). Although the concentration of GATA3 remains low in such cultures, GATA3 is still essential for T_H2 cell differentiation, as constitutively active STAT5A fails to induce T_H2 cells differentiation in the absence of *Gata3* (REF. 17). Thus, GATA3 expression and STAT5 activation are two crucial elements for T_H2 cell differentiation. Indeed, both GATA3 and STAT5 bind to key elements in the T_H2 cytokine locus[16] (FIG. 1).

Although the functions of T_H2 cells and the requirements of cytokines and transcription factors for their differentiation have been extensively studied *in vitro*, the factors that initiate and amplify T_H2 cell responses *in vivo* have only recently begun to be clarified. Some T_H2-associated cytokines, including TSLP, IL-25 and IL-33, have been shown to be important in certain T_H2-associated disease models. Here, we discuss the activation of immune cells including epithelial cells, basophils and dendritic cells (DCs) by allergens and helminth-derived products, and how IL-4, TSLP, IL-25 and IL-33 produced by these cells promotes the development of T_H2 cell responses *in vivo*.

Innate sensing of allergens and helminths

Adaptive immune responses depend on signals from innate immune cells. Discrimination of self versus non-self and danger versus non-danger signals by innate cells and the type of initial activation of these cells determines the nature and magnitude of adaptive immune responses. The first step in the initiation of T_H2 cell responses occurs at the tissue sites, including skin, lungs and gut, where allergens or parasites are encountered and the products of allergens and helminths are sensed.

The house dust mite (HDM) allergen is usually contaminated with low levels of lipopolysaccharide (LPS). It has been shown that low levels of LPS enhance T_H2-type responses to inhaled antigens, whereas high levels of LPS result in T_H1 cell responses[18]. Recently, it has been reported that Toll-like receptor 4 (TLR4) expression by lung cells (probably lung epithelial cells), but not DCs, is necessary and sufficient for HDM allergen-mediated DC activation and T_H2 cell differentiation[19]. Following activation through TLR4, lung epithelial cells produce TSLP, IL-25 and IL-33 (FIG. 2). How the amount of LPS influences the pattern of cytokine production by lung epithelial cells is not known. Activated lung epithelial cells also produce chemokines, such as CC-chemokine ligand 20 (CCL20), that recruit lung DCs to the airways. Once DCs are activated in the airways under the influence of the LPS-responsive airway epithelial cells, they migrate to the draining lymph nodes where they present antigens to T cells, which subsequently differentiate into T_H2 cells. Interestingly, the main HDM allergen, Der p 2, is structurally homologous to MD2 (also known as LY96), a molecule that is required for LPS binding to TLR4 (REF. 20). Therefore, it is possible that Der p 2 induces allergic inflammation in a TLR4-dependent but MD2-independent manner through the activation of airway epithelial cells and the production of T_H2-associated cytokines.

Many allergens are cysteine proteases. *In vitro* treatment of basophils with the cysteine protease papain results in their production of IL-4 and TSLP[21] (FIG. 2). Basophils are transiently recruited to the draining lymph nodes in response to allergen challenge and their local production of IL-4 and/or TSLP may explain how T_H2 cell responses are stimulated by cysteine protease-containing allergens. The expression of TSLP can also be induced in cells of a human airway epithelial cell line treated with papain or trypsin; IL-4 further promotes such induction[22]. The effect of trypsin on a human epithelial cell line is mediated by protease-activated receptor 2 (PAR2), whereas the induction of TSLP by papain only partially depends on PAR2.

Omega-1 (REFS 23,24), a T2 ribonuclease glycoprotein derived from *Schistosoma mansoni* egg antigen (SEA), has recently been reported to be a potent T_H2 cell-inducing factor (FIG. 2). Omega-1 functions by inhibiting DC activation and lowering the strength of the TCR-dependent signals that naive $CD4^+$ T cells receive, thus enhancing GATA3 production and T_H2 cell differentiation (BOX 1). Omega-1 also suppresses IL-12 production by DCs, diminishing T_H1 cell induction and, importantly, it induces T_H2 cell differentiation *in vivo* in the absence of IL-4 signalling. How DCs sense omega-1 activity is not known.

Box 1

TCR signal strength regulates T cell differentiation

T cell receptor (TCR) signal strength regulates T helper 1 (T_H1) and T_H2 cell differentiation[65,101,102]. Weak TCR signalling favours T_H2 cell differentiation, whereas strong TCR signalling results in T_H1 cell differentiation[102]. When naive $CD4^+$ T cells are stimulated *in vitro* with low concentrations of cognate peptide[12,65,66], they preferentially develop into T_H2 cells. Such T_H2 cell differentiation can also be achieved by stimulating

naive CD4+ T cells with higher concentrations of altered peptide ligands[67]. The induction of interleukin-4 (IL-4)-producing cells by weak TCR stimulation seems to be also dependent on CD28-mediated co-stimulation[66], which is required for the production of IL-2, an essential cytokine for inducing IL-4 production *in vitro*. Weak TCR stimulation induces IL-4-independent GATA-binding protein 3 (GATA3) upregulation and early IL-4 production[12]. Extracellular signal-regulated kinase (ERK) activation in response to TCR signalling strength has a crucial role in regulating T_H1 and T_H2 cell differentiation[12]. When naive CD4+ T cells are stimulated with low concentrations of cognate peptide, weak and transient ERK activation is observed. Such weak ERK activation is necessary for inducing sufficient amounts of IL-2 needed for further T_H2 cell polarization but is not sufficient to repress TCR-mediated GATA3 induction. When naive CD4+ T cells are stimulated with high concentrations of cognate peptide, ERK activation is high and prolonged. Such strong ERK activation suppresses TCR-mediated GATA3 upregulation and IL-2-mediated signal transducer and activator of transcription 5 (STAT5) phosphorylation, two crucial events for inducing IL-4 production, as blockade of the ERK pathway by an ERK kinase inhibitor allows the T cells stimulated with high concentrations of peptide to increase GATA3 transcription and to mediate STAT5 activation in response to IL-2, resulting in IL-4-independent early IL-4 production[12].

Although omega-1 seems to be responsible for much of the ability of SEA to induce T_H2 cell differentiation *in vitro*, omega-1-depleted SEA can still induce T_H2 cell differentiation *in vivo*. It has been reported that the IL-4-inducing principle of *S. mansoni* eggs (IPSE) can mediate FcεRI-dependent IL-4 production by basophils[25]. Other components of SEA such as lacto-*N*-fucopentaose III may also be responsible for eliciting T_H2 cell responses *in vivo*[26]. Specific components from other parasites such as *Trichuris muris* and *Nippostrongylus brasiliensis* that are responsible for the induction of T_H2-type responses have not been identified. Whether all helminths produce agents that favour T_H2 cell differentiation by diminishing TCR signalling strength in a manner similar to omega-1 is not known.

Epithelial cells, basophils and DCs

Lung, skin and intestinal epithelial cells are not only physical barriers to invaders, but also produce cytokines in response to allergens[18] and products of helminths[27]. In humans, epithelial cells, especially keratinocytes from patients with atopic dermatitis, express high levels of TSLP[28]. Lung epithelial cells respond to HDM and cysteine proteases by producing TSLP[18,22]. In addition, *T. muris* infection induces TSLP production by intestinal epithelial cells (IECs), which correlates with nuclear factor-κB (NF-κB) activation in IECs[27]. Deletion of the NF-κB regulator IκB kinase-β (IKKβ) in IECs reduces their TSLP expression during *T. muris* infection; *T. muris*-infected mice in which IKKβ is not expressed in IECs fail to develop T_H2-type responses and to expel the helminth, implying a central role for this pathway in *T. muris*-mediated T_H2 cell differentiation.

As mentioned earlier, basophils can produce IL-4 and TSLP in response to cysteine protease allergens or IPSE. Basophils are also effective antigen-presenting cells (APCs) and can promote the differentiation of naive T cells into effector T_H2 cells both *in vitro* and *in vivo*. It has been reported that when acting as APCs, basophils favour T_H2 cell responses, whereas DCs mainly induce T_H1 cell responses when the same antigen is presented[29]. The lower level of MHC class II molecule expression by basophils compared with DCs is consistent with the observation that low-strength TCR signalling results in T_H2 cell differentiation.

Administration of antigen–IgE immune complexes induces T_H2-type responses both through the FcεRI-mediated activation of basophils and the targeting of antigen to these cells,

promoting their role as APCs[29]. In the papain allergen-induced model of T_H2 cell differentiation, basophils seem to be necessary and sufficient as the APCs for T_H2 cell induction; DCs are apparently not required[30]. However, for ovalbumin–alum-induced T_H2 cell responses *in vivo*, DCs have been shown to be crucial[31]. Similarly, conditional depletion of airway DCs abolishes eosinophilic airway inflammation to inhaled antigen, implying that DCs are essential for the development of asthma[32,33]. Interestingly, eosinophil-derived neurotoxin with ribonuclease activity serves as an endogenous alarmin to activate myeloid DCs through the TLR2–myeloid differentiation primary-response protein 88 (MYD88) pathway and promotes T_H2 cell responses[34,35].

The role of basophils during *T. muris* infection seems to be more complex; depletion of basophils results in failure of helminth expulsion, and mice in which MHC class II expression is restricted to DCs have impaired immunity to *T. muris*[36]. However, in mice in which MHC class II expression is restricted to DCs, blocking of interferon-γ (IFNγ) restores T_H2 cell-mediated immunity, suggesting that in the absence of IFNγ, basophils are not essential for T_H2 cell development. Indeed, depletion of DCs resulted in fewer primed $CD4^+$ T cells than in wild-type mice that had been infected with *T. muris*, although T_H2-type cytokine production was not altered[36]. By contrast, other APCs, such as macrophages and B cells, are not essential for *T. muris*-induced T_H2 cell responses and worm expulsion[36,37]. These results suggest that both basophils and DCs are involved in the immune responses to *T. muris*; however, whether basophils can actually process and present *T. muris* antigens to $CD4^+$ T cells *in vivo* remains to be determined.

Basophils are recruited to the draining lymph node two days after exposure to SEA[36]; however, the overall role of basophils during *S. mansoni* infection has not been assessed. As omega-1-treated DCs are sufficient to induce T_H2 cell responses, basophils may not be as important for the initial T_H2 cell-biased immune response in *S. mansoni* infection as in *T. muris* infection. It has been recently reported that the recruitment of basophils to the draining lymph nodes after *N. brasiliensis* infection completely depends on IL-3; however, $Il3^{-/-}$ mice or mice depleted of basophils develop normal T_H2 cells[38]. There are also numerous reports showing that DCs are important APCs during T_H2 cell responses to allergens and helminths[39–47].

Thus, epithelial cells and basophils have important roles in the initiation of T_H2 cell responses by producing T_H2-associated cytokines in response to allergen or helminth-derived products. Basophils are also involved in the initiation of some T_H2 cell responses by serving as APCs. However, the differential requirements for basophils or DCs as APCs for the induction of T_H2 cell responses seem to depend on the nature of the antigens or helminths and/or the particular adjuvant used.

IL-4 and T_H2 cell differentiation

Traditionally, IL-4 has been viewed as the keystone of the T_H2 cell response. However, although the IL-4–STAT6 pathway is crucial for T_H2 cell induction *in vitro* and in some *in vivo* models of T_H2-associated disease, including allergen-induced AHR and *T. muris* infection[48–50], this pathway is dispensable in other *in vivo* T_H2 cell responses (see below).

Initial sources of IL-4 *in vivo*

IL-4, through its activation of STAT6, upregulates GATA3 expression[8,9,17,51] and also suppresses T_H1 and T_H17 cell responses, partly through the upregulation of growth factor independent 1 (GFI1), a transcriptional repressor of IFNγ and IL-17 production[52]. Identifying the initial source of IL-4 is crucial to understanding the initiation of IL-4-dependent T_H2 cell responses.

Natural killer T (NKT) cells produce large amounts of IL-4 immediately after TCR engagement[53]. However, mice lacking NKT cells such as CD1d- and β_2-microglobulin-deficient mice can mount normal T_H2 cell responses in various *in vivo* models, including those of helminth infections and induction of AHR[54]. A report showed that NKT cells were essential for allergen-induced AHR but were not required for T_H2 cell differentiation in this model, implying that they orchestrate or mediate the effector response rather than T_H2 cell induction[55]. These investigators have also reported that there are large numbers of NKT cells in the bronchial alveolar lavage fluid of patients with asthma, suggesting that NKT cell-derived cytokines may have an important role in human asthma[56].

It has long been known that basophils produce large amounts of IL-4 when activated by FcεR1 cross-linking or through other cell surface receptors, both in mice[57,58] and in humans[59]. Recent reports have shown that basophils transiently enter lymph nodes during immune responses to papain[21] and that they are essential for IgE production and T_H2 cell responses in mice immunized with papain[30]; however, whether IL-4 production is the sole or even main mechanism through which basophils induce these T_H2 cell responses *in vivo* is still uncertain.

Naive $CD4^+$ T cells can also produce IL-4 independently of IL-4 signalling when they are activated. In response to peptide stimulation, naive $CD4^+$ T cells from TCR-transgenic IL-4Rα-deficient mice secrete amounts of IL-4 sufficient to induce T_H2 cell differentiation, particularly when IFNγ and IL-12 are absent from the culture[60]. *In vitro*, autocrine and/or paracrine IL-4 induces and consolidates T_H2 cell differentiation[12,61], but whether it does so *in vivo* is not known.

IL-4-independent T_H2 cell responses

Although the IL-4–IL-4R–STAT6 pathway is not essential for all forms of T_H2 cell differentiation *in vivo*[58,62–64], GATA3 activation is necessary[17,51]. TCR signalling may directly induce GATA3 expression, and this is particularly true when naive $CD4^+$ T cells are stimulated *in vitro* with low concentrations of cognate peptide[12,65,66] or with higher concentrations of altered peptide ligands[67] (BOX 1). It is likely that low TCR signal strength also favours TCR-mediated induction of GATA3 expression *in vivo* and may result in IL-4-independent T_H2 cell differentiation, although that has not been directly shown.

Other T_H2 cell-promoting cytokines

In addition to IL-4, other cytokines, including TSLP, IL-25 and IL-33, have crucial roles in the induction of some T_H2 cell responses *in vivo*. Depending on the T_H2 cell-associated model under study, the relative importance of each cytokine varies, similar to the involvement of IL-4 in different settings. Below, we discuss the functions of these cytokines in allergen-induced T_H2 cell responses, as well as during different helminth infections.

Functions of TSLP: initiation, amplification or both?

TSLP is produced by epithelial cells, mast cells and basophils[21,28,68,69]. Its expression is increased in the lungs of mice with airway inflammation, and lung-specific overexpression of TSLP induces T_H2-related airway inflammation suggesting that TSLP can be an initiator of allergic airway inflammation[68]. In addition, treatment of human airway epithelial cells with IL-4 and IL-13 results in the upregulation of TSLP expression[70], suggesting that an IL-4–TSLP or IL-13–TSLP loop may be involved in the amplification of T_H2 cell responses (FIG. 2). Furthermore, the basophil-mediated T_H2 cell response to papain is partially dependent on TSLP production by basophils[21]. During helminth infection, however, TSLP is only crucial for T_H2 cell responses to some parasites (see below).

TSLP acts on $CD4^+$ T cells, presumably through its activation of STAT5 (REFS 3,71,72). TSLPR-deficient mice fail to develop allergic responses to inhaled antigen; instead, these mice developed strong T_H1 cell responses. Transferring wild-type $CD4^+$ T cells into TSLPR-deficient mice restores their allergic responses, implying that the function of TSLP in this model is mainly through its direct action on $CD4^+$ T cells[73]. A more recent study reported that TSLP has a crucial role in a T_H2-mediated allergic skin inflammation model by acting exclusively on $CD4^+$ T cells[74]. In TSLPR-deficient mice, there was decreased infiltration of eosinophils and less production of T_H2 cell-associated cytokines in the skin. However, no widespread defect in DC maturation or in T_H2 cell development was evident, suggesting that TSLP affects already differentiated T_H2 cells to control their effector cytokine production. It has been recently reported that human $CD4^+$ T cells express low levels of TSLPR and respond to TSLP poorly. The effects of IL-7 (which shares a receptor subunit with TSLP) on human $CD4^+$ T cells are much more robust than those of TSLP in terms of inducing STAT5 phosphorylation and promoting T cell proliferation, suggesting the effects of TSLP on human $CD4^+$ T cells are limited[75]. However, because much of the effect of TSLP may occur in tissues, a careful evaluation of $CD4^+$ T cells from human skin, lung and gut for TSLPR expression is needed before a definitive conclusion on this important point is reached.

TSLP also acts on other immune cells. TSLP-treated human DCs produce T_H2 cell-attracting chemokines, including CCL17 and CCL22 (REF. 28), that bind to CC-chemokine receptor 4 (CCR4), which is expressed by T_H2 cells [76,77]. These TSLP-treated DCs can also prime naive human $CD4^+$ T cells to preferentially become T_H2 cells[28]. TSLP-treated DCs upregulate OX40L cell surface expression and blockade of the OX40L–OX40 interaction diminishes T_H2 cell cytokine production induced by TSLP-treated DCs *in vitro*[45]. Although OX40L–OX40 interaction is important for T_H2 cell responses, T_H1 cell responses may also require OX40L–OX40 interaction; all activated T cells upregulate OX40 expression. However, it is possible that the signalling triggered by OX40L has a unique role in promoting T_H2 cell differentiation in the absence of IL-12 (REF. 45). Given that TSLP also suppresses IL-12 production by DCs, this may be the main mechanism through which TSLP biases DCs towards inducing T_H2-type responses[45,78,79]. However, in the presence of CD40L–CD40 signalling, TSLP can still stimulate human DCs to induce T_H2 cell differentiation without blocking IL-12 production, suggesting TSLP also affects other DC functions[80]. TSLP produced by epithelial cells also activates mast cells[81]. Interestingly, TSLP has been reported to increase the number of IL-4-producing basophils in the peripheral blood[36], which may have an important role in certain T_H2 cell responses.

In contrast to the need for TSLP in allergic airway inflammation, it is not required for T_H2 cell responses to some helminths, such as *Heligmosomoides polygyrus* and *N. brasiliensis*. TSLPR-deficient mice have normal T_H2 cell differentiation and protective immunity against these parasites[78]. However, TSLP is required for T_H2-type immune responses to *T. muris*, possibly through its suppression of T_H1 cell responses, as neutralization of IL-12 or IFNγ reverses the defect in T_H2 cell responses in TSLPR-deficient mice[78,79]. Intestinal DCs from IEC-specific conditional *Ikkb*-knockout mice infected with *T. muris* produce higher levels of tumour necrosis factor (TNF) and the IL-12 and IL-23 subunit p40, which correlates with the increased IFNγ and IL-17 production by $CD4^+$ T cells from these mice[27], suggesting that a cytokine (or several cytokines) produced by IECs (possibly TSLP) has an important role in regulating DC function.

Thus, TSLP can regulate the functions of T cells, DCs, mast cells and basophils in allergic responses and helminth infections. The relative importance of TSLP on the function of each cell type may vary in individual T_H2-associated models, where the potential T_H1 or T_H17 cell response varies and thus the need to repress them.

Functions of IL-25: initiation, amplification or both?

IL-25 is an IL-17-related cytokine produced by T_H2 cells[82]. Administration of recombinant IL-25 to naive mice induces IL-4, IL-5 and IL-13 production and systemic T_H2 cell responses, including IL-4-mediated IgE induction, IL-5-mediated eosinophilia and IL-13-mediated histopathological changes in lungs and gastrointestinal tracts[82]. Interestingly, IL-25 also induces eosinophilia and histopathological changes in recombination-activating gene (*Rag*)-knockout mice, which is consistent with the ability of IL-25 to promote IL-5 and IL-13 production by MHC class $II^{hi}CD11c^{low}F4/80^{low}CD4^{-}CD8^{-}$ NBNT cells[82]. IL-4 induction by IL-25 occurs in wild-type but not *Rag*-knockout mice, indicating that IL-25 induction of IL-4 production requires B and/or T cells. It has been recently reported that adipose tissue-associated $LIN^{-}KIT^{+}SCA1^{+}IL\text{-}7R\alpha^{+}$ NBNT cells produce IL-5 and IL-13 in response to IL-2 plus IL-25 stimulation[83]. Such cells are present in *Rag*-knockout mice but not in mice deficient for the common cytokine receptor γ-chain (γ_c), and these cells are crucial for IL-13-mediated goblet cell hyperplasia[83].

IL-25-deficient mice infected with *N. brasiliensis* show delayed worm expulsion and induction of IL-5 and/or IL-13, whereas administration of IL-25 results in accelerated worm expulsion through the induction of T_H2-associated cytokines made by $KIT^{+}Fc\varepsilon RI^{-}$ NBNT cells[84]. Whether the NBNT cells capable of producing T_H2-associated cytokines that were reported by three groups[82–84] are the same population requires further investigation. Furthermore, whether such cells can be APCs during T_H2-type immune responses to allergens or helminth products is not known. Interestingly, administration of IL-25 induces worm expulsion in *Rag1*-knockout mice infected with *N. brasiliensis*[84], suggesting that the IL-25-responsive cell population may serve as effector cells and IL-4 and/or IL-13 production by T_H2 cells may not be essential. Therefore, IL-25 produced by epithelial cells may initiate T_H2-type immune responses by activating innate immune cells, and IL-25 produced by T_H2 cells further boosts such an effect.

IL-25-deficient mice on a C57BL/6 background fail to expel *T. muris,* correlating with a decreased T_H2- and increased T_H1-type response[85]. Blocking IL-12 and IFNγ in these mice restores their T_H2-type response to *T. muris* and results in worm expulsion. Conversely, administration of IL-25 to AKR mice, which are normally susceptible to *T. muris*, conveys resistance to infection by the helminth, indicating that IL-25 has an important role in regulating the balance between T_H1- and T_H2-type responses during parasite infections.

IL-25 is also expressed by allergen-activated epithelial cells and it can directly act on $CD4^{+}$ T cells to initiate T_H2 cell differentiation in an IL-4-dependent manner[86]. Matrix metalloproteinase 7 (MMP7) produced by airway epithelial cells during allergic inflammation dramatically increases the activity of IL-25 by cleaving it[87]. *Mmp7*-knockout mice have less AHR, which correlates with reduced T_H2-type cytokine production in response to allergen challenge, suggesting IL-25 cleavage by MMP7 may be important for AHR induction.

Activated human basophils, eosinophils and mast cells express IL-25, which can upregulate GATA3 expression in human memory T_H2 cells. Increased IL-25 and IL-25R expression have been detected in patients with asthma suggesting that IL-25 may serve as an amplification factor in human allergic diseases[88].

Functions of IL-33: initiation, amplification or both?

IL-33 is a member of the IL-1 family[89]; one component of its receptor, ST2 (also known as IL-1RL1), is selectively expressed by the T_H2 subset of T_H cells[90,91]. Administration of IL-33 to naive mice induces splenomegaly, eosinophilia, increased serum IgE, IL-5 and IL-13 production, and histopathological changes in lungs and gastrointestinal tract[89].

Blocking IL-33 function by an ST2 fusion protein decreases eosinophilic airway inflammation, which is positively correlated with a decrease in IL-4 and IL-5 expression[91]. Although some strains of ST2-deficient mice displayed substantial reduction in pulmonary granuloma formation in response to SEA injection, consistent with reduced IL-5 expression and eosinophil infiltration in these mice[92], other strains of ST2-deficient mice cleared *N. brasiliensis* infection normally[93].

IL-33 is upregulated during the early phase of *T. muris* infection, and administration of IL-33 results in increased TSLP production[94]. IL-33 together with IL-3 can directly act on human basophils to induce IL-4 production[95,96] and IL-33 has also been shown to activate mast cells[97]. IL-13 induces ST2 expression by macrophages and IL-33, in turn, promotes further differentiation of alternatively activated macrophages[98]. Furthermore, stimulation of T_H2 cells with IL-33 together with TSLP or other STAT5 activators results in TCR-independent IL-13 production[99]. Adipose tissue-associated $LIN^-KIT^+SCA1^+IL\text{-}7R\alpha^+$ NBNT cells also express ST2 and they produce IL-5 and IL-13 in response to IL-33 (REF. 83). Therefore, IL-33 can initiate and amplify T_H2-type responses under certain circumstances.

Thus, IL-4, TSLP, IL-25 and IL-33 are all associated with certain types of T_H2-associated immune responses. In the model of T_H2-associated inflammation discussed above, one or more of these cytokines produced by epithelial cells or basophils in response to allergens or helminth These cytokines products initiates T_H2 cell differentiation. are also involved in the amplification of T_H2-type immune responses at later stages by forming positive feedback loops. The cell sources, target cells and the functions of T_H2-inducing cytokines are summarized in TABLE 1.

Putting the 'T_H2 pieces' together

In vivo functions of IL-4 and TSLP

Both TSLP and IL-4 seem to be important for allergen-induced T_H2-type immune responses (FIG. 3). T_H2 cell differentiation in response to infection with some parasites, including *N. brasiliensis,* can occur in a TSLP- or IL-4-independent manner but T_H2-type responses to other helminths, such as *T. muris,* require TSLP and IL-4. It remains to be determined to what extent T_H2-type responses that are either IL-4- or TSLP-independent can occur in the absence of both these cytokines.

The mouse genetic background influences the initiation of T_H1- and T_H2-type immune responses (BOX 2). It is known that the balance between IL-4 and IFNγ production determines the resistance or susceptibility of different mouse strains to infection with *T. muris*. Blocking IL-4 in resistant mice results in a failure of worm expulsion, whereas blocking IFNγ or administration of recombinant IL-4 to susceptible mice induces T_H2-type responses and parasite expulsion [48]. Therefore, the initiation of T_H2-type responses to infection with particular parasites or to allergen exposure differs, possibly because some stimuli that can induce T_H2-type responses may also contain components capable of inducing T_H1- or T_H17-type responses. Simultaneous induction of T_H1-, T_H2- and T_H17-associated responses of different magnitudes in various models results in a differential requirement of certain T_H2 cell-inducing factors in the control of T_H2-type responses. In cases in which mixed T_H1, T_H2 and T_H17 cell-associated responses are triggered, TSLP and IL-4 may be required to suppress T_H1- and T_H17-type responses so that a preferential T_H2-type response can occur. However, when T_H2-type responses are already dominant during initial T cell activation, TSLP and IL-4 may no longer be crucial for T_H2 cell differentiation. Changes in the balance of cytokines with cross-regulatory activities (such as IL-4 versus IFNγ, IL-4 versus TGFβ and TSLP versus IL-12) may result in changes of the type of

immune responses induced. Therefore, when studying a T_H2-type response, other types of responses should also be assessed at the same time.

Box 2

Genetic background influences T_H2-type immune responses

The genetic background of the mice used in models of T helper 2 (T_H2)-mediated inflammation has an important role in determining the balance of the T_H cell responses. One striking example is the response to *Leishmania major* infection[103]. C57BL/6 mice develop a protective T_H1-type response but BALB/c mice are susceptible owing to a T_H2-biased immune response. Many gene loci involved in T_H2-type responses have been identified, one of which is the MYC-induced nuclear antigen (*Mina*) locus on chromosome 16. MINA is expressed at higher levels in many T_H1-biased mice strains, including C57BL/6 mice, than in T_H2-biased mice such as BALB/c mice[104]. MINA binds to the *Il4* promoter and represses IL-4 production. Therefore, genetically determined differential expression levels of MINA at an early stage of $CD4^+$ T cell activation may influence the balance between T_H1 and T_H2 cells. Responses to infection with some helminths such as *Trichuris muris* also vary among mouse strains. C57BL/6 mice are resistant to *T. muris* infection owing to the development of protective T_H2 cell responses, whereas AKR mice are susceptible because of bias towards T_H1 cell responses. The molecule (or molecules) responsible for such a difference remains to be determined.

In vivo functions of basophils and DCs

Basophils have a crucial role in sensing cysteine protease antigens, such as papain (FIG. 3a). However, in response to other T_H2-inducing factors, the main function of basophils may be to regulate the balance of T_H1 and T_H2 cell responses (FIG. 3b). Although DCs can induce both T_H1 and T_H2 cell responses, basophils seem to function specifically as T_H2-promoting APCs. Therefore, basophils are needed to induce more T_H2 cells in the models in which T_H1 cells are also induced by IL-12-producing DCs. It is also possible that basophils, through TSLP expression, suppress IL-12 production by DCs and/or promote the development of T_H2-related DCs. However, if DCs are already conditioned to induce T_H2 cell responses, such as in response to the *S. mansoni* product omega-1, basophils may no longer be essential (FIG. 3c). In this regard, basophils are not crucial APCs during T_H2-type responses to *T. muris* infection when T_H1 cell-inducing factors are blocked, and these cells are not essential for T_H2-type responses to *N. brasiliensis* infection[38], which are also IL-4 and TSLP independent.

The strength of T cell signalling and the cytokine milieu are two crucial determinants for T_H2 cell differentiation. Freshly isolated DCs expressing low levels of MHC class II and B7 molecules (also known as CD80 and CD86) preferentially induce T_H2 cell differentiation, whereas T_H1 cell differentiation is driven by activated IL-12-producing DCs[100]. DCs treated with omega-1 do not produce IL-12 and display a resting phenotype. Thus, T_H2 cell differentiation occurs when $CD4^+$ T cells receive low-strength TCR signalling, consistent with many *in vitro* studies. Low levels of MHC class II expression on basophils, in addition to their production of IL-4 and TSLP, may also contribute to the ability of basophils to preferentially induce T_H2 cell differentiation.

Conclusions and perspective

The products of allergens and helminths, as the initiators of T_H2-type immune responses, are crucial in determining the activation of their target cells and the production of T_H2-

promoting cytokines by these stimulated cells. Many different cell types, including lung and intestinal epithelial cells, DCs and basophils, are responsible for sensing these products and thus involved in the initiation of T_H2-type immune responses *in vivo*. The initiation of T_H2-type responses takes place in the tissue sites where allergens or parasites are encountered. Activated DCs and basophils migrate from tissues to the draining lymph nodes to stimulate proliferation and differentiation of antigen-specific $CD4^+$ T cells. The amplification of T_H2-type responses starts in the lymph nodes when naive $CD4^+$ T cells begin to differentiate towards T_H2 cells and continues to occur until the differentiated T_H2 cells reach the tissue sites to orchestrate immune responses. At that stage, T_H2 cells may directly communicate with epithelial cells and many types of immune cells that are recruited to the tissue sites to further regulate the magnitude of the T_H2-type responses. Crosstalk among different cells participating in T_H2-type responses through the production of T_H2-related cytokines, such as IL-4, IL-25, TSLP and IL-33, results in powerful feedback loops. When over-produced, each of these cytokines can initiate T_H2-type responses. In response to allergens or helminths, each of these cytokines can make some contribution to the overall T_H2 cell responses but the relative importance of each and the signalling pathways that are induced may vary in different models. In some T_H2-associated models, such as *T. muris* infection in resistant or susceptible mouse strains, the combination of TSLP, IL-25, IL-33 and IL-4 becomes crucial in determining the initiation of the T_H2 cell response. Whether *T. muris* is less efficient than other helminths in inducing T_H2-type responses or it is more potent than others in triggering T_H1-type responses is not certain; therefore, although valuable, data from *T. muris* infection studies may not represent the overall principles of *in vivo* T_H2-type immune responses.

The molecular mechanisms for T_H2 cell differentiation *in vivo* are poorly understood. Both GATA3 expression and STAT5 activation are crucial for the initiation of T_H2 cell differentiation *in vitro*. However, T_H2 cell differentiation can occur even when GATA3 is expressed at low levels but a strong STAT5 signal is provided. As IL-4 is the only factor known to induce high levels of GATA3 expression *in vitro* and T_H2 cell differentiation often occurs *in vivo* in the absence of IL-4, it is crucial to determine GATA3 expression levels in T_H2 cells generated *in vivo* in various models. If GATA3 expression is high in T_H2 cells that develop in the absence of IL-4 *in vivo*, then what is inducing GATA3 expression and how? However, it remains possible that the expression GATA3 need not be upregulated especially for IL-4-independent T_H2-type responses, although it is essential for these responses. If GATA3 is not upregulated in an IL-4-independent T_H2-type response *in vivo*, focus should then be on studying the regulation of STAT5 activators, such as IL-2, IL-7 and TSLP, and their actions on T cells, which may be a key event for the initiation of T_H2-type immune responses.

Future studies should also focus on the molecular mechanisms through which allergens and helminths are sensed by innate immune cells, including epithelial cells and basophils, through which T_H2-inducing cytokines IL-4, TSLP, IL-25 and IL-33 are induced in these stimulated innate cells. Understanding the molecular basis for the initiation of T_H2 cell differentiation and the cross-regulation between T_H2- and other T_H-type responses will greatly enhance our ability to design immune interventions and to treat many T_H2-related diseases, such as allergic inflammation and chronic parasite infections.

Note added in proof

Two recent reports[115,116] on further studies of the IL-25-responsive NBNT cells have shown that these cells are important during the initiation and amplification of T_H2-type responses and that they also function as effector cells. By using an *Il13*–enhanced green fluorescent protein (eGFP) reporter mouse strain, McKenzie and colleagues[115] showed that the NBNT

cells (designated 'nuocytes') comprise 80% of the IL-13-producing cells that are induced in mice treated with IL-25 or IL-33. These cells express inducible T cell co-stimulator (ICOS), ST2, IL-17RB and IL-7Rα, although only a fraction of them express KIT. Nuocytes are induced during helminth infection through the action of IL-25 and IL-33. Such cells enhance T cell responses in an IL-13-independent manner and their expansion requires T cells. By contrast, IL-13 production by these cells is crucial for accelerating worm expulsion. By using KIT and *Il4*–eGFP as markers, Artis and colleagues[116] reported that IL-25 induces both KIT^+GFP^- and KIT^+GFP^+ NBNT cells in gut-associated lymphoid tissues. Interestingly, these NBNT cells expressed no or low levels of ST2 and variable levels of IL-7Rα. IL-25-induced KIT^+ cells promote T_H2-type responses *in vivo* and rescue the T_H2 cell defects in IL-25-deficient mice in response to *T. muris* infection. IL-25-induced KIT^+GFP^+ cells give rise only to mast cells after *in vitro* culture with stem cell factor and IL-3, whereas KIT^+GFP^- cells can generate mast cells, basophils, macrophages and other $CD11b^+$ cells. KIT^+GFP^- but not KIT^+GFP^+ cells express MHC class II molecules and can induce IL-4Rα-mediated T_H2 cell differentiation *in vitro*, suggesting these cells may also be T_H2 cell-inducing APCs.

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Glossary

Asthma	A chronic disease of the lung, characterized by airway hyperresponsiveness and inflammation. The most common form of the disease, allergic asthma, results from inappropriate immune responses to common allergens in genetically susceptible individuals. Allergic asthma is characterized by infiltration of the airway wall with mast cells, lymphocytes and eosinophils. $CD4^+$ T cells producing T_H2-type cytokines are thought to have a crucial role in orchestrating the recruitment and activation of these effector cells of the allergic response
Airway hyperresponsiveness	Increased narrowing of the airways, initiated by exposure to a defined stimulus that usually has little or no effect on airway function in normal individuals. This is a defining physiological characteristic of asthma
Non-B non-T cells	(NBNT cells). Cells that are different from basophils, eosinophils, mast cells and NKT cells and can produce IL-5 and IL-13 but little or no IL-4 in response to IL-25 or IL-33 stimulation. They may produce IL-4 in response to phorbol 12-myristate 13-acetate (PMA) plus ionomycin stimulation. These cells were described as MHC class $II^{hi}CD11c^{low}$ $F4/80^{low}CD4^-CD8^-$ or $KIT^+FcεRI^-$ or $LIN^-KIT^+SCA1^+IL\text{-}7Ra^+ST2^+$ in three different reports, and they may comprise three different cell types
WNT	A signalling mediator named both for its mutant phenotype in *Drosophila melanogaster* (Wingless) and for its role as a preferential retrovirus integration site in murine leukaemia virus-induced leukaemias (Int-1). WNT signalling activates the T cell factor 1 (TCF1) and lymphoid enhancer-binding factor 1

	(LEF1) families of transcription factors by stabilizing their co-activator β-catenin and mobilizing it from the cytoplasm to the nucleus
Cysteine proteases	Enzymes requiring a cysteine thiol in their catalytic pockets to cleave polypeptides by hydrolysis of the peptide bonds. Common cysteine proteases include papain and bromelain
β_2-microglobulin	(β_2m). A single immunoglobulin-like domain that non-covalently associates with the main polypeptide chain of MHC class I molecules. In the absence of β_2m, MHC class I molecules are unstable and are therefore found at low levels at the cell surface
Altered peptide ligands	(APLs). Peptide analogues that are derived from the original antigenic peptide. They commonly have amino acid substitutions at TCR-contact residues. TCR engagement by these APLs usually leads to partial or incomplete T cell activation. Antagonistic APLs can specifically antagonize and inhibit T cell activation that is induced by the wild-type antigenic peptide
Recombination-activating gene (*Rag*)-knockout mice	*Rag1* and *Rag2* are expressed by developing lymphocytes. Mice that are deficient in either RAG protein fail to produce B and T cells owing to a developmental block in the gene rearrangement that is required for receptor expression
Alternatively activated macrophage	A macrophage stimulated by IL-4 or IL-13 that expresses arginase 1, the mannose receptor and IL-4Rα. There may be pathogen-associated molecular patterns expressed by helminths that can also drive the alternative activation of macrophages

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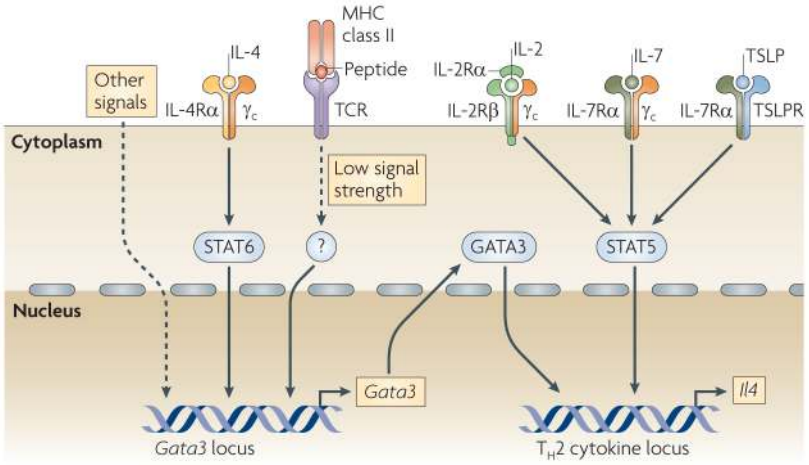

Figure 1. T_H2 cell differentiation requires both GATA3 expression and STAT5 activation

GATA-binding protein 3 (GATA3) and activated signal transducer and activator of transcription 5 (STAT5) bind to crucial regulatory elements of the T helper 2 (T_H2) cytokine locus and are indispensable for interleukin-4 (IL-4) production and thus T_H2 cell differentiation. IL-2, IL-7 and thymic stromal lymphopoietin (TSLP) activate STAT5. Several pathways are involved in regulating GATA3 expression. IL-4, through the activation of STAT6, is important for GATA3 upregulation *in vitro*. Low signal strength T cell receptor (TCR) activation induces GATA3 expression in an IL-4- and STAT6-independent manner. Other signalling pathways, including the Notch and WNT pathways, have been reported to regulate *Gata3* transcription, although whether their effect is direct is currently being investigated. γ_c, common cytokine receptor γ-chain; R, receptor.

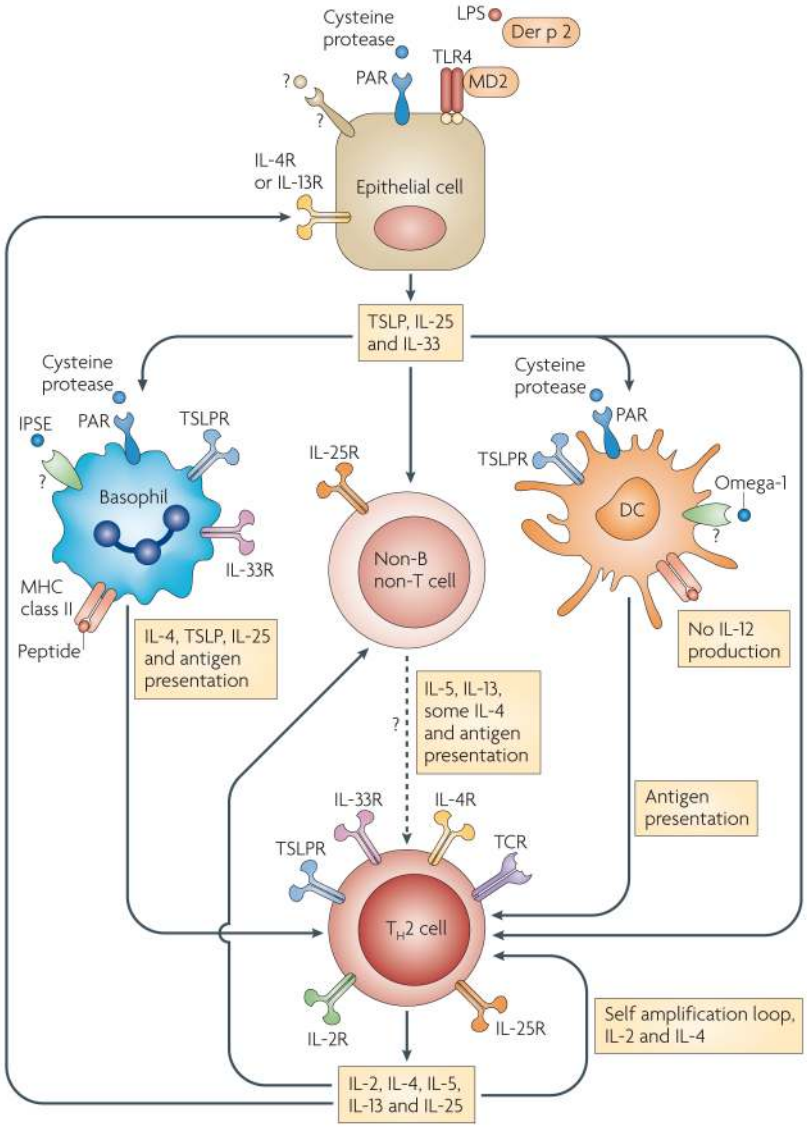

Figure 2. Cytokines have crucial roles in the initiation and amplification of T_H2-type immune responses

Cysteine protease- and/or lipopolysaccharide (LPS)-containing allergens, as well as helminth products, can activate lung and intestinal epithelial cells to produce thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and IL-33, which initiate T helper 2 (T_H2)-type immune responses by acting on basophils, dendritic cells (DCs) and/or non-B non-T cells. The allergen Der p 2 is structurally homologous to MD2, a component of Toll-like receptor 4 (TLR4) signalling complex. A high dose of Der p 2 enhances allergic inflammation in a TLR4-dependent MD2-independent manner. Some cysteine proteases and helminth products, such as IL-4-inducing principle of *Schistosoma mansoni* eggs (IPSE), can also directly stimulate basophils to produce TSLP and IL-4. Omega-1, a component of *S. mansoni* egg antigen, modulates DC function to favour a T_H2 cell promoting phenotype. Basophils, DCs and possibly other cells can serve as antigen-presenting cells to drive T_H2 cell differentiation under the influence of various cytokines such as TSLP, IL-4 and IL-25. Cytokines produced by T_H2 cells, including IL-2, IL-4 and IL-25, can self-amplify the differentiation process. At the effector stage, T_H2 cells and epithelial cells may further

amplify T_H2-type responses through a cytokine-mediated positive regulatory loop. Although they are not shown in the figure, other immune cells, including natural killer (NK) cells, NKT cells, γδ T cells, macrophages, B cells, eosinophils and mast cells, may also participate in the initiation and amplification of T_H2-type responses by creating a T_H2-biased cytokine environment. In addition, IL-4 may induce IL-12 production by DCs[105] or kill T_H2-inducing DCs[106], suggesting there are also negative regulatory mechanisms for T_H2-type immune responses. PAR, protease-activated receptor; R, receptor; TCR, T cell receptor.

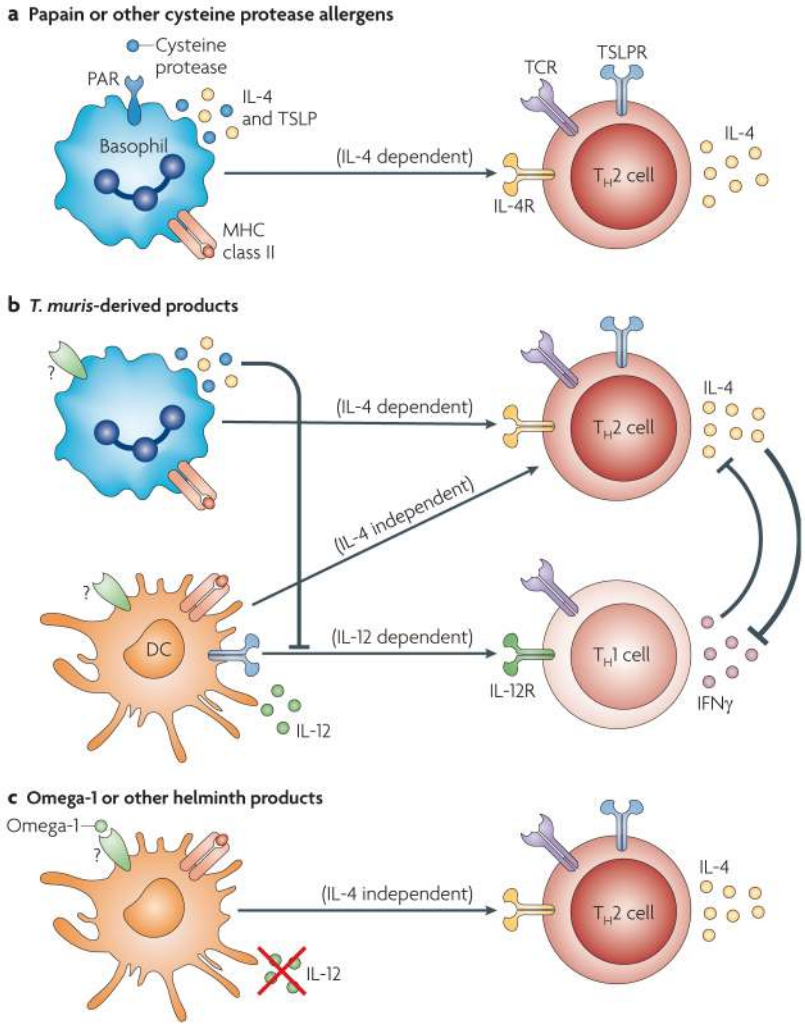

Figure 3. Basophils and dendritic cells, functioning as antigen-presenting cells, are differentially involved in various T_H2-type immune responses

Both basophils and dendritic cells (DCs) are involved in the fate determination of naive $CD4^+$ T cells through cytokine production and antigen presentation; however, the relative importance of these two cell types seem to be different in various models. a | In papain-induced (and possibly other cysteine protease allergen-induced) T helper 2 (T_H2)-type responses, basophils seem to be crucial, whereas DCs are not essential. Interleukin-4 (IL-4) and thymic stromal lymphopoietin (TSLP), produced by activated basophils, are important for such T_H2 cell differentiation. b | Different *Trichuris muris*-derived products may simultaneously activate basophils and DCs. Basophils are predominantly involved in T_H2 cell induction, whereas DCs induce both T_H1 and T_H2 cell differentiation. TSLP produced by basophils may be required for suppressing IL-12 production by DCs, promoting the development of T_H2 cell-inducing DCs and inducing IL-4 production by T cells. IL-4 produced either by basophils or T cells is also crucial for inhibiting interferon-γ (IFNγ) production in T cells and amplifying T_H2-type responses. c | In some helminth infection models, helminth products including omega-1 can down-modulate the functions of activated DCs and suppress IL-12 production; therefore, IL-4-independent T_H2 cell differentiation occurs without the involvement of basophils. T_H2-type responses to *Nippostrongylus*

brasiliensis do not require basophils, and such responses are both IL-4 and TSLP independent. PAR, protease-activated receptor; R, receptor; TCR, T cell receptor.

Table 1

Cytokines involved in the initiation and amplification of T_H2-type immune responses

Cytokine	Induced by	Main source	Main targets	Functions related to T_H2-type immune responses
IL-4	Antigen[12,60,61], IPSE[25], IgE[29], IL-2 (REF. 1), IL-3 (REF. 29), IL-4 (REF. 1), IL-25 (REF. 86) and TSLP[71–75]	Naive CD4+ T cells[12,60,61], T_H2 cells[1], NKT cells[53] and basophils[21,25,29,30,57–59]	T cells[6,7], B cells[107,108], macrophages[109] and epithelial cells[22,70]	Induction of T_H2-associated cytokines[6,7], IgE class switching[107,108], alternative macrophage activation[109] and induction of TSLP expression[22,70]
IL-2	Antigen[3]	Activated CD4+ T cells[3]	T cells[3]	Induction of IL-4 (REFS 15,16), IL-4Rα[3] and IL-2Rα[3] expression
TSLP	Allergens[21], helminth-derived products[27], IL-4 and IL-13 (REFS 22,70)	Epithelial cells[19,22,27,28,68–70], basophils[21,69] and mast cells[28,69]	DCs[28,45,75], T cells[71–75], basophils[36] and mast cells[81]	Suppression of IL-12 production[45,78–80] and induction of T_H2-associated cytokines [71,72]
IL-25	Allergens[19,86], helminth-derived products[84,85] and IL-4 (REF. 82)	T_H2 cells [82], epithelial cells[19,86], basophils[88], eosinophils[88] and mast cells[88]	T cells[86] and NBNT cells[82–84]	Induction of T_H2-associated cytokines[82,84,86]
IL-33	Allergens[19] and helminth-derived products[94]	Epithelial cells[19,110], endothelial cells[110], airway smooth muscle cells[111] and adipocytes[112]	T_H2 cells [90,91,99], DCs[113], basophils[95,96], mast cells[97], macrophages[98,114] and NBNT cells[83]	Induction of T_H2-associated cytokines[89,91,95,96,99], TSLP expression[94] and amplification of alternatively activated macrophages[98]

DC, dendritic cell; IL, interleukin; IPSE, IL-4-inducing principle of *Schistosoma mansoni* eggs; NBNT, non-B non-T; NKT, natural killer T; T_H2, T helper 2; TSLP, thymic stromal lymphopoietin.