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Cellular networks controlling Th2 polarization in allergy and immunity

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Abstract

In contrast to the development of Th1 (type 1 T helper cells), Th17 and Treg (regulatory T cells), little is known of the mechanisms governing Th2 development, which is important for immunity to helminths and for us to understand the pathogenesis of allergy. A picture is emerging in which mucosal epithelial cells instruct dendritic cells to promote Th2 responses in the absence of IL-12 (interleukin 12) production and provide instruction through thymic stromal lymphopoieitin (TSLP) or granulocyte-macrophage colony stimulating factor (GM-CSF). At the same time, allergens, helminths and chemical adjuvants elicit the response of innate immune cells like basophils, which provide more polarizing cytokines and IL-4 and reinforce Th2 immunity. This unique communication between cells will only be fully appreciated if we study Th2 immunity *in vivo* and in a tissue-specific context, and can only be fully understood if we compare several models of Th2 immune response induction.

Introduction: Th2 lymphocytes, the lesser gods of adaptive immunity

Th2 cell immunity is something of a two-edged sword. These cells evolved to fight off parasites, but they are also responsible for allergic diseases. Recent advances in understanding Th2 immunity bring us closer to more effective treatments for allergic diseases like allergic asthma and rhinitis, atopic dermatitis and food allergy. These are clearly on the rise in western societies, and pose a significant burden on the health of millions of patients and on health expenditure.

The immune system evolved to neutralize or kill invading pathogens, while at the same time avoiding reactivity to self, harmless commensal organisms and environmental antigens like allergens. Most often, pathogens are neutralized through the effector mechanisms of innate immunity, such as the activation of complement, and phagocytosis and/or killing by macrophages, neutrophils or eosinophils. These innate responses are reinforced by adaptive immunity, in that humoral immunity facilitates complement activation and phagocytosis by innate immune cells and that particular subsets of T lymphocytes help innate effector cells through release of cytokines. $CD4^+$ T helper lymphocytes are divided into broad categories based on the cytokines produced. Th1 lymphocytes produce interferon (IFN)-γ and stimulate the phagocytosis and killing of intracellular bacteria by macrophages. Th17 lymphocytes produce IL-17, which stimulates neutrophils to kill extracellular bacteria and fungi. Th2 lymphocytes produce IL-4, IL-5 and IL-13. IL-5 stimulates the differentiation of eosinophils, which have important roles in killing helminths and other parasites, whereas IL-4 and IL-13 stimulate contraction of smooth muscle and overproduction of mucus, which helps in expulsion of helminths from the gut and lung. The IL-4 (and, to a lesser extent IL-13) produced by Th2 cells also drives the class switching of B cell immunoglobulin production towards immunoglobulin E. Antigen-specific IgE subsequently arms effector cells, like basophils and mast cells, that express the high affinity IgE receptor (FcεRI, Fc ε receptor I), which rapidly degranulate upon

re-encounter with the antigen and help in parasite expulsion or resistance to reinfection [1]. Not surprisingly, therefore, Th2 immune responses are often accompanied by activated eosinophils, basophils, and mast cells, as well as goblet cell hyperplasia and functional changes to the surrounding tissues. These activation loops of innate and adaptive immunity need to be closely regulated. Naturally occurring and induced Treg dampen overt inflammatory reactions to microorganisms, and also suppress immunity to self, by suppressing the activation of innate immune cells, the antigen presenting capacity of dendritic cells and the effector function of Th1, Th2 and Th17 cells.

Despite the wealth of information and explosion of recent research on how Th1, Th17 and Treg responses are programmed, relatively less is known about the initiation of Th2 responses. Understanding Th2 immunity is important, as it is central to understanding allergic diseases. Like helminth infection, these diseases are characterized by increased production of IgE antibodies (to inhaled or ingested harmless allergens) and eosinophilic infiltration of the affected tissues. One possible contributing factor to the increase in allergies in the west is that the most commonly used adjuvant for vaccines in humans aluminum hydroxide is also a known Th2 inducer in mice and humans, so understanding its mechanism of action might have great implications for design of better adjuvants [1]. We will not describe the precise molecular mechanisms of Th2 lineage decisions during Th polarization and development, as this is the subject of several recent excellent review articles [2-4]. It has been shown that dendritic cells are at the very heart of inducing T cell responses; however, there has been a lot of debate about how, and even if, they are involved in Th2 response induction. Here, we will discuss the role of dendritic cells in different Th2 models and focus on the communication of dendritic cells with their neighboring epithelial cells and the cells of the innate immune response like basophils, mast cells and eosinophils.

The role of dendritic cells in different Th2 models

Dendritic cells perform a unique sentinel function in the immune response in that they recognize antigens through expression of ancient pathogen pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), NOD-like receptors, and C-type lectin receptors. These receptors will recognize motifs on virtually any pathogen, allergen, or substance. In addition, dendritic cells have been shown to be sensitive to more generic stress responses, such as oxidative stress, increased rates of protein synthesis and hypoxia, that could also signal the presence of xenobiotics, local tissue injury and disturbance of homeostasis [5,6]. Dendritic cells take up, process and present antigens on their surface, and posses the ability to migrate from the tissues to the draining lymph node. Having all these capabilities, dendritic cells are at the crossroads between innate and adaptive immunity [7].

The study of the functional importance of dendritic cells in various Th2 diseases has been greatly aided by the availability of transgenic models in which dendritic cells can be conditionally depleted or rendered functionally incapable of antigen presentation [9-12]. In one such model, in which *cd11c*DTR mice were subjected to house dust mite exposure, it was shown that Th2 immunity, as measured by the early production of IL-4 in $CD4^+$ T lymphocytes and the development of airway eosinophilia and IL-4, IL-5 and IL-13 production by mediastinal lymph node T cells, failed to develop [8]. Also, it was shown that Th2 immunity and features of Th2-dependent asthma did not develop following inhalation of the harmless protein antigen ovalbumin in the lung when dendritic cells were eliminated [9,10]. This dependence of Th2 immunity on dendritic cells was also seen when mice with chronic airway remodeling (typically seen in asthma of long duration) were exposed to a new allergen [16]. When dendritic cells were depleted during infection with the parasitic helminth *Schistosoma mansoni*, Th2 immunity failed to develop and responses skewed towards a Th1 dominated response [11]. In a more chronic model of the intestinal parasite *Heligmosomoides polygyrus*, Th2 effector responses in the gut were severely affected by dendritic cell depletion [12]. Finally, depletion of $CD11c^{hi}$ dendritic cells in mice exposed to ovalbumin antigen in the Th2 adjuvant alum completely abolished Th2 immunity, as measured by the induction of IgE responses and eosinophilic airway inflammation upon ovalbumin aerosol re-exposure in immunized mice [13]. It was shown that a large part of the adjuvant effects of alum were mediated by the *in vivo* release of the endogenous danger signal uric acid. When uric acid crystals are mixed with harmless ovalbumin and injected intraperitoneally, this also induced Th2 immunity, and this response was abolished in *cd11c*DTR mice depleted of dendritic cells [14]. These experiments showed that $CD11c^{hi}$ dendritic cells are necessary for Th2 immunity. However, it has to be noted that by using the *cd11c* promoter to deplete dendritic cells, there are also some off target effects. It has been shown that alveolar macrophages and a proportion CD8+ T cells and plasma cells also express CD11c and will, thereby, also be depleted by this treatment [10,15]. However, adoptive transfer of these affected cell types showed that the effect seen by depleting cells expressing CD11c was due to the depletion of dendritic cells [10].

Having established that dendritic cells are necessary for induction of Th2 immunity, we asked whether they are sufficient. When we transferred as few as 30,000 house dust mite-pulsed lung-derived dendritic cells into the lungs of naïve mice, a Th2 response to house dust mite was induced and eosinophilic airway inflammation developed upon re-exposure of the mice to house dust mite [8]. More precise studies are warranted to define with certainty whether specific subsets of dendritic cells (inflammatory dendritic cells versus subtypes of $CD24^+CD8\alpha^+CD103^+$ or $CD24^-CD11b^+$ conventional dendritic cells) are differentially endowed with potential to induce Th2 immunity. However, this question can be partially, yet indirectly, answered by the fact that Th2 sensitization can be induced by adoptive transfer of GM-CSF cultured bone marrow dendritic cells, most closely resembling mature monocyte-derived $CD11b^+$ dendritic cells, but not by Flt3L cultured bone marrow-derived dendritic cells that more resemble the immature, steady-state dendritic cells resident in the lymph nodes and spleen [14,16,18,19]. Lung dendritic cells can be divided into several subsets [17], grossly divided into $CD11c^+$ conventional dendritic cells and $CD11c^{low}$ plasmacytoid dendritic cells. Conventional dendritic cells can be further divided based on expression of either the myeloid marker CD11b or the integrins CD103 ($\alpha E\beta 7$) and langerin (CD207) [20]. During inflammation, monocyte-derived inflammatory dendritic cells are also attracted to the site of inflammation [13].

Function can also be site-dependent. In the skin and gut, $CD103^+$ dendritic cells are primarily involved in cross-presentation of self or foreign antigens to $CD8^+$ T cells, the generation of gut-tropic effector T cells and the induction of Treg. In the lung, however, it has recently been shown that $CD11b^+$ dendritic cells were more efficient at inducing Th2 cells producing IL-4 and IL-10, whereas $CD103^+$ dendritic cells induced greater frequencies of $CD4^+$ T cells producing IFN-γ and IL-17A [18]. The role of plasmacytoid dendritic cells in the induction of Th2 immunity is unclear. Several experiments from several groups have shown that plasmacytoid dendritic cells dampen Th2 immunity to inhaled antigens in vivo [19-21]. However, plasmacytoid dendritic cells have been shown to activate memory Th2 cells *in vitro* [22]. Recently, it was shown that increased PD-L1 and PD-L2 expression in plasmacytoid dendritic cells activated Th2 effector cells [23]. The precise role of plasmacytoid dendritic cells in suppressing Th2 development in the lung is the subject of intense research. The function of plasmacytoid dendritic cells is in balance with that of conventional dendritic cells and determined by the cytokine osteopontin [24], as well as by activation of the complement system [25,28].

Dendritic cell-independent development of Th2 immunity

Recent papers have proposed that basophils, rather than dendritic cells, are the true inducers of Th2 lymphocyte responses by serving as an early source for the Th2 instructive cytokine IL-4 and, at the same time, acting as antigen presenting cells [26,27]. These authors also suggested that for some antigens, like the model allergen papain or for the helminth *Trichuris muris*, dendritic cells were neither sufficient nor necessary for Th2 induction. These conclusions were based on the use of mice expressing MHCII exclusively from the *cd11c* promoter, and reconstituted with $CD4^+$ wild type T cells. These mice poorly reconstitute MHCII expression on migratory inflammatory dendritic cells, which might explain the lack of evidence in this model for a role of dendritic cells as sufficient APCs for inducing Th2 immunity. Another caveat to these studies was the use of the MAR1 antibody to the FcεRI. We, and others, have found that inflammatory dendritic cells are also depleted by this antibody [8,28]. Studies employing genetic strategies to deplete basophils using Cre/lox technology (*mcpt8*Cre mice) have found that Th2 immunity to papain and the helminth *Nippostrongylus brasiliensis* is unaffected in the absence of basophils, yet severely depleted when dendritic cells are genetically targeted using *cd11c*DTA mice [29]. Another recent study showed that *in vivo* basophils did not interact with antigen-specific T cells in the lymph node and that IL-4 producing basophils could only be found in the affected peripheral tissues [30]. We concur with the view of others that the most likely scenario is that basophils cooperate with dendritic cells to promote Th2 immunity, but do not necessarily have to present antigen to perform this function (Figure 1) [8,31].

Direct dendritic cell – T cell interaction and Th2 instruction

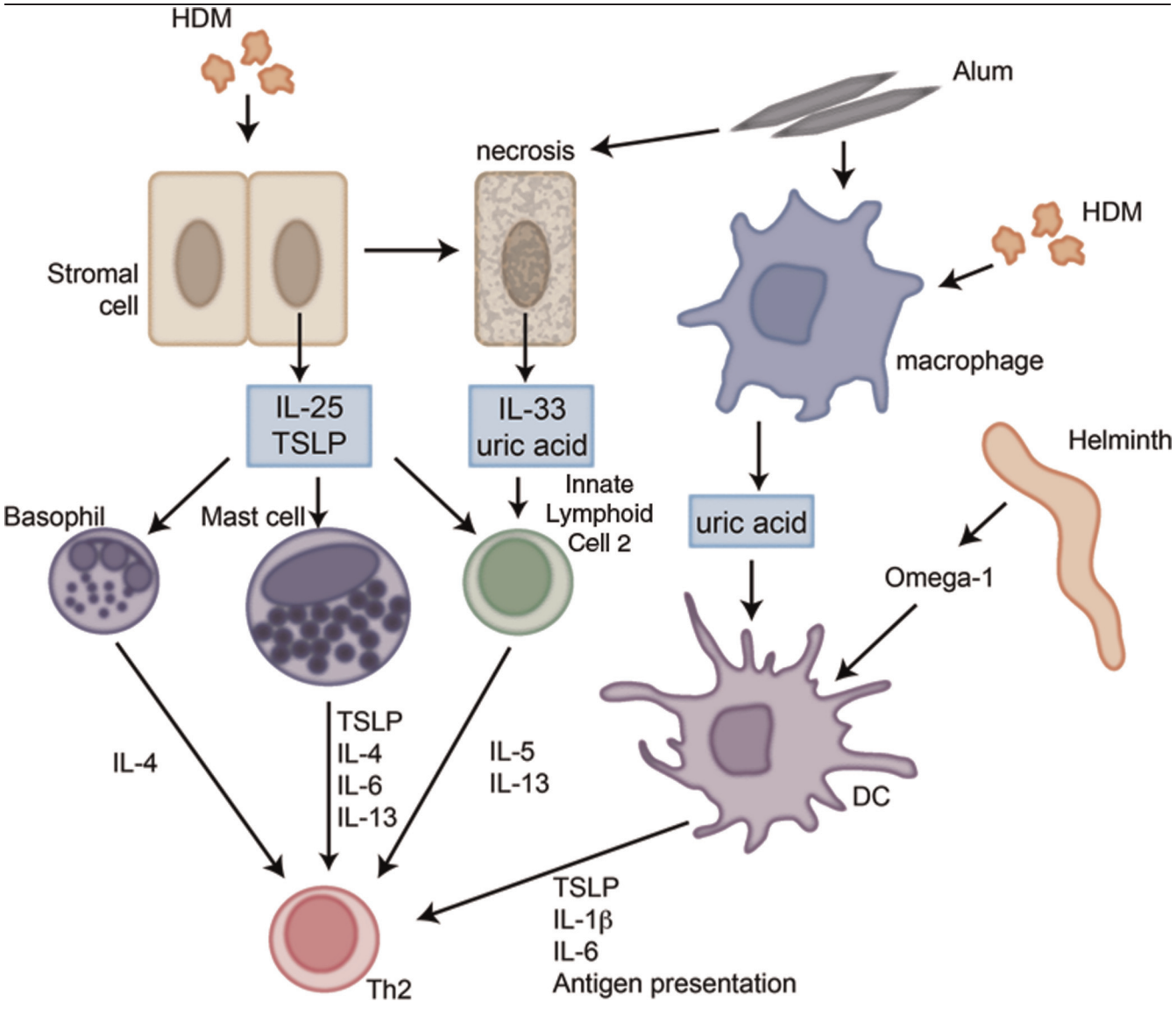
In the draining lymph node, dendritic cells interact with naïve Th cells and induce their differentiation. Whereas activated $CD4^+$ T cells differentiate into the Th1 lineage in response to IL-12 provided by the dendritic cells, similar signals that initiate Th2 differentiation remain poorly characterized. Th2 differentiation is induced through the actions of the cytokine IL-4 in the absence of IL-12 production by dendritic cells. When we retrovirally overexpressed IL-12, GM-CSF cultured dendritic cells were no longer capable of inducing Th2 immunity in the lungs [32]. Others have proposed that production of IL-6 could be decisive in Th2 instruction [33-35], since $IL\text{-}4^{KO}$ mice can still mount a Th2 response [36,37].

Differentiation of naïve Th cells into Th2 cells requires the upregulation of the transcription factor GATA3 [38] and requires activation of STAT-5 (through IL-2 or TSLP) and STAT-6 transcription factors [39]. GATA3 and STAT-6

activation can be upregulated either through IL-4R signalling or Jagged-Notch signalling [40,41]. Notch-dependent signals have been shown to directly regulate GATA-3 expression and critically control Th cell fate *in vivo* [40,42,43]. However, it has also been suggested that Notch signals provide survival and proliferative advantages to committed Th cells rather than direct commitment to the Th cell fate [44]. Nonetheless, recently Jagged1, and not Jagged2, expression on dendritic cells has been shown to be critical for IL-4 induction and the promotion of allergic responses. Where exactly the STAT-5 activating signal comes from is less well understood. Dendritic cells have been shown to produce IL-2 and TSLP, but these could also be produced by T cells in an autocrine manner upon T cell activation [45].

Besides the expression of Jagged and production of cytokines, other surface markers on dendritic cells can

Figure 1. A complex cellular network underlies the initiation of type 2 immune responses



Antigen stimulation leads to TSLP (thymic stromal lymphopoietin) or IL(interleukin)-25 production from stromal cells, which subsequently stimulates type 2 effector cytokine expression from various cell types, including innate lymphoid cells, basophils and mast cells. Alternatively, IL-33, which induces many of the features similar to IL-25 and TSLP, is released as an active form from necrotic cells and acts as an alarmin. Besides IL-33, uric acid is released from dying cells and produced by macrophages after alum or house dust mite stimulation. In addition, certain antigens such as Omega-1 from the helminth *S. mansoni* prime dendritic cells, so that they guide $CD4^+$ T cells towards a Th(T helper cells)2 response. Abbreviations: DC, dendritic cell; HDM, house dust mite; IL, interleukin; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

influence Th2 differentiation. The expression of OX40L on dendritic cells has also been shown to be required for optimal Th2 priming [46-48]. The expression of OX40L on dendritic cells is dependent upon signalling through CD40 [47,49,50]. Furthermore, CD40 expression itself is important for Th2 induction as $CD40^{-/-}$ dendritic cells were incapable of inducing Th2 responses to helminth antigens [50]. CD40 interacts with CD154 on T cells and this also seems to be necessary for Th2 immunity. When mice deficient in CD154 were infected with *S. mansoni* helminths, they did not induce Th2 immunity and suffered from severe morbidity and mortality [51]. More confirmation is provided by the observation that *S. mansoni* egg preparations prime Th2 cells via the functional modulation of dendritic cells [46,52]. Dendritic cells exposed to parasitic helminth-derived antigens, including SEA, are distinguished by their low production of IL-12, which is thought to be a prerequisite for their Th2-inducing capacity [53]. The omega-1 antigen from *Schistosoma* applied to dendritic cells *in vitro* stimulates Th2 development independent of IL-4Rα signalling *in vivo* [54].

Interaction of dendritic cells with epithelial cells leads to polarization of dendritic cells

Stromal cells have been shown to be important in instructing dendritic cell behavior, particularly in mucosal tissues where epithelial cells represent the first line barrier to the outside world, making them candidates for orchestrating immune responses [55-58]. Some supporting evidence for this comes from the finding that certain dendritic cells are located just below the epithelial lining in the lung, making them easily assessable for epithelial cell-derived factors (Figure 2) [17]. Indeed, chemokines like CCL2 and CCL20 that attract immature dendritic cells and their precursors are produced by airway epithelial cells exposed to Th2 stimuli like house dust mite [59-62]. In response to inhaled allergens, airway epithelial cells secrete a variety of cytokines (GM-CSF, TSLP, IL-25, IL-33, and IL-1 family members), which contribute to dendritic cell maturation and drive them into a Th2-activating mode [59,63].

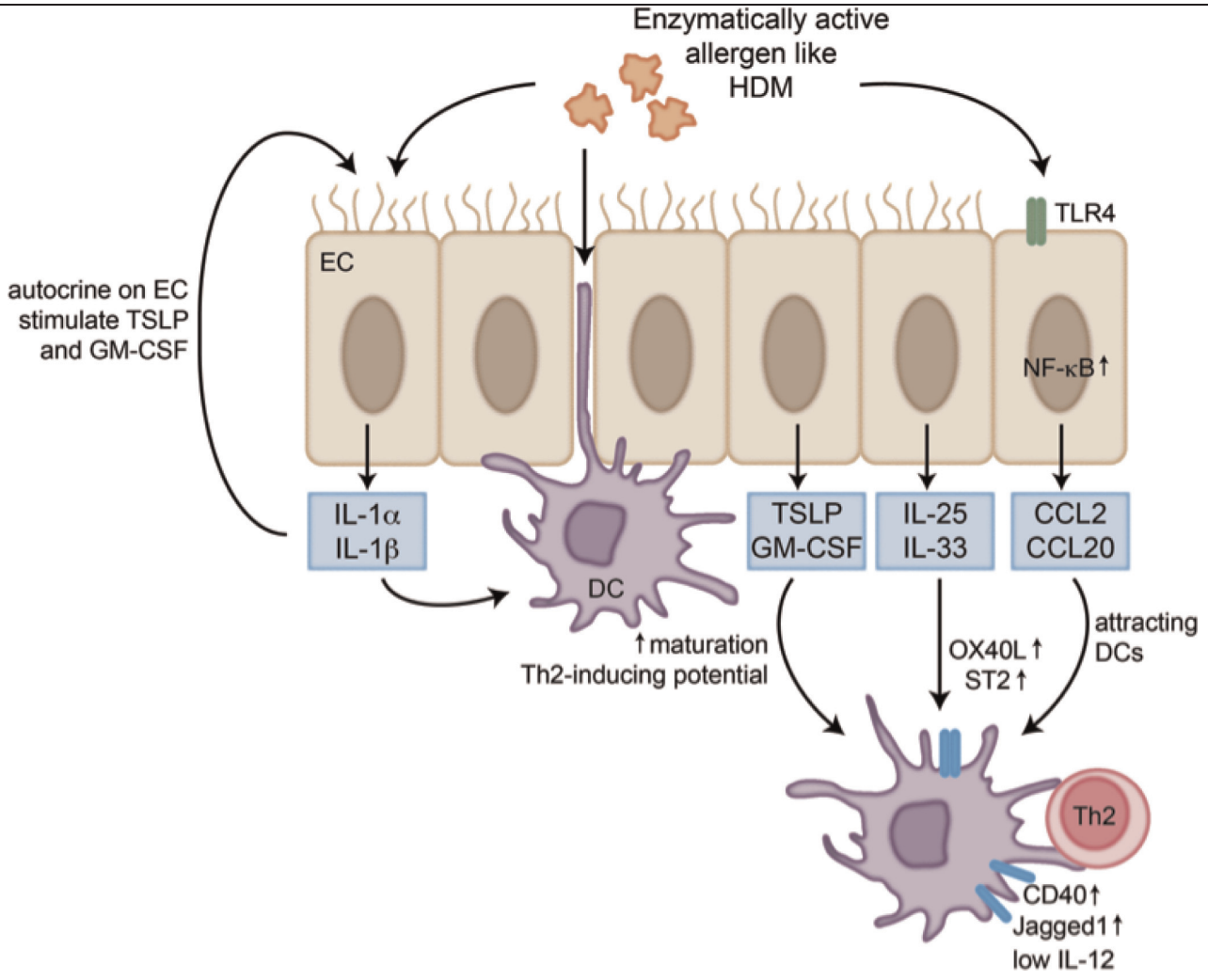
One example of this was shown in mice overexpressing GM-CSF, who showed a break of tolerance to the inhaled harmless antigen ovalbumin, and developed a strong Th2 allergic airway inflammation driven by mature dendritic cells [64]. Also, in a mouse model of house dust mite-induced asthma, GM-CSF was shown to be necessary (but not sufficient) for proper Th2 responses [65-68].

Another well-described Th2-inducing cytokine produced by epithelial cells (but also by mast cells and dendritic cells themselves under inflammatory conditions) is TSLP [45,59,69]. Initially, TSLP was found to potently enhance the maturation of $CD11c^{+}$ dendritic cells, and TSLP-primed dendritic cells were shown to promote Th2 differentiation. TSLP was reported to exert its Th2-promoting properties through a dendritic cell-mediated pathway that involved induction of OX40L [59,70-72]. Mice overexpressing TSLP in the lung epithelium had increased asthma features [73], whereas blockade of the TSLP-R inhibited key features of allergic asthma [74]. Besides the effects on dendritic cells, TSLP also influences the function of mast cells and basophils, cell types involved in Th2 responses, by acting as a growth factor [75,76]. In specific helminth infections, like *H. polygyrus*, *N. brasiliensis* and *S. mansoni*, TSLP plays a role in the clearance of worms induced by Th2 immunity [77]. While, TSLP is not necessary for clearing all helminth infections, for *Trichuris muris* it was shown to be indispensible; this could be because *T. muris* is less efficient in Th2 induction and more potent than other helminths in triggering Th1 responses [3].

IL-25 (also known as IL-17E) was initially reported as a Th2 cell-derived cytokine, but it can also be produced by basophils [72] and airway epithelial cells in response to allergens and respiratory viruses [78,79]. In mice, overexpression of IL-25 in lung epithelial cells led to allergic inflammation, likely due to the capacity of IL-25 to activate dendritic cells to induce Th2 responses [80]. Injection of neutralizing anti-IL-25 antibodies was able to strongly reduce allergic airway inflammation and airway remodelling [78].

The last group of Th2 instructive cytokines discussed here are the IL-1 family members. Some IL-1 family members are produced as pro-cytokines that require cleavage by caspase-1 through the inflammasome activation to be released [81]. IL-1α and IL-1β both bind to the IL-1 receptor 1 (IL-1RI), which is present on almost all cell types, including structural cells such as airway epithelial cells [82,83]. IL-1β is released from cultured airway epithelial cells following protease allergen exposure and enhances the release of the dendritic cell-attracting chemokine CCL20, and of the dendritic cell maturation cytokines TSLP and GM-CSF [84,85]. IL-1R signalling involves the adaptor molecule MyD88, also found downstream of several TLRs. Interestingly, house dust mite-induced Th2 responses in the lung were found to be strongly reduced in $MyD88^{-/-}$ mice [86]; however, pathology induced by *S. mansoni* infection was unaltered [87]. Also, dendritic cells have been shown to express ST2, the receptor for the IL-1 family member IL-33. This cytokine is expressed in airway epithelial cells where it is constitutively stored in nuclei. Its location is unexpected,

Figure 2. Interactions between airway epithelial cells and dendritic cells



Dendritic cells (DCs) sample the airway lumen by forming dendritic extensions between epithelial cells. Enzymatically active allergens, like house dust mite can stimulate airway epithelial cells, via TLR(toll-like receptor)4 followed by NF-κB (nuclear factor-κB) activation, to produce chemokines and cytokines that attract and activate DCs. Certain cytokines, like IL(interleukin)-25 and IL-33 will lead to the upregulation of OX40L, CD40 and ST2, which will lead to polarization of $CD4^+$ T cells towards a Th2 phenotype. Other cytokines like IL-1α and β activate DCs, but also have a positive autocrine feedback on epithelial cells and further stimulate the production of TSLP and GM-CSF. Abbreviations: DC, dendritic cell; EC, epithelial cell; GM-CSF, granulocyte-macrophage colony stimulating factor; HDM, house dust mite; IL, interleukin; NF-κB, nuclear factor-κB; TLR, toll-like receptor; TSLP, thymic stromal lymphopoietin.

and how it is released into the extracellular environment remains unclear. It has been postulated, however, that IL-33 might act as an alarmin in case of allergen exposure [88]. Dendritic cells exposed to IL-33 increased their expression of maturation markers, such as CD40 and OX40L and, thereby, became very potent at inducing Th2 responses [89,90]. Both IL-33 and IL-25 have also been shown to induce an allergic phenotype or helminth clearance independent of Th2 lymphocytes [91,92]. In Rag deficient mice, which lack T and B cells, innate lymphoid cells producing IL-5 and IL-13 are induced by IL-25 or IL-33 [93].

PRR expression by radioresistant stromal cells determines Th2 immune response induction by dendritic cells

Several groups have used radiation chimeric models to study the relative importance of PRRs of the TLR or NLR (NOD-like receptors) family to induction of Th2 immunity. Using chimeric $Tlr4^{-/-}$ animals, we and others have demonstrated that the expression of TLR4 on epithelial cells is crucial in inducing dendritic cell recruitment and intramucosal migratory behaviour in response to LPS and house dust mite [59,94]. In response to house dust mite inhalation, TSLP, GM-CSF, IL-25 and IL-33 are made in an epithelial TLR4-dependent manner [59]. TLR4 is triggered

by endotoxin found inside the house dust mite extract and this is facilitated by the house dust mite allergen Der p 2, which behaves like the MD2 chaperone and is important for TLR4 activation [95]. This seems to be a common theme, as many natural and synthetic allergens like cat allergen Fel d 1 and nickel also trigger TLR4. Although some helminths like *S. mansoni* activate dendritic cells via TLR2 and TLR3, these receptors are dispensable to control infection and pathology [96].

In a recent study, it was shown that Th2 immunity, induced by injection of ovalbumin with agonists of the NLR receptors NOD1 and NOD2, was also dependent on stromal expression of these receptors, acting to induce the systemic production of TSLP and induction of dendritic cell maturation [97]. The precise role of other NLRs like NLRP3 (involved in the formation of the IL-1 and IL-18 inducing inflammasome) in Th2 immunity to natural allergens and alum is very controversial. Initially, it was proposed that Th2 immunity to alum was completely abolished in the absence of Nlrp3 [98], but others have refuted this idea [14,99,100], and it has long been known that alum-induced Th2 asthma models were IL-1R and MyD88-independent [101]. Papers show either an abrogation of alum response in the absence of NLRP3 [98,102], no need for NLRP3 [103,104], or a selective need for NLRP3 [105]. The differences found by the different groups could be due to the type of alum and ovalbumin used and/or mouse strain background.

For natural Th2 immunity to house dust mite in the lung, we and others have found the NLRP3 inflammasome to be irrelevant [14], whereas others have found a lack of the NLRP3 inflammasome to cause a deficiency in Th2 induction when house dust mite was applied to the skin [106]. These studies have certainly aroused interest in inflammasomes, and it remains to be determined how other NLRs are involved in Th2 immune responses to allergens and helminths. Finally, stromal cells (like epithelial cells, and also dendritic cells) express C-type lectin receptors like dectin-2 that have been shown to be involved in Th2 immune responses to house dust mite allergen [107]. Signalling through these receptors often involves the spleen tyrosine kinase pathway that increasingly appears to be crucial for Th2 development [14,34], through, as yet, unidentified mechanisms.

Conclusion

Recent advances are starting to dissect the mechanisms of Th2 development, and a picture is emerging that mucosal epithelial cells instruct dendritic cells to promote Th2 responses by inducing their activation in the absence of IL-12 production. At the same time Th2 stimulates innate immune cells like basophils, mast cells and innate lymphoid cell 2 to produce more polarizing cytokines and ILl-4, which reinforce Th2 immunity. This unique communication network of cells will only be fully appreciated if we study Th2 immunity *in vivo* in a tissue specific context, and if we compare several models of Th2 immune response induction, like helminth infection, allergen exposure and chemical adjuvants. Given the role of dendritic cells in promoting allergy, greater understanding may yield new targets for prevention and treatment.

Abbreviations

GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; NLR, NOD-like receptors; PRR, pattern recognition receptor; Th, T helper cell; TLR, toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

Competing Interests

The authors declare that they have no competing interests.

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