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Lung dendritic cell–epithelial cell crosstalk in Th2 responses to allergens

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Dendritic cells (DC) have been shown to be responsible for the initiation and maintenance of adaptive Th2 responses in asthma. It is increasingly clear that DC functions are strongly influenced by crosstalk with neighboring cells like epithelial cells, which can release a number of innate cytokines promoting Th2 responses. Clinically relevant allergens often interfere directly or indirectly with the innate immune functions of airway epithelial cells and DC. A better understanding of these interactions might lead to a better prevention and ultimately to new treatments for asthma.

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Introduction

Radioresistant cells such as epithelial cells lining the respiratory tract constitute the primary cellular barrier. Epithelial cells are uniquely positioned at the interface between ‘inside versus out,’ making them candidates for orchestrating immune responses. Epithelial cells possess microbial-detection mechanisms, and they express a tightly regulated and specifically localized set of pattern recognition receptors (PRRs), which enables them to respond to antigens and allergens. An emerging concept is that the epithelial barrier influences the development of antigen-specific immunity, suggesting that the type of immune response is defined by the local tissue micro-environment. It is therefore very likely that antigen recognition by epithelial cells determines the functional properties of tissue-residing DCs, thereby instructing the outcome of antigen-specific immunity. This concept has important implications for the regulation of mucosal homeostasis and for the initiation of innate and adaptive immune responses.

Allergen recognition in the airways involves pattern recognition receptors

Allergens are a complex mixture of biologically active molecules such as proteases, chitins [1], glycans, endotoxin, and a variety of still unidentified components. During the past years, it has become increasingly clear that most of the environmental allergens express pathogen associated molecular patterns that might trigger innate receptors such as Toll Like receptors (TLRs), NOD like receptors and also C-type lectin receptors [2]. Interestingly, polymorphisms in several PRRs have been found associated with allergen sensitization and asthma [3]. As an example, both chitin that is present in house dust mite (HDM) and cockroach frass are able to induce T cell responses that are TLR2-MyD88-dependent [4–6]. However, although both compounds trigger the same TLR, the outcome of immune response induced differed dramatically. Indeed, chitin was found to induce Th2 responses and to promote allergen sensitization whereas cockroach frass appeared to be protective against the development of allergic airway inflammation [4]. A possible explanation is that the recognition of complex allergens involves the simultaneous triggering of several PRRs and signalling pathways. Some allergens, like HDM, can for instance also trigger TLR4. Kim Bottomly’s group has shown years ago that the low amounts of LPS contained in the model allergen ovalbumin lead to a TLR4/MyD88-dependent Th2 response in the airways [7–9]. The fact that TLR4/MyD88 axis was able to mediate a Th2 response was somewhat surprising since LPS, the prototypical ligand for TLR4, had been shown to protect from Th2 sensitization [7]. However, the involvement of TLR4 signalling in mediating Th2 responses has been recently supported by groups using relevant allergens, like HDM, to induce Th2 sensitization [10•,11•]. TLR4 triggering by allergens has often been attributed to their endotoxin content [7], although there seems to be a more intimate link between allergic sensitization and TLR4 signalling. Indeed, it has been reported that Derp 2, one of the major allergen of HDM, was a homolog of MD2, the LPS-binding member of the TLR4 signalling complex [12•]. In this way, Derp 2 might promote or facilitate TLR4 signalling. It is important to note that TLRs are not the only PRRs triggered by environmental allergens. In fact, some airborne allergens contain proteases or glucans that can facilitate allergen sensitization by stimulating various PRRs (protease-activated receptors, C-type lectins) on various immune cells [13–16].

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Th2 immunity to inhaled allergens depends on PRR signalling in DCs

In the recent years, the focus has been put on trying to dissect the molecular mechanisms underlying allergenicity and Th2 sensitization. Certainly, the triggering of PRRs on DCs by allergens and environmental triggers seems to be essential. Studies have shown that HDM can trigger TLR4 and Dectin-2 directly on DCs. Indeed, allergens such as house dust extracts or cockroach frass induced DC maturation [17] and promoted the production of LTC4 [18,19], of the pro-Th17 cytokines IL-6 and IL-23, and of low levels of IL-12p70 [17,20,21]. The activation of DCs by HDM relied on downstream MyD88 signalling, although others have shown the involvement of IRF3 and Syk signalling [19,22]. Pollen extracts were also shown to modulate bone marrow-derived (BM)-DC responses in a process partially dependent on TLR4 triggering [23].

Crosstalk between epithelial cells and lung DCs leads to Th2 immunity

Although DCs can directly respond to allergens *in vitro*, one major caveat is that most of the studies performed have used bone marrow-derived DCs in mice or monocyte-derived DCs in humans to mimic lung DC responses. The direct effect of allergens on purified lung DCs remains unclear. There is evidence that allergens administered in the airways of mice or humans can recruit and activate lung DCs. However, this activation is not always necessarily direct. Stromal cells in the airways can certainly respond to allergens and influence the behavior of dendritic cells. *In vitro* studies have shown that airway epithelial cells (AECs) exposed to HDM produced CCL2 and CCL20, chemokines attracting immature DCs and their precursors [16,24]. CCL20 secretion was not dependent on TLR2/4 expression or on the protease activity of allergens, but relied on beta-glucan moieties within HDM [16,25]. Proteases in pollens, cockroach and house dust mite were found to disrupt epithelial tight junctions and, in this way, gain access to DCs. Allergens induced the production of inflammatory and instructing pro-Th2 cytokines by AECs [26–29]. All these data obtained *in vitro* or *ex vivo* point to the fact that allergen-activated AECs might contribute to instruct DCs to promote Th2 sensitization. This has been confirmed *in vivo* in a series of experiments using bone marrow chimeric mice lacking TLR4 on either immune cells or radioresistant epithelial cells, where the response to HDM was substantially altered when epithelial cells could not sense the endotoxin in the allergen [10,30]. Interestingly, NF- κ B activation was often observed in epithelial cells exposed to allergens and several studies have demonstrated that lung epithelial cell-specific deletion of NF- κ B lead to decreased cytokines responses [31–33]. On the opposite, the selective activation of NF- κ B in airway epithelial cells was enough to drive allergic airway inflammation [34,35].

Epithelial cell-derived factors instruct lung DCs to induce Th2 responses to allergens

In response to inhaled allergens, AECs secrete a variety of cytokines (GM-CSF, TSLP, IL-25, IL-33 and IL-1 family members), which contribute to mature DCs and to drive them into a Th2-activating mode [10,36] (Figure 1).

GM-CSF

GM-CSF is produced by AECs exposed to allergens [25,37]. The importance of GM-CSF in Th2 responses came from data obtained in mice overexpressing GM-CSF in the lung. When exposed to the harmless antigen ovalbumin, mice overexpressing GM-CSF showed a break of inhaled tolerance and developed a strong allergic airway inflammation driven by mature DCs [38]. Along this line, BMDCs grown in the presence of GM-CSF were found to be very effective at inducing Th2 priming [39,40]. Moreover, the administration of HDM in the airways also leads to Th2 sensitization that was partially mediated by endogenous GM-CSF [41]. On the contrary, in a mouse model of HDM-induced asthma, GM-CSF neutralization led to reduced Th2 responses [42,43].

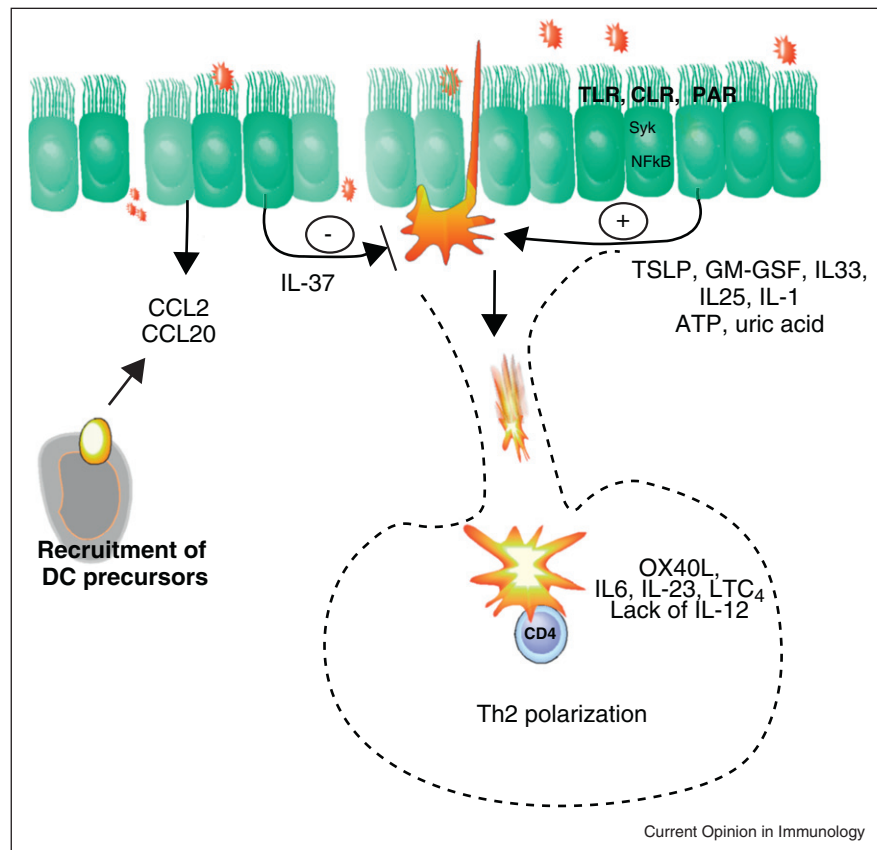
TSLP

Another well-described cytokine affecting DCs, B cells and Th2 cells is TSLP. It is produced not only by epithelial cells [10] but also by mast cells and DCs themselves under inflammatory conditions [44,45]. Various groups have reported correlations between TSLP and asthma or allergic rhinitis development [46–48]. Its role in Th2 responses came from the fact that mice lacking TSLP receptor (TSLPR) expression have attenuated Th2 features in an experimental asthma model [49] whereas mice overexpressing TSLP in the lung epithelium had increased asthma features [50]. Recently, TSLP has also been shown to break inhaled tolerance by inhibiting the generation of induced allergen-specific regulatory T cells [51]. Moreover, the blockade of TSLP by using a soluble TSLPR *in vitro* lead to reduced expression of maturation markers on TSLP-activated DCs and administration of this soluble TSLPR before sensitization reduced eosinophilia, IgE levels and Th2 cytokines *in vivo* [52]. The way TSLP induces Th2 responses is probably through its capacity to activate DCs to upregulate OX40L, allowing them to expand Th2 memory cells and to enhance the expression of IL-25R (IL-17RB) on these memory cells [53–55].

IL-25

IL-25 (also known as IL-17E) has initially been reported as a Th2 cell-derived cytokine. However, it can also be produced by basophils [56] and epithelial cells in response to allergens and respiratory viruses [57,58]. The number of IL-25-expressing and IL-25R-expressing cells is increased in biopsies of asthmatic patients [59,60]. In mice, overexpression of IL-25 in lung epithelial cells

Figure 1



Both lung DCs and epithelial cells express pattern recognition receptors (PRRs) and can be activated directly by allergens. In response to allergens, lung epithelial cells produce chemokines (CCL2, CCL20) that attract immature cDCs and inflammatory monocytes. Activated epithelial cells produce instructing cytokines (like IL-1, GM-CSF, and TSLP) and danger signals (ATP, uric acid), which favor DC maturation and their migration to the MLN where they will induce Th2 responses. Some epithelial-derived cytokines like IL-37 are able to suppress immune responses by inhibiting DC activation.

led allergic inflammation [57], probably owing to the capacity of IL-25 to activate DCs to induce Th2 responses [58]. Injection of neutralizing anti-IL-25 antibodies was able to strongly reduce allergic airway inflammation and airway remodelling [57,61].

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 [62]. IL-1 α and IL-1 β both bind to IL-1 receptor 1 (IL-1RI), which is present on almost all cell types, including structural cells such as AECs [63,64]. IL-1 β is released from cultured airway epithelial cells following protease allergen exposure and enhances the release of the DC-attracting chemokine CCL20, and of the DC maturation cytokines TSLP and GM-CSF, by epithelial cells [65,66]. IL-1R signalling involves the adaptor molecule MyD88, also found downstream several TLRs. Interestingly, HDM-induced Th2 responses in the lung were found strongly reduced in MyD88 $^{-/-}$ mice [11 $^{\bullet}$]. In this study, DC

migration to the LNs was altered in MyD88 $^{-/-}$ but not in TLR4 $^{-/-}$ mice, suggesting that some aspects of DC biology might be controlled by IL-1 family members signal through MyD88. DCs have been shown to express ST2, the receptor for the IL-1 family member IL-33. This cytokine is expressed in AECs where it is constitutively stored in nuclei. Its location is unexpected and how it is released in the extracellular environment remains unclear. It has been postulated, however, that IL-33 might act as an alarm in case of allergen exposure [67]. DCs exposed to IL-33 increased their expression of maturation markers, such as CD40, CD80 and OX40L and became very potent at inducing Th2 responses [68,69]. Recently, more attention has been put on trying to elucidate the role of other IL-1 family members. IL-37 was reported to be different from other members of the family since it was able to suppress inflammatory responses. When expressed in lung epithelial cells or in macrophages, IL-37 decreased the production of pro-inflammatory cytokines, such as IL-1 α , TNF α and IL-6 by these cells [70]. Also, little information is

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available about another member called IL-1F9. Elevated levels of this cytokine have been detected in AECs of allergen-challenged mice and it was shown to promote inflammation [71]. Whether this epithelial-derived cytokine is able to instruct lung DCs to induce Th2 responses to inhaled allergens remains to be elucidated.

Endogenous danger signals

Although triggering of PRRs might be a way allergens induce Th2 immunity, another could be that allergens induce the production of endogenous danger upon physical or metabolic stress [72]. We have previously reported that a single administration of HDM in the airways of mice induced the release of both ATP and uric acid [73^{••}]. HDM-induced UA promoted Th2 sensitization by amplifying the production of AEC-derived DC-instructing cytokines like TSLP, GM-CSF, and IL-25. Interestingly, we found that airway AECs were a source of uric acid, and that the release of uric acid was TLR4-dependent [73^{••}].

Conclusion

In the lung, both DCs and epithelial cells express a set of PRRs to sense the presence of inhaled antigens. It is increasingly clear that most of DC functions are controlled by factors produced by epithelial cells. Ultimately, a better understanding of epithelial cell-DC interactions in the lung will provide new opportunities for the prevention and treatment of allergic disorders.

Conflict of interest

The authors have no conflict of interest to disclose.

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- This is the first paper describing that house dust mite can induce the production of the endogenous danger signal, uric acid, by airway epithelial cells. This uric acid production was dependent on TLR4 triggering by house dust mite.