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Epithelial–dendritic cell interactions in allergic disorders

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Airway epithelial cells act through multiple mechanisms to function as an important component of the pulmonary defence strategy that is crucial to the maintenance of immune homeostasis. Dendritic cells are uniquely potent inducers of immune responses and it is increasingly clear that epithelium has the capacity to modulate the functional activity of dendritic cells, and vice versa, through production of a diverse array of mediators. Bidirectional interactions between epithelial cells and dendritic cell networks can thus impact upon the development and progression of immunity/tolerance in respiratory tissues. In this brief review we highlight the most recent advances in understanding how airway epithelial/dendritic cell interactions contribute to allergic disorders.

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Introduction

Networks of airway mucosal dendritic cells (AMDC) reside within and below the epithelium, function as sentinels in local immune surveillance, and dynamically influence the induction and regulation of innate and adaptive immunity in the airways. Following migration to draining lymph nodes, antigen-bearing AMDC can interact with and activate antigen specific naïve T-cells. The class of immune response generated is largely dependent on the collective translation of signals received by AMDC, which in turn reflect properties of the inductive inflammatory stimulus and the signals that AMDC receive during their sojourn in the mucosal microenvironment.

The extensive epithelial surface is a dominant feature of the respiratory mucosa and under normal circumstances

effectively separates internal tissues from the external environment. Airway epithelial cells (AEC) represent the point of first exposure to inhaled material, and it is clear that AEC play important roles in the maintenance of pulmonary homeostasis. Given the close proximity of AEC and AMDC (and other cells of the innate immune system such as alveolar macrophages), it is not surprising that AEC regulate innate and adaptive immunity in the lung. AEC achieve this by expressing various molecules that can modulate immune responsive cells such as AMDC in both the steady state and during inflammatory episodes. In allergic airways disease Th2 responses are exaggerated and/or dysregulated and there is increasing evidence that both direct and indirect interactions between AEC and AMDC are important contributors to sensitisation, initiation and progression to chronic disease.

Altered epithelial barrier function: implications for developing asthma

Recently there has been a resurgence of interest in the role of epithelial barrier function in the development of allergic asthma. A structurally or functionally defective epithelial barrier may lead to easier access of aeroallergens to AMDC and enhanced signalling between AEC and AMDC [1]. Genetic studies have highlighted polymorphisms in epithelial barrier proteins and cytokine genes associated with asthma and airway hyper-responsiveness, and these potentially impact upon AEC/DC communication [2,3]. It is likely that many of the environmental risk factors associated with allergic sensitisation interfere with both epithelial permeability and AEC/DC communication [4–8].

Allergens and epithelial cells

Antigens responsible for causing allergic disease are chemically diverse, often have enzymatic activity, and may contain or be co-exposed with varying amounts of microbial or other environmental contaminants. Allergen interaction with DC and development of Th2 immunity to inhaled allergen has been shown to depend in varying degrees on factors including protease activity [9,10], potential to induce TLR signalling [11*,12**,13**], triggering of non Toll-like receptors [14,15], and adjuvant effects of other co-exposed material [16].

Pattern recognition receptors on epithelial cells

AEC express an array of pattern recognition receptors (PRRs), including TLRs, NLRs and PARs, which can trigger mediator release [17,18]. PRRs enable the strategic recognition of organisms encountered in the respiratory mucosa and additionally facilitate direct AEC interaction with allergens, which can have profound

2 Allergy and hypersensitivity

effects on DC. Recent studies employing chimeric mice lacking TLR4 have demonstrated that responses to allergens are profoundly altered when AEC cannot detect endotoxin associated with the allergen. Notably, TLR4 triggering on structural cells, but not on DC, appears necessary and sufficient for DC activation and priming of effector Th2 responses to HDM [11[•]]. By contrast, other investigators report that Th2 sensitisation requires TLR4 signalling in both stromal cell *and* DC compartments [12^{••}]. Earlier work suggested that the concentration of LPS during sensitisation is crucial in determining Th-cell differentiation, high versus low dose inducing Th1 and Th2 responses respectively [19,20]. Interestingly, when TLR4 signalling was limited to the stromal cell compartment, high LPS exposure promoted the maturation of Th2 inducing DC that upregulate the Notch-ligand Jagged-1 rather than the Th1 inducing Delta-4 [12^{••}]. It is thought that in normal mice, Th2 immunity is not induced by high level LPS, because the Th2 signal provided by stromal cells is overcome by the Th1-selective DC response [21]. These contrasting findings may reflect differences in the time frame between exposure and analysis. Additionally, HDM probably contains other activating signals that can also act on AEC and/or DC, and in this regard the allergen Der p 2 may enhance responses to LPS by virtue of direct interaction due to functional homology with the TLR4 complex, thereby facilitating signalling [13^{••}].

Airway epithelial cells express various factors that can alter DC function

CD200

AEC can express the ligand for the inhibitory immune receptor CD200R that is expressed on lung macrophages. Mice lacking CD200 display increased macrophage activity and enhanced susceptibility to influenza infection [22,23]. While it is not yet clear if this pathway is directly involved in the interaction between AEC and DC, it is likely that this axis contributes at least indirectly to the control of DC function.

Collectins

Lung collectins have major effects on immune function in the peripheral lung, including regulation of DC function. Surfactant protein D (SP-D) deficient mice showed spontaneous activation of myeloid DC, while addition of SP-D to bone marrow derived DC inhibited their maturation [24]. Similarly, SP-D can inhibit mite allergen induced changes in DC-SIGN expression on human DC [25]. By contrast, SP-D deficient mice reportedly have reduced allergic airway inflammation, and moreover a polymorphism in the SFTPD gene is linked to a reduced risk of atopy in humans [26]. Additionally the SIRP α /CD47 regulatory axis, which is implicated in the control of migration and phagocytosis may play a role in AEC mediated regulation. Lung surfactant proteins SP-A and SP-D interact with SIRP α ,

and may provide constitutive signalling during steady state conditions, blocking interaction with CD47 and regulation of lung macrophage phagocytic function [27]. Evidence for a direct effect on AMDC is lacking, though AMDC express SIRP α and the expression of CD47 (which binds SIRP α) has been linked to the control of CD103 DC migration and development of Th2-mediated inflammation [28].

Vitamin D

The role of vitamin D in immune function is increasingly recognised, and locally produced vitamin D is believed to have important immunomodulatory effects [29]. Lung EC have recently been found to express high baseline levels of the activating enzyme 1 α -hydroxylase that converts vitamin D to its active form [30], and there are numerous reports of links between vitamin D deficiency and asthma (for example [31]).

Thymic stromal lymphopoietin (TSLP), IL-25 and IL-33

These three closely related cytokines can be expressed by AEC, can condition DC to favour Th2 polarisation, and appear to be crucial for the development of atopic disease. TSLP promotes DC survival and activation by upregulation of MHC class II and CD40L that then induces expansion of Th2-memory cells (as reviewed by [32]). An intact Th2 response is an essential downstream element in TSLP-driven allergic airways inflammation, as blocking STAT 6 signalling or IL-4/IL-13 function reverses the TSLP induced response [33]. Overexpression of TSLP in the lungs of mice induces spontaneous inflammation that resembles human asthma, though complete disease expression requires both TSLP and antigenic stimulation [34]. A number of stimuli relevant to asthma can induce TSLP expression in AEC including ds-RNA [35], vitamin D, allergen-derived proteases, Fc ϵ R1 overexpression and Th2-associated cytokines such as IL-25.

AEC also influence DC control of Th2 differentiation via local production of Th2-trophic cytokines such as IL-25 (e.g. [36]) and IL-33, which has been shown to condition DC to induce naive T-cells to produce atypical Th2 immunity characterised by IL-5/IL-13 secretion without IL-4 [37[•]]. Recent evidence suggests that IL-33 is an 'alarmin' [38[•]] and therefore is proposed to play an important role in sensing damage. AEC are known producers of IL-33 and elevated levels (compared to relevant controls) are found in asthma models and asthmatic individuals [39–41]. This can potentially be linked to allergen (as well as pathogen and other environmental stimuli) induced damage of AEC. Defective IL-25 signalling can result in reduced levels of cytokine production by AEC and eosinophils. EC-derived MMP-7 can mediate activation of IL-25, while also inhibiting regulatory T-cell development, thus coordinating allergic airway inflammation [42].

Foxa2

Foxa2, a member of the forkhead box family of transcription factors, is expressed in respiratory EC [43^{*}]. Conditional deletion of Foxa2 from respiratory EC during lung development led to Th2 mediated eosinophilic lung inflammation, goblet cell metaplasia and myeloid DC recruitment and activation during early postnatal life. Interestingly, overexpression of Foxa2 in respiratory EC in adult mice did not alter allergen mediated inflammatory responses, highlighting the fact that the regulatory properties of Foxa2 are most apparent during development.

Cadherins

AEC from asthmatics show reduced expression of E-cadherin and other junctional proteins [44,45]. This appears to be a key aspect of the epithelial–mesenchymal transition seen in airway remodelling. This is also likely to have major effects on immune function [46], though detailed studies of how this might alter lung DC function have not been reported.

Chemokines

In the airways DC are largely recruited as immature monocytic precursors from blood, and AEC contribute to this process through release of various chemokines. In this context, Nathan and co-workers have recently highlighted the role of AEC production of CCL20 after *in vitro* exposure to mite allergen [15]. Induction of CCL20 is dependent on β -glucan moieties within the allergen extract possibly interacting with the dectin-1 receptor, rather than TLR signalling or protease activity [15].

AEC-DC co-culture studies

Improved understanding of the interactions between human AEC and DC has emerged from a number of coculture studies. Ward *et al.* 2009 studied the influence of resting primary human EC on the differentiation of monocytes into DC [47]. EC conditioned medium skewed the differentiation towards macrophages rather than DC, and this was mediated by an unidentified soluble factor. In addition, supernatant from two human airway EC lines inhibited DC activation, an effect partly mediated via TGF- β [48]. Primary murine tracheal EC also inhibited the activation of bone marrow-derived DC, inducing these cells to express arginase-1, a marker of alternatively activated macrophages [48].

By contrast, findings from our group indicate that the capacity of AEC to regulate the differentiation of monocyte into DC is largely dependent on direct cell–cell contact [49^{*}]. AEC induced the differentiation of more activated DC that expressed higher antigen uptake/processing, with enhanced responsiveness to LPS and polyI:C. Importantly, AEC-conditioned DC showed a reduction in capacity to support Th2-memory responses, but no change in Th1 cytokine production. Blocking

experiments implicated key roles for AEC-derived IL-6 and in particular type I interferon in modulating DC function [49^{*}]. It is currently unclear whether this regulatory network is disturbed in asthma, but type I interferon synthesis in AEC of asthmatics is reportedly reduced [50,51].

When AEC are activated, they lose the capacity to inhibit DC activation. Bleck *et al.* 2008 showed that diesel exhaust particles can induce AEC to secrete TSLP that in turn activates DC and conditions them for Th2 polarisation [4].

The interaction between EC and DC is certainly not unidirectional. Obregon C *et al.* 2009 showed that DC can secrete exovesicles containing TNF α , class II MHC and co-stimulatory molecules, which can activate EC, thereby amplifying the magnitude of the innate immune response [52].

AEC:DC interactions in the context of respiratory infection

In a paramyxovirus infection model, mice deficient in the interferon signalling molecule Stat1 showed increased viral replication and inflammation relative to wild type mice, and this deficit was not corrected by reconstitution with wild type bone marrow [53^{*}]. By contrast, wild type mice that received bone marrow from Stat1 deficient mice were resistant to infection. These findings emphasise the crucial role of resident structural cells in the lungs, especially AEC, in innate immune function, though AEC:DC interactions were not studied directly.

Wang and colleagues [54] examined lung EC regulation of T-cells and DC in mice. EC inhibited T-cell function directly and indirectly via DC, through a variety of mechanisms including both cell contact and secreted factors. The regulatory capacity of lung EC was lost after RSV infection. Notably, RSV can induce rat lung EC to produce TSLP that in turn activates myeloid DC [55]. By contrast, others have reported that RSV infection does not alter the ability of human AEC to induce the differentiation of monocytes into DC with tolerogenic properties [56].

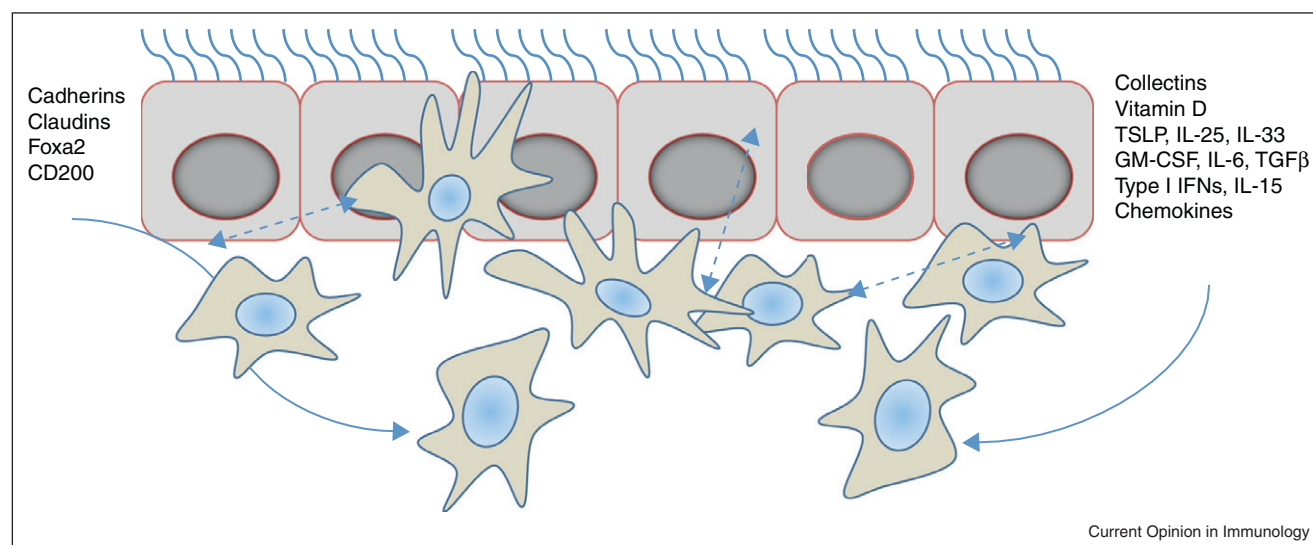
Korpi-Steiner *et al.* 2010 showed that co-culture of AEC with blood monocytes markedly enhances release of CXCL10 during rhinovirus infection [57]. This effect was mediated by type I IFN release by monocytes. Though not specifically examined in this study, DC are highly likely to have a similar effect to enhance AEC release of CXCL10.

Conclusion

Bidirectional interactions between AEC and local DC networks play a crucial role in the maintenance of immunological homeostasis in airway tissues, as outlined

4 Allergy and hypersensitivity

Figure 1



Interactions between airway epithelial cells and dendritic cells. Epithelial can modulate DC function via both cell membrane associated molecules and secreted soluble mediators, while DC can also alter epithelial cell function. Due to space constraints, not all the numerous potential mediators are included in the diagram above.

schematically in Figure 1. In particular, AEC produce a battery of immune modulators the role of which is to limit activation of innate immune surveillance mechanisms, thus setting the immunological ‘rheostat’ within the respiratory mucosa that ultimately determines the threshold that must be overcome before induction of adaptive immunity can occur.

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