

### Epithelium: At the interface of innate and adaptive immune responses

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Several diseases of the airways have a strong component of allergic inflammation in their cause, including allergic rhinitis, asthma, polypoid chronic rhinosinusitis, eosinophilic bronchitis, and others. Although the roles played by antigens and pathogens vary, these diseases have in common a pathology that includes marked activation of epithelial cells in the upper airways, the lower airways, or both. Substantial new evidence indicates an important role of epithelial cells as both mediators and regulators of innate immune responses and adaptive immune responses, as well as the transition from innate immunity to adaptive immunity. The purpose of this review is to discuss recent studies that bear on the molecular and cellular mechanisms by which epithelial cells help to shape the responses of dendritic cells, T cells, and B cells and inflammatory cell recruitment in the context of human disease. Evidence will be discussed that suggests that secreted products of epithelial cells and molecules expressed on their cell surfaces can profoundly influence both immunity and inflammation in the airways. (*J Allergy Clin Immunol* 2007;120:1279-84.)

**Key words:** Epithelium, innate immunity, adaptive immunity, airway inflammation, immune regulation

Epithelial cells play important roles in host defense, inflammation, and regulation of immune responses. This review highlights new data suggesting that epithelial cells mediate innate immune responses and regulate adaptive immune responses involving dendritic cells (DCs), T cells, and B cells, three cell types that are of central importance in allergic and other inflammatory diseases of the airways.

#### Abbreviations used

BAFF: B-cell-activating factor of the TNF family  
CSR: Class-switch recombination  
DC: Dendritic cell  
pIgR: Polymeric immunoglobulin receptor  
TLR: Toll-like receptor  
Treg: Regulatory T cell  
TSLP: Thymic stromal lymphopoietin

We have included information regarding the relevance of these new findings to asthma and other allergic diseases, where available. A picture emerges in which epithelial cells mediate innate host defense through secretion of dozens of distinct antimicrobial products. When innate immune responses fail, epithelial cells direct early adaptive immune responses by helping to program the DC response to antigen exposure. Epithelial cells also directly influence the response of antigen-specific T and B cells through the release of cell subtype-specific chemokines and the expression of soluble and cell surface-expressed molecules that regulate differentiation, proliferation, activation, and survival of T and B lymphocytes. Epithelial activation is a characteristic of asthma, rhinitis, chronic rhinosinusitis, chronic obstructive pulmonary disease, and other airways diseases. In some cases, deficiencies in the ability of the epithelium to maintain the immunologic and physical barrier might play a role in susceptibility to these diseases.

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#### EPITHELIAL CELLS AND INNATE IMMUNITY

Accumulating evidence indicates that epithelial cells play important roles in the initiation, maintenance, and regulation of both innate and adaptive immune responses in the airways. Epithelial roles in innate immunity have been known for decades, since Sir Alexander Fleming reported in 1922 that lysozyme and other mucosal substances prevent the growth of bacteria and other microorganisms. In addition to their mucociliary clearance function, epithelial cells are now known to kill or neutralize microorganisms through the production of several families of molecules,

including enzymes (lysozyme, phospholipases, peroxidases, and complement components), permeabilizing peptides (eg, defensins, cathelicidins, bacterial permeability-increasing protein [BPI], and palate, lung, and nasal epithelium clone [PLUNC]), collectins (eg, SP-A, SP-D, and MBL), pentraxins (eg, PTX-3 and CRP), protease inhibitors (eg, secretory leukocyte proteinase inhibitor [SLPI] and elafin), small molecules (ROS, thiocyanate, and nitric oxide), binding/neutralizing proteins (eg, mucins, serum amyloid A [SAA], and lactoferrin) and others.<sup>1</sup> Recent studies indicate that the production of many of these substances is initiated by pathogen-recognition receptors (see Fig 1), including Toll-like receptors (TLRs; TLR1 through TLR10), nucleotide-binding oligomerization domain [NOD]-like receptor [NLR] family receptors (eg, NOD1), helicases (eg, retinoic acid-inducible gene 1 [RIG-I] and melanoma differentiation-associated gene 5 [MDA5]), the double-stranded RNA binding kinase PKR, and others. It is now quite clear that epithelial cells routinely protect the airways from colonization or infection by most microorganisms.

An important component of the epithelial armamentarium in innate immunity is the maintenance of barrier function. There is evidence for deficient barrier function in keratinocytes of patients with atopic dermatitis and to some extent in airway epithelial cells of patients with asthma because of insufficient expression of the epidermal differentiation complex, a cassette of genes that includes the protease inhibitor serine protease inhibitors of the Kazal type (SPINK5), profilaggrin, and other genes that either form or protect tight junctions and other structures involved in epithelial integrity.<sup>2-4</sup> Reduced barrier function might increase susceptibility to sensitization and lower the threshold of antigen exposures required to drive local antigen-dependent inflammation. Recently, null mutations in profilaggrin have been linked to asthma incidence, as well as severity, suggesting that altered barrier function in either the skin or the airways is an important risk factor for allergic diseases.

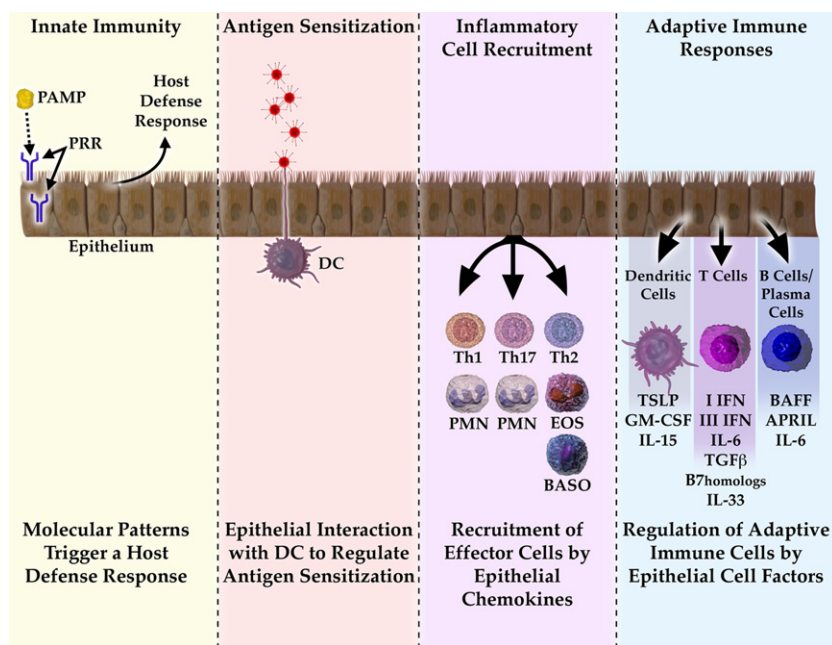
Epithelial cells also play an important role in the initiation of adaptive immune responses in the airways. Epithelial cells can trigger and modify the activation and differentiation of DCs, B cells, and T cells. When the innate immune functions of epithelium mentioned briefly above fail, adaptive immune responses to potential pathogens are necessary and lifesaving. In addition, epithelial restraint of inflammatory immune responses might be helpful to prevent excessive or unnecessary damage to the airways. Although responses of cells armed with antigen-specific immunoglobulins (eg, mast cells, basophils, eosinophils, and neutrophils) can play a role in the adaptive response, they will not be considered here.

## EPITHELIAL EFFECTS ON DCs

There is a highly meshed network of DCs within the respiratory epithelium. A subset of these DCs, referred to as intraepithelial DCs, has a distinct phenotype,

expressing  $\alpha_E\beta_7$ , Fc receptors, langerin, and tight junction proteins (claudin-1, claudin-7, and Zona occludens 2 [ZO 2]).<sup>5,6</sup> Intraepithelial DCs extend processes into the airway lumen between epithelial cells, presumably to collect antigenic material from the mucosal surface. These cellular processes interact with epithelial cells through the unusual membrane-associated chemokine fractalkine (CX3CL1), which is primarily expressed by epithelial cells.<sup>7</sup> Fractalkine and its receptor, CX3CR1, have been shown to mediate DC-epithelial interactions in the gut<sup>8</sup> and are increased in asthmatic airways.<sup>9</sup> Mucosal M cells are a type of specialized epithelial cell found in the intestine that have high permeability and permit antigen tissue entry for access to subepithelial DCs. Analogous cells do not appear to be found in normal human airway or in bronchus-associated lymphoid tissue, which is generally only present in inflamed human airways.<sup>10</sup> There is growing evidence that epithelial cells play a role in the recruitment and local survival of DCs because they produce the chemokine CCL20 (macrophage inflammatory protein 3 $\alpha$  [MIP-3 $\alpha$ ]) and the cytokine GM-CSF, respectively, which promote these processes.<sup>11,12</sup>

The nature of the immune response that occurs after DC exposure to antigen (eg,  $T_H1$ ,  $T_H2$ , regulatory T cell [Treg], and  $T_H17$ ) is determined by the state of activation of DCs and the context in which they present antigen to T cells (eg, level and type of costimulatory molecules and cytokine pattern expressed by the DCs). Although factors associated with antigen, such as the presence of TLR ligands, can have a profound outcome on the nature of the DC response, it is now clear that epithelial cells can also influence the subsequent DC activation status. The epithelial-derived factor thymic stromal lymphopoietin (TSLP) has been shown to skew DCs so that they activate formation of  $T_H2$  cells. TSLP is a 4-helix bundle cytokine related to IL-7 that binds to a specific receptor comprised of the IL-7 receptor  $\alpha$  chain and the TSLP receptor.<sup>13</sup> Production of TSLP occurs primarily by keratinocytes in the skin and epithelial cells in the airways. Besides activating DCs, epithelial TSLP has been shown recently to activate cytokine secretion by mast cells.<sup>14</sup> Increased TSLP expression has been demonstrated in both atopic dermatitis and asthma.<sup>15,16</sup> A feature of its effects on DCs is that it activates costimulation processes without triggering DC generation of IL-12, a cytokine with potent  $T_H1$ -skewing activity. Epithelial expression of TSLP is triggered by the TLR3 ligand double-stranded RNA, by rhinovirus, and by  $T_H2$  cytokines, and the process involves activation of nuclear factor  $\kappa B$  (NF- $\kappa B$ ) and IRF-3 in the case of double-stranded RNA and signal transducer and activator of transcription 6 in the case of IL-4.<sup>17</sup> Other epithelial-derived factors that are likely to influence the T cell-skewing characteristics of DCs are type I IFN (IFN- $\alpha$  and IFN- $\beta$ , which skew toward  $T_H1$ ) and type III IFN (IFN- $\lambda$ , IL-28, and IL-29, which skew toward Treg).<sup>18,19</sup> In asthmatic patients the type I and type III IFN airway epithelial interferon response to rhinovirus infection is impaired and correlated with worse respiratory



**FIG 1.** Model summarizing the influence of epithelial cells on innate and adaptive immune responses in the airways. Epithelial cells express pattern-recognition receptors and release antimicrobial products into the airways. They also interact with interepithelial DCs and subepithelial DCs to alter the ability of DCs to skew T cells. During inflammatory and immune responses, epithelial cells release specific chemokines that recruit subsets of granulocytes and T cells that are appropriate to the particular immune response. Finally, epithelial cells regulate the adaptive immune response by expression of soluble and cell-surface molecules that alter the function of DCs, T cells, and B cells in the airways. *PAMP*, Pathogen-associated molecular pattern; *PRR*, pathogen-recognition receptor; *PMN*, polymorphonuclear leukocyte; *EOS*, eosinophil; *BASO*, basophil; *APRIL*, a proliferation-inducing ligand.

symptoms.<sup>20,21</sup> This impaired epithelial response could lead to reduced  $T_H1$  and Treg responses in asthma. Epithelial cells are an inducible source of the IL-1 family members IL-1F9 and IL-33, the latter a ligand for ST2, a receptor that strongly induces  $T_H2$  cell skewing.<sup>22</sup> The potential role of these molecules in  $T_H2$  diseases in human airways is under investigation.

## EPITHELIAL EFFECTS ON T CELLS

Epithelial cells can shape the tissue response during adaptive immune effector responses to conform to the nature of the T-cell response and the leukocytes required. They release chemokines that attract neutrophils for  $T_H1$  and  $T_H17$  responses and eosinophils and basophils for  $T_H2$  responses. They also release chemokines that attract the T cells themselves:  $T_H1$  (CXCL10/IFN-inducible protein [IP]-10 and CXCL9/monokine induced by IFN- $\gamma$  [MIG] in response to IFN- $\gamma$ ) and  $T_H2$  (CCL1/I-309, CCL22/macrophage-derived chemokine [MDC], and CCL17/thymus and activation-regulated chemokine [TARC] in response to IL-4 and IL-13).<sup>23</sup> Epithelial cells produce CXCL8/IL-8 and CXCL1-3/growth-related oncogene (GRO)- $\alpha$ - $\gamma$  in response to IL-17 to recruit neutrophils.<sup>24,25</sup>  $T_H17$  cells comprise a relatively recently

recognized subset of T cells that are thought to mediate immunity to extracellular organisms, as well as several autoimmune diseases.<sup>26</sup> The chemokines responsible for  $T_H17$  recruitment have not been evaluated, but it is reasonable to expect that they will be partly epithelial cell derived. As discussed above, epithelial TSLP can influence the phenotype of outgoing DCs to modify the differentiation of the T cells to which they present antigen in draining lymph nodes. Epithelial cells might participate in T-cell responses in other ways because they express receptors for other factors that drive the T-cell differentiation process, such as IL-31 that might regulate both  $T_H1$  and  $T_H2$  cells, TGF- $\beta$  that skews toward  $T_H17$ , and IFN- $\lambda$  that might promote Treg responses.<sup>27,28</sup> It has not been tested whether epithelial cells have receptors for other such factors that influence the nature of the T-cell response, such as IL-25 that skews toward  $T_H2$ , TSLP that skews toward  $T_H2$ , or IL-23 that skews to  $T_H17$ . However, IL-22 appears to be a prominent cytokine produced by  $T_H17$  cells, and epithelial cells (keratinocytes) display a robust response to this cytokine.<sup>29</sup>

Several recent studies have shown that airway epithelial cells express high levels of certain B7 family members, notably B7-H1 and B7-DC (also known as PD-L1 and PD-L2).<sup>30-32</sup> These molecules are important regulators of T-cell activation, function, survival, and differentiation. Although B7-H1 and B7-DC levels are increased in

chronic rhinosinusitis and after viral infections, their relevance to immune regulation and disease pathogenesis awaits clarification. Epithelial cells also express Fas ligand, which can limit lymphocyte survival,<sup>33</sup> and CD40, which can stimulate epithelial production of RANTES, monocyte chemoattractant protein 1, IL-8, and intercellular adhesion molecule 1 when cross-linked.<sup>34,35</sup> A picture is emerging that suggests that epithelial cells can shape the nature of an adaptive immune response by altering the phenotype of both DCs and T cells.

## EPITHELIAL EFFECTS ON B CELLS

Studies in the 1970s demonstrated that IgA- and IgE-expressing B cells are found in the airways and that these cells produce IgE and IgA specific to known inhaled antigens. Several studies have shown that levels of aeroallergen-specific IgE are much higher in the airways than in the serum when normalized to total IgE or albumin. A survey study found that 19% of patients with rhinitis and polyposis had specific IgE in the nose, although not in the serum.<sup>36</sup> Recent studies concluded that the majority of the total body aeroallergen-specific antibodies of the IgE and IgA isotypes are produced in the airways and that systemic sensitization largely reflects spillover of immunoglobulins from the mucosal site of their production into the circulation.<sup>37</sup> It has been suggested that IgE is tightly regulated in this way to avoid the danger of anaphylaxis that accompanies the presence of high concentrations of circulating IgE. It is now clear that antigen-specific B cells are activated and undergo class-switch recombination (CSR) in the gut and airways. It thus becomes important to consider the role that local factors in the mucosae play in the recruitment, differentiation, activation, and survival of B cells. Epithelial cells, especially in the gut, have been shown to release chemokines that attract B cells in general and IgA-secreting B and plasma cells in particular. These chemokines include CCL25/thymus-expressed chemokine (TECK), CCL28/mucosae-associated epithelial chemokine (MEC), CXCL13/B lymphocyte chemoattractant (BLC), and CXCL12/stromal cell-derived factor (SDF)-1 $\alpha$ . In many cases studies have been restricted to the mucosal epithelium of the intestine.<sup>38</sup> In the airways epithelial production of CCL28 has been largely of interest because it attracts eosinophils and T<sub>H</sub>2 cells through CCR3 and CCR10.<sup>39</sup> However, this chemokine is also likely to be an important epithelial-derived chemokine that attracts B cells in both the gut and the airways.<sup>40,41</sup> CXCL12 is another known B cell-attracting chemokine that has nonetheless been of interest in airways disease for another reason; it has recently also been shown to play a role in the recruitment of epithelial stem cells to injured trachea as part of the repair process mediated by keratinocyte growth factor.<sup>42,43</sup>

Recent studies indicate that epithelial cells produce several factors that can modify the differentiation of B cells, much in the same way that has been described above for DCs and T cells. Epithelial cells have long been known

to be a rich source of IL-6 and TGF- $\beta$ , cytokines that have profound B cell-activating properties. In addition, recent studies indicate that epithelial cells produce B-cell-activating factor of the TNF family (BAFF)/B lymphocyte stimulator (BLyS), or TNFSF13B, which is a member of the TNF superfamily that is essential for B-cell development through the BAFF receptor and that can mediate B-cell CSR through another receptor, transmembrane activator and CAML interactor (TACI).<sup>44</sup> More studies are needed to determine the relative importance of epithelial-derived BAFF (and the related molecule APRIL) versus other sources of BAFF on local CSR and plasma cell differentiation of B cells in the airways. In the intestine it has been concluded that epithelial BAFF is the major trigger for regulating immunoglobulin class switching and that this process is promoted further by epithelial-derived TSLP and regulated by the protease inhibitor SLPI.<sup>45</sup>

Epithelial cells perform a well-known role in the transport of IgA and IgM across the epithelium into mucosal secretions.<sup>46,47</sup> This process is likely to be of importance both in innate and adaptive immunity because natural IgA antibodies (ie, those not generated by somatic hypermutation) can be produced locally in mucosal tissues, in some cases without the participation of T cells. Mucosal B cells produce dimeric IgA or pentameric IgM with monomers joined by the J chain. These multimers bind to the polymeric immunoglobulin receptor (pIgR), which transports them across epithelial cells into the airway lumen. This process occurs to a significant extent in airway mucosal glands, as well as in the lamina propria of the intestine and conducting airways.<sup>48</sup> During the process of transport of IgA (or IgM) by pIgR, the transported antibodies are covalently linked to a portion of pIgR that becomes the secretory component to produce the secretory forms sIgA or sIgM. This process is quite important in mucosal immunity, as well as in the neutralization of potential antigens in the gut and airways (immune exclusion). pIgR and secretory component have important immunologic roles beyond immunoglobulin transport. It has been established that pIgR expression and function is regulated by numerous cytokines, hormones, and pathogen-associated molecular patterns.<sup>46</sup> There are reports suggesting that defective epithelial transport of IgA might play a role in mucosal airways diseases, such as chronic obstructive pulmonary disease, chronic rhinosinusitis, and asthma.<sup>49-51</sup> More information is needed to determine the role of local B-cell responses in inflammatory disease, protective immunity, and immune exclusion (neutralization of antigens) in the airways.

It should be clear from this brief review that several lines of evidence now support the concept that epithelial cells are primary innate immune effector cells that also regulate the adaptive immune responses in the airways at the level of DCs, T cells, and B cells. Epithelial facilitation of adaptive immune responses probably occurs when antigen exposure is high and accompanied by a ligand for a pattern-recognition receptor. A high load of antigen could reflect the failure of epithelial innate



immune responses to clear the antigen source or could reflect high ambient exposure in inhaled air. Once adaptive responses are mobilized, it is clear that epithelial cells regulate them at every phase of the response (sensitization, effector responses, and termination). Finally, airway diseases associated with excessive or aberrant innate or adaptive immune responses might in some cases initially result from inappropriate responses of epithelium.

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