

E-cadherin: gatekeeper of airway mucosa and allergic sensitization

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The airway epithelium plays a role in immune regulation during environmental challenge, which is intertwined with its barrier function and capacity to limit submucosal access of environmental factors. In asthma, mucosal barrier function is often compromised, with disrupted expression of the adhesion molecule E-cadherin. Recent progress suggests that E-cadherin contributes to the structural and immunological function of airway epithelium, through the regulation of epithelial junctions, proliferation, differentiation, and production of growth factors and proinflammatory mediators that can modulate the immune response. Here, we discuss this novel role for E-cadherin in mediating the crucial immunological decision between maintenance of tolerance versus induction of innate and adaptive immunity.

Asthma and the airway epithelial phenotype

Asthma is an inflammatory airway disease that affects up to 300 million people worldwide and is characterized by paroxysmal and chronic symptoms, such as wheezing, sputum production, variable airflow limitation, and airway hyperresponsiveness to endogenous or exogenous bronchospasmogenic stimuli.

The airway epithelium forms a continuous, highly regulated physical barrier lining of the airway lumen, which prevents invasion of inhaled environmental agents such as aeroallergens, pollutants and pathogens. A number of observations suggest that the airway epithelium is disrupted in asthma. These include the detachment of columnar ciliated cells, presence of epithelial cell aggregates in sputum, increased permeability to allergens, and disrupted expression of the junction molecule E-cadherin at sites of epithelial detachment, when compared to healthy epithelium [1,2]. These structural and functional abnormalities (Boxes 1 and 2) might lead to enhanced signaling between the epithelium and underlying immune and structural cells. This might drive both allergic sensitization and airway remodeling, including goblet cell hyperplasia, subepithelial fibrosis and increased smooth muscle mass [3–5], thus contributing to airway narrowing. Furthermore, increased epithelial damage is known to correlate with more severe airway hyperresponsiveness.

The loss of mucosal barrier function in asthma might result from increased fragility of the airway epithelium [2] and/or an impaired repair mechanism with inability to restore cell–cell contacts upon damage (Box 3). Expression of the junction molecules E-cadherin and zona occludens-1 (ZO-1) is reduced *in vitro* in differentiated bronchial epithelium from asthma patients compared with healthy persons [2,6], which indicates that asthma epithelium inefficiently forms intercellular contacts. By contrast, increased expression of repair mediators, including epidermal growth factor receptor (EGFR) and transforming growth factor (TGF)- β at sites of ciliated cell detachment supports a role for aberrant repair in the asthmatic epithelial phenotype [7]. In line with this, asthmatic airway epithelium has been demonstrated to contain higher numbers of cells that express the basal cell markers cytokeratin-5 and -14 and p63 [6], which represent the main transient amplifying cell population in the airway epithelium [8]. These data imply that aberrant epithelial repair processes in asthma contribute to epithelial damage and loss of effective barrier function. Although it remains unanswered whether these changes are causal or secondary to the development of respiratory diseases, many of the recently identified asthma susceptibility genes, including *DPP10*, *GPCRA*, *CHI3L1* and a protocadherin gene family member *PCDH1* [9] are expressed in airway epithelial cells. Moreover, biopsy studies in children suggest that the damaged epithelial phenotype occurs early in disease pathogenesis, even before a definitive diagnosis of asthma [10]. Thus, there is suggestive evidence that events at the epithelial surface are decisive for the initiation and chronicity of asthma [11]. Furthermore, respiratory virus infections, which are associated with the development of asthma in children, can induce loss of epithelial E-cadherin-mediated contacts (Box 4). A direct link between compromised barrier function and allergy has been provided by recent findings in atopic dermatitis. Mutations in the epidermal barrier protein filaggrin (*FLG*) gene lead to a defect in epithelial barrier function, which results in increased epithelial permeability and penetration of exogenous substances (e.g. allergens and bacteria) [12]. Moreover, *FLG* mutations can lead to enhanced allergen sensitization [12,13] and *FLG* mutations combined with eczema in the first year of life have been associated with

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Box 1. E-cadherin regulation and epithelial-mesenchymal transition

In dynamic tissues such as the airway epithelium, cells can remodel and recycle AJs to control tissue structure by ubiquitination of E-cadherin, which triggers clathrin-mediated endocytosis and degradation by the endocytotic machinery [57,58]. Loss of junctional E-cadherin expression appears to be a pivotal step in EMT; a process in which cells lose epithelial characteristics to adopt a mesenchymal phenotype. Association of the cytoplasmic tail of E-cadherin with β -catenin is essential for effective junctional localization. When AJs are intact, E-cadherin limits the cellular availability of β -catenin. Upon liberation from disrupted AJs, β -catenin is targeted to the early endosome and endocytic recycling compartment [59]. Here, it can be recycled towards the cell membrane, or contribute to the free cytosolic pool of β -catenin [59], which is rapidly targeted for proteosomal degradation by GSK-3 β . Degradation of β -catenin can be prevented by inactivation of GSK-3 β through activation of the Frizzled receptors by Wnt/Wnt ligands and subsequent downstream signaling [60], or through activation of growth factor receptors, such as TGF- β receptor and EGFR [61]. Upon its stabilization, free cytosolic β -catenin can translocate to the nucleus

and associate with the transcription factor TCF/LEF-1 to activate transcription of genes known to be relevant to asthma, for example, genes involved in tissue repair (e.g. EGFR and CD44); airway remodeling (e.g. vascular endothelial growth factor and MMP-2, MMP-7 and MMP-9); and inflammatory responses (e.g. cyclooxygenase-2, IL-6, IL-8 and periostin, see Figure 2). β -Catenin stabilization also maintains epithelial cells in an undifferentiated phenotype [62] and promotes goblet cell hyperplasia, as has been demonstrated by the expression of an activated β -catenin isoform [Catnb ^{Δ (ex3)}] in respiratory epithelial cells of mouse fetal lungs [63]. In addition, free β -catenin can further promote AJ disassembly through transactivation of the E-cadherin suppressor genes Sna-1 and Sna-2, and by specific MMPs involved in E-cadherin degradation [64]. In line with these data, a central role for Wnt/ β -catenin signaling genes has recently been proposed in the development of impaired lung function in asthma [65], although it has still to be determined if downstream mediators of Wnt signaling are dysregulated and whether they contribute to AJ disruption in asthma.

later development of asthma and hay fever [14]. Furthermore, in eosinophilic esophagitis, a food-allergy-related disorder that is characterized by accumulation of eosinophils and a basal esophagus epithelial phenotype, recent genome-wide association studies have identified the junction protein desmoglein 1 as a susceptibility gene for the disease [15].

To date, attempts to ameliorate asthma severity or progression in humans have been disappointing, especially in terms of preventing airway remodeling. In this review, we focus on the crucial role of E-cadherin in mediating the decision between maintenance of tolerance and the induction of immunity, and discuss data that show that E-cadherin acts to maintain barrier function and a tolerogenic epithelial phenotype in a cell-autonomous fashion. We propose that E-cadherin is a novel therapeutic target, based on its central role in integrating structural and immunological barrier functions.

E-cadherin: the epithelial gatekeeper

Intercellular epithelial junctions form the structural adhesive forces of the mucosal barrier, which separate the

underlying tissue from the environment and enable communication between cells, establishment of cell polarity, and transcellular ion transport. These intercellular junctions are comprised of tight junctions (TJs), adherens junctions (AJs) and desmosomes (Figure 1). TJs localize apically and are considered the main regulators of paracellular permeability and movement of ions and solutes between cells. TJs are composed of the interacting transmembrane proteins occludin, claudins and junction-adhesion-molecules (JAMs). JAMs bind the cell polarity proteins Par-3 and Par-6, whereas occludin and claudins are anchored to the cytoskeleton by ZO-1, ZO-2, and ZO-3 and cingulin. Claudins function to regulate the permeability of the plasma membranes between adjacent cells, whereas occludin is involved in the regulation of *de novo* assembly of TJs [16]. In line with the paradigm that TJs largely contribute to epithelial permeability, high epithelial resistance is accompanied by continuous circumferential membrane expression of ZO-1 [17].

AJs mechanically connect adjacent cells and initiate the formation and maturation of cell-cell contacts through E-cadherin, a type I cadherin transmembrane

Box 2. Implications of EMT for asthma

The regulation of E-cadherin expression during EMT has been most extensively studied during embryogenesis and in epithelial tumors, where it has been demonstrated that E-cadherin expression can be downregulated by members of the Snail family, that is, Snail-1 (Sna-1) and Slug (Sna-2), and Zeb transcriptional repressor families [64]. In addition to E-cadherin loss, hallmarks of EMT include loss of cytokeratin expression and induction of mesenchymal markers, for example, fibroblast-specific protein (FSP)-1, fibronectin and α -smooth muscle actin (α -SMA). Strikingly, similar features related to AJ remodeling and EMT have been observed during re-epithelialization after tissue damage and/or during chronic inflammatory conditions. With regard to pathology of the respiratory system, the role of EMT is still largely unclear. EMT has been implicated in aberrant epithelial repair and scar tissue formation in idiopathic lung fibrosis and bronchiolitis obliterans [42,66,67]. In a mouse model of experimental asthma induced by chronic HDM treatment, EMT was convincingly shown using cell-fate mapping of airway epithelial cells, which were found to migrate to subepithelial layers of the airway wall. Epithelial cells showed reduced expression of E-cadherin and increased expression of vimentin and α -SMA [68]. In asthma patients, delocalization of E-cadherin has also been observed in bronchial biopsies. In line with

this, TGF- β induced downregulation of E-cadherin and expression of the mesenchymal markers FSP-1 and vimentin in various bronchial epithelial cell types [68–72]. TGF- β levels are increased in asthmatic airways and have a well-established role in airway remodeling [7,73]. TGF- β 1 induces Sna-1 and Sna-2-mediated downregulation of E-cadherin in primary airway epithelial cells during EMT [70]. Importantly, it has been observed that air-liquid interface (ALI)-cultured primary airway epithelial cells from asthma subjects have more widespread TGF- β -induced EMT throughout the ALI compared with cultures from healthy subjects [70]. Next to TGF- β , asthmatic airways display increased EGFR activity/expression, which potentially leads to disruption of E-cadherin-mediated junctions [7,50,73,74]. Recently, it has been demonstrated that disruption of cell-cell contacts is indispensable for transcriptional activation of EMT genes in kidney tubular cells [75]. Thus, breakdown of epithelial cell-cell contacts, as observed in asthma, might reflect an important step in EMT development. The observation that the proteolytically active allergen HDM in combination with TGF- β synergistically induces EMT features and transcriptional activation of β -catenin in bronchial epithelium fits with this hypothesis [71]. These data together implicate EMT as a relevant contributor to the cellular pathology of asthma.

Box 3. Effects of cigarette smoke and pollutants on epithelial E-cadherin expression

The inhalation of gaseous and particulate inorganic air pollutants is a well-known risk factor for the development of asthma and can cause damage to the airway epithelial layer. Several studies have suggested that exposure to cigarette smoke (CS) can directly impair barrier function of the respiratory epithelium and facilitate penetration of allergens across epithelial layers, which supports the challenging hypothesis that smoking promotes sensitization to allergens [76]. This hypothesis is supported by data from a mouse model, in which exposure to aerosolized ovalbumin in combination with CS leads to allergic sensitization at the expense of tolerance [77]. CS condensate and extract both induce damage to human airway epithelium, including disassembly of TJs [78,79]. Additionally, CS extract has been shown to downregulate epithelial resistance, decrease E-cadherin and ZO-1 expression, and induce EMT in the lung alveolar carcinoma cell line

A549 [80] and in the non-malignant esophageal epithelial cell line Het-1A [81]. Furthermore, it is of interest to note that exposure of asthmatic epithelium to tobacco smoke extract results in a stronger reduction in barrier function compared to normal epithelium [2].

Diesel exhaust particles (DEPs) have also been demonstrated to increase epithelial permeability, possibly by the induction of airway inflammation. Many studies have shown a role for DEPs as adjuvants for several allergens, including ovalbumin and HDM, during sensitization *in vivo*, which results in allergen-specific IgE and aggravated pulmonary inflammation and goblet cell proliferation in these models [77]. Direct effects of DEPs have also been shown on solute permeability in primary murine tracheal epithelium monolayers [82]. However, it is currently unknown whether DEPs affect E-cadherin expression or localization.

glycoprotein. E-cadherin is composed of an extracellular domain that forms homotypic, calcium-dependent adhesions between epithelial cells [18,19] and a highly conserved cytoplasmic tail. This cytoplasmic domain is structured and stabilized in the membrane only when bound to the anchor proteins p120 catenin, β -catenin, and α -catenin, which form an interface with the microtubule network and actin cytoskeleton. The actin microtubule cytoskeleton is a dynamic structure that maintains cell shape, enables cilia motion, and is important in intracellular vesicle transport and cellular division/proliferation. In addition to cell architecture, E-cadherin is able to regulate cell proliferation and differentiation through various transcription factors including ZO-1-associated nucleic acid binding protein [20].

At the basolateral side of E-cadherin-mediated cell–cell contacts, the so-called desmosomes provide mechanical strength to tissues. Desmosomes consist of non-classical cadherins and form adhesive bonds with the filament cytoskeleton of the cells, such as the armadillo proteins plakoglobin and plakophilin, and desmoplakin interacts with cytokeratin-5.

E-cadherin is thought to provide the architecture that is required to form other junctional complexes, including TJs. When E-cadherin is not properly expressed in the epidermis, delocalization of the TJ proteins ZO-1, occludin and claudins occurs, which leads to distorted TJ

architecture [21]. Additionally, siRNA knockdown of E-cadherin results in decreased ZO-1 expression in association with reduced epithelial resistance in bronchial epithelial monolayers [17]. These data identify the AJ protein E-cadherin as a crucial regulator of the establishment and maintenance of epithelial cell–cell contacts in the airway epithelium.

E-cadherin regulates airway epithelial innate immune function

The regulation of the response to environmental stimuli by E-cadherin extends well beyond the cell-autonomous regulation of the epithelial phenotype and barrier function. The airway epithelium is part of the innate immune system, and has a prominent regulatory role in the immune response to environmental triggers [22,23]. Many of the signaling pathways activated by environmental stimuli converge on the transcriptional activation of nuclear factor (NF)- κ B in the airway epithelium, and NF- κ B activity can lead to loss of inhalation tolerance and induction of immunity [24,25]. Induction of E-cadherin expression represses NF- κ B activity [26], whereas loss of E-cadherin-mediated cell–cell contacts induces NF- κ B signaling in carcinoma cell lines [27]. Thus, the balance between E-cadherin expression and NF- κ B activity could constitute an epithelial molecular switch between a tolerogenic and a proinflammatory/immunogenic phenotype.

Box 4. Effects of bacteria and viruses on E-cadherin-mediated epithelial cell–cell contacts

According to the hygiene hypothesis, an inverse relationship between allergic diseases and bacterial infections in early childhood exists, although the presence of low levels of endotoxin in allergen extracts might be crucial for allergic sensitization. Limited and conflicting data are present on the role of TLR signaling in microbial-induced changes in epithelial barrier function. TLR2 signaling has been described to increase integrity of intestinal epithelial cells by increasing the expression of ZO-1 in TJs [83,84]. By contrast, activation of TLR2 has been implicated in breakdown of intercellular junctions through calpain activation [45]. No direct effects of TLR signaling have been described on E-cadherin localization and/or expression, although high TLR3 expression levels have been associated with low E-cadherin protein levels in papillary thyroid carcinoma cell lines [85]. In line with this, exposure to dsRNA viruses, which are recognized by TLR3, has been demonstrated to induce EMT in biliary epithelial cells [86]. Furthermore, human papillomavirus and Epstein–Barr virus can reduce expression of E-cadherin in Langerhans cells and keratinocyte cell lines, respectively [87]. Similar effects have been reported for RV and RSV. This is of

interest since RSV is a primary cause of lower respiratory tract infections and is associated with the development of asthma in children, whereas RV infections are a major cause of asthma exacerbations. RV infection has been demonstrated to reduce mRNA levels of ZO-1, occludin, claudin-1, and E-cadherin, as well as epithelial resistance in primary cultured human nasal epithelial cells [88]. Intranasal inoculation of mice with RV-1B also appears to cause loss of ZO-1 in bronchial epithelial tight junctions *in vivo* [89]. In addition, RSV infection alters the expression of E-cadherin on A549 cells, and infection of human epithelial cells with RSV results in a significant decrease in transepithelial electrical resistance [90]. Loss of E-cadherin has also been demonstrated after RSV infection in mice. Furthermore, exposure to HDM following RSV infection in a mouse model of asthma results in increased allergic sensitization, enhanced allergic inflammation, and mucus production combined with reduced lung function [91]. Thus, viral infections might have important consequences for E-cadherin-mediated structural and immunological barrier function of the airway epithelium, although the mechanism and involvement of specific TLRs remains unresolved.

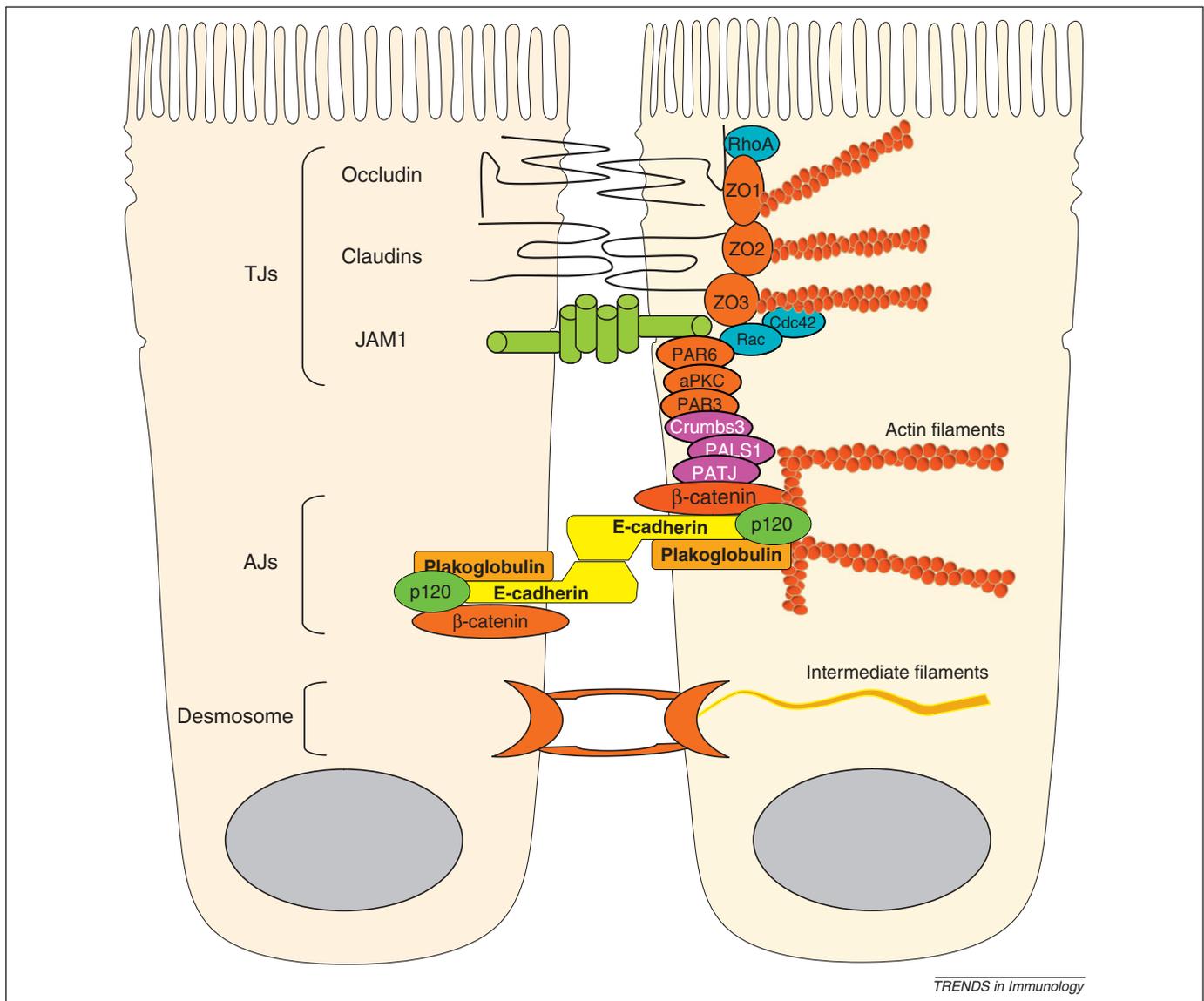


Figure 1. Schematic representation of the basic structural components of epithelial junctions. TJs are located most apically and comprise interacting transmembrane proteins claudins, occludin and JAMs. JAMs bind the cell polarity proteins Par-3 and Par-6. Occludin and claudins are linked to the cytoskeleton by ZO-1, ZO-2, and ZO-3 and cingulin. AJs are located more basolaterally and their main component is E-cadherin, which interacts with the cytoplasmic proteins p120 catenin, β -catenin, and α -catenin to connect with the actin cytoskeleton. Desmosomes are localized at the basolateral side of AJs and consist of non-classical cadherins.

In line with this hypothesis, downregulation of E-cadherin by siRNA leads to increased proinflammatory activity of bronchial epithelium with respect to the expression of Th2-promoting factors chemokine ligand (CCL)17 and thymic stromal lymphopoietin protein (TSLP) [28]. Loss of negative feedback control over EGFR activity appears to be involved in this effect, which might subsequently induce NF- κ B activation and CCL17 production [28,29]. Furthermore, the loss of epithelial integrity and increased permeability of asthmatic airway epithelium to allergens is accompanied by a stressed and activated phenotype, with increased NF- κ B activity [30]. Taken together, these data indicate that E-cadherin is crucially important to maintain a tolerogenic phenotype of airway epithelium.

Role of E-cadherin and CD103⁺ immune cells in tolerance induction

In addition to the cell-autonomous control of proinflammatory epithelial activity, E-cadherin is a ligand for the

cognate receptor CD103 ($\alpha_E\beta_7$ integrin), which is expressed on cells of the innate and adaptive immune system, including T cells and dendritic cells (DCs). CD103 marks mucosal intraepithelial T cell populations in the intestine, urogenital tract and airway mucosa. CD103 is also expressed on a specific population of regulatory CD4⁺CD25⁺Foxp3⁺ T cells (Tregs), which are capable of suppressing Th2-driven asthma manifestations, and might be essential for homing of these cells to sites of tissue inflammation [31]. Furthermore, CD103 is expressed on the majority of CD8⁺ T cells and a significant fraction of effector CD4⁺ T cells in the epithelial lining or bronchoalveolar lavage (BAL) fluid in healthy individuals. The CD103⁺ fraction of BAL CD4⁺ T cells increases in asthma with severity of disease [32]. Thus, loss of E-cadherin might lead to reduced capacity for Tregs to be retained in the airway mucosa, and additionally serve to facilitate transmigration of effector intraepithelial T cells into the airway lumen.

CD103 additionally identifies a novel subset of DCs that also expresses E-cadherin, TJ proteins and Langerin [33]. Mucosal DCs are situated in the intraepithelial, basolateral space [22]. Under homeostatic conditions, a network of resident CD103⁺ DCs probably samples the airway lumen through protrusions of dendrites that are extended across the airway epithelium [22,34]. The expression of TJ and AJ proteins might allow these dendrites to interact with the epithelium and pass epithelial junctions without disruption of the barrier [33]. Moreover, this homotypic interaction might serve to suppress DC-mediated immunity, which maintains a tolerogenic DC phenotype [35,36]. Importantly, disruption of E-cadherin-mediated adhesion induces typical features of DC maturation, including the upregulation of co-stimulatory molecules, MHC class II, and chemokine receptors. A similar role for these E-cadherin-mediated interactions has been described in epidermal Langerhans cells (LCs) [33,37].

A functional role for epithelial E-cadherin interaction with CD103 on DCs is implicated in the induction of Tregs and tolerance. CD103⁺ DCs contribute to the control of inflammatory responses and intestinal homeostasis by triggering the development of Foxp3⁺ Tregs from naïve T cells [38]. In the airway mucosa, CD103-expressing DCs might be relevant to maintain the balance between Th2 effector and Treg activities [22]. Indeed, CD103⁺ DCs contribute to tolerance induction to inhaled allergen [39], although they are also crucial for the clearance of several respiratory viral infections [33,39–42].

Finally, E-cadherin can bind to killer cell lectin-like receptor G1 (KLRG1), an inhibitory receptor that is expressed on a subset of recently activated natural killer cells, effector/memory T cells and Foxp3⁺Tregs. KLRG1 engagement inhibits secretion of inflammatory cytokines by DCs, thereby exerting immunosuppressive effects [43].

It is tempting to speculate that, in the absence of damage and typical danger signals, resident DCs actively maintain tolerance through interaction with intact epithelium via E-cadherin during antigen sampling. By contrast, stimuli that constitute potential danger and disrupt E-cadherin-mediated cell–cell contacts might promote DC and T cell activation.

Inside-out traffic: E-cadherin in transepithelial migration

Under physiological conditions, leukocytes can migrate across the epithelium into the airway lumen without disrupting the epithelial barrier [44]. Under pathological conditions, however, the transepithelial migration of large numbers of leukocytes inflicts epithelial damage; both through mechanical forces and release of soluble mediators that induce the loss of AJs and TJs [44], which leads to loss of barrier function and even epithelial denudation [44]. For instance, release of elastase by transmigrating neutrophils induces E-cadherin degradation and abrogates membrane localization of E-cadherin, β -catenin and ZO-1. In addition, transepithelial migration of neutrophils is highly dependent on the cleavage of the intracellular domains of E-cadherin and occludin by the endogenous protease calpain [45]. Granulocytes have also been demonstrated to cause disruption of cell–cell contacts in nasal

epithelium *in vivo*, with eosinophils inducing the most pronounced effects [46].

Effects of inhaled environmental allergens on the regulation of E-cadherin

Proteolytically active allergens can directly and indirectly cause disruption of E-cadherin-mediated contacts, by proteolytic activity and by inducing activation of pattern-recognition receptors (PRRs). Various allergens contain protease activity, including house dust mite (HDM), cockroach, fungi, cat and pollen [47,48]. HDM can induce proteolytic cleavage of the TJ protein occludin and to a lesser extent E-cadherin. This proteolytic activity has been proposed as a major determinant in the allergenicity and induction of an allergic immune response [47]. Similarly, tree and pollen peptidases have been shown to disrupt TJs.

In addition to direct proteolytic cleavage, proteases in HDM, cockroach, fungi and mold extracts might activate the protease-activated receptor (PAR)-2 [47]. It has been demonstrated that PAR-2 activation results in loss of E-cadherin mediated cell–cell adhesion in human primary airway epithelium [49]. In line with this, HDM exposure in human bronchial epithelium induces a rapid delocalization of E-cadherin, at least in part because of serine protease activity, which leads to activation of PAR-2 and subsequent a Disintegrin and Metalloproteinase (ADAM)-dependent EGFR transactivation [50].

Allergen extracts are often contaminated with lipopolysaccharide (LPS) from Gram-negative bacteria, which can be recognized by Toll-like receptor (TLR)4. The airway epithelium is known to express TLR1–6 [51], 8 and 9 [52], which recognize pathogen-associated molecular patterns from viruses, bacteria, fungi, protozoa and multicellular parasites [53]. The HDM allergen Der p2 exhibits structural homology with MD2, the LPS-binding member of the TLR4 signaling complex, thus facilitating TLR4 signaling [53]. TLRs have been proposed to play a key role in the initiation of innate immune responses, yet their precise role in allergen-induced inflammation is currently unclear. It has recently been demonstrated that TLR4 expression on structural (presumably epithelial) cells is crucial for DC activation in the lung, and priming of effector T helper responses to HDM-driven allergic airway inflammation [23]. Although the role of TLR4 in allergenicity is emerging, its involvement in allergen-induced epithelial barrier dysfunction is still largely unknown. TLR4 signaling might play a role in the regulation of E-cadherin, as indicated by the finding that loss of E-cadherin was prevented in TLR4-deficient mice in a model of fibrotic renal injury [54].

C-type lectin receptors (CLRs) are a third group of innate immune receptors that are expressed by the airway epithelium that can be activated by allergens. These receptors recognize carbohydrates that are present on allergens, including β -glucan and chitin. Although little is known about the effect of CLR activation on epithelial barrier function, activation of specific CLRs can induce Ca²⁺ fluxes [55] and might contribute to proinflammatory epithelial activity [56], as well as the activation of the intracellular

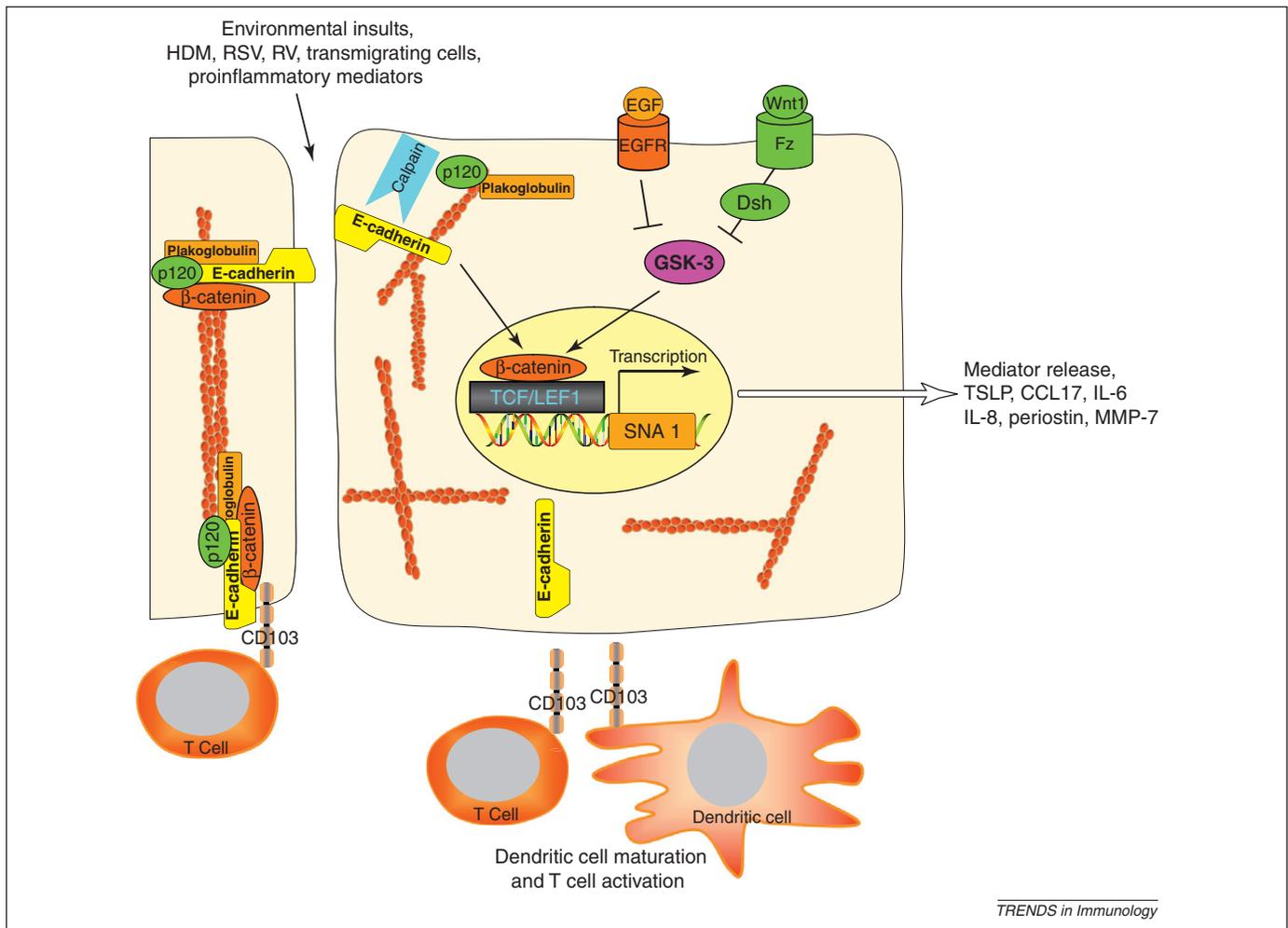


Figure 2. Overview of the role of E-cadherin as integrator of barrier function and immunological function in epithelial cells. Environmental exposures, including HDM and viruses [rhinovirus (RV) and respiratory syncytial virus (RSV)], can disrupt E-cadherin-mediated cell–cell contacts through activation of PARs and/or PRRs, which potentially leads to calpain activation and subsequent E-cadherin cleavage. Disruption of E-cadherin-mediated junctions might also result from the release of proinflammatory mediators and mediators released by transmutating cells. E-cadherin is the essential transmembrane protein in AJs between airway epithelial cells. Disruption of E-cadherin-mediated cell–cell contacts leads to β-catenin into the cytoplasm. EGFR or Wnt/Frizzled signaling inhibits glycogen-synthase kinase (GSK)-3β activity, which results in β-catenin dephosphorylation, stabilization and translocation to the nucleus. β-Catenin acts as cofactor for lymphoid enhancer binding factor/T-cell factor (LEF/TCF) in the transcriptional induction of genes involved in epithelial-to-mesenchymal transition (EMT) [e.g. SNA-1, matrix metalloproteinase (MMP)-7] and inflammation (e.g. IL-8 and periostin). Loss of E-cadherin-mediated cell–cell contacts can also increase EGFR activity and subsequent expression of TSLP and CCL17, which are upregulated in asthma. In addition to epithelial specific functions, loss of AJs can enhance DC maturation and T cell activation through loss of DC CD103 interaction with E-cadherin expressed on the epithelial cell surface.

protease calpain, which leads to disruption of E-cadherin-mediated cell–cell contacts [45].

Concluding remarks: a role for E-cadherin in asthma

The phenotype of the airway epithelium that is induced by the interaction of genotype and environment might play a central role in the pathogenesis of allergic asthma. The pathways that govern the immunological and structural phenotype of the asthmatic airway epithelium are functionally and molecularly closely intertwined. E-cadherin is present on the airway epithelium, and data suggest that it controls the outcome of the response to allergens through its interaction with Tregs and DCs, to suppress the production of allergenic mediators [28] and promote the establishment of tolerance (see Figure 2 for an overview). We suggest that future studies in conditional *Chd1* (E-cadherin) knockout mice will provide further insight into the role of E-cadherin in allergic airway inflammation. We propose that E-cadherin could be a novel target to

ameliorate disease severity or progression in humans, based on the various roles it has in epithelial adhesion, integrity, repair and immunomodulation.

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