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Epithelial cells as immune effector cells: The role of CD40

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Abstract

Through the expression of inflammatory mediators and immune-related molecules, epithelial cells function as immune effector cells in a wide-variety of tissues; the expression of the CD40 receptor on these cells contributes this role. Engagement of CD40 activates epithelial cells and results in their release of pro- and anti-inflammatory mediators as well as pro-fibrotic molecules. As such, epithelial CD40 has been implicated in the pathogenesis of inflammatory disorders, generation of self-tolerance, and rejection of allografts.

1. CD40: an introduction

CD40 is a member of the TNFR family, which includes TNFRI (p55), TNFRII (p75), CD30, Fas, and low-affinity nerve growth factor receptor (reviewed in ^{1, 2}). CD40 and its natural ligand, CD154, play a central role in the regulation of humoral and cell-mediated immunity ³. In a variety of local microenvironments, protein-protein interactions between CD40 and CD154 alter cell proliferation, differentiation, apoptosis, isotype switching, and inflammatory mediator production ⁴. Distribution of CD40 expression includes a diversity of cell types, such as B lymphocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, and smooth muscle cells ⁵. In this review, the expression and function of CD40 on epithelial cells are described.

2. Epithelial cell biology: an overview

Epithelial tissues are comprised of aggregated cells, which create tight barriers to protect underlying tissue from the external environment. The primary functions of these tissues include protection, secretion, sensation, absorption, and contractility. As such, epithelial cells have been described classically as barrier cells that are involved in homeostasis; these cells respond to a variety of environmental stimuli resulting in the alteration of their cellular functions such as ion transport and movement of secretions.

1.1 Epithelial cell types, structure, and function

Epithelial cells are divided into two groups as determined by their structure and function; these groups include covering and glandular epithelia (reviewed in ⁶). These groupings are

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subjective, however, as covering epithelia can contain cells that secrete while glandular epithelial cells may be found mixed with covering epithelial cells. Covering epithelia line body cavities and are classified with regard to organization and morphology; simple, stratified, and pseudostratified are types of covering epithelia. Examples of covering epithelial cells include ciliated cells located in the lung and kidney. Glandular epithelial cells synthesize, store, and secrete proteins, lipids, or complexes of carbohydrates and proteins. Examples of glandular epithelial cells include goblet cells, which secrete mucus, within the lung and small intestine. In general, epithelial cells have two distinct surfaces, the apical (luminal) and the basolateral (serosal). The apical surface is exposed to the environment directly while the basolateral surface is protected from the environment through the existence of tight junctions. Tight junctions facilitate selective transport of materials across the epithelial barrier and dictate sequestration of proteins made by epithelia to either the apical or basolateral compartment.

1.2 Epithelial cells as immune effector cells

Recent evidence suggests that, through their expression and secretion of immune molecules, such as lipid mediators, oxygen radicals, adhesion molecules, and cytokines, epithelial cells function as immune effector cells in a wide-variety of tissues. In particular, epithelial cells express the cytokine thymic stromal lymphopoietin (TSLP), an important regulator of immune responses. Epithelial cells, keratinocytes, and stromal cells are major producers of TSLP. TSLP was identified initially in conditioned medium supernatants from the mouse thymic stromal cell line, Z210R.1; it sustained the long-term growth of a pre-B cell line and enhanced the proliferation of unfractionated thymocytes (reviewed in ⁷). More recent work has shown that TSLP, which is expressed primarily in the lung, gut, and skin, promotes the generation of functional B and T lymphocytes, supports the differentiation of Th2 cells, and induces the activation and maturation of dendritic cells ⁷. It is through the varied actions of TSLP that the epithelium can play a key role in the development and maintenance of immune homeostasis both locally and systemically.

Through the expression of MHC (major histocompatibility complex) molecules and co-stimulatory ligands, epithelial cells have the capacity to function as nonprofessional antigen-presenting cells (APC). For example, previous work has demonstrated that airway epithelial cells express MHC class II molecules and the B7 family members B7-H1, B7-H2, B7-H3, and B7-DC constitutively ⁸⁻¹⁰. Further, it has been reported that airway epithelial cells take up soluble antigen that is then colocalized with class II molecules in different antigen-processing compartments, including early and late endosomes, acidic compartments, and lysosomes ¹⁰. Similarly, epithelial cells located in the thymus, intestine, cornea, and kidney express MHC and B7 molecules and function as nonprofessional APC. Collectively, these studies suggest that epithelial cells play a role in local antigen presentation.

Because epithelial cells can function as immune effectors, it is not surprising that these cells express the CD40 receptor. As such, numerous studies have reported the expression of CD40 molecules on a variety of epithelia, including epithelial cells of the lung, thymus, and kidney. The expression and function of epithelial CD40 in these tissues and related pathologies are discussed below; this discussion does not include the topic of epithelial derived cancers as that subject has been well reviewed previously ^{11; 12}.

3. Lung epithelia and airway disease

2.1 CD40 expression and function in airway epithelia

We and others have described CD40 expression on airway epithelial cells, including immortalized cell lines and primary cells. Using the 9HTEo- tracheal epithelial cell line, we have demonstrated that airway epithelial cells express CD40 constitutively at both the apical

and basolateral surfaces¹³. Further, we have shown that CD40 engagement on these cells stimulates the expression of inflammatory mediators, including the chemokines IL-8, RANTES, and MCP-1 and the adhesion molecule ICAM-1, via a signaling pathway that involves NF- κ B and TRAF3^{13; 14}. Unexpectedly, we also observed that cross-linking CD40 on 9HTEo- cells decreases CD40 surface protein half-life via a mechanism that involves TRAF6 but not TRAF2/3¹⁵. These results indicate that CD40 engagement may initiate a 'negative feed-back' loop to attenuate CD40-mediated responses. Similarly, Gormand and co-workers have reported that bronchial epithelial cell lines express constitutive levels of CD40 and that its ligation enhanced the expression of IL-6 and GM-CSF; however, TNF α and IFN γ increased the basal expression of CD40 on these cell lines¹⁶. Amsellem and colleagues also observed that IFN γ upregulated CD40 basal expression in the cystic fibrosis (CF) airway epithelial cell lines CFT-1 and CFT-2 and the non-CF tracheal epithelial cell line NT-1¹⁷. Likewise, Cagnoni and co-workers detected CD40 expression on normal respiratory epithelial cells *in vivo* and in primary cell cultures; CD40 expression was increased by IFN β and IFN γ ¹⁸. In addition, these investigators demonstrated that cross-linking CD40 on primary cells enhanced the secretion of IL-6 and IL-8 via a JAK3-dependent pathway¹⁸. Together, these reports suggest that the functional expression of CD40 on airway epithelial cells may be enhanced during an on-going inflammatory response.

2.2 Role of epithelial CD40 in asthma and allergic airway disease

T lymphocytes play a major role in the pathogenesis of allergic airway disease, including asthma-associated inflammation. Elevated numbers of activated T cells, which express the CD40 ligand CD154, have been observed in the bronchial alveolar lavage fluid and bronchial tissue of asthmatic patients (reviewed in¹⁹). It is likely that, as these cells migrate from the circulation and into the airway lumen, they encounter and interact with CD40 expressed on airway epithelium (see Figure 1). Notably, Vignoli and co-workers and Cagnoni et al. have each demonstrated that CD40 expression is increased in asthmatic and inflamed bronchial epithelium^{18; 20}. As suggested above, the consequences of such T cell - epithelial cell interactions may trigger the epithelium to express increased amounts of inflammatory mediators. The production of these mediators amplifies the migration and activation of leukocytes, such as eosinophils, neutrophils, and monocytes, into the pulmonary compartment; as a consequence, these cells release toxic products into the local milieu and damage the airway epithelium. A recent report by Merendino and colleagues highlights a CD40-mediated mechanism that protects the airway epithelium from oxidant-mediated injury²¹. Oxidants, which are derived from inflammatory cells as well as environmental sources, have been well described in the pathogenesis of airway inflammatory diseases²². In their report, Merendino et al. show that cross-linking epithelial CD40 increased cell survival in the presence of oxidant stress; this increase was associated with activation of the transcription factors NF- κ B and AP-1 and increased expression of the inhibitor of apoptosis, c-IAP1²¹. In light of these observations, it appears that the engagement of epithelial CD40 within the airways triggers a dual-action pathway; such a pathway both activates recruited immune cells and protects the lung epithelium from the mediators released by these cells.

3. Kidney epithelia and renal disease

3.1 CD40 expression and function in kidney epithelia

Within the kidney, CD40 expression has been observed on epithelial cells of the glomerulus as well as the proximal tubule. Yellin and co-workers reported initially that, in normal kidney, CD40 is expressed on parietal epithelial cells²³. Subsequent analyses have described both basal and inducible CD40 expression in primary cultures of renal proximal tubule epithelial cells. van Kooten and colleagues have demonstrated that IL-1 upregulates CD40 expression on proximal tubule epithelial cells²⁴; other groups have indicated that IFN γ and TGF β also

increase CD40 expression on these cells²⁵. In addition, van Kooten and colleagues have shown that engagement of CD40 in the presence or absence of other stimuli, such as IL-1 and IL-17, induces the production of IL-6, IL-8, RANTES, MCP-1 and/or IL-15 from these cells via an NF- κ B-dependent pathway^{24; 26; 27}. Likewise, Li and Nord have reported that CD40 ligation on renal proximal tubule epithelial cells increases the expression and function of the adhesion molecule ICAM-1 via the p38 mitogen-activated protein kinase signal transduction pathway²⁸. Further, Pontrelli and colleagues have shown that CD40 engagement on these cells induces the expression of plasminogen activator inhibitor-1 (PAI-1), a potent profibrotic mediator, in a time-dependent manner²⁹.

3.2 Role of epithelial CD40 in renal inflammation and renal allograft rejection

Tubulointerstitial inflammation and chronic allograft nephropathy are both characterized by an influx of inflammatory cells, including activated, CD154+ T cells, into the local microenvironment. Interactions between these cells and resident structural cells, such as epithelial cells, promote an ongoing inflammatory response (see Figure 1). As described above, engagement of CD40 expressed on renal proximal tubular epithelial cells enhances their production of inflammatory mediators, such as IL-6, IL-8, RANTES, MCP-1, IL-15 and PAI-1; in turn, these mediators cause tubular injury and promote renal allograft rejection. In particular, an increase in PAI-1 expression is associated with chronic tubulointerstitial diseases that are characterized by progressive fibrosis, including chronic allograft nephropathy²⁹.

Despite these pro-inflammatory actions, CD40 expressed on renal proximal tubular epithelial cells may also protect the inflamed epithelium from injury. To this end, Laxmanan et al. have reported that cross-linking CD40 on renal proximal tubule epithelial cells induces the expression of heme oxygenase-1 (HO-1), which serves as an antiapoptotic gene, via a pathway that involves NF- κ B³⁰. It is interesting to note that CD40-mediated expression of the anti-apoptotic HO-1 enzyme in the renal epithelium parallels the CD40-mediated expression of the apoptosis inhibitor c-IAP1 in airway epithelium²¹. Together, these findings suggest that, as observed within the pulmonary compartment, epithelial CD40 in the kidney can elicit both pro- and anti-inflammatory responses.

4. Thymic epithelia and self-tolerance

4.1 CD40 expression and function in thymic epithelia

The structure of the thymus is divided into two compartments, the cortex and medulla; each compartment contains specialized thymic epithelial cells. CD40 expression on both cortical and medullary thymic epithelial cells was described originally by Galy and Spits³¹. Expression of CD40 was maintained in culture and upregulated in the presence of IL-1 α , TNF α , and IFN γ , but not IL-4. The authors also reported that engagement of CD40, in conjunction with IL-1 and IFN γ stimulation, increased GM-CSF release from thymic epithelial cells. More recently, Akiyama et al. have reported that cooperation between CD40- and RANK (receptor activator NF- κ B)-mediated signals is required for the development of medullary thymic epithelial cells and subsequent establishment of the medullary microenvironment³². Further, these authors demonstrated that CD40 ligation on fetal thymic stroma induced medullary thymic epithelial cell development in a TRAF6-, NF- κ B inducing kinase (NIK)- and I κ B kinase β -dependent manner. Spence and Green have shown that CD40 expression on either thymic dendritic cells or epithelial cells is sufficient for the development of Foxp3+ regulatory T cells³³.

4.2 Role of epithelial CD40 in self-tolerance

Systemically, tolerance to self-antigens is governed by a combination of T cell tolerance and peripheral organ-specific tolerance. T cell tolerance is achieved mainly in the thymus, where

T cells develop and undergo negative selection. Because the autoimmune regulator (Aire) gene is expressed preferentially in thymic medullary epithelial cells, it is well accepted that these cells are essential in the clonal deletion of auto-reactive T cells. In contrast, organ-specific tolerance in the periphery is the result of anergy and regulatory T cell functions. As described above, engagement of CD40 expressed on thymic epithelia promotes the development of the thymic medullary microenvironment and the Foxp3+ regulatory T cell population; therefore, epithelial CD40 plays a direct role in the establishment of self-tolerance both within the thymus and in the periphery.

5. CD40 expression and function in other epithelia

Although not as completely characterized as the tissues described above, CD40 expression has been examined in other compartments, including the intestine and cornea. Cruickshank and co-workers reported that intestinal epithelial cells, which encounter enteric antigens, express CD40 together with other costimulatory molecules; however, these cells were unable to promote mitogen or antigen driven activation of CD4 T cells³⁴. With regard to corneal epithelium, Iwata and colleagues have shown that CD40 is expressed on primary limbal epithelial cells and also on cultured corneal epithelial cells with high proliferative potential³⁵. CD40 expression on cultured cells was enhanced in the presence of IFN γ and TNF α . Likewise, Bourcier et al. demonstrated that conjunctival epithelial cells isolated from normal and inflamed eyes expressed CD40; CD40 expression was further increased in the presence of IFN γ and TNF α ³⁶.

6. Concluding remarks and future directions

The CD40 receptor is expressed on epithelial cells in a wide variety of tissues. Its expression and function in these cells contributes to their role as immune effectors in the respective, local microenvironments. Engagement of epithelial CD40 activates these cells and results in their release of pro- and anti-inflammatory as well as pro-fibrotic mediators. As a consequence, epithelial CD40 has been implicated in the pathogenesis of inflammatory disorders, generation of self-tolerance, and chronic rejection of allografts. Future studies will likely include the generation of mouse models that express CD40 exclusively in tissue-specific epithelia; such an approach will provide focused information regarding the role of epithelial CD40 in immune responses. Moreover, such studies may yield insights into novel therapies that target epithelial CD40 actions.

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Fig 1.

Model of potential epithelial and T lymphocyte cell-cell interactions via CD40-CD154. Through expression of CD40, epithelial cells may interact with activated, CD154-expressing T lymphocytes. This cell-cell interaction may occur at either that basolateral and/or apical epithelial cell surfaces as the T cell migrates from the circulation into the tissue lumen.