REVIEW

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Regulation of local immunity by airway epithelial cells

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Abstract

Epithelial cells are the first line of defense against invading microbial pathogens. They are important contributors to innate mucosal immunity and generate various and sophisticated anti-microbial defense mechanisms, including the formation of a tight barrier and secretion of anti-microbial substances as well as inflammatory mediators. To provide these active defense mechanisms, epithelial cells functionally express various pattern-recognition receptors. Toll-like receptors have been shown to recognize conserved microbial patterns mediating inducible activation of innate immunity. Mucosal surfaces, however, are prone to contact with pathogenic as well as non-pathogenic microbes and, therefore, immune-recognition principles have to be strictly regulated to avoid uncontrolled permanent activation. This review will focus on mechanisms by which epithelial cells regulate mucosal immune responses, thus creating an organ-specific microenvironment. This includes local adaptations in microbial recognition, regulation of local immune homeostasis, and modulation of antigen-presenting cells and adaptive immune responses. These regulatory mechanisms serve the special needs of controlled microbial recognition in mucosal compartments.

Key words: epithelial cells, immunity, lung, Toll-like receptors.

Abbreviations: PAMP – pathogen-associated molecular pattern, PRR – pattern-recognition receptor, TLR – Toll-like receptor.

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INTRODUCTION

Mucosal surfaces are the major route for pathogen entry and sites for the development of infections. Airway epithelial cells represent the body's largest epithelial surface and, due to the amount of gas exchange with the external environment, are prone to microbial encounter. The upper airways regularly come into contact with airborne microbes and are therefore equipped with a variety of mechanisms to avoid the establishment of infections [15]. In particular, bronchial epithelial cells possess tight junctions which build up a physical barrier and hinder pathogen access to the body's interior. Moreover, bronchial epithelial cells are covered by a mucus layer which entraps microorganisms and the mechanical movement of cilia constantly clears the airways from inhaled microbes. In addition, mucosal epithelium in general produces a hostile environment for invading pathogens by continuously secreting anti-microbial substances, including lysozyme, lactoferrin, collectins, and highly active anti-microbial peptides. All these functions are constantly activated and, until recently, mucosal epithelial cells were mainly regarded as a static barrier. New results are now changing our understanding of the function of mucosa epithelial cells.

Over the last years it has been found that epithelial cells express receptors belonging to the class of pattern--recognition receptors (PRRs) which serve the function of recognizing microbial compounds [6, 20, 63]. PRRs are known to play a crucial role in the activation of professional innate immune cells, including macrophages and dendritic cells (DCs) [52, 78]. The existence of such receptors on airway epithelial cells suggests that the epithelium itself can discriminate self from foreign and can thus actively recognize and respond to pathogen encounter. Indeed, multiple reports now show that upon bacterial or viral infection, the epithelium contributes to the inflammatory reaction of the host by, for example, secretion of soluble mediators, including chemokines [30]. This change in the activation status is mediated especially by Toll-like receptors (TLRs), which is the most important family among the PRRs.

However, these recent findings also raised the question as to how epithelial cells, especially in non-sterile

compartments, regulate their sensitivity to commensal or non-pathogenic microbes. Obviously, mucosal surfaces which frequently encounter microbes would be prone to constant inflammation if regulatory mechanisms did not exist or if adaptation of common microbial recognition principles were not achieved. Recent experimental data now suggest that epithelial cells at various anatomic locations indeed show differences in terms of pathogen recognition compared with professional innate immune cells [11, 33, 51]. Although all these cells make use of the same PRRs, the resulting activation patterns differ. Moreover, epithelial cells actively regulate local immune responses by establishing a specific local microenvironment [67, 77]. Microenvironment regulation has now entered the focus of research in mucosal immunity [28], and this will be the topic of this review. This report mainly addresses airway epithelium. However, many fundamental experiments with respect to mucosal epithelium have been obtained with intestinal cells. Where these findings are probably valid for mucosal epithelium in general, they will be cited as well.

ORGAN-SPECIFIC REGULATION OF INNATE IMMUNE RESPONSES: A CONCEPT

Innate immunity mediates the first-line of defense against invading pathogens. A breakthrough in the understanding of the function of innate immunity was the conceptual and experimental description of PRRs, first provided by Charles Janeway [52]. In this concept, PRRs recognize pathogen-associated molecular patterns (PAMPs) and mediate the activation of innate immune cells. PAMPs are conserved microbial structures which are structurally different from host molecules and thus enable foreign/self discrimination. In principle, this concept has now been proven, and TLRs, which recognize compounds derived from bacteria, viruses, fungi, or parasites, are the most important and well-studied group among PRRs [3]. However, a major question arose when it became clear that structures recognized by PRRs are by far not confined to pathogenic microbes, but occur as well on non-pathogenic microorganisms [40]. Thus, PRRs are not able to discriminate virulent, pathogenic, and potentially dangerous microorganisms from harmless ones. In other words, opportunists may not be distinguished from pathogens.

Whereas this is no problem in microbial recognition in sterile compartments within the body, it immediately becomes obvious that the recognition principles at non-sterile mucosal surfaces (e.g. skin, intestine, oral cavity) must differ. However, TLRs have now been found not only on monocytes and DCs within sterile environments, but also on epithelial cells with constant contact with bacteria [1, 53].

Taking these observations into account, Raz [66] recently proposed the concept of "graded immune responses". He suggested that each organ senses infectious danger in a different way. Thus the specific organ's physiology shapes and instructs local immune responses. An important variable is the "degree of sterility", or the existence of commensal local microbial flora. Thus bacterial encounter in otherwise sterile blood will induce different responses than in the intestine. This is due to a different threshold for activation by microbial compounds [51, 53], organ-specific, non-canonical signaling pathways [1, 75], as well as specific regulatory adaptations [18, 34] and the unique weaponry of different organs [35, 51]. With such a concept of organ-specific immunity in mind, two important assumptions would be that the activation of PRRs has to be tightly controlled at non-sterile surfaces and that professional immune cells are controlled by organ-specific stroma cells.

In principle, three major compartments may be defined in which organ-specific regulation will differ (Fig. 1). In a sterile environment, every microbial contact is indicative of infectious danger and should mount a maximal response. In other words, sensitivity should be maximal, and this is what is normally observed when examining leukocytes from the blood or spleen. In molecular terms, maximal sensitivity is achieved by high expression of a full repertoire of PRRs and co-receptors

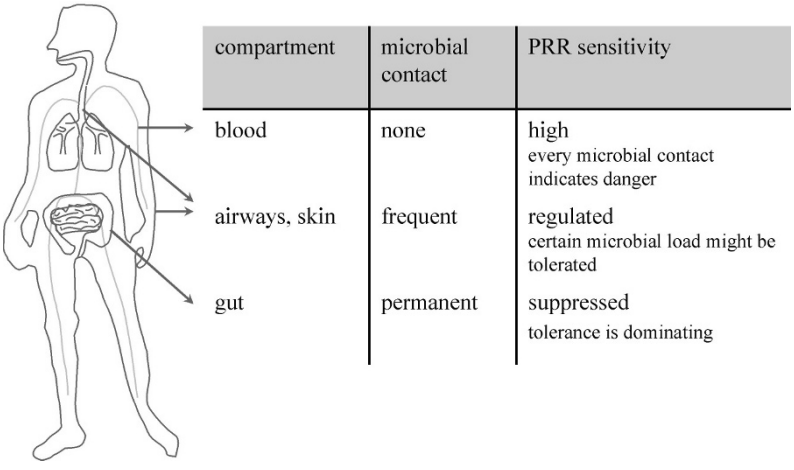

Fig. 1. Organ-specific regulation of immune responses. Microbial recognition within the innate immune system is achieved by use of PRRs that are also found on epithelial cells. However, PRRs in general are not able to discriminate pathogenic from non-pathogenic microbes. Thus, pattern recognition must be modulated and regulated in an organ-specific manner, especially within non-sterile compartments. It is proposed that PRR sensitivity is organ-specifically regulated, and an important control variable is microbial load at a given anatomical site.

and negative regulatory signaling circuits are suppressed. The opposite is realized in the colon: Constant contact with bacteria leads to a general suppression of TLR-sensitivity. This is achieved by the induction of negative regulatory molecules (e.g. IRAK-M, SIGIRR, Tollip) [41, 86, 89], expression of TLRs at different anatomical locations instead of the cell surface [1, 33], or by missing expression of co-receptors [74]. However, virulent, pathogenic bacteria that invade enterocytes or traverse the barrier can still evoke an epithelial response; therefore, this is not "anergy". A third reaction pattern may be defined for organs in which a limited repertoire of bacteria and only low numbers are frequently encountered, as observed, for example, in the upper airways or the skin. Here, TLR sensitivity has to be intermediate in order to tolerate avirulent microbes, but to defend against pathogenic microorganisms. Again, sensitivity has to be more tightly controlled than in the sterile compartment because inflammation in the lung poses the threat of severe organ dysfunction due to immunopathology.

Based upon such a concept of organ-specific regulation of immunity, it becomes clear that experimental results obtained under "sterile settings" (for example using blood leukocytes) cannot necessarily be transferred to the situation at mucosal surfaces.

AIRWAY EPITHELIAL CELLS ARE ABLE TO SENSE INFECTIOUS DANGER

A precondition for the concept of organ-specific immunity based on a graded degree of microbial contact is that non-professional immune cells (including epithelial cells that cover surfaces) are able to sense the presence of infectious danger. Indeed, over the last years it has been found that epithelial cells at different mucosal sites express functional PRRs. We were able to show that primary bronchial epithelial cells express TLRs 1-6 and -9 [51, 63]. Expression of TLRs in airway epithelial cells has been shown by a variety of other groups [6, 20, 23, 29] and is reviewed in detail elsewhere [21, 30]. An interesting observation was that the expression profiles of TLRs in epithelial cells and monocytes differed, with only low copy numbers of TLR-2 being detected in epithelium [51]. This coincided with reduced responsiveness towards some TLR-2 ligands and Gram-positive bacteria. Another observation was the low or missing expression of functional TLR7-9 [22, 51], although this is still a matter of debate in airway epithelial cells [54]. As these receptors are expressed intracellularly, active phagocytosis as observed in professional innate immune cells is a prerequisite for function and this could be the reason why epithelial cells do not use this recognition principle extensively. Thus the TLR profiles indeed support a concept of organ-adapted expression.

Interestingly, TLR expression has also been extensively studied and shown on intestinal epithelial cells [1, 10, 34, 46], keratinocytes [62], renal epithelial cells [85], and even on myocytes [17] and adipocytes [7]. The expression of prototypical PRRs will probably also be detected on many further cell types. This could indicate that, in principle, many organ-specific cells are able to use this common receptor system for the recognition of infecting microbes and, in turn, might mediate an organ-specific modulation of professional immune responses.

Further PRRs have been detected in airway epithelial cells: Our own work identified transcripts for CD14, fMLP, mannose receptor, and NOD1 in BEAS-2B cells [51] and others have also found NOD2 [80]. Recent interest has been focused on intracellular RNA receptors, and RIG-I and MDA5 have indeed been shown to be functionally expressed in airway A549 epithelial cells [58]; RIG-I was reported to be crucial for early responses to respiratory syncytial virus [48]. Moreover, NALP1, which belongs to a family of NOD-like receptors, has also been detected in tracheal epithelium [44].

The results clearly indicate that airway epithelial cells themselves are able to sense the presence of infecting microorganisms employing the common recognition principle of pattern recognition [72]. However, adaptations have to exist in order to fit microbial recognition to the specific needs of different organs.

LOCAL ADAPTATIONS IN THE RECOGNITION OF MICROBES AT EPITHELIAL SURFACES

The initial observation of TLR expression in intestinal epithelial cells which are in constant contact to commensal bacteria raised the question of organ-specific adaptations in TLR signaling. Intestinal epithelium has thus been analyzed intensively and prototypical regulatory mechanisms have been identified. As outlined above, some of these findings may also apply for mucosal immunity in compartments with less frequent bacterial contact (e.g. airway epithelium). However, it is probable that additional regulation takes place in the airways.

Epithelial cells show polarity, and in the intestine TLR-4 and -5 are expressed intracellularly [33] or at the baso-lateral side [18], which hinders activation by luminal bacteria from the apical side. This expression pattern for TLR-4 is actively induced by bacterial colonization shortly after birth [49]. Similar findings have been observed for the lipopolysaccharide (LPS) co-receptor MD2, which is not expressed on the surface of intestinal epithelial cells [1]. Intestinal macrophages down-regulate LPS-sensitivity via missing expression of yet another co-receptor, CD14 [74].

In line of these findings it has been reported that respiratory epithelial cells also show intracellular compartmentalization of TLR-4 [24]. Moreover, it is becoming clear that the level of receptor expression also determines the activation threshold [49]. Thus our own findings of reduced TLR-2 expression might explain a reduced sensitivity of BEAS-2B cells to certain TLR-2-dependent microbial lipopeptides as well as Gram-

-positive bacteria [51]. Indeed, increasing the level of receptor expression by transfection coincided with restored sensitivity towards Gram-positive bacteria. Moreover, increasing expression of TLR-2 could be induced by stimulation with interferon (IFN)-γ and tumor necrosis factor (TNF)-α, which might mimic the situation during chronic infection [32]. Indeed, cystic fibrosis coincided with increased sensitivity towards TLR-2 stimulation [54, 73]. As the underlying mechanism it was shown that healthy airway epithelium down-regulates TLR-2 expression via CG-methylation of the promoter, yet the methylation pattern was altered during chronic inflammation. In line with these findings, patients suffering from chronic inflammation due to psoriasis also had an increased TLR-2 sensitivity within epidermal epithelial cells [5].

Beside the regulation of receptor levels, the expression of co-receptors also plays a role in microbial sensing in airway epithelium. We could recently show that the hyporesponsiveness of bronchial epithelial cells towards Gram-positive bacteria was also due to lack of expression of CD36 [51], which serves as a co-receptor for lipopetide signaling [31] and mediates phagocytosis of Gram-positive bacteria [76]. Restoring CD36 expression increased sensitivity to Gram-positive bacteria.

It might be speculated that within the airway compartment, especially the sensitivity towards low amounts of Gram-positive bacteria is regulated, whereas recognition of high-grade Gram-positive infection and Gram-negative bacteria with typical LPS is retained [19, 30, 71].

Additional regulatory mechanisms within epithelial cells have been described. Thus, inhibitory molecules for TLR-signaling, including SIGIRR [87], Tollip [16, 53, 89], IRAK-M [41], or A20 [69], are or might be of special importance in different epithelial cells. Moreover, it has been suggested that induction of peroxisome proliferator-activated receptor γ by commensal bacteria in the intestine uncouples nuclear factor (NF)-κB activation from gene transcription, which contributes to epithelial tolerance [39].

Epithelium-specific activation of additional signaling pathways has also been proposed. It was shown that TLR2-mediated PI3K/Akt activation increased intestinal epithelial cell survival in a model of colitis [12]. In airway epithelium, *Pseudomonas aeruginosa* DNA had pro-inflammatory properties inducing interleukin (IL)-8 by a so-far non-classical activation pathway [14]. Low-dose LPS stimulation in airway epithelial cells activated a novel signaling pathway involving reactive oxygen species and epidermal growth factor receptor phosphorylation [42].

Considering all the above, it has become clear that PRR signaling in epithelial cells undergoes a variety of adaptations in order to serve the specific demands in different organs (Fig. 2).

INTRINSIC EPITHELIAL DEFENSE PROGRAMS

An important question which is still not fully answered is what kind of response programs are activated within epithelial cells upon stimulation of PRRs. From a variety of studies it is clear that airway epithelial cells upon TLR triggering respond with increased expression of chemokines and certain pro-inflammatory cytokines and induce the secretion of anti-microbial effectors. We have analyzed the whole transcriptom of BEAS-2B cells upon stimulation with the lung pathogens *Staphylococcus aureus*, *P. aeruginosa*, and RSV [51]. We observed that *S. aureus* only provoked a minor response, which is in line with the above-described decreased TLR-2 sensitivity. For the other two pathogens we found that they induced a common as well as a specific response program. The common program, which defines the core response of epithelial cells to microbial danger, comprised genes with functions in inflammation, cellular attraction, and the regulation of apoptosis; many of these genes were NF-κB dependent. The importance of intrinsic epithelial NF-κB activation for anti-microbial responses was recently demonstrated

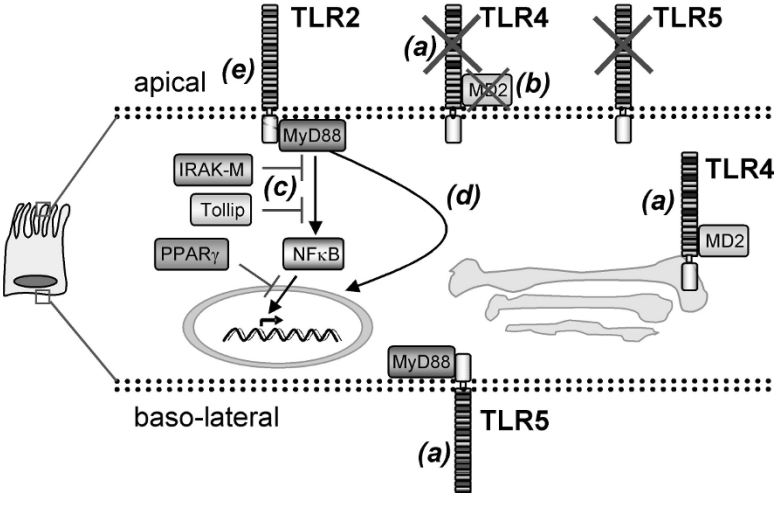

Fig. 2. Epithelium-specific adaptations in pattern recognition. Epithelial cells which are prone to contact with non-pathogenic microbes show alterations in PRR signaling. This results in organ-specific sensitivity of microbial recognition and activation. The proposed mechanisms that control PRR, especially TLR, sensitivity are: (**a**) restriction of apical TLR expression, (**b**) missing co-receptors, (**c**) inhibitory signaling molecules, (**d**) epithelium-specific signaling pathways, (**e**) reduced sensitivity of TLRs to activation by microbial compounds.

by the targeted manipulation of NF-κB in epithelial cells using adenoviral vectors. Administration of RelA enhanced clearance of *P. aeruginosa*, whereas expression of a dominant inhibitor of NF-κB inhibited anti-microbial defense [68]. Moreover, it was shown that within the first 4 h of infection, NF-κB activation was mainly observed in the bronchial epithelium, underlining the importance of the mucosa itself for immune defense.

Interestingly, different pathogens also induced specific response signatures in the bronchial epithelium. In general, these findings on global transcriptional changes upon microbial stimulation of epithelial cells are interpreted as a contribution of the bronchial epithelium to the host's anti-microbial defense, and this is achieved by inducing core as well as pathogen-adapted inflammatory programs. Supporting this concept of a contribution of epithelial cells to anti-microbial defense and inflammatory responses it was shown that epithelium-specific activation of the NF-κB pathway by expression of IκB kinase 2 under control of the CCL10 promoter was crucial for controlling inflammation and lung injury [13]. Furthermore, using bone-marrow chimeric MyD88-deficient mice it was shown that hemopoietic and resident cells were necessary for full-blown responses to inhaled LPS [56]. Finally, it was shown that bronchial epithelial cells from asthmatic patients have a defect in coping with rhinovirus infection [83]. All these findings support the importance of intrinsic epithelial pattern recognition.

So far, the role of TLRs in airway epithelium has mainly been analyzed under the assumption of a role of these receptors in mounting a professional immune response. However, it is also possible to ask whether TLR stimulation in epithelial cells evokes a more cell-specific response. From transcriptome analysis it became clear that microbial stimulation also regulated a variety of genes involved in cellular apoptosis. A very interesting report along this line now indicates that epithelial cell surface high-molecular-mass hyaluronan protected lung epithelium from apoptosis [36]. This was in part dependent on TLR-4 and basal activation of NF-κB. Similar findings have been reported for the intestine, where MyD88-deficient mice showed increased lethality in a noninfectious model of colitis [64, 65]. It was concluded that steady-state, and probably low-grade, activation of TLRs has protective effects on epithelium integrity. Interestingly, hyaluron fragments increased inflammation in injured tissue in a MyD88-dependent manner. This indicates that the degree of PRR activation might induce different outcomes and is thus an additional restriction point in epithelial cell PRR sensitivity. Corroborating these results for a role of PRRs in epithelial integrity, it was shown in the intestine that epithelium-specific inhibition of NF-κB by conditional ablation of NEMO resulted in spontaneous inflammation with increased apoptosis [55]. In airway epithelial cells it was reported that low-dose LPS stimulation accelerated wound repair by a signaling pathway involving transforming growth factor (TGF)-α and epidermal growth factor receptor signaling [42]. Again, high-dose LPS signaling was detrimental. Taken together, it is probable that TLR signaling in epithelial cells, beside its role in the defense against microbes, plays an additional, intrinsic role in mucosal homeostasis and this might be dependent on the magnitude of signaling.

An additional thought would be to analyze whether organ-specific responses are regulated by epithelial PRRs. It has been shown that such a specific response in the airways might be the secretion of surfactant. In the intestine it was recently shown that TLR-2 stimulation increased tight-junction-associated epithelial barrier integrity in a model of colitis [12]. This indicates that TLR activation in epithelial cells induces intrinsic changes that mediate cell-autonomous microbial resistance. Thus one might assume that TLR signaling is hard-wired to organ-specific gene induction, possibly by specific pathways (e.g. PI3K/Akt) or by epigenetic modifications. In turn, such an assumption would indicate that future experiments should aim to identify such organ-specific programs instead of focusing on general inflammatory reactions. It might well be that TLR-mediated microbe recognition in adipocytes affects metabolism, whereas in the kidney the filtration function is altered and in other organs TLR stimulation induces further changes. It is worth mentioning that both reaction patterns can be observed during sepsis.

AIRWAY EPITHELIAL CELLS REGULATE LOCAL IMMUNE HOMEOSTASIS

Based on the concept of graded immune responses in organs with different microbial load, we postulate that inhibitory mechanisms in non-sterile compartments predominate under noninfectious conditions. Epithelial cells, which at the first line of defense sense microbes, might be key players in such a scenario. Indeed, recently a unique regulatory, lung-specific, and TLR-dependent mechanism was described that ascribed to the epithelium a role in maintaining immune homeostasis [77]. It was shown that alveolar macrophages in noninfectious settings are continuously inhibited by epithelial cells. This steady-state suppression is mediated by TGF-β bound to $\alpha_v\beta_6$ integrin on epithelial cells. Tonic inhibition thus characterizes this compartment. However, during infection TLR activation seems to transiently release macrophages from epithelium inhibition. It was suggested that changes in macrophage cell-shape upon activation remove inhibition by epithelial surface TGF-β. In turn, epithelial cells transiently down-regulate $\alpha_v\beta_6$ integrin expression. In the further course, secretion of matrix metalloproteinase activates latent TGF-β, thus re-inducing $\alpha_v\beta_6$ expression and also re-inducing tonic inhibition. In such a scenario, epithelial cells are crucial for the establishment of a local inhibitory microenvironment. Similarly, the same group showed that in the lung, TLR stimulation induced indoleamine 2,3-dioxygenase,

which inhibited T cell-mediated immunity [27]. This reinforces the existence of an organ-specific microenvironment. It is permitted to speculate that "release of inhibition" during infections might also be induced by an initial epithelium-derived signal because these cells are at the frontline of defense against microbial encounter and are actively able to sense infectious microorganisms.

MODULATION OF ANTIGEN-PRESENTING CELLS BY AIRWAY EPITHELIUM

Mucosal DCs are known to differ from splenic DCs in many ways. Mucosal DCs have a propensity to induce T_{h2}-directed immune responses [2, 4] and to stimulate B lymphocytes to IgA switching [70]. Moreover, mucosal DCs were reported to have lower expression of TLRs [79]. Lamina propria DCs of the intestine even lack TLR-4, thus avoiding recognition of commensal bacteria, but express TLR-5 to become activated by pathogenic flagellated bacteria [81]. It was suggested that epithelial cells induce a specific microenvironment which is responsible for organ-specific immune responses and different mediators have been proposed to play a role in this setting, including TGF-β, prostaglandins and nitric oxide [8]. In the intestine it was shown that DCs express fewer costimulatory molecules and induce less T-lymphocyte proliferation [9]. TGF-β was identified as modulating cytokine secreted by stromal cells and affecting phagocytosis of intestinal macrophages [74]. More recently it was suggested that, again in the intestine, thymic stromal lymphopoietin (TSLP) modulated DCs to secrete the T_{h2}-attracting chemokines CCL17 and CCL22 and to inhibit DC activation. In patients with chronic inflammatory bowel disease, TSLP-mediated DC suppression or T_{h2} differentiation was decreased [67]. TSLP within bronchial epithelium was found to play a role in asthma, here mediating T_{h2} differentiation [87]. TSLP was induced in normal airway epithelial cells by TLR-3 stimulation and upon rhinovirus infection [38]. Interestingly, IKK-β deficiency within epithelial cells resulted in reduced TSLP expression and affected T_{h2} responses in a model of *Trichuris* infection [88]. Moreover, lack of epithelial IKK-β resulted in increased IL-12p40 and TNF-α expression as well as increased $CD4^+$ T cell-derived IFN-γ and IL-17. This was discussed to play a role in epithelium-mediated organ homeostasis. In airway epithelial cells it was also found that TSLP is controlled by NF-κB [45].

Recently it was shown that the epithelium-derived anti-microbial peptide LL-37 inhibited DC activation by TLR stimulation [37]. Cytokine secretion as well as expression of co-stimulatory molecules was suppressed and it was proposed that LL-37 might function as a regulator of the interface epithelium/professional immune cells.

Our own unpublished results show that bronchial epithelial cells constitutively secrete factors that inhibit DC activation by TLR stimulation. Supporting the above-described findings in the lung and in the intestine, we observed reduced co-stimulatory molecule expression, IL-12 secretion, and T-cell proliferation. Furthermore, it was shown by others that DCs conditioned by bronchial epithelial cells induced T cells to produce more IL-10 [61]. Also, pulmonary DCs produced IL-10 themselves upon allergen exposure and stimulated the development of regulatory T cells [2]. These results again reinforce the notion that the epithelium is an important regulator of local immunity. A so-far unanswered question is whether during infectious encounter epithelial cells might switch their inhibitory activity towards a stimulating one, thereby releasing DCs from inhibition.

MODULATION OF ADAPTIVE IMMUNE RESPONSES BY AIRWAY EPITHELIUM

T-helper cells within the lung are prone to a T_{h2} reaction pattern. This is in part mediated by the generation of organ-specific tolerogenic DCs, and epithelium-derived TSLP and TGF-β have been implicated in this process. Moreover, TGF-β, which is abundantly found in the lung, plays an important role in the inhibition of T_{h1}/T_{h2} differentiation, but induces adaptive regulatory $FoxP3^+$ T cells [47, 82]. Our own unpublished results indicate that airway-epithelium conditioned T cell activation is inhibited and that this is partly dependent on secreted TGF-β.

Recently, another population of T-helper cells has been identified which secretes IL-17A and IL-17F and which was termed T_{h17} [26, 59]. These T_{h17} cells played a role in the defense of infection with lung pathogen *Klebsiella pneumoniae* [25]. Interestingly, TGF-β in combination with IL-6 was shown to play a role in T_{h17} induction, which is further supported by IL-23 [50]. Recent results indicate that an autocrine IL-21 loop also contributes to T_{h17} induction [43, 57, 90], and in humans TGF-β seems to be dispensable, but IL-1β is important [84]. Also, TLR-activated DCs secreted IL-6 which, together with another co-factor, reverted the generation of regulatory T cells [60]. IL-1 acted synergistically. It has been shown that airway epithelial cells secrete IL-1 and IL-6 upon TLR stimulation. It is therefore tempting to speculate that the following scenario characterizes organ-specific airway immunity (Fig. 3). Under non-infectious conditions, airway epithelial cells mediate tonic inhibition of DCs and inhibit inflammatory T cell responses. TGF-β activity additionally results in the generation of regulatory T cells. Further soluble mediators, such as retinoic acid and IL-2, promote these cells and suppress T_{h17} differentiation. However, upon sensing virulent microbes, epithelial cells produce IL-1 and IL-6, release DCs and macrophages from inhibition, and mediate switching to T_{h17} immunity. Such a concept would place airway epithelial cells in the center of the regulation of local immune responses.

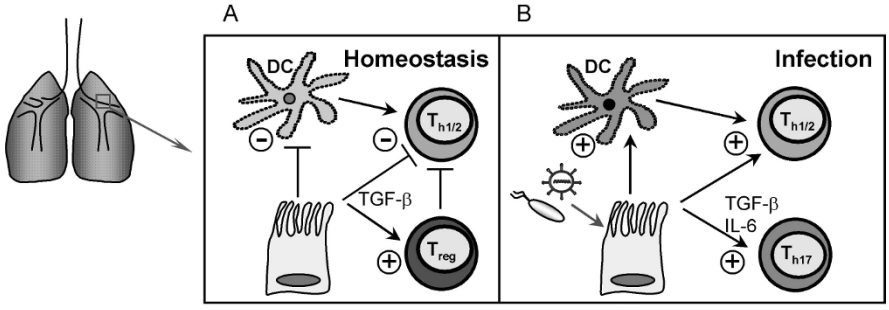

Fig. 3. Immunity in airway epithelium: a model. **A** – under noninfectious conditions, epithelial cells inhibit DCs and T cells in order to adapt to the local necessities of the airway compartment, which regularly encounters airborne microbes. This inhibition is achieved by soluble factors, including TGF-β and, possibly, TSLP. Cell-contact-dependent suppression is additionally proposed. Moreover, adaptive regulatory T cells are activated that contribute to tonic inhibition. TGF-β and further factors, including retinoic acid and IL-2, promote the induction of regulatory T cells. **B** – Infections are sensed by epithelial cells, which change their activation status and now transiently release professional immune cells from inhibition. Epithelium-derived factors, including IL-1 and IL-6, now switch T cell immunity to a T_{h17} response pattern and professional antigen-presenting cells are activated.

CONCLUSIONS

Recent findings indicate that immune responses are regulated in an organ-specific manner. At mucosal surfaces, the degree of microbial contact regulates the threshold and the nature of local immunity. It has been shown that airway epithelial cells functionally express PRRs which enable them to sense infectious danger. However, within the framework of organ-specific immunity, airway epithelial cells show an increased activation threshold to limit potentially harmful inflammatory reactions. Moreover, under noninfectious conditions, airway epithelial cells mediate tonic inhibition of antigen-presenting cells and T lymphocytes. Upon sufficient activation of PRRs, airway epithelial cells induce a pathogen-adapted gene expression program that 1) results in intrinsically anti-microbial responses, 2) contributes to the establishment of an inflammatory response (e.g. by chemotaxis), and 3) transiently releases professional immune cells from tonic inhibition. This ascribes a much more active role to epithelial cells in the regulation of local immune responses than anticipated so far.

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