Lung epithelium as a sentinel and effector system in pneumonia – molecular mechanisms of pathogen recognition and signal transduction

Stefan Hippenstiel*, Bastian Opitz, Bernd Schmeck and Norbert Suttorp

Address: Department of Internal Medicine/Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany
Email: Stefan Hippenstiel* - stefan.hippenstiel@charite.de; Bastian Opitz - bastian.opitz@charite.de; Bernd Schmeck - bernd.schmeck@charite.de; Norbert Suttorp - norbert.suttorp@charite.de
* Corresponding author

Abstract

Pneumonia, a common disease caused by a great diversity of infectious agents is responsible for enormous morbidity and mortality worldwide. The bronchial and lung epithelium comprises a large surface between host and environment and is attacked as a primary target during lung infection. Besides acting as a mechanical barrier, recent evidence suggests that the lung epithelium functions as an important sentinel system against pathogens. Equipped with transmembranous and cytosolic pathogen-sensing pattern recognition receptors the epithelium detects invading pathogens. A complex signalling results in epithelial cell activation, which essentially participates in initiation and orchestration of the subsequent innate and adaptive immune response. In this review we summarize recent progress in research focussing on molecular mechanisms of pathogen detection, host cell signal transduction, and subsequent activation of lung epithelial cells by pathogens and their virulence factors and point to open questions. The analysis of lung epithelial function in the host response in pneumonia may pave the way to the development of innovative highly needed therapeutics in pneumonia in addition to antibiotics.

Types of pneumonia, different types of pathogens, economic burden of pneumonia

Pneumonia is the third leading cause of death worldwide and the leading cause of death due to infectious disease in industrialized countries. In developing countries, approximately 2 million deaths (20% of all deaths) of children are due to pneumonia [1]. The majority of patients with community-acquired pneumonia (CAP) in industrialized countries are treated as outpatients with a low mortality rate usually less than 1%. In patients requiring inpatient management, the overall mortality rate increases up to approximately 12%. Of note, lethality rate in hospitalized patients differs significantly among different patient groups due to comorbidity (COPD, stroke, etc.) or risk factors (age, patients from nursing homes) [2].

In nosocomial pneumonia (hospital-acquired pneumonia, HAP; health-care associated pneumonia, HCAP) mortality increases substantially. HAP accounts for 15% of all nosocomial infections, its mortality rate exceeds 30%, although the attributable mortality is lower [3-5]. Requirement of mechanical ventilation is a high risk factor for the development of HAP with high mortality. This form of CAP, called ventilator-associated pneumonia

Published: 08 July 2006
Respiratory Research 2006, 7:97 doi:10.1186/1465-9921-7-97
This article is available from: http://respiratory-research.com/content/7/1/97
© 2006 Hippenstiel et al; licensee BioMed Central Ltd.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
(VAP) occurs in up to 47% of all intubated patients and varies among patient populations [6]. It definitely results in an increased length of stay. Moreover, high mortality rates are reported ranging from 34% in mixed medical/surgical intensive care unit patients [7] to up to 57.1% in heart surgical patients [8].

Consequently, CAP and HAP represent an enormous economic burden to the public health systems. CAP alone causes costs to the US economy of about US$ 20 billion in the United States [9] due to more than 10 million visits to physicians, 64 million days of restricted activity and over 600,000 hospitalizations per year [10].

Increasing antimicrobial resistance of pathogens causing CAP (e.g. *Streptococcus pneumoniae* [11,12]) and VAP (e.g. *Pseudomonas aeruginosa, Staphylococcus aureus* [6,13]) as well as the increasing number of humans with increased susceptibility to pneumonia (e.g. geriatric and/or immunocompromised people [14]) will aggravate the problem. Consequently, the development of new preventive and therapeutic strategies is urgently warranted.

Table 1: Important pathogens causing pneumonia

| Pathogen | CAP | HAP/HCAP | Adults | Children |
|----------|-----|----------|--------|----------|
| **Bacteria** | | | |
| *S. pneumoniae* | +++ | +++ | +++ | +++ |
| *H. influenzae* | ++ | ++ | ++ | ++ |
| *M. pneumoniae* | +++ | + | ++ | +++ |
| *Chlamydia spp.* | + | (+) | | ++ |
| *Klebsiella spp.* | + | ++ | | |
| *Legionella spp.* | + | +++ | | |
| *S. aureus* | ++ | +++ | +++ | + |
| *Acinetobacter spp.* | + | +++ | | |
| **Viruses** | | | |
| *RSV* | ++ | + | +++ | |
| *Rhinovirus* | ++ | | | ++ |
| *Influenza virus* | ++ | (+) | | |
| *Parainfluenza virus* | ++ | | | ++ |
| **Fungi** | | | |
| *Candida spp.* | ++ | | | |
| *Aspergillus spp.* | ++ | | | |
| *P. jiroveci* | + | | | |

+ indicates the relative importance of the pathogen and the frequency of isolation in adults or children. 1 of importance in immunocompromised hosts. 2 important opportunistic pathogen in HIV/AIDS patients. CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; HCAP, health-care associated pneumonia. Based on collective data [2,5,6,15-18,23,252,253].

Interestingly, in children, a high rate of co-infections with viruses such as influenza A or B as well as respiratory syncytial virus (RSV) is observed in pneumococcal pneumonia [18]. Tsolia et al. recently provided evidence for high prevalence of viral infections, in particular rhinovirus infections, in school-age children hospitalized due to CAP [19]. Such infections have to be considered in the context of asthma attacks in children as well as in asthma and COPD exacerbations of adults [20-22].

Overall, in young infants, viruses such as RSV, parainfluenza and influenza virus are the most common cause of pneumonia (Table 1). In immunocompromised adults, in patients with asthma, chronic bronchitis or COPD, viruses are more frequently identified as the causative agent of pneumonia than in immunocompetent adult beings [23,24]. Cytomegalovirus-related pneumonia continues to be a major cause of morbidity and mortality in transplant recipients.

In addition to viruses, fungi like *Candida* spp. or *Aspergillus* spp. induce pneumonia in the immunocompromised host (post-transplantation, post-chemotherapy, etc.) [25].

Pneumonia due to infections with the opportunistic pathogen *Pneumocystis jirovecii* (former *P. carinii*) is a major cause of illness and death in HIV/AIDS patients [26].

Bacteria are the most common cause of pneumonia in adults. Most CAP-cases are due to infections with *S. pneumoniae, Haemophilus influenzae*, and *Mycoplasma pneumoniae* (Table 1) [15,16]. In patients with severe CAP, *Legionella* spp. as well as gram-negative bacilli and *S. aureus* have to be considered besides pneumococci [15,16]. The majority of late onset-VAP cases is caused by *S. aureus*, including antibiotic-resistant subtypes, *Pseudomonas* spp., *Klebsiella* spp., as well as *Acinetobacter* spp. [17].
The pulmonary innate immune system
A large variety of pathogens are known to cause pneumonia. The innate immune system serves as the first line host defense system against invading pathogens. Localized at the interface between the environment and the host, the airway epithelium does not only form a large mechanical barrier, but it is also predisposed as a sentinel system to detect pathogens entering via the airways and to initiate the initial host immunological response.

Pseudostratified and columnar tracheobronchial epithelium consisting of ciliated cells, secretory goblet cells and cells with microvilli provide mechanisms for mucociliary clearance. In the bronchioles, cuboidal epithelium and secretory Clara cells line the airways. Alveolar type I cells and type II cells constitute the alveolar epithelium. About 95% of the internal lung surface is built by alveolar type I cells. Fused to endothelial cells by their basement membranes both cell types together form the gas exchange barrier. Alveolar type II cells fulfill many known functions, including the regulation of the lung surfactant system [34], alveolar fluid content [35], and are important for the replacement of injured type I cells [34,36]. Although not evaluated systematically, it seems predictable that differentiated lung epithelial cells from different origin in the lung will have a cell-type specific response to a given pathogen. This might be due to varying expression of pattern recognition receptors (PRR), and/or cell-specific protein expression (e.g. surfactant protein expression) [37] as well as to different susceptibility to injury [38].

Although all pathogens causing pneumonia may directly interact with tracheobronchial as well as alveolar epithelium, the molecular mechanisms and consequences of these interactions are poorly understood. For some of the important pathogens mentioned, little or nothing is known about the consequences of epithelial infection.

Taking the enormous global burden of pneumonia, the increasing number of antibiotic-resistant bacteria, and the emergence of new pulmonary pathogens into account, an exact analysis of molecular mechanisms of disease is mandatory to form a rational basis for the development of innovative interventional procedures in pneumonia. In this review we focus on current molecular aspects of pathogen-lung epithelial interactions.

Recognition of entering pathogens by lung epithelium
A prerequisite for the initiation of host responses is the recognition of pathogens by the host immune system. A tremendous progress in this field was the discovery that the 10 germline-encoded human TLRs comprising the TLR family act as transmembrane pattern recognition receptors (PRR) detecting a large variety of conserved pathogen-associated molecular pattern (PAMP) as well as presumably even self-molecules [39-43]. TLR activation initiates expression of important mediators of the subsequent immune response. In addition, recent research points to the existence of cytosolic PRRs, which may serve as a second sentinel system detecting particularly but not exclusively invasive pathogens. These include members of the NACHT (domain present in NAIP, CIITA, HET-E, TP-1)-LRR (leucine-rich repeats) (NLR) family [44-46], as well as the caspase-recruitment domain (CARD)-containing RNA-helicases retinoic acid inducible gene-1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5)
Both, the TLRs and the NLRs, but not the CARD-helicases, possess LRR domains, which seem to be crucial for pathogen recognition.

Transmembraneous receptors

In brief, TLR1, TLR2, and TLR6 are at least partly located on the cell surface, and may collaborate to discriminate between the molecular structures of triacyl and diacyl lipopeptides, as well as lipoteichoic acid. TLR4 recognizes bacterial lipopolysaccharide (LPS) [53], whereas TLR5 detects bacterial flagellin on the cell surface [54]. In contrast, TLR3 [55], TLR7, TLR8 [56,57] and TLR9 [58] are located in endosomal compartments and perceive microbial nucleic acids: TLR3 recognizes viral dsRNA, whereas TLR7 and TLR8 recognize viral single stranded (ss)RNA. Bacterial and viral cytosine-phosphate-guanosine (CpG)-containing DNA motives are recognized by TLR9. The ligand for TLR10 has not been identified yet [59,60] (Fig. 1).

Distribution and subcellular expression of TLRs differ between immune cells and epithelial cells. Most results, however, were obtained by analysis of different (immortalized) cell lines and a systematic exploration of TLR receptor expression in healthy human lungs or inflamed (humanized) cell lines and a systematic exploration of TLR receptor expression in healthy human lungs or inflamed (inflammation)-induced information on the role of lung epithelial TLR expression [61,62]. Moreover, TLR1-5 as well as TLR9 protein was shown to be expressed in tracheal and bronchial epithelial cell lines [61]. Expression of TLR2, TLR4, and TLR5 has been documented in vivo in human airway epithelial cells [63-65] as well as TLR2 expression in alveolar epithelial cells [66].

Besides lung epithelial cells hematopoietic cells (resident in the lung or infiltrating during the host-pathogen combat) also contribute to the host response in pneumonia. Studies analyzing global responses in pneumonia by using TLR-deficient mice (or C3H/Hej mice, which express a non-functional TLR4), therefore give only limited information on the role of lung epithelial TLR expression in pneumonia. Furthermore, most studies published focused on e.g. lethality, global bacterial burden or immune cell recruitment. Nevertheless, studies by Wang et al. [67] and Chu et al. [68] demonstrated important epithelium-related information obtained from these models by specific analysis of the lung epithelium. Thus, Wang et al. showed that H. influenza induced TLR4-dependent TNFα and MIP1α expression in lung airway epithelial cells in vivo [67]. Moreover, by the use of TLR2-deficient mice Chu et al. reported reduced airway mucin expression in M. pneumoniae infected TLR2-deficient mice [68].

The expression and localization of TLRs may differ between lung epithelial and classical immune cells. For example, TLR4 apparently is not expressed on the surface of the tracheobronchial epithelial cell line BEAS-2B and the alveolar epithelial cell line A549. In these cells – which only responded to purified TLR4 ligand LPS and only expressed TLR4 in vivo – TLR4 ligand LPS and its receptor TLR4 appeared to be expressed in an intracellular compartment, although the role of TLR4 in the cell membrane with subsequent increasing susceptibility to LPS took place as documented by studies using RSV infected lung epithelial cells [70]. Nevertheless, an increasing number of studies clearly indicate that lung epithelial cells are sufficiently activated by a broad variety of TLR ligands [39,40,71].

Lipoteichoic acid [72], commercially available peptidoglycan [73], and M. pneumoniae [68] activated cultured human pulmonary epithelial cells in a TLR2-dependent manner. Results obtained with S. pneumoniae-infected epithelial cells indicated a cooperative recognition of these bacteria by TLR1 and TLR2 but not by TLR2 and TLR6 [74]. P. aeruginosa flagella as well as the C-terminus of its cytotoxin ExoS stimulated lung epithelial cells TLR2 and TLR5-dependently [75]. In an elegant study, Soong et al. showed that lipid rafts-associated complexes of TLR2 and asialoGM1 presented at the surface of airway epithelial cells formed broadly responsive signalling complexes reactive to important lung pathogens like P. aeruginosa or S. aureus [76]. Notably, by using TLR2-deficient mice, the role of TLR2 for M. pneumoniae-induced airway mucin expression was demonstrated recently [68]. Taken together, TLR2 represents an important functionally active PRR on the surface of lung epithelial cells.

Double-stranded RNA, a byproduct of viral replication, is recognized by TLR3 within the endocytoplasmic compartment. Thus, TLR3 reportedly participates in the recognition of influenza A virus [77], rhinovirus [78] and detects the synthetic viral dsRNA analog polyribocytidylic acid [poly(I:C)] [78,79] in lung epithelial cells. Moreover, in a model of RSV infection in TLR3-deficient mice, Rudd et al. demonstrated that TLR3 was not required for viral clearance in the lung, but it had a large impact on mucus production [80].

TLR4 contributes to the recognition of various bacterial pathogens by lung epithelial cells [61,69,72]. In H. influenzae infection, activation of the transcription factor NF-κB and subsequent TNFα and MIP1α expression was reduced in lung epithelial cells of TLR4-deficient mice compared to wild-type cells, demonstrating the critical role of TLR4 in vivo for epithelial cell activation by this pathogen [67]. Consistent with this notion, two common, co-segregating
missense mutations (Asp299Gly and Thr399Ile) affecting the extracellular domain of TLR4 reduced the response to inhaled LPS in humans [81]. Besides LPS, other pathogen-derived factors may also be recognized by lung epithelial TLR4. For example, the important pneumococcal virulence factor pneumolysin was found to induce a TLR4-dependent activation of epithelial cells [74,82] and chlamydial heat shock protein also initiated TLR4- and TLR2-related signalling [83,84]. In addition, TLR4 together with CD14 might be involved in the recognition of RSV fusion protein, thereby contributing to anti-viral host defence in the lung [85]. Accordingly, TLR4 mutations (Asp299Gly and Thr399Ile) may be associated with increased risk of severe RSV bronchiolitis in human infants, thus implicating a role of TLR4 in this virus infection [86].

Flagellin is a major structural component of flagella, a locomotive organell present on a wide range of bacteria [87]. It induces TLR5-dependent signalling on the surface of host cells, which might also involve TLR4 [87]. Lung epithelial cells were stimulated by flagella of e.g. Bordetella bronchiseptica [88], P. aeruginosa [65,89], and L. pneumophila [90]. The importance of this interaction was highlighted by the observation that a common dominant TLR5 stop codon polymorphism leading to impaired flagellin signalling is associated with increased susceptibility to Legionaires’ disease [90].

In contrast to TLR2-6, little is known about the expression and function of TLR7-8 in lung epithelium. However, TLR6 may function in heterodimers with TLR2 thereby contributing to the recognition of diacylated lipoproteins [41-43]. It is not clear if lung epithelium expresses functionally active TLR7 and TLR8 although these receptors recognize guanosine- and uridine-rich single-stranded (ss)RNA found in many viruses.

Functionally active TLR9 was expressed in the human alveolar tumour epithelial cell line A549 as demonstrated by Droemann et al [66]. Although immunization of mice with CpG motives reduced the burden of Cryptococcus neoformans in the lung, it is unclear if this effect was dependent on lung epithelial TLR9, or more likely, induced by TLR9-expressing immune cells causing promotion of a sufficient Th1-type immune response [91]. However, promotion of lung TLR9 signalling by using synthetic agonists may enhance the host defence and may even be beneficial in patients with acquired immune deficiency.

From an analytical perspective the use of purified virulence factors has been essential for understanding PRR function. However, infection of lung epithelial cells with “complete” pathogens containing different PAMPs results in a more complex, but also more realistic stimulation (e.g. pneumococci possesses TLR2-stimulating LTA [92] as well as TLR4-stimulating pneumolysin [74,82]). In addition, more than one TLR may be activated by one PAMP as demonstrated for the bifunctional type-III secreted cytotoxin ExoS from P. aerogenosa, which was shown to activate both, TLR2 and TLR4 signalling [93].

The situation is furthermore complicated by the fact that pathogens may modulate the expression pattern of TLRs and induce a re-localization of the PRRs. For example, pneumococci increased the expression of TLR1 and TLR2 in bronchial epithelial cells, but displayed no effect on TLR4 and TLR6 expression [74]. In mice, inhalation of LPS induced a strong increase in TLR4 protein expression in the bronchial epithelium as well as in macrophages within 24 hours [94]. Poly(I:C) may elevate the expression of TLR1-3 but decrease the expression of TLR5 and TLR6 [79]. Increased expression as well as membrane localization of TLR3 [95] and TLR4 [70] have been observed after RSV infection of airway epithelial cells. The effect of mixed infections with different pathogens (e.g. influenza virus and pneumococci) on TLR expression/localization and subsequent cell activation is widely unknown (see below). Thus, during an infection process, the recognition of pathogens is a dynamic process influenced by varying TLR expression on pulmonary epithelium. Furthermore, the liberation of cytokines (e.g. TNF-α, IFN-γ) during the initiated host response as well as therapeutic interventions (e.g. corticosteroids) influences expression of TLRs [96].

Of note, besides the traditional membranous PRRs, other membrane receptor molecules may also be critically involved in epithelial activation by pathogens (Fig. 1). S. aureus protein A binds to TNFRI presented on airway epithelial cells thereby inducing pneumonia [97]. In addition, stimulation of platelet-activating factor receptor by S. aureus LTA, and subsequent epidermal growth factor receptor activation may stimulate mucus expression and cell activation in lung epithelium independently of TLR2 and TLR4 [98]. Angiotensin converting enzyme 2 (ACE2) expressed in the lung has recently been identified as a potential SARS coronavirus receptor and SARS and the Spike protein of this virus reduced the expression of ACE2 [99,100]. Notably, blocking of the renin-angiotensin pathway reduced the worsening of disease induced by injection of Spike protein in mice [100]. Thus, non-classical pathogen-recognition transmembranous receptors may also be important for the pathophysiology of pneumonia.

**Cytosolic receptors**

Various bacterial lung pathogens like C. pneumoniae [101,102], L. pneumophila [103,104], and S. pneumonia [105,106] are able to invade and replicate efficiently.
within epithelial cells. Inside the cells, these pathogens are protected against detection and attack by various defense mechanisms of the innate immune system. Not only whole bacteria are sensed intracellularly, the same is true for bacterial proteins or genetic material after injection into host cells via various bacterial secretion systems (e.g. type III or IV secretion system) [107-110]. Moreover, many viruses replicate very efficiently within the lung epithelium. Recent research provided evidence that cytosolic PRRs exist which detect these invasive pathogens and initiate an appropriate immune response [44-46] (Fig. 2).

The human NLR family, currently consisting of 22 proteins, contains NALP (NACHT-, LRR-, and pyrin domain-containing proteins), NOD (nucleotide-binding oligomerization domain), CIITA (class II transactivator), IPAF (ICE-protease activating factor) and NAIP (neuronal apoptosis inhibitor protein). These proteins are implicated in the detection of intracellular pathogens or other general danger signals [44-46]. Two of the best characterized members of the NLRs are NOD1 and NOD2 [44,45,111]. In general, the importance of NOD proteins has been highlighted by the findings that critical mutations are associated with inflammatory granulomatous disorders (e.g. Crohn's disease, Blau syndrome) [112]. In addition, an insertion-deletion polymorphism of the NOD1 gene effecting the LRR domain has been associated with asthma and high IgE levels as suggested recently [113,114].

NOD proteins share a tripartite domain structure: The carboxy-terminal LRR domain seems to mediate ligand recognition (Fig. 2). The central NOD (NACHT) domain exhibits ATPase activity and facilitates self-oligomerization. An amino-terminal localized caspase-recruitment domain (CARD) (one CARD domain in NOD1, two in NOD2) mediates protein-protein interaction [44-46]. NOD1 is activated by peptidoglycan-derived peptides containing γ-D-glutamyl-meso-diaminopimelic acid found mainly in Gram-negative bacteria [115,116], whereas NOD2 mediates responsiveness to the muramyl dipeptide MurNac-L-Ala-D-isoGln conserved in peptidoglycans of basically all bacteria [117,118]. However, as for many of the TLRs and their agonists, there is no formal proof for the binding of the peptidoglycan motifs to the LRR domains of NOD1 and NOD2.

So far it is unclear how cytoplasmic NODs find their ligands: Some bacteria such as Shigella and Listeria reach the free cytosol of host cells [119]. Furthermore, injection of peptidoglycan-derived molecules in the host cell cytosol by type IVb secretion system-expressing bacteria (e.g. L. pneumophila [109]) has also to be considered since this mechanism was evidenced in experiments with Helicobacter pylori [110]. In addition, the peptide transporter PEPT1 was suggested to play a role in the uptake of muramyldipeptide and subsequent proinflammatory intestinal epithelial cell activation [120]. Thus, it is reasonable to speculate that the high-affinity peptide transporter PEPT2 expressed in the respiratory tract epithelium [121] is involved in NOD-peptidoglycan-related lung cell activation.

Although residing in the cytosol, it was shown that in intestinal epithelium, membrane recruitment of NOD2 was essential for NF-κB activation by muramyl dipeptide [122]. As known so far, NOD1 is ubiquitously expressed whereas NOD2 is primarily found in antigen presenting cells and epithelial cells. In human lung epithelium, we detected expression of NOD1 and lower expression of NOD2 in resting human BEAS-2B cells [106]. Further analysis revealed that intracellular pneumococci were recognized by NOD2 but not by NOD1 in epithelial cells. Moreover, NOD1 was implicated in lung infections with P. aeruginosa [123], and NOD2 in Mycobacterium tuberculosis infection [124]. In addition, our unpublished experiments indicated an important role of NOD1 in lung epithelial cell activation by L. pneumophila. Moreover, the respiratory pathogen C. pneumoniae activated human endothelial cells via NOD1 suggesting a role of this mole-

---

**Figure 2**
Recognition of pathogens by cytosolic PRRs. (A) As an example, NOD1 is shown. NOD1 is activated by peptidoglycan-derived peptides. The carboxy-terminal LRR domain is involved in agonist recognition, whereas the central NOD (NACHT) domain has ATPase activity and facilitates self-oligomerization. At the amino-terminal a protein-protein interaction mediating caspase-recruitment domain (CARD) is localized (one CARD domain in NOD1, two in NOD2). Recruitment of the kinase-activity containing adaptor molecule RICK transmits the signal to the NF-κB pathway and it may also participate in MAPK stimulation. (B) The cytosolic PRRs MDA5 and RIG-I recognize dsRNA leading to a complex signalling pathway involving molecules like IPS-1, Rip, FADD promoting NF-κB activation, whereas IPS, TBK and IKKi mediate IRF3 activation.
cule also in lung infection [125]. The observation that NOD1 was involved in infection with *H. pylori* [110] and *Listeria monocytogenes* [126] further strengthened the hypothesis that NOD proteins act as important cytosolic PRRs.

After infection of pulmonary epithelial cells with *S. pneumoniae*, expression of NOD1 and NOD2 increased in these cells *in vitro* and overall expression was up-regulated in mouse lungs infected with pneumococci [106]. IFNγ has been shown to increase NOD1 expression in epithelial cells [127], and TNFα as well as IFNγ, up-regulated expression of NOD2 [128]. Thus, as already explained for TLRs, the expression of cytosolic PRRs may also vary during the hassle with pathogens and the subsequent activation of the host immune system.

Besides NOD1 and NOD2, additional members of the NLR family may have a role in pneumonia. For example, *L. pneumophila* replicates in macrophages derived from A/J mice, but not in cells derived form other mouse-inbred strains. The higher susceptibility of A/J mice towards *L. pneumophila* infection may have a role in pneumonia. For example, Naip5 together with IPAF or ASC recognizes Legionella flagellin and controls intracellular replication of Legionella within mice macrophages, and mediates IL-1β secretion, respectively [131-133]. Thus, at least in mice, bacterial flagellin is recognized by both, TLR5 on the cell surface and Naip5 within the cytosol.

As a great number of other members of the NLR protein family, such as NALP proteins (with exception of NALP10) also contain LRR domains implicated in pathogen recognition, additional members of this family may function as cytosolic PRRs or may be involved in inflammatory signalling [44,45,134,135]. For example, Nalp3/cryopyrin has recently been demonstrated to mediate IL-1β and IL-18 secretion induced by a diverse variety of stimuli such as bacterial or viral RNA, muramyl dipeptide, TLR agonists, together with ATP, native bacteria (e.g. *S. aureus*) and bacterial toxins [136-139].

An important question is how activation of transmembranous and cytosolic receptors acts together in host cell responses. For example, a synergistic stimulation of cytokine induction by NOD1 or NOD2, together with TLRs has been observed in human dendritic and monocyte cells [140-143], while NLR proteins may act as inhibitors of TLR signalling. Overexpression of the NALP12 for example was shown to reduce TLR2/4- and *M. tuberculosis*-related activation of myeloid/monocytic cells [144]. Moreover, *in vivo* studies in NOD2-deficient mice or mice carrying a common Crohn’s disease-associated NOD2 mutation yielded controversial results regarding functional NOD2/TLR2 interaction [145-147].

dsRNA is produced as an intermediate product during virus replication and recent observations point to the existence of cytosolic PRRs recognizing viral dsRNA (Fig. 2). Both, RIG-I and MDA5 recognizes dsRNA leading to activation of an antiviral response [47,48]. RIG-I and MDA5 comprise a carboxy-terminal DexD/H-box RNA helicase domain which seems to mediate recognition of dsRNA, whereas amino-terminal CARD domains mediate the recruitment of downstream signalling adaptor molecules [47,48]. Matikainen et al. reported that IFNβ and TNFα induced the expression of RIG-I in A549 cells. Expression of dominant-negative form of RIG-I inhibited influenza A virus-related activation of an IFNβ promoter suggesting a role of lung epithelial RIG-I in host defense [148]. Very recent studies in mice deficient in RIG-I or MDA5 indicated that RIG-I mediated IFN response to RNA viruses including influenza virus and MDA5 recognized picornavirus-infection [149]. Increased susceptibility of RIG-I-deficient mice towards influenza virus infection highlights the importance of this molecule for lung infection [149].

Besides these studies, however, nothing more is currently known about the expression of these molecules and their functional role in lung epithelial inflammation and disease.

**Downstream signalling pathways**

The recognition of PAMPs by PRRs activates a network of signal transduction pathways. Although it is reasonable to suggest that most of these pathways function in pulmonary epithelial cells and in classical immune cells similarly in principle, most data have not been verified in human lung epithelial cells or in the lung *in vivo*. In the following, a brief introduction in basic mechanisms is given with special emphasis on signalling pathways known to be operative in lung epithelium.

In general, a central aspect of inflammatory activation by PRRs is the stimulation of NF-κB-dependent gene transcription [40,44,59,60]. On the other hand, increasing evidence points to an important role of interferon-regulating factor (IRF)-dependent gene transcription leading to the generation of type I interferons (IFN) and subsequent expression of co-called IFN-stimulated genes (ISGs) [150-152].

The ability of the TLRs to activate transcription factors leading to gene transcription differs and depends on differential engagement of the four TIR (Toll-interleukin-1 receptor) domain containing adaptor molecules MyD88 (differentiation primary response gene 88), TIRAP (toll-
IL-1R domain-containing adaptor protein; Mal), TRIF (Toll/IL-1R domain-containing adaptor inducing IFNβ) and TRAM (Fig. 3). Thus, whereas all TLRs except TLR3 engage MyD88 in order to activate NF-κB and AP-1 [153,154], only TLR3 and TLR4 signal via TRIF and TRIF/TRAM, respectively, leading to additional activation of IRF3 and potentially IRF7 [155-158]. The forth adaptor TIRAP is recruited to TLR2 as well as TLR4 and is involved in the MyD88-dependent transcriptional activation of NF-κB [159,160]. In case of the conserved MyD88-dependent signalling leading to NF-κB activation, further signalling molecules, such as IRAK4 (interleukin-1 receptor-associated kinase-4), IRAK1, as well as TRAF6 (tumor necrosis factor receptor-associated factor-6), are additionally recruited downstream of MyD88 to the receptor complex [43,59]. Downstream of TLR7-9, a similar signalling module leads to the activation of IRF5 and IRF7 [161-165].

Small GTP binding Rho proteins like Rac1 may also participate in TLR-driven NF-κB dependent gene transcription, as recently shown for pneumococci infected human lung epithelial cells [74]. The canonical NF-κB pathway downstream the TLRs involves phosphorylation of IκB molecules sequestering NF-κB in the cytosol in unstimulated cells by the IKK (IκB kinase) complex finally leading to the proteosomal-mediated degradation of IκB [59,166]. Free NF-κB molecules translocate into the nucleus and initiate NF-κB dependent gene transcription [59,166].

Stimulation of this NF-κB activation was observed e.g. after infection of lung epithelial cells with pneumococci [74,167], Moraxella catharrhalis [168], P. carinii [169], P. aerogenosa [170], or exposure to purified virulence factors like LPS [171]. In addition to stimulation of transmembrane TLRs, activation of NOD1 and NOD2 also results in NF-κB activation. Both NODs recruit the adaptor molecule RICK/Rip2 through CARD-CARD interaction [172,173] and we recently implicated the downstream signalling molecules IRAK1, IRAK2, TRAF6 as well as NIK (NF-κB-inducing kinase), TAB2 (transforming growth factor-β activated kinase binding protein) and TAK1 (transforming growth factor-β activated kinase) in S. pneumoniae initiated NOD2-dependent NF-κB activation in epithelial cells [106].

The important role of NF-κB activation for lung inflammation was furthermore emphasised by Sadikot et al., who demonstrated that selective overexpression of constitutively active IκB kinase in airway epithelial cells by adenoviral vectors was sufficient to induce NF-κB activation, inflammatory mediator production and neutrophilic lung inflammation in mice [174]. Moreover, by using the same experimental approaches, this group showed most recently that inflammatory signalling through NF-κB in lung epithelium is critical for proper innate immune response to P. aeruginosa [175]. In addition, inhibition of NF-κB by airway epithelium selective overexpression of an IκB suppressor reduced the inflammatory response upon intranasal application of LPS [171]. Overall, NF-κB activation is a central event in pathogen exposed lung epithelium.

As mentioned above, a key feature of some but not all TLRs is the initiation of IRF-dependent gene transcription. The cytosolic PRRs RIG-I and MDA5 are also capable to induce IRF3 and IRF7 activation [47,48] (Fig. 2). However, in contrast to the well-established canonical NF-κB pathway, the mechanisms of IRF activation are much more elusive and require further investigation. The complexity of these pathways may be illustrated by exemplarily focussing on IRF3, which is crucial for e.g. initial IFNβ expression. Different molecules like IFNβ promoter stimulator 1 (IPS-1, also known as MAVS, VISA, Cardif) (Fig. 2), TBK1, IKKi, or PI3 kinase pathway are implicated in the IRF3 activation process [176-182]. Activation of IRFs is vital for the regulation of type I (IFNβ-subtyps, IFNβ, -ω, -ε, -x, -α) expression, participating in the host response against viruses and, notably, intracellular bacteria [183,184]. Besides acting on classical immune cells,
expression of type I IFNs resulted in auto- and paracine stimulation of cells through specific receptors (IFNAR), stimulation of janus kinases, STATs, and subsequent expression of ISGs in epithelial cells [183,184]. Thus, although intracellular bacteria and viruses are important lung pathogens, neither the expression of central signalling molecules nor the resulting signalling events are known to date in lung epithelial cells.

Another important signalling pathway involves mitogen-activated protein kinases (MAPK). Pro-inflammatory signalling induced by several TLRs [59,185] as well as NOD1 and NOD2 involves the activation of ERK (extracellular signal-regulated kinase), INK (c-Jun N-terminal kinase), and p38 MAPK [126,145,186]. Activation of these kinases was also observed e.g. in pneumococci- [74,167] or virus-infected [187] lung epithelium and in pneumococci-infected mice lungs [167].

The finding that e.g. the p38 MAPK pathway converges with the NF-κB pathway in IL-8 regulation illustrates the complex signalling network in infected epithelial cells: Blockade of p38 MAPK activity did not affect pneumococci-induced nuclear translocation and recruitment of NF-κB/RelA to the il8 promoter but reduced the level of phosphorylated RelA (serine 536) at the il8 promoter [167]. The inhibition of serine 536-RelA phosphorylation blocked pneumococci-mediated recruitment of RNA polymerase II (Pol II) to il8 promoter thereby averting IL-8 expression [167] (Fig. 4). Thus, p38 MAPK kinase contributes to pneumococci-induced chemokine transcription by modulating p65 NF-κB-mediated transactivation in human lung epithelial cells. DNA in euchromatin must be processed to allow for access of activated transcription factors. Increasing evidence indicates that histone modifications may serve as combinatorial code for the transcriptional activity state of genes in many cellular processes by loosening the DNA-histone interaction and unmasking of transcription factor binding sites [188]. In chromatin, 146 base pairs of DNA are wrapped in 1.65 turns around a histone octamer (H2A, H2B, H3, H4) [189]. A wide range of specific covalent modifications of accessible N-terminal histone tails are decisive for transcription repression or gene activation [190]. To date, acetylation (mostly lysine), phosphorylation (serine/threonine), methylation (lysine), ADP-ribosylation, and ubiquitination of histones have been described [191,192]. Phosphorylation at Ser-10 on H3 and acetylation at Lys-14 of H4 seem to have a special impact on gene regulation [189]. For example, it was found that LPS stimulation of dendritic cells induced p38 MAPK-dependent phosphorylation at Ser-10 on H3 and acetylation at Lys-14 on H4 specifically occurs at il8, and mcp1, but not at tnfα or mip1α genes [193]. Both modifications have been correlated with the immediate early gene induction. In addition, L. monocytogenes-related recruitment of histone acetylase (HAT), CBP and Pol II to the il8 promoter and subsequent il8 gene expression in human endothelial cells depended on p38 MAPK-related acetylation (Lys-8) of histone H4 and phosphorylation/acetylation (Ser-10/Lys-14) of histone H3 at the il8 promoter [194]. Furthermore, we recently demonstrated that M. catharrhalis enhanced global acetylation of histone H3 and H4 and at the il8 gene in human bronchial epithelial cells [168]. For this infection, global histone deacetylase (HDAC) expression as well as its activity decreased [168]. Considering that patients with chronic obstructive pulmonary disease (COPD) which are often colonized by Moraxella also display decreased HDAC activity [195,196], acute and chronic effects of histone-related (epigenetic) modifications should be taken into account in host-infection.

Besides the signaling pathways mentioned, other pathways, including e.g. tyrosine kinases [197] or protein kinase C [198], may also play an important role, but have not been analyzed yet in detail in pulmonary epithelium.

Importantly, most investigations focused on the effects purified virulence factors (e.g. LPS) or – at the most – of one pathogen. This approach does not take into account that mixed or sequential infections with different pathogens (e.g. influenza virus and pneumococci) causing severe pneumonia may occur. In a sequential infection model RSV infection lead to impaired clearance of S. pneumoniae, S. aureus or P. aerugenosa [199]. In addition, reduced clearance of pneumococci was observed after influenza A virus infection [200]. Polymicrobial colonization of lung epithelial cells by pneumococci and H. influenzae led to strong NF-κB activation and synergistic IL-8 expression and synergistic inflammation in mice in vivo [202]. Virus infection in concert with endogenous pro-inflammatory mediators may alter PRR expression in lung epithelium as evidenced for TLR3 [201] and RIG-I [148]. Thus, co-infections or mixed infections certainly will influence pathogen recognition, signal transduction and host gene transcription thereby opening up an important new field of research.

In conclusion, a complex network of signalling events is started through the recognition of pathogens by lung epithelial cells.

Consequences for lung epithelial cell activation
The complex response of the lung epithelium to pathogen recognition reflects the great variety of stimuli and signalling pathways activated. The epithelial response includes production and secretion of inflammatory mediators such as cytokines and chemokines, the up-regulation of epite-
Up-regulation of adhesion molecules like intercellular adhesion molecule 1 (ICAM-1) or vascular cell adhesion molecule-1 (VCAM-1) in pulmonary epithelium was observed after exposure to diverse stimuli such as LPS [40,61,207], outer membrane protein A from *K. pneumoniae* [208] or infection with *P. carinii* [209]. The liberation of immunodulatory cytokine- and chemokines and up-regulation of adhesion molecules mediates the acute immune response by e.g. recruitment of leucocytes to the site of infection and modulates the initiation of adaptive immune response. In addition, systemic effects of lung epithelial inflammation by the release of e.g. granulocyte-macrophage colony-stimulating factor (GM-CSF) by activation of immature precursor cells have to be considered [210]. GM-CSF secretion was shown in *S. pneumoniae*-infected bronchial epithelial cells as well as in pneumococci-infected mice lungs [167].

Antimicrobial substances like defensins and cathelicidins secreted by pulmonary epithelium [203] are capable of killing Gram-positive and -negative bacteria, some fungi as well as enveloped viruses [211-213]. Some of these factors, like human β-defensin (hBD)-2 have shown to be up-regulated by cytokines as well as by bacteria like *P. aerogenosa* in lung epithelial cells [214].

In addition, inflamed epithelium may show increased arachidonic acid metabolism. In pneumococci-infected lung epithelium as well as in pneumococci-infected mice lung increased cyclooxygenase-2 expression and subsequently increased prostaglandin E₂ (PGE₂) liberation was noted [215]. PGE₂ in turn may influence immune cells, blood perfusion distribution as well as lung function [216].

The epithelium thereby closely interacts with other cellular components of the innate immune system such as phagocytes (neutrophils, macrophages), natural killer cells and others [217-221]. Of note, today the exact contribution of parenchymal lung versus hematopoietic cells to the initiation and control of the immune response within the lung is not entirely clear and seems to be pathogen-specific as evidenced by studies using chimeric mouse models. In *P. aerogenosa*-infected mice lungs, expression of MyD88 in non-bone marrow derived cells is required for the early control of infection, including cytokine production and neutrophil recruitment, whereas on the long run both, parenchymal and hematopoietic cells were required to control pathogen replication [222]. After inhalation of endotoxin, the cytokine response seems to be mediated by hematopoietic cells in a myeloid differentiation primary response gene (88) (MyD88)-dependent way, whereas bronchoconstriction depended on resident cells as indicated by experiments with chimeric mice [223]. In studies using TLR4-deficient chimeric mice, expression of TLR4 on hematopoietic cells
and macrophages seemed crucial to initiate the LPS-induced recruitment of neutrophils within the alveolar space [224]. On the other hand, inhibition of the nuclear factor-κB (NF-κB) pathway in distal lung epithelium lead to reduced neutrophilic lung inflammation and cytokine expression [171,225].

In addition, the interaction of lung epithelium with hematopoietic cells may alter the immune response of both cell types. Transmigration across lung epithelial cells decreased apoptosis of polymorphonuclear leucocytes [226,227] and migration over the surface of alveolar epithelial cells facilitated alveolar macrophage phagocytic activity in a ICAM-1-dependent manner [228]. On the other hand, LPS-exposed mononuclear phagocytes induced the expression of human β-defensin-2 in lung epithelial cells, thereby strengthening the epithelial innate immune response [229]. Moreover, the complex interaction is further highlighted by the observation that defensins produced by neutrophils may stimulate the release of cytokines by epithelial cells and promote epithelial cell proliferation [230-232].

Overall, it is reasonable to suggest that the pulmonary epithelium contributes significantly to the initiation of an appropriate immune response in pneumonia. Furthermore, the transition of the innate to adaptive immune response might significantly be modulated by epithelial-related actions. Finally, although poorly examined and not discussed here, the lung epithelium may also possess mechanisms to negatively control and terminate inflammatory responses [233].

**Concluding remarks**

Pulmonary epithelium is well equipped to act as an interactive sentinel system detecting entering pathogens. Recognition of pathogens or their products by transmembraneous and intracellular receptors activated signalling cascades leading to a complex activation status of pulmonary epithelium and influences local and systemic immune response. Although pneumonia is a common worldwide disease, causing millions of deaths annually, central mechanisms of pathogen-lung epithelial interaction are still obscure. Basic questions, like the expression of functional active transmembrane and cytosolic PRRs in normal and inflamed human lungs, are widely unanswered. Results about PRR function are often obtained in classical immune cells and transferred to pulmonary epithelial cells function although important differences may exist (e.g. TLR4 expression and localization). For many important lung pathogens only fragmentary information about their interaction is available. In addition, the modulatory role of alveolar fluid containing immunoregulatory surfactant proteins needs further investigation [234-237]. Finally, the complexity, which is introduced by co-infections and subsequent infection must be appreciated in further studies.

Overall, it seems imperative to accelerate the verification of important general mechanisms of innate immunity for the organ lung with respect to pneumonia. In addition, the lung is a unique organ and it is important to identify organ specific mechanisms of innate immunity. The relative ease of transnasal or tracheal application of small interference RNA might allow a relatively fast verification of important newly identified molecules in vivo without the time-consuming establishment of knock out models [238-240].

In addition to the analysis of host response initiation, the understanding of control mechanisms of local inflammation within the lung (resolution of inflammation, repair mechanisms) is crucial [241-243]. In the lung, a high degree of organ function must be preserved on a minute basis to allow for sufficient gas exchange. In this sense, lungs differ from gut or kidney, because inflammation in the lungs must be controlled much more tightly. Of note, as noticed for the intestinal epithelium [244,245], lung epithelial PAMP recognition may be somewhat restricted to avoid frequent epithelial-mediated inflammation. Ambient air contains bacteria and endotoxin [246], and the aerosolized concentrations of e.g. endotoxin is increased in e.g. agricultural environments [247,248]. Limitation of pro-inflammatory lung epithelial activation may be due to restriction of PRR expression on epithelial surfaces [69,70], reduced expression of co-signalling molecules (as shown for e.g. MD-2 [249]), or increased expression of inhibitory molecules (e.g. TOLLIP [250,251]).

Overall, there are a lot of important questions about the molecular mechanisms by which the lung epithelium acts in pneumonia. Their analysis may help to develop future innovative therapeutic strategies in pneumonia.

**Acknowledgements**

The authors apologize for not citing more original manuscripts due to space limitations and hope that the cited reviews will provide more detail. This work was supported by the German Federal Research Ministry (BMBF) competence-network CAPNETZ to N.S., B.S. and S.H., the Deutsche Gesellschaft für Pneumologie to S.H., and the Deutsche Forschungsgemeinschaft (DFG Hi-789/6-1) to S.H.

**References**

1. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C: Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002, 2:225-32.
2. Mandell LA: Epidemiology and etiology of community-acquired pneumonia. *Infect Dis Clin North Am* 2004, 18:761-76, vii.
3. Chastre J, Trouillet JL, Vugnat A, Joly-Guillou ML, Clavier H, Dombrat MC, Gibert C: Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998, 157:1165-1172.
4. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C: Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993, 94(2):281-288.

5. Lynch JP II: Hospital-acquired pneumonia: risk factors, microbiology, and treatment. Chest 2001, 119:373S-384S.

6. Shaw MJ: Ventilator-associated pneumonia. Curr Opin Pulm Med 2005, 11:236-241.

7. Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, Slutsy AS, Stewart TE: Critically ill patients with severe acute respiratory syndrome. JAMA 2003, 290:367-373.

8. Bouza E, Perez A, Munoz P, Jesus PM, Rincon C, Sanchez C, Martin-Rodanan V, Vicario M: Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. Crit Care Med 2003, 31:1964-1970.

9. Marrie TJ: Community-acquired pneumonia. Clin Infect Dis 1994, 18:501-513.

10. Selwyn PW: Economic costs of respiratory tract infections in the United States. Am J Med 1985, 78:45-51.

11. Bishai WR: Clinical significance of pneumococcal pneumonia and factors influencing outcomes. Treat Respir Med 2005, 4 Suppl 1:I9-23.

12. File TM: Overview of virus-induced airway disease. Chest 2005, 128:598-606.

13. Combes A, Luyt CE, Fagon JY, Wollf M, Trouillet JL, Gibert C, Chastre J: Impact of methicillin resistance on outcome of Staphylococcus aureus ventilator-associated pneumonia. Am J Resp Crit Care Med 2004, 170:786-792.

14. Janssens JP: Pneumonia in the elderly (geriatric) population. Curr Opin Pulm Med 2005, 11:226-230.

15. File TM: Community-acquired pneumonia. Lancet 2003, 362:1991-2000.

16. Gant V, Parton S: Community-acquired pneumonia. Curr Opin Pulm Med 2000, 6:226-233.

17. Koller MH: Bench-to-bedside review: antimicrobial utilization strategies aimed at preventing the emergence of bacterial resistance in the intensive care unit. Crit Care Med 2005, 33:459-464.

18. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, Kauppila J, Leinonen M, McCracken GJH: Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004, 113:701-707.

19. Tsoltsa MN, Psarras S, Bossios A, Audi H, Paldanius M, Gourgiotis D, Kallergi K, Kafetzis DA, Constantopoulos A, Papadopoulos NG: Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections. Crit Care Med 2004, 32:681-686.

20. Hayden FG: Rhinovirus and the lower respiratory tract. Rev Med Virol 2004, 14:17-31.

21. Johnston SL: Overview of virus-induced airway disease. Proc Am Thorac Soc 2005, 2:150-156.

22. Tan WC: Rhinovirus in asthma exacerbations. Curr Opin Pulm Med 2005, 11:21-26.

23. Greenberg SB: Respiratory viral infections in adults. Curr Opin Pulm Med 2002, 8:201-208.

24. Ison MG, Fishman JA: Human metapneumovirus and human coronavirus. Curr Opin Infect Dis 2005, 18:4-10.

25. Pound MW, Drew RH: Human metapneumovirus. Curr Opin Infect Dis 2005, 18:411-418.

26. Crowe JE: Human metapneumovirus as a major cause of human respiratory tract disease. Pediatr Infect Dis J 2004, 23:521S-522S.

27. Williams JV, Harris PA, Tollefsen SJ, Halburnt-Rush LL, Pinkerhous JM, Edwards KM, Wright PF, Crowe JE: Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004, 350:443-450.

28. Chen H, Deng G, Li Z, Tian G, Li Y, Jiao P, Zhang L, Liu Z, Webster RG, Yu K: The evolution of H5N1 influenza viruses in ducks in southern China. Proc Natl Acad Sci U S A 2004, 101:10452-10457.

29. Li KS, Guan Y, Wang J, Smith GJ, Xu KM, Duan L, Raharajo AP, Puthavathana P, Buranathai C, Nguyen TD, Etoepangestie AT, Chaisingh A, Aungkawalin P, Long Jang NT, Webb RJ, Poon LL, Chen H, Shortridge KF, Yuen KY, Webster RG, Peiris JS: Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature 2004, 430:209-213.

30. Fouchier RA, Hartwig NG, Bestebroer TM, Niemeyer B, de Jong JC, Simons JH, Osterhaus AD: A previously undescribed coronavirus associated with respiratory disease in humans. Proc Natl Acad Sci U S A 2004, 102:6212-6216.

31. Wang JT, Chang SC: Severe acute respiratory syndrome. Curr Opin Infect Dis 2004, 17:143-148.

32. Enemark H: Alveolar macrophage type II cell: defender of the alveolus revisited. Respi Res 2001, 2:33-46.

33. Matthay MA, Folkesson HG, Clerici C: Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002, 82:569-600.

34. Chinenov YD: Cell cycle kinetics in the alveolar epithelium. Am J Physiol 1997, 272:L1031-L1045.

35. Crouch E, Wright JR: Surfactant proteins a and d and pulmonary host defense. Ann Rev Physiol 2001, 63:521-541.

36. Naka H, Matute-Bello G, Lin SJ: The role of surfactant proteins in the immune response. Annu Rev Physiol 2003, 65:171-196.

37. Nakamura M, Matute-Bello G, Lin SJ: The role of surfactant proteins in the immune response. Annu Rev Physiol 2003, 65:171-196.

38. Nakamura M, Matute-Bello G, Li J, Hase Y, Hayashi S, Kajikawa O, Lin SJ: Surfactant proteins a and d and pulmonary epithelial cells to fas-induced apoptosis. Am J Pathol 2004, 164:1949-1958.

39. Basu S, Fenton MJ: Toll-like receptors: function and roles in lung disease. Am J Physiol Lung Cell Mol Physiol 2004, 286:L887-L892.

40. Genske CM, McEvany NG: Toll-like receptor expression and function in airway epithelial cells. Arch Immunol Ther Exp (Warsz) 2005, 53:418-427.

41. Janeway CAJ, Medzhitov R: Innate immune recognition. Annu Rev Immunol 2002, 20:197-216. Epub;2001 Oct 4;197-216.

42. Kawai T, Akira S: TLR signaling. Annu Rev Immunol 2004, 22:191-213.

43. Takeda K, Kaisho T, Akira S: Toll-like receptors. Annu Rev Immunol 2004, 22:335-376. Epub;2002 Dec 19;335-376.

44. Inohara, Chamaillard, McDonald C, Nunez G: NOD-LRR proteins: role in host-microbial interactions and inflammatory disease. Annu Rev Biochem 2005, 74:355-83-355-383.

45. Martinon F, Tschopp J: NLRs join TLRs as innate sensors of pathogens. Trends Immunol 2005, 26:447-454.

46. Pham-Huy DJ, Girardin SE: The role of Toll-like receptors and NOD proteins in bacterial infection. Mol Immunol 2004, 41:1099-1108.

47. Andrejeva J, Childs KS, Young DF, Carlos TS, Stock N, Goodbourn S, Randall RE: The V proteins of paramyxoviruses bind the IFN- inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter. Proc Natl Acad Sci U S A 2004, 101:17264-17269.

48. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, Taira K, Akira S, Fujita T: The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nature 2003, 425:76-81.

49. Aliprantis AO, Yang RB, Mark MR, Sugget S, Devaux B, Radolf JD, Klimpel GR, Godowski P, Zychlinsky A: Cell activation and apoptosis by bacterial lipopolysaccharides through toll-like receptor-2. Science 1999, 285:736-739.

50. Buwitz-Beckmann U, Heige H, Wiesmuller KH, Jung G, Brock R, Akira S, Ulmer AJ: TLR1 and TLR6-independent recognition of bacterial lipopolysaccharides. J Biol Chem 2006, 281:...
55. Alexopoulos L, Holt AC, Medzhitov R, Flavell RA: Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptors 7 and 8. *Nature* 2003, 421:732-738.

56. Diebold SS, Kaito T, Hemmje H, Akira S, Sousa R: Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* 2004, 303:1529-1531.

57. Heil F, Hemmje H, Hochrein H, Amstnderfer F, Kirschning C, Akira S, Lipford G, Wainger H, Bauer S: Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science* 2004, 303:1529-1529.

58. Hemmje H, Takeuchi O, Kawai T, Kaito T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wainger H, Takeda K, Akira S: A Toll-like receptor recognizes bacterial DNA. *Nature* 2000, 408:740-745.

59. Akira S, Takeda K: Toll-like receptor signalling. *Nat Rev Immunol* 2004, 4:499-511.

60. Beutler B: The Toll-like receptors: analysis by forward genetic methods. *Immunogenetics* 2005, 57:385-392.

61. Wang K, Carroll TP, Smith SG, Taggart CC, Devaney J, Griffin S, O'Neill S, McElvaney NG: TLR-induced inflammation in cystic fibrosis and non-cystic fibrosis airway epithelial cells. *J Immunol* 2005, 174:1638-1646.

62. Muir A, Soong G, Sokol S, Reddy B, Gomez MI, Van Heeckeren A, Prince A: Toll-like receptors on normal and cystic fibrosis airway epithelial cells. *Am J Respir Cell Mol Biol* 2004, 30:777-783.

63. Hauber HP, Tulic MK, Tsicopoulos A, Wallart B, Olivenstein R, Daigneault P, Hamid Q: Toll-like receptors 4 and 2 expression in the bronchial mucosa of patients with cystic fibrosis. *Can Respir J* 2003, 10:123-138.

64. Hertz CJ, Wu Q, Porter EM, Zhang YJ, Weisumiller KH, Godowski PJ, Ganz T, Randell SH, Modlin RL: Activation of Toll-like receptor 2 on human tracheobronchial epithelial cells induces the antiviral peptide human beta defensin-2. *J Immunol* 2003, 171:680-686.

65. Zhang Z, Louboutin JP, Weiner DJ, Goldberg JB, Wilson JM: Human airway epithelial cells sense Pseudomonas aeruginosa infection via recognition of flagellin by Toll-like receptor 5. *Infect Immun* 2005, 73:7151-7160.

66. Bauber HP, Tulic MK, Tsicopoulos A, Wallart B, Olivenstein R, Daigneault P, Hamid Q: Toll-like receptors 4 and 2 expression in the bronchial mucosa of patients with cystic fibrosis. *Can Respir J* 2003, 10:123-138.

67. Malley R, Hennke P, Morse SC, Cieslewicz MJ, Lipstich M, Thompson CI, Kwon EJ, Paton JC, Weisel MR, Golenbock DT: Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. *Proc Natl Acad Sci U S A* 2003, 100:1966-1971.

68. Costa CP, Kirschning CJ, Busch D, Durr S, Jennen L, Heinemann U, Prebeck S, Wagner H, Miehlke T: Role of chlamydial heat shock protein 60 in the stimulation of innate immune cells by Chlamydia pneumoniae. *Eur J Immunol* 2002, 32:2460-2470.

69. Da Costa CU, Wanita N, Kirschning CJ, Busch DH, Rodriguez N, Wagner H, Miehlke T: Heat shock protein 60 from Chlamydia pneumoniae elicits an unusual set of inflammatory responses via Toll-like receptor 2 and 4 in vivo. *Eur J Immunol* 2004, 34:2874-2884.

70. Kurt-Jones EA, Popova L, Swenson KL, Haynes LM, Jones LP, Tripp RA, Waller EA, Freeman MW, Golenbock DT, Anderson LJ, Finberg RW: Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus infection. *Infect Immun* 2004, 72:5713-5719.

71. Harn KB, Weisumiller KH, Godowski PJ, Ganz T, Randell SH, Modlin RL: Activation of Toll-like receptor 2 on human tracheobronchial epithelial cells induces the antiviral peptide human beta defensin-2. *J Immunol* 2003, 171:680-686.

72. Monick MM, Varovssky TO, Powers LS, Butler NS, Carter AB, Gudmundsson G, Hunninghake GW: Respiratory syncytial virus up-regulates TLR4 and sensitizes airway epithelial cells to endotoxin. *J Biol Chem* 2003, 278:53035-53044.

73. Chaudhuri N, Dower SK, Whyte MK, Sabroe I: Toll-like receptors and chronic lung disease. *Clin Sci (Lond)* 2005, 109:125-133.

74. Bäumler AJ, Jäger KM, Röber F, Willden IR, Tesley TD, Milner AB: Expression of functional toll-like receptor 2- and 4- on alveolar epithelial cells. *Am J Respir Cell Mol Biol* 2004, 31:241-245.

75. Okada Y, Asai Y, Hashimoto S, Mizumura K, Ijichi I, Matsumoto S, Ra C, Morita T: A20 inhibits toll-like receptor 2- and 4-mediated interleukin-8 synthesis in airway epithelial cells. *Am J Respir Cell Mol Biol* 2004, 31:330-336.

76. Romeo A, Gugliotta D, Lanzavecchia A: Toll-like receptors on lung epithelial cells are functionally active during respiratory syncytial virus infection. *Am J Physiol Lung Cell Mol Physiol* 2005, 288:L1209-L1223.
ent domains of Pseudomonas aeruginosa exoenzyme S activate distinct TLRs. J Immunol 2004, 173:2031-2040.

94. Saito T, Yamamoto T, Kazaura T, Gejyo H, Naito M: Expression of toll-like receptor 2 and 4 in lipopolysaccharide-induced lung injury in mouse. Cell Tissue Res 2005, 321:75-88.

95. Rudd BD, Burstein E, Duckett CS, Li X, Lukacs NW: Differential role for TRIM3 in respiratory syncytial virus-induced chemokine expression. J Virol 2005, 79:3350-3357.

96. Homma T, Kato A, Hashimoto N, Batcelor J, Yoshikawa M, Imai S, Wakuguchi H, Saito H, Matsumoto K: Cytoskeletal and cytokines synergistically enhance toll-like receptor 2 expression in respiratory epithelial cells. Am J Respir Cell Mol Biol 2004, 31:463-465.

97. Gomez ML, Lee A, Reddy B, Muir A, Soong G, Pitt A, Cheung A, Prince A: Staphylococcus aureus protein A induces airway epithelial inflammatory responses by activating TNFR1. Nat Med 2004, 10:842-846.

98. Lemjabbar H, Basbaum C, Kocijancic J, Cossart P, Sansonetti PJ: Nod2 is a sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem 2003, 278:8869-8872.

99. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M, Foster SJ, Moran AP, Fernandez-Luna JL, Nunez G: Host recognition of bacterial muramyl dipeptide mediated through Nod2. Implications for Crohn's disease. J Biol Chem 2003, 278:5509-5512.

100. Cossart P, Sansonetti PJ: Bacterial invasion: the paradigms of enteroinvasive pathogens. Science 2004, 304:242-248.

101. Nod1 detects a unique muramyl dipeptide from gram-negative bacterial peptidoglycan. Science 2003, 300:1584-1587.

102. Weidinger S, Klopp N, Rummler L, Wagenpfeil S, Bertin J, Sansonetti PJ,Philpott DJ: Nod1 detects a unique muramyl dipeptide from gram-negative bacterial peptidoglycan. Science 2003, 300:1584-1587.

103. Inohara N, Kabesch M, Moffatt MF, Schedel M, Carr D, Zheng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng N, Ohtsuka T, Leong-Poi H, Crackower MA, Fu. J Immunol 2004, 173:5599-5606.

104. NOD1 participates in the innate immune response to Pseudomonas aeruginosa. Nat Med 2004, 10:367-372.

105. Bacterial invasion: the paradigms of enteroinvasive pathogens. Science 2004, 304:242-248.

106. Nod2 is a sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem 2003, 278:8869-8872.

107. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M, Foster SJ, Moran AP, Fernandez-Luna JL, Nunez G: Host recognition of bacterial muramyl dipeptide mediated through Nod2. Implications for Crohn's disease. J Biol Chem 2003, 278:5509-5512.

108. Cossart P, Sansonetti PJ: Bacterial invasion: the paradigms of enteroinvasive pathogens. Science 2004, 304:242-248.

109. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M, Foster SJ, Moran AP, Fernandez-Luna JL, Nunez G: Host recognition of bacterial muramyl dipeptide mediated through Nod2. Implications for Crohn's disease. J Biol Chem 2003, 278:5509-5512.

110. Cossart P, Sansonetti PJ: Bacterial invasion: the paradigms of enteroinvasive pathogens. Science 2004, 304:242-248.

111. Inohara N, Kabesch M, Moffatt MF, Schedel M, Carr D, Zheng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng N, Ohtsuka T, Leong-Poi H, Crackower MA, Fu. J Immunol 2004, 173:5599-5606.

112. NOD1 participates in the innate immune response to Pseudomonas aeruginosa. Nat Med 2004, 10:367-372.

113. Bacterial invasion: the paradigms of enteroinvasive pathogens. Science 2004, 304:242-248.

114. Nod2 is a sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem 2003, 278:8869-8872.

115. Inohara N, Kabesch M, Moffatt MF, Schedel M, Carr D, Zheng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng N, Ohtsuka T, Leong-Poi H, Crackower MA, Fu. J Immunol 2004, 173:5599-5606.

116. NOD1 participates in the innate immune response to Pseudomonas aeruginosa. Nat Med 2004, 10:367-372.
Ren T, Zamboni DS, Roy CR, Dietrich WF, Vance RE: Flagellin-Deficient Legionella Mutants Evade Caspase-1- and Naip5-Mediated Phagosome Maturity. J. Infect. Dis. 2006, 193:18.

Zamboni DS, Kobayashi KS, Kohlsheidt T, Ogura Y, Long EM, Vance RE, Kuida K, Mariathasan S, Dixit VM, Flavell RA, Dietrich WF, Roy CR. The Bircle cytosolic pattern-recognition receptor contributes to the detection and control of Legionella pneumophila infection. Nat Immunol. 2006.

Chamaillard M, Girardin SE, Viale J, Philpott DJ. Nodds, Naips and Naip: intracellular regulators of bacterial-induced inflammation. Cell Microbiol. 2003; 5:581-592.

Ting JP, Davis BK: CATERPILLER: a novel gene family impor- tant in immunity, cell death, and diseases. Annu Rev Immunol. 2005; 23:387-414. 874-84.

Kanneganti TD, Ozoren N, Body-Malapel M, Amer A, Park JH, Ting JP, Davis BK: Nalp3 is critical for NLRP3/Caspase-1 activation in response to inflammasome activators. J Clin Invest. 2006; 116:1397-1411.

Williams KL, Lich JD, Duncan JA, Reed W, Rallabhandi P, Moore C, Williams KL, Lich JD, Duncan JA, Reed W, Rallabhandi P, Moore C, Marrows to synthesize Toll-like receptor agonists synergize with lipopolysaccharide in cytokine induction. J Biol Chem. 2004; 279:8694-8700.

Uehara A, Yang S, Fujimoto Y, Fukase K, Kusumoto S, Shibata K, Ohteki T, Takada H: Synergistic effect of Nod1 and Nod2 agonists with Toll-like receptor agonists on human dendritic cells to generate interleukin-12 and T helper type 1 cells. Infect Immun. 2005; 73:7967-7976.

Traub S, Kubasch N, Morath S, Kresse M, Hartung T, Schmidt RR, Herrmann C: Structural requirements of synthetic muropeptides to synergize with lipopolysaccharide in cytokine induction. J Biol Chem. 2004; 279:8694-8700.

Uehara A, Yang S, Fujimoto Y, Fukase K, Kusumoto S, Shibata K, Sugawara S, Takada H: Muramyldipeptide and diaminopimelic acid-containing desmureamylpeptides in combination with chemically synthesized Toll-like receptor agonists synergistically induced production of interleukin-8 in a NOD2- and NOD1-dependent manner, respectively, in human monocyte-like cells. Cell Microbiol. 2005; 7:FS3-6.31.

Williams KL, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffield VM, Accaviti-Loper MA, Su L, Vogel SN, Braunstein A, Reed W, Duncan JA, Reed W, Ballabandi P, Moore C, Kurtz S, Coffeld...
ACTIVITY REDUCTION. Am J Physiol Lung Cell Mol Physiol 2006, 73:276-2777.

176. Fitzgerald KA, McWhirter SM, Faia KL, Rowe DC, Latz E, Golenbock

177. Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, Ishii KJ,

178. Sarkar SN, Peters KL, Elco CP, Sakamoto S, Pal S, Sen GC:

179. Strahl BD, Allis CD:

180. Hippenstiel S, Kratz T, Krull M, Seybold J, Eichel-Streiber C, Suttrop

181. Sharma S, tenOever BR, Grandvaux N, Zhou GP, Lin R, Hiscott J:

182. Pichavant M, Delneste Y, Fevrier C, Brichet A, Tonnel

183. Chung KF, Barnes PJ:

184. Bals R, Hiemstra PS:

185. Wang J, Gigliotti F, Jagielski S, Johnston C, Finkelstein JN, Wright

186. Joseph T, Look D, Ferkol T: NF-kappaB activation and sustained IL-12

187. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

188. Hippenstiel S, Krutzik P, Meinl U, Seybold J, Eichel-Streiber C, Suttrop

189. Muegge K: Preparing for the target of the bullet. Nat Immunol 2002, 3:16-17.

190. Oshiro BD, Allis CD: The language of histone modifications. Nature 2000, 403:41-45.

191. Clark S, Lubbert M: Epigenetic targets in hematopoietic malignancies. Oncogene 2003, 22:6489-6496.

192. Jenuwein T, Allis CD: Translating the histone code. Science 2001, 293:1074-1080.

193. Saccani S, Pantano S, Natoli G: p38-Dependent marking of inflammatory genes for increased NF-kappa B recruitment. Nat Immunol 2002, 3:69-75.

194. Schmick B, Beermann W, van LV, Zahrnt J, Opitz B, Witzenrath M, Hong AC, Chakraborty T, Kracht M, Rosseau S, Suttrop N, Hippenstiel S: Intracellular bacteria differentially regulated endothelial cytokine release by MAPK-dependent histone modification. J Immunol 2005, 175:2843-2850.

195. Barnes PJ, Adcock IM, Ito K: Histamine deactivation and deacetylation importance in inflammatory lung diseases. Eur Respir J 2005, 25:552-563.

196. Ito K, Ito M, Elliott WM, Cosio G, Caramori G, Von OM, Barczyk A, Hayashi S, Adcock IM, Hogg JC, Barnes PJ: Decreased histone deacetylation activity in chronic obstructive pulmonary disease. N Engl J Med 2003, 349:1148-1151.

197. Ulanova M, Puttagunta L, Marce-Elpamos M, Duszyk M, Steinhoff U, Duta F, Kim MS, Krakow K, Schreiber AD, Syk tyrosine kinase participates in beta-1 integrin signaling and inflammatory responses in airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 2005, 288:L507-L517.

198. Hippenstiel S, Krutzik P, Meinl U, Seybold J, Eichel-Streiber C, Suttrop N: Rho protein inhibition blocks protein kinase C translocation and activation. Biochem Biophys Res Commun 1998, 245:830-834.

199. Stark JM, Stark MA, Coloastro GN, LeVine AM: Regulation of inflammatory gene expression in lung epithelial cells through a TNF-alpha-mediated mechanism. Am J Physiol Lung Cell Mol Physiol 2001, 281:L685-L696.

200. Groskreutz DJ, Monick MM, Powers LS, Yarovinsky TO, Look DC, Cunninghake GW: Respiratory syncytial virus induces TLR3 protein and protein kinase R, leading to increased double-stranded RNA responsiveness in airway epithelial cells. J Virol 2003, 77:1713-1740.

201. Ratner AJ, Lysenko ES, Paul MN, Weiser JN: Synergistic proinflammatory responses induced by polymicrobial colonization of epithelial surfaces. Proc Natl Acad Sci U S A 2005, 102:429-434.

202. Groskreutz DJ, Monick MM, Powers LS, Yarovinsky TO, Look DC, Cunninghake GW: Respiratory syncytial virus induces TLR3 protein and protein kinase R, leading to increased double-stranded RNA responsiveness in airway epithelial cells. J Virol 2003, 77:1713-1740.

203. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

204. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

205. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

206. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

207. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

208. Pichavant M, Delneste Y, Fevrier C, Brichet A, Tonnel

209. Hippenstiel S, Eichel-Streiber C, Suttrop N: Macrophages

210. Chung KF, Barnes PJ:

211. Hippenstiel S, Krutzik P, Meinl U, Seybold J, Eichel-Streiber C, Suttrop

212. Koczulla AR, Bals R: Antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnol Lett 2005, 27:1337-1347.

213. Koczulla AR, Bals R: Antimicrobial peptides: current status and therapeutic potential. Drugs 2003, 63:389-406.
