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Innate Immunity of Airway Epithelium and COPD

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1. Introduction

The mammalian immune system consists of two branches- innate and adaptive immune systems and together they provide protection against infection. Innate immunity is a first line of host defense and is responsible for immediate recognition of pathogens to prevent microbial invasion. In addition innate immune responses also stimulate adaptive immune system (Medzhitov and Janeway, 1997). Cellular components of innate immune system include mucosal epithelial cells, macrophages, neutrophils, natural killer cells, basophils, eosinophils and others. The airway mucosa represents the body's largest mucosal surface and is the first point of contact for inhaled microorganisms, environmental pollutants, airborne allergens and cigarette smoke (Diamond et al., 2000). Airway mucosa provides protection against potentially hazardous inhaled factors by multiple mechanisms. For instance, mucus secreted by the airway epithelium covers the apical surface of airway epithelium and traps inhaled microorganisms, allergens and particulate material. The trapped material is then cleared by mucociliary escalator away from lungs and towards the pharynx. Tight junctions between the polarized airway epithelial cells restrict the paracellular movement of solutes and ions, and prevent pathogens from gaining access to the submucosal compartment. In addition to its role as a physical barrier between environmental factors and internal milieu, airway epithelial cells also play a critical role in bridging innate and adaptive immune defenses (Hammad and Lambrecht, 2011; Kato and Schleimer, 2007). Airway epithelial cells express number of innate immune receptors also known as pattern recognition molecules, which recognizes pathogen-associated molecular patterns (PAMPS) or danger-associated molecular patterns (DAMPS) to initiate appropriate innate defense mechanisms. This includes elaboration of antimicrobial molecules, pro-inflammatory cytokines and chemokines that recruits and activates other mucosal innate immune cells. The responses of activated innate immune cells lead to recruitment of immune cells into epithelium or airway lumen and initiate adaptive immune responses. Continuous exposure to environmental stimuli, such as cigarette smoke, noxious gases or other environmental hazards may lead to prolonged and aberrant activation of airway epithelial cells resulting in excessive expression of pro-inflammatory cytokines and chemokines that recruit large number of inflammatory cells into airway lumen. This in turn leads to persistent inflammation, airway damage and abnormal repair, impaired innate immune responses. There are reports suggesting that exposure to cigarette smoke also

dampens the needed innate immune responses to infection, thereby promoting the persistence of infecting organism. This may result in delayed but sustained inflammation that can lead to progression of lung disease. In this chapter, we will discuss how the impaired innate immune defense mechanisms fail to provide protection against invading pathogens and its impact on progression of lung disease in patients with chronic obstructive pulmonary disease (COPD).

2. Barrier function of airway epithelium

Airway epithelium lines the entire airway mucosa. In normal adult human, the large airways are cartilaginous and mainly made up of ciliated cells, mucus producing goblet cells, undifferentiated columnar cells and basal cells with a capacity to multiply and differentiate into ciliated or goblet cells. Large airways are also surrounded by submucosal and serous glands. As the large airways branches out, it gradually becomes non-cartilaginous, loses surrounding submucosal and serous glands, the cells become more columnar and cuboidal, and Clara secreting cells replace goblet cells in the small airways. Airway epithelium also consists of other minor cell types such as neuroendocrine cells, dendritic cells and others.

The three essential components that contributes to barrier function of airway epithelium are mucociliary apparatus (Knowles and Boucher, 2002), intercellular tight and adherens junctions (Pohl et al., 2009) that regulates epithelial paracellular permeability, and secreted antimicrobial products that kill the inhaled pathogens (Bals and Hiemstra, 2004).

2.1 Mucociliary clearance

The primary players of mucociliary apparatus are mucus produced by goblet cells and submucosal glands that overlay the airway epithelium and cilia. Mucociliary dysfunction results in recurrent and persistent respiratory infections as evidenced in patients with cystic fibrosis, ciliary dyskinesia and COPD (Bhowmik et al., 2009; Jansen et al., 1995; Livraghi and Randell, 2007; Sethi, 2000). In COPD patients, the dysfunction of mucociliary clearance is due to combined effect of mucus hypersecretion, increased viscosity of mucus and dysfunction or loss of cilia (Mehta et al., 2008). The airway mucus is a viscoelastic gel and contains more than 200 proteins, and it is secreted by goblet cells that are present in the airway epithelium and by submucosal glands. The main components of airway mucus are mucins, which are high molecular weight glycoproteins and cross link to form structural framework of mucus barrier (Rose et al., 2001; Thornton et al., 2008). At least 12 mucins are detected in human lungs, of these MUC5AC and MUC5B are the predominant mucins in normal airways (Rose and Voynow, 2006). Airways infection with virus or bacteria, exposure to toxic agents such as cigarette smoke and pollutants that induce airway inflammation and oxidative stress have been shown to upregulate expression of MUC5AC and MUC5B (Borchers et al., 1999; Casalino-Matsuda et al., 2009; Dohrman et al., 1998; Gensch et al., 2004; Haswell et al., 2010; Shao et al., 2004). Cigarette smoke induces expression of number of inflammatory mediators including IL-1 β , IL-8, TNF- α , MCP-1, leukotrienes through oxidative stress-related pathways from airway epithelial cells, resident macrophages and infiltrated neutrophils, which can increase mucus secretion (Adcock et al., 2011; Choi et al., 2010; Cohen et al., 2009; Mebratu et al., 2011). Cigarette smoke also causes

mucus hypersecretion by increasing expression of hypoxia-induced factor 1 and growth factors such as TGF- β , and EGF ligands (Yu et al., 2011a, b). Smokers with COPD also show goblet cell metaplasia and submucosal gland hypertrophy (Innes et al., 2006). Increased EGF receptor expression and activation and increased expression of platelet activating factor caused by cigarette smoke are thought to play a role in development of goblet cell metaplasia (Curran and Cohn, 2010; Komori et al., 2001; O'Donnell et al., 2004). Cigarette smoke decreases water and ion transport by inhibiting apical chloride channel and basolaterally located potassium channel in primary human and mouse airway epithelial cells (Cohen et al., 2009; Savitski et al., 2009). This essentially reduces the periciliary liquid layer in which cilia can beat rapidly and also increases the viscosity of mucus resulting in reduced clearance of mucus from the airways. In addition, respiratory epithelial cells exposed to cigarette smoke extract or condensate showed 70% less cilia and shorter cilia compared to control cells (Tamashiro et al., 2009). Mice exposed to cigarette smoke although showed slight increase in ciliary beat frequency at 6 weeks and 3 months, it was significantly reduced at 6 months and these mice also showed significant loss of tracheal ciliated cells (Simet et al., 2010). Decreased number of cilia, reduced ciliary function combined with hypersecretion of mucin, increased viscoelasticity of secreted mucus in COPD patients can lead to airways obstruction and promote persistence of trapped pathogens in the airways (Rose and Voynow, 2006; Voynow et al., 2006). Persistence of bacteria or viruses can further increase production of mucus in the airways (Baginski et al., 2006).

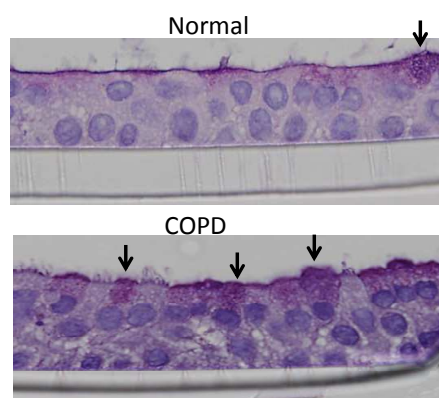


Fig. 1. Airway epithelial cells isolated from COPD patient cultured at air/liquid interface show more goblet cells (arrows) than the similarly grown normal airway epithelial cells.

Another feature that is frequently noted in airways of COPD patients is squamous metaplasia (Araya et al., 2007) and it correlates with the severity of airway obstruction (Cosio et al., 1978). The airway epithelium exposed to cigarette smoke responds by secreting TGF- β (de Boer et al., 1998), which is required for repair of injured epithelium and maintain homeostasis. However, chronic exposure to cigarette smoke can induce sustained production of TGF- β and increased TGF- β activation leading to expression of the $\beta 6$ integrin, a TGF- β responsive gene (Wang et al., 1996). This in turn contributes to a phenotypic switch from columnar ciliated to squamous epithelium (Masui et al., 1986a; Masui et al., 1986b). Squamous epithelial cells secrete increased amounts of IL-1 β , which acts as a paracrine factor with adjacent airway fibroblasts to further activate TGF- β (Araya et al., 2006), thereby increasing squamous metaplasia and further contributing to impaired barrier function and persistence of inhaled pathogens.

In our laboratory, we observed that cultured airway epithelial cells isolated from COPD patients show goblet cell metaplasia, decreased number of ciliated cells (Figure 1), and increased MMP activity suggesting that epigenetic changes that occur *in vivo* are maintained even when cells are expanded *ex vivo* (Schneider et al., 2010). COPD epithelial cells also showed increased viral load following rhinovirus challenge compared to normal cells. Similarly, we also found that elastase/LPS exposed mice which show typical features of COPD, including emphysema, airway remodeling, diffuse lung inflammation and goblet cell hypertrophy, also showed increased persistence of virus compared to normal mice following rhinovirus challenge and majority of the virus particles were observed in the airway epithelium (Sajjan et al., 2009). Rhinovirus infection increased mucin expression further in these mice. Since goblet cells are the target for rhinovirus infection (Lachowicz-Scroggins et al., 2010) we suggest that COPD airway epithelial cultures which have increased number of goblet cells are more susceptible to rhinovirus infection than the controls. Patients with COPD, cystic fibrosis and asthma show goblet cell metaplasia and this may be one of the reasons these patients are more susceptible to rhinovirus infection. In addition, airway epithelial mucins also interact with several other respiratory pathogens including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Burkholderia cenocepacia*, influenza virus, adenovirus and coronavirus (Landry et al., 2006; Matrosovich and Klenk, 2003; Plotkowski et al., 1993; Ryan et al., 2001; Sajjan and Forstner, 1992; Sajjan et al., 1992; Walters et al., 2002). The bound pathogens which are cleared under normal conditions, persist in the airway lumen when the mucociliary clearance is impaired and initiate inflammatory response and damage the airway epithelium.

2.2 Junctional adherens complexes and airway epithelial permeability

Epithelial permeability is maintained through the cooperation of two mutually exclusive structural components: Tight junctions and adherence junctions on the lateral membranes (Pohl et al., 2009). While tight junctions regulate the transport of solutes and ions across epithelia, adherence junctions mediate cell to cell adhesion (Hartsock and Nelson, 2008; Schneeberger and Lynch, 2004; Shin et al., 2006). Under homeostatic conditions, these intercellular junctions prevent inhaled pathogens and also serve as signaling platforms that regulate gene expression, cell proliferation and differentiation (Balda and Matter, 2009; Koch and Nusrat, 2009). Therefore disassociation or sustained insult that affects junctional complex will disrupt not only barrier function, but also prevent normal repair of airway epithelium. Compared to control nonsmokers, airway epithelium is leaky, hyperproliferative and abnormally differentiated in smokers (Hogg and Timens, 2009). Consistent with this observation, various *in vivo* and *in vitro* studies showed that cigarette smoke increases airway epithelial permeability (Boucher et al., 1980; Gangl et al., 2009; Olivera et al., 2007; Serikov et al., 2006). Recently, transcriptome analysis of airway epithelial cells from normal and COPD patients revealed global down-regulation of physiological tight junction complex gene expression (Shaykhiev et al., 2011). Further, normal airway epithelial cells exposed to cigarette smoke extract also showed similar down-regulation of genes related to tight junction complex. This was associated with decreased expression of PTEN and FOXO3A, a transcriptional factor in the PTEN pathway, suggesting that cigarette smoke down-regulates expression of apical junctional complex genes by modulating PTEN signaling pathway. Consistent with this notion, cigarette smoke in combination with IL-1 β

has been shown to induce disassembly of tight junction complex in endothelial cells by suppressing PTEN activity (Barbieri et al., 2008). Chen et al showed that cigarette smoke also alters epithelial permeability by disrupting cell polarity via activation of EGFR, dissociation of β -catenin and E-cadherin from adherence junctional complex and redistribution of apical MUC1 membrane bound mucin to cytoplasm (Chen et al., 2010). In a homeostatic epithelium, β -catenin cooperates with E-cadherin to form apical junctional complex and maintain cell polarity (Xu and Kimelman, 2007). In airway regeneration or oncogenic formation β -catenin translocates to nucleus, and activates canonical Wnt signaling pathway (Mazieres et al., 2005; Tian et al., 2009). Similar to β -catenin, the cytoplasmic tail of MUC1 also supports structural barrier during homeostasis (Chen et al., 2010). Since cigarette smoke causes aberrant activation of both EGFR and canonical Wnt/ β -catenin signaling (Khan et al., 2008; Lemjabbar et al., 2003), it is plausible that chronic cigarette smoke exposure decreases barrier function and promote microbial invasion of airway epithelium.

2.3 Antimicrobial products of airway epithelium

In addition to acting as a physical barrier, airway epithelial cells also secrete antimicrobial substances, which include enzymes, protease inhibitors, oxidants and antimicrobial peptides. Lysozyme is an enzyme found in airway epithelial secretions and exerts antimicrobial effect against wide range of gram-positive bacteria by degrading peptidoglycan layer (Ibrahim et al., 2002). Lysozyme is also effective against gram-negative bacteria in the presence of lactoferrin, which disrupts the outer membrane allowing lysozyme to gain access to peptidoglycan layer (Ellison and Giehl, 1991). Lactoferrin is an iron-chelator and inhibit microbial growth by sequestering iron which is essential for microbial respiration (Ganz, 2002). Lactoferrin also display antiviral activity against both RNA and DNA viruses either by inhibiting binding of virus to host cells or by binding to virus itself (van der Strate et al., 2001; Laube et al., 2006). Lactoferrin levels increase in response to bacterial and viral infections. Epithelial cells produce protease inhibitors, such as secretory leukoprotease inhibitor (SLPI), elastase inhibitor, α 1-antiprotease and antichymotrypsin. These protease inhibitors mitigate the effects of proteases expressed by pathogens and recruited innate immune cells. Administration of SLPI decreased the levels of IL-8 and elastase activity in airway secretion of cystic fibrosis patients (McElvaney et al., 1992).

Human beta defensins (hBD) are the most abundant antimicrobial peptides expressed on the surface of airway epithelium and are effective against wide range of bacteria and viruses (Ganz, 2003; Kota et al., 2008; McCray and Bentley, 1997). While hBD1 is constitutively expressed, hBD2 to hBD4 expression is induced by LPS via NF- κ B activation and also by IL-1 (Becker et al., 2000; Singh et al., 1998). hBD2 is induced by *P. aeruginosa* infection in normal but not in cystic fibrosis airway epithelia (Dauletbaev et al., 2002). Environmental factors such as air pollutants decrease defensin gene expression in the airways (Laube et al., 2006). In CF airway epithelia activity of hBD2 is also decreased due to increased salt concentration (Goldman et al., 1997). Cathelicidins are another class of antimicrobial peptides and LL37 is the only human cathelicidin identified to date. LL37 bind to LPS and inactivate its biological function. Overexpression of human LL37 in CF mouse model increased killing of *P. aeruginosa* and reduced the ability of this bacterium to colonize the airways (Bals et al., 1998).

Airway epithelial cells also generate oxidants such as nitric oxide (NO) and hydrogen peroxide. Three NO synthases contribute to production of NO in airway epithelia: the constitutively expressed NOS1 and NOS3 and inducible NOS2. Viral infections and pro-inflammatory cytokines induce expression of NOS2 and defective NOS2 expression is responsible for increased viral replication in cystic fibrosis and overexpression of NOS2 provides protection against viral infection (Zheng et al., 2003; Zheng et al., 2004). Hydrogen peroxide is produced by dual oxidase 1 and 2. These belong to a family of NADPH oxidases and are located in the plasma membrane and secrete hydrogen peroxide to extracellular milieu. The dual oxidase-generated hydrogen peroxide in combination with thiocyanate and lactoperoxidase generates the microbicidal oxidant hypothiocyanite, which effectively kills both gram positive and gram negative bacteria and this innate defense mechanism is defective in cystic fibrosis airway epithelium due to impaired transport of thiocyanate (Moskwa et al., 2007).

In COPD patients, levels of lysozyme and SLPI decrease with bacterial infection, while lactoferrin levels remain unchanged (Parameswaran et al., 2011). Lower levels of salivary lysozyme in clinically stable COPD patients correlated with increased risk of exacerbations (Taylor et al., 1995). Reduced lysozyme levels in COPD is thought to be due to degradation by proteases elaborated by bacterial pathogens or neutrophils (Jacquot et al., 1985; Taggart et al., 2001). These proteases also inactivate SLPI (Parameswaran et al., 2009). In addition, SLPI forms complexes with neutrophil elastase and binds to negatively charged membranes, thus decreasing the levels of SLPI further in the airway secretions during infection. In clinically stable patients however, the levels of SLPI were increased compared to smokers without COPD and never smokers (Tsoumakidou et al., 2010). In contrast, hBD2 was absent in COPD patients. Herr et al showed that hBD2 is significantly reduced in pharyngeal wash and sputum of current or former smokers compared to non-smokers, and exposure of airway epithelium to cigarette smoke *in vitro* inhibited induction of hBD2 by bacteria (Herr et al., 2009). Recently, we showed that COPD airway epithelial cells show a trend in decreased expression of NOS2 and Duox oxidases and this was associated with impaired clearance of rhinovirus (Schneider et al., 2010).

3. Innate immune receptors of airway epithelium

Airway epithelium in addition to providing a physical barrier, it also plays a pivotal role in recognition of pathogens and releasing appropriate chemokine and cytokines to initiate an inflammatory response. This inflammatory response includes recruitment of phagocytes to clear pathogens that are not cleared by barrier function of epithelium, and immune cells, such as dendritic cells and lymphocytes that initiate adaptive immune response. Airway epithelium recognizes pathogens or pathogen associated molecular patterns (PAMPS) by innate immune receptors also known as pattern recognition receptors (PRRs), which are germ-line encoded receptors. One of best characterized PRRs are Toll-like receptors (TLRs) (Akira et al., 2001; Medzhitov, 2001).

3.1 Toll-like receptors

TLRs are type I transmembrane receptors with an extracellular domain that contains leucine-rich-repeat motifs, a transmembrane domain and a cytoplasmic domain known as

the toll/interleukin-1 receptor (TIR) homology domain (Hoffmann, 2003) (Figure 2). To date thirteen TLRs have been identified in mammalian system. Only TLRs1 to 10 are expressed in humans. TLRs1, -2, -4, -5 and -6 are expressed on the cell surface and TLRs3, -7,- 8 and -9 are expressed in the endosomes, lysosomes and the endoplasmic reticulum. (Kawai and Akira, 2009). TLRs recognize a wide range of PAMPs- lipoproteins by TLRs 1, -2, and -6 (Aliprantis et al., 1999; Schwandner et al., 1999; Takeuchi et al., 2001; Takeuchi et al., 2002), LPS by TLR4 (Poltorak et al., 1998), flagella by TLR5 (Hayashi et al., 2001), DNA by TLR9 (Hemmi et al., 2000), and RNA by TLR3, -7 and -8 (Alexopoulou et al., 2001; Diebold et al., 2004; Heil et al., 2004). TLR4 also recognizes respiratory syncytial virus (Kurt-Jones et al., 2000).

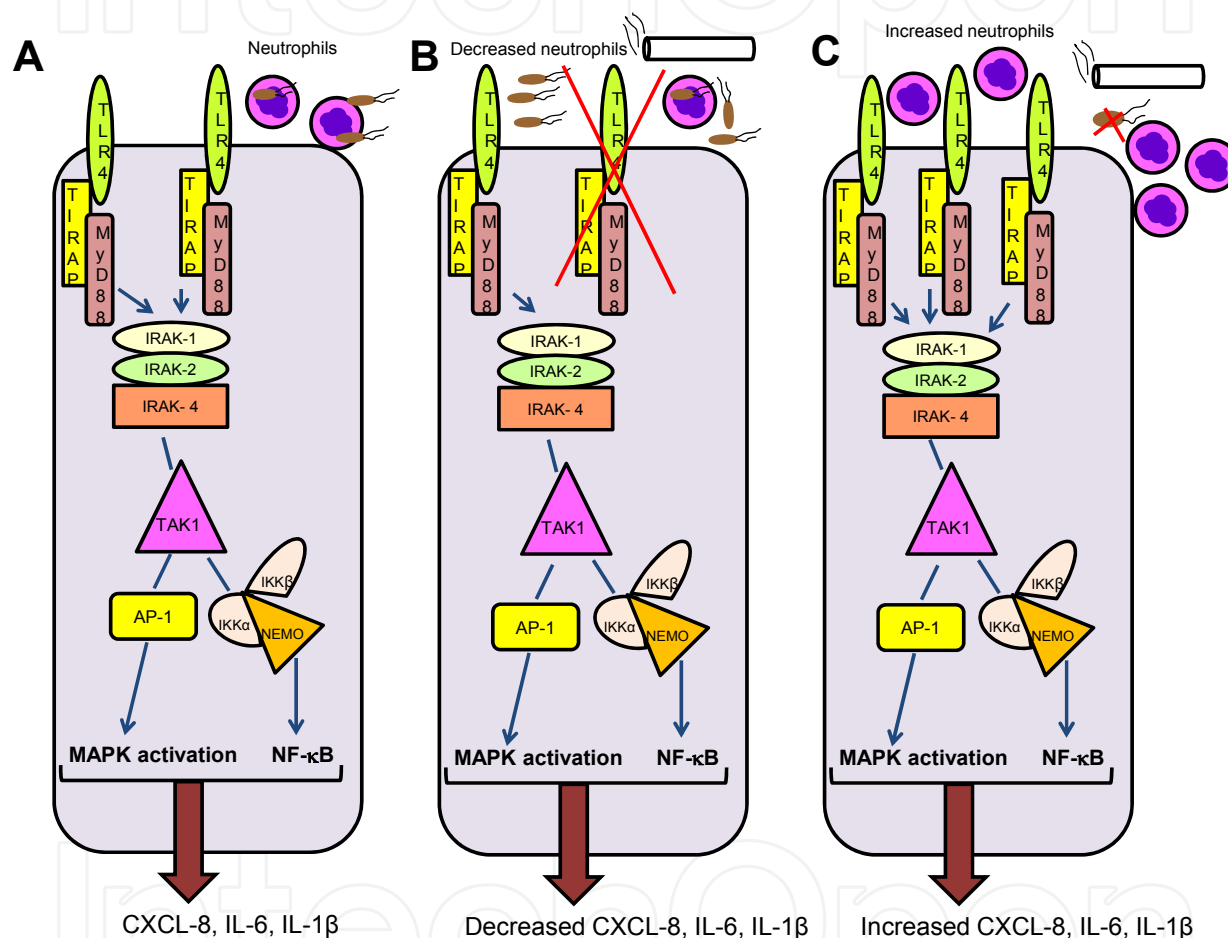


Fig. 2. Impact of cigarette smoke on persistence of bacteria and inflammation. Under homeostasis, TLR4 recognizes infecting bacteria and activates both MAP kinase and NF-κB pathway to stimulate normal levels of CXCL-8, IL-6 and IL-1β to recruit neutrophils, which clear bacteria. Decreased expression of TLR4 caused by acute exposure to cigarette smoke attenuates release of CXCL-8, IL-6 and IL-1β, there by decreasing the neutrophil infiltration and increasing the bacterial persistence. Under chronic exposure as noted in COPD patients, if the TLR4 expression is increased, then chemokine and cytokine expression is increased leading to decreased bacteria coupled with increased inflammation.

TLRs initiate signaling by MyD (myeloid differentiation primary-response protein) 88-dependent and -independent pathways. Except for TLR3, all TLRs initiate signaling by MyD88-dependent pathway to activate NF-κB. MyD88 is located in the cytoplasm and is similar to

TLR in structure and has an N-terminal death domain, an intermediary domain and C-terminal TIR domain. Upon recognition of PAMPs by TLRs, the TIR domain of TLR interacts with TIR domain of MyD88 directly or indirectly via MyD88-adaptor like protein (MAL)/TIR adaptor protein (TIRAP)(Horng et al., 2002; Li et al., 2005). TLR5, -7, -8 and -9 does not require TIRAP to initiate signaling events that leads to NF- κ B activation (Horng et al., 2002). Association of MyD88 to TLR leads to recruitment of IL-1R associated kinase (IRAK)-4, IRAK-1, TNFR-associated factor 6 (TRAF6), which then through a number of kinases activates NF- κ B and AP-1 and stimulates expression of CXCL-8, IL-6, IL-1 β and TNF- α (Adachi et al., 1998; Mukaida et al., 1990; Jeong and Lee, 2011). TLR4 also signals via MyD88-independent pathway and the first supporting evidence came from the studies on MyD88 knockout mice, which failed to respond normally to TLR2, -5, -7 and -9 ligands, but not to TLR4 (Kawai et al., 1999). Later TLR4 endocytosed upon binding to LPS was shown to signal through TIR-domain-containing adapter-inducing interferon (IFN)- β (TRIF) pathway similar to TLR3 (Alexopoulou et al., 2001; Hoebe et al., 2003; Kagan et al., 2008). TLR2 was shown to be internalized and stimulate type I interferon (IFN) response by MyD88-dependent pathway in virus-, but not bacteria infected inflammatory monocytes (Barbalat et al., 2009).

The airway epithelium expresses all 10 TLRs, but the expression of TLR2 to TLR6 is stronger than the others. Expression of TLRs7 through -10 is variable depending on type of cells used (Mayer et al., 2007; Platz et al., 2004; Sha et al., 2004). Expression of TLRs 1 through -6 and -9 on the cell surface was confirmed by flow cytometry (Greene et al., 2005). However the signaling from these TLRs depends on the expression of adaptor molecules and co-receptors. Primary airway epithelial cells are hyporesponsive to LPS despite expressing TLR4 and this is because of reduced surface expression of co-receptor CD14 and low expression levels of co-stimulatory molecule MD2 (Jia et al., 2004). This may be necessary to restrict TLR4 activation under unstimulated conditions to prevent chronic inflammation of airways that is constantly exposed to inhaled bacteria and endotoxin. On the contrary, LPS was shown to activate TLR4 signaling in small airway and alveolar epithelial cells even though the TLR4 was localized to cytoplasmic compartment (Guillot et al., 2004). More recently John et al attributed chronic colonization of bacteria in CF airways to decreased expression of TLR4 in CF airway epithelial cells (John et al., 2010). TLR2, which is expressed on the apical surface of polarized airway cells is mobilized into an apical lipid raft receptor complex following *P. aeruginosa* infection and initiate signalling (Soong et al., 2004). TLR5 recognizes flagella of *P. aeruginosa* and *Burkholderia cenocepacia* and activate NF- κ B (Adamo et al., 2004; Urban et al., 2004; Zhang et al., 2005). *Haemophilus influenzae* traverses polarized airway epithelial cells by interacting with TLR2, which then activates p38 mitogen activated protein (MAP) kinase and TGF- β Signalling(Beisswenger et al., 2007). TLR3 recognizes double stranded (ds)-RNA, an intermediate generated during RNA virus replication and elicits chemokine and type I IFN responses by MyD88- independent signaling mechanism (Gern et al., 2003; Wang et al., 2009). Upon ligation of ds-RNA, TRIF and TRAM (TRIF-related adaptor molecule) are recruited to TIR domain of TLR3 and TRAM acts as a bridge between TLR and TRIF and this allows activation of TRIF-dependent signaling leading to activation of IRF3 via IKK ϵ /TBK-1 to stimulate IFN production or activation of NF- κ B via IKK α /IKK β to stimulate CXCL-8 expression (Kawai and Akira, 2008). The recognition of double-stranded RNA by TLR3 also increases expression of hBD2 (Duits et al., 2003). Viral or bacterial infection transcriptionally upregulates TLR3 expression (Liu et al., 2007; Sajjan et al., 2006; Wang et al., 2009; Xing et al., 2011), thereby increasing viral induced cytokine and

chemokine responses further. Stimulation of TLR2 or TLR3 also induces mucin expression by activating MAP kinases and inducing EGF receptor signaling (Chen et al., 2004; Kohri et al., 2002; Li et al., 1997; Zhu et al., 2009). MUC1, a transmembrane mucin is a negative regulator of TLRs and therefore may play an important role in limiting TLR- induced inflammatory responses (Ueno et al., 2008).

There are conflicting reports with regards to expression of TLRs and their role in innate immune responses in patients with COPD. Airway epithelial cells from patients with severe COPD showed decreased expression of TLR4, but not TLR2 (MacRedmond et al., 2007). In contrast, recently Pace et al observed increased neutrophils and decreased apoptosis of neutrophils in the bronchoalveolar lavage and increased expression of TLR4 in airway epithelium of COPD patients providing evidence that increased TLR4 may contribute to airway neutrophilia in COPD (Pace et al., 2011). Pace et al also demonstrated increased TLR4 expression and concurrent increased CXCL-8 in response to LPS challenge in cigarette smoke exposed airway epithelial cells (Pace et al., 2008), while other investigators showed decreased TLR4 expression which was associated with reduced CXCL-8 and hBD2 production (Kulkarni et al., 2010; MacRedmond et al., 2007). Our preliminary studies involving primary airway epithelial cells from COPD patients suggested heightened expression of CXCL-8 in responses to *P. aeruginosa* infection compared to normal airway epithelial cells (Ganesan and Sajjan, unpublished results). However, role of TLR in this context is yet to be established. Whether TLR4 expression is decreased or increased it has important implications in COPD airway inflammation and obstruction (Figure 2). The decreased expression of TLR4 may lead to decreased innate immune responses and increased persistence of infecting organism. On the other hand increased expression of TLR4 increases neutrophil recruitment and mucus production in response to bacterial or viral infection, thereby leading to increased airways inflammation and obstruction.

3.2 RIG-I like receptors

Another family of PRRs that play a role in innate defense mechanisms of airway epithelial cells is retinoic acid inducible (RIG)-I like receptors (RLR). This family of PRRs includes RIG-I, MDA-5 (melanoma differentiation associated protein 5) and LGP-2 (Laboratory of genetics and physiology 2). RLRs are the primary sensor molecules for detection of viral RNA in the cytoplasm (Meylan and Tschopp, 2006; Sun et al., 2006). Both RIG-I and MDA-5 contain a caspase recruitment domain (CARD) and a RNA helicase domain (Kang et al., 2002; Yoneyama et al., 2005; Yoneyama et al., 2004). On the other hand, LPG-2 has only RNA helicase domain but not CARD domain, which is required for recruiting adaptor protein MAVS (also known as VISA, Cardiff) (Yoneyama et al., 2005). Therefore recognition of viral RNA by RIG-I and MDA-5 leads to IFN or chemokine response, and LPG-2 suppresses this response (Yoneyama et al., 2005). RIG-I and MDA-5 recognize different RNA species. RIG-I recognizes single stranded (ss)RNA viruses, such as influenza virus, paramyxoviruses and deficiency in RIG-I increases the susceptibility of mice to RNA viruses (Kato et al., 2005). RIG-I specifically binds to the 5'-triphosphate moiety, the signature of which is exposed in the process of viral entry or replication. The host RNA which loses 5'triphosphate moiety during processing is therefore not recognized by RIG-I preventing cytokine and chemokine response due to self-recognition. RIG-I also recognizes short dsRNA (<1 kb) in 5'triphosphate-

independent manner and induces IFN responses (Kato et al., 2008). On the other hand, MDA-5 recognizes long dsRNA that is >1 kb. Since viruses from picornaviridae family including rhinovirus generate long dsRNA in infected cells, innate immune responses to these viruses depends on recognition of viral RNA by MDA-5 (Kato et al., 2006; Wang et al., 2009). Mice deficient in MDA-5 show increased inflammatory response, delayed IFN response and significantly increased viral load up to 48 h after rhinovirus infection (Wang et al., 2011). Both RIG-I and MDA-5 uses a common adaptor protein called interferon beta promoter stimulator-1 (IPS-1, also known as MAVS, VISA, CARDIF)(Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005). IPS-1 has a CARD domain which is homologous to RIG-I and MDA-5 and has a transmembrane domain at its C-terminal end that spans the mitochondrial membrane (Seth et al., 2005). IPS-1 after binding to RIG-I or MDA-5 through CARD-CARD interaction, activates IRF3 and NF- κ B via TBK1/IKK ϵ and RIP-1/IKK α /IKK β respectively. IPS-1 also interacts with receptor-interacting protein-1 (RIP-1), which is a death domain and is implicated in virus infection-induced IFN expression (Balachandran et al., 2004). However IPS-1 interaction with RIP-1 via the non-CARD region facilitates NF- κ B activation, rather than IRF3 activation. Therefore IPS-1 regulates both IRF3 and NF- κ B activation upon binding to RIG-I or MDA-5. IPS-1-deficient mice fail to activate IRF3 and NF- κ B, with concomitant loss of type I IFN and inflammatory cytokine induction after viral infection and show increased persistence of virus (Kawai and Akira, 2008). Recently, cigarette smoke extract was demonstrated to inhibit RIG-I-stimulated innate immune responses to influenza infection in bronchial organ culture model (Wu et al., 2011). Exposure to cigarette smoke extract also interfered with STAT1 activation by IFN- γ , a type II interferon which stimulates expression of various antiviral proteins (Modestou et al., 2010). Further, cigarette smoke also attenuated the inhibitor effect of IFN- γ on RSV mRNA and protein expression. Eddleston et al demonstrated that exposure of airway epithelial cells to cigarette smoke extract suppressed mRNA induction of CXCL-10 and IFN- β by human rhinovirus and also viral dsRNA mimic polyinosinic:polycytidylic acid (poly I:C) (Eddleston et al., 2011). This was found to be due to decrease in activation of the IFN-STAT-1 and SAP-JNK pathways. Inhibition of antiviral responses, in particular IFN and CXCL-10 responses appear to be due to acute exposure to cigarette smoke that occurs *in vitro*, because the airway epithelial cells obtained from COPD patients showed antiviral responses to rhinovirus infection which was in fact significantly higher than the cells obtained from non-smokers (Schneider et al., 2010). Similar to our observations, mice exposed to cigarette smoke and poly I:C or influenza virus showed increased IFN responses and this was attributed to pathogenesis of COPD (Kang et al., 2008).

3.3 NOD-like receptors

Nod-like receptors (NLR) are a family of proteins and sense microbial signatures in the cytosol. There are at least 22 identified NLRs in humans, although only few of them have been functionally characterized. All of them have a central nucleotide binding domain and C-terminal leucine-rich repeat domain, which possibly mediate ligand binding. In addition, they also contain different N-terminal effector domains such as CARD domain, pyrin domains or baculovirus inhibitor repeats and thus activate diverse downstream signaling pathways (Chen et al., 2009; Fritz et al., 2006). The most widely studied among the CARD containing NLRs are NOD1 and NOD2. NOD1 primarily recognizes peptidoglycan (PGN)

derivative, γ -D-glutamyl-mesodiaminopimelic acid from gram-negative bacteria (Chamaillard et al., 2003; Girardin et al., 2003a), whereas, NOD2 is considered as a general sensor of PGN through muramyl dipeptide (Girardin et al., 2003b). Upon recognizing PGN, both NOD1 and NOD2 activate NF- κ B-mediated proinflammatory response via RIP-2 (Hasegawa et al., 2008). Both NOD1 and NOD2 are highly expressed in immune and inflammatory cells (Fritz et al., 2005; Kanneganti et al., 2007). These two NODs are also expressed in airway epithelium and are induced by bacterial stimuli (Bogefors et al., 2010; Mayer et al., 2007; Opitz et al., 2004; Travassos et al., 2005). NOD1 and NOD2 contribute to innate immune responses to different bacteria including *Pseudomonas aeruginosa*, *Chlamydia pneumonia*, *Haemophilus influenza* and *L. pneumophila* both *in vivo* and *in vitro* (Clarke et al., 2010; Frutuoso et al., 2010; Shimada et al., 2009; Zola et al., 2008).

NOD2 not only recognizes bacterial peptidoglycan, but also viral ssRNA. NOD2 deficiency results in impaired type I IFN expression *in vitro* upon stimulation with viral ssRNA (Sabbah et al., 2009). This was dependent on NOD2 interaction with IPS-1 and activation of IRF3, but not on activation of RIP-2. NOD2 deficient mice were also found to be more susceptible to infection with respiratory syncytial virus and influenza virus than the wild-type mice.

Pyrin domain containing NLRs are normally called as NLRP. There are 14 members in this NLR subfamily. At least NLRP1-3 form multiprotein complex named "inflammasomes" which consists one or two NLRs, an adaptor molecule ASC (apoptosis-associated speck-like protein containing a CARD), and caspase-1 (Martinon et al., 2002). Inflammasomes respond to several PAMPS or DAMPS and regulate caspase-1 mediated cell death called pyroptosis and production of IL-1 β and IL-18 at post-transcriptional level. Therefore, unlike other cytokines, IL-1 β production requires two signals. Signal I is often provided by TLRs which activates NF- κ B dependent pro-IL-1 β , and signal II comes from inflammasomes, which mediate caspase 1-dependent cleavage of pro-IL-1 β to its mature form. The activators of NLRP3 are microbial RNA, bacterial pore forming toxins, certain types of DNA and MDP (Kanneganti et al., 2006; Mariathasan et al., 2006; Martinon et al., 2004; Meixenberger et al., 2010; Muruve et al., 2008). Accordingly, NLRP3 null mice were shown to be susceptible to influenza virus, *Streptococcus pneumoniae* and *K. pneumonia* infection (Kanneganti, 2010; Allen et al., 2009; Ichinohe et al., 2010; Thomas et al., 2009). In addition NLRP3 is also activated by necrotic cells, uric acid metabolites, ATP, biglycan, hyaluronan that might be released after tissue injury (Babelova et al., 2009; Iyer et al., 2009; Mariathasan et al., 2006; Martinon et al., 2006; Yamasaki et al., 2009).

In addition to NLRP, NLRC4 (NLR family CARD domain containing) and NAIP5 (NLR family, BIR domain containing) also form inflammasomes. While NAIP is expressed in both lung macrophages and epithelial cells, NLRC4 is expressed only in macrophages (Diez et al., 2000; Vinzing et al., 2008). NLRC4 inflammasome recognizes *L. pneumophila* and *P. aeruginosa* flagellin present in the host cytosol, independently of TLR5 (Franchi et al., 2006; Miao et al., 2006). NAIP controls intracellular replication of *L. pneumophila* depending on the recognition of flagellin (Vinzing et al., 2008).

The widely expressed NLRX1 (NLR family member X1) is the only NLR receptor that is localized to mitochondria and it negatively regulates RIG-I and MDA-5 receptors. NLRX-1 mediates production of reactive oxygen species upon bacterial infection (Moore et al., 2008; Tattoli et al., 2008) and decreased dsRNA-stimulated IFN response.

Although, there is no evidence that NLRs play a role in innate immune responses to bacterial or viral infection in COPD so far, the emerging literature indicate inflammasome forming NLRs may contribute to COPD pathogenesis. Inhaled cigarette smoke, oxidative stress, necrotic cell death, hypoxia, hypercapnia may cause tissue injury and release of DAMPs (uric acid, ATP) and this in turn activates NLRP3 inflammasome (Wanderer, 2008). Consistent with this notion, uric acid concentration was increased in the bronchoalveolar lavage of COPD patients (Wanderer, 2008). COPD patients also had significantly increased amounts of IL-1 β and this correlated with severity of the disease (Sapey et al., 2009). Mice exposed to cigarette smoke also showed increased IL-1 β in their lungs (Doz et al., 2008) and finally mice overexpressing mature IL-1 β in epithelial cells showed typical feature of COPD including emphysema, lung inflammation with increased neutrophils and macrophages and airway fibrosis (Lappalainen et al., 2005). ASC (inflammasome adaptor protein) null mice showed attenuated inflammation after exposing to elastase and less uric acid. Elastase-induced inflammation was significantly reduced in wild-type mice treated with uricase or treated with IL-1R antagonist (Coullin et al., 2009). All these evidences suggest contribution of inflammasome forming NLRP3 to COPD pathogenesis.

4. Innate immunity and co-infections

Nontypeable *H. influenzae* (NTHi), *S. Pneumoniae* and *P. aeruginosa* are detectable in lower airways of approximately 25 to 50% of clinically stable COPD patients (Sethi and Murphy, 2008). Chronic colonization can alter the responses of airway epithelial cells and other innate and adaptive immune cells to subsequent viral or bacterial infections leading to increased severity of disease. Exacerbations due to concurrent or sequential infections was shown to be associated with increased severity of disease at least in one-quarter of COPD patient population (Papi et al., 2006; Sethi et al., 2006; Wilkinson et al., 2006). Risk of secondary bacterial infection following a viral infection dates back to 19th century, when cases of pneumonia correlated with influenza (flu) epidemic (McCullers, 2006). Influenza infection increases risk of secondary bacterial infection by increasing binding or invasion of bacterial pathogen to airway epithelial cells, desensitizing innate immune receptors such as TLRs, and causing immunosuppression by increasing glucocorticosteroid expression (Beadling and Slifka, 2004; Hament et al., 1999; Jamieson et al., 2010; McCullers, 2006; Seki et al., 2004; Sun and Metzger, 2008). Respiratory syncytial virus infection increased persistence of *P. aeruginosa* in mice and increased *P. aeruginosa* and NTHi binding to airway epithelial cells (de Vrankrijker et al., 2009; Jiang et al., 1999; Van Ewijk et al., 2007). Respiratory syncytial virus also increased persistence of NTHi by dysregulating the expression of β -defensin in chinchilla model of respiratory infection (McGillivray et al., 2009). Rhinovirus which causes common cold, in combination with *S. pneumoniae* was associated with severe cases of community-acquired pneumonia in children (Honkinen et al., 2011). Various *in vitro* studies showed that rhinoviruses also increase bacterial binding to airway epithelial cells by increasing the expression of bacterial receptors on airway epithelial cells or by facilitating invasion of cells by bacteria (Ishizuka et al., 2003; Passariello et al., 2006). We demonstrated that rhinovirus infection also increases paracellular permeability and promote bacterial traversal across mucociliary- differentiated airway epithelium (Sajjan et al., 2008). Rhinovirus infection also decreases bacterial PAMPS-induced proinflammatory response by desensitizing TLRs (Oliver et al., 2008).

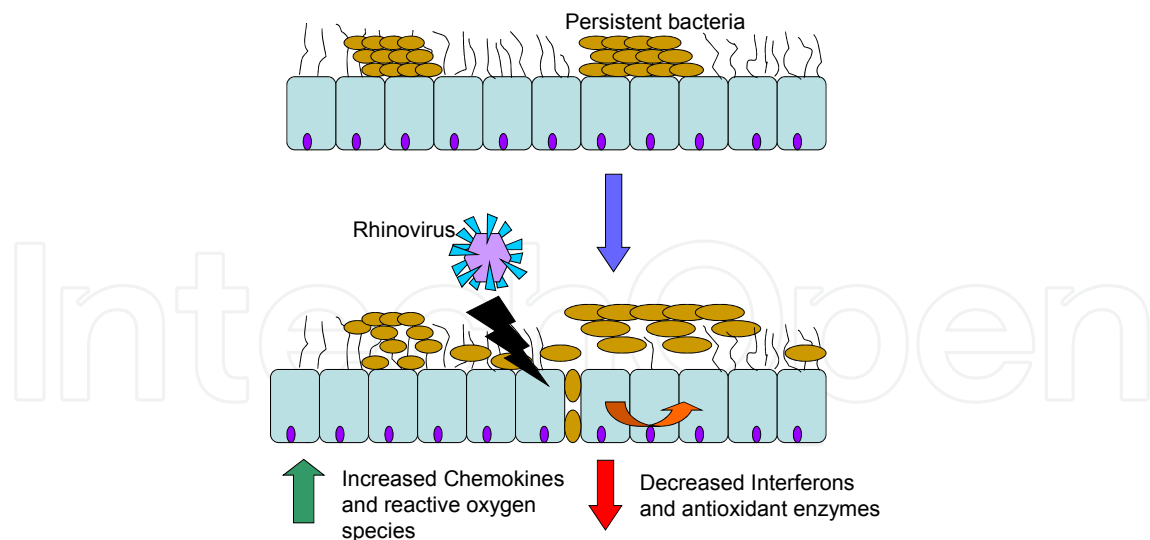


Fig. 3. COPD airway epithelial cells are impaired in clearing infecting bacteria. This leads to colonization of bacteria on the apical surface of airway epithelium. Subsequent rhinovirus infection disrupts barrier function and promotes traversal and interaction of bacteria with basolateral receptors leading to exaggerated chemokine response. At the same time COPD airway epithelial cells also show increased generation of reactive oxygen species and attenuated expression of antioxidant enzymes resulting in increased oxidative stress. This in turn suppresses interferon (antiviral) response stimulated by secondary rhinovirus infection. Together this may lead to persistence of bacteria and virus, and increased inflammation.

Impact of secondary viral or bacterial infection in patients colonized with bacteria is being increasingly recognized in recent years. For instance, despite chronic colonization with *P. aeruginosa*, cystic fibrosis patients show exacerbations periodically and some incidences are associated with acquiring secondary viral or bacterial infections (Ong et al., 1989; Ramsey et al., 1989; Wat et al., 2008). Similarly, in COPD patients who are chronically colonized with NTHi, exacerbations were associated with acquisition of new strain of NTHi, other species of bacteria or respiratory virus (Murphy, 2000; Murphy et al., 2008; Murphy et al., 2007; Papi et al., 2006; Sykes et al., 2007; Wilson, 2000). Recently, we showed that secondary bacterial infection in primary cystic fibrosis airway epithelial cells preinfected with *P. aeruginosa* increases C-X-C chemokine responses by increasing the load of planktonic bacteria which are more pro-inflammatory than their counterpart biofilm bacteria and also increased paracellular invasion of bacteria in differentiated airway epithelial cells (Chattoraj et al., 2011b). We also demonstrated that cystic fibrosis, but not normal airway epithelial cells infected with bacteria show suppressed type I IFN response to subsequent rhinovirus infection (Chattoraj et al., 2011a). This was due to increased oxidative stress in cystic fibrosis airway epithelial cells. Airway epithelial cells from COPD patients show increased oxidative stress similar to cystic fibrosis patients. Therefore we expect that bacterial preinfection may suppress innate immune responses to subsequent virus infection in COPD cells. Consistent with this notion, our preliminary studies indicate that infection with *P. aeruginosa* or NTHi infection increases oxidative stress further and decreases expression of antioxidant genes in COPD airway epithelial cells. In addition, we also observed suppression of IFN response in COPD airway epithelial cells infected with bacteria to subsequent rhinovirus infection (unpublished observations). Similar to our observations, LPS treatment was demonstrated

to suppress IFN- β production in response to dsRNA in mice as well as in monocytes and macrophages (Piao et al., 2009; Sly et al., 2009). This was due to increased expression of SHIP, a MPA kinase phosphatase in LPS treated monocytes. In airway epithelial cells however, *P. aeruginosa* infection induced suppression of IFN response to rhinovirus infection was not due to increased expression of SHIP, but rather due to decreased Akt phosphorylation (Chattoraj et al 2011) which is required for maximal activation of IRF3 (Dong et al., 2008; Sarkar et al., 2004). Previously, we have shown that expression of IFN response to rhinovirus infection requires activation of IRF3 in airway epithelial cells (Wang et al., 2009). Based on these experimental evidences, it is possible that 30% of COPD patients who are chronically colonized with *NTHi* or *P. aeruginosa* in their lower airways may show suppressed antiviral responses and increased chemokine expression (Figure 3). This may lead to increased lung inflammation and progression of lung disease in COPD patients following exacerbation due to co-infections.

5. Conclusion

The airway epithelium contributes significantly to innate immune system in the lungs. It acts as a physical barrier that protects against inhaled substances and pathogens. Airway epithelial cells also express plethora of innate immune receptors which recognizes both PAMPS and DAMPS and stimulate appropriate responses to either clear the infecting organism and to repair of injured epithelium. However in COPD, chronic exposure to cigarette smoke or environmental hazards causes airway remodeling and also modulate innate immune responses of airway epithelial cells to infection (Figure 4). This results in impaired clearance of infecting organisms and aberrant cytokine and growth factor expression and increased lung inflammation leading to progression of lung disease.

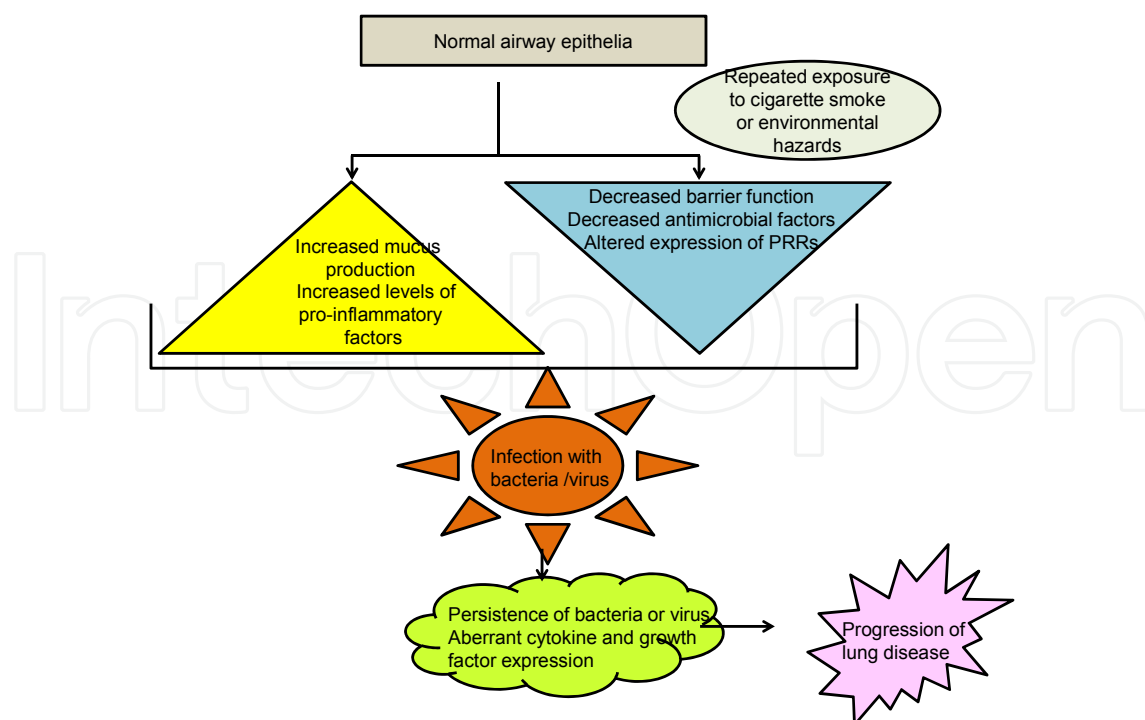


Fig. 4. A schematic representation depicting the combined effects of cigarette smoke or other environmental hazards and bacterial infection on the progression of lung disease in COPD

6. Acknowledgements

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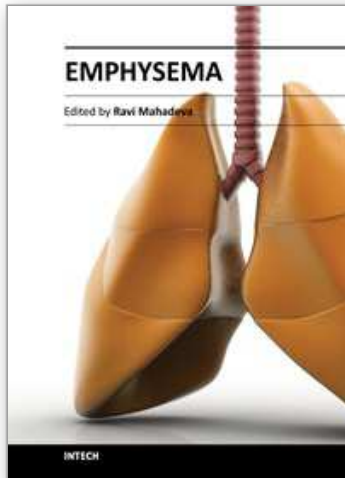
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Emphysema

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Chronic Obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality world-wide. The most common cause is chronic cigarette smoke inhalation which results in a chronic progressive debilitating lung disease with systemic involvement. COPD poses considerable challenges to health care resources, both in the chronic phase and as a result of acute exacerbations which can often require hospital admission. At the current time it is vital that scientific resources are channeled towards understanding the pathogenesis and natural history of the disease, to direct new treatment strategies for rigorous evaluation. This book encompasses some emerging concepts and new treatment modalities which hopefully will lead to better outcomes for this devastating disease.

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