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REVIEW

Respiratory epithelial cells in innate immunity to influenza virus infection

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Abstract Infection by influenza virus leads to respiratory failure characterized by acute lung injury associated with alveolar edema, necrotizing bronchiolitis, and excessive bleeding. Severe reactions to infection that lead to hospitalizations and/or death are frequently attributed to an exuberant host response, with excessive inflammation and damage to the epithelial cells that mediate respiratory gas exchange. The respiratory mucosa serves as a physical and chemical barrier to infection, producing mucus and surfactants, anti-viral mediators, and inflammatory cytokines. The airway epithelial cell layer also serves as the first and overwhelmingly primary target for virus infection and growth. This review details immune events during influenza infection from the viewpoint of the epithelial cells, secretory host defense mechanisms, cell death, and recovery.

Keywords Innate immunity · Influenza · Epithelial cells · Virus infection · Secretory innate defenses

Introduction

Each year, seasonal influenza affects 5%–15% of the population in the northern hemisphere. Whereas most cases are mild and do not require professional medical intervention, some 3–5 million infections worldwide are severe enough to cause hospitalization or death (http://www.euro.who.int/en/what-we-do/health-topics/diseases-and-conditions/influenza/seasonal-influenza 2010). Because of its usefulness as a model for localized mucosal immune responses, influenza infection has often been studied in the context of innate and adaptive immunity, with a focus on cellular infiltration of the lung and the efficacy of these responses in viral clearance. However, less attention has been given to the actual damage associated with viral infection itself, which is known to cause respiratory and multi-organ failure (Abdel-Ghafar et al. 2008; Gu et al. 2007; Ng and To 2007). These processes can be generated or exacerbated by the antiviral immune response or by the direct interaction of the virus with the host epithelium. Regardless of the specific intervening pathological mechanisms, the initiation and consequence of the antiviral response, ranging from recovery to severe morbidity or mortality, can generally be traced to the original source of virus infection and growth, viz., the epithelial lining of the respiratory tract.

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Respiratory epithelial cell populations and functions

The respiratory system is divided into the upper and lower tracts, with the larynx, grouped with either region, serving as the mid-point. The upper tract comprises the nasal sinuses and the pharynx, and the lower tract consists of the trachea or windpipe, which branches first into the two bronchi and then into the bronchioles that terminate in the air sacs or alveoli. The diaphragm stretches along the base of the ribcage and functions to promote respiration by enlarging the thoracic cavity during respiration, creating suction that pulls air into the lungs, before relaxing during exhalation. The oxygen and carbon dioxide gas exchange

processes, which constitute respiratory function, occur in the alveoli, specifically the extremely thin (50–100 nm in depth) layer of alveolar epithelial type I cells (ATI) that line these delicate sacs and interface with the apposing blood capillaries (Dobbs et al. 2010).

Down to the most distal bronchioles, the human respiratory tract is lined by a pseudo-stratified layer of epithelial cells of variable cellular composition. This complex cellular organ consists of mucus- and inspired particulate- sweeping columnar ciliated cells, mucus-producing goblet cells, surfactant-secreting Clara cells, sensory neuro-epithelial (NE) cells, and basal cells, which act as progenitors for other select cell types. The relative prominence of these different populations changes progressively from the trachea to the terminal bronchi. For example, the NE cells, which secrete substance P and serotonin and communicate with smooth muscle, are found in small clusters near branch points in the bronchi and bronchioli and then decrease in numbers at more distal regions (Morrisey and Hogan 2010). Basal cells comprise roughly 30% of the pseudostratified epithelium (Morrisey and Hogan 2010). Studies of mouse tracheal epithelium suggest that basal cells give rise to Clara and ciliated cells, both during normal maintenance and under conditions of damage (Morrisey and Hogan 2010; Rock et al. 2009). The ratio of secretory (Clara and goblet) cells to ciliated cells is comparable throughout this epithelial region, with fewer ciliated cells in the distal region. Goblet cells also drop off in number toward the bronchioles. Mice have relatively fewer goblet cells than humans, although, following exposure to cytokines and allergens, these numbers increase (Wan et al. 2004). Differences in cellular composition may account for variations in the patterns of infection and host response for any particular section of the lung.

The alveolar epithelium consists of two main populations: alveolar type I (ATI) and type II (ATII) epithelial cells. The ATI cells constitute roughly 10% of the alveolar population and account for about 95% of the surface that interfaces with inspired air (Crapo et al. 1982; McElroy and Kasper 2004; Stone et al. 1992). The ATII population provides only around 5% of the alveolar surface in normal adult mammals (Crapo et al. 1982; McElroy and Kasper 2004). This difference in number to cell surface occupancy reflects the spread-out "stretchy" nature of ATI cells. The extensive anti-microbial, pro-respiratory, and pro-healing responses of ATII cells have garnered them the title of "defenders of the alveolus" (Mason and Williams 1977). The sparsely distributed ATII cells produce surfactant (a substance that provides for proper respiration), play an important role in fluid balance and alveolar trans-epithelial ion transport, and act as stem cells for both themselves and the ATI population (Berthiaume et al. 1999). By contrast, the ATI cells are not readily grown in culture, and there are few identifying molecular markers (Williams 2003). Beyond gas exchange, their functions have not been well analyzed, although evidence has been provided for basal apolipoprotein E and transferrin production, which increase in response to oxidative stress (Chen et al. 2006). Thus, both ATI and ATII cells contribute to the maintenance of lung homeostasis following damage by extrinsic agents such as the influenza A viruses.

Secretory innate defenses against infection

We inhale on average 10,000 liters of air per day, ensuring constant exposure to environmental insults (Whitsett 2002). Human lungs contain various bioactive molecules and active processes that, at steady-state, are generally effective against minor irritants, such as dust and particulates, and low-level infectious diseases. Following encounters with more severe pathogens such as the influenza A viruses, the cells of the respiratory tract respond by mobilizing the normal "background" defenses and inducing more powerful and effective anti-microbial mechanisms. However, differences in virus strain, which lead to variations in cell tropism, efficiency of infection and replication, and the capacity to interfere with host defenses, modulate the degree to which the host system mounts an effective defense.

Interferons

Virus-infected cells secrete interferons (IFNs), viz., biologically active substances that induce neighboring uninfected cells to upregulate anti-viral mechanisms. Epithelial cells are known to produce two classes of IFNs. The type I IFNs include IFNα, IFNβ, IFN-κ, IFN-ε, and limitin, which signal through the universally expressed IFN α/β receptor (IFNAR) and induce identical biological effects via Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways (Sommereyns et al. 2008). The type III IFNs, viz., IFN-λ1, IFN-λ2, and IFN-λ3, signal via interleukin-28R (IL-28R), a distinct receptor complex restricted in expression to epithelial cells and a limited number of other cell types (Mordstein et al. 2010).

Type I IFNs represent the most powerful innate defense against influenza virus infection and replication. The susceptibility of IFNAR-deficient mice establishes the essential nature of this pathway for the initial control of many virus infections (Hwang et al. 1995; Muller et al. 1994). Signaling through JAK-STAT induces the transcription factor ISGF3, which regulates expression of a multitude of IFN-stimulated genes, such as the 2′–5′ oligoadenylate synthetases (OAS), protein kinase R (PKR), and orthomyxovirus resistance GTPases (Mx; Stark

et al. 1998). Briefly, the products of IFN-induced genes act to limit virus replication and spread by degrading viral (and cellular) RNA (OAS), inhibiting cellular translation machinery (PKR), interfering with primary transcription in the nucleus (Mx1), and limiting posttranslational activities (MxA) and interaction with the viral polymerase complex, leading to the blockade of virus replication (Mx1 and MxA; Garcia-Sastre and Biron 2006; Pavlovic et al. 1992; Sadler and Williams 2008; Samuel 2001).

The type III IFNs are believed to play less of a protective role in antiviral responses. Indeed, mice deficient in the IFNλ receptor show a mild defect in response to influenza virus infection (Mordstein et al. 2008). Although the type III and type I IFNs induce similar downstream anti-proliferative and anti-viral activities, limited expression of the type III IL-28R on host cells may explain the weaker phenotype in deficient mice (Dumoutier et al. 2004; Zhou et al. 2007). Interestingly, mice lacking receptors for both type I and type III IFNs show faster and increased levels of mortality to influenza A virus infection when compared with mice deficient for just one of the receptors (Mordstein et al. 2010). Thus, the type I and type III IFNs probably provide additive protection.

The kinetics and magnitude of IFN secretion can vary for different influenza A viruses. Comparison of a highly virulent H5N1 strain with a much less pathogenic human H3N2 virus has shown that the H5N1 strain induces a later, and much decreased, profile of IFNβ production from polarized human bronchial epithelial (Calu-3) cells (Zeng et al. 2007). Likewise, a virulent H7 virus induces poor IFNβ production in Calu-3 cells (Maines et al. 2008). Such delayed and depressed IFN secretion probably compromises early innate and antiviral defenses, thereby exacerbating virus spread and contributing to morbidity.

Cytokines and chemokines

Epithelial cells at the site of infection produce the earliest wave of cytokines (Table 1), which in turn trigger local inflammatory and systemic responses (Van 2000). The first cytokines made in this cascade are IFN-α, tumor necrosis factor α (TNFα), IL-1α, and IL-1β, soon followed by IL-6 and a variety of chemotactic cytokines such as IL-8 (KC in mouse) a neutrophil attractant, monocyte chemoattractant proteins (MCPs), and macrophage inflammatory proteins (MIPs; Bielefeldt-Ohmann 1995). In humans, the measurement of nasal cytokines induced by infection with A/Texas/91 (H1N1) virus has shown IFN-α, TNFα, and IL-6 at maximum levels on day 2, with IFNα levels being highest among the three. Then, a second TNFα peak and the first IL-8 peak occurs on day 4 (Treanor 2010). Various H3N2 and H1N1 influenza strains induce TNFα production from porcine lung epithelial cells within 24 h (Seo and Webster 2002). TNFα, IL-6, IL-1, and IFNα are associated with the systemic infection symptoms of fever, anorexia, and sleepiness. TNFα and IL-1 induce endothelial adhesion molecules, which promote the entry of innate inflammatory cells such as monocyte/macrophages, blood-bourne dendritic cells (DCs), and neutrophils into the site of infection. These same cytokines subsequently stimulate the local activation of these cells, which function directly to kill the virus and to remove infected host cells by phagocytosis. However, damage to bystander cells via the release of lytic granules is thought to be a common side effect of this cytokine/chemokine/inflammatory cell influx and activation.

Virulent influenza viruses generally induce higher levels of pro-inflammatory cytokines from airway epithelial cells in comparison with milder strains. Despite similar levels of virus replication, the pathogenic 1997 and 2004 H5N1 isolates stimulate higher levels of IFN-β, IL-6, IP-10 (IFN-gamma-inducible protein-10), and RANTES (regulated upon activation, normal T cell expressed and secreted) production from bronchial epithelial cells (NHBE) and human primary alveolar cells (type II alveolar epithelial cells) than a standard human H1N1 virus (Chan et al. 2005). The H5N1 VN04 strain induces significantly higher RANTES and IP-10 levels than a seasonal H1N1 strain after 24 h of infection of undifferentiated normal human bronchial epithelial (NHBE) cells (Chan et al. 2010). However, the extent of IP-10 protein secretion is comparable for well-differentiated NHBE cells exposed to the HK98/H1N1 and VN04/H5N1 viruses (Chan et al. 2010). A 2004 human H5N1 Vietnam isolate, which targets type II pneumocytes, induces higher and sustained expression of type I IFNs, IL-6, and TNFα in macaque lung tissue (Baskin et al. 2009).

The pleiotropic cytokine IL-6 functions as an acute-phase protein, in hematopoiesis, and in Th2 skewing, whereas IP-10 has been found to act as a chemoattractant for monocyte/macrophages, DCs, T cells, and natural killer (NK) cells and to induce effector T cell generation and trafficking (Dufour et al. 2002). RANTES, or CCL5, is chemotactic for T cells, eosinophils, and basophils, stimulates T cell activity (Dairaghi et al. 1998; Taub et al. 1996), and increases the adherence and extravasation of monocytes. Chemokines produced by airway epithelial cells may assist in host defense by promoting increased immune cell numbers and activation. Nevertheless, chemokines such as IP-10 and RANTES can also act to damage host tissue by this same recruitment of immune cells that enhances the inflammatory processes. Such negative aspects are apparent in disease models such as arthritis, atopic dermatitis, nephritis, colitis, and other autoimmune/inflammatory disorders (Appay and Rowland-Jones 2001; Rossi and Zlotnik 2000). Thus, epithelial cells respond to

Table 1 Cytokines produced by airway epithelial cells in response to influenza (*NHBE* normal human bronchial epithelial cells, *A549* human lung carcinoma cell line, *NCI-H292* bronchiolar epithelial cells, *DCs* dendritic cells, *MHC* major histocompatibility complex, *APC* antigen-presenting cell, NK natural killer)

Cytokine	Cell types	Function	References
TNFα (tumor necrosis factor α)	Porcine lung epithelial cells	•Fever •Activation of neutrophils, macrophage function •Upregulation of leukocyte adhesion molecules	Seo and Webster 2002
IL-6 (interleukin-6)	NHBE , ATII, NCI-H292	•Fever •Acute phase protein synthesis •Platelet production •Ig secretion	Chan et al. 2005; Adachi et al. 1997; Brydon et al. 2003; Wang et al. 1999
Type I IFNs (interferons)	NHBE, ATII	•Anti-viral •Upregulation of MCP-1, MCP-3, and IP-10 gene expression •Upregulation of MHC gene expression •APC maturation •T cell survival •IL-12, IL-18 receptor expression •IFN-gamma production from human NK and T cells	Chan et al. 2005; Zeng et al. 2007; Maines et al. 2008; Stark et al. 1998; Matikainen et al. 2000; Cella et al. 1999; Marrack et al. 1999; Sareneva et al. 2000, 1998
IP-10 (IFN-gamma-inducible protein-10)	NHBE, ATII	•Attracts monocytes, macrophages, DCs, T cells •Effector T cell production, trafficking	Chan et al. 2005
RANTES (regulated upon activation, normal T cell expressed and secreted)	NHBE, ATII, NCI-H292, A549	•Chemoattractant for monocytes, T cells, basophils, eosinophils	Chan et al. 2005; Adachi et al. 1997; Matsukura et al. 1998; Brydon et al. 2003; Julkunen et al. 2000; Wang et al. 1999
IL-8	NCI-H292, A549, ATII	•Chemoattractant for neutrophils	Adachi et al. 1997; Brydon et al. 2003; Julkunen et al. 2000; Wang et al. 1999
MIP-1 (macrophage inflammatory protein-1)	ATII	•Granulocyte activation •Induction of synthesis and release of IL-1, IL-6, and TNFα	Wang et al. 1999
MCP-1 (monocyte chemoattractant protein-1)	A549, ATII	•Chemotactic for monocytes, DCs, T cells	Julkunen et al. 2000; Wang et al. 1999

highly pathogenic influenza strains by inducing the more robust secretion of inflammatory cytokines; this, intriguingly, might not necessarily be a function of increased viral replication. Characteristics particular to high (versus low) pathogenicity virus strains, such as certain viral gene products, preference for one or several airway epithelial cell types over others, or the microenvironment of preferred targets, might cause the greater production of key inflammatory mediators from host epithelial cells.

Virus-damaged airway epithelial cells may also assist in host defense by promoting their own demise. The induction of "self-apoptosis" might be mediated via intrinsic or extrinsic mechanisms, with the intrinsic varieties encompassing internal sensing and initiation of death pathways, and the extrinsic types resulting from outside signals for death induction, e.g., TNF-related apoptosis-inducing ligand (TRAIL)/TRAIL-R interactions (Wiley et al. 1995). A necessary requirement for some extrinsic pathways of epithelial cell apoptosis is the upregulation of surface molecules to facilitate recognition by cytolytic host cells or mediators.

Epithelial cell death

Influenza viruses cause host cell death by several mechanisms. Direct infection can induce cell lysis, which releases new virions together with potentially inflammatory or harmful cellular contents into the extracellular space at around 20–40 h after infection (Julkunen et al. 2001). Influenza virus may also induce apoptosis via classical programmed cell death pathways. In normal uninfected tissues, apoptotic cell death reflects a series of specific cellular actions that result in the removal of damaged cells in a relatively un-inflammatory manner. Apoptosis comprises three discrete phases: initiation, which can be induced by a variety of means and leads to the activation of intracellular signaling pathways; a commitment phase, in which the cells reach a point at which death is imminent; and the execution phase, in which the cytopathic effects of DNA fragmentation, cell shrinkage, and membrane blebbing occur. In humans, viral replication peaks around days 2–3, and shedding is minimal by day 5–6 (Taubenberger and Morens 2008). The effect of damage to epithelial cells that line the respiratory tract will thus span 5–6 days of virus replication and cycling. Alveolar epithelial cell destruction can lead to direct respiratory failure via the induction of alveolar edema and poor respiratory gas exchange function. Lung autopsies of patients who have died of influenza are surprisingly similar among those infected with diverse strains and of varied pre-existing health status and show extensive alveolar denudation, alveolar edema, and pneumocyte hyperplasia, amongst other signs of respiratory failure (Nakajima et al. 2010; Treanor 2010). An understanding of the way that influenza viruses kill or otherwise damage the various cellular elements that make up the respiratory mucosa may help us to develop approaches to prevent the compromise in function that leads to respiratory failure.

Both extrinsic and intrinsic (e.g., cellular stress) pathways of apoptosis induction have been described for influenza-virus-infected respiratory epithelium. Exposure to IFNα/β is known to promote apoptosis via induction of the FADD/Caspase-8 death signaling pathway (Balachandran et al. 2000; Ludwig et al. 2006). Apoptosis of H3N2-infected human nasal and bronchiolar cells is significantly limited in the presence of pan-caspase and specific caspase-8 inhibition (Brydon et al. 2003). The double-stranded RNA that is produced intermediately during virus replication is a well-characterized inducer of nuclear factor kappa B (NF-κB)-dependent responses. Within 8 h, influenza A virus infection of human airway epithelial cells triggers the NF-κB-dependent expression of TRAIL, Fas, and FasL (Wurzer et al. 2004), all of which are pro-apoptotic proteins. Virus non-structural protein-1 (NS1)-mediated induction of NF-κB leads to increased IFNβ production in mouse embryonic fibroblasts, human embryonic kidney 293 cells, and Vero cells (Brydon et al. 2003; Wang et al. 2000) and enhanced apoptosis in MDCK, chicken fibroblasts, and chicken embryos (Zhirnov et al. 2002), although whether these pathways operate in influenza-infected airway epithelial cells is unclear.

Intrinsic pathways of apoptosis are dependent on the involvement of endogenous factors, such as cell stress, that initiate the cell death cascade. Avian influenza virus infection has been found to induce mitochondrial/cytochrome-C-mediated apoptotic pathways in human bronchial epithelial cells (Choi et al. 2006; Xing et al. 2010). Induced by interferons and activated by double-stranded RNA and cellular stress, PKR plays a role in both the extrinsic and intrinsic induction of cell death (Stark et al. 1998). Together with Fas antigen upregulation and increases in intracellular calcium and transforming growth factor-β (TGFβ), PKR activation has been linked to influenza-A-induced apoptosis (Schultz-Cherry et al. 1998; Takizawa et al. 1996). The influenza A virus protein neuraminidase activates latent TGFβ, which initiates apoptotic pathways (Schultz-Cherry and Hinshaw 1996). Recently, the influenza A virus M2 ion channel protein has been found to halt autophagosome degradation during the course of infection, a process that prolongs cell survival (Gannage et al. 2009).

Host cells recruited to the site of infection participate in the induction of apoptosis in the airway epithelium. Antigen-specific CD8+ T cells can use several different mechanisms to eliminate influenza-virus-infected targets, operating via the perforin/granzyme B, Fas/FasL, and

TRAIL pathways (Mirandola et al. 2004; Topham et al. 1997). Analysis of mRNA for TRAIL and its receptor DR-5 (TRAIL-R2) shows evidence of increased levels in lung tissue following influenza infection, and immune T cells, in particular, express TRAIL under such conditions (Yoneyama et al. 2005). Upregulation of DR5 has been confirmed for pulmonary epithelia, with the effect being approximately five times higher for directly infected cells, suggesting a mechanism for enhancing lysis via the TRAIL pathway (Brincks et al. 2008).

Different influenza A viruses have been found to vary in their capacity to induce epithelial cell death, both from the aspect of target cell type and efficiency. The 1918 H1N1, the H5N1, and the 2009 H1N1 influenza A viruses all cause epithelial cell destruction in the large airways plus diffuse alveolar damage, whereas the pathology characteristic of recent seasonal H3N2 and pre-2009 H1N1 viruses is more limited to the large airways, with less extension into the alveoli (Guarner and Falcon-Escobedo 2009; Gu et al. 2007). Cell death, particularly apoptosis, of airway epithelium during influenza virus infection is thought to serve multiple purposes in host protection. Apoptosis might function to decrease the magnitude of the disease process by removing the source of replicating virus. This will in turn both limit the further spread of the virus in the respiratory tract and decrease the levels of potentially damaging pro-inflammatory cytokines, a probable cause of severe outcomes (Cheung et al. 2002). However, the situation is not simple: the upregulation of TRAIL and FasL on human airway epithelial cells has been found to increase the efficiency of influenza A virus propagation, and epithelial cell death may also boost cytotoxic T lymphocyte function via the increased uptake of influenza-infected apoptotic bodies by antigen-presenting macrophages and DCs (Ludwig et al. 2006; Wurzer et al. 2004). Nevertheless, the death of cells that are vital for proper respiration is obviously not trivial, as respiratory failure might be a direct reflection of the extent of airway epithelial cell denudation. Thus, a proper balance needs to be struck in order to clear the virus with minimal damage to the host. Differences in the tropism and pathogenicity of influenza virus strains can evidently operate to skew this balance.

Recovery after infection

Extensive airway epithelial cell destruction is a frequent outcome of influenza virus infection. Given the vital function of these cells in homeostasis, host defense, and respiration, the regeneration of this cell population is required for host survival.

The wound healing response involves a complex mixture of specific cell types, proteins, and signaling pathways that operate in a highly regulated, timed, and cooperative manner to ensure the proper recovery of the epithelial cell layers and underlying basement membrane. The general healing response in any tissue comprises multiple overlapping phases, the staging of which may vary depending upon the extent of damage and the availability of key factors. The initial innate inflammatory process begins immediately following injury and continues for roughly 2–4 days. This overlaps, and is followed by, re-epithelialization, angiogenesis, matrix production, and matrix remodeling.

Fibroblasts can clearly play a part in maintaining the integrity of ATII cells. Both supernatants of fibroblast cultures and direct cell contact between the two populations function to increase ATII proliferation rates (Adamson et al. 1991). Keratinocyte growth factor (KGF), hepatocyte growth factor, and fibroblast growth factor-10, all members of the fibroblast growth factor family, contribute to airway epithelial repair processes (Ware and Matthay 2002). Of these, KGF is best documented to provide protection from injury and facilitation of the repair process. Derived mainly from fibroblasts, KGF promotes surfactant synthesis, fluid clearance, and the proliferation and migration of ATII cells (Atabai et al. 2002; Panos et al. 1993; Ulich et al. 1994; Wang et al. 1999; Yano et al. 2000).

Airway epithelial layers contain a variety of progenitors with regenerative potential, both for self-renewal and for other cell types. One issue to consider when thinking of epithelial repair during influenza recovery is that the nature of airway damage can influence the type of progenitor epithelial cell involved in the process (Kotton and Fine 2008). Moreover, the extent and duration of host tissue damage will influence the time needed for full recovery and, in turn, determine the extent of functional dysregulation (Didierlaurent et al. 2007; Goulding et al. 2007; Meneghin and Hogaboam 2007). The “decision” as to whether acute damage to the delicate alveoli can be corrected to full recovery, or whether the loss of structure is so extensive that there can be no restoration to function, may ultimately be dictated by the integrity of the basement membrane (BM; Strieter 2008). Four main structures dominate BM composition: entactin, laminin, perlecan, and type IV collagen (Charonis et al. 2005; West and Mathieu-Costello 1999). Additional to being a permeability barrier, the BM operates as a scaffold for cell adhesion, trafficking, spread, and the production cellular communication factors (Charonis et al. 2005; West and Mathieu-Costello 1999). Studies with models of chronic inflammation and epithelial/endothelial proteinases have found that diminished BM integrity contributes to inappropriate ATII re-epithelialization and defective re-endothelialization as a consequence of improper vascular remodeling and fibrosis, a combination that leads inexorably to the loss of alveolar structure and diminished lung function (Strieter 2005; Wallace et al. 2007; Keane et al. 2005; Treanor 2010).

Concluding remarks

The functional analysis of respiratory damage, including epithelial and endothelial cell physiology and repair pathways, has, for the most part, been confined to models of acute mechanical lung injury and asthma. Very little that is specific is known about repair following virus-induced lung damage, despite the important part such processes play in the resolution and ultimate clinical consequences of infection. The characteristic of early host immunity, including the participation of various secreted molecules and cell-cell interactions involving the epithelial, leukocytic, and lymphocytic compartments, probably have profound effects on the initiation, and then the resolution, of damage. The extent and duration of such a compromise will, in turn, depend upon the degree of functional and physical pathology and the effectiveness and rapidity of corrective recovery pathways. Future research focused on both understanding these processes and identifying novel targets for therapeutic interventions that mitigate influenza-associated morbidity and mortality is clearly worthwhile.

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