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Chapter 53

Virus Infection of Airway Epithelial Cells

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Chapter Outline

SUSCEPTIBILITY OF THE EPITHELIUM TO RESPIRATORY VIRAL INFECTION

The airway epithelium represents the first line of defense against viral infection of the lower respiratory tract, and several mechanisms are employed in the initial control of infection. Mechanical defense occurs through the combination of mucus production by secretory cells and mucus movement by ciliated cells that together clear viral particles from the respiratory tract via the mucociliary escalator (Knight and Holgate, 2003; Voynow and Rubin, 2009). In addition, healthy airway epithelium maintains an impermeable physical barrier to viral entry through cell–cell barriers that include tight junctions, adherens junctions, and desmosomes (Roche et al., 1993). These junctions function to limit submucosal spread and restrict access to specific viral receptors that may be present on the basolateral membrane (Bergelson, 2003). In addition, airway epithelial cells can release antimicrobial defensins that can prevent viruses from entering their target cells (Gong et al., 2010; Chong et al., 2008; Jiang et al., 2009).

Progressive improvements in viral detection methods have enabled better definition of common and emergent viruses as pathogens of the human respiratory tract. Some of the most common types of human viral pathogens include rhinoviruses (RVs), influenza A virus (IAV), parainfluenza virus (PIV), respiratory syncytial virus (RSV), adenovirus (AdV), metapneumovirus, coronavirus, and several enteroviruses (Debiaggi et al., 2012). Although rodents (including mice) are not generally the natural host for these types of viruses, there are well-characterized mouse models that take advantage of mouse-adapted viral strains to provide detailed analysis of immune pathways involved in the host response to respiratory viral infection (Oldstone, 2013). An example of this strategy is the use of mouse-adapted IAV strains that replicate efficiently even in rodent airway epithelial cells (O'donnell and Subbarao, 2011). Other human pathogens, such as RSV and RV, replicate inefficiently in the adult mouse (Graham et al., 1988; Yin and Lomax, 1986), so that studies of these viruses in the mouse model have significant limitations. Neonatal mice infected with both RSV and RV appear to develop at least some of the features of chronic airway disease found in humans and have therefore been pursued as suitable models of the disease process (You et al., 2006; Schneider et al., 2012). Even in these cases, however, replication of human viruses remains limited in mouse models and therefore makes it difficult to fully model the corresponding human condition. Accordingly, several laboratories (including ours) have turned to natural rodent pathogens to model the infectious process and its consequences for lung disease (Kohlmeier et al., 2008; Takamura et al., 2010; Walter et al., 2002). In particular, there is now a well-characterized mouse model that incorporates infection with mouse parainfluenza virus type 1 (mPIV-1), commonly known as Sendai virus (SeV). This approach has facilitated investigation of airway epithelial responses during acute viral infection and illness as well as a role for these responses in the development of chronic airway disease (Agapov et al., 2009; Byers et al., 2013; Grayson et al., 2007; Kim et al., 2008; Shornick et al., 2008).

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In addition to work on the host epithelial and immune responses to respiratory viral infection, there has been some definition of the first steps of viral entry into airway epithelial cells. However, specific viral entry mechanisms have been defined for only a few types of respiratory viruses, and even in these cases, there is only partial characterization of the viral entry mechanism. Influenza and PIV bind sialic acids present on epithelial surfaces through hemagglutinin proteins within the viral envelope, and this interaction mediates fusion with host cell membranes through cleavage by viral neuraminidases (reviewed in Luo (2012), Moscona (2005)). The molecular recognition of host glycans by variants of these viral receptors is a major determinant of host cell tropism (Suzuki et al., 2000; Markwell and Paulson, 1980; Ibricevic et al., 2006). Similarly, RSV attachment to epithelial cell surface glycosaminoglycans and viral fusion occur through glycoproteins G and F, respectively (Techaarpornkul et al., 2001). Recent structural elucidation of the RSV F protein in a prefusion state will enable better definition of this process and guide vaccine development (Mclellan et al., 2013). The major RV subgroups enter epithelial cells through intracellular adhesion molecule-1, whereas a minor group utilizes the low-density lipoprotein receptor (Greve et al., 1989; Tomassini et al., 1989; Marlovits et al., 1998). In contrast, AdVs gain entry only through disrupted epithelium via the coxsackievirus and AdV receptor, which is normally sequestered by tight junctions and therefore not accessible to the virus within an intact, mature airway epithelium (Cohen et al., 2001). Further studies of viral access and attachment are needed to develop better methods to prevent and disrupt viral infection.

ACUTE EPITHELIAL RESPONSES TO RESPIRATORY VIRAL INFECTION: INDUCING THE "ANTIVIRAL STATE"

Because epithelial cells are the initial portal of entry and site of replication for respiratory viruses, they are primed to respond to infection through distinct pattern recognition receptors (PRRs) and coordinated antiviral signaling programs. Similar to other surveillance cells in barrier tissues, epithelial cells express PRRs that are categorized into three major groups: Toll-like receptors (TLRs), retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs).

Toll-like receptors are a family of integral membrane proteins that recognize a wide variety of pathogen-associated molecular patterns (PAMPs) and signal through common Toll/interleukin-1 (IL-1) receptor domain-containing adaptor molecules (Kawai and Akira, 2010). Of the 13 known receptors, TLRs 3, 7, 8, and 9 appear to respond to virus-associated molecular patterns, specifically viral nucleic acids, with recognition occurring primarily within intracellular endosomes (Barton and Kagan, 2009). Each of these viral recognition TLRs is expressed on airway epithelial cells and is capable of inducing type I and III interferons as well as proinflammatory cytokines. TLR3 appears to be especially relevant to the response of airway epithelial cells to respiratory viruses, including RSV (Groskreutz et al., 2006), RV (Hewson et al., 2005; Kato et al., 2007), and IAV (Guillot et al., 2005). Virus-associated ligands have been identified for TLRs 7, 8, and 9 (double- and single-stranded RNA and CpG DNA, respectively) (Diebold et al., 2004; Heil et al., 2004; Hemmi et al., 2000; Triantafilou et al., 2011), though their specific roles in the response to viral infection remain less certain. One particular question is the relative role of the epithelial TLR system in controlling infection during acute illness versus inflammation during chronic disease, and further studies are under way to address this issue.

RIG-I and the related melanoma differentiation-associated protein 5 (MDA-5) are RNA helicases that also recognize viral nucleic acids, specifically double- and single-stranded RNA, respectively (Yoneyama et al., 2004; Gitlin et al., 2006; Kato et al., 2006). In contrast to TLRs, the RLR group of sensors recognize intracellular viral RNA within the cytoplasm and signal through caspase recruitment domains as well as the adaptor mitochondrial antiviral signaling protein (MAVS/IPS-1/VISA/Cardif) to induce interferon regulatory factor 3 (IRF-3) and subsequent interferon production (Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005). MDA-5 has been reported to sense small RNA viruses, such as RV, whereas RIG-I recognizes negative-sense single-stranded viral RNAs, such as IAV and RSV (Kato et al., 2006). However, MDA-5 can also specifically protect against SeV in mice (Gitlin et al., 2010), suggesting that RLR-dependent recognition may be more generally used for defense against respiratory viral infection.

NLRs have been more recently recognized as an important component of the initial epithelial response to viral infection (Ichinohe et al., 2009; Thomas et al., 2009). For example, the NOD-like receptor protein 3 (NLRP3) inflammasome complex (Lamkanfi and Dixit, 2012) provides a signal for procaspase-1 activation and subsequent processing and release of select IL-1 family cytokines, including IL-1β and IL-18, that mediate paracrine signals to neighboring cells (Muruve et al., 2008). It is still uncertain whether NLRP3 functions as a PRR directly or mediates a signal through other PRRs in any system, including the airway epithelial barrier (Allen et al., 2009).

PRR pathways lead to activation of several transcription factors, namely NF-κB, IRF-3, and IRF-7, which induce interferon production and signaling and the consequent establishment of a cellular "antiviral state" (Levy and Garcia-Sastre, 2001; Samuel, 2001; Schoggins and Rice, 2011). Type I interferon is produced in a biphasic pattern via early IRF-3 and late IRF-3 and IRF-7 activation and autocrine/paracrine IFN-α/β signaling through the interferon receptor complex (IFNAR-1 and -2) (Iversen and Paludan, 2010). Type III

interferons can be induced either by a combination of IRF-3 and -7 (IFN-λ1) or predominantly by IRF-7 (IFN-λ2, -3) (Osterlund et al., 2007) and appear to act specifically on epithelial cells (Sommereyns et al., 2008). Type III interferons distinctly signal through a complex that includes the IL-10 receptor β chain and interferon-λ receptor-1 chain (Kotenko et al., 2003; Sheppard et al., 2003). However, both type I and type III interferons activate Janus kinase/signaling transducer and activator of transcription signaling pathways and induce the expression of interferon-stimulated genes (ISGs). These ISGs orchestrate cellular processes aimed at inhibiting viral replication directly or stimulating immune cell recruitment and programmed death of infected cells to prevent viral dissemination (Der et al., 1998). Viruses such as RSV and IAV have been shown to induce specific type I and III interferon response patterns in airway epithelium (Jewell et al., 2007; Ioannidis et al., 2012; Okabayashi et al., 2011). Among the genes induced in airway epithelial cells are several cytokines that function in proinflammatory, anti-inflammatory, and reparative processes during infection. The role of epithelial cytokines in the normal host response to respiratory viral infection and in the development of virus-associated chronic airway disease is developed in the next section.

ACUTE EPITHELIAL RESPONSES TO RESPIRATORY VIRAL INFECTION: CYTOKINE NETWORKS IN NORMAL HOST DEFENSE

In addition to interferons, several other cytokines are secreted by airway epithelial cells to recruit immune cell populations and orchestrate innate and adaptive responses to viral infection. Well-studied responses of airway epithelial cells include production of pleiotropic cytokines such as IL-6, IL-1α/β, IL-18, and tumor necrosis factor-α as well as growth factors such as granulocyte/macrophage and granulocyte colony-stimulating factors that directly recruit immune cell populations and mediate activation of proinflammatory cytokine cascades ((Shornick et al., 2008; Piper et al., 2013), and reviewed in Bals and Hiemstra (2004), Diamond et al. (2000), Kato and Schleimer (2007), Schleimer et al. (2007), Shaykhiev and Bals (2007)). Other cytokines, such as IL-15, IL-17C, and IL-12 can be released by epithelial cells in response to viruses or virus-associated PAMPs to activate T cells and T cell subsets, natural killer (NK) cells, dendritic cells (DCs), macrophages, and at least some types of epithelial cells themselves (Ramirez-Carrozzi et al., 2011; Pfeifer et al., 2013; Verbist and Klonowski, 2012; Rajan et al., 2013; Zdrenghea et al., 2012; Walter et al., 2001).

Chemokines are also potently produced by airway epithelial cells to recruit specific immune populations. During the early postinfection phase, epithelial cell-derived CXCL8 is released to recruit neutrophils (Choi and Jacoby, 1992; Johnston, 1995; Turner, 1988) and CCL20 to recruit DCs (Wareing et al., 2007; Kallal et al., 2010; Grayson et al., 2007). During subsequent adaptive responses, additional immune cell subsets are recruited, with CXCL9, CXCL10, CCL5, and CCL28 primarily attracting T cells and NK cells (Spurrell et al., 2005; Saito et al., 1997; Groom and Luster, 2011; Grayson et al., 2007), CCL2 and CCL5 recruiting monocytes (Herold et al., 2006; Schneider et al., 2013), and CCL3, CCL5, CCL11, and CCL24 recruiting eosinophils (Van Wetering et al., 2007; Lukacs et al., 1996; Papadopoulos et al., 2001). CCL5 may also act as a survival factor for lung macrophages during respiratory viral infection, and this function is critical for viral clearance and host survival (Tyner et al., 2005).

ACUTE EPITHELIAL RESPONSES TO RESPIRATORY VIRAL INFECTION: T-HELPER TYPE 2 (TH2)-ASSOCIATED CYTOKINES

In addition to cytokines that are conventionally linked to antiviral function, it also appears that airway epithelial cells (and perhaps epithelial barrier cells in general) can express cytokines with the capacity to regulate Th2-polarized mucosal immune responses (Saenz et al., 2008). These cytokines include the IL-17 family member IL-25 (IL-17E), IL-1 family member IL-33 (IL-1F11, NF-HEV), and IL-7 family member thymic stromal lymphopoietin (TSLP). Each of these cytokines has been shown to promote development of type 2 immune responses (Paul and Zhu, 2010). Because these cytokines can be expressed even at baseline in the epithelial cell barrier, it appears that mucosal surfaces are primed to release these cytokines under infectious or inflammatory conditions. Although the receptors for IL-25, IL-33, and TSLP are widely expressed on immune cell populations, the precise roles of these cytokines in the antiviral response are uncertain. To support such roles, investigators have shown that RSV and TLR3 agonists increase TSLP expression in primary culture airway epithelial cells (Lee et al., 2012; Calven et al., 2012; Qiao et al., 2011; Kato et al., 2007). Other labs have shown that TSLP induces protective antiviral T cell responses to control RSV and IAV through enhancement of DC function (Han et al., 2012; Yadava et al., 2013), although some labs found no requirement for TSLP in the responses to IAV (Plumb et al., 2012). Lung epithelial cells also express IL-25 particularly in response to allergen (Angkasekwinai et al., 2007), but any role for IL-25 in the acute epithelial response to viral infection has not yet been described. In studies of transgenic mice, investigators showed that IL-33 is widely expressed in epithelial barriers at baseline, being easily detectable in skin, lung, vagina, and gastrointestinal tract (Pichery et al., 2012). IL-33 is unusual in possessing dual function as both a nuclear factor and a cytokine (Carriere et al., 2007). Similar to TSLP, IL-33 derived from a nonhematopoietic source has been implicated in protective antiviral T cell responses

to control RNA and DNA virus replication in mice (Bonilla et al., 2012). However, this study did not include common respiratory viruses, and a more recent analysis showed no difference in viral titer, histology, or body weight loss using the SeV model and IL-33-deficient mice (Byers et al., 2013).

Precisely how these cytokines are released from epithelial cells to engage their cognate receptors on the surface of immune cells remains enigmatic, but most probably occurs through a nonclassical secretory mechanism (Malhotra, 2013). IL-33 had been previously ascribed the function of an "alarmin," being stored within the nucleus of cells at mucosal barriers and released upon cell damage to activate local inflammatory cells (Moussion et al., 2008). However, this functional description requires modification, as more recent data suggest that both IL-33 and IL-25 may in fact be released by a regulated mechanism from intact cells in response to PAMPs or signals of cellular stress (Kouzaki et al., 2011, 2013; Byers et al., 2013). Unraveling the basis for IL-33 release from epithelial cells in response to virus-associated stimuli and whether the mechanism is shared among related and distinct cytokines will require further study.

INTERPLAY BETWEEN VIRUS INFECTION, EPITHELIAL TYPE 2 CYTOKINES, AND THE DEVELOPMENT OF CHRONIC AIRWAY DISEASE

Chronic obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are characterized by a long-term inflammatory process that may be linked to viral infection (Holgate et al., 1992; Holtzman, 2012). In asthma, the airway inflammation often includes at least some component of a type 2 immune response, with IL-4, IL-5, and/or IL-13 production that is classically associated with allergy (reviewed in Schuijs et al. (2013), Byers and Holtzman (2011)). In fact, animal models that involve specific allergen challenge are routinely used to define the underlying immune basis for this type of disease in humans (Zosky and Sly, 2007; Stevenson and Belvisi, 2008). These models have been useful for studying asthma; however, they utilize antigenic stimuli and/or sensitization protocols that may not incorporate the role of infection in the airway disease process (Kumar and Foster, 2012; Stevenson and Birrell, 2011).

In fact, there is a strong relationship between respiratory viral infection and initiation, exacerbation, and progression of asthma and COPD in studies of human patients (Papadopoulos et al., 2011; De Serres et al., 2009; Papi et al., 2007; Busse et al., 2010). Similarly, respiratory viral infection can induce persistent type 2 inflammation in susceptible strains of mice, and the associated airway disease exhibits characteristic features of human asthma and COPD (Buchweitz et al., 2007; Hashimoto et al., 2004; Walter et al., 2002; You et al., 2006; Schneider et al., 2012). Thus, a more physiologically relevant paradigm for the study of chronic airway disease should incorporate the role of viral infection as the stimulus for development and/or exacerbation of disease. In the mouse model of chronic airway disease that develops after mPIV-1 (SeV) infection, a long-term type 2 immune response is responsible for driving IL-13 production and consequent airway mucus production and hyperreactivity (Walter et al., 2002; Kim et al., 2008; Tyner et al., 2006). During the acute infectious phase of this model, DC-derived CCL28 recruits IL-13-producing $CD4^+$ T cells to sites of infection (Grayson et al., 2007). However, in the subsequent weeks an innate immune program emerges that involves semi-invariant natural killer T (NKT) cells and Th2-polarized monocytes and macrophages that develop independent of an adaptive immune response (Kim et al., 2008). Interactions between monocyte/macrophage CD1d and NKT cell TCR-β result in amplified lung production of IL-13 that persists for months. Sustained production of IL-13 drives airway epithelial production of mucus that also continues long after clearance of infectious virus.

Because IL-13 is a potent stimulus for airway mucus production (Wills-Karp et al., 1998; Zhen et al., 2007; Alevy et al., 2012) and a target for inhibition in asthma (Corren et al., 2011), there has been considerable interest in identifying the factors that control IL-13 production. As introduced above, IL-25, IL-33, and TSLP are candidates to control IL-13 levels in epithelial cell barriers in many clinical settings, including asthma and COPD (Moffatt et al., 2010; Prefontaine et al., 2010; Wang et al., 2007; Ying et al., 2005; Calven et al., 2012). Antibody blockade and targeted gene deficiency have been used extensively to study the role of type 2 cytokines in allergic lung disease and helminth infection (Oliphant et al., 2011; Monteleone et al., 2010; Omori-Miyake and Ziegler, 2012; Smith, 2011). However, few studies have focused on the roles of these cytokines in respiratory viral infection or the postviral airway disease that develops after this type of infection. One study showed increased expression of TSLP in airway epithelial cells isolated from asthmatic subjects and suggested a role for TSLP in driving RSV-induced Th2 cells and associated pathology in mice (Lee et al., 2012). Similarly, others found increased TSLP production due to RV infection in primary culture bronchial epithelial cells (Calven et al., 2012). In addition, it was reported that IL-33 receptor (T1/ST2/IL-1RL1) signaling promoted a skewed Th2 cell response to RSV in RSV-G-primed mice (Walzl et al., 2001). More recent work has identified a type 2 innate lymphoid cell (ILC2) population that responds to IL-33 and IL-25 by producing IL-13 and IL-5 ((Scanlon and Mckenzie, 2012), reviewed in (Spits et al., 2013; Hwang and Mckenzie, 2013)). This ILC2 population is activated in response to allergen challenge and helminth infection, but the role of these cells during respiratory viral infection is less certain. One group suggested that IL-33-producing

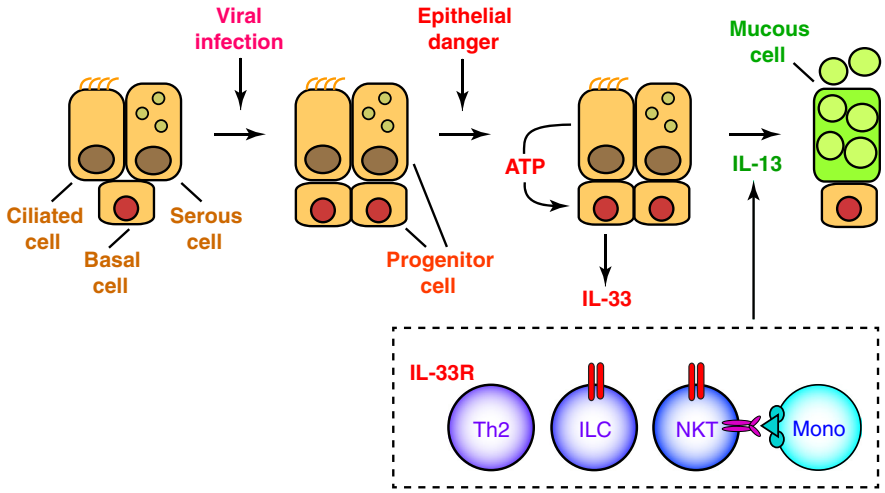

FIGURE 1 Scheme for IL-33/IL-13 immune axis in chronic obstructive lung disease. Respiratory viral infection leads to an increase in lung epithelial progenitor cells (airway basal cells in humans and perhaps airway serous cells and alveolar type 2 cells in mice) that are programmed for increased IL-33 expression. Subsequent epithelial danger signals stimulate ATP-regulated release of IL-33 that acts on immune cells in the lung, e.g., $CD4^+$ T helper type 2 cells (Th2), innate lymphoid cells (ILC), and semi-invariant NKT cells (NKT) with interacting monocytes and macrophages (Mono) to stimulate IL-13 production and consequent mucous cell metaplasia. *Reprinted from Byers et al. (2013), with permission.*

alveolar macrophages and IL-33-responsive ILCs drive airway hyperreactivity that develops after IAV infection in mice (Chang et al., 2011). However, other work indicates that IL-33 is derived from airway epithelial progenitor cells in the setting of chronic inflammatory disease that develops after SeV infection in mice (Byers et al., 2013). Moreover, a homologous IL-33-expressing population of airway epithelial progenitor cells was also found in patients with COPD who manifest chronic airway disease. Together, these results have provided for a proposed scheme in the development of chronic obstructive lung disease that might be initiated or exacerbated by respiratory viral infection (Figure 1). Under this scheme, viral infections might skew airway epithelial cell programming toward a renewable source of IL-33 production and release and therefore increased susceptibility to long-term inflammatory disease.

CONCLUDING REMARKS

The airway epithelial barrier is especially situated and wired to respond to respiratory viral infection. Epithelial cells are particularly designed to produce and respond to cytokines that regulate the downstream immune cell trafficking and activation that results in viral clearance. Under most circumstances, these events are probably necessary for antiviral immunity, although formal proof of an essential role for airway epithelial cells in host defense still needs to be rigorously established. In some cases, however, specific viruses and host genetic susceptibility can lead to an airway epithelial response that is skewed toward type 2 immunity and the activation of innate and perhaps adaptive immune pathways that lead to chronic airway inflammation and characteristic features of chronic obstructive lung disease. Epithelial-derived cytokines are central to this inflammatory process and appear to derive from a multipotent, self-renewing population of airway progenitor cells that can perpetuate the disease process. Further studies are needed to determine the precise basis for this type of epithelial cell programming and whether it is linked to specific viral or host factors. Together, this work could provide a new paradigm for airway epithelial cell function that includes an essential role in normal antiviral defense and a pathogenic role in the development of chronic inflammatory lung disease.

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