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Current Opinion in Virology

Recent insights into pulmonary repair following virus-induced inflammation of the respiratory tract

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A hallmark of infection by respiratory viruses is productive infection of and the subsequent destruction of the airway epithelium. These viruses can also target other stromal cell types as well as in certain instances, CD45$^+$ hematopoietic cells either resident in the lungs or part of the inflammatory response to infection. The mechanisms by which the virus produces injury to these cell types include direct infection with cytopathic effects as a consequence of replication. Host mediated damage is also a culprit in pulmonary injury as both innate and adaptive immune cells produce soluble and cell-associated pro-inflammatory mediators. Recently, it has become increasingly clear that in addition to control of excess inflammation and virus elimination, the resolution of infection requires an active repair process, which is necessary to regain normal respiratory function and restore the lungs to homeostasis. The repair response must re-establish the epithelial barrier and regenerate the microarchitecture of the lung. Emerging areas of research have highlighted the importance of innate immune cells, particularly the newly described innate lymphoid cells, as well as alternatively activated macrophages and pulmonary stem cells in the repair process. The mechanisms by which respiratory viruses may impede or alter the repair response will be important areas of research for identifying therapeutic targets aimed at limiting virus and host mediated injury and expediting recovery.

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Current Opinion in Virology 2012, **2**:233–241

This review comes from a themed issue on
Viral pathogenesis
Edited by Diane Griffin and Veronika von Messling

Available online 17th May 2012

1879-6257/$ – see front matter

http://dx.doi.org/10.1016/j.coviro.2012.04.006

Introduction

The respiratory tract (RT) is a dynamic organ whose role in gas exchange is vital for life. Because a large volume of air is exchanged by the lungs (i.e. up to 10 L/min), the lungs are continuously exposed to microbial and chemical insults [1]. The importance of respiratory viruses (RV) as a major threat to mankind is evidenced by the outbreak of infection by the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), the sporadic human infections with high pathogenic avian H5N1 influenza, and the recent pandemic caused by swine origin influenza H1N1 infection. As more and more evidence has emerged, it is becoming increasingly clear that the pathogenicity associated with RV infection reflects not only the efficiency of virus replication and the tropism of a given virus/strain for particular cell types within the RT but also the magnitude and characteristics of the host anti-viral immune response. Recovery from RV infection requires the elimination of virus/virus-infected cells, the resolution of injury-associated inflammation, and importantly, cellular and molecular repair mechanisms necessary for restoration of normal lung structure and function. This review will first briefly summarize virus and host immune mediated damage to the RT and then focus on recent findings implicating specific cell types in repair and recovery from pulmonary injury following RV infection.

Virus induced respiratory tract inflammation and injury

A variety of RT cell types can potentially serve as targets of infection by RV. These include lung resident cells, most notably: firstly, airway and alveolar respiratory epithelial cells (REC) whose destruction (or dysregulation) can, if severe, compromise respiratory function and secondly, hematopoietic origin (bone marrow-derived CD45$^+$) inflammatory and immune cells which can, like virus, induce tissue damage and compromise lung function potentially triggered following infection of RT resident or recruited CD45$^+$ cells by certain RV (Table 1). For example, SARS-CoV and Type A Influenza virus (IAV) can productively infect certain REC types triggering extensive necrosis and apoptosis of infected cells which in turn results in the accumulation of cellular debris leading to edema and mucous production within the airways [2••,3]. SARS-CoV has been reported to have a cellular tropism either for alveolar REC or more recently, respiratory epithelial stem cells involved in REC regeneration (see below) [4–6]. SARS-CoV exploits the angiotensin-converting enzyme 2 (ACE2), a negative regulator of the renin–angiotensin system for blood pressure homeostasis, as a receptor for entry into epithelial cells

Table 1

Direct effects of virus infection on respiratory tract target cells

Target Cell:	Primary Effect:	Direct Consequences:
Respiratory Epithelium	**Cell Death** (i.e. Apoptosis/Necrosis)	- Accumulation of Cellular Debris - Compromised Lung Function and Gas Exchange - Loss of Barrier Function & Epithelial Integrity - Stimulation (or Suppression) of Epithelial Stem Cell Response
	Induction of Innate Viral Recognition Pathways (e.g. PAMP Receptors)	- Anti-Viral State - Cytokine/Chemokine/IFN Production - Mucus Production
Hematopoietic Cells (e.g. Macrophages, Neutrophils, RDCs)	**Cell Death** (i.e. Apoptosis/Necrosis)	- Accumulation of Cellular Debris - Inhibition of Viral Clearance
	Induction of Innate Viral Recognition Pathways (e.g. PAMP Receptors)	- Activation/Maturation (e.g. RDCs, Macrophages) - Anti-Viral State - Cytokine/Chemokine/IFN Production - Reduced Immune Suppression (e.g. Alveolar Macrophages)
	Migration (e.g. Macrophages, RDCs)	- Induction of Adaptive Immune Responses - Systemic Spread (i.e. H5N1, SARS-CoV)

PAMP = pathogen associated molecular pattern; RDCs = respiratory dendritic cells.

[7,8]. Subsequent downregulation of ACE2 expression following SARS-CoV infection of REC has been linked to increased lung edema and severe acute lung injury [7,9,10].

In most instances, productive infection of REC by RV is necessary for virus propagation and as a consequence, contributes to RT inflammation/injury. However, infection of bone marrow-derived $CD45^+$ RT resident cells (e.g. respiratory dendritic cells (RDCs)) and recruited inflammatory myeloid lineage cells (e.g. inflammatory mononuclear cells and possibly neutrophils) may profoundly influence the course and ultimate outcome of RV infection [11,12•]. Both SARS-CoV and highly pathogenic avian H5N1 IAV can productively infect cells of hematopoietic origin, which may account for the propensity of these agents to leave the RT and disseminate systemically [13–15]. RV infection of resident RDC and alveolar macrophages results in the engagement of intracellular pathogen associated molecular pattern (PAMP) receptors (e.g. TLR and/or RLR) and initiates robust cytokine production [11,16]. Of note, the infection of RDC by IAV may also be a pivotal step for the activation of the $CD8^+$ T lymphocyte response [17]. However, one or more subsets of RT resident RDC, notably RDC expressing CD103 may be specialized to take up viral antigen without infection and efficiently initiate an adaptive immune response [18]. Interestingly, alveolar macrophages, through a mechanism dependent on TLR3 engagement, inhibit RDC activation during SARS-CoV infections, which in turn results in lymphopenia and prolongation of virus-induced inflammation [19•]. During the evolution of virus infection, infection of or at least viral antigen uptake by $CD45^+$ inflammatory cells in the infected RT may also serve as a potent stimulus for the development of an excessive host immune response through interaction of these RV antigen expressing inflammatory cells with adaptive immune effector T lymphocytes [20,21•].

Host immune mediated respiratory tract inflammation and injury

Engagement of epithelial and hematopoietic cell PAMP receptors by viral proteins and nucleic acids during infection upregulates a number of chemoattractant mediators (e.g. MCP-1 and KC), which recruit various innate immune cell types. While contributing to viral clearance, these innate immune cells are also notable for their role in promoting pulmonary tissue damage [11,16,22,23]. Excessive accumulation of neutrophils and inflammatory mononuclear cells (a heterogeneous cell type encompassing monocytes and TNF/inducible nitric oxide synthase producing DCs (tipDCs)) is strongly correlated with severe lung pathology in cases of human SARS-CoV, avian influenza, and respiratory syncytial virus (RSV) infections [24–26]. In murine models of RV infection, however, it is clear that the extent of inflammatory cell infiltration into the RT alone is not the sole factor accounting for host-mediated pulmonary injury [27••,28]. Rather, RT damage is linked to the characteristics of the soluble and cell-associated inflammatory mediators produced or expressed by innate immune cells (Table 2). Release of soluble factors by phagocytic cells (e.g. pro-inflammatory cytokines and free radicals) can damage bystander un-infected cells in addition to infected cell targets resulting in excessive pulmonary tissue damage [29,30•]. Also, inflammatory mononuclear cells express the surface molecule TNF-related apoptosis-inducing ligand (TRAIL) which can induce apoptosis in cells expressing the corresponding ligand(s) as can occur in IAV infection [31•]. Because un-infected REC express TRAILs, albeit at lower levels than

Table 2

Immune mediators of pulmonary injury during respiratory virus infection

Soluble mediators	Cell-associated mediators
Chemokines - for example, MCP-1, MIP1α, KC - Leukocyte recruitment	Fas ligand - Expressed by pDCs, T cells - Induce epithelial cell apoptosis
Cytokines - for example, IL-1, IL-6, TNF - Induce epithelial cell apoptosis - Fever promotion - Trigger mucous production - Stimulate cytokine release	Perforin/granzymes - Expressed by T cells, NK cells - Induce epithelial cell apoptosis - Stimulate cytokine release
Interferon - for example, IFNα, IFNβ, IFNγ, IFNλ - Induce epithelial cell apoptosis - MHC upregulation - Stimulate cytokine release	TRAIL - Expressed by inflammatory mononuclear cells, T cells - Induce epithelial cell apoptosis
Proteases - for example, MMP, plasminogen - Disrupt extracellular matrix - Promote viral replication	
Free radicals - for example, H_2O_2, NO^-, O_2^- - Induce epithelial cell apoptosis	

KC (CXCL1) = keratinocyte derived chemokine; MCP-1 (CCL2) = monocyte chemoattractant protein-1; MHC = major histocompatibility complex; MIP1a (CCL3) = macrophage inflammatory protein-1; MMP = matrix metalloproteinases; pDCs = plasmacytoid dendritic cells; TRAIL = TNF-related apoptosis-inducing ligand 2.

IAV-infected alveolar REC, inflammatory mononuclear cells have the potential to indiscriminately eliminate REC, contributing to increased airway permeability and alveolitis. While exuberant neutrophil and inflammatory mononuclear cell accumulation and activation does enhance pulmonary inflammation and excess mortality in murine models of IAV infection, the depletion or absence of these innate immune effector cells can paradoxically result in augmented tissue damage, possibly reflecting the contribution of these innate immune cells directly to IAV clearance or feedback control of the host immune response [32–36]. Thus, not surprisingly, the role of innate immune cells in virus clearance and/or tissue damage in the RT undoubtedly represents a complex interplay between the host and the particular infecting RV. Thus, there is a delicate balance between the extent of accumulation of innate immune cells in the infected RT and the activation state of the cells, which is in part controlled by the properties of the infecting RV.

The adaptive immune response to primary RV infection consists of infiltrating antigen-specific T lymphocytes and humoral immunity. These adaptive immune components gain access to the RT several days post infection and typically are associated with RV clearance. As with innate immune cell types, T lymphocytes employ a variety of soluble and cell-associated mediators that contribute to RV elimination and inflammation (see Table 2). $CD8^+$ T lymphocytes, and to a lesser extent $CD4^+$ T lymphocytes, employ cell-associated mediators (e.g. perforin/granzyme, FasL) to trigger apoptosis in target cells [21•,37]. Since cytolysis induction requires engagement of the T lymphocyte antigen receptor by the viral peptide/MHC molecule complexes, T cell-mediated apoptosis is largely limited to the RV-infected cells. With one notable exception [38], T lymphocyte mediated cytolysis is considered to play a minor role in the development of tissue injury produced by adaptive immune cells during RV infection [39,40]. In contrast, T cell derived soluble inflammatory mediators (e.g. TNF, MIP-1α, IFNγ) can damage uninfected cells within the RT and augment the infiltration of injury-promoting innate immune cells. The extent of this pro-inflammatory cytokine production may ultimately be determined by viral tropism of infiltrating $CD45^+$ inflammatory cells. Our laboratory and others have recently noted that co-stimulation, along with antigen, is required to drive effector T cell pro-inflammatory cytokine responses and proliferation within the RT during IAV infections [20,21•,41]. Because co-stimulatory molecule expression is principally limited to hematopoietic cells, the ability of a particular RV to infect these recruited $CD45^+$ inflammatory cells may be an important factor in determining the extent of adaptive immune mediated tissue damage during RV infection.

Factors regulating pulmonary inflammation

The factors controlling the extent of pulmonary inflammation during RV infection have been recently reviewed [42,43]. For adaptive immune cells, it is the encounter of the antigen receptor with its target viral antigen that ultimately controls the number and function of these cells. Likewise for innate immune cells, it is the presence of mediators produced by responding adaptive cells and/or engagement of intracellular sensors within innate immune cells in the infected RT by viral PAMPs that regulates the response of these effector cells. Therefore, it is the cessation of virus replication and the elimination of viral antigen that is the primary factor controlling both host and virus induced injury and inflammation. Furthermore, the downregulation of co-stimulatory receptors/ligands on immune cells and the upregulation of inhibitory receptors (e.g. NKG2A, CD200R) and their ligands on $CD45^+$ immune cells (and in some cases $CD45^-$ REC) may be important factors in controlling excess inflammation during respiratory viral infections [44–46].

There is also important regulatory elements within the immune response that dampen ongoing inflammation during RV infection. First, a number of regulatory cytokines are produced to attenuate an inflammatory response. Effector T lymphocytes, in conjunction with

their production of pro-inflammatory cytokines, have been noted to produce high levels of the regulatory cytokine IL-10 during IAV and RSV infections [47,48•,49]. Blockade of IL-10 signaling during the effector T cell phase of influenza infection increases pro-inflammatory cytokine production and mortality [48•]. In addition, release of active TGF-β can reduce inflammation and increase survival during RV infection [50,51]. As another facet for inflammation resolution, $Foxp3^+$ regulatory T (Treg) cells can dampen anti-viral responses, notably in RSV and IAV infections, by regulating the extent of adaptive immune responses within the RT [52–56]. Thus, regulatory elements within the anti-viral immune response and eventual viral clearance ultimately curtail the extent of pulmonary inflammation. The subsequent steps of repairing and re-modeling the RT following RV infections, however, are not as fully understood and appreciated.

Re-establishing the epithelial barrier and maintaining barrier integrity

A hallmark of RV infection is replication of virus in and the subsequent destruction of the airway epithelium. Therefore, by necessity, the repair of the epithelium is essential for recovery. The stages of airway repair have been studied in great detail for a variety of chemically induced injury models [57,58]; however, the unique set of conditions imposed by RV infection (e.g. viral load and the tropism of a given RV for a particular RT cell type) can potentially modify the repair process in ways that are not well understood.

New research has highlighted the importance of initiating and maintaining a proper repair response during and following respiratory virus infection and has demonstrated a renewed interest in an active repair process, rather than simply a passive dampening of inflammation.

RV infection, including IAV and SARS-CoV, results in large numbers of apoptotic and necrotic epithelial cells, leaving denuded basement membranes of the upper and/or lower airways. In addition to virus-induced cell death, infiltrating leukocytes secrete large quantities of matrix metalloproteinases (MMP) that damage and degrade the basement membranes of the endothelium and epithelium, which results in the loss of the microarchitecture of the conducting airways and alveoli. Therefore, the lung must initiate a robust repair response to reconstitute the extracellular matrix, return to homeostasis, and rebuild barrier function. Furthermore, impaired repair processes in the RV-infected lung may also enhance susceptibility to secondary microbial infection.

The restoration of the respiratory epithelium following injury can be divided into three sequential stages: provisional matrix deposition, epithelial proliferation, and epithelial differentiation. In order for new epithelial cells to regenerate, fibroblasts and epithelial cells surrounding the infected foci secrete a provisional matrix made predominantly of the structural protein fibronectin [59]. TGFβ, another potent stimulator of the fibro-proliferative response, is released by virally infected epithelial cells [60], which can subsequently stimulate secretion of provisional matrix proteins from fibroblasts and other non-hematopoietic cell types. Upon completion, the newly formed extracellular matrix can provide a platform for epithelial progenitor cells to proliferate and give rise to new epithelial cells that can regenerate those lost to infection. A myriad of factors regulate pulmonary epithelial proliferation, most notably TGFβ [58]. It was recently found that the transcription factor Elf3 is an upstream inducer of TGFβII receptor expression and important for bronchiolar airway cell proliferation [61]. Finally, once the cells have proliferated to cover the denuded areas, they then receive signals (e.g. Notch-dependent and Smad-dependent signaling) to differentiate into the specific cell types found within the airways [62–64]. Thus, there are many pathways that converge to mount a proper repair response in the infected RT; however, emerging studies have highlighted the role of the innate immune system and distinct stem cell populations in this process.

The role of the innate immune system: the second act

Although the innate immune system plays a clear role in the induction of inflammation and injury associated with RV infection during the acute phase, a number of studies have demonstrated the importance of innate immune cells, particularly of the newly described family of innate lymphoid cells (ILC), to the maintenance and regeneration of mucosal epithelia.

Lymphoid tissue inducer (LTi) cells, first described as $CD3^-CD4^+$ lineage negative cells, are important for the development of lymphoid tissues via the production of lymphotoxins [65–67]. Recently, they have been shown to secrete the 'tissue-protective' cytokine IL-22 in adult mice [68]. IL-22 levels are reduced in the IAV-infected lung; however, levels return to baseline immediately following virus clearance from the lung [69]. Although IL-22 does not seem to have any direct anti-viral properties in the lung, it does stimulate pulmonary epithelial cells to upregulate antibacterial genes, such as lipocalin-2, and may be essential for resistance against many Gram negative bacterial pneumonia [70]. IL-22 can also protect airway epithelial cells from apoptosis, which is correlated with increased levels of the anti-apoptotic genes *Bcl2* and *Bcl2l1* [71]. Thus, IL-22 may be an important factor in maintaining the epithelial barrier. LTi-like cells, which are phenotypically similar to LTi cells but also express the NK cell receptor NKp46 in adults (often referred to as NKR^+LTi, ILC22, or NK22), are also potent producers of IL-22. To date, ILC22 cells have been best described in the intestinal lamina propria but can be found in the liver and mesenteric lymph nodes [72]. However, as more is

learned about inducible bronchi associated lymphoid tissue (iBALT) [73,74], ILC2*2* cells may very well be found within these structures in the lungs and contribute to repair. NK cell receptor (CD161)-expressing innate lymphoid cells have also been identified in humans; however, these cells functionally more resemble the innate lymphoid cell type 2 [75], described below.

As another member of the innate lymphoid family, natural helper cells or innate lymphoid cell type 2 (ILC2), were variously described by several groups [76••,77–79]. These ILC2 are potent producers of type 2 cytokines, namely IL-5 and IL-13. Although originally described in fat associated lymphoid clusters [76••], these ILC2 have been identified in many organs including the spleen, bone marrow, and various regional lymph nodes. Of interest, a relatively large number are also found within the RT [78,80]. The ability of these cells to secrete large quantities of IL-5 and IL-13 (on the order of 30 ng per 5000 cells) has made them a target for limiting virus induced asthma exacerbations [81]. However, ILC2 are also essential for epithelial integrity, lung function, and proper airway remodeling during IAV infection via their secretion of the epidermal growth factor ligand, amphiregulin [82•]. Amphiregulin can limit lung inflammation during bleomycin-induced injury [83]; however, this new demonstration of its role in actively participating in and/or regulating airway repair following RV infection merits further research. In addition to amphiregulin, it is also formally possible that ILC2 are secreting other factors that directly or indirectly modulate the repair response. ILC2 are early producers of the type 2 cytokine IL-9 [84], which although a culprit in asthma and allergy, can protect epithelial cells from apoptosis by upregulating *Bcl2* [85]. ILC2 are located near the bronchi and bronchioles [80] and thus are well situated to mediate the repair response following a RV infection. ILC2 produce large amounts of IL-5 and IL-13 when stimulated by IL-33 or IL25. IL-33 is present in the IAV-infected lung, with the predominant sources being necrotic epithelial cells [86], alveolar macrophages [81], and NKT cells (Gorski and Braciale; unpublished observation). Thus, IL-33 may be the signal to initiate ILC2 into the repair phase. Whether IL-25 has a direct role in RV infection, outside of virus induced asthma exacerbation [87], is not yet clear.

The propensity of innate immune cells to produce predominantly type 2 cytokines in order to orchestrate a pulmonary repair response rather than simply exacerbate asthma is not outside the realm of possibilities. Type 2 immune responses can also be thought of as a reparative response [88]. Type 2 immune responses largely depend on signaling through the IL-4R alpha chain. Both IL-4 and IL-13 signal through IL-4Ra, and mice deficient in IL-4Ra have delayed wound repair responses [89,90]. In addition, IL-13 is highly pro-fibrotic, which when present in small amounts and under tight regulation, may be able to promote a repair response, particularly in generating a provisional matrix. Signaling through the IL-4Ra via IL-4 and/or IL-13 is also important for the generation of alternatively activated macrophages (so-called 'M2' macrophages) [91]. M2 are known to be anti-inflammatory and involved in tissue repair in a variety of injury models [92]. M2 express a set of signature molecules including arginase, Ym1/Chi3I3, Fizz1, and MRC1. Arginase in particular is known to be involved in the synthesis of collagen [93] and thus may again be important in provisional matrix deposition. M2 expressing arginase and Ym1 are significant contributors to lung fibrosis, but this effect is dependent on the pro-inflammatory $Ly6C^{hi}$ monocytic subset [94]. Therefore, in the right context (i.e. in the absence of strong inflammation as occurs following virus clearance in the lung), M2 may have a role to play in promoting a reparative response. In support of this hypothesis, M2 generation during RSV infection was found to limit inflammation, and in their absence, there was sustained epithelial cell damage in the infected lung [95•]. The generation of M2 during RSV infection was found to be IFNβ dependent, which was essential for regulating IL-4, IL-13, and IL-4Ra expression, thereby providing a link between RV infection and the induction of M2. Thus, viruses that inhibit the interferon response, such as IAV and RSV, could potentially interfere with the proper repair response via inhibition of M2 generation [96].

Activating stem cells

The epithelial proliferation and differentiation phase of repair requires the presence of a pulmonary progenitor cell that is either resident in the lung or recruited following RV infection. These progenitor cells give rise to the specialized epithelial cells that will regenerate on the denuded areas of the lung. Interest in the role of stem cell activation following RV infection has increased recently with the better characterization of region-specific stem cell populations that can regenerate different cell types of the lung. The factors that regulate pulmonary stem cells, both their activation and/or recruitment, are not well understood, and the study of this population is further complicated by the lack of defined surface markers.

Multi-potent progenitor cell populations, such as 'bronchioalveolar stem cells (BASC)' have been identified in the lung [97]. These cells have been described as $CD45^{-}CD31^{-}CD34^{+}Sca\text{-}1^{+}$, although many groups maintain that this set of markers represent a heterogeneous population of stem cells that differentially give rise to various lung cell types [98,99]. BASC have been characterized as being able to repopulate both bronchiolar and alveolar epithelia [97,100]; however, recent studies show that distinct progenitor cells can exist for both of these regions as well as the trachea [2••,101,102]. Of relevance, SARS-CoV has been shown to infect BASC and therefore, could potentially contribute to virus-induced pathology via

a mechanism that inhibits pulmonary repair [103]. Since many RV have the ability to infect the lower airways, in the case of severe disease, understanding the mechanisms of how BASC and/or other regional stem cell populations are regulated is paramount to expediting the repair response.

In support of the regional specific stem cell populations, Kumar *et al*. found that following H1N1 influenza infection of mice, $p63^+$ progenitor cells, which are thought to mark basal cells in the trachea [104,105], begin forming clusters around damaged foci into distinct keratin 5^+ ($Krt5^+$) pods [2••]. Within these pods, distal airway stem cells (DASCs), distinct from the upper airway stem cell populations, are capable of differentiating into cells that appear to be of alveolar lineage. What factors and mediators control the DASC differentiation event are not known. This becomes of further importance during secondary bacterial infection, particularly following the 2009 H1N1 influenza pandemic, where loss of epithelial repair mechanisms was shown to be a major contributor to pathogenesis, as opposed to a heightened inflammatory response [106].

Summary

A part of RV pathogenesis is damage to lung epithelium, either directly or via immune-induced damage, and in the process, viruses can impede epithelial repair mechanisms. The absence of a proper repair response can lengthen morbidity and can certainly contribute to an increase in mortality. Understanding the mechanisms that contribute to an appropriate reparative response following RV infection will undoubtedly provide insight about the inappropriate (i.e. over-exuberant, disregulated, or prolonged) repair response that leads to pulmonary fibrosis or asthma exacerbations. We argue that an active repair process, which includes the cooperative action of innate immune cells and regional stem cells that maintains barrier integrity under homeostatic conditions and reestablishes it in the event of epithelial loss associated with RV infection, must be considered to be an essential part of the overall host response to both RV and other infections of the RT.

Acknowledgements

We would like to thank the members of the Braciale laboratory, in particular T.S. Kim, for their insight and editorial assistance. This work was supported by grants from the National Institutes of Health (RO1 AI-15608, RO1 AI-37293, RO1 HL-33391, and U19AI-83024) to T.J. Braciale and a training grant award to S.A. Gorski.

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