Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Recent insights into pulmonary repair following virus-induced inflammation of the respiratory tract

Stacey A Gorski\(^1,2,4\), Matthew M Hufford\(^1,2,4\) and Thomas J Braciale\(^1,2,3\)

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.

Addresses
\(^1\)Beine B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908, USA
\(^2\)Department of Microbiology, University of Virginia, Charlottesville, VA 22908, USA
\(^3\)Department of Pathology, University of Virginia, Charlottesville, VA 22908, USA
\(^4\)Authors contributed equally to this manuscript.

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.
[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

| 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.
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 cells, 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 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 IL-25. 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-4Rα, and mice deficient in IL-4Rα 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/Chi3L3, 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 ‘bronchialveolar stem cells (BASC)’ have been identified in the lung [97]. These cells have been described as CD45^-CD31^-CD34^-Sca-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 epithelium [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 in distinct keratin 5 (Krt5)+[238] pods [239]. 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 (ROI AI-15608, ROI AI-37293, ROI HL-33391, and U19AI-83024) to T.J. Braciale and a training grant award to S.A. Gorski.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Kohlmeier JE, Woodland DL: Immunity to respiratory viruses. Annu Rev Immunol 2009, 27:61-82.

2. Kumar PA, Hu Y, Yamamoto Y, Hoe NB, Wei TS, Mu D, Sun Y, •• Joo LS, Dagher R, Zielonka EM et al.: Distal airway stem cells yield alveoli in vitro and during lung regeneration following H1N1 influenza infection. Cell 2011, 147:525-538.

This paper nicely demonstrates the existence of distal airway stem cells that can regenerate alveoli following IAV infection.

3. Roberts A, Deming D, Paddock CD, Cheng A, Yount B, Vogel L, Herman BD, Sheahain T, Heise M, Gennrich GL et al.: A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog 2007, 3:e5.

4. Chen Y, Chan VS, Zheng B, Chan KY, Xu X, To LY, Huang FP, Khoos US, Lin CL: A novel subset of putative stem/progenitor CD34+Oct-4+ cells is the major target for SARS coronavirus in human lung. J Exp Med 2007, 204:2529-2536.

5. Ling TY, Kuo MD, Li CL, Yu AL, Huang YH, Wu TJ, Lin YC, Chen SH, Yu J. Identification of pulmonary Oct-4+ stem/progenitor cells and demonstration of their susceptibility to SARS coronavirus (SARS-CoV) infection in vitro. Proc Natl Acad Sci U S A 2006, 103:9530-9535.

6. Nicholls JM, Butany J, Poon LL, Chan KH, Beh SL, Poutanen S, Peiris JS, Wong M: Time course and cellular localization of SARS-CoV nucleoprotein and RNA in lungs from fatal cases of SARS. PLoS Med 2006, 3:e27.

7. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W et al.: A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005, 11:875-879.

8. Li W, Moore MJ, Vasilevna N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC et al.: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003, 426:450-454.

9. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H et al.: Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005, 436:112-116.

10. Li X, Molina-Molina M, Abdul-Hafez A, Uhal V, Xaubet A, Uhal BD: Angiotensin converting enzyme-2 is protective but downregulated in human and experimental lung fibrosis. Am J Physiol Lung Cell Mol Physiol 2008, 295:L178-L185.

11. Hao X, Kim TS, Braciale TJ: Differential response of respiratory dendritic cell subsets to influenza virus infection. J Virol 2008, 82:4906-4919.

12. Manicassamy B, Manicassamy S, Belicha-Villanueva A, • Pisanelli G, Pulendran B, Garcia-Sastre A: Analysis of in vivo dynamics of influenza virus infection in mice using a GFP reporter virus. Proc Natl Acad Sci U S A 2010, 107:11531-11536. This paper details susceptible cell types within an IAV-infected mouse lung utilizing a novel GFP reporter IAV strain.

13. Spiegel M, Schneider K, Weber F, Weidmann M, Hufert FT: Interaction of severe acute respiratory syndrome-associated coronavirus with dendritic cells. J Gen Virol 2006, 87:1953-1960.

14. Thitithyanont A, Engering A, Ekchariyawat P, Wiloboon-sut S, Limsalakpetch A, Yongvanitchit K, Kum-Arb U, Kanchongkittiphon W, Utaiasinchareon P, Sirisinha S et al.: High susceptibility of human dendritic cells to avian influenza H5N1 virus infection and protection by IFN-alpha and TLR ligands. J Immunol 2007, 179:5220-5227.

15. Wang SF, Huang JC, Lee YM, Liu SJ, Chan YJ, Chau YP, Chong P, Chen YM: DC-SIGN mediates avian H5N1 influenza virus infection in cis and in trans. Biochem Biophys Res Commun 2008, 373:561-566.

16. Herold S, von Wulfen W, Steinmueller M, Pleschka S, Kuziel WA, Mack M, Srivastava M, Seeger W, Maus UA, Lohmeyer J: Alveolar epithelial cells direct monocyte transepithelial migration upon influenza virus infection: impact of chemokines and adhesion molecules. J Immunol 2006, 177:1817-1824.

17. Molledo B, Li W, Yount JS, Moran TM: Unique type I interferon responses determine the functional fate of migratory lung dendritic cells during influenza virus infection. PLoS Pathog 2011, 7:e1002345.

18. Kim TS, Braciale TJ: Respiratory dendritic cell subsets differ in their capacity to support the induction of virus-specific cytotoxic CD8+ T cell responses. PLoS ONE 2009, 4:e4204.
19. Zhao, J., Zhao, J., Van Rooijen, N., Perlman, S.: Evasion by stealth:
• inefficient immune activation underlies poor T cell response and severe disease in SARS-CoV-infected mice. PLoS Pathog 2009, 5:e1000636.
This study highlights a potential mechanism for lymphopenia associated with SARS-CoV infection.

20. Dolfi DV, Duttagupta PA, Boeuestau AC, Mueller YM, Oliai CH, Borowski AB, Katsakis PD. Dendritic cells and CD8+ T cell responses during the effector phase in vivo. J Immunol 2011, 186:4599–4608.

21. Hufford MM, Kim TS, Sun J, Braciale TJ: Antiviral CD8+ T cell
• effector activities in situ are regulated by target cell type. J Exp Med 2011, 208:167–180.
This study demonstrates that CD45+CD11chi cells during IAV infection drive CD8+ T lymphocyte IFNγ production in vivo in a mechanism dependent on co-stimulation.

22. Bonville CA, Bennett NJ, Koehnlein M, Haines DM, Ellis JA, DeVecchio AM, Rosenberg HF, Domachowske JB: Respiratory dysfunction and proinflammatory chemokines in the pneumonia virus of mice (PVM) model of viral bronchiolitis. Virology 2006, 349:87–95.

23. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN: House dust mite allergens induce asthma via Toll-like receptor 4 triggering of airway structural cells. Nat Med 2009, 15:410–416.

24. Bem RA, Domachowske JB, Rosenberg HF: Animal models of human respiratory syncytial virus disease. Am J Physiol Lung Cell Mol Physiol 2011, 301:L148-L156.

25. Cleri DJ, Ricketti AJ, Varnaio JR: Severe acute respiratory syndrome (SARS). Infect Dis Clin North Am 2010, 24:175-202.

26. Xu T, Qiao J, Zhao L, Wang G, He G, Li K, Tian Y, Gao M, Wang J, Wang H et al.: Acute respiratory distress syndrome induced by avian influenza A (H5N1) virus in mice. Am J Respir Crit Care Med 2006, 174:1011-1017.

27. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, • Martinborough E, Peach R, Oldstone MB, Rosen H: Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell 2011, 146:380-391.
This paper highlights the regulation of immune system pre-inflammatory cytokine and chemokine production during IAV infection by type I interferon and endothelial cells.

28. Walsh KB, Teijaro JR, Wilker PR, Jatzek A, Fremgen DM, Das SC, Watanabe T, Hatta M, Shinya K, Suresh M et al.: Suppression of cytokine storm with a saponoside analog provides protection against pathogenic influenza virus. Proc Natl Acad Sci U S A 2011, 108:12018-12023.

29. Jayasekara JP, Vinuesa CG, Karupiah G, King NJ: Enhanced antiviral antibody secretion and attenuated immunopathology during influenza virus infection in nitric oxide synthase-2-negative mice. J Gen Virol 2006, 87:3361-3371.

30. Lin KL, Suzuki Y, Nakano H, Ramsburg E, Gunn MD: CCR2-
• monocyte-derived dendritic cells and exudate macrophages produce influenza-induced pulmonary immune pathology and mortality. J Immunol 2008, 180:2562-2572.
This paper nicely details macrophage cell types present in the IAV-infected lung and the role of inflammatory mononuclear cells during infection.

31. Herold S, Steinmueller M, von Wulffen W, Cakarova L, Pinto R, • Plesschka S, Mack M, Kuzel WA, Corazza N, Brunner T et al.: Lung epithelial apoptosis in influenza virus pneumonia: the role of macrophage-expressed TNF-related apoptosis-inducing ligand. J Exp Med 2008, 205:3065-3077.
This study demonstrates the role of TRAIL in inflammatory mononuclear cell mediated viral clearance, alveolar leakage, and enhanced mortality associated with IAV infection.

32. Aldridge JR Jr, Moseley CE, Boltz DA, Negovetch NJ, Reynolds C, Franks J, Brown SA, Doherty PC, Webster RG, Thomas PG: TNF/ INOS-producing dendritic cells are the necessary evil of lethal influenza virus infection. Proc Natl Acad Sci U S A 2009, 106:5306-5311.

33. Dessing MC, van der Slujs KF, Florquin S, van der Poll T: Monocyte chemoattractant protein 1 contributes to an adequate immune response in influenza pneumonia. Clin Immunol 2007, 128:328-336.

34. Narasaratju T, Ng HH, Phoon MC, Chow VT: MCP-1 antibody treatment enhances damage and impedes repair of the alveolar epithelium in influenza pneumonia. Am J Respir Cell Mol Biol 2010, 42:732-743.

35. Tate MD, Deng YM, Jones JE, Anderson GP, Brooks AG, Reading PC: Neutrophils ameliorate lung injury and the development of severe disease during influenza infection. J Immunol 2009, 183:7441-7450.

36. Tumpey TM, Garcia-Sastre A, Taubenberger JK, Palese P, Swayne DE, Panin-Jackwood MJ, Schultz-Cherry S, Solorzano A, Van Rooijen N, Katz JM et al.: Pathogenicity influenza viruses with genes from the 1918 pandemic virus: functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. J Virol 2005, 79:14933-14944.

37. Brown DM, Ditzer AM, Meents DL, Swain SL: CD4 T cell-mediated protection from lethal influenza: perforin and antibody-mediated mechanisms give a one-two punch. J Immunol 2006, 177:2888-2898.

38. Bem RA, van Woensel JB, Lutter R, Domachowske JB, Medema JP, Rosenberg HF, Bos AP: Granzyme A- and B-cluster deficiency delays acute lung injury in pemuenovirus-infected mice. J Immunol 2010, 184:931-938.

39. Bruder D, Srikatkhachorn A, Enelow RI: Cellular immunity and lung injury in respiratory virus infection. Viral Immunol 2006, 19:147-155.

40. La Gruta NL, Kedzierska K, Stambas J, Doherty PC: A question of self-preservation: immunopathology in influenza virus infection. Immunol Cell Biol 2007, 85:85-92.

41. McGill J, Van Rooijen N, Legge KL: IL-15 trans-presentation by pulmonary dendritic cells promotes effector CD8 T cell survival during influenza virus infection. J Exp Med 2010, 207:521-534.

42. Kim TS, Sun J, Braciale TJ: T cell responses during influenza infection: getting and keeping control. Trends Immunol 2011, 32:225-231.

43. Snelgrove RJ, Godlee A, Huston T: Airway immune homeostasis and implications for influenza-induced inflammation. Trends Immunol 2011, 32:328-334.

44. Ryljei TP, Rijkers ES, de Ruiter T, Stolte EH, van der Valk M, Rimmelzaan GF, Boon L, van Loon AM, Coenjaerts FE, Hoen RM et al.: Lack of CD200 enhances pathological T cell responses during influenza infection. J Immunol 2009, 183:1990-1996.

45. Snelgrove RJ, Goulding J, Didierlaurent AM, Lyonga D, Vekaria S, Edwards L, Gwyer E, Sedgwick JD, Barclay AN, Huston T: A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. Nat Immunol 2008, 9:1074-1083.

46. Zhou J, Matsuoka M, Cantor H, Homer R, Enelow RI: Cutting edge: engagement of NKp2A on CD8+ effector T cells limits immunopathology in influenza pneumonia. J Immunol 2008, 180:25-29.

47. Sun J, Cardani A, Sharma AK, Laubach VE, Jack RS, Muller W, Braciale TJ: Autocrine regulation of pulmonary inflammation by effector T-cell derived IL-10 during infection with respiratory syncytial virus. PloS Pathog 2011, 7:e1002173.

48. Sun J, Madan R, Karp CL, Braciale TJ: Effector T cells control • lung inflammation during acute influenza virus infection by producing IL-10. Nat Med 2009, 15:277-284.
The first paper to demonstrate effector T lymphocyte production of the regulatory cytokine, IL-10, during respiratory virus infection.

49. Weiss KA, Christiaansen AF, Fulton RB, Meyerholz DK, Varga SM: Multiple CD4+ T cell subsets produce immunomodulatory IL-10 during respiratory syncytial virus infection. J Immunol 2011, 187:3143-3154.

50. Carlson CM, Turpin EA, Moser LA, O’Brien KB, Cline TD, Jones JC, Tumpey TM, Katz JM, Gauldie J et al.: Transforming growth factor-beta: activation by neuraminidase and role in
highly pathogenic H5N1 influenza pathogenesis. PLoS Pathog 2010, 6:e1001136.

51. Williams AE, Humphreys IR, Cornere M, Edwards L, Rae A, Russell T: TGF-beta prevents eosinophilic lung disease but
impairs pathogen clearance. Microbes Infect 2005, 7:365-374.

52. Antunes I, Kassiotis G: Suppression of innate immune
pathology by regulatory T cells during Influenza A virus
infection of immunodeficient mice. J Virol 2010, 84:12564-12575.

53. Betts RJ, Prabhu N, Ho AW, Lew FC, Hutchinson PE, Rotzscheke O, Macary PA, Kemeny DM: Influenza A virus infection results in a
robust, antigen-responsive and widely disseminated Foxp3+
regulatory T cell response. J Virol 2011.

54. Fulton RB, Meyerholz DK, Varga SM: Foxp3+CD4 regulatory T
cells limit pulmonary immunopathology by modulating the
CD8+ T cell response during respiratory syncytial virus
infection. J Immunol 2010, 185:2382-2392.

55. Lee DC, Harker JA, Tregoning JS, Atabani SF, Johansson C, Schwarze J, Ospenhau PJ: CD25+ natural regulatory T cells are
critical in limiting innate and adaptive immunity and resolving
disease following respiratory syncytial virus infection. J Virol 2010, 84:8790-8798.

56. Ruckwardt TJ, Bonaparte KL, Nason MC, Graham BS: Regulatory T cells promote early influx of CD8+ T cells in the
lungs of respiratory syncytial virus-infected mice and diminish immunodominance disparities. J Virol 2009, 83:3019-3028.

57. Beens MF, Morrisey EE: The three R’s of lung health and
disease: repair, remodeling, and regeneration. J Clin Invest
2011, 121:2065-2073.

58. Crosby LM, Waters CM: Epithelial repair mechanisms in the lung. Am J Physiol Lung Cell Mol Physiol 2010, 298:L715-L731.

59. Herard AL, Pierrot D, Hinrnsnky J, Kaplan H, Sheppard D, Puchelle E, Zahn JM: Fibronectin and its alpha 5 beta 1-integrin
receptor are involved in the wound-repair process of airway epithelium. Am J Physiol 1996, 271:L728-L733.

60. Roberson EC, Tully JE, Guala AS, Reiss JN, Godburn KE, Pociask DA, Alcorn JF, Riches DW, Dizier O, Janssen-
Heininger YM et al.: Influenza induces ER stress, caspase-12-
dependent apoptosis and JNK mediated TGF-beta release in
lung epithelial cells. Am J Respir Cell Mol Biol 2011.

61. Oliver JR, Kushwah R, Wu J, Pan J, Cutz E, Yeger H, Waddell TK, Hui J: Eif2a plays a role in regulating bronchial epithelial repair
kinetics following Clara cell-specific injury. Lab Invest 2011, 91:1514-1529.

62. Buckley S, Shi W, Barsky L, Warburton D: TGF-beta signaling
promotes survival and repair in rat alveolar epithelial type 2
cells during recovery after hyperoxic injury. Am J Physiol Lung
Cell Mol Physiol 2008, 294:L739-L748.

63. Rock JR, Gao X, Xue Y, Randell SH, Kong YY, Hogan BL: Notch-
dependent differentiation of adult airway basal stem cells. Cell
Stem Cell 2011, 8:639-648.

64. Rogel MR, Sori PN, Treon JR, Stitkov A, Trejo HE, Ridge KM:
Vimentin is sufficient for required wound repair and
remodeling in alveolar epithelial cells. FASEB J 2011, 25:3873-3883.

65. Mebius RE, Rennert P, Weismann IL: Developing lung nodes
collect CD4+CD3-LTbeta+ cells that can differentiate to APC,
NK cells, and follicular cells but not T or B cells. Immunity 1997, 7:531-534.

66. Yokota Y, Mansouri A, Mori S, Sugawara S, Adachi S, Nishikawa S, Gruss P: Development of peripheral lymphoid organs and
natural killer cells depends on the helix-loop-helix inhibitor
Id2. Nature 1999, 397:702-706.

67. Fukuyama S, Hiroi T, Yokota Y, Rennert PD, Yanagita M,
Kinoshita N, Terawaki S, Shikina T, Yamamoto M, Kuroko Y et al.: Initiation of NALT organogenesis is independent of the IL-7R,
LTbetaR, and TGF-beta signaling pathways but requires the Id2
gene and CD3(−)CD4+(−)CD45(+) cells. Immunity 2002, 17:31-40.

68. Sonnenberg GF, Fouser LA, Artis D: Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier
surfaces by IL-22. Nat Immunol 2011, 12:383-390.

69. Guo H, Topham DJ: Interleukin-22 (IL-22) production by
pulmonary Natural Killer cells and the potential role of IL-22
during primary influenza virus infection. J Virol 2010, 84:7750-7759.

70. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA,
Reinhart TA, McAllister F, Edeal J, Gaus K et al.: IL-22 mediates
mucosal host defense against Gram-negative bacterial pneumonia. Nat Med 2008, 14:275-281.

71. Sonnenberg GF, Nair MG, Kim TJ, Zaph C, Fouser LA, Artis D: Pathological versus protective functions of IL-22 in airway
inflammation are regulated by IL-17A. J Exp Med 2010, 207:1293-1305.

72. Sanos SL, Vonarbourg C, Mortha A, Diefenbach A: Control of epithelial cell function by interleukin-22-producing
ROPr gammam+ innate lymphoid cells. Immunology 2011, 132:453-465.

73. Moyron-Quiroz JE, Rangel-Moreno J, Kusser K, Hartson L, Sprague F, Goodrich S, Woodland DL, Lund FE, Randall TD: Role of
inducible bronchus associated lymphoid tissue (iBALT) in
respiratory immunity. Nat Med 2004, 10:927-934.

74. Rangel-Moreno J, Carragher DM, de la Luz Garcia-Hernandez M, Hwang JY, Kusser K, Hartson L, Kolls JK, Khader SA, Randall TD: The
development of inducible bronchus-associated lymphoid tissue
depends on IL-17. Nat Immunol 2011, 12:639-646.

75. Mjøsberg JM, Truffi S, Crellin NK, Peters CP, van Drunen CM, Piet B, Fokkens WJ, Cupedo T, Spits H: Human IL-25- and IL-9-
responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol 2011, 12:1055-1062.

76. Moro K, Yamada T, Tanabe M, Takeuchi I, Ikawa T, Kawamoto H, Furusawa J, Ohtani M, Fuji H, Koyasu S: Innate production of
T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. Nature 2010, 463:549-554.

77. Elegant demonstration of the existence of natural helper cells and their production of type 2 cytokines.

78. Neill DR, Wong SH, Bellios A, Flynn RJ, Daly M, Langford TK, Bucks C, Kane CM, Fallon PG, Pannell R et al.: Nuocytes
represent a new innate effector leukocyte that mediates type-
2 immunity. Nature 2010, 464:1367-1370.

79. Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, Locksley RM. Systemically dispersed innate IL-13-expressing
cells in type 2 immunity. Proc Natl Acad Sci U S A 2010, 107:11489-11494.

80. Saenz SA, Siracusa MC, Perrigueu JG, Spencer SP, Urban JF Jr, Tocke JR, Budeisky AL, Kleinschek MA, Kastelein RA, Kambayashi T et al.: IL-25 elicits a multipotent progenitor cell
population that promotes T(H)2 cytokine responses. Nature 2010, 464:1362-1366.

81. Itakura M, Yanagibashi T, Ogasawara M, Tsuneyama K, Yamamoto S, Hatton Y, Kouro T, Ikura A, Nagai Y, Takaki S et al.: Identification of innate IL-5-producing cells and their role in lung eosinophil regulation and antitumor immunity. J Immunol 2012, 188:703-713.

82. Chang YJ, Kim HY, Albacker LA, Baumgart N, McKenzie AN, Smith DE, Dekryuyt RH, Umematu DT: Innate lymphoid cells
mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. Nat Immunol 2011, 12:631-638.

83. Monticelli LA, Sonnenberg GF, Abt MC, Allegnkat T, Ziegler CG,
• Deering TA, Angelosanto JM, Laidlaw BJ, Yang CY, Sathalihawala T et al.: Innate lymphoid cells promote lung-
tissue homeostasis after infection with influenza virus. Nat Immunol 2011, 12:1045-1054.

84. First demonstration of ILC2 producing factor other than type 2 cytokines that is important for lung homeostasis.

85. Fukumoto J, Harada C, Kawaguchi T, Suetsugu S, Maeyama T, Inoshima I, Hamada N, Kuwano K, Nakanishi Y: Amphiregulin
attenuates bleomycin-induced pneumonia in mice. Am J
Physiol Lung Cell Mol Physiol 2010, 298:L131-L138.
Recent insights into pulmonary repair following virus infection

Gorski, Hufford and Braciale 241

84. Wilhelm C, Hirota K, Stiegitz B, Van Snick J, Tolaini M, Lahl K, Sparwasser T, Helmbry H, Stockinger H: An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. Nat Immunol 2011, 12:1071-1077.

85. Singhera GK, MacRedmond R, Dorscheid DR: Interleukin-9 and -13 inhibit spontaneous and corticosteroid induced apoptosis of normal airway epithelial cells. Exp Lung Res 2008, 34:579-598.

86. Le Goffic R, Anshad MI, Rauch M, L’Helgoualc’h A, Delmas B, Piquet-Pellorce C, Samson M: Infection with influenza virus induces IL-33 in murine lungs. Am J Respir Cell Mol Biol 2011, 45:1125-1132.

87. Kalko GE, Phipps S, Angkasekwinai P, Dong C, Foster PS: NK cell deficiency predisposes to viral-induced Th2-type allergic inflammation via epithelial-derived IL-25. J Immunol 2010, 185:4681-4690.

88. Allen JE, Wynn TA: Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. PLoS Pathog 2011, 7:e1002003.

89. Chen F, Liu Z, Wu W, Rozo C, Bowbridge S, Millman A, Van Rooijen N, Urban JF Jr, Wynn TA, Gause WC: An essential role for T(H)2-type responses in limiting acute tissue damage during experimental helminth infection. Nat Med 2012, 18:260-266.

90. Loke P, Gallagher I, Nair MG, Zang X, Brombacher F, Mohrs M, Allison JP, Allen JE: Alternative activation is an innate response to injury that requires CD4+ T cells to be sustained during chronic infection. J Immunol 2007, 179:3926-3936.

91. Gordon S, Martinez FO: Alternative activation of macrophages: mechanism and functions. Immunity 2010, 32:593-604.

92. Varin A, Gordon S: Alternative activation of macrophages: immune function and cellular biology. Immunobiology 2009, 214:630-641.

93. Hesse M, Modell M, La Flamme AC, Schito M, Fuentes JM, Cheever AW, Pearce EJ, Wynn TA: Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-arginine metabolism. J Immunol 2001, 167:6533-6544.

94. Gibbons MA, MacKinnon AC, Ramachandran P, Dhaliwal K, Duffin R, Phyrnan-Adams AT, van Rooijen N, Haslett C, Howie SE, Simpson AJ et al.: Lyf6Chi monocytes directly alternatively activated probiotic macrophage regulation of lung fibrosis. Am J Respir Crit Care Med 2011, 184:569-581.

95. Shirey KA, Pletnev AA, Puche AC, Keegan AD, Prince GA, Blanco JC, Vogel SN: Control of RSV-induced lung injury by alternatively activated macrophages is IL-4R alpha-, TLR4-, and IFN-beta-dependent. Mucosal Immunol 2010, 3:291-300. Alternatively activated macrophages limit tissue damage during RSV infection of mice.

96. Snten AP, Taylor RH, Lei W, Campbell SA, Tipper JL, Martinez MJ, Witt TL, Clay CC, Harrod KS: Respiratory syncytial virus impairs macrophage IFN-alpha/beta- and IFN-gamma-stimulated transcription by distinct mechanisms. Am J Respir Cell Mol Biol 2010, 42:404-414.

97. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, Crowley D, Bronson RT, Jacks T: Identification of bronchoalveolar stem cells in normal lung and lung cancer. Cell 2005, 121:823-835.

98. Teisalu RM, Lagasse E, Whitesides JF, Stripp BR: Prospective isolation of bronchiolar stem cells based upon immunophenotypic and autofluorescence characteristics. Stem Cells 2009, 27:612-622.

99. McQuater JL, Brouard N, Williams B, Baird BN, Sims-Lucas S, Yuen K, Nilsson SK, Simmons PJ, Bertoccelli I: Endogenous fibroblastic progenitor cells in the adult mouse lung are highly enriched in the sca-1 positive cell fraction. Stem Cells 2009, 27:623-633.

100. Nolen-Walston RD, Kim CF, Mazan MR, Ingento EP, Gruntman AM, Tsai L, Boston R, Woolfenden AE, Jacks T, Hoffman AM: Cellular kinetics and modeling of bronchoalveolar stem cell response during lung regeneration. Am J Physiol Lung Cell Mol Physiol 2008, 294:L1158-L1165.

101. Rawlins EL, Okubo T, Xue Y, Bragg DM, Auten RL, Hasegawa H, Wang F, Hogan BL: The role of Scgp1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. Cell Stem Cell 2009, 4:525-534.

102. Rock JR, Onatis MW, Rawlins EL, Lu Y, Clark CP, Xue Y, Randell SH, Hogan BL: Basal cells as stem cells of the mouse trachea and human airway epithelium. Proc Natl Acad Sci USA 2009, 106:12771-12775.

103. Mallick B, Ghosh Z, Chakrabarti J: MicroRNA analysis unravels the molecular basis of SARS infection in bronchoalveolar stem cells. PLoS ONE 2009, 4:e7837.

104. Daniely Y, Liao G, Dixon D, Linnoila RI, Lori A, Randell SH, Oren M, Jetten AM: Critical role of p63 in the development of a normal esophageal and tracheobronchial epithelium. Am J Physiol Cell Physiol 2004, 287:C171-C181.

105. Senoo M, Pinto F, Crum CP, McKeon F: p63 is essential for the proliferative potential of stem cells in stratified epithelia. Cell 2007, 129:523-536.

106. Kash JC, Walters KA, Davis AS, Sandauk A, Schwartzman LM, Jagger BW, Chertow DS, Li O, Kuestner RE, Ozinsky A et al.: Lethal synergism of 2009 pandemic H1N1 influenza virus and Streptococcus pneumoniae coinfection is associated with loss of murine lung repair responses. mBio 2011:2.