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T Cell Responses during Acute Respiratory Virus Infection

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Abstract

The T cell response is an integral and essential part of the host immune response to acute virus infection. Each viral pathogen has unique, frequently nuanced, aspects to its replication, which affects the host response and as a consequence the capacity of the virus to produce disease. There are, however, common features to the T cell response to viruses, which produce acute limited infection. This is true whether virus replication is restricted to a single site, for example, the respiratory tract (RT), CNS etc., or replication is in multiple sites throughout the body. In describing below the acute T cell response to virus infection, we employ acute virus infection of the RT as a convenient model to explore this process of virus infection and the host response. We divide the process into three phases: the induction (initiation) of the response, the expression of antiviral effector activity resulting in virus elimination, and the resolution of inflammation with restoration of tissue homeostasis.

Lung Dendritic Cells and Control of T Cell Activation and Initial Differentiation

While the respiratory tract (RT) contains various cell types that support the productive infection and replication of viral pathogens, these cells often provide the first line of defense against a broad array of common respiratory viral pathogens such as influenza A virus (IAV), respiratory syncytial virus (RSV), rhinovirus, and coronaviruses (i.e., severe acute respiratory syndrome coronavirus (SARS-CoV)) (Table 1). Initially envisioned as a passive barrier between the host and the environment, the cell types comprising the RT represent an active robust immune surveillance system. These cells include epithelial cells (e.g., ciliated cells, club cells, goblet cells, and type I and II alveolar cells), bone marrow origin (CD45⁺) innate immune cells (e.g., alveolar macrophages (AM), natural killer T (NKT) cells etc.) as well as highly specialized CD45⁺ professional antigen-presenting cells (APCs), the dendritic cells (DCs), which are distributed throughout the conducting airways, alveoli, and the lung parenchyma (reviewed in Braciale et al., 2012; Holt et al., 2008; Lambrecht and Hammad, 2012).

DCs are essential for efficient antigen presentation to T cells and therefore play a pivotal role in initiating the immune response to foreign antigens (e.g., viral pathogens). They also serve a companion function in the maintenance of tolerance to self-antigens. As in other body surfaces (gut and skin), the lung contains two major types of DCs – conventional DCs (cDCs) and plasmacytoid DCs (pDCs) (Braciale et al., 2012; Neyt and Lambrecht, 2013). cDCs are further grouped into two distinct subsets: (1) cDC1 which further expresses cell surface markers characteristic of their localization to lymphoid tissue (i.e., CD8 α) or nonlymphoid tissue (i.e., CD103) and (2) cDC2 which expresses CD11b (CD11b⁺ cDC) independent of tissue localization.

Following viral infection of the RT, one of the most important functions of cDC is the capture of antigens derived from the virus for delivery to the site of induction of adaptive immune responses, the lung-draining lymph node (DLN) (Lambrecht and Hammad, 2012; Legge and Braciale, 2003; Lukens et al., 2009; Varga and Braciale, 2013; Figure 1). The lung-resident DC ‘samples’ the inhaled foreign materials and pathogens entering the airways. The sampling activity of cDCs depends primarily on their anatomical distribution within the lung. CD103⁺ cDCs are localized mainly at the basolateral side of the epithelial layer. To sample antigens they extend dendrites into the lumen of the alveoli and conducting airways. CD11b⁺ cDCs localize primarily to and sample the deeper RT sites below the epithelium (i.e., submucosal and interstitial sites) (Neyt and Lambrecht, 2013; Sung et al., 2006). Following an inflammatory stimulus like virus infection, these viral antigen-bearing, activated cDCs then leave the virus-infected lung and emigrate in a CCR7-dependent manner via the lymphatics to the DLN (Kim and Braciale, 2009; Heer et al., 2008; Figure 1).

Early data supported the concept of a dichotomy among cDC subsets in driving either CD4 or CD8 T cell differentiation; thus DC2 (CD11b⁺ cDC) was considered to be critical for driving CD4 T cell responses, whereas DC1 (CD8 α /CD103⁺ cDC) was specialized for induction of CD8⁺ T cell responses (del Rio et al., 2007; Dudziak et al., 2007). However, this view has been challenged by a growing body of recent data demonstrating that a given cDC subset can trigger both CD4 T and CD8 T cell responses but along different differentiation and resulting effector pathways. Whereas CD11b⁺ cDCs preferentially induce CD4⁺ T differentiation toward the T helper cell type 2 (Th2) (Plantinga et al., 2013) or T-helper cell type 17 (Th17) (Schlitzer et al., 2013) effector responses, CD103⁺ DCs are geared to generate CD4⁺ T-helper cell type 1 (Th1) (Furuhashi et al., 2012) or Th2 responses (Nakano et al., 2012). Likewise, whereas both lung migratory CD103⁺ and CD11b⁺ cDC subsets can serve as primary APCs capable of

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Table 1 Common pathogenic viruses infecting the respiratory tract (RT)

Family (genome)	Virus	Primary target cell in the RT	Common symptoms
Paramyxoviridae (–, RNA)	Respiratory syncytial virus	Ciliated epithelial cell	Bronchiolitis and pneumonia (<2 years and elderly), colds (elderly)
	Measles	Epithelial and endothelial cell, dendritic cell	Fever, coughing, conjunctivitis, runny nose, rash
	Human metapneumovirus	Ciliated epithelial cell	Bronchiolitis, pneumonia, colds
Orthomyxoviridae (–, RNA)	Influenza A/B	Epithelial cell, pneumocyte	Fever, runny nose, coughing, nasal congestion, fatigue
Coronaviridae (+, RNA)	SARS-CoV/MERS-CoV	Epithelial cell, pneumocyte	Severe and often fatal pneumonia
	Coronavirus	Epithelial cell	Common colds, pneumonia
Picornaviridae (+, RNA)	Rhinovirus	Epithelial cell	Common colds
Adenoviridae (DNA)	Adenovirus	Epithelial cell	Colds, pneumonia, bronchitis
Herpesviridae (DNA)	Cytomegalovirus	Pneumocyte	Congenital damage, glandular fever (mononucleosis)
	Epstein–Barr virus	Pneumocyte	Glandular fever, fatigue

SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-Cov, middle east respiratory syndrome coronavirus.

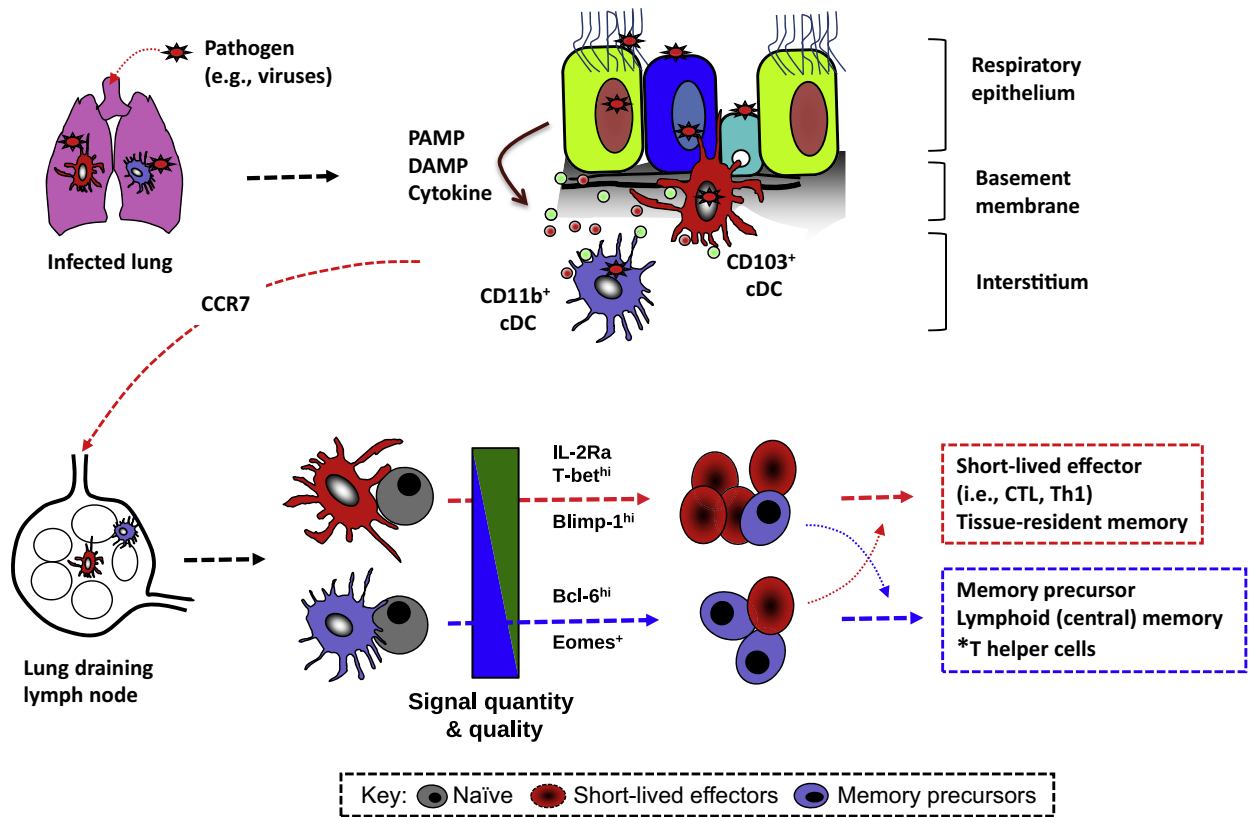


Figure 1 Initiation of T lymphocyte activation and differentiation during respiratory virus infection. Responding to viral infection, CD103⁺ cDCs (conventional dendritic cells) and CD11b⁺ cDCs acquire viral antigens in the lung and migrate from the infected lungs to the regional draining lymph node (DLN). These lung cDC subsets differ in the expression of peptide displayed on MHC class I, surface expression of costimulatory molecules, and soluble mediators. Lung CD103⁺ cDC rapidly accumulates in the DLN and displays a highly potent antigen-presenting cell activity stemming from the stronger CD8 T cell activation signals which they provide (i.e., greater amounts of signal 1 and 2) to trigger virus-specific T cells. This DC subset favors the induction of lung-tropic effectors (i.e., interleukin (IL)-2R α ^{hi}, Tbet^{hi}, and Blimp-1^{hi}), contributing to the elimination of virally infected cells. A fraction of effectors that has survived after virus clearance may become lung tissue-resident memory T cells. On the other hand, CD11b⁺ cDCs display a weaker capacity to activate CD8⁺ T cells. This favors the programming of naïve CD8 T cells preferentially into activated CD8⁺ T cells with memory potential (i.e., Bcl6^{hi} and Eomes^{hi}) that ultimately become circulating central memory cells primarily resident in lymphoid tissues. *CD4 T cells that differentiate into follicular helper subset (Tfh) utilize Bcl6 (and IL-6/21) as a critical regulator of Tfh cell differentiation.

activating naïve virus-specific CD8⁺ T cells in the DLN, the migrant lung CD103⁺ cDCs in the DLN have been found during IAV infections to play the primary role in the induction of the antiviral CD8⁺ effector T cell responses, that is, the production of large numbers of activated CD8 T cells with potent antiviral effector activities (i.e., cytotoxicity and cytokine production) (Helft et al., 2012; Kim and Braciale, 2009; Molledo et al., 2011). This may in part be due to the fact that CD103⁺ cDCs have the unique ability to capture nonreplicating viral particles as well as take up apoptotic cells and ‘cross-present’ apoptotic cell-derived antigens to naïve CD8⁺ T cells (Kim and Braciale, 2009; Desch et al., 2011). Further CD103⁺ cDCs have superior antigen MHC class I-loading machinery (Ho et al., 2011) and a higher levels of costimulatory molecule expression (e.g., CD24 (Kim et al., 2014)) compared to those of CD11b⁺ cDCs. CD11b⁺ cDCs, on the other hand, support the differentiation of activated CD8⁺ T cells into memory cells. These findings suggest a temporal regulation of viral antigen presentation by these two distinct cDC subsets during immunity to acute viral infections. Indeed CD103⁺ DC appears to play a more prominent role as APC early in viral infection (at least with IAV) resulting in the preferential development of effector CD8⁺ T cells (critical for infected cell clearance), whereas CD11b⁺ DC assumes a more prominent role later in the infection as APC favoring the formation of a memory CD8⁺ T cell response (important for resistance to reinfection) (Ballesteros-Tato et al., 2014, 2010; Figure 1).

The potential complexity of the initial interactions of naïve T cells with lung-draining DC within the DLN is further highlighted from recent work suggesting that the chronological age at the time of infection may have profound effects on the DC usage and therein ultimately the range of effector activity displayed during the developing T cell response. Early in life, the distribution of DC subsets in the lungs appears greatly skewed toward the CD103⁺ subset. The consequence of this is evident in animal models, where infection of mice within the first 2 weeks of life with RSV results in a greater number of infected DC in the lungs, altered viral antigen uptake and processing by cDC, a skewing of cDC migrating to the DLNs to the CD103⁺ lineage, and an overall reduced CD86 and CD80 expression by these migrant DCs. The overall result in these changes is a reduced naïve CD8 T cell response to infection. Similarly, recent findings in SARS-CoV and to a lesser degree IAV infection suggest that advancing age is associated with alterations in the response of pulmonary DC to infection which in turn can reduce CD8 T cell immunity. Prostaglandin PGD₂ levels within the lungs increase with aging and following infection with certain viruses, for example, SARS-CoV. This aging and/or SARS-CoV-induced elevated PGD₂ expression inhibits the migration of DC from the lungs to the DLN. In addition, SARS-CoV reduces MHC II, CD80, and CD86 expression on DC. As a result there is a profound reduction in DC activation of a SARS-CoV-specific CD8 T cell response and a corresponding delay of viral clearance and increased disease severity (Channappanavar et al., 2014; Zhao et al., 2011). In sum, these data would suggest that the timing of the viral infection (i.e., neonatal vs adult vs aged) may alter the DC and CD8 T cell immune response generated and therein ultimately control the eventual outcome of the infection.

In addition to the role of DC in the initial activation of naïve CD8 T cells within the DLN, recent studies have shown that the effector fate of the developing antiviral effector CD8 T cell is strongly influenced by encountering distinct DC subsets before egress from the LN to the lungs. Specifically, during lethal dose inoculum or infection with highly pathogenic strains of IAV, pDC within the DLN expresses high levels of FasL in an interleukin (IL)-12 p40 homodimer-dependent manner. As the naïve T cells are activated and begin to upregulate Fas (i.e., the receptor for FasL), the T cells are killed by the pDC. In this manner, the overall magnitude of the CD8 T cells found downstream in the lungs is greatly reduced leading to lack of viral control and eventual death. Interference with IL-12 p40 homodimer or the FasL:Fas interaction prevents the death of the T cells and allows viral control (Boonnak et al., 2014; Langlois and Legge, 2010; Legge and Braciale, 2005).

Effector T Cell Responses during Acute Virus Infection

Upon their arrival in the infected lungs, the activated differentiated CD8 and CD4 T cells initiate the effector phase of the T cell response to acute pulmonary viral infections (Figure 2). The action of the CD8 cells is usually essential for the elimination of virus-infected cells and eventual resolution of the infection. Indeed analyses in experimental models have revealed that the loss of CD8 T cells during IAV, middle east respiratory syndrome coronavirus (MERS-CoV), RSV, and SARS-CoV result in delayed or insufficient viral clearance and in many cases more severe disease (Bender et al., 1992; Channappanavar et al., 2014; Epstein et al., 1998; Graham et al., 1991; Thomas et al., 2006; Topham and Doherty, 1998; Varga and Braciale, 2013; Zhao et al., 2014, 2010, 2009). The effector response of CD8 T cells can be divided into two primary activities: (1) functions directed toward the elimination of infected cells, and (2) production of cytokines and chemokines that will recruit and direct the responses of additional innate and adaptive immune cells as well as contribute to the overall antiviral state.

The direct elimination of virus-infected cells in the lungs by antiviral effector CD8 T cells occurs via two mechanisms: release of lytic granules and engagement of death-inducing receptors on the cell surface of infected cells by ligands on the surface of the T cells (Figure 2). Upon immune synapse formation with the infected cell, the CD8 T cell can release perforin (a membrane-perturbing molecule) and granzymes (serine proteases that induce apoptosis) from lytic granules across the synapse to target the selective elimination of the infected cell. Further, engagement of the CD8 T cell surface molecules, FasL and TRAIL, with their ligands, Fas and DR5, respectively, on the infected cells, triggers the apoptosis of the infected cells. The importance of each of these effector molecules in CD8 T cell-mediated control of acute respiratory infections has been well characterized during experimental IAV infection in mice where the elimination of these effector molecules or their ligands via targeted knockout or blockade reduces the cytolytic potential of the antiviral T cell response and viral control (Brincks et al., 2008; Topham et al., 1997). Similar to IAV infection, deficiency of FasL or perforin during acute RSV

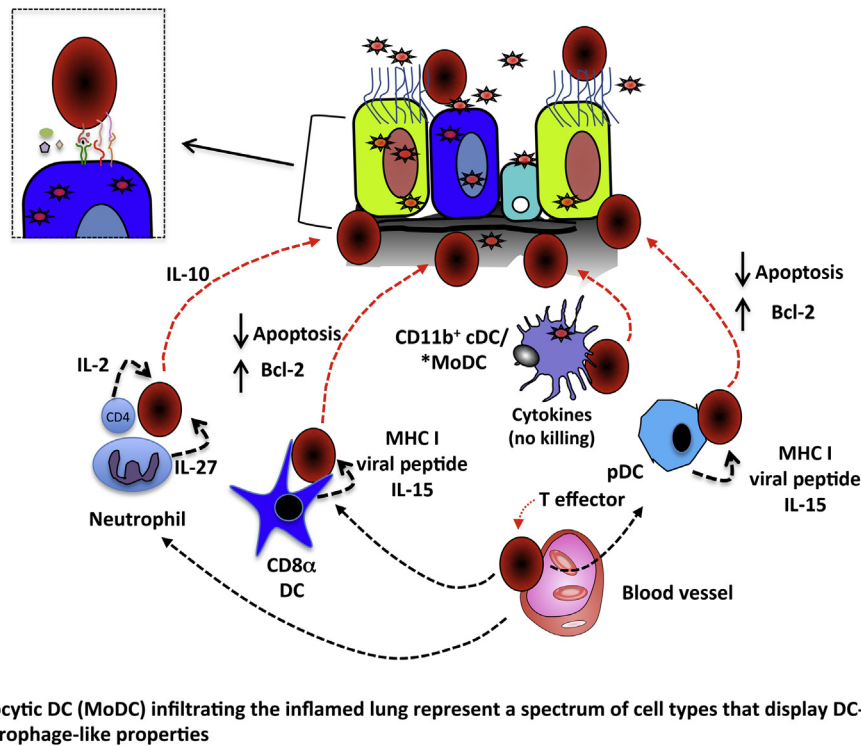


Figure 2 Effector T cell responses during acute respiratory virus infection. Upon entry into the inflamed lung after activation in the draining lymph node, effector T cells undergo additional differentiation and rounds of proliferation regulated by local antigen-presenting cells (APCs) and locally produced soluble mediators. An array of cytokines and chemokines produced *in situ* by APC-stimulated effector T cells promote virus clearance via direct killing mechanisms (i.e., perforin, granzyme, TRAIL, and FasL) or indirect pathways (i.e., cytokines). T cell triggering also allows T cell production of chemokines used to recruit additional immune cells into the response. Notably, recruited inflammatory cells (i.e., neutrophils) cooperate with CD4 and CD8 T effectors to drive the production of regulatory cytokines such as interleukin (IL)-10. Insert: T cell interaction with epithelial cells engages cytotoxic pathways to mediate direct viral control with minimal production of inflammatory cytokines such as interferon γ . DC, dendritic cell; pDC, plasmacytoid DC; cDC, conventional DC.

infections has been shown to delay viral clearance (Aung et al., 2001; Rutigliano and Graham, 2004).

In addition to the above cytotoxic functions, effector CD8 T cells, upon recognition of viral antigens, can also produce and secrete the cytokines, interferon (IFN) γ , TNF, IL-2, and IL-10, as well as chemokines, such as CCL2, CXCL9, and CXCL10. These chemokines recruit additional immune cells (CD8 as well as CD4 T cells, DCs, NK cells, monocytes/macrophages) into the site of infection where they can further modulate the immune response. The recruited cells can have both positive (i.e., additional antiviral) as well as negative (i.e., immunopathological) effects on the control of viral infection and disease severity. Although IFN γ production is a hallmark of the response of IAV-, MERS-CoV-, RSV-, and SARS-CoV-specific effector CD8 T cells, the impact of IFN γ produced by CD8 T cells on viral replication is likely dependent on the infectious agent. Thus, *in vivo* elimination of IFN γ during infection by neutralizing antibody administration or adoptive transfer of IFN γ -deficient CD8 T cells during RSV infection reduces virus control (Ostler et al., 2002), whereas IFN γ -deficient T cell clones are still able to control IAV infections (Graham et al., 1993). A direct role for T cell-produced IFN γ in virus control is currently less clear during SARS-CoV and MERS-CoV infections but experiments have demonstrated that IFN γ supplementation during

MERS-CoV and prior to SARS-CoV infection reduces virus titers suggesting that it may play an important role in viral control (Zhao et al., 2014, 2012).

In addition to the CD8 T cell mediated influence on other immune cells within the lung during acute virus infection, it is now increasingly clear that these cell-to-cell interactions exert additional bidirectional influences on the phenotype and overall health of the CD8 T cells (Figure 2). Although it has long been appreciated that recognition of signal 1 (i.e., MHC class I + virus peptide by TCR) is required for induction of cytotoxicity, recent studies suggest that signal 2 (costimulation) and signal 3 (cytokine) interactions have a major influence on the local lung-specific CD8 T cell response during acute viral infections. These additional interactions include the long-appreciated CD4 T cell help and production of IL-2 as a growth factor but also include recent work demonstrating differential T cell effector responses and fitness upon interactions with differing cells types within the lungs. For instance, virus-specific CD4 T cells produce IL-2 in conjunction with IL-27 produced by inflammatory mononuclear cells/neutrophils which in turn supports the production of the anti-inflammatory cytokine IL-10 by IAV-specific CD8 T cells responding to viral antigen (Sun et al., 2011b). This IL-10 production is critical in the control of the overall inflammation and protection

from immunopathology. Interestingly the modulation of CD8 T cell effector ability within the lungs is regulated not just by the inflammatory milieu but can be specifically tuned by the cell that the T cell is interacting with at the time. During IAV infections, CD8 T cell interactions with CD45⁺ cells expressing the costimulatory molecules, CD80 and CD86, drive both cytokine and cytolytic effector responses, whereas interaction with CD45⁺ cells in the absence of CD80/CD86 interactions or epithelial cells results in only cytolytic effector ability (Hufford et al., 2011). Further, effector CD8 T cell interactions with APCs expressing cognate MHC class I–viral peptide, various costimulatory molecules and transpresenting IL-15 have been implicated in providing important antiapoptotic signals to the effector CD8 T cells allowing them to survive the harsh inflammatory environment of the lungs and expand to the levels required to control the virus infection (Hufford et al., 2012; McGill et al., 2008, 2010).

It is important to note that although an effector CD8 T cell response to IAV, RSV, MERS-CoV, and SARS-CoV has been shown to be critical for viral control, the overall CD8 T cell effector response during SAR-CoV, unlike IAV and RSV, is substantially reduced in mice consistent with observations in humans (Zhao et al., 2011). This is due in part to the above described effects of SARS-CoV on DC during the induction phase of the response (i.e., reduced migration, costimulation, MHC expression). It is, however, worth noting, given the important role delineated for local APC interactions with the effector T cells within the lungs described above for IAV (McGill

et al., 2008, 2010), that defective APC function during the effector phase of the CD8 T cell response (e.g., SAR-CoV infection) in the lungs may have additional negative effects on the magnitude of the effector T cell response and consequent diminished control of virus replication.

Role of T Cells in the Resolution of Pulmonary Inflammation Following Respiratory Virus Infection

Following the clearance of infectious viruses, the host undergoes a resolution process to quiet/resolve inflammatory responses in the RT and to repair the damaged epithelium (Figure 3). Complete resolution of host inflammation and rapid tissue repair are crucial for the restoration of normal lung homeostasis and gas-exchange function (Gorski et al., 2012). Many immune and structural cell types such as IL-22-producing NK cells, amphiregulin-expressing innate lymphoid type 2 cells, type 2 macrophages, and tissue stem cells (Gorski et al., 2012; Kumar et al., 2013a,b; Li et al., 2011; Monticelli et al., 2011; Shirey et al., 2014; Vaughan et al., 2015; Zuo et al., 2015) are required for host resolution of infection and lung repair, although when and how these cells co-opt to do so remain largely undefined. T cells, including both effector and regulatory T cells (Treg cells), are an integral component of the cellular machinery required for resolution of inflammation and tissue recovery following the T cell response to respiratory virus infection (Braciale et al., 2012; Sun and Braciale, 2013).

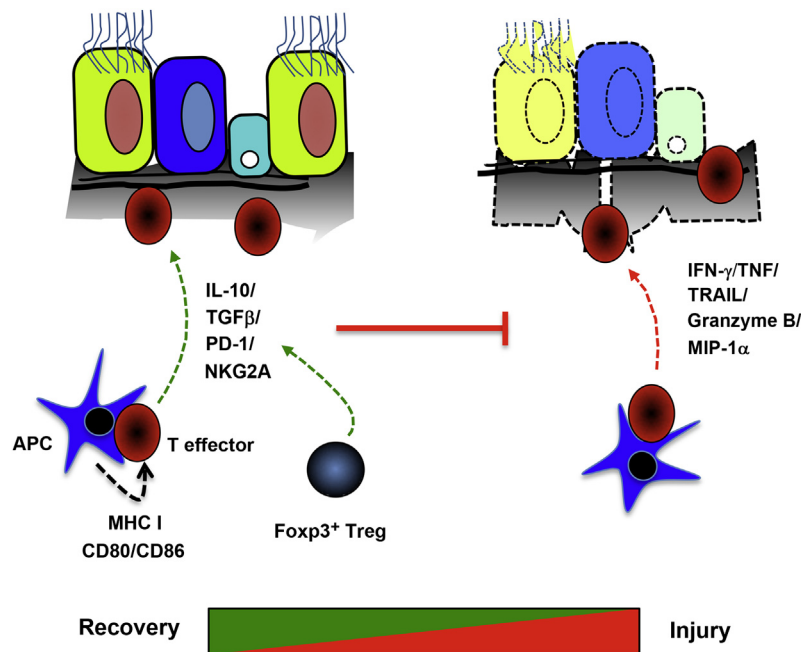


Figure 3 Role of T cells in the resolution of pulmonary inflammation following respiratory virus infection. During and after viral clearance, effector T cells and Foxp3⁺ regulatory T cells (Treg cells) infiltrating the infected lung produce regulatory cytokines (i.e., anti-inflammatory interleukin (IL)-10 and anti-inflammatory TGFβ) and express suppressive surface molecules (i.e., program death 1 (PD-1) and natural killer group protein 2, member A (NKG2A)). These immunoregulatory mediators/molecules play a critical role in limiting tissue injury by suppressing the production of pro-inflammatory cytokines produced by the effector T cells and inflammatory innate cells. This balancing act between effector and Treg cells is crucial in promoting recovery with minimal infection-associated immunopathology in the site of infection. APC, antigen-presenting cell.

Forkhead box P3 (Foxp3⁺) Treg cells accumulate in large numbers in the RT during the resolution phase of both IAV and RSV infection (Fulton et al., 2010; Lee et al., 2010; Liu et al., 2010; Moser et al., 2014; Figure 3). These Treg cells are largely generated intrathymically and react to viral antigens in the lung (Bedoya et al., 2013; Liu et al., 2010). These lung Treg cells also exhibit a unique 'effector' phenotype and produce high levels of anti-inflammatory cytokine IL-10 and other immune-regulatory molecules including granzyme B (Bedoya et al., 2013; Cretney et al., 2011; Loebbermann et al., 2012b), which could enhance the ability of Treg cells to control pulmonary inflammation following infection. The local induction of these 'effector' Treg cells depends on several transcription factors including interferon regulatory factor 4 (IRF4), B lymphocyte-induced maturation protein 1 (Blimp1), and T-box expressed in T cells (T-bet) (Bedoya et al., 2013; Cretney et al., 2011). Importantly, depletion of Treg cells results in overactive and persistent tissue inflammation and delays host recovery from IAV and RSV infection (Fulton et al., 2010; Lee et al., 2010; Liu et al., 2010; Moser et al., 2014). Conversely, promotion of the expansion of Treg cells or transfer of Treg cells into the infected lungs diminishes exuberant respiratory inflammation and promotes rapid host recovery from IAV infection (Lee et al., 2010; Sakthivel et al., 2014). Thus, Treg cells are essential for resolving host inflammation and promoting tissue recovery during acute respiratory virus infection.

As discussed above, effector T cells are essential for viral clearance in the RT through their ability to kill virus-infected cells. However, upon antigenic stimulation, lung effector T cells also produce large quantities of inflammatory cytokines and mediators *in situ* (Hufford et al., 2015), which can promote host inflammation and cause tissue damage (Braciale et al., 2012; La Gruta et al., 2007) during both IAV and RSV infection (La Gruta et al., 2007; Openshaw and Chiu, 2013; Figure 3). Thus, the production of inflammatory mediators by lung effector T cells (i.e., T cell inflammatory activities) needs to be tightly regulated to avoid excess tissue inflammation and damage following respiratory virus infection. To this end, stimulation of T cell inflammatory activities requires the encounter of T cell receptor by MHC and peptides derived from viral antigens and costimulatory signals including CD80/86 expressed on APCs (Hufford et al., 2011, 2015). As the amount of antigen deposition in the tissue drastically decreases following the clearance of virus-infected cells, inflammatory activities of the effector T cells rapidly wane (Hufford et al., 2011, 2015), which helps to resolve T cell-mediated inflammation. In addition, effector T cells also bear several regulatory factors to actively dampen inflammatory responses induced by T cells themselves or other immune cells (Sun and Braciale, 2013). For example, lung effector CD4 and CD8 T cells produce high levels of the regulatory cytokine IL-10 during both IAV and RSV infections (Loebbermann et al., 2012a; McKinstry et al., 2009; Sun et al., 2011a,b, 2009; Weiss et al., 2011). As noted above, blockade of IL-10 function at the time of T cell infiltration to the lung increases proinflammatory cytokine levels in the RT and delays host recovery during IAV and RSV infection (Loebbermann et al., 2012a; Sun et al., 2011a; Sun et al., 2009; Weiss et al., 2011), suggesting that IL-10 derived from effector T cells functions to promote the resolution of

pulmonary inflammation and recovery. Notably, certain polymorphisms of the IL-10 gene are associated with a higher risk of severe RSV bronchiolitis, pointing to the possibility that IL-10 may control the severity of acute respiratory virus infection in humans (Helminen et al., 2008).

In addition to IL-10, effector T cells in the lung also express high levels of coinhibitory receptors including program death 1 (PD-1) and natural killer group protein 2, member A (NKG2A) during IAV and RSV infection (Ely et al., 2014; Erickson et al., 2012; McNally et al., 2013; Rutigliano et al., 2014; Yao et al., 2014; Zhou et al., 2008; Figure 3). PD-1 expression on effector T cells is linked to their functional impairment in the lung and may delay the clearance of virus infection during IAV and human metapneumovirus (HMPV) infection (Erickson et al., 2012; McNally et al., 2013; Rutigliano et al., 2014; Zhou et al., 2008). On the other hand, the blockade of the interaction of PD-1 and its ligand PD-L1 results in exaggerated and prolonged respiratory inflammation without altering viral clearance during RSV infection, indicating that this immune-regulatory mechanism is also important in limiting T cell inflammatory activities in the lung and contributes to the resolution of tissue inflammation during RSV infection (Yao et al., 2014). Notably, PD-1 is expressed on T cells in nasal washes of RSV-infected children (Yao et al., 2014), suggesting that, similar to mice, PD-1 could likewise function in controlling respiratory inflammation in humans. In addition to PD-1, lung effector CD8 T cells express increased levels of NKG2A as a result of migration from DLN to the inflammatory lung environment (Ely et al., 2014; Zhou et al., 2008). Similar to PD-1, NKG2A appears to be important in restricting CD8 T cell effector function and limiting immune-pathology as the disruption of NKG2A in CD8 T cells or the ablation of NKG2A ligand in the lung leads to exaggerated pulmonary inflammation and damage during IAV infection (Ely et al., 2014; Zhou et al., 2008).

As noted above, effector T cells gain the expression of important regulatory molecules, including IL-10, PD-1, and NKG2A, upon migration to the infected lungs from DLN. In conjunction with this, effector CD8 T cells in the lung also downregulate their capability to produce IFN γ following antigen stimulation (Arimilli et al., 2008, 2010; Fulton et al., 2008). Together, although it remains to be determined whether those tissue effector T cells could pass through a stable and transmissible differentiation state, these data suggest that the lung local environment could reshape the differentiation status of effector T cells to restrict their production of inflammatory mediators and to promote their expression of anti-inflammatory factors. Understanding the associated mechanisms regulating the balance and timing of the production of proinflammatory versus anti-inflammatory mediators may offer opportunities to promote rapid resolution and recovery of respiratory virus infection while limiting immune-mediated disease.

Concluding Remarks

This Encyclopedia article has dealt primarily with the induction, effector function, and control of inflammation of CD8⁺ T cell responses during acute virus infection. Many of the topics

addressed in this section, for example, T cell activation, costimulation, DC as APC, are dealt with at great depth in other sections of this Encyclopedia. Likewise, the contribution of CD4 T cell responses to acute and chronic virus infection are dealt with in detail in other sections of the Encyclopedia. The reader is referred to these sections.

See also: Anatomy and Microanatomy of the Immune System: Lymph Node Structure. Cells of the Innate Immune System: Dendritic Cells and Dendritic Cell Subsets; ILC2 in Immunity. Cytokines and Their Receptors: IL-10. Immunity to Viral Infections: CD4 T Cell Immunity to Viral Infection; CD8 T Cell Memory to Pathogens; Dendritic Cells in Viral Infection; Immune Responses to Viruses in the CNS. T Cell Activation: Conventional Dendritic Cells: Identification, Subsets, Development, and Functions; Cytotoxic Lymphocytes; Modification of T Cell Functions at Sites of Infection and Inflammation; Th1 Cells; Treg Cells.

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