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Role of T cell immunity in recovery from influenza virus infection

Jie Sun[1,2,*] and **Thomas J. Braciale**[3]

[1]Department of Pediatrics, Herman B. Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

[2]Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

[3]Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908, USA.

Abstract

Influenza virus infection has the potential to induce excess pulmonary inflammation and massive tissue damage in the infected host. Conventional $CD4^+$ and $CD8^+$ as well as nonconventional innate like T cells respond to infection and make an essential contribution to the clearance of virus infected cells and the resolution of pulmonary inflammation and injury. Emerging evidence in recent years has suggested a critical role of local interactions between lung effector T cells and antigen presenting cells in guiding the accumulation, differentiation and function of effector T cells beyond their initial activation in the draining lymph nodes during influenza infection. As such, lung effector $CD4^+$ and $CD8^+$ T cells utilize multiple effector and regulatory mechanisms to eliminate virus infected cells as well as fine tune the control of pulmonary inflammation and injury. Elucidating the mechanisms by which conventional and nonconventional T cells orchestrate their response in the lung as well as defining the downstream events required for the resolution of influenza infection will be important areas of future basic research which in turn may result in new therapeutic strategies to control the severity of influenza virus infection.

Introduction

Influenza virus is a leading cause of upper and lower respiratory infection and constitutes an ongoing threat to global health. Current strategies for influenza prevention and treatment include yearly vaccination and anti-viral drugs. However, frequent changes in the surface antigens of influenza virus due to the antigenic shift and drift allow influenza viruses to escape antibody-mediated immunity following vaccination. Anti-viral treatment is generally only effective during a very short time period early after influenza infection, and furthermore, many circulating influenza virus strains have developed resistance to the current antiviral drugs. Thus, it is of urgent need to understand the pathophysiology and the protective immune responses to influenza virus infection for the development of future preventive and therapeutic means. In this article, we review recent advances in the understanding of the role of adaptive $CD4^+$ and $CD8^+$ T cell immune responses as well as

[*]Corresponding author: Dr. Jie Sun, R4, Room 274, 1044 W. Walnut Street, Indianapolis, IN 46202, Tel: 317-278-8544, Fax: 317-274-5378, sun32@iupui.edu.

nonconventional T lymphocytes in the protection and recovery of influenza infection with special focuses on the effector mechanisms and the regulation of the T cell responses in the infected site, i.e. the lungs.

Role of CD8$^+$ T cells in anti-influenza immunity

Local control of CD8$^+$ T cell responses in the lung

Following influenza infection, respiratory dendritic cells (DCs), mainly CD103$^+$ DCs, carry influenza antigen and migrate to the draining lymph nodes (dLN) to encounter naive CD8$^+$ (and CD4$^+$) T cells therein [1]. Subsequently, influenza specific CD8$^+$ T cells undergo a stepwise process of activation, proliferation and differentiation to become effector T cells and migrate to the lung to eliminate virus infected cells. Classically, the activation and differentiation of CD8$^+$ T cells are believed to be completed in the secondary lymphoid organs. However, recent advances have suggested that CD8$^+$ effector T cells receive additional signals from local antigen presenting cells (APCs), in particular DCs, to guide their further activation, differentiation and effector activities upon arrival to the lung. Studies from Mcgill et al have demonstrated that the depletion of lung DCs after T cell activation in the dLNs resulted in diminished maintenance and accumulation of CD8$^+$ effector T cells in the lung and thus impaired the clearance of virus in the respiratory tract [2]. Further studies have demonstrated that lung DCs provide cognate antigens and trans-presented IL-15 to promote the proliferation and survival of local effector CD8$^+$ T cells [2,3]. Interestingly, similar to the activation and expansion of naïve CD8$^+$ T cells, Dolfi et al demonstrated that effector T cells require CD28 co-stimulation from lung DCs to sustain their proliferation and survival in the lung [4]. Besides providing signals required for the proliferation and survival of effector T cells, local APCs also produce cytokines to drive further differentiation of CD8$^+$ effector T cells in the lung. For example, effector CD8$^+$ T cells activated in the draining LN are capable of producing high levels of effector cytokine IFN-γ but minimal regulatory cytokine IL-10 [5]. Upon migration to the infected lungs, effector CD8$^+$ T cells acutely acquire the capacity to produce the regulatory cytokine IL-10 to dampen respiratory inflammation associated with the anti-viral immune response (see below) [5]. Lung local APCs, including DCs, macrophages and neutrophils, produce the cytokine IL-27 and play important roles in driving the acquisition process of IL-10 production by lung effector T cells [6]. Thus, the interaction of lung APCs and effector CD8$^+$ T cells in the lung promote further differentiation of effector T cells (i.e. acquisition of a regulatory feature).

Activated CD8$^+$ T cells are capable of producing effector cytokines and cytolytic molecules, however, they do not spontaneous secrete effector cytokines and release cytolytic molecules without further interaction with antigen bearing target cells, including CD45$^+$ APCs and influenza infected epithelial cells localized within the infected respiratory tract [7,8]. Interestingly, effector T cells exhibit differential effector activities when interacted with CD11c$^+$ APCs or epithelial cells. The interaction with lung CD11c$^+$ APCs triggers effector T cells to release both cytolytic molecules and effector cytokines, while the interaction with epithelial cell triggers the release of cytolytic molecules but not effector cytokines [7]. Clearly, both epithelial cells and CD11c$^+$ APCs bear influenza antigen and so can stimulate effector T cells via TCR signaling. However, lung CD11c$^+$ APCs but not epithelial cells express high levels of the co-stimulatory ligands CD80/86 (murine B7.1/.2) molecules and thus can additionally trigger CD28 signaling in effector T cells [7]. Inhibition of CD28 signaling at the time of effector T cell infiltration to the lung acutely abolished effector cytokine production during influenza infection [7]. Thus, anti-viral effector T cell activities in the lung are differentially regulated by the strength of interaction with their target cell types; strong interaction between APCs and effector T cells (involving with both TCR and costimulatory signals) triggers full spectrum of effector T cell activities, while weak

interaction only triggers the release of cytolytic molecules to kill target cells. The uncoupling of the release of inflammatory cytokines and the secretion of cytolytic molecules by effector T cells may have important implications in designing novel therapeutics for influenza infection as it is possible in the future to selective inhibit pathogenic cytokine responses of effector T cells but retain their ability to clear virus. However, as CD28 signaling can also promote the survival of effector T cells in the lung [4], such approaches should be also undertaken with extra caution not to affect the accumulation of antiviral T cells in the infected lung.

Effector mechanisms of $CD8^+$ T cells

Classically, $CD8^+$ T cells are believed to clear influenza virus infection through Fas/Fas-L and perforin-dependent mechanisms. However, recent studies have suggested that effector T cells may also use other mechanisms to contribute to the resolution of influenza infection in the lung (Figure 1). TRAIL deficient mice exhibited enhanced morbidity and influenza virus titer in response to influenza infection and the transfer of TRAIL deficient $CD8^+$ T cells failed to protect lethal challenge of influenza virus infection [9]. Thus, TRAIL expression by $CD8^+$ T cells appear to contribute to the clearance of influenza infected cells during primary influenza infection. Effector $CD8^+$ T cells also express many anti-viral cytokines and chemokines that could potentially attract additional innate and adaptive immune cells to facilitate viral clearance. A recent report have suggested that effector $CD8^+$ T cells may use multiple redundant effector mechanisms, including direct killing of target cells via perforin and death receptors and the production of effector cytokines and chemokines, to protect against influenza infection [10]. Furthermore, like $CD4^+$ T cells [11], effector $CD8^+$ T cells were able to elicit the activation of an early host innate response and thus provide bystander protection against the virus that could not be recognized by the transferred $CD8^+$ T cells [10]. In addition, besides classical IFN-γ producing Tc1 cells, experiments have established that IL-4 producing Tc2 and IL-17 producing Tc17 cells are able to provide protection to influenza virus infection [12]. Whether these differentially polarized Tc subsets use distinct mechanisms to protect influenza infection warrant further investigation. Likewise, the extent to which Tc2 and Tc17 cells contribute to virus clearance and recovery/immunopathology during experimental (as well as human) influenza infection remains to be determined.

Control of pulmonary inflammation by $CD8^+$ effector T cells

The control and clearance of influenza virus infection by the innate and adaptive immune system can be accompanied by strong inflammatory responses generated within the infected respiratory tract. The recovery of influenza infection requires that these accompanying inflammatory responses be well controlled to minimize immune-mediated pathology in the process of viral clearance. Multiple immune counter-regulatory mechanisms help to retain the inflammatory responses in control during influenza infection [1]. In particular, as mentioned above, anti-viral effector $CD8^+$ T cells in the lung gain the ability to produce IL-10 during influenza infection. Although multiple cell lineages in the lung can produce IL-10 during influenza infection [13,14], effector $CD8^+$ T cells appeared to be the major producers of IL-10 as determined by $CD8^+$ T cell depletion and in vivo cytokine staining [5]. Importantly, the blockade of IL-10 function, at the time of T cell infiltration to the lung, resulted in excessive pulmonary inflammation and lethal injury [5]. These data suggest that effector $CD8^+$ T cells are able to fine tune respiratory inflammation during influenza infection. Both APC-derived IL-27 and Th-cell derived IL-2 were required for the development of IL-10 producing effector $CD8^+$ T cells in the lung during influenza infection [6]. These IL-10 producing effector $CD8^+$ T cells were characteristic of terminal differentiated effector T cells as they express high levels of effector molecules and the transcription factor Blimp-1. Interestingly, the generation of these IL-10 producing effector

T cells are mainly restricted to the primary infection as memory $CD8^+$ T cells progressively lose responsiveness to IL-27 [15].

Role of $CD4^+$ T cells in anti-influenza immunity

The recovery from influenza infection requires the action of both $CD8^+$ and $CD4^+$ T cells. Classically, $CD4^+$ T cells were believed to participate in the anti-viral immune responses by providing the help for $CD8^+$ T and B cell responses to promote viral clearance. During the primary $CD8^+$ T cell responses, $CD4^+$ T cells appeared not critical for the development of $CD8^+$ T cell responses due to the direct activation of DCs by influenza virus [16]. However, $CD4^+$ T cells provide IL-2 to instruct the production of IL-10 by effector $CD8^+$ T cells and thus are required for the full spectrum of cytokine production by effector $CD8^+$ T cells [6]. Recently, a newly described subset of $CD4^+$ T cells, follicular helper T cells (Tfh), were identified as a specialized type of $CD4^+$ T cells to provide the essential help for B cell responses. Influenza infection induces the generation of Tfh cells which can promote germinal center (GC) formation as well as support high affinity antibody production by B cells [17]. Tfh cells induced during influenza infection are for the most part induced within lymphoid organs draining the site of infection, that is mediastinal lymph nodes and requires a novel late activator antigen-presenting cell (LAPC) for optimal induction in the draining LNs [18,19]. LAPCs migrate from the infected lungs to the dLN "late," i.e., 6 d after infection through CXCR3-dependent mechanisms, which is concomitant with Tfh differentiation. Tfh cell development induced by LAPCs required ICOS-ICOSL-dependent signaling [19]. Furthermore, the signaling from IL-6 and IL-21 also controlled the development of Tfh cells during influenza infection [20]. In contrast, IL-2 signaling inhibited the development of Tfh and GC B cell responses during influenza infection [21].

In addition to their role in helping $CD8^+$ T cells and B cells, $CD4^+$ T cells also exhibit direct effector activities against influenza infection. A recent report has identified that lung $CD4^+$ T cells expressed cytolytic molecules such as Granzyme B (Gzmb) and perforin and exhibited direct cytotoxicity against influenza-infected cells [22]. Interestingly, the up-regulation of Gzmb and perforin expression in influenza-specific $CD4^+$ T cells is restricted to the infection site [22], suggesting that the lung microenvironment promotes the generation of these cytotoxic $CD4^+$ T cells. Notably, these Gzmb and perforin-expressing $CD4^+$ T cells express the Th1 signature cytokine IFN-γ, indicating that they can be characterized into broader Th1 lineage [22]. Future studies are needed to identify the molecular mechanisms guiding the development of these cytotoxic $CD4^+$ T cells and to clarify their relationship with classic Th1 cells. Nevertheless, following adoptive transfer, these $CD4^+$ T cells provide both cytolytic and IFN-γ dependent protection again influenza challenge, suggesting these $CD4^+$ T cells employ multiple effector mechanisms to protect and promote recovery from influenza virus infection [22]. Currently the exact physiological function of cytotoxic $CD4^+$ T cells during influenza infection warrants further studies, however, a recent clinical study has implicated that pre-existing $CD4^+$ T cells may directly kill target cells through perfroin dependent mechanisms and in the case of type A influenza infections contribute to protection against infection with heterologous viruses i.e heterosubtypic immunity in humans [23]. Thus, $CD4^+$ T cells are able to protect against influenza infection via multiple mechanisms including both direct cell contact dependent cytolytic effector activity and indirect “help” to other immune cells. An elegant recent study has suggested that these multiple mechanisms of $CD4^+$ T cells may act in a synergistic manner to provide complete protection against influenza virus infection [24].

Role of unconventional T cells in the protective immunity to influenza

Beyond conventional $CD4^+$ and $CD8^+$ T cells, innate like T cells such as NKT cells and γδ T cells were recently shown to play important roles in the recovery of influenza infection. CD1d or invariant NKT cell (Jα18 deficient) deficient mice exhibited enhanced susceptibility to influenza virus infection, and the activation of NK T cells through the injection of α-GalCer protected the host from influenza infection [25,26]. NKT cells exert their function to protect the host through multiple mechanisms. NKT cells were able to suppress the function of myeloid-derived suppressor cells (MDSCs), which promoted anti-viral T cell responses and viral clearance [27]. iNKT cells can also affect the maturation of DCs in the dLN to affect the development of $CD8^+$ T cells responses against influenza infection [28]. Beyond their function in promoting T cell immunity, NKT cells can reduce lung injury induced by influenza infection through the elimination of inflammatory monocytes [29], which were previously shown to be a major contributor to lung injury during influenza infection [1]. Furthermore, NKT cells are a major source of IL-22 and so may help to preserve lung epithelium integrity following influenza infection [30]. Innate-like γδ T cells constitutes a small fraction lymphocytes that express γδ TCR and be able to rapidly respond to infection, potential danger or cellular stress [31]. γδ T cells were originally shown to be able to provide heterotypic immunity against influenza infection. Recently, using a humanized mouse model, it was demonstrated that aminobisphosphonate pamidronate-expanded γδ T cells were able to kill influenza virus–infected cells in vitro and protect humanized mice from lethal influenza infection in vivo [32]. This study raises the possibility that aminobisphosphonate pamidronate and related compounds may be useful as novel therapeutic approaches for protection from and treatment of influenza virus infection in the human.

Conclusion

In this brief review we have identified and described some of the recent findings emerging from the analysis of the role of T lymphocytes in protection and recovery from influenza virus infection. While some of these findings can be extrapolated to infection with other respiratory viruses (and perhaps to a limited extent to the host response to bacterial infection in the respiratory tract), there will be differences in the response of T cells following different species or strains of respiratory viruses. Research within the past two decades has provided us with considerable insight into the processes involved in the induction of innate and adaptive immune responses, the expression of innate and particularly adaptive immune effector activities such as T-cell mediated cytolysis and the mechanisms underlying these processes. An emerging frontier for new research involves understanding the role of the host immune response in orchestrating and regulating the events association with the resolution of infection (i.e. the repair of damage tissue) and in the case of viral and bacterial infections of the respiratory tract, the restoration of normal pulmonary structure and function.

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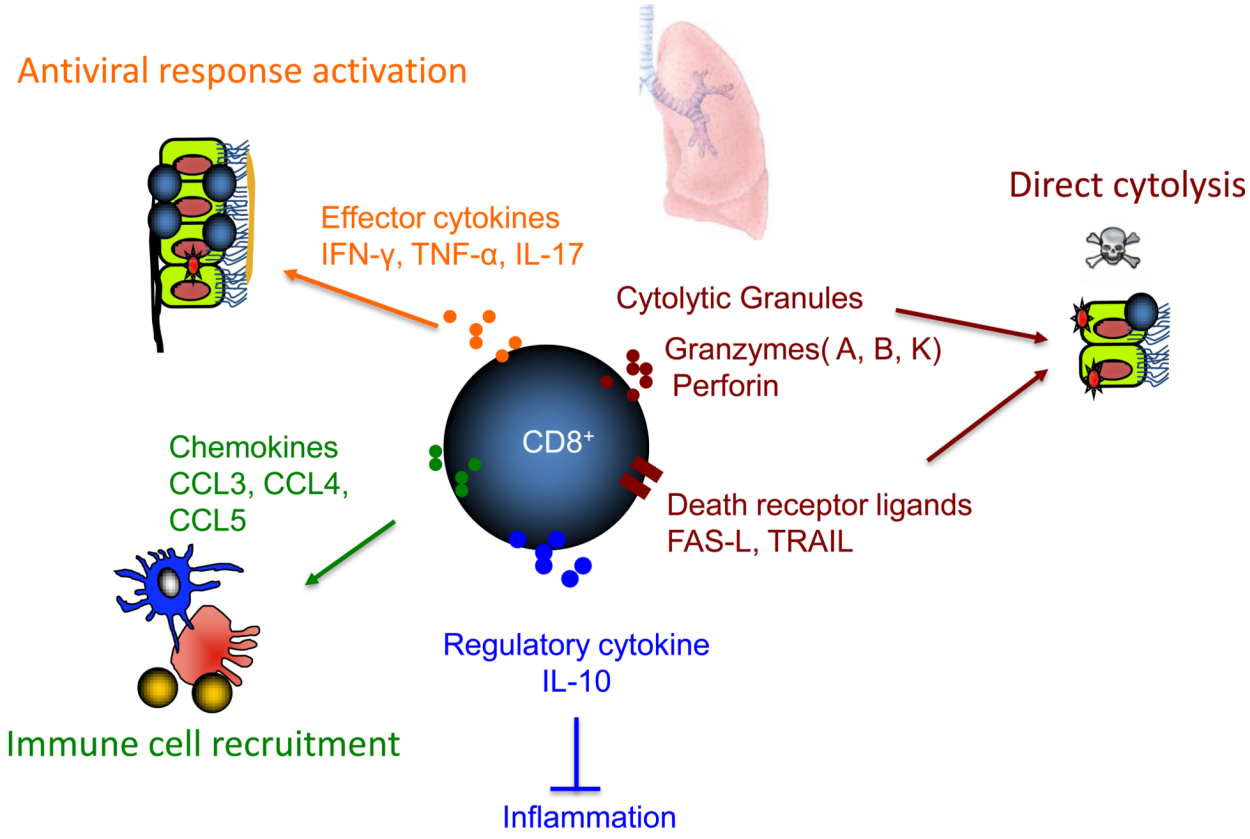
Highlights

- Local interaction between APCs and T cells controls influenza T cell responses
- Effector T cells use multiple mechanisms to restrict influenza infection
- Target cell types determine effector T cell activities in situ
- Nonconventional T cells help to clear virus and limit tissue injury



Influenza-specific effector T cells use multiple mechanisms to help to resolve influenza infection in the lung.
I) Effector CD8⁺ T cells express cytolytic granules and death receptor ligands to directly kill virus infected cells.
II) Effector CD8⁺ T cells express antiviral effector cytokines to stimulate antiviral responses in epithelial cells.
III)) Effector CD8⁺ T cells express multiple chemokines to recruit other immune cells to the lung.
IV) Effector CD8⁺ T cells express the regulatory cytokine IL-10 to control excessive pulmonary inflammation.

Figure 1.