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T cell responses in respiratory viral infections and chronic obstructive pulmonary disease

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Abstract

Respiratory viruses are major human pathogens that cause approximately 200 million pneumonia cases annually and induce various comorbidities with chronic obstructive pulmonary disease (COPD), resulting in significant health concerns and economic burdens. Clinical manifestations in respiratory viral infections and inflammations vary from asymptomatic, mild, to severe, depending on host immune cell responses to pathogens and interactions with airway epithelia. We critically review the activation, effector, and regulation of T cells in respiratory virus infections and chronic inflammations associated with COPD. Crosstalk among T cells, innate immune cells, and airway epithelial cells is discussed as essential parts of pathogenesis and protection in viral infections and COPD. We emphasize the specificity of peptide antigens and the functional heterogeneity of conventional $CD4^+$ and $CD8^+$ T cells to shed some light on potential cellular and molecular candidates for the future development of therapeutics and intervention against respiratory viral infections and inflammations.

Keywords: Chronic obstructive pulmonary disease; Coronavirus disease 2019; Inflammation; Respiratory virus; T cells

Introduction

Respiratory viral infections are the most frequently occurring diseases worldwide, clinically recognized as "common cold," flu, bronchiolitis, pneumonia, and so on, with approximately 200 million viral pneumonia cases alone annually.[1] Adaptive and innate immune systems, together with airway epithelial tissues, become a major battlefield against viral infections, and a robust immune response is essential for viral clearance. However, an immunological paradox in various respiratory viral infections is that strong immune and inflammatory responses usually lead to tissue inflammation, cytokine storm, acute lung dysfunction, chronic tissue damage, or the exacerbation of pre-existing inflammatory diseases. Reversely, persistent or chronic lung inflammation can interfere with protective immune responses in combating new infections. Complex interactions between infections and inflammations were more specifically derived from the overlapped cellular and molecular compositions that are protective in anti-viral immune defenses but can be pathogenic to induce tissue damage. In innate immune responses, monocytes, macrophages (MΦs), granulocytes, and airway epithelial cells mediate viral entry into host cells and produce various inflammatory mediators partially for viral clearance and often lead to tissue damage. In adaptive immune responses, T cells respond to the viral peptides presented by viral-infected antigen-presenting cells (APCs) to control viral infections. However, T cells can induce both protective and pathogenic responses, as Yin-Yang interactions at the cellular and molecular levels or as a mysterious Roman mythological figure "Janus" with two faces looking in opposite directions.

Chronic obstructive pulmonary disease (COPD) designates a complex of lung inflammatory pathologies, including emphysema, chronic bronchitis, chronic bronchiolitis,[2,3] which manifest persistent or progressive airflow limitation, lung dysfunction, and airway tissue damage and remodeling. Ranked as the third leading cause of global mortality following heart diseases and stroke,[4] COPD killed >3 million people worldwide in 2016 and affected around 10% and 25% of middle-aged and senior (>70 years of age) populations, respectively, in the Australian cohorts.[5] In

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etiology, COPD involves mixed genetics and environmental factors, including genetic elements prone to inflammatory pathology, exacerbation by bacterial and viral infections, and exposure to various environmental pollutants.[6,7] In pathogenesis, COPD is initiated by inflammatory responses through a complex interaction of airway epithelial, stromal, and immune cells, together with systemic inflammatory cells and mediators.[8] These interactions further lead to functional dysregulation, structural damage, and obstructive reconstruction of airway tissues, reducing respiratory capacity symptomatically. Since various innate immune mechanisms in respiratory viral infections and COPD have been comprehensively reviewed,[9-11] we briefly summarize key innate compositions below and emphasize T cell-mediated immune responses as critical viral-specific responders and regulators in the crosstalk between lung infections and inflammations.

Comorbidity and Innate Immune Responses in Respiratory Viral Infections and COPD

Considerably abundant evidence supports that viral infections are critical factors to induce the pathogenesis and acute exacerbation of COPD (AECOPD) [Table 1]. Implementation of molecular genetic approaches has facilitated the demonstration of viral infections in half of all AECOPD,[12,13] with the positivity of viral genetic elements ranging approximately from 22% to 64% in AECOPD patients from 20 cohorts[14,15] and 24 cohorts,[11] or at an average of 36.7% in COPD patients from 28 cohorts.[16] The positive rate of each respiratory virus in AECOPD varies, with human rhinovirus (HRV) at a range of 12% to 63% as the most detected virus[14] [Table 1]. Stable COPD patients show a lower percentage of a total viral infection rate in comparison to AECOPD patients. For example, 12%[17] or 19%[18] of total viral infection has been detected in stable COPD. The most common viruses detected in stable COPD were respiratory syncytial virus (RSV) (24%), HRV (7.3%), and coronavirus (5.9%) in the London cohort.[13] Comorbidity rates between respiratory viral infections and COPD are impacted by various confounding factors. For example, a low viral prevalence in the London cohort was likely confounded by a relatively high influenza vaccination rate (74%).[19]

Host-pathogen interactions and innate immune responses in respiratory viral infections and COPD involve airway epithelial cells, stromal cells, and innate immune cells[9-11] as major components forming the activation (input) and effector (output) arms of T cell immunity. Various inflammatory mediators produced by these cells, such as circulating cytokines, chemokines, small molecular mediators, and reactive oxygen species (ROS), are up-regulated to damage airway tissue structures and lung function, eventually reducing respiratory capacity and inducing severe clinical symptoms. As a result, these innate responses will enhance mucus production, disrupt mucociliary clearance and physical integrity of the epithelial barrier, and mediate immune cell migration in the airway. Two major categories of innate molecules critically regulate T cell responses in viral infection and inflammation. First, pattern recognition receptors are important host receptors to interact with pathogen-associated molecular patterns (PAMPs) from viruses to initiate the production of inflammatory mediators for immune regulation.[56] For example, endocytic toll-like receptor (TLR) 3 and TLR7–9 bind viral PAMPs to initiate signaling cascades and activate various transcription factors to regulate cytokine production. Specifically, transcription factors interferon (IFN) regulatory factor (IRF) 3 and IRF7 regulate the production of type I interferons, while transcription factors activator protein 1 and nuclear factor κB mediate the production of pro-inflammatory cytokines.[56,57] Second, cytokines and chemokines produced by innate cells in viral infections further display a broad effector function, such as regulating the pathogenesis mediated by airway epithelia, recruiting other hematopoietic cells, and promoting peptide antigen presentation for T cell activation. For example, chemokine (C-X-C motif) ligand (CXCL) 1/growth regulated oncogene-α, CXCL5/epithelial-derived neutrophil-activating peptide 78, and CXCL8/interleukin (IL)-8 attract neutrophils and monocytes to lung tissues.[8] CXCL9 (monokine induced by IFN-γ), CXCL10 (IFN-γ-induced protein 10 kDa or IP-10), and CXCL11 (interferon-inducible T cell α-chemoattractant) attract type 1 helper T (Th1) cells and cytotoxic T cells to lung tissues.[8] Moreover, interferon production is known to up-regulate the expression of human leukocyte antigen (HLA) class I proteins and co-stimulatory molecules on APCs, such as monocytes, MΦs, and dendritic cells (DCs), for T cell activation.[58]

T Cell Responses in Respiratory Viral Infections and COPD

T cells can be activated at least by three mechanisms, antigen presentation, co-stimulation or co-inhibition, and cytokine stimulation.[59,60] Antigen presentation defines the specificity of T cell responses to viral peptides presented by viral-infected cells. For example, the intracellular infection of influenza viruses stimulates the presentation of viral peptides by either HLA class I proteins to $CD8^+$ T cells or HLA class II proteins to $CD4^+$ T cells. Co-stimulation and co-inhibition involve cell contact-based molecular interactions between APCs and T cells, for example, the interaction of CD80 or CD86 molecules on APCs with CD28 molecule on T cells for the stimulation of T cell responses or with cytotoxic T lymphocyte-associated antigen 4 protein on T cells for the inhibition of T cell responses.[61] Cytokine stimulation has been most often studied and discovered in respiratory inflammation. There are many examples of cytokines contributing to T cell activation and the regulation of lung inflammation.[62] For example, IL-33, a cytokine of the IL-1 family, can be released from epithelial cells to interact with cell surface receptor suppression of tumorigenicity 2 (ST2) to stimulate $ST2^+CD4^+$ T cells and other $ST2^+$ immune cells for the induction of steroid-resistant type 2 inflammation.[63] In addition to conventional T cells, unconventional T cells can be activated at the early time of primary infections, such as the responses of natural killer (NK) T cells and mucosal-associated invariant T cells.[59,60,64] After 2 to 4 weeks of infection, conventional T cells expand clonally and accumulate in infection sites to induce anti-viral immune responses.[60]

Whether T cell responses contribute to the pathogenesis of COPD or lung inflammation is an intriguing and challenging question for further investigations. As a proof of concept, T cells transferred from cigarette smoke-exposed

Table 1: Viral pathogeneses, innate immune responses, and comorbidity in COPDs.

Viruses	Features and pathogeneses	Innate immunity	Comorbidity in COPD
Human rhinovirus (HRV)	Positive sense, single-stranded RNA, picornaviridae family. More than 150 serotypes.[25] More than 60% serotypes bind ICAM-1[20] to invade bronchial epithelial cells and alveolar MΦs.	Replicates in bronchial epithelial cells to produce CXCL10,[21] IL-8. Infects alveolar MΦs to produce TNF-α, CXCL10, CCL5 (RANTES), eotaxin-1, ICAM-1, and neutrophil elastase via NF-κB activation.[22] Production of CXCL10, CCL5, and TNF-α attracts naïve T cells. Infects primary human airway fibroblast to produce chemokines for neutrophils.[23]	HRV causes most frequent viral infections in COPD.[14] HRV is positive in 17.3%,[24] 16.4% of 2000 COPD cases.[14] HRV is positive in 12% to 63% childhood community-acquired pneumonia and/or bronchiolitis from 19 cohorts.[25] 90% HRV infections in COPD patients cause exacerbation in three cohorts.[11]
Respiratory syncytial virus (RSV)	Negative single-stranded RNA-enveloped virus. A common cause for bronchiolitis. Enter host cells through micropinocytosis followed by proteolysis of the fusion (F) protein.[26]	Induces high expression of inflammatory markers.[13] Interacts with PRR (TLR3) in lung epithelial cells[27] to produce cytokine and inflammatory mediators *via* NF-κB activation and further recruit neutrophils and activate T cells.[28] RSV RNA interaction with TLR3 is associated with declining lung function in COPD.[27]	RSV is positive in 5.3% exacerbated COPD.[24] RSV is 9.9% positive in 2000 COPD cases.[14]
Influenza virus	Segmented negative-sense, mostly single-stranded, orthomyxoviridae. Causes seasonal flu. HA and NA interact with N-linked glycans to induce endocytosis for cell entry.[29]	Replicates in alveolar epithelial cells to recruit $CCR2^{hi}$ inflammatory monocytes[30] and induce alveolar MΦ apoptosis. Infects neutrophils to induce apoptosis, impair phagocytosis, and reduce reactive oxygen species production, further causing tissue damage and inflammatory pathology.[31,32] Infects alveolar MΦs to produce TNF-α.	Influenza virus is positive in 7.4% exacerbated COPD.[24] Influenza virus is 7.8% positive in 2000 COPD cases.[14] Influenza virus is positive in 25%[18] or 36%[33] of COPD cases.
Herpes simplex virus (HSV-1)	Double-stranded DNA, alpha herpes virus. Causes persistent infection.	Infects MΦs, DCs through interacting with TLR2/9 to reduce IL-1β and nitric oxide synthase but enhances type I IFN and MCP-1.[34] Reduces lung function and increases mortality.[9]	HSV-1 is positive in 19% of COPD patients[9]
Adenovirus	Double-stranded DNA, non-enveloped. Causes life-threatening infections of the lower respiratory tract in immune-compromised individuals. Infects bronchial epithelia and integrates the viral *E1A* gene to the host genome in COPD.[35]	Infects airway epithelia, persists without detectable replication[36], and amplifies inflammation in cigarette smoke exposure.[36] Adenovirus early region 1A (E1A) protein interacts with ICAM-1 promoter region in lung epithelial and enhances ICAM-1 expression.[35] E1A protein enhances growth factor production and up-regulates pro-inflammatory signaling to regulate airway remodeling in COPD.[37] Adenovirus 19-kDa protein inhibits HLA class I production and minimizes $CD8^+$ T cell activation.[36]	Adenovirus is 2.1% positive in 2000 COPD cases.[14] Adenovirus is 7% to 10% positive in exacerbated COPD.[38]
Epstein-Barr virus (EBV)	Double-stranded DNA, enveloped, gammaherpesvirus. Infects 95% world population.[39] Interacts with CD21[40] on B cells and Ephrin receptor A2 on epithelial cells[41] for cell entry.	Inhibits antigen presentation. Likely increases GM-CSF in monocytes to inhibit monocytes from maturation for antigen presentation,[9] maintain pro-inflammatory function, and promote neutrophils migration from the blood.	EBV infection increases in COPD.[42]
Human immunodeficiency virus (HIV)	Positive-sense, single-stranded, enveloped RNA virus, genus lentivirus, and family retroviridae. ~35 million people live with HIV. Enters the airway epithelium through breaking down cell junctions. Infects MΦs by binding of viral gp120 to CCR5 or CXCR4 and infects $CD4^+$ T cells by binding of viral gp120 to CD4.	Increases inflammatory cytokines IL-6 and CRP, but not IL-8 or TNF-α.[43] Infects monocytes and MΦs to produce circulating sCD163[43] and sCD14[44] as monocyte markers which are associated with severe inflammation and high risk of radiographic emphysema. Circulating endothelin-1 is a biomarker for airflow obstruction in HIV^+ individuals.[43] HIV^+ COPD shows a high frequency of activated $CD8^+$ T cells in blood and BALF and high activated alveolar MΦs[45] to produce IFNγ. HIV^+ emphysema shows a low frequency of $CD4^+$ cells and $CD4^+/CD8^+$ T cells, but a high level of sCD14.[44]	HIV is positive in 2% to 37% cases of emphysema or airflow obstruction.[46] 25% HIV^+ individuals have COPD.[47] 6.8% to 21.0% HIV^+ individuals show COPD.[48] 26% HIV^+ smokers show airflow obstruction.[49]

(*continued*)

Table 1
(continued).

Viruses	Features and pathogeneses	Innate immunity	Comorbidity in COPD
Human coronavirus (HCoV)	Positive-sense, single-stranded, enveloped RNA virus. 150 serotypes were divided into alpha, beta, and gamma coronavirus. HCoV is positive in 15% of adult patients diagnosed as common colds.	Binds to ICAM-1 for cell entry. Alpha-coronavirus-229E isolate binds CD13. Alpha-coronavirus-NL63 binds ACE2.	HCoV is positive in 4.1% of 2000 COPD cases[14] and is linked to COPD exacerbation.[50]
Severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2	SARS-CoV binds ACE2.[25] SARS-CoV-2 uses ACE2, CD26, CD147, and TMPRSS2 as cellular receptors.[51,52]	SARS-CoV infects cells and is released from cells through endosomal fusion. SARS-CoV and SARS-CoV-2 induce acute lung inflammation, respiratory syndromes, and mortality, as associated with pre-existing COPD. ACE2 expression level high on the bronchial epithelial cells in overweight COPD patients.[53]	A higher risk of more severe COVID-19 is shown in COPD patients at a relative risk of 1.88,[54] or at a much higher odds ratio (OR) of 5.69.[55]

ACE2: Angiotensin-converting enzyme 2; BALF: Bronchoalveolar lavage fluid; CCL5: CC chemokine ligand-5; CCR: C-C chemokine receptor; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CXCL10: Chemokine (C-X-C motif) ligand 10; CXCR: C-X-C chemokine receptor; DCs: Dendritic cells; GM-CSF: Granulocyte-macrophage colony-stimulating factor; gp120: HIV envelope glycoprotein; HA: Hemagglutinin; HLA: Human leukocyte antigen; ICAM-1: Intercellular adhesion molecule 1; IFN: Interferon; IL: Interleukin; MΦs: Macrophages; MCP-1: Monocyte chemoattractant protein 1; NA: Neuraminidase; NF-κB: Nuclear factor κ light chain enhancer of activated B cells; PRR: Pattern recognition receptor; RANTES: Regulated on activation, normal T cell expressed and secreted; sCD163: Soluble CD163; sCD14: Soluble CD14; TLR: Toll-like receptor; TMPRSS2: Transmembrane protease, serine 2; TNF-α: Tumor necoris factor-α.

mice are sufficient to cause lung tissue inflammation and destruction in immunodeficient recipient mice without cigarette smoke exposure.[65] Although cigarette smoke-exposed mice do not represent COPD, the transferrable T cell-mediated lung pathology may be implicated in COPD, since COPD patients show the oligoclonal expansion of $CD4^+$ T cells. Particularly, the $CD4^+$ T cell subsets with specific autoreactivity to elastin antigens induce T cell proliferation and cytokine production in COPD, demonstrating the pathogenicity of autoreactive $CD4^+$ T cells.[66] $CD8^+$ T cells can be stimulated by intracellular microbial infections, such as viral-infected cells in viral-induced pneumonia.[67] It is critical to understand how viral-specific $CD8^+$ T cells are different from or similar to the "persistently activated" cytotoxic $CD8^+$ T cells as a large population of lymphocytes in the airway of COPD.[67] These persistently activated $CD8^+$ T cells are considered contributors to COPD pathogenesis because their abundance is positively associated with COPD progression and reduced value of forced expiratory volume in 1 second (FEV_1) in smokers.[68]

$CD8^+$ T cells

Activation kinetics

In respiratory viral infections, infected DCs and MΦs migrate from lung tissues to the draining lymph nodes or mucosal-associated lymphoid tissues to activate $CD8^+$ T cells by presenting antigenic viral peptides, the costimulatory interaction of surface molecules, and the stimulation of innate cytokines. Activated $CD8^+$ T cells emerge and fluctuate in tracheal aspirates of individuals within the first 10 days upon the onset of respiratory symptoms in the "common cold" infections of HRV, RSV, human coronavirus, or influenza A virus (IAV).[69] Similarly, primary H1N1 IAV infection in rhesus monkey brings activated $CD8^+$ T cells (not necessary to be antigen-specific) to appear in blood and lung tissues on days 5 to 7 and peak on days 7 to 10 post-inoculation[70] [Figure 1]. Reinfection of H1N1

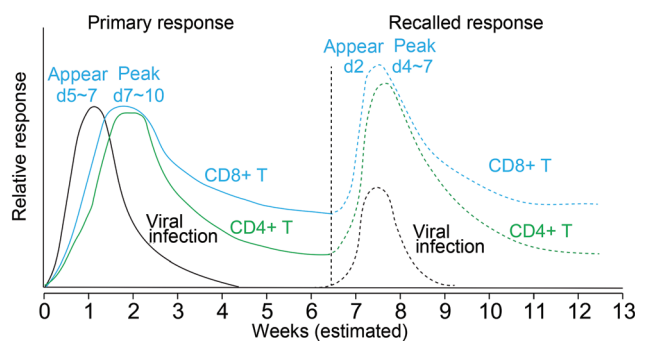

Figure 1: Hypothetical kinetics of $CD4^+$ and $CD8^+$ T cell responses in viral infections. The estimated days of $CD8^+$ T cell responses are based on H1N1 influenza A virus infection in a non-human primate model, considering multiple viral infections (HRV, RSV, HCoV, and influenza viruses) diagnosed as "common cold" in humans. D5–7 means the days of 5 to 7 upon the onset of clinical symptoms. HCoV: Human coronavirus; H1N1: Hemagglutinin 1 neuraminidase 1; HRV: Human rhinovirus; RSV: Respiratory syncytial virus.

speeds up the appearance of $CD8^+$ T cells in the lung as early as day 2 post-inoculation with a peak on days 4 to 7.[70] The antigen-specific $CD8^+$ T cells stained with the matched HLA class I proteins and predicted RSV peptides emerge during the first week upon the onset of symptoms, peak in the second week, and gradually disappear in the eighth week. Reinfection of RSV will stimulate a spike of $tetramer^+$ $CD8^+$ T cells for 2 weeks and then maintain at a lower level.[69] Results demonstrate that antigen-specific $CD8^+$ T cells undergo the contraction of effector $CD8^+$ T cells and the differentiation of a memory subset that remains within the lung. In terms of tissue tropism, the RSV- and IAV-specific $CD8^+$ T cells were enriched in the lung with less frequency in the blood,[71] facilitating anti-viral effector and memory responses in infected tissues.

Effector responses

In addition to $CD8^+$ T cells isolated from human tracheal aspirates, $CD8^+$ T cells are more accessible from other

sources, such as bronchoalveolar lavage fluid (BALF) and blood to test their responses. Peptides from RSV, IAV, or HRV similarly activate blood CD8$^+$ T cells to produce IFN-γ, tumor necrosis factor-α (TNF-α), and IL-2. Activated CD8$^+$ T cells from individuals with "common cold" viral infections express various activation markers [Figure 2], including pan-leukocyte marker CD11a, IL-2 receptor α (CD25), an inhibitory receptor CD94/NK group 2 member A, activation markers CD44, CD38, human leukocyte antigen DR-locus (HLA-DR), and a proliferation marker Ki-67,[69] together with reduced expression of lymphoid homing receptor CD62-ligand (L-selectin).[72] Activated CD8$^+$ T cells particularly display cytolytic effector responses to provide immune defense against intracellular viral infection [Figure 2]. The surface up-regulation of lysosomal-associated membrane protein-1 (LAMP1 or CD107a) is a cytolytic marker of CD8$^+$ T cell degranulation for the secretion of perforins and granzymes, which together punctuate the membrane of viral-infected cells and kill viruses. Activated CD8$^+$ T cells also produce abundant IFN-γ and TNF-α cytokines to facilitate the cytolytic immune responses by enhancing the intracellular viral-killing mechanisms, such as the generation of ROS.

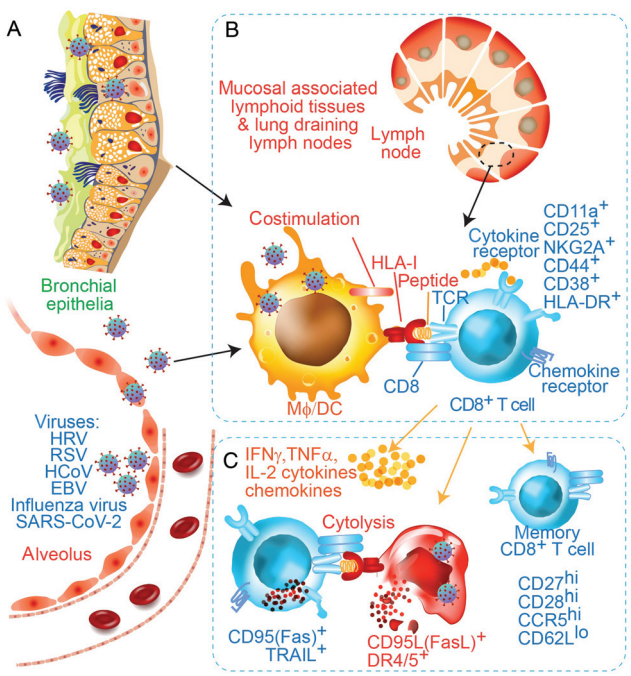

Figure 2: Peptide antigen presentation and CD8$^+$ T cell responses in respiratory viral infections. (A) Respiratory viruses infect bronchial and alveolar epithelial cells to replicate inside and produce innate cytokines or chemokines to attract blood cells to lung tissues. (B) Epithelial cells, MΦs, or DCs with infected viruses encounter naïve T lymphocytes in airway submucosa, mucosal-associated lymphoid tissues, or lung draining lymph nodes for antigen presentation and T cell activation. CD8$^+$ T cell activation is mediated by HLA class I proteins–peptide antigen-TCR interaction, costimulatory molecular interaction, and cytokine stimulation. (C) Activated CD8$^+$ T cells produce cytokines (eg, IFN-γ, TNF-α) and chemokines, and mediate cytolytic activities for viral killing and clearance. Upon the control of viral infection, survived CD8$^+$ T cells develop memory phenotypes. CCR5: C-C chemokine receptor type 5; CD62L: CD62-ligand; DC: Dendritic cell; DR4/5: Death receptors 4 and 5; EBV: Epstein-Barr virus; Fas: Fas cell surface death receptor; FasL: Fas ligand; HCoV: Human coronavirus; HLA: Human leukocyte antigen; HRV: Human rhinovirus; IFN-γ: Interferon γ; IL-2: Interleukin-2; MΦ: Macrophage; NKG2A: Natural killer group 2 member A receptor; RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TCR: T cell receptor; TNFα: Tumor necrosis factor α; TRAIL: TNF-related apoptosis-inducing ligand.

Viral clearance

Intensive studies using adoptive transfer or depletion of activated CD8$^+$ T cells in the mouse system demonstrated the protection of clonal and polyclonal CD8$^+$ T cells to reduce the titers of infected RSV and IAV.[73] Limited human studies also established the role of CD8$^+$ T cells in eliminating respiratory viruses. Experimental infection of RSV in human adults demonstrates a correlation between the number of pre-existing viral-specific CD8$^+$ T cells in airways and a reduced viral load in the nasal cavity and bronchial brushings.[74] Human adults infected with influenza virus similarly display an association between CD8$^+$ T cell cytolytic activity and the clearance of viral shedding in nasal washes[75] by showing that a low IFN-γ$^+$ CD8$^+$ T cell frequency is associated with higher viral titers in H7N9 IAV infection.[76] Multiple mechanisms have been demonstrated in CD8$^+$ T cells to play a cytolytic effector function to clear viral infections. In addition to the cytolytic function mediated by perforins and granzymes, CD8$^+$ T cells can further induce cell death through the cell contact-dependent interaction between CD95 (Fas) and CD95L (FasL) that leads to the apoptosis of virally infected cells for viral clearance [Figure 2], as demonstrated in RSV infection.[77] Moreover, cell contact-dependent interaction can be further mediated by TNF-related apoptosis-inducing ligand (TRAIL) on CD8$^+$ T cells with TRAIL-R1/R2 (death receptor [DR]4/5) on viral-infected cells.[30]

Memory responses

Factors determining the differentiation of memory subsets from naïve precursors remain poorly understood. Chemokine receptors CC chemokine receptor-5 (CCR5) and C-X-C chemokine receptor (CXCR) 5 appear to be involved in this decision-making process after influenza virus infection in mice. CCR5$^{-/-}$CXCR3$^{-/-}$ CD8$^+$ T cells cannot be fully activated and further contract after viral clearance, supporting the chemokine-directed localization of T cells within infected tissues is critical for antigen encounter, activation, differentiation, and memory formation of CD8$^+$ T cells.[78] A naive (CD45RA) or memory (CD45RO) marker combined with a chemokine receptor CCR7 for lymphoid tissue trafficking or a molecule CD27 for co-stimulation are generally used to label different subsets of memory T cells in humans. Briefly, CD45RA$^+$ CCR7$^+$ labels naïve CD8$^+$ T cells; CD45RA$^-$ CCR7$^+$ labels central memory CD8$^+$ T (T_{CM}) cells; CD45RA$^-$ CCR7$^-$ labels effector memory CD8$^+$ T (T_{EM}) cells; and CD45RA$^+$ CCR7$^-$ labels terminally differentiated effector memory CD8$^+$ T (T_{EMRA}) cells.[79] In RSV infection,[74] viral-specific memory CD8$^+$ T cells typically enrich with the T_{EM} subset that expresses a high level of CD27, CD28, and CCR5, and low CD62L, allowing rapid reactivation in lung tissues [Figure 2]. Recently, tissue-resident memory was used to describe tissue-resident memory T (T_{RM}) cells that localize in regional tissues and rapidly respond to infections. In RSV or IAV infection, induced T_{RM} cells are considered to localize in the lung parenchyma, along the wall of large airways, in tissues surrounding bronchioles and alveoli, airway lumen, but not in the lung-draining lymph nodes that are for T_{CM} cells.[73] The generation of T_{RM} cells in influenza[80] and RSV vaccinations[81] through an intranasal route rather than a systemic pathway interestingly supports the tissue

residency of T_{RM} cells. Phenotypically, RSV-specific T_{RM} cells expressing high CD69 and CD103 (αE subunit in the integrin αEβ7 molecules) in human BALF[74] are different from $CD8^+$ T cells in the blood, $CD8^+$ T cells newly trafficked to lung tissues, or T_{EM} cells primarily surrounding blood vessels or within the vasculature tissues.

Secondary responses

Viral-specific $CD8^+$ T cells can persist for several months and years post-infection, such as upon the infection of RSV[74] or severe acute respiratory syndrome (SARS)[82] viruses, although a speedy declination of viral-specific memory $CD8^+$ T cells appears in the elderlies with RSV infection.[83] Upon encountering the same or cross-reactive viral pathogens in reinfection, memory $CD8^+$ T cells rapidly expand [Figure 3] to produce effector cytokines and cytolytic molecules, including IFN-γ, TNF-α, and granzymes, for viral clearance.[84,85] As essential frontline defenders, T_{RM} cells can more rapidly expand *in situ* for cytokine production and effector responses before the recruitment of circulating memory $CD8^+$ T cells, as demonstrated in mice with IAV infection.[86] CXCR3 and CCR5 are critical for memory $CD8^+$ T cell expansion upon reinfection, supporting the important roles of chemokine-mediated migration.[78]

Protection

Multiple vaccination studies, such as vaccination using $CD8^+$ T cell epitopes against RSV,[87] mediate the reduction or clearance of lung viral titers following RSV challenge. Memory $CD8^+$ T cells are usually known to protect against the infection of the same subtype of viruses. Moreover, the protection against the infection of heterosubtypic viruses has been interestingly evidenced for IAV vaccination. IAV is known for antigenic drifting by mutating residues in surface hemagglutinin (HA) and neuraminidase (NA) proteins, leading to the loss of protection from prior vaccination using a different IAV subtype. However, cross-subtype protection can be mediated by memory $CD8^+$ T cells, as demonstrated in H1N1 IAV-immunized mice for controlling a lethal challenge of H2N2 IAV without inducing anti-H2N2 neutralizing antibodies[88] or controlling a challenge of the highly virulent subtype of H7N7 without anti-H7N7 neutralizing antibodies[89] [Figure 3A]. This cross-subtype protection mediated by memory $CD8^+$ T cells has been shown in non-human primates as well[70] [Figure 3A]. In humans, cross-subtype protection against respiratory viral infection has been similarly implied and demonstrated. For example, $CD8^+$ T cell responses induced by unattenuated live IAV intranasally are cross-reactive to different subtypes of IAV, while antibody responses remain specific for each IAV subtype.[75] Pre-existing H3N2-specific memory $CD8^+$ T cells are associated with reduced viral shedding in later pandemic H1N1 IAV infection[90] [Figure 3A]. Moreover, pre-existing RSV-specific memory $CD8^+$ T cells in experimental RSV infections correlate with a lower symptom score.[74] Therefore, to improve the efficacy and protection relies on a better understanding of the pathway of vaccination and infection, conservation of subtype antigens, and the induction of antigen-specific $CD8^+$ T_{RM} cells, as in IAV infections[85,91] and animal studies.[70,89]

Exacerbation

As an opposite side of protection, a potential risk is that cytolytic $CD8^+$ T cells may be able to exacerbate COPD through inducing cytolysis[92,93] and cell death.[8,30,77] Moreover, can TNF-α and IFN-γ cytokines produced by activated $CD8^+$ T cells promote inflammatory pathologies, such as in RSV or IAV infection?[94] Different from anti-viral protection mediated by activated $CD8^+$ T cells upon IAV or SARS vaccination,[91,95] these $CD8^+$ T cells potentially induce immunopathology.[94] However, both cytokines can be systematically produced in abundant innate immune cells, so further investigation with controls on cell type- and subset-specific cytokine production is required to address the role of $CD8^+$ T cell-derived cytokines in a cytokine storm or inflammation. Another hypothesis is that suboptimal activation of $CD8^+$ T cells upon viral infection likely leads to relatively lower enhancement of CD69 expression and minimal contraction of activated $CD8^+$ T cells through Fas-mediated apoptosis. Thus, the accumulation of several suboptimally activated $CD8^+$ T cells may lead to pro-inflammatory responses through cytolysis and inflammatory cell recruitment in lung tissues, as consistent with an increased number but a suboptimal function of $CD8^+$ T cells in COPD.[8]

$CD8^+$ T cells in COPD

The frequency of $CD8^+$ T cells in the lung tissue and blood of COPD patients is high and inversely associated with FEV_1 value.[92,96] The $CD8^+$ T cell subsets in COPD are also functionally altered in cytolytic gene expression and inflammatory cytokine production. In comparison to control subjects without COPD or without viral infection, $CD8^+$ T cells from COPD patients with low FEV_1 values show enhanced messenger RNA (mRNA) expression of perforin and granzyme B but not FasL upon *in vitro* stimulation of IL-18 or IL-15.[93] IL-17-expressing $CD8^+$ T cells increase in the lungs and blood of COPD patients, likely contributing to the pathogenesis of COPD.[97,98] Using an *ex vivo* infection model, $CD8^+$ T cells from COPD human subjects are defective in response to the influenza virus (H3N2). The $CD8^+$ T cells from COPD patients show reduced anti-viral cytotoxicity and highly express PD-1 protein, contributing to the defective immune defense reactivity of $CD8^+$ T cells.[99] Moreover, $CD8^+$ T cell dysfunction in COPD is also shown with down-regulated CD247 (CD3ζ) expression.[100] This is consistent with the known mechanisms by which various viruses escape immune recognition and antigen presentation for T cell activation.[101]

$CD4^+$ T cells

$CD4^+$ T cells play important heterogeneous regulatory roles in anti-viral immune responses and inflammations. $CD4^+$ T cells regulate B cell differentiation and antibody production against viral infection, the activation of viral-specific $CD8^+$ T cells,[102] and the activation and recruitment of innate immune cells [Figure 4]. Interestingly, $CD4^+$ T cells can similarly mediate cytolytic functions[103] to enhance host resistance to various viruses, including IAV infection.

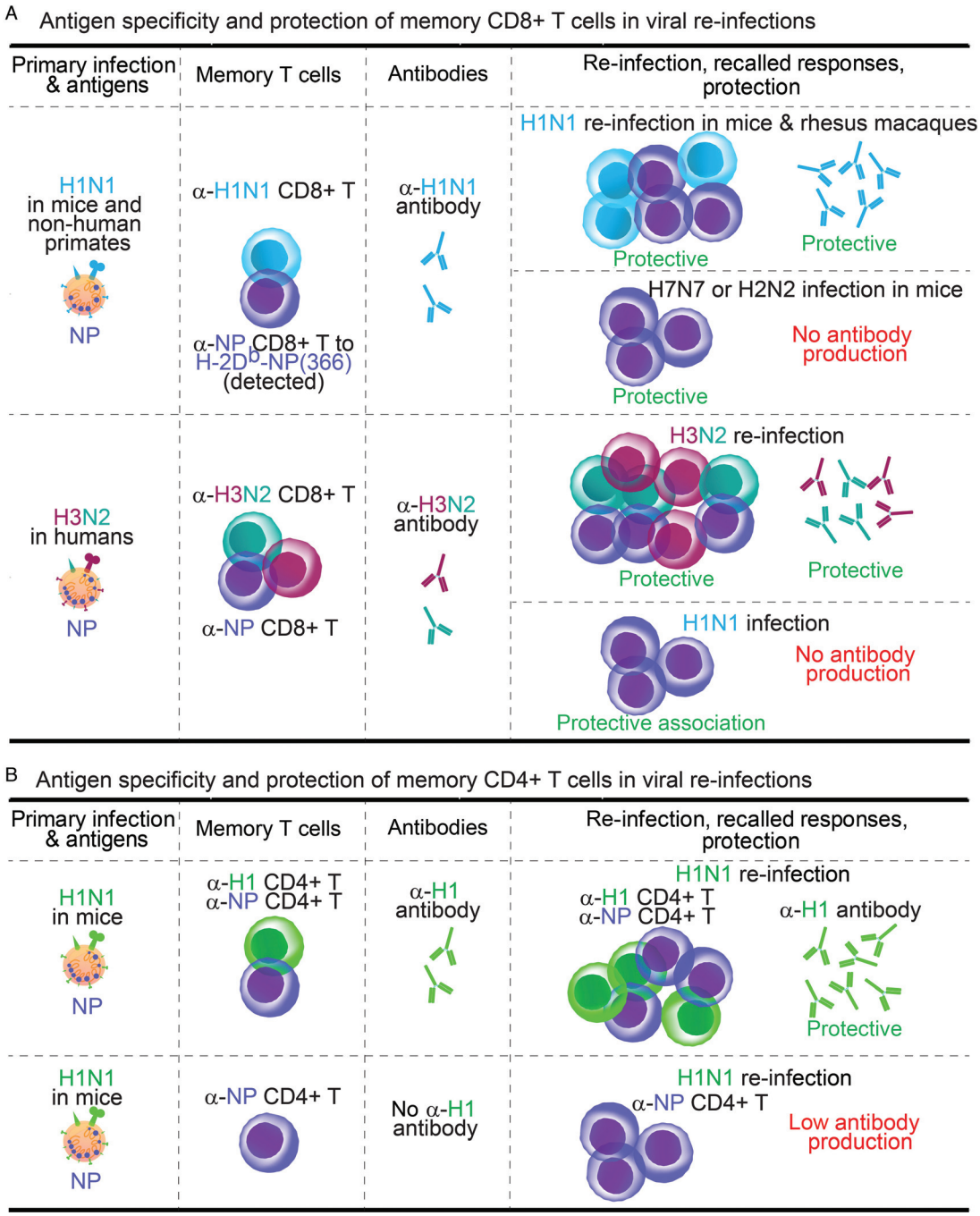

Figure 3: Antigen specificity and protection of memory T cells. Influenza virus has been used as a model to study the protection of memory $CD8^+$ (A) and $CD4^+$ (B) T cells against the re-infections of the same or a different influenza virus subtype. The hemagglutinin (subtype 1 refers to H1) and neuraminidase (subtype 1 refers to N1) are surface-exposed envelop proteins and often stimulate antibody production. The nucleocapsid (NP) protein is embedded and rarely stimulates antibody production but can induce T cell responses. H: Hemagglutinin; N: Neuraminidase; NP: Nucleocapsid protein.

Activation

In comparison to $CD8^+$ T cells, similar mechanisms but different molecules activate $CD4^+$ T cells. Specifically, $CD4^+$ T cells use HLA class II protein-mediated antigen presentation for activation and cytokine stimulation to differentiate helper or regulatory $CD4^+$ T cells [Figure 4]. In addition to viral peptide presentation, innate cytokine stimulation is quite unique for $CD4^+$ T cell activation [Figure 4A]. Different sets of cytokines facilitate the differentiation of various helper $CD4^+$ T cell subsets, each of which is controlled by various master transcription factors[104] [Figure 4]. These cytokines and transcription factors are essential to facilitate the differentiation of Th1, Th2, Th17, regulatory T (Treg), and follicular helper (Tfh) $CD4^+$ T cells [Figure 4B], as detailed in the elegant review.[104] For example, in HRV infection, the HRV-derived proteinase 2A stimulates monocyte-derived den-

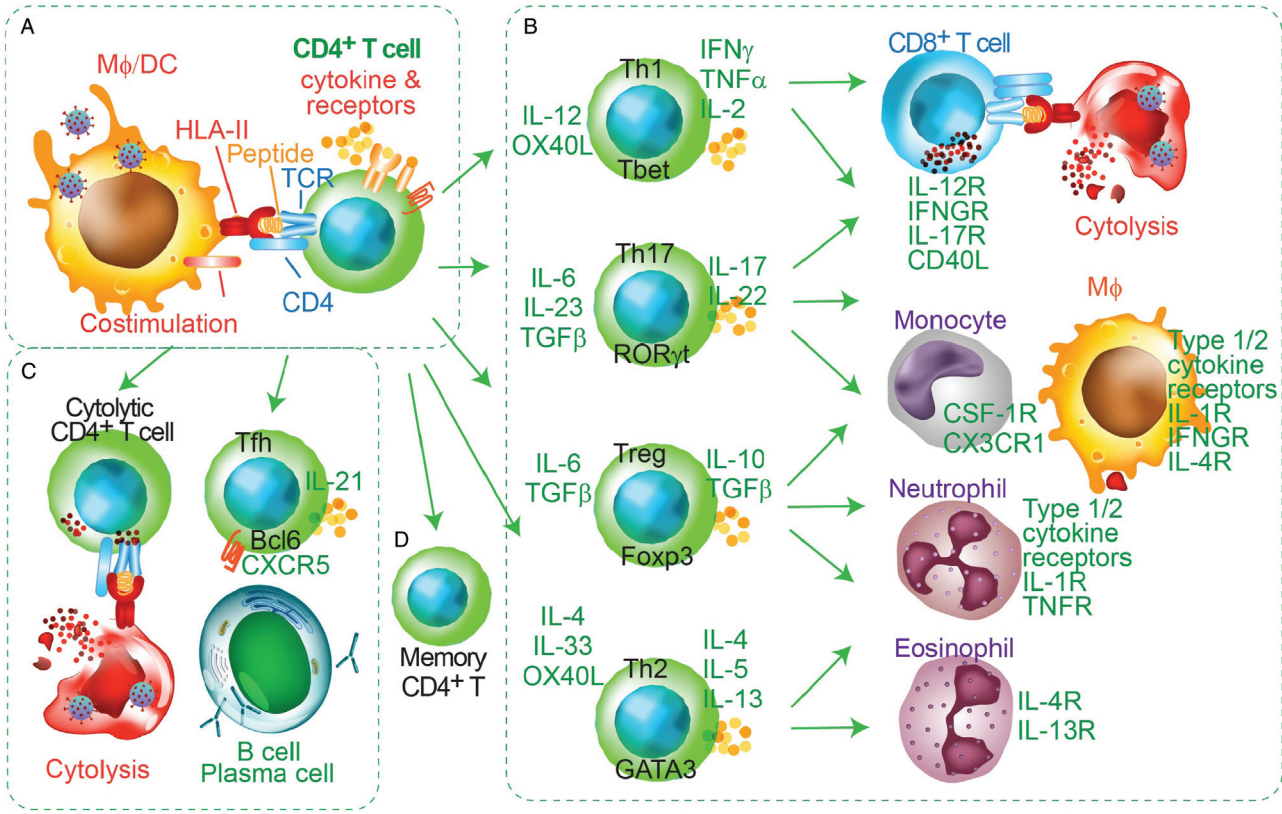

Figure 4: Peptide antigen presentation and CD4$^+$ T cell responses in respiratory viral infections. (A) Respiratory viruses infect MΦs and DCs to present peptide antigens to naïve CD4$^+$ T lymphocytes in airway submucosa, mucosal-associated lymphoid tissues, or lung draining lymph nodes. CD4$^+$ T cell activation is mediated by HLA class II proteins-peptide antigen-TCR interaction, costimulatory molecular interaction, and cytokine stimulation. (B) Activated CD4$^+$ T cells differentiate into different helper CD4$^+$ T cell subsets and produce various cytokines and chemokines to mediate effector responses of cytolytic CD8$^+$ T cells, granulocytes, MΦs, and other cells. (C) Activated CD4$^+$ T cells differentiate into follicular helper T cells to regulate antibody production and differentiate into cytolytic CD4$^+$ T cells to lyse viral-infected host cells. (D) Upon the control of viral infection, survived CD4$^+$ T cells develop memory phenotypes. Bcl6: B-cell lymphoma 6; CD40L: CD40 ligand; CSF-1R: Colony stimulating factor 1 receptor; CX3CR1: CX3C motif chemokine receptor; CXCR5: C-X-C motif chemokine receptor 5; DCs: Dendritic cells; Foxp3: Forkhead box P3; GATA3: GATA binding protein 3; HLA: Human leukocyte antigen; IFNγ: Interferon γ; IFNGR: IFN-γ receptor; IL: Interleukin; MΦs: Macrophages; OX40L: *OX40 ligand;* Tbet: T-box protein expressed in T cells; TCR: T cell receptor; Tfh: T follicular helper cell; TGFβ: Transforming growth factor β; Th: Helper T cells; TNFα: Tumor necrosis factor α; TNFR: Tumor necrosis factor receptor; Treg: Regulatory T cells; RORγt: Retineic-acid-receptor-related orphan nuclear receptor gamma t.

dritic cells to further activate CD4$^+$ T cells for the differentiation of Th1 and Th2 cells.[105]

Effector responses and protection

Activated CD4$^+$ Th1 cells express multiple cytokines, such as IFN-γ, TNF-α, and IL-2 [Figure 4B], and contribute to anti-viral immune responses. It is known that IFN-γ acts on phagocytes, such as monocytes, MΦs, and DCs, to suppress viral replication and up-regulate HLA protein expression, which reversely enhances T cell activation as in an indirect positive feedback loop. Differently, IL-2 induces the expansion and differentiation of T cells using direct positive feedback. CD4$^+$ T cells can further regulate CD8$^+$ T cell activation and function through stimulating DCs for the expression of CD40 co-stimulatory molecule to interact with CD40 ligand (CD40L) on CD8$^+$ T cells and the production of cytokine IL-12 to stimulate CD8$^+$ T cells[106] [Figure 4B]. CD4$^+$ T cells alone can be hyper-polarized by IL-2 and antigens to express perforin and granzymes as cytolytic T cells to lyse viral-infected target cells and clear the influenza virus[103] [Figure 4C]. For B cell responses, CD4$^+$ T cells use the Tfh cell subset featured with the expression of surface CXCR5 and signature transcription factor B-cell lymphoma 6 (Bcl6) to regulate B cell differentiation, antibody production, and antibody class switching[107,108] [Figure 4C]. Tfh cells mainly localize in the B cell follicles of secondary lymphoid organs[107] and can be detected in non-lymphoid lung tissues.[108] Furthermore, Treg cells are imperative in respiratory viral infections[109] by suppressing over-stimulated inflammatory responses and tissue damage mediated by other innate and adaptive immune components, and potentially inhibiting anti-viral immune responses. Different cytokines critically regulate Treg expansion and function. For example, the pro-inflammatory cytokines IL-6 or type I IFN impairs Treg activity in acute viral infections, including coronavirus disease 2019, SARS, and IAV infections. In contrast, T cell cytokine IL-2 promotes Treg expansion and response to inhibit inflammatory responses by producing IL-10 and transforming growth factor-beta (TGF-β).[110,111]

Effector responses and exacerbation

Potentially functioned as a negative side in anti-viral immune responses, Th2 and Th17 subsets of CD4$^+$ T cells differentiate in different respiratory virus infections

[Figure 4B]. Although RSV infection elicits protective Th1 and cytolytic T cells, RSV infection also stimulates Th2 responses to release IL-4, IL-5, and IL-13 for the recruitment of eosinophils, which further induce lung tissue damage.[112] For example, F and G protein of RSV may interestingly skew $CD4^+$ T cells to Th1 or Th2 subsets, respectively.[113] Overall outcomes of excess Th2 responses are known to further induce elevated airway hyperactivity, airflow difficulty, and lung function deterioration.[114] Th17 cells produce IL-17 and IL-22 and recruit neutrophils. Unsurprisingly, IL-17 production contributes to the influx of neutrophils, inflammation, and tissue damage, as in RSV infection.[115] Moreover, IL-17 can bind to interleukin-17 receptor (IL-17R) to inhibit the anti-viral function of $CD8^+$ T cells.[116]

Memory responses

In respiratory viral infections, memory $CD4^+$ T cells often express an activated phenotype, have a lower frequency than memory $CD8^+$ T cells, and contract within a few months [Figure 1].[117,118] Similarly, memory $CD4^+$ T cells can be maintained and ready for reactivation during secondary infections [Figure 4D]. The reactivated $CD4^+$ T_{EM} cells rapidly express cytokines and surface co-stimulatory receptors such as CD40L, to regulate antigen presentation, B cell differentiation, inflammatory cell recruitment, and $CD8^+$ T cell responses.[119] Memory $CD4^+$ T cells generated upon respiratory viral infections are antigen-specific in memory responses for regulating B cell activation. IAV-specific memory $CD4^+$ T cells are heterogeneous in peptide antigen specificities and functional outcomes, by responding to peptides derived from variable surface HA and NA proteins, and conserved nucleoprotein (NP) and matrix 1 proteins [Figure 3B]. Regarding antigen specificity, $CXCR5^+$ Tfh-like cells from the circulation of healthy adults were enriched for clonal reactivity to more variable HA protein than the conserved NP, while other $CD4^+$ T cells without CXCR5 expression were preferentially reactive to conserved NP. Further tests show that HA-specific $CD4^+$ T cells (Tfh or Tfh-like cells) potentially regulate neutralizing antibody responses, which are more likely elicited by the surface variable protein HA. Through interacting with the viral-infected or viral protein-endocytosed B cells, $CD4^+$ T cells are activated and differentiated by recognizing the peptides derived from the surface-exposed HA proteins to regulate antibody production against this source protein[118] [Figure 3B].

$CD4^+$ T cells in COPD

Autoreactive $CD4^+$ T cells occur in human COPD. The $CD4^+$ T cells isolated from the blood and lung samples of COPD patients with emphysema are shown with a Th1 phenotype, which correlates with emphysema severity. Anti-elastin antibodies are detected in individuals with emphysema. Unlike the protection induced by antigen-specific $CD4^+$ T cells in influenza viral infections,[118] helper $CD4^+$ T cells responding to elastin peptides from patients with emphysema may be detrimental.[66] In this elegant study, blockade of major histocompatibility complex class II molecules inhibits $CD4^+$ T-cell responses to elastin peptides, confirming their antigen specificity. Activated $CD4^+$ T cells in emphysematous lungs exhibit a predominantly Th1 effector phenotype and secrete CXCL10. The fold increase of IFN-γ and IL-10 produced by $CD4^+$ T cells is associated with disease severity. In addition to a Th1 cytokine secretion pattern (such as IFN-γ production) from most studies with COPD clinical specimens,[120,121] Th2 responses (with IL-4 production) were also reported in different studies complexed by various confounding factors and disease severity.[122] As major cells regulating autoimmune and inflammatory responses, Treg cells detected with a $CD4^+CD25^{hi}$ phenotype often reduce in COPD.[66] However, $CD4^+$ T cells labeled with transcription factor Foxp3 can increase in lung tissues,[123] potentially due to Foxp3 expression in effector and memory human T cell subsets as well.[124] Following the reduction of CD25, $CD4^+CD25^-Foxp3^+$ T cells appear to lose Treg-associated molecules and functions.[125] Therefore, functional and cytokine measurements are essential to characterize Treg cells.[123] For example, decreased $TGF\text{-}\beta^+$ and $IL\text{-}10^+$ cells in small airways, and impaired suppressive function are relevant to persistent inflammation in COPD.[126,127]

Conclusion remarks

T cells interact with innate immune components to receive input signals for activation and deliver effector responses as outputs in respiratory viral infections and COPD. Viral-infected APCs stimulate T cells to differentiate into various subsets [Figures 2 and 4] in lung tissues and reversely regulate innate cells to orchestrate immune responses for inhibiting viral infections or exacerbating inflammations. Each cellular or molecular factor has unique features to interplay in this infection and inflammation microenvironment. In particular, the peptide-reactive T cells are characterized by antigen specificity, receptor-ligand recognition, response to non-self, persistence at a low frequency, precise response to stimulation, kinetically diverse, clearing viruses, memory to primary stimulation, regulation of inflammation, and apoptosis to minimize damage. These T cell characteristics allow effective anti-viral immune responses and precise protection during various stages of viral infections. Ideally, T cells can be regulated to provide bidirectional protection by enhancing hyporeactive and suppressing hyperreactive immunity. Several molecules and cellular subsets, including T_{RM} cells, Treg, memory $CD8^+$ T cells, and viral peptide antigens, can be targeted for future vaccine or therapeutic development.

However, streamlined pathways for the activation and effector function of different immune cells remain mostly unknown and unpredictable in the context of cellular interactions, imposing challenges in designing vaccination and therapeutic strategies. Understanding the following fundamental aspects in T cell responses will significantly forward our knowledge and methodology to induce immune protection against respiratory viral infections and chronic inflammations represented by COPD. For example, can and how peptide specificity lead to different effector functions, or can peptide antigen specificity of $CD4^+$ and $CD8^+$ T cells predict protection? Can $CD4^+$ Tfh cells that regulate B cell differentiation and antibody

production link the peptide specificity of Tfh cells with antibody specificity? As initiated in the studies of IAV-stimulated $CD4^+$ T cell responses, experiments in mice support that memory $CD4^+$ T cells responding to NP peptides cannot recall the production of anti-HA antibodies [Figure 3B]. Notably, memory $CD4^+$ T cells responding to HA peptides regulate an enhanced antibody production to HA protein, leading to lower viral titers in the lungs.[118] Similar questions can be raised to understand viral-specific $CD8^+$ T cells. Moreover, how can we predict the protection or exacerbation of T cell and innate immune responses in viral infections to balance viral clearance and excessive inflammation? How do the investigations on viral virulence and invasion pathways provide knowledge to understand immunological processes that potentially exacerbate COPD? Precise and comprehensive understandings of the activation and regulation pathways of various $CD4^+$ and $CD8^+$ T cells in respiratory viral infections and COPD are fundamental to provide optimal targets for designing intervention and therapeutic strategies for disease control.

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Conflicts of interest

None.

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