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Review

The role of T cells in influenza infection and vaccination

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ABSTRACT

Influenza virus infections cause significant illness or death every year, becoming a serious health risk. Currently, influenza vaccines mainly induce responses to antibodies against specific strains, but they do not effectively induce effective T cell-mediated immunity. Humoral immunity relies on the production of antibodies that bind to surface proteins (such as hemagglutinin and neuraminidase) to combat the virus. These antibodies envelope the virus to prevent it from invading cells and also label the virus for phagocytic cells to clear. T cell-mediated immunity relies on cytotoxic cells to kill infected cells to combat the virus. Cytotoxic T cells rely on viral proteins on the surface of infected cell to recognize them. This enables the detection of more viral proteins, such as internal proteins like nucleoproteins. A better understanding of the mechanism by which T cells combat influenza is helpful for vaccine development. In this review, we elaborate on the role of T cells in enhancing anti-influenza immune defense. In addition, we explore the possibility that new influenza vaccines can induce such T cell responses.

INTRODUCTION

Every year, a large number of diseases or deaths around the world are caused by influenza viruses, which threaten public health. There are four subtypes of influenza viruses, namely A, B, C, and D (Hampson and Mackenzie, 2006; Hause et al., 2014). Subtype C induces milder clinical manifestations in adults, thereby posing a reduced health risk to the public. Subtype D circulates robustly in bovine herds (Hause et al., 2014). Sera from cattle-industry workers reveal high, occupation-linked seroprevalence (White et al., 2016). Yet data proving efficient human-to-human transmission remain scarce. In contrast, subtypes A and B are capable of causing more severe illness and are responsible for seasonal outbreaks (Baigent and McCauley, 2003; Wang et al., 2023).

The influenza A virus (IAV) is distinguished by its surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), which delineates the specific subtypes of IAV strains. Up to now, 19 distinct variants of hemagglutinin (H1–H19) and 11 variants of neuraminidase (N1–N11) have been recognized. For the influenza B virus (IBV), it is classified into two distinct lineages that are both antigenically and genetically unique, which are B/Victoria and B/Yamagata (Koutsakos et al., 2016). Due to the selective pressures from antibodies specific to the HA and NA (Thyagarajan and Bloom, 2014), the IAV experiences alterations in these proteins, which enables it to evade the immune system through a mechanism referred to as antigenic drift (Sandbulte et al., 2011). A subset of stable interior proteins, including polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), polymerase acidic protein (PA) and nucleoprotein (NP), is instrumental for detection by T cells. These protein sequences are ultra-conserved and are key targets of T-cell responses for assisting viral immunity (Assarsson et al., 2008).

Humoral immunity mediates strain-specific protection. T cell-mediated cell immunity provides broad cross-reactivity against viral

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subtypes and drift variants (Assarsson et al., 2008). T cells rely on major histocompatibility complex (MHC) to recognize viral peptide sequences on the surface of infected cells or antigen-presenting cells (APCs). Presentation of viral antigens interacts with T cell receptor (TCR), as well as cytokines and costimulatory signals (Bugeon and Dallman, 2000), triggering activation, proliferation and differentiation of naïve T cells. Most activated T cells undergo programmed cell death after infection. Nonetheless, antigen-reactive memory T cells still exist. They wait to respond to subsequent influenza virus infections. T cells can recognize epitopes on internal conserved viral proteins and have broader potential for cross-protection (McMichael et al., 1983).

T cells play a key role in anti-influenza immunity. An ideal vaccine needs to be able to trigger a strong cross-protective T cell response and reduce the disease burden of seasonal influenza or influenza outbreaks. In this review, the role of T cells in fighting influenza and vaccine strategies to stimulate T cell immunity are summarized.

$CD4^+$ T CELL RESPONSE

$CD4^+$ T cells can recognize viral peptide segments composed of 12–16 amino acids on MHC II molecules (Rossjohn et al., 2015). The current influenza vaccine mainly triggers the immune response of $CD4^+$ lymphocytes to the HA viral epitope. Mouse studies have found that the H1 viral epitope is in two regions of HA, and some HA regions have no epitopes. It is not clear whether other subtypes such as H3, H5, and H7 have this characteristic (Knowlden et al., 2019). There are studies carried out in various environments, showing that $CD4^+$ T cells play a key role in the influenza immune response (Wilkinson et al., 2012). Pre-existing $CD4^+$ T cells can enhance antibody production during infection (Besavilla et al., 2023). The defense against influenza strains is associated with $CD4^+$ T cell responses (Tsang et al., 2022). The cross-protective immune response against influenza may be due to the conserved matrix protein 1 (M1), matrix protein 2 (M2) and NP sequences in different influenza strains (Eickhoff et al., 2019). Enhancing $CD4^+$ T cell responses can come from a single mutation in the HA320-335 of influenza A virus (Hulin-Curtis et al., 2024). Studies show that epitope mutations can change the flanking amino acids in the TCR-human leukocyte antigen (HLA) complex, and enhance TCR affinity through the side chains of the core 9-mer peptide. Understanding the structural characteristics of influenza virus cross-reactive epitopes recognized by human $CD4^+$ T cells and their affinity for T cell receptors can help enhance the adaptive immunity induced by vaccines.

$CD4^+$ T cell subsets

Situations such as influenza virus infection or vaccination can make naïve $CD4^+$ T cells differentiate into subsets with different phenotypes and cytokine expression patterns, mainly including T helper 1 (Th1), T helper 2 (Th2), and regulatory T (Treg) cells, among others (Swain et al., 2012) (Fig. 1). The functional attributes of different subsets are quite different.

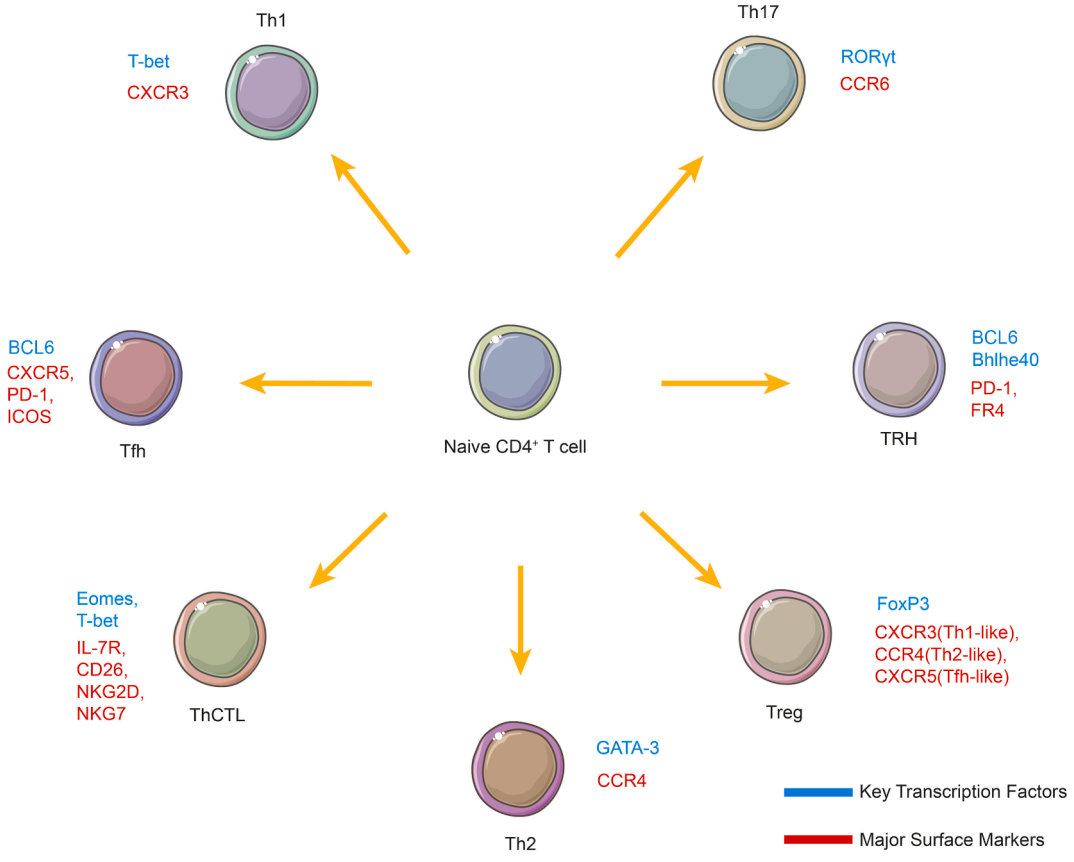


Fig. 1. Main $CD4^+$ subsets in influenza infection or vaccination. During influenza immunity, the dominant $CD4^+$ subsets recorded are Th1, Th2, Th17, Tfh, TRH, ThCTL and Treg. Their signature transcription factors and surface identifiers are itemized in the figure (t-lymphocyte icon by Servier https://smart.servier.com/is licensed under CC-BY 3.0 Unported https://creativecommons.org/licenses/by/3.0/).Abreactions: BCL6, B-cell lymphoma 6; Bhlhe40, basic helix-loop-helix family member e40; CCR4, C–C motif chemokine receptor 4; CCR6, C–C motif chemokine receptor 6; CD26, cluster of differentiation 26; CXCR3, C-X-C motif chemokine receptor 3; CXCR5, C-X-C motif chemokine receptor 5; Eomes, eomesodermin; FoxP3, forkhead box P3; FR4, folate receptor 4; GATA-3, GATA binding protein 3; ICOS, inducible T-cell costimulator; IL-7R, Interleukin-7 receptor; NKG2D, natural killer group 2 member D; NKG7, natural killer cell granule protein 7; PD-1, programmed cell death protein 1; RORγt, RAR-related orphan receptor gamma t; T-bet, T-box expressed in T cells; Th, T helper; Tfh, follicular helper T cells; TRH, tissue-resident helper T cells; ThCTL, cytotoxic $CD4^+$ T lymphocyte; Treg, regulatory T cell.

Th1 cell

Th1 cells produce IFN-γ to fight viruses, and persistent IFN-γ drives inflammation or causes tissue damage (Bermejo-Martin et al., 2009). It is important to clarify the mechanisms of Th1 response initiation and termination. After H1N1 virus attack, T cells isolated from the lung release IFN-γ, which can trigger excessive inflammatory damage to the tissue in the alveolar microenvironment of mice (Ding et al., 2024). Also, IFN-γ is a key molecule driving the progressive remodeling of influenza-related pulmonary aspergillosis and interstitial lung disease (Hiller and Mizgerd, 2024; Seldeslachts et al., 2024).

Recently, research has found that the intrinsic arginase 1 (Arg1) is related to the lifespan of Th1 cells in humans and mice, and also related to Th1-related tissue pathology in influenza infection. Selectively removing Arg1 from $CD4^+$ T cells accelerates the Th1 effector reaction specific to influenza virus and their subsequent recuperation, which results in effective viral elimination and a reduction in pulmonary pathological reactions. The authors further revealed that the regulatory role of Arg1 may be mediated through the modulation of the metabolic equilibrium between glutamine and arginine (West et al., 2023), but previous studies have failed to demonstrate the existence of Arg1 within $CD4^+$ T cells (Geiger et al., 2016).

Overall, the programming of Th1 cells depends on T-box expressed in T cells (T-bet) to clear numerous intracellular pathogens. They serve as principal transcription factors to facilitate the differentiation of T cells (Szabo et al., 2000). However, recent studies have indicated that T-bet may not be indispensable for the efficient clearance of IAV infections. Although the expression of T-bet exerts a broad influence on the cytokine generation, the efficacy of effector cells lacking T-bet is only slightly reduced, exhibiting no pronounced defects in contrast to wild-type mice. This slight decrease is due to diminished expression of C-X-C motif chemokine receptor3 (CXCR3), resulting in an inadequate concentration of T-bet-lacking, activated cells within the infected pulmonary regions (Dhume et al., 2019).

Th1-polarized memory cells produce a large amount of IL-2, which is often considered to enhance protective immunity and can enhance the activity of other immune cells [such as natural killer cells (NK cells) and $CD8^+$ T cells] (Seder et al., 2008). However, in mouse IAV infection, memory $CD4^+$ T cells lacking IL-2 are more effective against IAV than wild-type memory cells producing IL-2. The lack of IL-2 down-regulates a variety of inflammatory cytokines in the infected lung and promotes virus clearance. This phenomenon may be related to the increased sensitivity of the lung environment during virus infection to IL-2-driven inflammation, leading to immunopathology (McKinstry et al., 2019). The activation and function of T cells are affected by the calcium release-activated calcium channel (CRAC), but blocking these CRAC channels has no effect on Th1-driven anti-IAV infection immunity, which is different from their inhibitory effect on Th2-mediated allergic airway inflammation (Wang et al., 2022).

New findings show that the role of Th1 cell characteristics in anti-influenza is considered to be of great significance in combating influenza, and further research is needed. Can these factors resist other diseases? Is there a difference in their role in influenza? Or can clarifying their regulatory mechanism better balance immune and inflammatory damage?

Th2 cell

Inactivated influenza vaccine (IIV) vaccination can trigger humoral immunity, which is mediated by Th2 cells. However, protective antibodies are mainly used to prevent viral infection, and the Th1 subset is the key to clearing viruses in host cells. When the virus infects, excessive Th2 activation will weaken the Th1 response by producing a large amount of IL-4 (Moran et al., 1996). Previous studies have shown that the Th2 response may mainly rely on recruiting more eosinophils to delay virus clearance and aggravate lung pathology (Graham et al., 1994). However, virus infection can also induce eosinophil recruitment independently of Th2 cells. It has been found that IL-4, IL-5, and IL-13 do not mediate eosinophil aggregation (Chang et al., 2023). Eosinophilia was once regarded as the main driving factor of immunopathology (Chin et al., 1969; Prince et al., 1986; Waris et al., 1996). However, recent studies have shown that eosinophils can also carry out antiviral activities against influenza viruses (Chang et al., 2023; LeMessurier et al., 2020; Tiwary et al., 2021). The authors believe that this dual characteristic may be related to the different proportions of eosinophil subsets, such as the increase in the proportions of iEos and rEos. Even so, there may be other eosinophil phenotypes that are not yet clear. Their association with Th2 responses and their role after influenza virus infection still need to be further studied.

Th17 cell

In addition to the Th1 cells unique to influenza viruses, Th17 cells can also provide antibody-independent protection (Dhume et al., 2019; Eliasson et al., 2018; McKinstry et al., 2009). However, it has been reported that Th17 cells may trigger inflammatory pathology (Crowe et al., 2009; Maroof et al., 2014). Recently, research on intranasal immunization with the CTA1-3M2e-DD fusion protein found that M2e-specific Th17 tissue-resident memory T (TRM) cells accumulate in the lungs, where they can independently control infection and protect tissues from damage. This effect is independent of Th1 or Treg cells (Omokanye et al., 2022). During anti-infection, Th17 TRM cells have pro-inflammatory functions, and during resolution, they mainly play a regulatory role. This transformation helps prevent inflammatory damage and promotes tissue repair. Th17 TRM cells can differentiate into cytotoxic $CD4^+$ T lymphocyte (ThCTL) cells, which is different from the traditional view that ThCTL cells are derived from Th1 effector cells (Omokanye et al., 2022). The author said that after pulmonary TRM cells are activated, the local microenvironment may affect the function of effector cells, such as Th17 cells. More experiments are needed to confirm this.

Tfh cell and TRH cell

In tradition, follicular helper T (Tfh) cells in lymphoid follicles interact with germinal center (GC) B cells to make antibodies produce well. Some Tfh cells exist in the blood in the form of circulating follicular helper T cells (cTfh). Strongly activated cTfh is related to enhancing influenza humoral immunity, and can also be achieved by enhancing the secretion of high-affinity antibody-secreting cells and increasing HA-restricted memory B cells (Nguyen et al., 2021).

In the research on influenza infection, the mechanism of driving a strong Tfh response at 6 days post-infection (dpi) involves local antigen recognition and the situation of persistent infection signals in Tfh differentiation (Devarajan et al., 2022). The authors observed that Tfh cells were detectable in small numbers at 5–6 dpi, peaked at 7–8 dpi, and GC B cell formation occurred after 6–7 dpi. Subsequently, the authors provided these effector signals by administering two doses of live attenuated influenza vaccine (LAIV) on day 0 and day 6, demonstrating that vaccination can also induce potent Tfh responses, supporting long-lasting antibody responses similar in strength to those observed during infection. However, the specific infection signals independent of antigen presentation were not clearly identified by the authors, although they may be related to certain inflammatory factors. One study described a series of immune cell reactions to influenza infection, finding that the formation of cTfh cells was correlated with high-titer antibody production, thereby augmenting populations that secrete high-avidity antibodies alongside expanding memory B lymphocytes specific to influenza hemagglutinin. Heightened concentrations of cytokines like IL-6, IL-8, MIP-1α/β, and IFN-γ were found to inhibit the responses of antibody-secreting cells and Tfh cells, suggesting that severe infection suppresses these responses (Nguyen et al., 2021). In elderly individuals, the transformation of HA-restricted memory T lymphocytes into cTfh cells is compromised. The impaired emergence of cTfh cells in older individuals parallels heightened transcription of pro-inflammatory modules within these cells, rather than a contraction

of the TCR repertoire linked to senescence. Following vaccination, the abnormal overproduction of inflammatory cytokines such as IL-2 and enhanced tumor necrosis factor (TNF) signaling were found to inhibit Tfh differentiation and result in lower antibody titers (Hill et al., 2021). It is not clear whether TNF mainly affects T cells or lymphoid organ structures. Moreover, vaccine-induced inflammation inhibition strategies may enhance antibody production in the elderly. In conclusion, in-depth understanding of Tfh is helpful to enhance the long-lasting antibody response after vaccine immunization.

Initial Tfh cells play a role during infection. After the initial stage of infection subsides, there is controversy whether they persist to assist B cells and the formation of $CD8^+$ T cell memory. Studies have found tissue-resident helper T cells (TRH) with Tfh and TRM characteristics (Son et al., 2021). After virus clearance, they appear in the lung microenvironment, optimizing and maintaining B cell and T cell recall responses. The development of TRH relies on Tfh/TRM-related transcription factors, such as Basic Helix-Loop-Helix Family Member E40 (Bhlhe40) and B-cell lymphoma 6 (BCL6) (Son et al., 2021). TRH supports the survival of $CD8^+$ T cells in chronic viral infections in an IL-21-dependent manner (Son et al., 2021). BCL6, which is required by TRH cells, is provided by B lymphocytes residing in the inducible bronchus-associated lymphoid tissue, which also serves as the homeostatic niche for TRH cells (Swarnalekha et al., 2021). Simultaneously stimulating strong B cell and $CD8^+$ T cell responses in mucosal tissues could be a vital approach for creating a universal influenza vaccine. The function of TRH cells in both vaccination and infection continues to be a promising field for additional research.

ThCTL cell

ThCTL cells exert cytotoxic effects to eradicate cells infected with the influenza virus, particularly when the recognition capacity of $CD8^+$ T cells is diminished because of the downregulation of MHC class I molecules on infected cells (Brown et al., 2012). Among these situations, ThCTL can also play a key immune role relying on MHC II molecules (Adhikary et al., 2006; Dhatchinamoorthy et al., 2021; Jellison et al., 2005; Soghoian et al., 2012). The mechanisms of ThCTL differentiation and Tfh differentiation have certain similarities, and they also need to re-recognize the virus-specific antigens presented by the lung antigen-presenting cells; effective ThCTL differentiation needs to rely on the signals given by the persistent influenza infection. These signals are specifically manifested by the stimulation of IL-15 through infection-induced type I interferons, which further supports the development of $CD4^+$ effectors into ThCTL (Devarajan et al., 2023). In this mechanism, the transformation of $CD4^+$ effector T cells into ThCTL cells can occur without the need for CD28 co-stimulation. However, CD28 co-stimulation is particularly crucial for Tfh differentiation (Devarajan et al., 2022). These two different yet similar multi-differentiation signal mechanisms may form a checkpoint to ensure that Tfh and ThCTL only fully develop when the infection persists, so as to prevent excessive immune responses after the virus is cleared and avoid unnecessary potential autoimmune responses. Tfh cells initiate antibody responses; ThCTL activates cytotoxic immunity. Live attenuated vaccines (LAIV) emit signals of live viruses. Decoding local signals of vaccine spatio-temporal alignment contributes to achieving protection over a wider range.

Treg cell

In vitro studies show that IL-12 induces Tregs to shift toward Th1 and simultaneously induces T-box transcription factor (T-bet), IFN-γ, and CXCR3 (Verma et al., 2014). During IAV infection, IFN-γ makes Tregs have a Th1-like effector cell phenotype and maintain stability and function. If Tregs lack the IFN-γ receptor but have the IL-12 receptor, they will inhibit Th1-like polarization (low T-bet, CXCR3, IFN-γ) and promote Th2-like differentiation (high GATA binding protein 3 (GATA-3), C–C motif chemokine receptor 4 (CCR4), IL-4) (Gocher--Demske et al., 2023). Th1-like regulatory T cells limit the effector function, proliferation, and memory cell formation of $CD8^+$ T cells in acute/chronic infections, while Th2-like regulatory T cells do not (Gocher-Demske et al., 2023). The Th1-like polarization of Tregs relies on exogenous IFN-γ, not autocrine. It may enable regulatory T cells to have the ability to assess the level of inflammation and judge the expansion or contraction of effector T cell responses, which can help correctly regulate immunosuppressive functions. When vaccinating, adjuvants can be used to polarize regulatory T cells to Th2 and enhance the immunogenicity of vaccines. However, there are always challenges in achieving this goal.

Another class of Treg cells, namely $CD4^+$ follicular regulatory T (Tfr) cells, are instrumental in enhancing antigen-specific responses within germinal center B cells during influenza virus infections. Furthermore, these Tfr cells contribute to bolstering memory antibody responses aimed at the conserved area of the HA stem (Lu et al., 2021). Without Tfr cells, influenza virus-specific GC B cells and antibody titers exhibit a declining trend, which further leads to the attenuation of humoral immunity (Lu et al., 2021). Tfr cells characteristically express C-X-C motif chemokine receptor 5 (CXCR5) and BCL6, with follicles and GCs being their primary localization sites following infection or immunization (Linterman et al., 2011). Contrary to previous studies, the authors assessed antigen-specific B cell reactions on day 30 post-infection, demonstrating a decline in virus-specific plasma cells in animals lacking Tfr cells. The authors speculate that the complexity of the antigen and its duration of persistence may have influenced Tfr cell function. Specifically, the use of live virus for infection in this study, as opposed to the antigen NP-OVA (protein-conjugated compound) employed in prior studies (Clement et al., 2019; Sage et al., 2016), may have contributed to these differences. Tfr cells may specifically suppress non-antigen-restricted GC B cells by modulating the intensity of their interactions with GC B cells, thus optimizing humoral immune responses. Further experimental evidence is required to substantiate this hypothesis.

$CD4^+$ T cell immune reactions elicited by infection and vaccination

The $CD4^+$ T cell immune response triggered by influenza viruses is different from that triggered by vaccines. Figuring out these differences is quite important for improving the protective power of vaccines.

Population-specific differences in $CD4^+$ T cell responses

In children, natural infection is stronger than IIV-induced $CD4^+$ T cell response to HA and NP. It is worth noting that the immune advantage of NP-specific immune response lasts until the second year after immunization, indicating that the memory response induced by infection is more persistent. Further research found that in infected patients $CD4^+$ T cells showed enhanced versatility, manifested as the coordinated release of a variety of cytokines, such as IFN-γ (Shannon et al., 2021).

The infection-mediated advantage is more obvious among recipients of solid organ transplantation (SOT). Empirical data show that the reactivity of $CD4^+$ T cells caused by natural exposure is significantly higher than that caused by vaccination, even considering the higher possibility of using corticosteroids (e.g., prednisone) in the influenza infection cohort. Specifically reflected in the proportion of IFN-γ^+, IL-4^+ and multifunctional $CD4^+$ T cells in individuals infected with influenza A/H1N1, and the ratio of TNF-α^+, IL-2^+ and multifunctional $CD4^+$ T cells in individuals infected with A/H3N2 and B influenza example (L'Huillier et al., 2020). These differences may be the reason for the more lasting cross-protection effect of natural infection on subsequent reinfection.

Spatial dynamics of immune responses

Infection reshapes the distribution of $CD4^+$ T cells. In the mouse IBV infection model, live virus infection has been proven to induce the

specific enrichment of antigen-specific CD4$^+$ T cells in the lung parenchyma, which have the characteristics of tissue residence (Rattan et al., 2022). There is currently a paucity of evidence to suggest that commonly used influenza vaccines can elicit such tissue-resident properties.

Regulatory mechanisms of vaccine-induced immunity

In the case of natural infection, the individual's pre-existing infection history usually enhances the robustness of T cell response when re-infection through other mechanisms mediated by memory T cells. However, this history of infection or vaccination does not seem to be enough to cause a stronger immune response after the flu vaccination. Studies show that the vaccine-induced CD4$^+$ T cell response is strictly regulated by the host's pre-existing immune state and is related to the individual's vaccination history (Wild et al., 2021). It is worth noting that repeated immunity leads to reduced activation of HA118-132-specific CD4$^+$ T cells, which hinders antibody induction. In addition, the magnitude of antibody response after immunization is inversely proportional to the pre-existing fluid immunity level. The production of vaccine-induced antibodies requires the activation of vaccine-specific CD4$^+$ lymphocytes and the development of Tfh characteristics. However, in individuals who have been vaccinated multiple times, the activation of CD4$^+$ T cells will prevent the vaccine from producing a strong antibody response. The author puts forward several possible explanations for this phenomenon. Repeated antigen stimulation may lead to low expression of CD127, which is crucial for the activation and homeostasis of T cells. In addition, pre-existing antibodies may weaken the ability of APCs to capture antigens, thereby destroying the presentation of antigens to CD4$^+$ T cells. Other studies have also shown that limited activation of CD4$^+$ T cells may be a potential cause of weakened or altered antibody response in people who have been vaccinated repeatedly (Lai et al., 2020; Richards et al., 2020).

CD8$^+$ T CELL RESPONSE

The activation of CD8$^+$ T cells targeting viruses depends on the interaction between their TCR and peptide-MHC I complexes, which mainly recognize peptide sequences of 8–11 amino acids (Rossjohn et al., 2015). Since the influenza virus mainly infects airway epithelial cells, these cells are likely to present antigens through MHC I molecules, thus initiating the CD8$^+$ lymphocyte response (Ilyushina and Wright, 2016). Studies show that alveolar epithelial cells can also activate lung CD103$^+$ dendritic cells (DCs) in a granulocyte-macrophage colony-stimulating factor dependence, so as to effectively remove influenza viruses through CD8$^+$ T cells (Unkel et al., 2012). For influenza viruses, polypeptides bound to MHC I molecules mainly come from highly conservative proteins inside the virus, such as NP, PB1, PB2 and PA proteins, which are located inside the core of the virus. However, there are also polypeptides from viral envelope proteins, such as M1 (located on the inner side of the enclosure structure) and NA (on the outer side). Studies show that the length of these peptide segments is crucial to determine the reaction of CD8$^+$ T cells to antigens (Assmus et al., 2020). Neuraminidase-derived peptides NA (181–190) (SGPDNGAVAV) and NA (181–191) (SGPDNGAVAVL) have complete sequence overlap. The only difference is that there is a single amino acid protrusion at the C end of the longer peptide. This smallest peptide structure variation causes IAV-infected C57BL/6 (B6) mice to form two completely independent and non-interactive T cell groups, each of which showed different functional properties.

A key role of CD8$^+$ CTLs is to detect and destroy virus-infected cells through granulase B (GZB) and perforin, and through the participation of Fas/FasL pathway (Topham et al., 1997). The death of programmed cells prevents the further production of progeny viruses. In addition, when CD8$^+$ T cells are activated, they produce cytokines including IFN-γ, which hinders the proliferation of the virus (Kreijtz et al., 2011). With the help of these two mechanisms, CD8$^+$ T cells can effectively remove the virus and promote the host's recovery from infection (Bender et al., 1992). Similar to CD4$^+$ Th17 cells, CD8$^+$ T lymphocytes (Tc17) that secrete IL-17 have been proven to play a beneficial immunomodulatory role in the host's synergistic response to influenza A virus H5N1, H1N1 and H3N2 subtypes (Hamada et al., 2009; Wang et al., 2011). Subsequent studies have shown that the infection of the avian H7N9 subtype can lead to significant contraction of Tc17 cells in the circulation, and the reconstruction of these CD8$^+$ T lymphocytes secreting IL-17 is considered to be serologically relevant in the recovery period of the affected individual (Bao et al., 2019). Interestingly, CD8$^+$ T cells may spare some cells previously infected by influenza virus, which can survive long-term without presenting IAV antigens. This may help to minimize pathological changes associated with IAV infection (Fiege et al., 2019a).

Epitopes identified by CD8$^+$ T cell

CD8$^+$ T cells reactive to the influenza virus predominantly identify epitopes on evolutionarily conserved proteins, leading to a robust cross-reactivity in cytotoxic T lymphocyte (CTL) responses to various influenza viruses. However, the conserved antigenic epitopes presented by HLA molecules vary among individuals. A multitude of highly conserved epitopes recognized by CD8$^+$ T cells for IAV and IBV has been identified (Habel et al., 2022; Hamza et al., 2024; Menon et al., 2024; van de Sandt et al., 2019), with particular attention given to epitopes presented by HLA-A24:02, HLA-A68:01, and HLA-A11:01 molecules. Because these HLA gene variants correlate with negative consequences during influenza infection. Therefore, the formulation of vaccines targeting these T cell epitopes may help protect individuals expressing risky HLA genes from severe influenza disease. Additionally, some CD8$^+$ T cells, reactive to several epitopes, display broad-reactivity between IAV and IBV, such as the PB2(550–558) epitope presented by HLA-A24:02 (Hensen et al., 2021). Recognition of such epitopes may facilitate the creation of vaccines designed to offer extensive and long-lasting immunity across various influenza strains.

CD8$^+$ T cell regulators

A variety of signaling molecules act in concert to modulate both the count and functionality of CD8$^+$ T cells in the period of influenza infection (Fig. 2). Recently, a study has shown that the transcription factor Runx3 modulates the proliferation dynamics of CD8$^+$ T cells within the mediastinal lymph nodes (mLN) and lung during H1N1 influenza virus infection, employing disparate mechanisms. Mouse models with the Runx3 gene knocked out exhibit enhanced lymph node enlargement and CD8$^+$ T cell proliferation but significantly suppressed generation of pulmonary CTLs (Hao et al., 2024). Moreover, the absence of Runx3 exerts no marked influence the programming death of pulmonary CD8$^+$ T cells (Hao et al., 2024). Thus, the Runx3 signaling cascade potentially regulates the movement of CD8$^+$ T cells from lymphoid tissues to the pulmonary compartment or their amplification within the lung tissue itself. MicroRNA-139 can regulate CTL responses (Trifari et al., 2013), but its expression is not necessary for the influenza-specific CTL response (Hope et al., 2022). Cytokines IL-7 and IL-33 critically orchestrate antiviral CD8$^+$ immunity by fostering the initial expansion of cytotoxic T lymphocyte clones within mediastinal nodes and by potentiating effector functions inside the pulmonary milieu, respectively (Kim et al., 2019; Sheikh et al., 2022). Type III interferon (IFN-λ) can direct CD8$^+$ T cell immunity against IAV by programming dendritic cells (Hemann et al., 2019). In infected tissue, the removal of neutrophils is crucial to enhance the effectiveness of cytotoxic T lymphocyte-driven immunity. Apoptotic neutrophils release epidermal growth factor, which promotes the differentiation of mononuclear cells into antigen-presenting tissue resident macrophages, thus triggering the CD8$^+$ T cell effect function (Lim et al., 2020). According to the study, blocking the CXCR3 pathway may help prevent influenza-related lung damage (Guo et al., 2024). The interaction between IFN-γ and IAV virulence factor can regulate the function of CD8$^+$

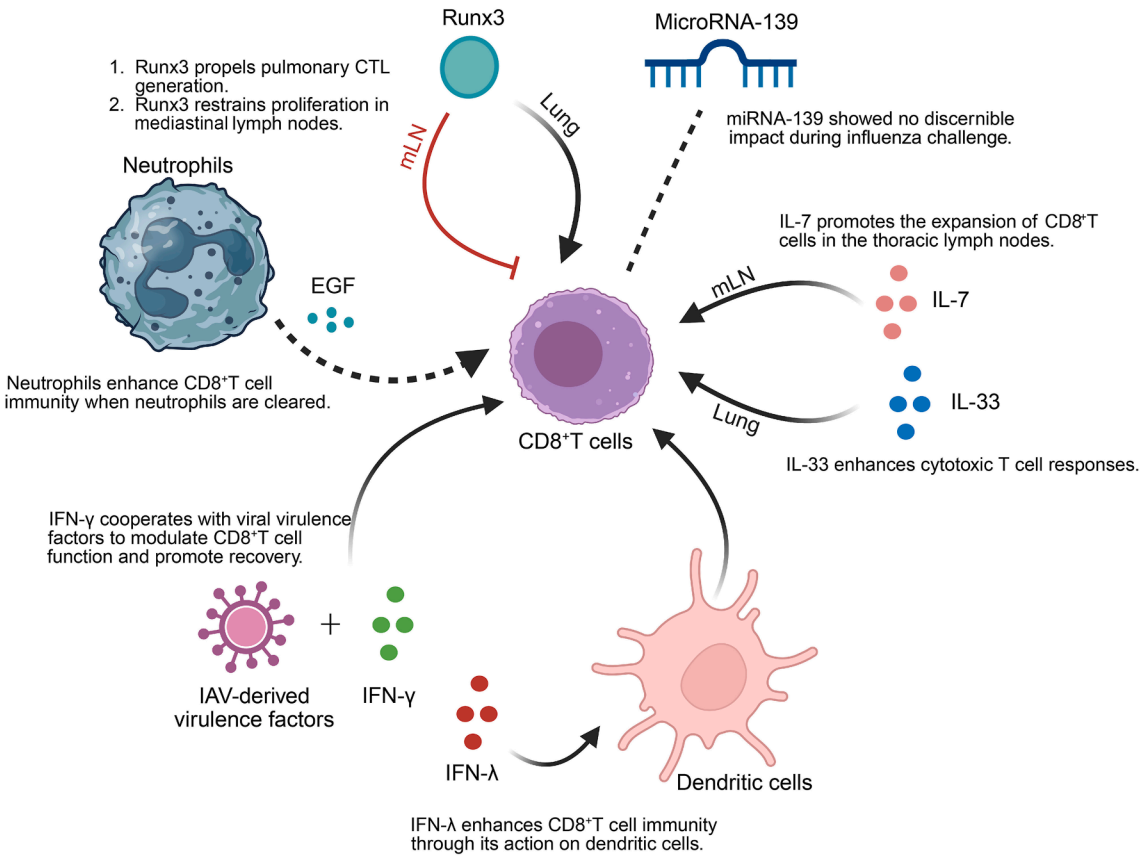


Fig. 2. Signal factors regulate $CD8^+$ T cells in influenza infection. Runx3 has a dual regulatory effect: it promotes the generation of lung CTL and inhibits the proliferation of mediastinal lymph nodes. It is worth noting that microRNA-139 did not show a significant effect during the flu attack. IL-7, IL-33, neutrophils (releasing EGF during apoptosis) and IFN-λ-regulated dendritic cells enhance $CD8^+$ T cell immunity or cytotoxicity output respectively. In the later stage of infection, IFN-γ and viral virulence factors coordinate to regulate $CD8^+$ T cell activity and promote body recovery. (Image created with BioRender.com). Abreactions: CTL, cytotoxic T lymphocyte; IFN-γ, interferon-gamma; IFN-λ, interferon-lambda; IAV, influenza A virus; IL-7, interleukin-7; IL-33, interleukin-33; mLN, mediastinal lymph node; Runx3, Runt-related transcription factor 3; EGF, epidermal growth factor.

T cells and promote the recovery of mice after infection (Barman et al., 2022).

$CD8^+$ T cells in older adults

The elderly have a high incidence and mortality rate after being infected with influenza, and are at high risk of influenza (Thompson et al., 2003). Concurrently, the effectiveness of influenza vaccines in providing protection is noted to decline as age increases (Chen et al., 2009). This age-related difference may be related to changes in $CD8^+$ T cells, including changes in their subgroup ratio, epitope recognition and TCR diversity. The proportion of $CD8^+$ T cells in total peripheral blood single nuclear cells (PBMCs) decreases, while the proportion of $CD28^{(null)}$ $CD8^+$ T cells increases, which may be the reason why the CTL response is limited and the protective effectiveness is reduced after the elderly are vaccinated against influenza (Xie and McElhaney, 2007). The author proposed that the number of $CD28^{(null)}$ $CD8^+$ T cells is negatively correlated with the number of granulase B $(GrB)^+CD62L^{(high)}$ $CD8^+$ central memory T cells, which are considered to be an early effect cell group against influenza virus infection. In the elderly, the proliferation of $CD8^+$ T cells with reduced expression of IL-7 receptor α (IL-7Rα) is associated with weaker antibody response after influenza vaccination (Park et al., 2019). Previous studies have shown that the decrease in the expression of IL-7Rα can be used as an indicator of the proliferation and exhaustion of memory $CD8^+$ T lymphocytes (Kim et al., 2006). Transcription factor MYC proto-oncogene, bHLH transcription factor (MYC), special AT-rich sequence-binding protein 1 (SATB1) and basic leucine zipper ATF-like transcription factor (BATF) may regulate the expression of aging-related genes in this cell subgroup (Park et al., 2019). Additionally, certain reduced subsets of $CD8^+$ lymphocytes, such as those expressing a tissue-resident phenotype and producing IFN-γ, are correlated with weaker antiviral immune reactions after influenza virus infection (T. H. Nguyen et al., 2021). Studies have indicated that the breadth of $CD8^+$ T cell reactions specific to subdominant epitopes of the influenza virus is diminished in the elderly population (Lee et al., 2011). This alteration may correlate to the age-related narrowing of T-cell receptor diversity within the elderly. However, another study found that despite reduced TCR diversity, the elderly retain TCRs with cross-reactivity to both IAV and Epstein-Barr virus (EBV) (Clark et al., 2022). Therefore, cross-immunity to these two viruses may be partially maintained in older individuals, although such cross-reactive TCRs may not necessarily represent the optimal specific immune response to either virus alone. One potential strategy to protect the elderly from influenza virus infections may involve boosting immunity during middle age, when the immune system still functions relatively well. Empirical study has revealed that augmenting previously activated $CD8^+$ T cell responses in middle-aged mice, initially triggered by natural infection, leads to IAV-restricted $CD8^+$ T cell responses that remain unaffected by the time elapsed between the initial natural infection and the subsequent boosting immunization (Lanfermeijer et al., 2024).

UNCONVENTIONAL T-CELL LINEAGES

Beyond classical $CD4^+$ and $CD8^+$ subsets, γδ T lymphocytes and natural killer T (NKT) cells shape influenza immunity. Dissecting their circuitry completes the cellular panorama.

γδ T cells

γδ T cells bear γδ rather than αβ TCRs. They dominate barrier surfaces and patrol against invasion (Chien et al., 2014). Once triggered, they secrete IL-17A (Wang et al., 2016), IFN-γ (Dong et al., 2018), M-CSF (Mamedov et al., 2018), IL-9 (Melandri et al., 2018) and amphiregulin (Krishnan et al., 2018), curbing H1N1, H5N1 and H3N2 infection (Carding et al., 1993; Dong et al., 2018; Guo et al., 2018). Upon H1N1 challenge, lung parenchyma is rapidly colonized by γδ T cells that release IL-17A without delay (Wang et al., 2011, 2016).

Most pulmonary γδ T cells recognize antigens via CD1d, a MHC class I-like molecule (Uldrich et al., 2013). H5N1 hemagglutinin can directly ligate sialylated receptors, eliciting IFN-γ release (Dong et al., 2018). Unlike MHC class I, CD1d presents lipids and microbial metabolites (Godfrey et al., 2008), yet viral ligands are scarce (Gaya et al., 2018). A recent study shows that infected epithelium releases cardiolipin lipids (CLs), which $CD1d^{+}$ B-1a cells capture and present to γδ T cells, driving IL-17A through the γδTCR-interferon regulatory factor 4(IRF4) axis (Wang et al., 2021). Other endogenous lipids may fuel the same circuit. Newly exported thymic γδ T cells seed the lung, acquire C-X-C motif chemokine receptor 6 (CXCR6) and adopt tissue-residency. Single-cell profiling identifies IL-17A-producing γδ T (Tγδ17) cells as TCR-$γδ^{hi}$ $CD3^{hi}$ aquaporin $3(AQP3)^{hi}$ $CXCR6^{hi}$ in both mice and patients. IL-17A output collapses when B-1a cells or B-cell CD1d are absent. Extended analysis of pneumonia patients uncovered a positive triad linking Vγ9Vδ2 cells—a dominant human Tγδ17 subset—to CLs accumulation within the respiratory tract and to disease severity, implying that extensive tissue damage liberates CLs and fuels Vγ9Vδ2 activation via a conserved lipid-sensing circuit. This convergence intimates that an analogous lipid-γδ T-cell axis operates in humans. This study reveals a functional γδ T-B-1a loop, which provides early congenital protection in the lung. Whether this dialogue demands cognate ligand recognition or involves co-stimulatory pairs like CD40L-CD40 and B7-CD28 remains unresolved.

In a cohort of adults, peripheral γδ T-cell frequency predicted H1N1 susceptibility more strongly than any other subset (Mettelman et al., 2023), contrasting with the protective role reported in children and mice (Carding et al., 1993; Dong et al., 2018; Guo et al., 2018). The discrepancy is ascribed to age-skewed TCR repertoires: adult Vγ9Vδ2 chains favor polycytotoxic profiles (Sant et al., 2019), whereas children display non-overlapping TCR landscapes (Clark and Thomas, 2020). Thus, γδ T cells may either defend or exacerbate disease depending on age and clonal composition.

NKT cells

NKT cells comprise type 1, type 2 and type 1a subsets; type 1 NKT cells (invariant NKT cells, iNKT) is most thoroughly delineated (Paget and Trottein, 2013). They express invariant Vα14-Jα18 (mouse) or Vα24-Jα18 (human) TCRs restricted to CD1d (Godfrey and Kronenberg, 2004) and rapidly secrete IFN-γ and IL-4 during early infection (Fujii et al., 2002; Lee et al., 2013; Paget and Trottein, 2013). They are deemed pivotal early-actuators and fine-tuners of the nascent immune response. Pulmonary iNKT curb H1N1 and H3N2 replication by amplifying innate responses in mice (Ho et al., 2008; Kok et al., 2011).

iNKT are widely viewed as sessile sentinels that remain anchored within tissues and eschew recirculation (Crosby and Kronenberg, 2018; Fan and Rudensky, 2016), yet two murine subsets exist: recirculating $CD244^{+}$ $CXCR6^{+}$ iNKT (C2 iNKT) and tissue-resident $CD244^{-}$ $CXCR6^{+}$ iNKT (C1 iNKT) (Cui et al., 2022). C2 iNKT depend on thymic IL-15, circulate through peripheral organs and display NK-like traits (high CD244, killer cell lectin-like receptor (KLRs)). Their absence during H1N1 infection blunts IAV-specific $CD8^{+}$ T and NK cell expansion while expanding myeloid-derived suppressor cells (MDSCs); adoptive transfer restores immunity. Researchers posit that the proliferative burst and functional priming of IAV-specific $CD8^{+}$ T and NK cells may stem from direct licensing by C2 iNKT cells (Paget et al., 2011), or indirectly via C2 iNKT-mediated suppression of MDSCs (De Santo et al., 2008). Conversely, C2-deficient mice lose less weight and survive lethal challenge, indicating that circulating C2 iNKT also fuel harmful inflammation.

A separate study revealed that NKT-derived LIGHT (TNFSF14), engaging lymphotoxin beta receptor (LTβR) on tissue-protective alveolar macrophages, amplifies their death and thereby exacerbates pulmonary pathology and susceptibility to lethal influenza infection (Shi et al., 2021). Although NKT deficiency protects against H1N1 and H7N9 (Shi et al., 2021), earlier work reported protection (De Santo et al., 2008; Ho et al., 2008; Paget et al., 2011). Differences in viral inoculum, $CD1d^{-/-}$ mouse lineage and husbandry protocol may skew the balance. As noted, mice lacking C2 iNKT lose less weight and face lower mortality after lethal IAV challenge, implying that shifts in the C2:C1 iNKT ratio may tilt NKT function toward protection or pathology. Because both NKT and NK cells release LIGHT, the massive NK influx after PR8 (H1N1) infection can override NKT loss, sustaining LIGHT-driven lung injury.

MEMORY T CELL SUBSETS

Adaptive immune reactions triggered by influenza virus are chiefly centered within the respiratory tract. T cells that harbor CXCR3, CXCR6, and/or C-C motif chemokine receptor 5 (CCR5) chemokine receptors are recruited to the pulmonary region of affected individuals in the period of influenza infection (Brownlie et al., 2022). Upon resolution of the infection, a portion of these T cells undergoes a transition to become memory T cells, conferring long-lasting immunity.

Lung-resident antigen-presenting cells engage with $CD4^{+}$ T cells in the initial phase of the immune reaction. This interaction regulates the localization of memory $CD4^{+}$ T cells and regulates the secretion of their cytokines (Hargrave et al., 2024). IL-2 enhances the memory adaptability of IAV-specific $CD4^{+}$ T cells (Alam et al., 2020). Unlike infantile $CD4^{+}$ lymphocytes, memory $CD4^{+}$ T cells mainly react to a few immune dominant peptides (Cassotta et al., 2020). This difference may come from different antigen processing mechanisms. After the flu infection was removed, various $CD8^{+}$ memory cell subgroups expressed CD49a. These cell groups can neutralize viruses not only through indirect cytotoxic pathways, but also by combining and maturing innate immune cells, and by disassembling cells damaged by virus invasion (Reilly et al., 2021). Migratory dendritic cells (mDCs) stationed in the lungs are transferred from the mLN of the drainage lung region to the spleen, where they initiate $CD8^{+}$ T cell activation. Subsequently, $CD8^{+}$ T cells in the spleen undergo differentiation to produce memory cells with long-term maintenance potential (Jenkins et al., 2021).

Some of these memory T lymphocytes reside within tissues, providing continuous defense against virus invasion and are termed TRM cells (Masopust and Soerens, 2019). They are characterized by an elevated presence of CD69 with or without the integrins CD103 and CD49a, which are phenotypic hallmarks (Booth et al., 2014; Okhrimenko et al., 2014; Wong et al., 2016). TRM and effector-memory T cells (TEM) share a C-C motif chemokine receptor 7 (CCR7)-negative phenotype, precluding entry into lymphoid niches. TEM shuttle endlessly between blood and non-lymphoid organs, never lodging in respiratory mucosa. Local vigilance therefore falls to TRM. Owing to their fixed stations, TRM react faster than circulating TEM. On rechallenge, $CD8^{+}$ TRM rapidly release IFN-γ and TNF (van de Wall et al., 2024; Xia et al., 2025), and a subset armed with granzyme B lyses infected cells outright (Mair et al., 2025). Yet pulmonary TRM pools are inherently unstable (Stolley et al., 2020), so durable protection cannot rest on them alone (Hayward et al., 2020; Wu et al., 2014). TEM can promptly compensate for the compromised cellular immunity resulting from TRM egress or depletion.

Recent lineage-tracing and single-cell transcriptomic interrogations have disclosed a strikingly heterogeneous landscape of $CD4^{+}$ TRM cells, encompassing cytotoxic ThCTL-like effectors (McKinstry et al., 2012), a

PD-1^{hi}CXCR5^{lo}BCL6^{int} follicular-helper–reminiscent subset (Son et al., 2021) (designated TRH), and IL-17–producing Th17-like populations (Omokanye et al., 2022). Such phenotypic diversification endows the CD4$^+$ TRM compartment with a versatile functional repertoire.

Paralleling this complexity, CD8$^+$ TRM bifurcate into two ontogenically and anatomically discrete subpopulations: airway-resident TRM (A-TRM) and interstitial TRM (I-TRM) (Takamura et al., 2019; Wein et al., 2019). CD8$^+$ I-TRM cells show strong cell dissolving potential, and selectively return to the tissue remodeling focus after secondary contact with the antigen, so as to coordinate the local repair process (Takamura et al., 2016). On the contrary, CD8$^+$ A-TRM cell is a powerful IFN-γ secretory cell, which can effectively inhibit the replication of the virus, but shows inhibited cytotoxicity during reinfection (McMaster et al., 2015).

The occurrence of TRM is inversely proportional to the intensity of the TCR signal. Paradoxically, T cells with low affinity may in fact have an advantage in forming TRM (Fiege et al., 2019b). However, previous human studies have shown that the intensity of TCR interaction may not affect the development of TRM cells. On the contrary, the formation of TRM cells is mainly determined by T-bet and CXCR3 stimulated by IL-12 (Iborra et al., 2016; Slütter et al., 2013). Mucosal imprinting and differentiation of TRM induced by C-C motif chemokine receptor 2 (CCR2)-mediated mononuclear cell migration negative regulation vaccine (Lee et al., 2021). NFκB signal cascade plays a crucial role in regulating virus-specific tissue resident memory and enhancing lung CD8$^+$ TRM response (Pritzl et al., 2023). The pharmacological isolation of circulating T lymphocytes realized by the antagonism of sphingosine-1-phosphate receptor (S1PR) with FTY720 prevents the substantial invasion of hematogenous T cells, thus allowing the clear separation of TRM autonomous function in the tissue microenvironment (Son et al., 2021).

Most TRM paradigms are drawn in mice. It is still difficult to transform into human medicine. Direct clinical data on human lung TRM is scarce because lung tissue is difficult to obtain ethically. Occasional surgical or post-mortem pathological samples confirmed TRM-like cells, but the surface features were vague. Different lung ecological positions and TCR group libraries between different species force us to re-evaluate the effectiveness and toxicity of TRM-oriented interventions.

The unified phenotype is only part of the obstacle. The strategy of using transplant anti-host allergic reaction (Slütter et al., 2017; Takamura et al., 2019) or removing circulating T cells through cell-dissolving antibodies in the vascular concentration (Fonseca et al., 2020; Watanabe et al., 2015) while retaining tissue-resident T cells is too dangerous for human routine use.

In order to reduce the difference, three aspects should be prioritized. Embrace humanized mice and explore the behavior of T cells in the humanized microenvironment. Excavate clinical specimens -paired blood and bronchial alveolar lavage fluid of vaccinated people or recovering from infection- and draw influenza-specific T cell maps through high-dimensional flow cytometry and single-cell transcriptomics. In rat-based vaccines or treatments, test early-stage trials on humans rapidly.

Further research on memory T cells and TRM developed by follow-up infection and vaccine will help artificially induce lasting immune protection against influenza viruses.

AVIAN AND SEASONAL INFLUENZA VIRUSES

Given that the avian influenza virus represented by H5N1 and H7N9 can spread between birds and humans and can induce serious diseases such as acute respiratory distress syndrome, it is essential to conduct a strict examination of the phenotype characteristics of avian influenza virus. As previously discussed, T cell immunity is essential for offering cross-protection against different seasonal influenza strains. Likewise, CD4$^+$ and CD8$^+$ effector lymphocytes, along with memory T cells, provide protection during both the acute and recovery stages of avian influenza infection. A strong CD8$^+$ T cell response in the initial phase of infection promotes faster recovery in avian influenza patients, while a delayed T cell response during the acute phase suggests a worse prognosis (Wang et al., 2015). During the convalescent phase, the expression of CD49a, a lung-homing marker, on virus-specific CD8$^+$ T cells is more pronounced at 6–8 months post-infection compared to 1.5–4 months. In patients who experienced severe infection within the first year post-infection, the quantity of virus-specific T cells that produce IFN-γ is on the rise (Zhao et al., 2018). The investigators attribute the observed effect to the transient contraction of virus-reactive IFN-γ-secreting T lymphocytes during the initial four months following infection. Furthermore, the research highlighted that CD8$^+$ memory T cells secreting cytokines peaked at 14 months post-infection, after which they gradually declined. CD4$^+$ T cells stimulated by seasonal influenza strains can cross-react with the HA of the H7 subtype (Richards et al., 2015). A similar cross-reactivity is also observed in CTLs (Kreijtz et al., 2008).

T CELL RESPONSE IN INFLUENZA VACCINATION

Assessing the capability of different influenza vaccines to prime T cell immunity through comparative studies is extremely advantageous for creating more effective new vaccines. The main purpose of widely used influenza vaccines, such as IIV, is to induce B-cell immunity and antibody response, but the ability to promote CD8$^+$ T cell immunity is limited. CD8$^+$ T cells that specifically target IAV are considered crucial in regulating and promoting recovery from influenza infection (Sridhar et al., 2013). Because the lack of cross-reactive antibodies and strong cellular immunity can accelerate the spread of the virus, this restriction may cause a pandemic when the virus mutates or zoonosis spreads to humans. For example, the H1N1 G4 subtype swine influenza virus that appeared in 2023 has very little cross-reaction with the human influenza vaccine on the T cell epitope, which poses an imaginable risk to public health (Tan et al., 2023). Given the capacity of T cell immune responses to display cross-reactivity, the design of an effective future vaccine should aim to trigger a robust cellular and humoral immune reaction. This would ensure dependable immune defense even in scenarios where protective antibodies are not present (Table 1.). The ambition demands departure from classical inactivated templates and deliberate integration of novel adjuvants, delivery routes and vaccine platforms.

Refining adjuvant-delivery pairings offers a precision conduit for eliciting airway-localized T-cell immunity. Licensed adjuvants now span aluminum salts, emulsions and Toll-like receptor agonists. MF59 emulsion and MPLA Toll-like receptor agonist skew responses toward Th1 (Chen, 2023; Yang et al., 2022). Yet the same adjuvant yields divergent phenotypes when delivered differently. Intranasal, but not subcutaneous, administration of an Adjuplex-formulated inactivated vaccine elicits pulmonary CD8$^+$ TRM and cross-subtype protection (Gasper et al., 2016). Mucosal entry thus imprints a frontline defense. LAIV replicates locally after nasal dosing and induces mucosal and systemic cross-reactive CD8$^+$ T cells in children (Mohn et al., 2020), although pre-existing immunity curtails efficacy in adults (Hoft et al., 2011). Immunizing children—key drivers of community transmission—may therefore indirectly shield adults. Non-structural protein 1 restructuring (Prokopenko et al., 2023) or neuraminidase-deficient backbones (Wu et al., 2020) further enhance LAIV-induced cytotoxicity.

Vaccines directed at conserved internal proteins (M2, NP) promise breadth. Subunit immunogenicity is historically modest, yet self-assembling peptide nanoparticles (20–200 nm) present these antigens as ordered multimers that drain efficiently to lymph nodes and markedly heighten both T-cell discrimination and the immunogenicity of short-peptide antigens. Nanoparticles bearing conserved HA, M2 and NA peptides provoke strong humoral immunity and T-cell responses (Pan et al., 2023; Zykova et al., 2023) and confer heterosubtypic protection spanning IAV and IBV (Pan et al., 2023). An H9 HA head-epitope mi3 nanoparticle elicits cross-reactive T cells against divergent H9N2 strains in mice (Hao et al., 2025), underscoring tolerance to drift. Viral-vector

Table 1
Potential influenza vaccines and vaccine delivery methods to induce T cell immunity.

Vaccine Type	Administration Route	Immune Responses Post-Vaccination
LAIV	Intranasal vaccination	In humans: Induces mucosal and systemic cross-reactive $CD8^+$ T cells in children; efficacy in adults is curtailed by pre-existing immunity. In mice: Engineering (e.g., non-structural protein 1 restructuring, neuraminidase-deficient backbones) can enhance cytotoxic T cell induction.
Subunit vaccine (e.g., with self-assembling nanoparticles)	Subcutaneous or intramuscular vaccination	Traditional subunit vaccines have modest immunogenicity. In mice: Self-assembling peptide nanoparticles presenting conserved antigens (HA, M2, NA): Markedly heighten T-cell responses, provoke strong humoral immunity (antibody titers) and confer heterosubtypic protection.
mRNA vaccine (e.g., LNP-formulated)	Intramuscular vaccination	In ferrets: An mRNA vaccine encoding conserved internal proteins primed robust heterosubtypic $CD8^+$ and $CD4^+$ T-cell responses. In humans: mRNA-1010 (encoding HA) elicited a superior polyfunctional $CD4^+$ T cell response but $CD8^+$ T-cell frequencies remained indistinguishable from controls.
Viral vector vaccine (e.g., MVA-NP/M1, MCMV)	Intramuscular or intranasal vaccination	In humans: MVA-NP/M1 failed to reduce viral load in adults, indicating insufficient T-cell immunity via this route. In mice: Intranasal administration of a MCMV vector expressing IAV epitopes mobilized mucosal $CD8^+$ T cells and controlled infection.
Inactivated vaccine + adjuvant (e.g., Adjuplex-formulated)	Intranasal vaccination vs. Subcutaneous vaccination	In mice: Intranasal administration: Elicits pulmonary $CD8^+$ TRM response and cross-subtype protection. Subcutaneous administration: Does not induce the same mucosal $CD8^+$ TRM response or protection.

Mucosal (intranasal) delivery is crucial to the $CD8^+$ TRM immunity of the immune front line and airway localization, while the systemic pathway (muscular/subcutaneous injection) mainly drives the antibody response. New platforms (engineered LAIV, antigen display nanoparticles, multi-antigen mRNA) are crucial to overcome the limited $CD8^+$ T cell induction of traditional inactivated vaccines. Abreactions: LAIV, live attenuated influenza vaccine; TRM, tissue-resident memory T cells; LNP, lipid nanoparticle; MVA, modified vaccinia Ankara; MCMV, murine cytomegalovirus; NA, neuraminidase; M1, matrix Protein 1; HA, hemagglutinin; M2, matrix Protein 2; IAV, influenza A virus; NP, nucleoprotein.

platforms likewise hold promise, yet their efficacy hinges critically on vector choice and the route of inoculation. MVA-NP/M1 (modified vaccinia Ankara, MVA) given intramuscularly failed to reduce adult viral load (Evans et al., 2024), whereas intranasal murine cytomegalovirus expressing IAV epitopes mobilized mucosal $CD8^+$ T cells and controlled infection (Zheng et al., 2019). Vector tropism and pre-existing immunity must therefore guide platform choice.

mRNA technology offers unrivalled modularity. Lipid nanoparticle (LNP) delivery sustains endogenous antigen expression, favoring MHC class I presentation and robust $CD8^+$ T-cell priming—an outcome rarely achieved by killed whole-virus or protein vaccines that traffic via the exogenous route. Rapid insertion of multiple conserved genes and built-in LNP adjuvanticity broaden and intensify immunity. A mRNA vaccine encoding the highly conserved internal proteins of influenza viruses primed and boosted heterosubtypic $CD8^+$ and $CD4^+$ T-cell responses in ferrets, with a $CD8^+$ bias (van de Ven et al., 2022). Quadrivalent HA-encoding mRNA-1010 has entered multiple clinical trials (Ananworanich et al., 2025; Lee et al., 2023; Soens et al., 2025), yet cellular read-outs remain scarce. One trial showed mRNA-1010 elicited a superior polyfunctional $CD4^+$ response—IFN-γ, IL-2, TNF-α and CD40L co-expression—versus placebo at day 8, persisting or intensifying by day 29 (Ananworanich et al., 2025). Th1-skewed $CD4^+$ T cells which co-express IFN-γ and CD40L outnumbered placebo at every dose on the same day, yet $CD8^+$ T-cell frequencies remained indistinguishable from controls. A shortcoming of mRNA-1010 is its exclusive encoding of HA, a surface glycoprotein that lacks the conservation of internal viral proteins; consequently, its capacity to elicit cross-reactive T cells and to counter antigenic drift may be limited. Henceforth, clinical trials must routinely quantify vaccine-elicited T-cell signatures to unlock the full cellular potential of mRNA platforms rather than merely gauging humoral endpoints.

The era of integrated vaccines is changing to reasonable combinations—such as adjuvants, mucosal delivery, engineering LAIV, nanoparticles and mRNA—where the mechanism is one of customized protective immunity.

CONCLUSION

Recent research emphasizes the importance of T cells in fighting the flu and accelerating recovery from infection. The current flu vaccine is insufficient in effectively inducing T cell immunity, which prompts people to strongly pursue new vaccines that can effectively trigger T cell response, especially in the $CD8^+$ T cell spectrum. However, deepening our understanding of influenza-specific T cell response is crucial to developing a vaccine strategy for broad immune protection for multiple lines of influenza virus. This vaccine will represent significant progress in this field, providing a wider range of protection and potentially revolutionary methods for influenza vaccines. The research of the next generation of influenza vaccines should focus on four aspects: optimization of adjuvant delivery to help form tissue resident T cells; platform targeting conservative antigen epitopes to ensure extensive protection; in-depth exploration of mRNA vaccines to enhance cytotoxic immunity; and a reasonable combination of these methods. These methods use the cross-reactivity of T cell immunity to provide reliable immunity against mutant viruses.

CONFLICT OF INTEREST

Heather Miller was employed by company Cytek Biosciences. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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