Expanding roles for CD4$^+$ T cells in immunity to viruses

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Abstract | Viral pathogens often induce strong effector CD4$^+$ T cell responses that are best known for their ability to help B cell and CD8$^+$ T cell responses. However, recent studies have uncovered additional roles for CD4$^+$ T cells, some of which are independent of other lymphocytes, and have described previously unappreciated functions for memory CD4$^+$ T cells in immunity to viruses. Here, we review the full range of antiviral functions of CD4$^+$ T cells, discussing the activities of these cells in helping other lymphocytes and in inducing innate immune responses, as well as their direct antiviral roles. We suggest that all of these functions of CD4$^+$ T cells are integrated to provide highly effective immune protection against viral pathogens.

Pattern-recognition receptors
(PRRs). Host receptors that can detect pathogen-associated molecular patterns and initiate signalling cascades, leading to an innate immune response. Examples include Toll-like receptors (TLRs) and NOD-like receptors (NLRs). PRRs can be membrane-bound receptors (as in the case of TLRs) or soluble cytoplasmic receptors (as in the case of NLRs, retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5)).

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Viruses can enter the body by diverse routes, infect almost every type of host cell and mutate to avoid immune recognition. Destroying rapidly dividing viruses efficiently requires the coordination of multiple immune effector mechanisms. At the earliest stages of infection, innate immune mechanisms are initiated in response to the binding of pathogens to pattern-recognition receptors (PRRs), and this stimulates the antiviral activities of innate immune cells to provide a crucial initial block on viral replication. Innate immune responses then mobilize cells of the adaptive immune system, which develop into effector cells that promote viral clearance.

Activation through PRRs causes professional antigen-presenting cells (APCs) to upregulate co-stimulatory molecules and promotes the migration of these cells to secondary lymphoid organs. Here, they present virus-derived peptides on MHC class II molecules to naive CD4$^+$ T cells and deliver co-stimulatory signals, thereby driving T cell activation. The activated CD4$^+$ T cells undergo extensive cell division and differentiation, giving rise to distinct subsets of effector T cells (BOX 1). The best characterized of these are T helper 1 (T_H1) and T_H2 cells, which are characterized by their production of interferon-γ (IFNγ) and interleukin-4 (IL-4), respectively[1]. Specialized B cell helpers, known as follicular helper T (T_{FH}) cells, and the pro-inflammatory T_H17 cell subset also develop, along with regulatory T (T_{Reg}) cells, which are essential for avoiding over-exuberant immune responses and associated immunopathology[2].

A key role of CD4$^+$ T cells is to ensure optimal responses by other lymphocytes. CD4$^+$ T cells are necessary as helpers to promote B cell antibody production and are often required for the generation of cytotoxic and memory CD8$^+$ T cell populations. Recent studies have defined additional roles for CD4$^+$ T cells in enhancing innate immune responses and in mediating non-helper antiviral effector functions. We discuss what is known about the T cell subsets that develop following acute viral infection and how different subsets contribute to viral control and clearance.

Following a rapid and effective antiviral response, infection is resolved and the majority of effector CD4$^+$ T cells die, leaving a much smaller population of memory CD4$^+$ T cells that persists long-term[3,4]. Memory CD4$^+$ T cells have unique functional attributes and respond more rapidly and effectively during viral re-infection. A better understanding of the functions of memory CD4$^+$ T cells will allow us to evaluate their potential contribution to immunity when they are induced by either infection or vaccination. We describe the antiviral roles of CD4$^+$ T cells during the first encounter with a virus and also following re-infection.

Generation of antiviral CD4$^+$ T cells

To develop into effector populations that combat viral infections, naive CD4$^+$ T cells need to recognize peptide antigens presented by MHC class II molecules on activated APCs. PRR-mediated signalling activates APCs to upregulate their expression of MHC class II molecules, co-stimulatory molecules (such as CD80 and CD86) and pro-inflammatory cytokines (such as type I IFNs, tumour necrosis factor (TNF), IL-1, IL-6 and IL-12)[5]. When the activated APCs migrate to draining lymph nodes, they prime naive virus-specific CD4$^+$ T cells, which then differentiate into antiviral effectors (FIG. 1). The priming environment can vary

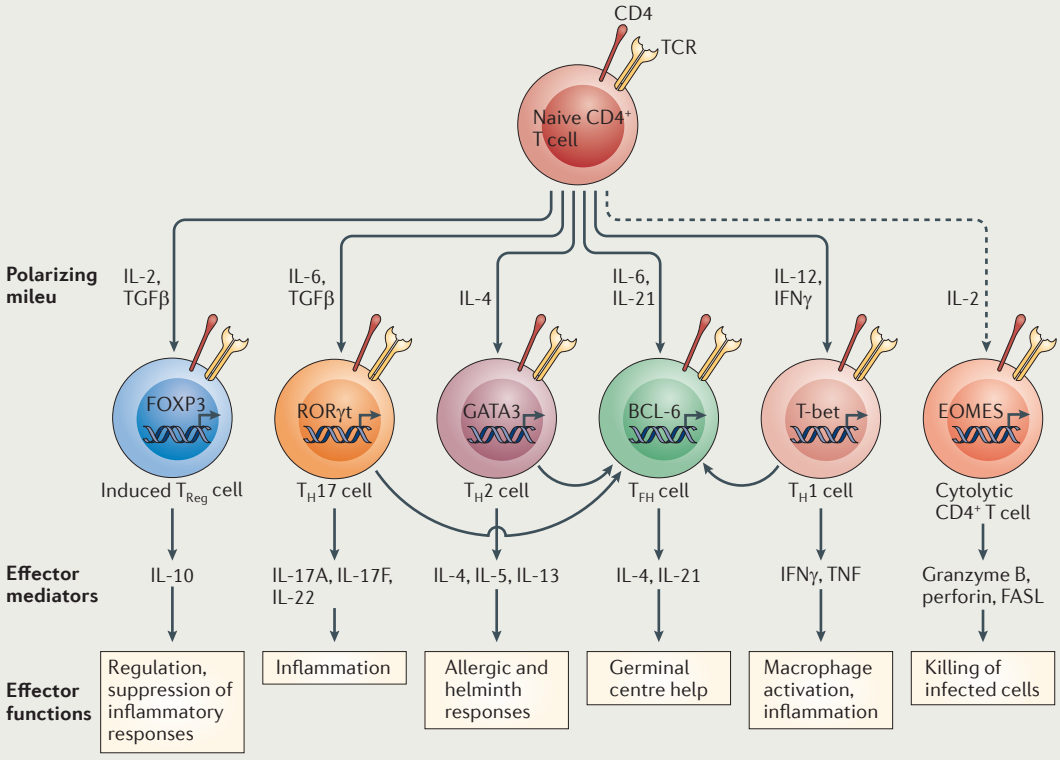
Box 1 | **Subsetting CD4⁺ T cell responses based on T_H cell polarization**

Following recognition of a specific antigen presented by an appropriately activated antigen-presenting cell, naive CD4⁺ T cells undergo several rounds of division and can become polarized into distinct effector T helper (T_H) cell subsets that differentially orchestrate protective immune responses (see the figure). The differentiation of polarized effector T cells is controlled by unique sets of transcription factors, the expression of which is determined by multiple signals but particularly by soluble factors that act on responding CD4⁺ T cells during their activation. The elucidation of the crucial cytokines that govern the differentiation of distinct T_H cell subsets has allowed researchers to examine the protective capacities of differently polarized CD4⁺ T cell subsets in several models of infectious disease.

Although the production of the signature cytokines interferon-γ (IFNγ), interleukin-4 (IL-4) and IL-17 is routinely used to assign subsets (T_H1, T_H2 and T_H17, respectively) to responding CD4⁺ T cells, it is increasingly clear that considerable plasticity exists within T_H cell subsets *in vivo*, especially during responses to pathogens. Moreover, certain cytokines (for example, IL-10) can be produced by subpopulations of cells within multiple effector subsets. Finally, the successful clearance of viral pathogens in particular often depends on complex CD4⁺ T cell responses that encompass multiple T_H cell subsets. Together, these T cell subsets are capable of mediating direct antiviral functions, of providing help for B cells, of regulating immunopathology and of mediating cytotoxic killing of virus-infected cells. CD4⁺ T cells with cytotoxic activity have been described in several models of viral disease as well as in the clinic. Following re-stimulation, memory CD4⁺ T cells retain their previous effector functions and rapidly produce effector cytokines. This property of primed CD4⁺ T cells represents a key advantage of the memory state.

Certain T_H cell subsets — including follicular helper T (T_{FH}) cells and regulatory T (T_{Reg}) cells — are often defined less by their cytokine profile and more by their functional attributes. Further studies will be required to determine whether populations of CD4⁺ T cells with specialized functions can include cytokine-polarized cells from several subsets.

BCL-6, B cell lymphoma 6; EOMES, eomesodermin, FASL, FAS ligand; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; RORγt, retinoic acid receptor-related orphan receptor-γt; TCR, T cell receptor; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.



T-bet
A member of the T-box family of transcription factors. T-bet is a master switch in the development of T helper 1 (T_H1) cell responses through its ability to regulate the expression of the interleukin-12 receptor, inhibit signals that promote T_H2 cell development and promote the production of interferon-γ.

dramatically during different viral infections and is influenced by many variables, including the route of infection, the viral dose and the organ or cell types targeted. As has been extensively reviewed elsewhere, the extent of T cell proliferation and the determination of T cell subset specialization are affected by the specific subset of APCs that is activated[6,7], the antigen load and the duration of antigen presentation[8], and the patterns and amounts of cytokines produced by different APCs[9].

Effector T_H cell subsets in viral infection

In contrast to T_H cell populations that are generated *in vitro*, effector T cells that are found *in vivo* are often characterized by plasticity and heterogeneity in terms of their cytokine-producing potential. Nevertheless, the CD4⁺ T cells that are generated in response to viral infection mainly have a T_H1-type phenotype and produce large amounts of IFNγ and express T-bet. This phenotype classically depends on the exposure of T cells to high levels of IL-12, type I IFNs and IFNγ in

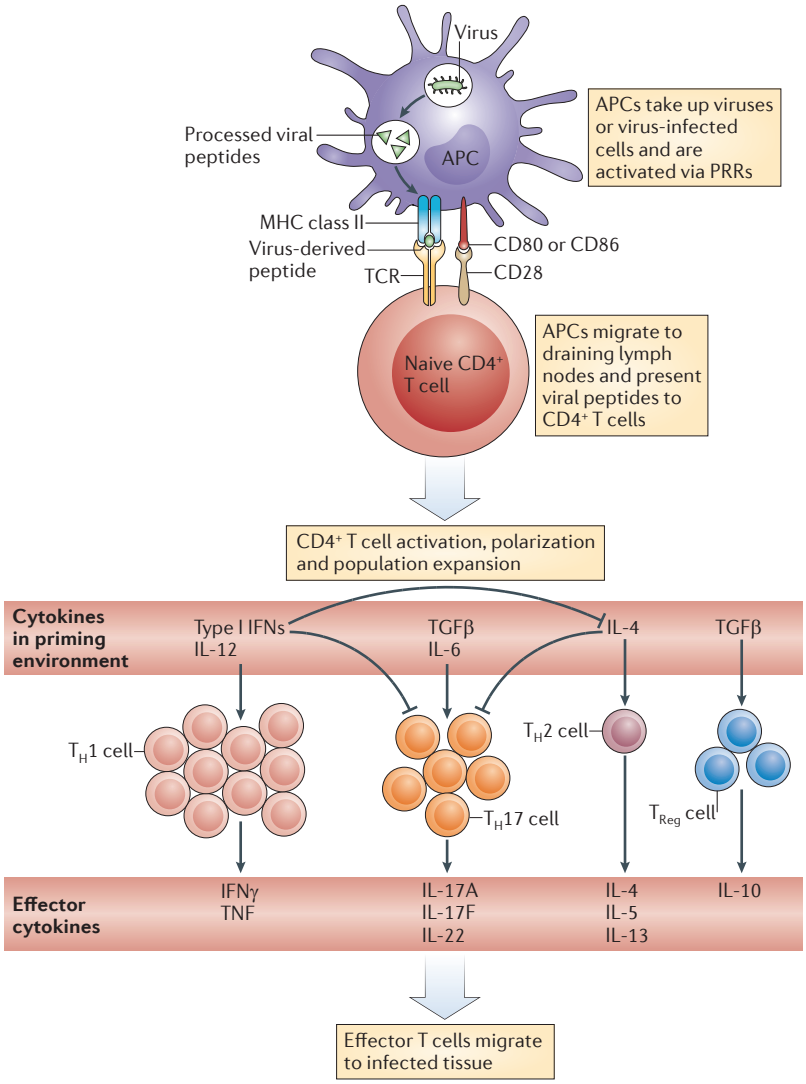


Figure 1 | **Generation of antiviral effector CD4⁺ T cells.** The crucial initial steps in generating primary antiviral T cell responses are the uptake of viral antigens by antigen-presenting cells (APCs) in infected tissue, the activation of APCs by pattern-recognition receptor (PRR) ligation, and the migration of these cells to draining lymph nodes. The nature of the viral infection, as well as PRR ligation, can influence the activation status of antigen-bearing APCs and the T helper (T_H) cell-polarizing environment. The recognition of antigens on activated APCs by naive T cells during viral infection predominately results in the generation of T_H1 cells owing to the presence of type I interferons (IFNs) and interleukin-12 (IL-12). However, T_H17, T_H2 and regulatory T (T_{Reg}) cell populations are also generated to some degree in certain viral infections. TCR, T cell receptor; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

the priming milieu[10], although T_H1 cell responses are generated in response to certain viruses independently of IL-12 or type I IFNs[11–13], suggesting that other factors can also contribute to T_H1 cell polarization. IL-12 and type I IFNs promote T_H1 cell differentiation both directly and indirectly (by repressing the development of other T_H cell subsets), and can even influence effector T cells that are already polarized. For example, polarized T_H2 cells that were transferred to hosts infected with lymphocytic choriomeningitis virus (LCMV) acquired a mixed T_H1/T_H2 cell phenotype, which was characterized by high levels of IFNγ production and diminished IL-4 production. Interestingly, most IFNγ-producing cells in the T_H1/T_H2 cell population co-produced IL-4 or IL-13, and IL-12 and type I IFNs were shown to drive this mixed T_H1/T_H2 cell phenotype[14]. *In vivo*, IL-12 can also reprogramme *in vitro*-polarized T_H17 cells to a T_H1-type phenotype[15,16].

Originally, it was thought that IL-4-producing T_H2 cells were needed to drive optimal humoral immune responses. Thus, the predominance of T_H1 cells over T_H2 cells during viral infection was somewhat surprising, given the important role of neutralizing antibodies in viral clearance and in providing long-term immunity to re-infection. However, adoptive transfer of either T_H1 cells or T_H2 cells was shown to provide efficient help for the generation of neutralizing antiviral IgG responses[17,18]. The signature T_H1-type cytokine, IFNγ, enhances IgG2a class switching, and this explains why IgG2a is usually the dominant isotype in IgG responses generated against viruses[19]. In fact, several studies have found that, far from promoting antiviral responses, T_H2 cell-associated mediators (and IL-4 in particular) have a strong negative impact on immune protection and drive immunopathology during infection with many viruses, including influenza virus[20,21], respiratory syncytial virus (RSV)[22], herpes simplex virus (HSV)[23] and vaccinia virus[24]. Instead, it is now clear that IL-4-producing T_{FH} cells provide much of the help required for IgG1 production (see below).

The roles of T_H17-type effector responses during viral infection are not well understood, but virus-specific IL-17-producing CD4⁺ T cells have been detected in mice following infection with mouse cytomegalovirus (MCMV)[25], HSV[26], vaccinia virus[27], Theiler's murine encephalomyelitis virus[28] or influenza virus[16], although at levels lower than those of T_H1 cells. The generation of polarized T_H17 cells during viral infection has been correlated with high levels of IL-6 and may also be influenced by transforming growth factor-β (TGFβ)[28]. T_H17 cells are implicated in driving harmful inflammation during autoimmunity, and IL-17 may contribute to immunopathology during responses against viruses, as demonstrated in studies using influenza virus or vaccinia virus[27,29]. However, in some cases, T_H17 cells contribute to host protection against viruses[16]. One protective mechanism mediated by T_H17 cells might be the promotion of enhanced neutrophil responses at sites of infection. IL-17 upregulates CXC-chemokines that promote neutrophil recruitment[30], and neutrophils can contribute to protection against certain viruses, including influenza virus[31]. We expect that other roles for T_H17 cells will be identified in future studies, as T_H17 cells often produce significant levels of IL-21 and IL-22 in addition to IL-17 (REF. 16). Although not extensively studied in viral systems, IL-22 production by T_H17 cells could be involved in regulating the expression of defensins, and could also play an important part in tissue repair (reviewed in REF. 32). IL-21 production may also regulate aspects of the innate immune response during viral infection. Moreover, IL-21 is involved in sustaining CD8⁺ T cell responses during chronic viral infection, as discussed below.

Roles of CD4+ T cells during primary infection

Although the best-studied pathways of CD4+ T cell-mediated help are those that promote antibody production by B cells, CD4+ T cells also enhance effector CD8+ T cell responses during certain viral infections and contribute to the maintenance of a functional memory CD8+ T cell pool (FIG. 2). Furthermore, effector CD4+ T cells regulate the inflammatory response and can directly mediate viral clearance.

CD4+ T cell-mediated help for B cells. Current licensed vaccines directed against viral pathogens are evaluated almost exclusively on their ability to generate strong neutralizing antibody responses. Antibody-mediated protection can be extraordinarily long-lived[33], and neutralizing antibodies present at the time of pathogen encounter can prevent rather than combat infection, thereby achieving 'sterilizing' immunity. Thus, it is crucial to understand the mechanisms by which CD4+ T cells help B cells during viral infection in order to define what is required for effective vaccination (FIG. 2a). CD4+ T cells that enter B cell follicles and provide help to B cells, resulting in germinal centre formation, are now referred to as T_{FH} cells. The generation and functions of T_{FH} cells have been expertly reviewed elsewhere[34,35], so we focus only on the roles of these cells during viral infection.

Following viral infection, the expression of SLAM-associated protein (SAP) by T_{FH} cells is necessary to direct the formation of germinal centres[36,37], where T_{FH} cells promote the generation of B cell memory and long-lived antibody-producing plasma cells[36,38]. Thus, T_{FH} cells are likely to be important for generating long-lived antibody responses and protective immunity to most, if not all, viruses. Indeed, CD4+ T cells have been shown to be required for the generation of optimal antibody responses following infection with coronavirus[39], vaccinia virus[40], yellow fever virus[41] or vesicular stomatitis virus (VSV)[42]. It is not yet clear how distinct cytokine-polarized CD4+ T cell subsets influence the B cell response during primary viral infection. One possibility is that distinct T_H cell subsets, such as T_H1, T_H2 and T_H17 cells, can each develop into T_{FH} cells and provide efficient help for B cells. This hypothesis is supported by a recent study demonstrating that such polarized subsets can be reprogrammed to express T_{FH} cell characteristics *in vitro*[43]. As different T_H cell subsets have been associated with distinct antibody class-switching responses, the broad range of protective antibody isotypes that is often found in individuals with immunity to a virus favours such a model.

Several co-stimulatory ligands expressed by CD4+ T cells contribute to the promotion of B cell activation and antibody production. One notable ligand is CD40 ligand (CD40L). Interactions between CD40 (which is expressed on B cells) and CD40L (which is expressed on activated CD4+ T cells) are crucial for generating optimal humoral responses against several viral pathogens, including LCMV, Pichinde virus, VSV, HSV and influenza virus[44–46]. The expression of inducible T cell co-stimulator (ICOS) by T_{FH} cells has also been shown to be important for germinal centre formation[34], and ICOS expression is required for optimal induction of humoral responses against LCMV, VSV and influenza virus[47]. The roles during viral infection of other co-stimulatory molecules expressed by T_{FH} cells are less clear. For example, OX40-deficient mice generate normal levels of class-switched antibodies during infection with LCMV, VSV or influenza virus[48]. Further studies are required to determine the importance of additional signals that pass between T_{FH} cells and B cells in generating protective antibody responses during viral infection.

CD4+ T cell-mediated help for CD8+ T cells. The mechanisms by which CD4+ T cells promote CD8+ T cell effector and memory responses are less well understood than B cell help. As in B cell help, CD40L–CD40 interactions between CD4+ T cells and APCs are crucial (FIG. 2). One possible mechanism — the 'licensing' of APCs by CD4+ T cells — may be of only minor importance during viral infection, as APCs can be activated effectively by viruses through PRRs[49,50], thus obviating the need for this process[50–52]. However, it is unclear whether APCs that are activated directly through PRRs are functionally similar to those licensed by CD4+ T cells[53]. An absence of CD4+ T cells has been shown to compromise the generation of primary cytotoxic T lymphocyte (CTL) responses against vaccinia virus[54] and HSV[55] (and influenza virus in some, but not all, studies[56–58]), suggesting that the two modes of APC activation are distinct. Whether CD4+ T cell-mediated help is required for the generation of optimal antiviral CD8+ T cell responses probably depends on which elements of the innate immune response are triggered following infection by a virus and to what extent. For example, the strong type I IFN response that is induced by administration of polyinosinic–polycytidylic acid (polyI:C) can bypass the otherwise obligate requirement for CD4+ T cell-mediated help in the generation of CD8+ T cell responses following vaccinia virus infection[59].

It is not clear whether different T_H cell subsets have distinct roles in helping CD8+ T cells. During the primary response, the licensing of APCs by CD4+ T cells probably occurs before the full polarization of effector CD4+ T cells, but fully polarized T_H cells might also promote efficient CD8+ T cell responses against viral pathogens through mechanisms other than APC licensing. For example, chemokines produced following antigen-specific interactions between APCs and CD4+ T cells can actively attract CD8+ T cells to the activated APCs[60], and CD40L–CD40 interactions between CD4+ T cells and APCs can protect APCs from CTL-mediated death[61], perhaps leading to more-efficient CD8+ T cell priming.

In addition, CD4+ T cells facilitate the development of functional, pathogen-specific memory CD8+ T cells that can respond following re-infection[51,52,62,63]. One mechanism by which CD4+ T cells promote this process involves the downregulation of TNF-related apoptosis-inducing ligand (TRAIL) expression on responding CD8+ T cells (FIG. 2). It is thought that CD8+ T cells that are helped by CD4+ T cells downregulate

Class switching
The process by which proliferating B cells rearrange their DNA to switch from expressing the heavy-chain constant region of IgM (or another class of immunoglobulin) to expressing that of a different immunoglobulin class, thereby producing antibodies with different effector functions. The decision of which isotype to generate is strongly influenced by the specific cytokine milieu and by other cells, such as T helper cells.

Germinal centre
A highly specialized and dynamic microenvironment that gives rise to secondary B cell follicles during an immune response. Germinal centres are the main site of B cell maturation, which leads to the generation of memory B cells and plasma cells that produce high-affinity antibodies.

Polyinosinic–polycytidylic acid
(PolyI:C). A substance that is used as a mimic of viral double-stranded RNA.

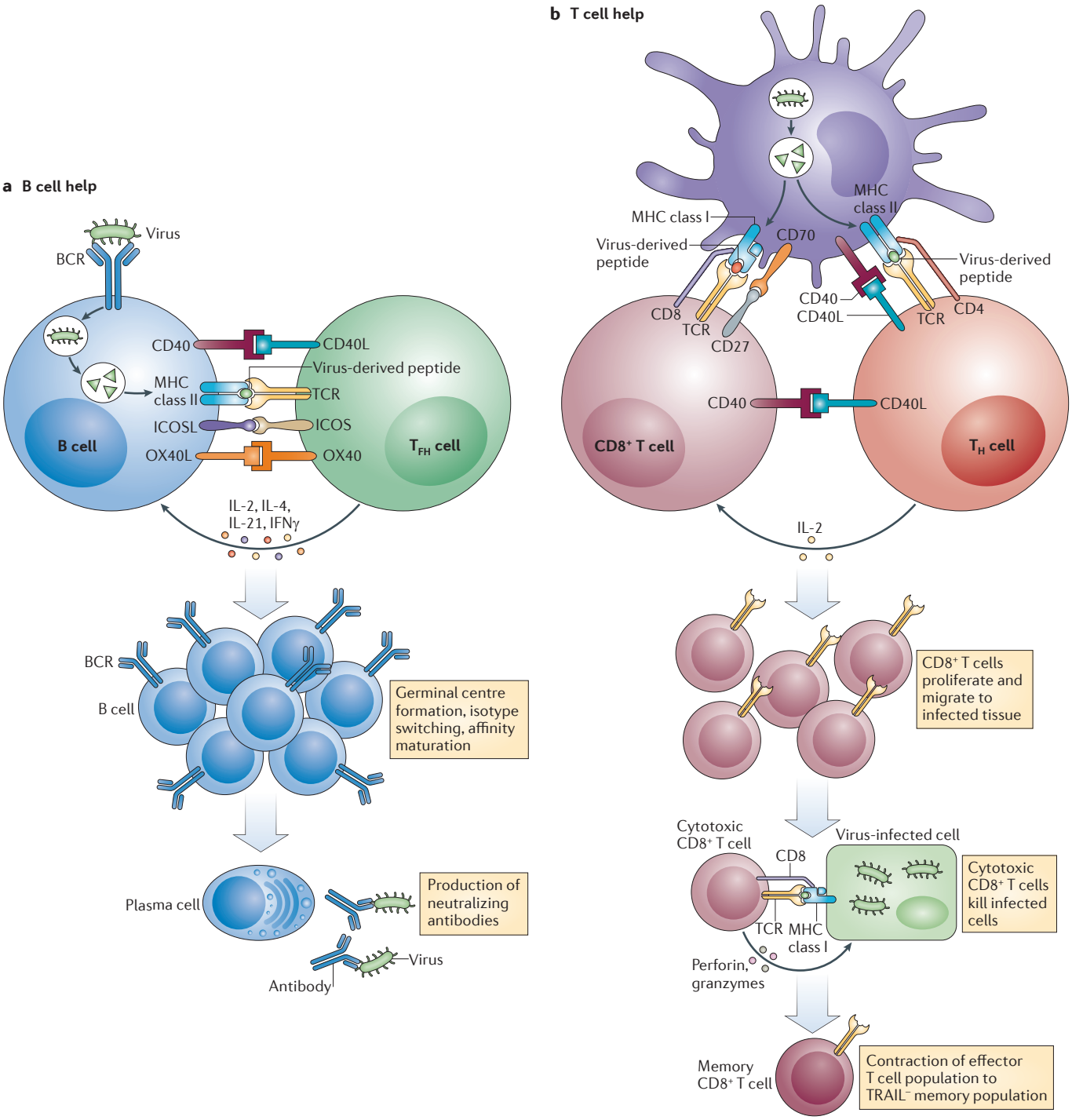


Figure 2 | **Helper functions of $CD4^+$ T cells. a** | The canonical function of $CD4^+$ T cells is the provision of help for B cells in germinal centre formation, isotype switching and affinity maturation of antibody responses. Follicular helper T (T_{FH}) cells are a specialized subset of $CD4^+$ T cells that provide help to B cells through both cell–cell interactions (most notably CD40L–CD40 interactions) and the release of cytokines. The generation of neutralizing antibodies is a crucial component of protection against many viral pathogens and the goal of most vaccine strategies. **b** | The best-characterized pathway of $CD4^+$ T cell-mediated help in the generation of $CD8^+$ T cell effectors involves the provision of interleukin-2 (IL-2) and the activation, known as 'licensing', of antigen-presenting cells (APCs) via CD40L–CD40 interactions. It is often unclear whether $CD4^+$ T cell-mediated help has a role in the initial generation of antiviral $CD8^+$ T cell effector responses, presumably because viruses can trigger pattern-recognition receptors and independently activate APCs. However, a clear role for $CD4^+$ T cell-mediated help in the generation of functional memory $CD8^+$ T cells has been demonstrated during viral infection. Downregulation of TNF-related apoptosis-inducing ligand (TRAIL) expression on $CD8^+$ T cells is a prominent feature of $CD8^+$ T cells that have been helped and at least in part facilitates their robust recall response during secondary infection. BCR, B cell receptor; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; TCR, T cell receptor; T_H, T helper.

TRAIL expression and become less susceptible[64], or have delayed susceptibility[65], to TRAIL-mediated apoptosis. By contrast, $CD8^+$ T cells that have not been helped undergo enhanced TRAIL-mediated apoptosis following antigen re-exposure. $CD4^+$ T cell-mediated help also controls the expression of other molecules. For example, $CD4^+$ T cells downregulate the expression of programmed cell death protein 1 (PD1) on $CD8^+$ T cells, and this can enhance the function of pathogen-specific memory $CD8^+$ T cells[66–68].

$CD4^+$ T cells may promote the generation of effector and memory $CD8^+$ T cell populations through many possible pathways. One such pathway involves enhancing the APC-mediated production of cytokines that augment initial $CD8^+$ T cell responses; these cytokines include IL-1, IL-6, TNF and IL-15 (REF. 69). Paracrine IL-2 produced by $CD4^+$ T cells during the initial priming of $CD8^+$ T cells in LCMV infection dramatically improves the $CD8^+$ T cell recall response potential[70]. Furthermore, $CD4^+$ T cells have been shown to upregulate the expression of CD25 (also known as IL-2Rα) on $CD8^+$ T cells during infection with vaccinia virus or VSV[71]. At later stages of the response, $CD4^+$ T cells produce additional cytokines, such as IL-21, which appears to be a crucial signal for downregulating TRAIL expression on $CD8^+$ T cells responding to vaccinia virus[72]. Finally, evidence suggests that direct ligation of CD40 on naive $CD8^+$ T cells by CD40L on $CD4^+$ T cells can enhance the generation of memory $CD8^+$ T cells[73] (FIG. 2).

$CD4^+$ T cells seem to be particularly important for maintaining memory $CD8^+$ T cell populations[74], and the presence of $CD4^+$ T cells during priming may influence the homing pattern and, ultimately, the tissue distribution of memory $CD8^+$ T cells[75]. Whereas a specialized T cell subset (namely, T_{FH} cells) provides help for B cells, no analogous helper subset for $CD8^+$ T cells has been identified to date. Defining the conditions that lead to the generation of $CD4^+$ T cells with potent $CD8^+$ T cell helper activity could be important for developing better vaccines against several viral pathogens.

More than just lymphocyte helpers

In addition to activating cells of the innate immune system and providing potent help to promote the functions of B cells and $CD8^+$ T cells during viral infection, $CD4^+$ T cells develop into populations of effector T cells that migrate to sites of infection[76]. Accumulating evidence suggests that effector $CD4^+$ T cells have potent protective roles during viral infection that are independent of their helper activities. Strong immune protection mediated by $CD4^+$ T cells has been described in animal models of infection by rotavirus[77], Sendai virus[78,79], gammaherpesviruses[80,81], West Nile virus (WNV)[82], HSV[83,84], influenza virus[85,86], dengue virus[87], Venezuelan equine encephalitis virus[88], coronavirus[89], VSV[90] and Friend virus[91,92]. In many cases, the direct protective mechanism used by $CD4^+$ T cells has not been defined. However, effector $CD4^+$ T cells have, in general, been shown to protect against viral pathogens through two distinct mechanisms: first, through the production of cytokines, most notably IFNγ and TNF[81,82,85,87,89,90,92]; and second, through direct cytolytic activity[78,81,82,87,92] mediated by both perforin and FAS (also known as CD95)[84,86] (FIG. 3). Cytotoxic $CD4^+$ T cells have also been observed following infection with LCMV[93].

The cytotoxic activity of $CD4^+$ T cell effectors does not depend on T_H1 cell polarization[94], and expression of the transcription factor eomesodermin, but not T-bet, may be crucial in driving the development of cytotoxic $CD4^+$ T cells *in vivo*[95]. Thus, $CD4^+$ T cells with cytotoxic activity could be considered a separate functional T cell subset. The fact that MHC class II expression is largely restricted to professional APCs under steady-state conditions may limit the protective potential of virus-specific cytotoxic $CD4^+$ T cells. However, cells other than professional APCs are capable of upregulating MHC class II expression following pathogen challenge and could therefore become targets of cytotoxic $CD4^+$ T cells during viral infection. For example, epithelial cells that are activated by infection[96] or IFNγ-mediated signals[97] strongly upregulate their expression of MHC class II molecules.

Although immune protection mediated by cytotoxic $CD4^+$ T cells requires direct recognition of virus-infected cells, soluble factors released by other effector $CD4^+$ T cells can act more broadly. For example, IFNγ can promote the establishment of an antiviral state in surrounding tissue and can also activate several innate immune cell populations, most notably macrophages, to mediate antiviral activity[98]. Thus, effector $CD4^+$ T cells that migrate to infected tissues probably promote viral clearance through both cytotoxic and cytokine-dependent mechanisms.

Immunoregulation by effector $CD4^+$ T cells

Effector $CD4^+$ T cells are capable of potent immunoregulation at sites of infection. A subset of T_H1 cells has been found to transiently produce both IFNγ and IL-10 at the peak of the effector $CD4^+$ T cell response in many models of infectious disease[99]. Several signals have been found to stimulate the generation of IL-10-producing effector $CD4^+$ T cells, including high levels of antigen, soluble factors such as IL-12 and IL-27, and co-stimulatory signals such as ICOS (reviewed in REF. 99). IL-10 is a pleiotropic cytokine that is most often associated with anti-inflammatory or inhibitory functions (FIG. 3). The impact of IL-10 production by effector $CD4^+$ T cells is complicated and can be variable, especially in situations in which strong immune responses (which are capable of serious immunopathology) are required to eliminate a rapidly replicating pathogen. For instance, the absence of IL-10 during influenza virus infection can lead, on the one hand, to improved host survival, owing to enhanced T cell[16] and antibody[100] responses, but also, on the other hand, to exacerbated inflammation and immunopathology, which result in increased mortality[101]. Similarly, ablating *Il10* has been found to enhance protection against WNV[102] and vaccinia virus[103], but to cause increased pathology following infection with RSV[104] and death following infection with mouse hepatitis virus[105] or coronavirus[106]. Finally, as well as producing IL-10 themselves, effector $CD4^+$ T cells can also promote IL-10 production by effector $CD8^+$ T cells during viral infection[107].

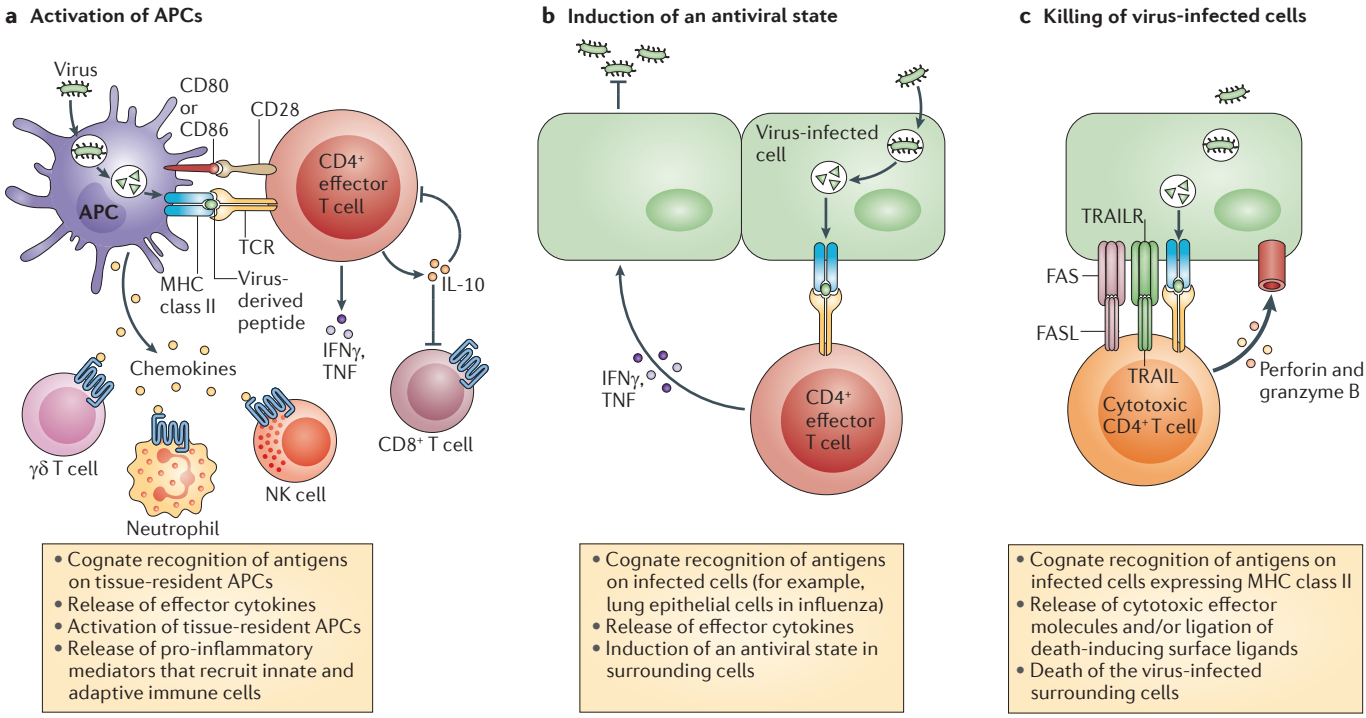


Figure 3 | **Antiviral functions of CD4⁺ T cells that are independent of their lymphocyte helper functions.** **a** | After migrating to sites of infection, effector CD4⁺ T cells that recognize antigens on antigen-presenting cells (APCs) produce an array of effector cytokines that contribute to the character of the inflammatory responses in the tissue. Some products of highly activated effector CD4⁺ T cells, such as interleukin-10 (IL-10), dampen inflammation and regulate immunopathology, whereas others, such as interferon-γ (IFNγ), are pro-inflammatory and activate macrophages, which in turn drive further inflammation. The production of IL-10 by effector CD4⁺ T cells can have a profound impact on the outcome of a viral infection. **b** | IFNγ, tumour necrosis factor (TNF) and other cytokines produced by CD4⁺ T cells help to coordinate an antiviral state in infected tissues. **c** | Cytotoxic CD4⁺ T cells can directly lyse infected cells through diverse mechanisms, including FAS-dependent and perforin-dependent killing. FASL, FAS ligand; NK, natural killer; TCR, T cell receptor; TRAIL, TNF-related apoptosis-inducing ligand; TRAILR, TRAIL receptor.

Regulatory CD4⁺ T cells

Increased frequencies of CD4⁺ T_{Reg} cells (of both the forkhead box P3 (FOXP3)⁺ and FOXP3⁻ populations) have been observed in numerous human and animal studies of viral infection. Most studies that have assessed the impact of T_{Reg} cells during viral infection have concentrated on models of chronic infection. In such settings, T_{Reg} cells have been found, depending on the particular pathogen, to have both beneficial roles, such as limiting collateral tissue damage, and detrimental roles, including diminishing the overall magnitude of antiviral immune responses[108]. The antigen specificity of T_{Reg} cells in the context of infectious disease has not been addressed often, but it is likely that T_{Reg} cell populations contain at least some virus-specific cells and that these populations are generated in concert with antiviral effector T cell responses. Indeed, this has recently been shown in a coronavirus infection model[109]. The accumulation of virus-specific FOXP3⁺ T_{Reg} cells during viral infection could be due to the expansion of pre-existing populations of thymus-derived 'natural' T_{Reg} cells that are specific for viral antigens, or could also reflect the *de novo* generation of 'induced' T_{Reg} cells from naive virus-specific CD4⁺ T cells. An important factor in the generation of induced T_{Reg} cells appears to be TGFβ[110,111], although how induced T_{Reg} cells affect viral infection is not yet well understood. For example, some viral pathogens may promote the development of T_{Reg} cell populations to limit the host antiviral response. Evidence for this hypothesis has been found in several models, mainly of chronic viral infection[112,113]. In acute viral infection, which has not been studied as fully as chronic infection, T_{Reg} cells have been shown to limit pathology during infection with WNV[114] or RSV[115,116] and in a model of influenza A virus infection[117]. A detailed account of T_{Reg} cell induction and responses during viral infection is available elsewhere[118].

CD4⁺ T cells and chronic viral infection

Compared with our understanding of CD8⁺ T cells[119], much less is known about how chronic infection affects CD4⁺ T cell phenotype and function. However, the impact of persistent viral infection on CD4⁺ T cell function and the importance of CD4⁺ T cells during chronic viral infection are receiving increasing attention. During persistent infection with LCMV clone 13, responding CD4⁺ T cells lose the ability to produce T_H1-type effector cytokines and to function optimally following viral rechallenge[120]. The loss of function of CD4⁺ T cells responding to persistent antigen is probably driven by

Box 2 | **CD4⁺ T cell help for CD8⁺ T cells during chronic viral infection**

The best-characterized function of CD4⁺ T cells during persistent viral infection is the maintenance of competent CD8⁺ T cells that retain robust effector functions long-term[153]. Although this has been most-rigorously studied in models of lymphocytic choriomeningitis virus (LCMV) infection, CD4⁺ T cells have also been found to affect CD8⁺ T cell responses to varying degrees in other models of chronic infection, including mouse cytomegalovirus[154], mouse polyomavirus[155] and gammaherpesvirus[156] infection. Recent studies using LCMV infection suggest that interleukin-21 (IL-21) production by CD4⁺ T cells during chronic infection is crucial for maintaining functional CD8⁺ T cells that are able to contain the infection[157–159]. Importantly, clinical evidence also correlates the presence of higher numbers of IL-21-producing CD4⁺ T cells with improved CD8⁺ T cell function and improved control of HIV infection[160,161]. These observations suggest new avenues that could improve vaccination strategies and adoptive transfer therapies[162] through the generation of CD4⁺ T cell populations specifically geared towards the provision of maximal help in the context of chronic infection.

high levels of antigen following the priming phase[121] and seems not to be regulated by the intrinsic changes in APCs that are caused by chronic viral pathogens[120].

Chronic infection may not lead to irreversible exhaustion of responding CD4⁺ T cells. For example, functionally impaired CD4⁺ T cells have been observed in patients with HIV, and treatment with antibodies that stimulate CD28 (REF. 122), block T cell immunoglobulin domain and mucin domain protein 3 (TIM3)[123] or block PD1 signalling[124] dramatically increased the proliferative potential of these T cells *in vitro*. Also, a recent study by Fahey *et al.* found that during chronic LCMV infection responding CD4⁺ T cells progressively adopt a functional T_{FH} cell phenotype[125]. That CD4⁺ T cells may retain specific functions during chronic infection helps to explain earlier observations that persistent LCMV infection is eventually cleared through mechanisms that are dependent on CD4⁺ T cells (BOX 2). For instance, interactions between exhausted CD8⁺ T cells and CD4⁺ T cells may restore CD8⁺ T cell function during chronic infection with LCMV[126]. These findings and others (reviewed in REFS 127,128) have important implications for the design of vaccines against viruses that cause chronic infection in humans (such as HIV, hepatitis B and hepatitis C).

Memory CD4⁺ T cell responses against viruses

Following the resolution of infection, or after successful vaccination, most virus-specific effector CD4⁺ T cells die. This leaves a small population of memory T cells, which ensures that the frequency of virus-specific T cells is greater than it was before priming. The population of CD4⁺ memory T cells diminishes with time and may require boosting. It is unclear which responding effector CD4⁺ T cells make the transition to a memory phenotype, but a recent study suggests that those with lower expression of LY6C and T-bet have a greater potential to do so[129]. A quantitative gain in antigen-specific cells represents one important advantage of the memory state, but memory T cells also differ from naive T cells by broad functional criteria. Compared with naive T cells, memory CD4⁺ T cells respond much faster, respond to lower antigen doses, require less co-stimulation and proliferate more vigorously following pathogen challenge[130]. In addition, subpopulations of memory CD4⁺ T cells have wider trafficking patterns and some are retained at or near sites of previous infection[131], and this contributes to their ability to be rapidly activated following local re-infection. Tissue tropism and/or retention of tissue-resident memory CD4⁺ T cells may depend on specific interactions between adhesion molecules and their receptors (BOX 3).

Memory CD4⁺ T cells enhance early innate immune responses following viral infection. Memory CD4⁺ T cell-mediated recognition of antigens presented by APCs following re-infection has rapid consequences. Within 48 hours of intranasal infection with influenza virus, antigen-specific memory CD4⁺ T cells cause an enhanced inflammatory response in the lung, and this is characterized by the upregulation of a wide array of pro-inflammatory mediators[132] (FIG. 4). In infected tissues, transferred T_H1-type and T_H17-type memory cells, as well as memory CD4⁺ T cells generated by previous infections, upregulate the expression of pro-inflammatory cytokines and chemokines, including

Box 3 | **Tissue-resident memory T cells**

Following the resolution of primary immune responses, most effector T cells die by apoptosis, leaving behind a small population of long-lived memory cells. Recent studies have demonstrated that, in addition to recirculating through lymphoid and non-lymphoid tissues, some memory cells reside at sites of infection. Although most of these studies have concentrated on CD8⁺ T cell memory, CD4⁺ T cells also appear to survive for long periods in peripheral tissues[163,164].

Often, the expression of distinct surface proteins distinguishes tissue-specific memory cells from conventional lymphoid memory populations. These molecules are likely to have a crucial role in the retention of memory T cells at different sites through specific interactions with ligands that are expressed in particular tissues. For example, the expression of α1β1 integrin (also known as VLA1) by airway-resident memory CD4⁺ T cells in the lungs can facilitate binding to collagen[164], and high levels of CD103 expression by brain- or skin-resident memory CD8⁺ T cells facilitates their interaction with cells that express E-cadherin[165,166].

Tissue-resident memory T cells act as a first line of defence. Combined with the ability of memory T cells, but not naive T cells, to be activated through the recognition of antigens in peripheral tissues[132,167], the location of memory CD4⁺ T cell populations at potential sites of re-infection represents a powerful advantage of the memory state over the naive state, in which a lag of several days precedes the influx of antigen-specific cells into infected sites. Tissue-resident memory cells may facilitate more-rapid recruitment and activation of innate cell populations that are capable of controlling initial viral titres. Moreover, these memory cells may simultaneously accelerate the development of pathogen-specific effector populations of B and T cells by promoting the earlier activation of antigen-presenting cells. Elucidating the important cues that drive the development of long-lived tissue-resident memory cells is likely to become an important area of research, especially as this understanding may lead to the design of improved vaccination strategies.

IL-1α, IL-1β, IL-6, IL-12p40, CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 9 (CXCL9) and CXCL10. By contrast, T_H2-type and non-polarized (T_H0) memory T cells have a minimal impact on pulmonary inflammation following influenza virus challenge. To induce innate inflammatory responses, memory CD4⁺ T cells must recognize antigens on CD11c⁺ APCs. These APCs become activated during interactions with memory CD4⁺ T cells, and this results in the upregulation of MHC class II and co-stimulatory molecule expression by the APCs. Activated APCs contribute to the subsequent innate inflammatory response through the production of pro-inflammatory cytokines, such as IL-6 and IL-1β. By contrast, the naive CD4⁺ T cell response *in vivo* does not have an appreciable impact on the tissue inflammatory response at 48 hours post-infection[132]. In other studies, naive CD4⁺ T cells could actually downregulate tissue inflammation following mouse hepatitis virus infection[133]. The ability of T_H1-type and T_H17-type memory CD4⁺ T cells, but not T_H2-type or non-polarized memory T cells, to promote an early inflammatory response may help to explain why transfer of virus-specific T_H1 and T_H17 effector cells, but not transfer of T_H2 or non-polarized T cells, promotes early control of viral loads in mice infected with influenza virus[16,86,132]. A similar impact of memory CD4⁺ T cells on early viral control during secondary influenza infection was recently reported by Chapman *et al.*[134], and this also correlated with a dramatic enhancement of innate immune responses against the virus. However, this effect has not yet been studied in other models of viral infection.

We suggest that the early activation of innate immune mechanisms by memory CD4⁺ T cells serves to lessen the 'stealth phase' of infection, during which titres of the virus are still too low to generate robust inflammatory responses[135]. This would prevent viruses from gaining a 'foothold' in the host by infecting and replicating in cells at a level that is below immune detection. Importantly, the induction of early innate immune responses by memory CD4⁺ T cells does not require PRR activation[132] and could therefore be important for enhancing protection against viral pathogens — such as vaccinia virus and influenza virus — that can actively antagonize key components of innate recognition pathways, such as dsRNA-dependent protein kinase (PKR)[136].

One intriguing finding is that memory CD4⁺ T cells specific for ovalbumin enhance antiviral immunity when ovalbumin is co-administered with an influenza virus that does not express ovalbumin[132]. Thus, we hypothesize that the induction of innate immune responses by memory CD4⁺ T cells could have an adjuvant effect, which could be exploited (and substituted for PRR stimulation[132]) to promote immune responses to vaccines that do not contain live viruses. For example, a vaccine could activate the innate immune system through antigen-specific stimulation of memory CD4⁺ T cells that are known to be widespread in the human population (for example, most individuals have memory CD4⁺ T cells specific for tetanus toxin). This method could possibly enhance the immunogenicity of 'weak' vaccines.

Heterologous memory responses. Heterologous viral immunity occurs when memory T cells that were generated in response to a particular virus cross-react with epitopes expressed by other, unrelated viruses. It has recently become clear that this is quite a widespread phenomenon that is likely to be important in the human population, as humans are exposed to numerous antigens as a result of infection and vaccination[137].

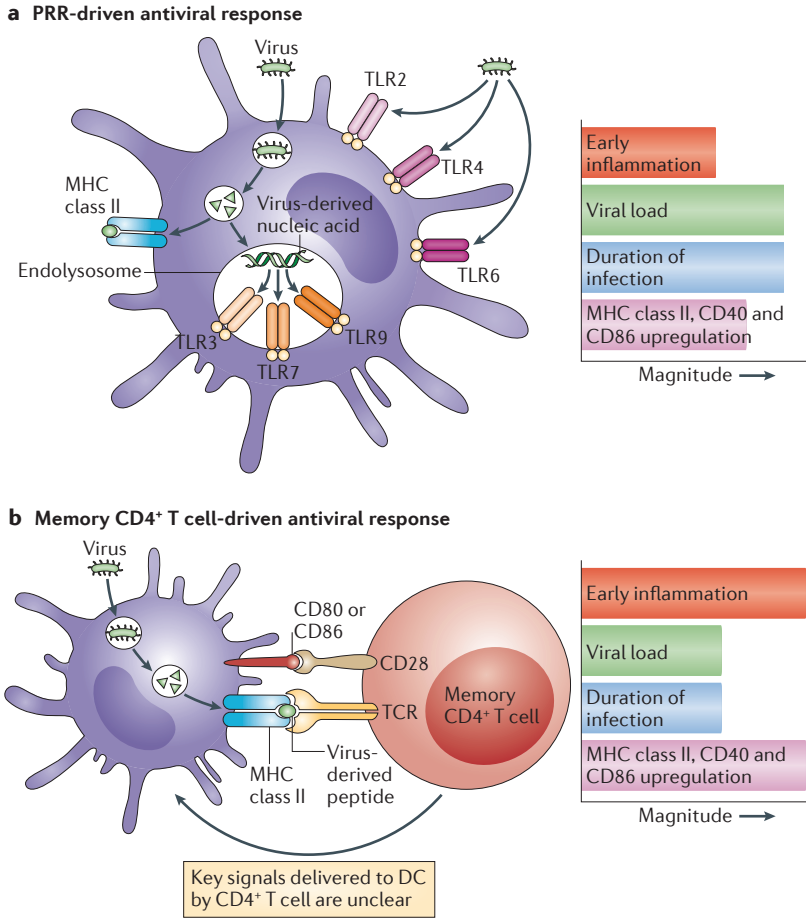


Figure 4 | **Activation of APCs through PRRs and through the recognition of antigens by memory CD4⁺ T cells. a** | Several classes of pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), sense the presence of viral pathogens, and the triggering of these receptors leads to the activation of antigen-presenting cells (APCs), including dendritic cells (DCs). Activated APCs upregulate their expression of MHC molecules and co-stimulatory molecules, which are important for the priming of naive virus-specific T cells. Triggering of PRRs at the site of infection induces local inflammation, which involves the activation of several populations of innate immune cells that can control viral titres and establish chemokine gradients to attract further antiviral effector cells. The efficiency of PRR triggering can determine whether viral replication or protective immunity gains the upper hand. **b** | Virus-specific memory CD4⁺ T cells can directly activate DCs through the recognition of antigens presented by MHC class II molecules, even in the absence of co-stimulation delivered via PRR-mediated signalling. The crucial signals delivered by memory CD4⁺ T cells to DCs in this process are unclear and could involve both cell-surface interactions and cytokine signals. The outcome of DC activation and the initiation of inflammatory responses are similar whether triggered through PRRs or memory CD4⁺ T cells but, in situations of infection with a rapidly replicating virus (such as influenza virus), memory CD4⁺ T cell-mediated enhancement of innate immunity is substantially quicker and more effective than that provided by PRR triggering. TCR, T cell receptor.

Although heterologous immune responses can be protective, they may in some cases be deleterious and can result in dramatic immunopathology[138]. It will be important to determine to what extent the ability of memory CD4+ T cells to induce innate immunity contributes to both beneficial and deleterious heterologous responses.

Helper functions of memory CD4+ T cells. Several studies indicate that memory CD4+ T cells are superior to naive T cells in providing help for B cells, and they have been shown to promote earlier B cell proliferation, higher antibody levels and earlier class-switching responses compared with naive CD4+ T cells[139–141]. In many cases, when pre-existing circulating antibodies are able to recognize the virus, re-infection may never occur. Faster antibody production could be particularly important after re-infection with rapidly mutating viruses (such as influenza virus), as the generation of neutralizing antibodies specific for new variants that evade previously generated antibodies could be necessary for immunity.

That memory CD4+ T cells are superior helpers for B cells compared with naive T cells is suggested by multiple criteria, and many mechanisms may contribute. Memory CD4+ T cells contain preformed stores of CD40L, an important signal in CD4+ T cell-mediated help for antibody production[142]. The location of memory CD4+ T cells may also be an advantage. For example, antigen-specific memory CD4+ T cells with a T_{FH} cell phenotype are retained in the draining lymph nodes of mice for over 6 months following immunization[143]. The increased levels and polarized profile of cytokines produced by memory CD4+ T cells, as compared with those of naive T cells, is likely to promote a more-robust B cell antibody response and to dictate the antibody isotype, which has a key role in the efficacy of antibodies specific for viruses such Ebola virus[144], WNV[145] and influenza virus[146]. Recent observations suggest that IL-4 and IFNγ produced by T_{FH} cells have a central role in driving not only immunoglobulin class switching in the germinal centre, but also B cell affinity maturation[147].

Whether memory CD4+ T cells are superior to naive CD4+ T cells at providing help for primary or secondary CD8+ T cell responses during viral infection has not been rigorously tested. However, the features of memory cells described here suggest that memory CD4+ T cells could promote an accelerated response by naive CD8+ T cells, both through more-rapid licensing of APCs and through faster and more-robust production of IL-2 and possibly other cytokines; these possibilities need to be explored. In support of this concept, a study using *Listeria monocytogenes* found that T_H1-type but not T_H2-type memory CD4+ T cells enhanced primary CD8+ T cell responses in terms of both magnitude and cytokine production, although the mechanism of memory CD4+ T cell-mediated help was not determined[148]. Whatever the pathways involved, the fact that memory CD4+ T cells enhance the generation of CD8+ T cell memory and that this process has a greater dependence on CD4+ T cell-mediated help when PRR stimulation is limited suggests that CD4+ T cell-mediated help will be of particular importance in achieving optimal CD8+ T cell memory responses with vaccines that do not contain live, replication-competent viruses.

Finally, we should point out that the impact of memory CD4+ T cells on the early innate immune response may also affect subsequent antigen-specific immune responses against viruses, owing to alterations in the expression of chemokines. For example, by upregulating local production of CC-chemokine receptor 5 (CCR5) ligands at the site of infection, memory CD4+ T cells can promote the recruitment of memory CD8+ T cells that contribute to early viral control in influenza virus infection[149]. In HSV-2 infection, IFNγ expression by CD4+ T cells is required to induce chemokines that recruit effector CD8+ T cells to the infected vaginal tissue[150]. Similar roles for CD4+ T cells in promoting CD8+ T cell recruitment may occur during infections with other viruses, although it is often difficult to separate the roles of CD4+ T cells in generating effector CD8+ T cells from their roles in modifying CD8+ T cell trafficking[39,85,151].

Secondary effector T cells

The presence of memory CD4+ T cells that are capable of producing multiple cytokines has been correlated with superior protective capacity in numerous studies[152], but how such cells achieve enhanced protection has not been addressed. One possibility is that 'secondary' effector CD4+ T cells that arise from memory precursors may be much more efficient in directly combating pathogens than primary effector CD4+ T cells that arise from naive cells. Our recent experiments that directly compared such primary and secondary effectors during influenza virus infection support such a view (T.M.S., K.K.M., L. M. Bradley and S.L.S., unpublished observations). We found that following adoptive transfer of either antigen-specific memory CD4+ T cells or an equal number of antigen-specific naive CD4+ T cell precursors, the secondary effector populations that developed from the memory CD4+ T cells showed greater expansion and contained higher frequencies of T cells that secrete multiple cytokines. Furthermore, although high levels of IL-10 were produced by primary effector CD4+ T cells during influenza virus infection, secondary effector cells produced much less IL-10. Thus, memory CD4+ T cells seem to give rise to secondary effector T cells that are distinct from and superior to the primary effectors derived from naive CD4+ T cells. We suggest that this results in more-protective recall responses, and we predict that further functions of secondary effectors will be discovered as additional comparative analyses are carried out.

Summary

Here, we have reviewed how CD4+ T cells contribute to protective immunity to viruses, during both primary and secondary infections. Several key principles emerge. Distinct CD4+ T cells subsets — including T_H1 cells, T_H17 cells, T_{FH} cells and CD4+ T cells with cytotoxic

functions — have important roles in the antiviral response. Key among these roles is the provision of help to B cells, but CD4$^+$ T cells also contribute to the antiviral response by producing cytokines and chemokines, by enhancing CD8$^+$ T cells responses and through direct cytotoxic effects on virus-infected cells.

Memory CD4$^+$ T cells have additional protective functions compared with naive cells. They induce early innate inflammatory responses in the tissue that contribute to viral control. Importantly, memory CD4$^+$ T cells provide more-rapid help to B cells, and probably to CD8$^+$ T cells, thereby contributing to a faster and more-robust antiviral immune response. Finally, secondary effectors derived from memory CD4$^+$ T cell precursors are likely to be more capable of mediating direct antiviral activity than primary effectors derived from naive CD4$^+$ T cells.

The picture that emerges is one in which CD4$^+$ T cells carry out an impressive variety of functions at different times and in different sites, and we suggest that the synergy of these distinct mechanisms can provide an extraordinarily high level of viral control. Depending on the particular pathogen and the level of infection, these mechanisms may often be redundant, but they are likely to each make key contributions following exposure to high doses of rapidly replicating viruses or to viruses that have evolved mechanisms to evade specific immune pathways. We point out that the study of the immune response to viral infections has revealed new mechanisms by which CD4$^+$ T cells function to protect against pathogens, and we predict that additional mechanisms will be identified in the future. Thus, this area of study will lead to a better understanding of how vaccines can be designed to harness the power of CD4$^+$ T cell memory.

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This study provides evidence that not only effector CD8$^+$ T cell functions but initiation of CD8$^+$ memory T cell responses can occur within extra-lymphoid tissues through interaction with CD4$^+$ T cells and recently recruited DCs.

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