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Review

Virus-specific T cells as correlate of (cross-)protective immunity against influenza

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ABSTRACT

Since inactivated influenza vaccines mainly confer protective immunity by inducing strain-specific antibodies to the viral hemagglutinin, these vaccines only afford protection against infection with antigenically matching influenza virus strains. Due to the continuous emergence of antigenic drift variants of seasonal influenza viruses and the inevitable future emergence of pandemic influenza viruses, there is considerable interest in the development of influenza vaccines that induce broader protective immunity. It has long been recognized that influenza virus-specific $CD8^+$ T cells directed to epitopes located in the relatively conserved internal proteins can cross-react with various subtypes of influenza A virus. This implies that these $CD8^+$ T cells, induced by prior influenza virus infections or vaccinations, could afford heterosubtypic immunity. Furthermore, influenza virus-specific $CD4^+$ T cells have been shown to be important in protection from infection, either via direct cytotoxic effects or indirectly by providing help to B cells and $CD8^+$ T cells. In the present paper, we review the induction of virus-specific T cell responses by influenza virus infection and the role of virus-specific $CD4^+$ and $CD8^+$ T cells in viral clearance and conferring protection from subsequent infections with homologous or heterologous influenza virus strains. Furthermore, we discuss vector-based vaccination strategies that aim at the induction of a cross-reactive virus-specific T cell response.

1. Introduction

Influenza viruses are a major cause of respiratory tract infections in humans. Annual epidemic outbreaks are typically caused by influenza A (H1N1 or H3N2 subtypes) or B viruses. Complications leading to morbidity and mortality following infection are predominantly observed in high-risk groups, such as the elderly and immunocompromised. Therefore, annual vaccination of these high-risk groups is recommended.

Currently used trivalent inactivated influenza vaccines (TIV) contain hemagglutinin (HA) of A/H1N1, A/H3N2 and influenza B vaccine strains that antigenically match the epidemic strains that are most likely to circulate in the coming influenza season. Recently, quadrivalent vaccines have become available that contain an additional, antigenically different influenza B virus component [1]. These vaccines aim at the induction of antibody responses against HA and to a lesser extent neuraminidase (NA) [2] and their use reduces morbidity and mortality in selected patient populations [3]. However, as a result of selective pressure exerted by virus-specific antibodies induced by previous vaccinations and/or infections, seasonal influenza viruses accumulate mutations in the antigenic sites of HA and NA [4–6]. Therefore, vaccine-induced antibodies do not provide efficient protection against infection with antigenically mismatching virus strains. In general, TIV inefficiently induce virus-specific $CD8^+$ T cell responses [7,8] that also substantially contribute to protective immunity by accelerating viral clearance. Live-attenuated influenza vaccines (LAIV) are also available in some countries and are especially used to vaccinate children [9]. LAIV are capable of inducing both humoral and cellular immune responses, and induce both cytotoxic and helper T cells [10].

In this review, we describe the induction of T cell responses by influenza virus infections. Subsequently, we discuss the role of both $CD4^+$ and $CD8^+$ T cells in the clearance of influenza virus infections and their contribution to heterosubtypic immunity. Furthermore, we discuss vector-based vaccination strategies that focus on efficient induction of a cross-reactive influenza virus-specific T cell response and afford heterosubtypic immunity.

2. Immune response to influenza virus

Influenza virus-specific serum antibodies are detected 7–12 days post primary infection. Neutralizing antibodies mainly

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target the HA and NA proteins and correspond well with protection from infection with homologous strains [11]. Infection with (seasonal) influenza virus also induces T cell responses [12–16]. Since influenza viruses infect epithelial cells of the respiratory tract, sentinel lung-resident CD103$^+$ dendritic cells (DC) present in the immediate proximity of respiratory epithelial cells are in a unique position to capture antigens from virus-infected cells, mature and migrate to lymph nodes (LN) and exert their function as professional antigen presenting cells (APC) by activating naive T cells [17–19]. In mice it was shown that respiratory infection with influenza virus leads to DC migration to the draining lymph nodes, DC maturation and efficient antigen presentation to lymphocytes [20,21].

After the T cell receptor (TCR) recognizes a MHC-peptide complex, there is clonal expansion of virus-specific CD4$^+$ or CD8$^+$ naive T cells into effector cells. Co-stimulatory signals are required to prevent abortive clonal expansion (reviewed in [22]). In the course of an influenza virus infection, primed T cells migrate from LN to the lungs where they exert their antiviral effects by eliminating influenza virus-infected epithelial cells. After clearance, immunological memory is established. There are various memory T cell subsets, however, the role of each subset during a secondary infection is incompletely understood. Generally, the memory T cells can be divided into long-lived central memory T cells (T^{CM}), effector memory T cells (T^{EM}) and tissue resident memory T cells (T^{RM}). Heterosubtypic immunity, *i.e.* virus-specific T cells that respond to a secondary infection with an antigenically different virus, can be established when memory T cells recognize conserved antigens (reviewed in [23]).

It has been shown that despite lack of a protective antibody response, primed B cell deficient mice are still able to clear an influenza virus challenge infection, albeit less efficient than in the presence of B cells [24]. Graham et al. also showed that mainly the CD8$^+$ T cell response was responsible for this B cell-independent clearance [24]. However, depletion of CD8$^+$ T cells from influenza virus-infected mice, also still led to viral clearance [25–28], indicating that other arms of the immune system were involved. Combining the two approaches, depletion of CD8$^+$ T cells from IgG deficient mice was detrimental to viral clearance and resulted in fatal infections [29]. Furthermore, depletion of CD4$^+$ T cells from mice resulted in a slightly delayed influenza virus clearance compared to mice with functional CD4$^+$ and CD8$^+$ T cell compartments [30,31]. Altogether, these data suggest a complex interplay, where influenza virus-specific antibodies, B cells, CD4$^+$ and CD8$^+$ T cells play an important role in facilitating viral clearance and protection from re-infection [31–33].

3. CD8$^+$ T cells

Decades ago, it was already recognized that influenza virus infections in mice lacking MHC class I restricted CD8$^+$ T cells result in delayed virus clearance and more severe diseases upon re-infection [27]. Moreover, in experimentally infected humans an inverse correlation between CD8$^+$ cytotoxic T lymphocytes (CTL) present in peripheral blood and virus shedding was observed [34]. Over the years the role of CD8$^+$ T cells in clearing influenza virus infections has been confirmed in various animal models [27,35,36]. More recently, it was demonstrated that pre-existing virus-specific CD8$^+$ T cells in humans correlated with protection against disease severity caused by infection with 2009 pandemic H1N1 influenza viruses [37].

Upon interaction of their TCR with a specific MHC class I-peptide complex, CD8$^+$ T cells are activated. An influenza virus infection induces CD8$^+$ T cells mainly specific for the relatively conserved internal proteins, like nucleoprotein (NP), matrix (M) protein and

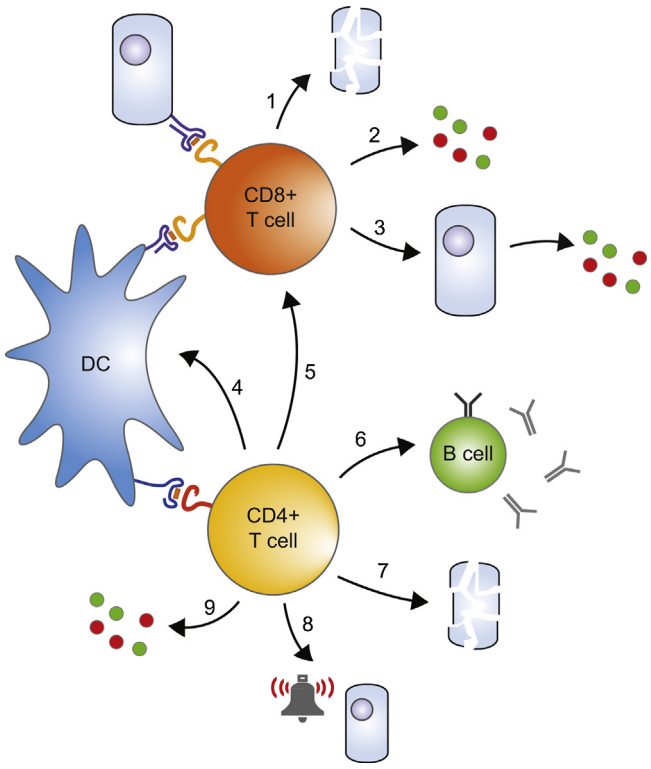

Fig. 1. T cell immunity against influenza virus. CD4$^+$ and CD8$^+$ T cells contribute to immunity against influenza virus through several mechanisms. After activation of T cells via MHC-restricted influenza virus antigen presentation, the main function of virus-specific CD8$^+$ T cells is (1) direct lysis of influenza virus-infected cells. In addition, virus-specific CD8$^+$ T cells (2) produce (antiviral) chemokines and cytokines and (3) stimulate epithelial cells to produce these molecules. Influenza virus-specific CD4$^+$ T cells aid in the activation of (4) APC, (5) CD8$^+$ T cells and (6) B cells. Furthermore, CD4$^+$ T cells (7) can have direct cytotoxic effects, (8) induce an antiviral state in cells in the vicinity and (9) activate the innate immune system through production of chemokines and cytokines.

the polymerase subunits [34,35,38,39]. CTL responses are often directed at only a fraction of all potential antigenic epitopes, which are defined as immunodominant epitopes [40]. Several factors have been implicated to influence immunodominance, but recently it was shown in mice that the prevalence of high-avidity T cells in a starting population predominantly determines this hierarchy in the T cell response [41].

After primary activation by APC, T cells migrate to the lung to exert their effector functions. McGill et al. showed that in the lung influenza virus-specific CD8$^+$ T cells require a second MHC-restricted antigen-dependent interaction with pulmonary DC [42]. Classically, CD8$^+$ T cells exert their effects via cytolytic contact-dependent pathways [43], however, CTL can also have a suppressor function by the secretion of cytokines [44] and chemokines [45]. Additionally, CD8$^+$ T cells produce chemokines upon antigen-specific interaction with epithelial cells [46] and promote chemokine production by epithelial cells themselves (Fig. 1) [47].

CD8$^+$ T cells can be divided in Tc1, Tc2 and Tc17 subgroups depending on the cytokine production profile. Tc1 and Tc2 have direct cytolytic capacity, whereas this is not the case for the Tc17 subset [48,49]. Direct cytolytic capacity is exerted via either release of perforin and granzymes, or via apoptosis triggered by Fas/Fas Ligand (FasL) or TNF receptor 1 interaction [43,50]. Tc17 can efficiently recruit B cells, neutrophils, NK cells, macrophages and T cells by the production of cytokines and chemokines [36].

By themselves, each of the Tc1, Tc2 and Tc17 subgroups were able to confer protection from infection with a lethal dose of