the cGAS-STING axis, including the control of the intracellular levels of second messenger 2′,3′-cGAMP or CDNs, the mechanism of STING translocation and NF-κB activation mediated by STING. Future work is also required to uncover new nucleic acid sensors and novel regulators of cytosolic nucleic acid sensing. In addition, it is worthwhile to unravel how viruses exploit these regulatory mechanisms to control type I IFN production and escape immune responses. How host self nucleic acids and pathogen-derived nucleic acids are accurately discriminated by nucleic acid sensors needs to be further investigated. A greater understanding of the mechanisms that regulate type I IFN production will guide and facilitate the discovery of new drugs and therapies that promote the eradication of pathogens and alleviate autoimmune diseases.

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**IMMUNOLOGY**

Special Topic: Infection and Immunity

**CD8+ cytotoxic T lymphocytes in human influenza virus infection**

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Influenza remains a global problem, resulting in 250,000–500,000 deaths in non-pandemic years according to the most recent WHO report (http://www.who.int/mediacentre/factsheets/fs211/en/). The currently available influenza vaccines mostly induce antibodies against the viral surface glycoproteins, haemagglutinin (HA) and neuraminidase, with the HA being by far the more important. Whilst neutralizing antibodies can provide sterilizing immunity by blocking infection, this protection is only specific for the immunizing and closely related strains and is ineffective against heterologous strains with serologically distinct HAS [1]. Influenza viruses continue to evolve and change antigenically. However, drastic antigenic changes are found when a new pandemic virus adapts to transmit efficiently between humans. A pandemic strain may even be of another subtype, such as the original H3N2 viral strain, or a distant variant of an already circulating virus, such as the 2009 pandemic H1N1 strain. The recent discovery of broadly neutralizing protective mAb targeting stalk region of HA and its ability of enhancing the engagement with Fc receptors shaded new lights in further vaccination strategies [2]; however, despite this, current seasonal influenza vaccines failed to boost responses to the conserved HA stem region [3]. Thus, existing antibody-based vaccines developed against current viruses, in humans or animal reservoirs, are unlikely to confer adequate protection against a pandemic strain, and there is an urgent need for another vaccine strategy. An alternative or additional approach would be to stimulate T-cell-mediated immunity, particularly virus-specific CD8+ cytotoxic T lymphocytes (CTLs), which target the highly conserved internal proteins.

We and others have demonstrated that memory T-cell responses in human to internal protein are highly cross-reactive between the different viral strains, including the recently occurring human infection of animal strains i.e. Avian H5N1, swine H1N1 and avian H7N9 [4,5]. While CTLs will not prevent the establishment of infection, there is good evidence in mice that T cells provide partial protection against...
influenza by promoting viral clearance and reducing the severity of symptoms. All human adults have been infected with influenza virus but the level of CTL immunity in individuals and the population is not stable over the years and it has been suggested that the level of T-cell immunity is related to the annual incidence of influenza infection [6]. The ‘Cleveland Family study’ showed that protection from influenza correlated with T-cell responses, and cross-reactive T-cell responses may contribute to the protection [7].

Pre-existing CTL responses have been associated with good control for the virus and disease severity regardless of the existence of neutralizing antibodies in influenza virus infection and challenge studies [8]. In a study where volunteers were challenged with influenza virus intranasally, those with measurable pre-exposure CTL responses, probably reflecting more recent influenza virus infection, shed less virus than those with no T-cell responses, implying a protective effect [9]. This observation is confirmed by a recent study that pre-existing cellular immune responses in particular CD8+ T-cell responses were correlated with the protection in a cohort of 342 healthy adults who were followed through the UK pandemic waves and before and after incident pH1N1 infection [8].

However there is a risk that an excess of antigen specific T cells could overreact to the virus, and aggravate the infection, especially if virus load is high. Therefore, it is important to further our understanding about what antigen specific T cells, especially cross-reactive CTL, do in humans infected with a virulent strain such as H5N1 or H7N9 in comparison to a relatively mild strain of the virus such as pdm2009H1N1. Studies on H5N1 influenza virus infection showed that the H5N1 virus is an extremely virulent strain which can persist in the body of those infected for up to 2 weeks, whereas in most seasonal influenza virus infections, the virus disappears approximately 2–3 days.

In human infections with avian influenza viruses H5N1 and H7N9, and in rare severe cases with pandemic or seasonal viruses, plasma proinflammatory cytokines are persistently raised [10], suggesting immune dysfunction. The high virus loads in human H5N1 virus infections raise the possibility of CTL-induced pathology.

CD8+ T cells are not homogeneous. There are multiple different phenotypes, which predict the functionality of the cells. Impaired T-cell function was observed in patients with acute pdm2009H1N1 influenza virus infection, possibly due to the expression of PD-L1 on both dendritic cells and T cells, lung alveolar and bronchiolar epithelial cells as well as on airway and lung tissue cells [11]. This could trigger an inhibitory signal via PD-1 expressed on T cells during the acute influenza virus infection. However, it is not clear if impaired T-cell function observed in these studies is the cause of, or an effect of, severe influenza virus infection.

Most of the current studies in human influenza virus infection consist of data generated from T cells in the circulation; these may have limited relevance to the lung, where the virus infection and disease occurs. Memory CD8 T cells to influenza virus accumulate in lung tissue [12]. A discordant distribution between influenza-specific T cells in lungs and blood was observed in pdm2009 severely infected individuals [13].

Overall, there is urgent need to study the determinant(s) of optimal CTL responses required for the control of the influenza virus in large-scale longitudinal human influenza virus infected patient cohorts. Special attention should be paid to immune responses, especially CTLs, in lung, a disease site for severe influenza virus infection, as well as consideration of additional factors including the circulating virus virulence, host genetics, age, gender and environmental effects.

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