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The immunopathology of dengue and Zika virus infections

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A large proportion of the world's population live in areas with dengue virus (DENV) transmission resulting in tens of millions of symptomatic dengue cases each year. Serious complications following DENV infection occur more frequently in those suffering from a second or subsequent infection implicating virus-specific immunity as having a role in pathogenesis. In recent years outbreaks of the related Zika virus (ZIKV) have been associated with birth defects and neurological complications. As DENV and ZIKV share a viral vector sequential infections can occur. Given the sequence homology between the two viruses, the generation of cross-reactive immune responses is highly likely. This review examines the role immunopathogenesis plays during DENV infection as well as highlighting recent studies that demonstrate DENV immunity may have an effect on the outcome of ZIKV infection.

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Introduction

Since dengue virus (DENV) was first isolated in 1943 the global incidence of disease has increased year on year. Recent estimates suggest that 390 million DENV infections occur each year of which 96 million manifest clinically [1]. Transmission has been reported in 128 countries with a collective population of 3.9 billion, as a result over half the world's population are at risk of contracting dengue [2].

Decades of research into the pathogenesis of dengue have implicated the virus-specific immune response in contributing to severe symptoms. This has complicated the development of a safe and effective vaccine. Sanofi-Pasteur has recently developed a vaccine that has been licensed for use in several countries, but can only be administered to certain age groups. Furthermore, it remains contentious as to whether the vaccine is completely avoiding the induction of harmful immune responses [3,4•].

Certain areas of DENV transmission have recently been experiencing outbreaks of the related Zika virus (ZIKV). Whilst initially found to cause relatively mild symptoms, current outbreaks of ZIKV have been linked to birth defects as well as serious neurological complications. As ZIKV and DENV share substantial sequence homology it will be important to establish if cross-reactive immune responses exist and how they might affect the outcome of both diseases.

Dengue virus

DENV is a member of the flavivirus family. It has a single-stranded positive sense RNA genome that is translated into a single polyprotein. This polyprotein is then cleaved into 3 structural proteins; capsid (C), Premembrane (PrM) and envelope (E) and 7 non-structural proteins NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5.

DENV is transmitted via the bite of infected *aedes* mosquitoes, whose distribution restricts circulation of the virus to tropical and subtropical regions. DENV exists as four related serotypes (DENV1-4) each of which co-circulates in endemic areas. As a result of this heterogeneity immunity to one serotype can provide only short-lived protection from a subsequent infection with another serotype. Therefore secondary infections are common.

DENV causes a spectrum of disease ranging from dengue fever (DF), a self-limiting febrile illness, to dengue haemorrhagic fever and dengue shock syndrome (DHF/DSS), which can be life threatening without medical intervention. DHF/DSS is characterised by increased capillary permeability leading to plasma leakage. In the absence of fluid replacement therapy, this can result in circulatory insufficiency, shock and organ failure.

Epidemiological evidence has demonstrated that severe complications from DENV infection occur more frequently in patients experiencing a secondary or subsequent infection [5,6]. Furthermore, whilst DHF/DSS are associated with increased viral loads [7], the critical phase of dengue disease manifests when the levels of

virus are receding. This suggests that the DENV-specific immune response itself may contribute to disease severity.

The exact mechanism that leads to an increase in vascular permeability during DENV infection is incompletely understood. Aside from the temporal disconnect between the presence of virus and the critical phase of disease, a direct role for virus particles in pathogenesis is further brought into question by the absence of extensive endothelial cell damage [8]. The fall in viral load and the manifestation of severe symptoms instead coincide with an inflammatory 'cytokine storm' again implicating the immune response in pathogenesis.

This cytokine storm results in high circulating levels of many pro-inflammatory mediators such as interferon-γ (IFN-γ), tumour necrosis factor (TNF), soluble TNF receptor 1 (sTNFR1), sTNFR2, CXC-chemokine ligand 8 (CXCL8), CXCL9, CXCL10, CXCL11, CC-chemokine ligand 5 (CCL5) and vascular endothelial growth factor A (VEGFA), as well as the anti-inflammatory cytokine interleukin-10 (IL-10) [7,9–11]. The origins and effects of these molecules during DENV infection are not fully understood but they are thought to underpin a complex interplay between immune cells and other cell types such as endothelial cells that have a role in pathogenesis.

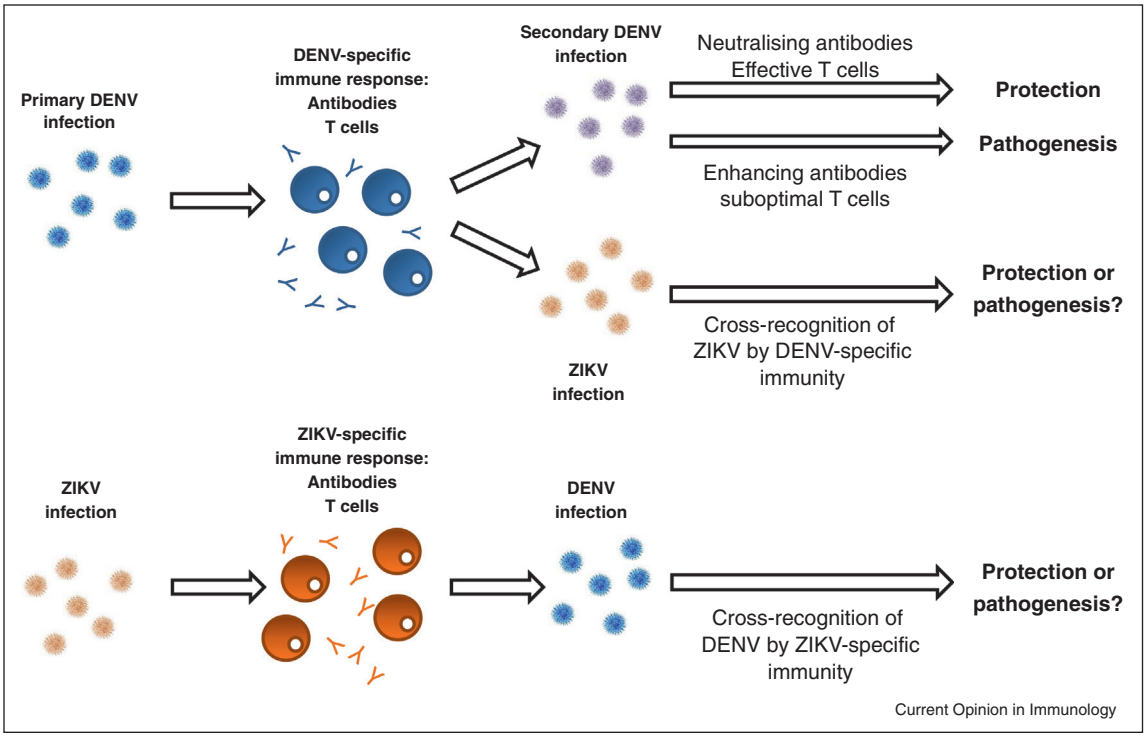
The role of DENV-specific antibodies in pathogenesis

Virion-specific antibodies

The most well characterised mechanism of immunopathology during DENV infection involves antibodies specific for proteins on the virion surface. PrM and E-specific antibodies generated during a primary infection may be poorly neutralising during a subsequent infection due to antigenic variation and insufficient titre (Figure 1).

This can lead to the opsonisation of the virus allowing for increased entry and replication in Fc receptor bearing cells such as macrophages, a major site of DENV replication. This mechanism of antibody dependent enhancement (ADE) has been demonstrated both *in vitro* [12–15] and *in vivo* [16–19]. In addition to enhancing viral replication, the interaction between opsonised virus and Fc receptors can lead to the induction of cytokines [20] that could further recruit inflammatory immune cells and contribute to the cytokine storm.

Figure 1



Cross-reactive DENV/ZIKV-specific immune responses have the potential to affect the outcome of both diseases. Immunopathogenesis has been implicated in contributing to the severe symptoms associated with DENV infection. Epidemiological evidence shows poor disease outcomes are associated with secondary infections and mechanisms involving both antibodies and T cells have been investigated. Due to the co-circulation and genetic relatedness of ZIKV and DENV it is of importance to understand what impact immune responses to one of these viruses will have on the outcome of infection with the other.