

# Immunology in zika virus infection and disease

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## Editorial

Human Zika-virus infection is begun when a blood-feeding female *Aedes* mosquito deposits the virus into human skin and the blood stream. Both human epidermal keratinocytes and dermal fibroblasts are permissive to Zika virus infection. The expression of pathogen recognition receptor (PRR)s, toll-like receptor (TLR), RIG-1 and MDA-5, which subsequently trigger the expression of type 1-IFNs, IFN stimulated genes, including OAS2, ISG-15 and MX-1, and inflammatory cytokines are upregulated by infection of dermal fibroblasts with Zika virus. Type 1- and 2-IFNs are known to be important for control of other flaviviruses infections. Both types of IFNs inhibit replication of Zika virus in human fibroblasts. The role of these cytokines in host- defense mechanisms is further confirmed in murine model, in which mice deficient in the type 1-IFN receptor (A129) or type 1- and type 2-IFN receptors (AG129) are highly susceptible to Zika virus infection, with viremia and age-dependent mortality. In contrast, the virus does not cause replication or disease in juvenile or adult immunocompetent mice.

Further investigation of the role of each type of these cytokines during Zika virus infection is urgently needed. The dendritic cell (DC) is one of the main target cells during infection by various flaviviruses, for examples, DENV, WNV and presumably the most potent antigen-presenting cell (APC)s. Blood DCs of convalescent Zika-virus infection patients demonstrated similarly effective antigen capturing functions as those of healthy donors, which indicates recovery from Zika virus disease could be related to restoration of normal APC function. The monocyte is another important innate-immune-cell type targeted by various flaviviruses, and triggers robust pro-inflammatory cytokine and chemokine responses upon infection. Monocytosis is already known to occur in DENV and WNV infections. Some patients with Zika virus disease are reported to have monocytosis during the acute phase, but become normal during the convalescent phase. Unlike DENV infection, no "cytokine storm effects" were identified in the serum during the acute phase of Zika-virus-disease patients with more pronounced elevation of chemokines than inflammatory cytokines. So, the role of monocytes in Zika virus infection remains undefined.

Serological analysis of patients with Zika virus disease demonstrated both anti-Zika-virus IgG and IgM and neutralizing antibodies, which were demonstrated to provide partial protection in infant and adult mice against lethal Zika virus infection. However, the extensive cross-reactivity of patient's serum antibodies against closely related flaviviruses, such as DENV and YFV frequently make unreliable serologic laboratory results to diagnose Zika virus infection. Furthermore, pre-existing antibodies against DENV or

YFV through either infection or vaccination do not seem to confer cross-protection against Zika virus disease. This is evidenced by the diagnosis of Zika virus infection in the two American scientists who had prior vaccination with YFV 17D vaccine before exposure to the virus and recent outbreaks involve countries that are hyperendemic for DENV. On the other hand, a recent study indicated that a high seroprevalence of pre-existing flaviviruses, such as Zika virus or DENV in Okwoko District of Nigeria did not prevent a YFV epidemic in 1970. Although cross-immunity does not inhibit related virus infection, it may decrease the severity of infection to some extent. For example, Rhesus monkeys immunized with Zika virus had a decreased viremia upon a subsequent challenge with YFV. B cells and specific antibodies are critical in the control of disseminated WNV infection, but are not sufficient to eliminate it from the host. During WNV infection, T cells lead to control of viral dissemination and viral clearance. In another recent study, analysis of serum cytokine levels of travelers returning from Brazil, the Pacific and Asia demonstrated increased Th-1 (interleukin (IL)-2), Th-2 (IL-4, IL-13), Th-9 (IL-9) and Th-17 (IL-17) responses during the acute phase, but revealing normal levels of those cytokines in the recovery phase. These results demonstrate that polyfunctional T-cell responses are induced upon Zika virus infection. Nevertheless, the role of the peripheral T cells remains unidentified.

In conclusions, neutralizing antibodies provide partial protection, whereas type 1- and type 2-IFNs are important in controlling Zika virus infection. Development of a useful animal model of Zika virus infection is urgently needed to support these investigations.

Transmission of Zika virus in humans is demonstrated via blood transfusion, sexual intercourse and perinatal transmission from mother to fetus at the time of delivery, in addition to the mosquito transmission. Fetus, placenta, eye, brain and testicles are the known immunologically privileged sites in the human body. Thus, identifying immune factors that lead to viral clearance in periphery will provide significant visions into the development of immunotherapy and vaccines against the Zika virus infection.

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## Conflicts of Interest

None.