Zika Virus Infection RIG-ged by Keratinocytes and Fibroblasts

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Zika virus is an emergent virus targeting the skin. Ji-Ae et al. (2018) explore the interactions between Zika virus and skin cells. They showed that human keratinocytes play an important role in control of initial infection via the interaction with retinoic acid-inducible gene receptors.


Zika virus (ZIKV) is an arbovirus that is transmitted by Aedes aegypti and Aedes albopictus mosquitoes. It was first isolated from a rhesus monkey in the Zika forest of Uganda in 1947. ZIKV has been associated with several epidemics in the Pacific region since 2007, in French Polynesia in 2013, and in Brazil in 2015 (Rodrigues Dias et al., 2018). These outbreaks affected an estimated 30,000 individuals in French Polynesia (about 11% of the population) and 220,000 individuals in Brazil (0.1% of the population) (Baud et al., 2017). ZIKV may be transmitted via several routes including sexual transmission, vertical transmission, and blood transfusion. Clinical manifestations associated with ZIKV are not fully characterized, but the virus is associated with congenital malformations in vertically infected newborns neurological complications such as meningoencephalitis and Guillain-Barré syndrome (Dirlikov et al., 2017; Fellner, 2016).

A skin rash is classically reported with ZIKV (Cordel et al., 2017). It predominantly affects the face, the upper limbs, the trunk, and the lower limbs and usually spares the palms and soles. The exanthema is most often micropapular, and itching is reported in nearly half of patients. Although the mechanisms of rashes associated with ZIKV are not clearly understood, ZIKV has been specifically detected in skin lesions with a higher concentration of viral DNA compared with serum, suggesting that ZIKV may be directly implicated in the rash pathogenesis (Cordel et al., 2018).

Because the most common route of ZIKV transmission is an insect bite and the most common clinical feature of ZIKV infection in humans is a skin rash, the potential role of skin cell types in ZIKV pathogenesis and resolution deserves to be better explored.

In this issue, Ji-Ae et al. (2018) used several methods to explore interactions between different types of skin cells and ZIKV. They elegantly showed that human keratinocytes play an important role in control of initial infection via interaction with retinoic acid-inducible gene receptors (RLRs). The investigators first showed that ZIKV can infect the transformed human keratinocytes (HaCat cells), primary keratinocytes, and human skin fibroblasts. After infection, RLRs are rapidly activated, strongly suggesting that they play a major role in host defense against the virus (Figure 1). Subsequently, Ji-Ae et al. showed that a significant increase of RLRs is associated with the secretion of interferon, a well-known antiviral molecule. Using microarrays, they next showed that RLR-dependent genes including RIG1, IFNB1, and CXCL10 are up-regulated after infection of HaCat.
Clinical Implications

- Zika virus can infect both keratinocytes and fibroblasts.
- Zika virus activates retinoic acid-inducible gene receptors (RLRs), which in turn favor the secretion of interferon to suppress the propagation of the virus.
- The protein NS1 of the Zika virus may block the activation of RLRs, and the virus escapes from the immune defense (Figure 1).

Pathogenesis of Zika Virus Infection

Although these in vitro results strongly suggest a role for RLRs in immune defense against ZIKV, it would be very interesting to explore the expression of RLR genes and proteins in the skin lesions of patients featuring exanthema associated with ZIKV primary infection and to further characterize interactions between ZIKV and the skin. Additionally, this study explored some of the interactions between ZIKV and keratinocytes and fibroblasts, interactions between immune skin cell types (e.g., Langerhans cells, dermal dendritic cells, macrophages, etc.) and ZIKV have not been studied. Moreover, it would be interesting also to determine which skin cells feature activation of the RLR pathway in animals, because both small and large animal models have been used in the past to uncover the characteristics of Zika virus exanthema in Guadeloupe. JAMA Dermatol 2017;153:326–8.

Targets of RLRs in Zika Infection

The pathogenesis of this emerging disease (Bradley and Nagamine, 2017).

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES


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