

Evasion of Innate Immunity by Dengue Virus Non-Structural Proteins through Interfering with Type I Interferon Production and Jak/STAT Signaling

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Editorial

Dengue Virus (DENV), a mosquito-borne virus, is a member of the Flaviviridae family and transmits to humans through the bites of infected mosquitoes of the genus *Aedes*, most often *Aedes aegypti* (*Ae. aegypti*) and *Ae. Albopictus*. DENV includes four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) [1]. Generally, infected patients experience a spectrum of clinical diseases ranging from an acute debilitating self-limited dengue fever (DF) to a life-threatening syndrome, dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS). At present, no specific antiviral drugs and vaccines are available against DENV. Therefore, DENV infections cause dramatic public health issues in more than 100 countries and regions, particularly in tropical and subtropical regions in the world. The geographic expansion of the vector contributes to a widespread of disease with various severities.

DENV is a single-stranded positive-sense ribonucleic acid (RNA) virus with approximately 11,000 nucleotides in length, which encodes a single cotranslationally cleaved poly protein consisting of three structural proteins (capsid, envelope, and prM) and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). NS proteins are essential for viral replication and largely conserved across DENV serotypes [2]. DENV has evolved complex mechanisms, especially through its NS proteins, to evade the innate immune responses by interfering with both type I IFN production and the Jak/STAT signaling.

NS proteins of dengue virus interfere with the production of type I interferons

As the first line of host defense, the innate immune system deploys pattern-recognition receptors (PRRs) to detect and respond to the invasion of pathogens. Upon PRRs recognize conserved molecular structures known as pathogen-associated molecular patterns (PAMPs), the endosomal Toll-like receptor (TLRs) and cytosolic sensors activate a signaling cascade that culminates in the production of type I interferons (IFN-I) [3]. In order to establish infection in its host cells, DENV must subvert and/or the production antiviral effects of IFN-I. DENV replication is inhibited by the prior addition of type I IFN, and preventing early IFN induction is critical to DENV replication *in vitro* and *in vivo* [4,5]. Previous studies have demonstrated that the host cells produce only a very low level of IFN-I after being infected with DENV [6], thus, DENV might develop various mechanisms to depress the production of IFN-I. In order to understand the detailed mechanisms, many researchers have performed a lot of relevant studies. Recently, it was found that NS2A and NS4B proteins from DENV serotypes 1, 2, and 4 inhibit RIG-I/MDA-5 induction by blocking tank binding kinase 1 (TBK1) activation [2]. In contrast, DENV1 uniquely encodes an extra IFN regulating protein, NS4A that inhibits TBK1 [2]. Furthermore, Aguirre et al. documented the inhibition of IFN- I production by the proteolytic activity of DENV NS2B3 protease complex in human

monocyte derived dendritic cells (MDDCs), and further identified the human adaptor molecule stimulator of the interferon gene (STING), which plays a key role in the inhibition of DENV infection and spread, as a target of the NS2B3 protease complex, but DENV NS2B3 only recognizes human STING [7]. Subsequently, a study reported that DENV NS4A interacted with mitochondrial antiviral signaling protein (MAVS), and further demonstrated that NS4A was associated with the N-terminal CARD-like domain (CL) and the C-terminal transmembrane domain (TM) of MAVS, and hence this association prevented the binding of MAVS to RIG-I, resulting in repression of RIG-I-induced IRF3 activation and, consequently, abrogation of IFN production [8].

Dengue virus NS proteins interfere with type I interferon-induced Jak/STAT signaling

IFN-I induces expression of a large array of antiviral genes through the activation of the Janus kinase (JAK)-signal transducer and of transcription (STAT) pathway to protect host cells against viral infections, and particularly against DENV infection, which has been demonstrated in various experimental studies to elegantly demonstrated how these cytokines can limit viral replication. Previous studies have described that *in vitro* treatment with IFN- α/β or IFN- γ prior to DENV infection suppressed viral replication in human HepG2 cells. However, if the IFN- α/β or IFN- γ treatment was performed after DENV infection, viral replication was not affected. These studies suggested that DENV has evolved the ability to alter the function of IFN-I-mediated Jak/STAT signaling pathway in the infected host cells [5,9]. Munoz-Jordan et al. discovered that expression of three DENV NS proteins, NS2A, NS4A, or NS2B enhanced replication of IFN-sensitive viruses in the presence of exogenous IFN-I, and NS4B partially blocked activation of STAT1 and interferon-stimulated response element (ISRE) promoters in cells stimulated with IFN-I; These three DENV NS proteins have been reported to be associated with cellular membranes and have been shown to inhibit STAT1 phosphorylation [10,11]. In addition to inhibiting STAT1 phosphorylation, DENV also interferes with STAT2 expression. The viral protein, NS5, interacts with the cellular protein,

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ubiquitin protein ligase E3 component recognin 4 (UBR4), to mediate the degradation of STAT2 [12,13].

Conclusion

DENV has evolved multiple mechanisms to evade the innate immune response to facilitate viral replication. Recent and ongoing research continues to uncover an increasing number of unique mechanisms used by DENV NS proteins to subvert the host innate immune response.

In summary, DENV NS proteins inhibit the induction and signaling cascade of IFN-I, thus preventing cellular pathways that lead to the expression of interferon response genes and antiviral mechanisms. Understanding the viral and host mechanisms that regulate the balance between immune-mediated pathology and protection is critical for the development of safe and effective drugs and vaccines against DENV.

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