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Review

Cellular and molecular mechanisms of chikungunya pathogenesis

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ABSTRACT

Chikungunya virus (CHIKV) is an arthropod-borne virus that causes chikungunya fever, a disease characterized by the onset of fever and rashes, with arthralgia as its hallmark symptom. CHIKV has re-emerged over the past decade, causing numerous outbreaks around the world. Since late 2013, CHIKV has reached the shores of the Americas, causing more than a million cases of infection. Despite concentrated efforts to understand the pathogenesis of the disease, further outbreaks remain a threat. This review highlights important findings regarding CHIKV-associated immunopathogenesis and offers important insights into future directions. This article forms part of a symposium in *Antiviral Research* on "Chikungunya discovers the New World."

Contents

1. Introduction

Chikungunya virus (CHIKV) is an alphavirus belonging to *the Togaviridae* family that was first isolated from a human patient in Tanzania in 1952. It is transmitted mainly by the *Aedes agypti* and *Aedes albopictus* mosquitoes. Infection causes a self-limiting febrile illness known as chikungunya fever (CHIKF) with symptoms such as myalgia, fever and rashes. Patients also typically exhibit polyarthralgia, which is a hallmark of the disease. Symptoms usually appear after an incubation period of 4–7 days. While many of the symptoms disappear within the following week, arthralgia may persist in some patients for up to a few years (Her et al., 2009; Kam

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et al., 2009). In some cases, CHIKF has been associated with neurological complications such as myeloradiculopathy and meningoencephalitis (Borgherini et al., 2007; Chandak et al., 2009). However, direct neurovirulence and neuroinvasiveness remain to be investigated.

In this article, we discuss interactions between CHIKV and the host immune response, with a focus on the balance between protection and pathology in defining CHIKV pathogenesis. Our paper forms part of a symposium in Antiviral Research on "Chikungunya discovers the New World." Readers interested in a general review of the disease should refer to the article "Chikungunya: Evolutionary history and recent epidemic spread" (Weaver and Forrester, 2015) published in this symposium.

2. The virus

CHIKV is an enveloped virus that is approximately 70 nm in diameter in neutral pH and contains a 11.8 kb single-stranded, positive-sense RNA genome (Strauss and Strauss, 1994; Leung et al., 2011; Rashad et al., 2014). The genome consists of a 5′ methylated terminal cap untranslated region (UTR), followed by RNA coding for 4 non-structural proteins (nsP1–4) and 5 structural proteins (C–E3–E2–6K–E1), and a 3′ terminal poly-A tail (Strauss and Strauss, 1994; Leung et al., 2011; Teng et al., 2011). The non-structural proteins and structural proteins, governed by 2 separate open-reading frames (ORFs), contribute to the propagation of new virions (Schwartz and Albert, 2010; Leung et al., 2011; Rashad et al., 2014).

The non-structural genes encode for nsP1 and nsP3, helicase (nsP2) and polymerase (nsP4). These proteins associate to form the viral replication complex needed for downstream viral genome replication (Solignat et al., 2009; Schwartz and Albert, 2010). On the other hand, the structural capsid protein is involved in the formation of the icosahedral fenestrated nucleocapsid of a mature virion, in which the viral RNA genome will be contained (Solignat et al., 2009; Schwartz and Albert, 2010; Rashad et al., 2014). The E1 and E2 glycoproteins associate as a heterodimer before being incorporated onto the surface of the mature virion as trimeric spikes and are involved in the attachment and entry of the virion into susceptible target cells during subsequent infection. A total of 80 trimeric spikes are present on the surface of a mature virion (Voss et al., 2010).

The role of the 6K protein remains ambiguous, but it is thought to be involved in virus assembly and budding (Leung et al., 2011;

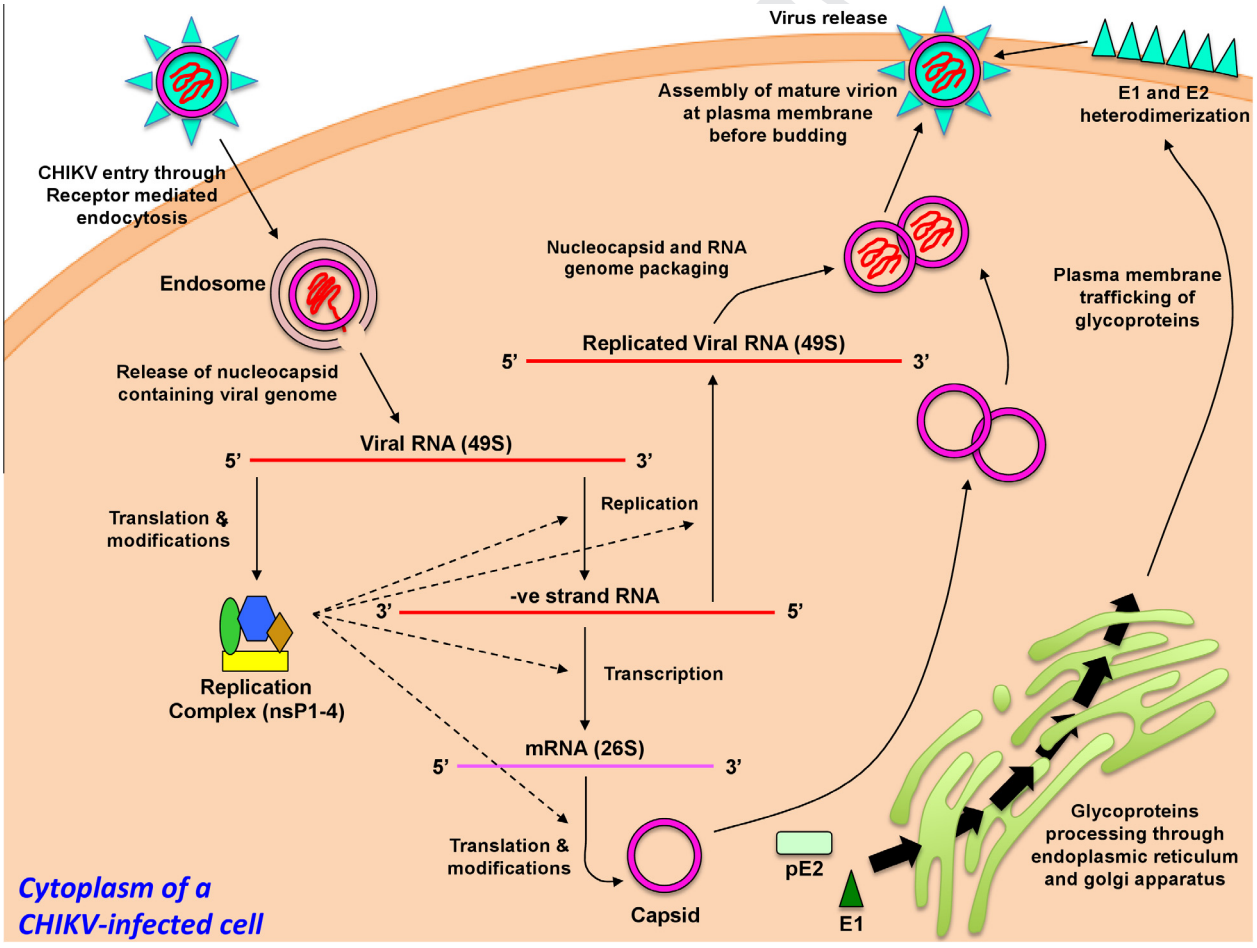

Fig. 1. CHIKV replication cycle. The virus enters susceptible cells through endocytosis, mediated by an unknown receptor. As the endosome is acidic, conformational changes occur resulting in the fusion of the viral and host cell membranes, causing the release of the nucleocapsid into the cytoplasm, The RNA genome is first translated into the 4 nsPs, which together will form the replication complex and assist in several downstream processes (depicted by dashed arrowed line). Subsequently, the genome is replicated to its negative-sense strand, which in turn will be used as a template for the synthesis of the 49S viral RNA and 26S subgenomic mRNA. The 26S subgenomic mRNA will be translated to give the structural proteins (C–pE2–6K–E1). After a round of processing by serine proteases, the capsid is released into the cytoplasm. The remaining structural proteins are further modified post-translationally in the endoplasmic reticulum and subsequently in the Golgi apparatus. E1 and E2 associate as a dimer and are transported to the host plasma membrane, where they will ultimately be incorporated onto the virion surface as trimeric spikes. Capsid protein will form the icosahedral nucleocapsid that will contain the replicated 49S genomic RNA before being assembled into a mature virion ready for budding. During budding the virions will acquire a membrane bilayer from part of the host cell membrane.

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