Antiviral Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Towards antivirals against chikungunya virus

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ARTICLE INFO

Article history:
Received 6 May 2015
Revised 18 June 2015
Accepted 24 June 2015
Available online xxxx

Keywords:
Chikungunya virus
Antiviral therapy
Monoclonal antibodies
Arbidol
Favipiravir
Ribavirin

ABSTRACT

Chikungunya virus (CHIKV) has re-emerged in recent decades, causing major outbreaks of chikungunya fever in many parts of Africa and Asia, and since the end of 2013 also in Central and South America. Infections are usually associated with a low mortality rate, but can proceed into a painful chronic stage, during which patients may suffer from polyarthralgia and joint stiffness for weeks and even several years. There are no vaccines or antiviral drugs available for the prevention or treatment of CHIKV infections. Current therapy therefore consists solely of the administration of analgesics, antipyretics and anti-inflammatory agents to relieve symptoms. We here review molecules that have been reported to inhibit CHIKV replication, either as direct-acting antivirals, host-targeting drugs or those that act via a yet unknown mechanism. This article forms part of a symposium in *Antiviral Research* on "Chikungunya discovers the New World."

Contents

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http://dx.doi.org/10.1016/j.antiviral.2015.06.017
0166-3542/© 2015 Published by Elsevier B.V.

1. Introduction

Chikungunya virus (CHIKV) is an alphavirus transmitted mainly by female mosquitoes of the species *Aedes aegypti* and *Aedes albopictus*. It causes an acute disease characterized by fever, arthralgia and in some cases a maculopapular rash (Thiberville et al., 2013). Infection is rarely fatal, but in many cases it evolves into a chronic stage of persistent disabling polyarthritis that can severely incapacitate the patient for weeks and even up to several years (Simon et al., 2011).

There are no vaccines or antivirals available for the prevention or treatment of CHIKV infection. Current therapy consists of the use of analgesics, antipyretics and anti-inflammatory agents, such as paracetamol and non-steroidal anti-inflammatory drugs

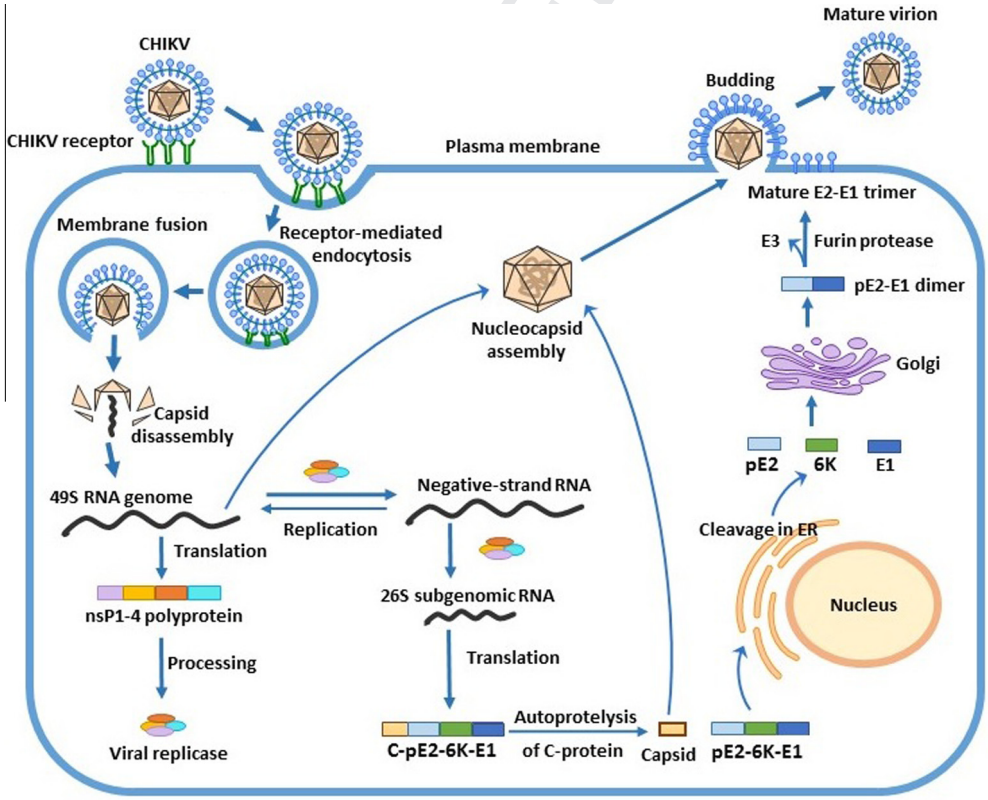

Fig. 1. Schematic representation of the replication cycle of chikungunya virus. CHIKV enters the cell by endocytosis following the binding of the E2 protein to specific receptor(s) on the cell surface. Within the endosome, the low pH triggers the fusion of the viral envelope with the endosomal membrane, leading to the release of the nucleocapsid into the cytoplasm. The nucleocapsid disassembles to liberate the viral genome, which is translated to produce the viral nonstructural proteins (nsP1–4). After processing, the nonstructural proteins complex to form the viral replicase, which catalyzes the synthesis of a negative-sense RNA strand to serve as a template for synthesis of both the full-length positive-sense genome and the subgenomic (26S) RNA. The subgenomic (26S) RNA is translated to produce the structural polyprotein (C-E3-E2-6K-E1), which is then cleaved to produce the individual structural proteins, followed by assembly of the viral components. The assembled virus particle is released by budding through the plasma membrane, where it acquires the envelope with embedded viral glycoproteins.

Please cite this article in press as: Abdelnabi, R., et al. Towards antivirals against chikungunya virus. Antiviral Res. (2015), http://dx.doi.org/10.1016/j.antiviral.2015.06.017