Institut Pasteur
Microbes and Infection xx (2016) 1–3
www.elsevier.com/locate/micinf

Review

Autophagy and viral diseases transmitted by *Aedes aegypti* and *Aedes albopictus*

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Received 22 December 2015; accepted 24 December 2015
Available online ■ ■ ■

Abstract

Despite a long battle that was started by Oswaldo Cruz more than a century ago, in 1903, Brazil still struggles to fight *Aedes aegypti* and *Aedes albopictus*, the mosquito vectors of dengue virus (DENV), Chikungynya virus (CHIKV) and Zika virus (ZIKV). Dengue fever has been a serious public health problem in Brazil for decades, with recurrent epidemic outbreaks occurring during summers. In 2015, until November, 1,534,932 possible cases were reported to the Ministry of Healthv [1]. More recently, the less studied CHIKV and ZIKV have gained attention because of a dramatic increase in their incidence (around 400% for CHIKV) and the association of ZIKV infection with a 11-fold increase in the number of cases of microcephaly from 2014 to 2015 in northeast Brazil (1761 cases until December 2015) [1]. The symptoms of these three infections are very similar, which complicates the diagnosis. These include fever, headache, nausea, fatigue, and joint pain. In some cases, DENV infection develops into dengue hemorrhagic fever, a life threatening condition characterized by bleeding and decreases in platelet numbers in the blood. As for CHIKV, the most important complication is joint pain, which can last for months.

Keywords: Autophagy; Dengue virus; Chikungynya virus; Zika virus; *Aedes aegypti*

Autophagy, a highly conserved cellular homeostatic biological process responsible for the lysosomal degradation of long-lived proteins, damaged organelles and parts of the cytosol, has been implicated in host-virus interactions. The first report describing the interaction of a virus with autophagy was in 1965, when the group of George Palade showed the presence of "autolytic vesicles", later known as autophagosomes, containing poliovirus particles during infection [2]. Today it is well recognized that many viruses induce an autophagic response in the infected cell, but the contribution of this pathway to either host antiviral defenses or viral replication is variable. For many viral infections, autophagy is an important antiviral effector mechanism that targets viral proteins for degradation and interferes with viral replication. For example, interferon-α production by VSV-infected plasmocytoid dendritic cells depends on the autophagic delivery of viral replication intermediates to Toll-like receptor-7 on late endosomes [3], and Sindbis virus is selectively targeted to autophagic degradation by direct interaction of the viral capsid with the autophagic adaptor p62 [4]. On the other hand, as a result of continuous co-evolution, many viruses have developed sophisticated mechanisms to directly or indirectly subvert autophagy in order to promote different stages of the viral life cycle.

DENV and ZIKV are both flaviviruses and share the common feature of manipulating the autophagic response in order to enhance their own replication and establish infection. DENV-induced autophagy is the best characterized so far and,

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http://dx.doi.org/10.1016/j.micinf.2015.12.006
1286-4579/

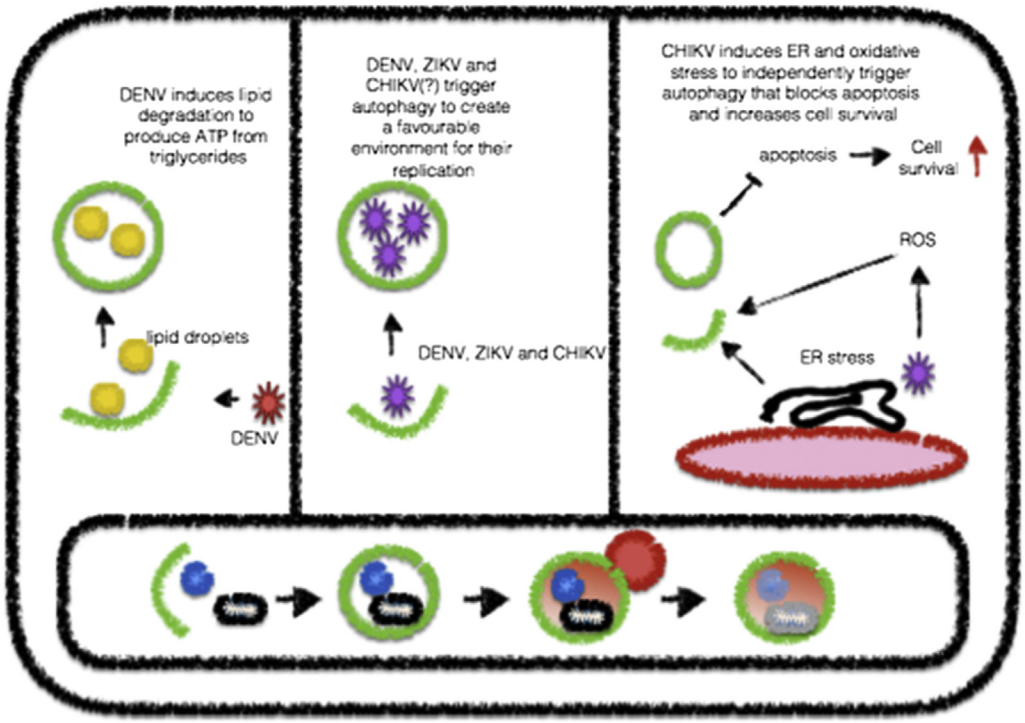

Fig. 1. Autophagy and its interaction with DENV, ZIKV and CHIKV: From left to right: DENV induces autophagy-dependent degradation of lipids to mobilze triglycerides to produce ATP via β-oxidation, hijacking cell host metabolism for its own replication. DENV, ZIKV and CHIKV increase autophagy to facilitate their replication. It is not clear if autophagosomes are used as a replicative niche for all of them. CHIKV induces ER and oxidative stress that, independently, increase autophagy to down regulate apoptosis and promote cell survival.

although the precise molecular mechanisms involved remain to be fully elucidated, it has been shown that DENV induces the reorganization of membranes to form autophagosomes that fuse with endosomes forming amphisomes [5]. Both autophagosomes and amphisomes are double membrane vesicles (DMVs), and DENV is known to replicate inside virally induced DMVs. Pharmacological or genetic inhibition of autophagy leads to inhibition of viral replication. In epithelial cells, hepatocytes and fibroblasts, up-regulation of autophagy prevents cell death and promotes DENV replication [6]. In addition, it has been suggested that autophagy supports DENV replication by suppressing the host's unfolded protein response (UPR) [7]. Conversely, in monocytes, induction of autophagy reduces viral yield. Finally, in hepatoma cells, DENV triggers lipophagy (lysosomal degradation of lipids) to obtain free fatty acids that are crucial for viral replication [8]. ZIKV-induced autophagy is less studied until now. So far, only one study has evaluated a potential role for autophagy in ZIKV infection [9], and the results showed that this virus induces the formation of autophagosomes that contain viral capsids. This event seems to be relevant for viral replication, as pharmacological inhibition of autophagy decreases the copy number of viral RNA.

The role of autophagy during CHIKV infection is still controversial. A first report suggested that autophagy was important for CHIKV replication, as inhibition of autophagy dramatically reduced CHIKV replication [10]. However, a more recent study showed that CHIKV infection induces both endoplasmic reticulum (ER) and oxidative stress, which act in an interdependent manner to trigger autophagy during the early phase of infection [11]. This prevents cell death and limits viral propagation. During the late phase of CHIKV infection, however, autophagic flux is reduced, which correlates with enhanced apoptotic cell death that favors viral particle release and viral spread. *In vivo*, mice with reduced induction of autophagy show higher sensitivity to CHIKV infection with a 2-fold increase in lethality when compared to wild-type mice [11].

In summary, autophagy may have multiple and opposing roles in different viral infections and can be exploited as a potential target for therapeutic purposes against viral infections transmitted by *A. aegypti* and *A. albopictus*.(Fig. 1). Q3

Acknowledgments

LAMC and LHT are funded by CNPq and FAPERJ. Q4

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Please cite this article in press as: Carneiro LAM, Travassos LH, Autophagy and viral diseases transmitted by *Aedes aegypti* and *Aedes albopictus*, Microbes and Infection (2016), http://dx.doi.org/10.1016/j.micinf.2015.12.006

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