Journal of Autoimmunity xxx (2018) 1–10

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

Current concerns and perspectives on Zika virus co-infection with arboviruses and HIV

Hussin A. Rothan [a], Mehdi R.M. Bidokhti [b], Siddappa N. Byrareddy [b, *]

[a] Department of Human Biology, International Medical University, Bukit Jalil, 57000 Kuala Lumpur, Malaysia
[b] Department of Pharmacology and Experimental Neuroscience, College of Medicine, University of Nebraska Medical Centre (UNMC), Omaha, NE 68198-5800, USA

ARTICLE INFO

Article history:
Received 16 November 2017
Received in revised form
30 December 2017
Accepted 8 January 2018
Available online xxx

Keywords:
Zika virus
HIV
Flavivirus
Dengue
Chikungunya
Co-circulation
Vaccination
Co-infection

ABSTRACT

Dissemination of vector-borne viruses, such as Zika virus (ZIKV), in tropical and sub-tropical regions has a complicated impact on the immunopathogenesis of other endemic viruses such as dengue virus (DENV), chikungunya virus (CHIKV) and human immunodeficiency virus (HIV). The consequences of the possible co-infections with these viruses have specifically shown significant impact on the treatment and vaccination strategies. ZIKV is a mosquito-borne flavivirus from African and Asian lineages that causes neurological complications in infected humans. Many of DENV and CHIKV endemic regions have been experiencing outbreaks of ZIKV infection. Intriguingly, the mosquitoes, *Aedes Aegypti* and *Aedes Albopictus*, can simultaneously transmit all the combinations of ZIKV, DENV, and CHIKV to the humans. The co-circulation of these viruses leads to a complicated immune response due to the pre-existence or co-existence of ZIKV infection with DENV and CHIKV infections. The non-vector transmission of ZIKV, especially, *via* sexual intercourse and placenta represents an additional burden that may hander the treatment strategies of other sexually transmitted diseases such as HIV. Collectively, ZIKV co-circulation and co-infection with other viruses have inevitable impact on the host immune response, diagnosis techniques, and vaccine development strategies for the control of these co-infections.

Contents

* Corresponding author.
E-mail addresses: hussinrothan@imu.edu.my (H.A. Rothan), mehdi.bidokhti@unmc.edu (M.R.M. Bidokhti), sid.byrareddy@unmc.edu (S.N. Byrareddy).

https://doi.org/10.1016/j.jaut.2018.01.002
0896-8411/

1. Introduction

Zika virus (ZIKV), an emerging mosquito-borne flavivirus, has attracted researcher's attention after the 2015–2016 imperative outbreak that has been associated with neurological complications. For years, the scientific research has focused on the most vital flaviviruses that have a significant impact on human health such as Dengue Virus (DENV), Yellow Fever Virus (YFV), Japanese Encephalitis Virus (JEV), and West Nile Virus (WNV) [1]. In February 2016, the World Health Organization has considered ZIKV infection a public health emergency [2]. ZIKV has a widespread distribution mainly in the countries of Africa, South America, and Southeast Asia; however, travelling has contributed to the expansion of ZIKV infection to non-epidemic nations of Europe, North America and Australia [3–5].

ZIKV was first found in macaque monkeys in the Zika forest in Uganda in 1947 and the first ZIKV infection in humans was reported in Nigeria, 1954 [6]. East Africa represents the African ZIKV lineage that was then transferred to Malaysia in Southeast Asia. The Asian lineage originated after virus dissemination to the Pacific Islands and the Americans [7]. The Asian-lineage ZIKV strain is currently circulating in the Western Hemisphere which can be differentiated from African-lineage ZIKV *via* molecular genomic and proteomic techniques [8].

Currently, ZIKV has spread to at least 33 countries and most recently in territories in the Americas [9,10]. Importantly, ZIKV infection disseminates in the DENV and Chikungunya virus (CHIKV) epidemic areas raising the possibilities of developing immunological complications and the incidence of viral co-infections. These areas are also endemic with other infections, most importantly HIV. The co-circulation and co-infection of ZIKV with these viruses represent the current biomedical and public health challenge in term of diagnosis, treatment and vaccine development.

In this review, we discuss the present aspects of ZIKV co-circulation and co-infection with DENV and CHIKV, ZIKV infection to HIV patients especially pregnant women, and the biological control of ZIKV and implications for vaccine design.

2. ZIKV co-circulation with other arboviruses

ZIKV is classified as a positive single-stranded RNA virus belonging to the *Flaviviridae* family, is transmitted by mosquito bite, and exists in two distinct lineages. The single open reading frame (ORF) RNA encodes a premature viral polyprotein. Host cell furin and viral protease cleave the viral polyprotein into three structural proteins (capsid, envelope and membrane precursor) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). The non-structural proteins are crucial for virus replication in the host cell [11].

The primary root of ZIKV infection in the epidemic zones is the mosquito bite. The warm tropical and subtropical regions of the world represent the preferred environment of *Aedes* mosquitos, the primary vector of flavivirus transmission [12,13]. The two mosquito species, *Aedes aegypti* and *Aedes Albopictus* are usually considered as a primary vector for ZIKV, DENV and the alphavirus, CHIKV transmission. However, ZIKV was also isolated from other mosquito species such as *Aedes africanus*, *Aedes apicoargenteus*, *Aedes luteocephalus*, *Aedes furciferand*, *Aedes taylori*, and *Aedes vittatus* [14–17]. Distribution of *Aedes Aegypti* and *Aedes Albopictus* in the terrestrial habitat leads to co-circulating of these viruses and creating significant practical difficulties in controlling and diagnosing these arboviruses infections [18,19]. These two species of mosquitoes can be infected with ZIKV, DENV and CHIKV and can transmit all combinations of these viruses simultaneously [20].

ZIKV, DENV and CHIKV share similar clinical symptoms; therefore, the diagnosis of ZIKV infection is particularly challenging in DENV or CHIKV endemic regions [21,22]. Patients with CHIKV or DENV portray with leukopenia and thrombocytopenia. Moreover, hepatomegaly and bleeding appear in patients with symptomatic chikungunya can be seen predominantly in DENV infection. Other symptoms like fever, arthralgias, myalgias and some with lymphedema, conjunctivitis, limbedema, could be observed in ZIKV, DENV, or CHIKV infections [23] (Fig. 1). A study by Colombo et al., 2017 showed the most common symptoms in the patients with ZIKV infection were rash (100%), arthralgia (77.1%), fever (74.0%), myalgia (74.0%) and non-purulent conjunctivitis (69.8%). In patients with DENV infections, the most frequently observed symptoms were rash (100%), arthralgia (70.1%), fever (79.1%), myalgia (74.6%) and headache (73.1%). The measure of association between clinical manifestations among ZIKV and DENV infected patients detected a significant difference only in abdominal pain, leukopenia, and thrombocytopenia [24].

Due to the similarity in infection symptoms of ZIKV, DENV, and CHIKV, the molecular-based techniques represent the optimal diagnostic method, in addition to conventional culture and serological tests. The serological test is inexpensive, simple, and available in resource limited settings. However, serum antibody cross-reactivity of DENV and ZIKV has been observed in the endemic areas [21]. Genomic and proteomic analysis of co-circulating viruses is essential to develop highly sensitive diagnostic tests. The most sophisticated molecular techniques are highly accurate in recognizing co-circulating viruses and even co-infection with viruses with high sequence similarity. For example, a validated real-time reverse transcription PCR assay using specific probes showed an accurate differentiation of ZIKV, CHIKV and the four serotypes of DENV [25–27]. Comparative proteomic analysis of co-circulating arboviruses to find a specific epitope could be an essential step to develop a simple, accurate, and affordable serological based diagnostic assay [28,29].

Epidemiological studies are required to elucidate the transmission, co-circulation, and infection complications of ZIKV, DENV, and CHIKV at the endemic areas of these viruses. The research consortium “ZIKAction” in Latin America, Europe and the Caribbean has been recently funded by the European Commission. It represents an excellent example of such studies illustrating the epidemiology and vertical transmission of ZIKV, the natural history of the consequences of ZIKV infection during pregnancy on the fetus's congenital and non-congenital syndromes [30]. The available resources of the recent epidemiological observation could facilitate the worldwide data dissemination of virus co-circulation. The Pacific Public Health Surveillance Network (PPHSN) provides an excellent source of information for communicable diseases, especially the outbreak of arboviruses including ZIKV, DENV and CHIKV [31]. An interactive map is available online [32] providing real-time data of the epidemic and emerging infectious diseases important for precaution preparations of the surrounding countries (Fig. 3).

3. Preceding ZIKV or DENV infections promote both diseases

3.1. T cells cross-reactivity

Heterologous immunity refers to a cross-reactivity of pathogen-specific memory T cells to a subsequent infection due to high homology of pathogen epitopes that can lead to a decrease or increase in infectivity of the second pathogen. The population of memory T cells could be affected by heterologous immunity creating a considerable alteration in the T cell pool, repertoire, and dominance causing a significant variation in viral infection [33]. This phenomenon has been observed in patients infected with influenza virus followed by acute infection with hepatitis C virus (HCV).

Please cite this article in press as: H.A. Rothan, et al., Current concerns and perspectives on Zika virus co-infection with arboviruses and HIV, Journal of Autoimmunity (2018), https://doi.org/10.1016/j.jaut.2018.01.002