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Advances in ZIKA virus host-cell interaction: Current knowledge and future perspectives

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Abstract
Emerging mosquito-transmitted RNA viruses, such as ZIKA virus (ZIKV) and Chikungunya represent human pathogens of an immense global health problem. ZIKV has emerged explosively since 2007 to cause a series of epidemics in the South Pacific and most recently in the Americans. Although typical ZIKV infection are asymptomatic, ZIKV infection during pregnancy is increasingly associated with microcephaly and other foetal developmental abnormalities. In the last few years, genomic and molecular investigation have established a remarkable progress on the pathogenic mechanism of ZIKV infection using invitro and *in vivo* models. Here, we highlight recent advances in ZIKV-host cell interaction studies, including cellular targets of ZIKV, ZIKV –mediated cell death mechanisms, host cell restriction factors that limit ZIKV replication, and immune evasion mechanisms utilized by ZIKV. By understanding the mechanism and machinery of ZIKV-host interaction at the cellular level will contribute crucial insights for the development of therapeutics and vaccines.

Keywords: ZIKA virus, cell death, cellular targets, innate immune evasion

Introduction
ZIKA virus is a mosquito-borne virus belong to the Spondweni serocomplex in the genus of Flavivirus of the family Flaviviridae that has become a new threat following the Ebola virus epidemic [1]. The expanding ZIKAV epidemic was declared an emergency by the world health organization on February 1 2016 [2].
ZIKA virus is a single stranded RNA virus that encodes a single Polyprotein that is cleaved o form mature protein, the capsid, envelop and precursor of membrane and non structural proteins.
Infectious disease have gained importance as a significant threat to public health following the recent outbreaks arthropod-transmitted viruses (arbovirus) in the western hemisphere. Global emergence of arbovirus such as dengue virus, chikungunya, yellow fever virus, and Zika virus has become possible due to several factors including urbanization, rapid population growth, and climate change [3]. Although environmental changes have given importance to the movement of human population, especially by air travel, the extent to which humans have reshaped the environment has also led to a dynamic spread of pathogens and their vectors. The dissemination of Arboviruses, in particular is dependent on their vectors, and reports of these pathogens in new global destinations should raise concern of the expansive distribution of the vectors, such as the Aedes species of mosquitoes. This review focuses on ZIKAV, which has rabies international health concerns due to its broad spectrum of transmission routes, autoimmune disorder in adults and newborns [4, 5]. ZIKAV belongs to the Flaviviridae family along with Japanese encephalitis virus (JEV), west Nile virus (WNV), All of which are medically important viruses transmitted by mosquitoes or ticks. As of January 2018, PAHO has reported 223, 477 confirmed ZIKAV cases that have cumulated world wide between 2015and 2018 [6]. Despite the global distribution of ZIKAV, there are no clinically approved vaccines or therapeutic treatment available to combat the infections [7]. As a result, international concern surrounding ZIKAV in terms of control, treatment, and prevention has classified the virus as a global threat to public health. Although most cases of ZIKAV infection result in asymptomatic or mild flu-like symptoms, such as fever, rash, and conjunctivitis, the series of outbreaks that started in yap islands in 2007 has emphasized just how wide of a phenotypic spectrum of disease can be caused in human by the virus. Recent incidences of infection have resulted in severe phenotype including Guillain-Barre syndrome, meningoencephalitis, and fetal abnormalities such as microcephaly and spontaneous abortion [8]. Diagnosis of ZIKAV infection has depended on molecular and serological testing, employing ELISA and RT-PCR platforms for IgM and RNA detection accordingly [9]. Laboratory testing of infants suspected of congential ZIKAV infection includes detection of viral RNA in serum and urine, and IgM Antibodies in serum and CSF of infants [10] World Health Organization has already established an etiological link between ZIKAV infection and birth defects like microcephaly in Brazil [9, 11]. Congential abnormalities induced by ZIKA infection have confirmed the possibility of vertical transmission. Despite the prevalence of birth defects, diagnosis of congenital microcephaly remains a challenge due to the existence of various etiological factors involved [12]. In addition to microcephaly exposure to ZIKAV during pregnancy can result in visual and hearing impairments in the newborn [13].
Flaviviruses can carry out their life cycle by utilizing the machinery of the host and functions of the host cell [14]. Although flavivirus-host cell interaction are essential for the pathogenesis many of these crucial interactions, however, remain elusive. In this review, we focus on ZIKV, a member of the flaviviridae family, and highlight the viral pathogenesis at the level of cellular mechanisms and interactions.

Structure of ZIKV
ZIKV is a single stranded, positive sense RNA virus whose

genome encodes a single polyprotein that is cleaved into three structural polyprotein, such as capsid(C), membrane precursor(prM), envelope (E) proteins, and seven non structural(NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5), as shown in Fig 1 [7]. While the virus is comprised of structural proteins nonstructural proteins are responsible for viral replication and assembly [7, 15]. The structure of ZIKV is similar to other flaviviruses. Flaviviral NS1 is involved in infection and viral replication and when it secreted extracellularly for immune evasion and pathogenesis it interacts with the host immune factors [16, 17, 18]. In addition NS1 has been suggested as a biomarker in diagnosis of flaviviruses such as DENV which results in early stages of infection corresponding to high levels of NS1 secreation [19].

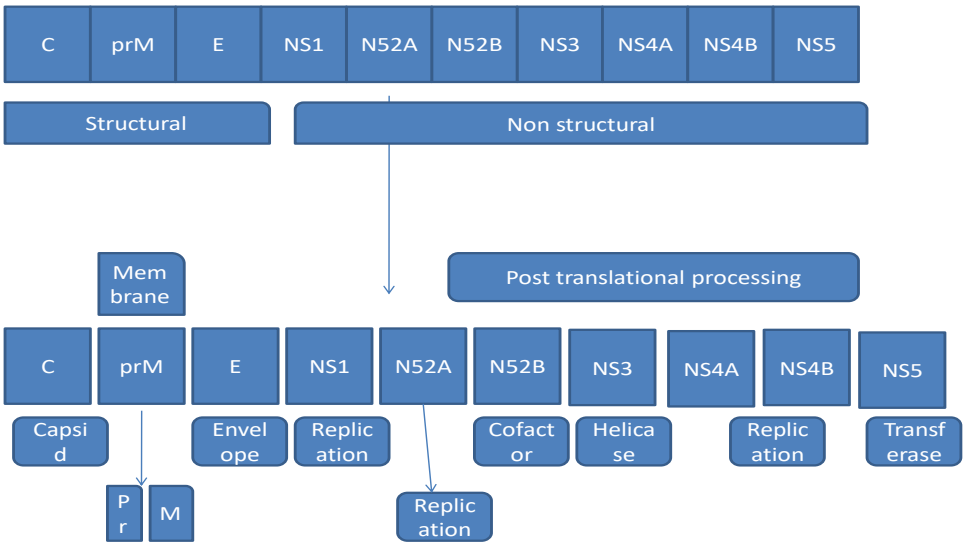

Fig 1: The structure of ZIKA virus Genome and its encoded proteins. The single open reading frames encode a polyprotein precursor that is post translationally cleaved into three structural protein (capsid, membrane and envelope) and seven non structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5).

NS3 consists of a protease domain which is linked to NS2B to form a protease complex in the case of ZIKV and a helicase domain [20]. The envelope (E) protein which mediates viral entry of ZIKV possesses a highly conserved fusion loop region that is also found in WNV, YFV, and DENV 1-4 [15, 21, 22]. Furthermore transposon mutagenesis screening has demonstrated the capacity of ZIKV to tolerate genetic diversity, as evident from ZIKV E gene's tolerance of mutations and this genetic flexibility within a viral genome has important implications on evasion mechanisms of adaptive immunity [23].

Cellular Entry and Targets of ZIKV

Since 2016 the scientific communities have dedicated that rapid and extensive research efforts on ZIKV with respect to its molecular pathogensis and associated celluar signaling pathways and factors.Table 1 shows that comprensive list of currently identified susceptible human cells to ZIKV infection. ZIKV exhibits broad tropism and the localization of its cellular targets that have been identified so far range from the brain, placenta and skin, testis, kidney, and retina. The entry of ZIKV is facilitated by the following receptor (TIM1, TIM4) and TAM (Axl, TYRO3) in human primary throphoblasts [24].

Table 1: Cellular targets and potential energy receptors for ZIKV

Origin	Cell targets	Potential entry receptor	References
Skin	Epidermal keratinocytes	Axl, Tim, Tyro3	32, 33
Skin	Dermal fibroblasts	Axl, Tim, Tyro3	32, 33
Blood	Dendritic cells	DC-SIGN	34
Blood	Monocytes	Unknown	35, 36
Placenta	Hofbauer cells	Axl, Tyro3, TIM1	37, 38, 39
Placenta	Trophoblasts	Axl, Tyro3, TIM1	40, 41
Placenta	Endothelial cells	Axl, Tyro3, TIM1	42

Fig-2 Innate immune evasion mechanism by ZIKV.During ZIKV Infection, viral RNA sensors and interferon – mediated signaling through downstream adaptor molecules and transcription factors can be targeted for immune evasion strategies. Viral proteins, indicated by red coor, can interfere with interferon (IFN) responses by suppressing the induction of signaling pathway at multiple steps [25, 26, 27, 28, 29, 30, 31].

Future Directions for ZIKV Studies

Although remarkable progress in ZIKV research has created opportunities for the development of vaccines as well as therapeutics, from which of them are currently advancing through clinical trials, and there are still some qution to be answered and should be focused with respect to future perspective. The mechanism by which ZIKV crosses the placenta and infects developing fetus are discussed in this

review paper as well as the host and viral factors contribute to ZIKV persistence in the placenta and other immune-privileged sites and also the roles of noncoding RNAs during ZIKV infection.

As we all know animal models provide useful platforms for supplementing and elevating cell-based in vitro studies so these techniques fail to reflect the physiological parameters and cellular communication occurring in human conditions. Because they are essential to understand the mechanisms of development and disease. The deficiency of human-derived models has given rise to organoids and organ chips that arise from a combination of microfluidic and microfabrication techniques. Organoid technology and organ-specific chip models such as placenta on a chip and eye on a chip are able to mimic the interactive contributions made by major cell types which are involved in virus pathogenesis and also overcoming the limitations of in vitro models [43, 44, 45, 46, 47]. The mechanism associated with virus–host cell interactions with increased virulence of ZIKV will provide a new way and also better way to design and develop beneficial and more potent drugs and therapeutics against ZIKV so as to prevent this infectious disease.

Conclusion and future perspectives

Zika virus, an arbovirus, shares the several characteristic feature with other members of the Flavivirus family. Recent evidences of autoimmune complications and maternal to fetal transmission of virus leading to microcephaly has widely accumulated. By Using state of the art methods to formulate the effective diagnostics, anti-viral drug, therapeutics, vaccines, and prevention and their control strategies would aid in addressing this emergent virus. There are some recent therapies which have shown promise in inhibiting ZIKAV infections and associated disease. These therapies include limiting viral entry into cells, targeting the ZIKAV helicase protein, use of nucleoside analogs like 2'-C-methylated nucleosides and 7-deaza-2'-C-methyladenosine to terminate the formation of nascent RNA strand, and use of antibodies that binds to ZIKAV but do not neutralize it, reducing the risk of ADE(Antibody dependent enhancement).Actually ADE is a major concern in the application of ZIKAV Therapies in geographical regions where other flavivirus are endemic. Thus to limit ADE, antibodies are being engineered in such a way which contain a Modified Fc region because Modification of the Fc region of antibodies not only prevents their attachment to Fc gamma region to inhibit internalization of the immune complex, but also it reduces complement binding which prevent ADE. In the future, several such engineered antibodies might be evaluated for synergistic effects in other therapeutic and prophylactic regimens.

Encouraging results with repurposed drugs, which have been shown by the use of chloroquine, which is a malaria drug that has led to the screening of several other FDA(food and drug administration)-approved drugs including niclosamide, emricasan, and daptomycin, palonosetron, kitasamycin, and many more, for ZIKV treatment. And the other strategy for the discovery of ZIKV preventives and anti-virals is the use of computational analysis.

More insights into genetic and molecular mechanisms associated with the recent increase in virulence of ZIKV could aid in the design and development of safer and more potent drugs and therapeutics against ZIKV. Along with the identification of novel drug targets, therapeutics, and vaccines, strengthening of appropriate prevention and control measures, including mosquito control, could help in limiting ZIKV infections, its associated complications, and its potential for further spread. It's the time for researchers, pharmaceutical companies, policy makers, regulators, and funding agencies to identify and implement strategies to counter it globally.

The declaration of the Zika epidemic as an international public health emergency by WHO in 2016, research on ZIKV has increased Much faster then before. However, there are many more areas that still not aware about this disease.

(1) The percent contribution of each route of ZIKV infection is not precisely understood which are based on mathematical modeling study and sexual transmission has been estimated to account for upto 3% of transmission, but contributions by other routes of infection are yet to be studied. This information may be helpful in designing precisely targeted inhibitory molecules to block infection at site of entry.

(2) Many FDA (food and drug administration) approved drugs which have been tested for resistivity against ZIKV; which can be repurposed for treating ZIKV infection in human. However, to date, no FDA category A drug has been identified clinically safe for use in mothers and fetuses before it come into the market.

(3) For engineered mab, only two mutations that prevent internalization of immune complexes, i.e., N297A substitutions, have been identified. More such mutations must be identified for optimal efficacy and synergism.

Conflict of Interest Statement

The authors declare that the review article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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