Mini Review

Contributions of Immune Response to Individual Differences in Zika Virus Infection

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Abstract

Zika virus has emerged as a public health crisis and is associated with a number of neurological deficits; however, only subsets of individuals who contract a Zika virus infection develop severe symptoms. The mechanism underlying Zika virus-induced neuropathogenesis is still poorly understood. Recent studies have implicated the host immune response as a key regulator in Zika virus neuropathology. Specifically, immune responses generated from previous flavivirus infection may contribute to antibody-dependent enhancement of Zika virus infection. Innate immunity may also play an important role for the broad array of individual symptomatic differences. Therefore, host immunity may serve as a therapeutic target to reduce Zika-associated neuropathogenesis.

ABBREVIATIONS

ZIKV: Zika Virus; NSC: Neural Stem Cells; DENV: Dengue Virus; WNV: West Nile Virus; ADE: Antibody-Dependent Enhancement

INTRODUCTION

Recently, Zika virus (ZIKV) has emerged as a rapidly increasing public health threat with local transmission increasing to 84 countries and territories since 2015 [1-3]. While ZIKV is associated with a number of neurological deficits such as microcephaly in infants and Guillain-Barré in adults, only 20% of individuals who contract a ZIKV infection develop clinical symptoms [4-7]. Furthermore, fetuses which contract ZIKV through infected mothers present a wide spectrum of ZIKV-induced neurological defects ranging from intracranial calcifications, ventriculomegaly, corpus callosum defects, to microcephaly [5,6,8-11]. It remains unclear what factors contribute to the variability, occurrence, and severity of these brain abnormalities in ZIKV-infected fetuses. Emerging evidence suggests that individual immune responses and previous flavivirus exposure may mediate ZIKV-associated neurological damage [12-15].

Numerous studies are rapidly enhancing our understanding of ZIKV neuropathogenesis; however the role of host immunity still presents a critical gap in knowledge [5,16]. In a recent study by McGrath and colleagues, three neural stem cell (NSC) strains isolated from three individual human fetal brains were infected with an Asian lineage strain of ZIKV, known to cause developmental neurological defects [17]. The infection rate of ZIKV was kept the same in these cells; however, two of three NSC strains displayed significantly reduced neurogenesis and transcriptome alterations [17]. Interestingly, the one strain that did not have decreased neurogenesis also showed a minimal change in transcriptome. Further analysis of the transcriptome alterations in the two susceptible strains revealed that pathways associated with innate immunity were significantly up-regulated [17]. This study suggests that innate immunity may play a role in mediating response of NSCs to ZIKV infection, and may contribute to individual differences observed clinically.

Other studies have investigated the relationship of previous exposure to other flaviviruses to ZIKV infection severity, specifically Dengue virus (DENV) and West Nile virus (WNV) [12,14,15]. This is particularly relevant given that ZIKV outbreaks and reports of ZIKV-associated neurological deficits are occurring largely in South and Central America as well as Southeast Asia. These regions have large populations of DENV and WNV sero-positive individuals, as well as local transmission of DENV, WNV, and ZIKV [2,12]. A study by Dejnirattisai in 2016 showed that DENV antibodies are cross-reactive with ZIKV in vitro and can enhance ZIKV infection through a mechanism referred to as antibody-dependent enhancement (ADE) [14]. This ADE phenomenon is already characterized in DENV, as there are four main serotypes [18]. Following infection with one serotype, an individual will gain lifelong immunity against that...
specific serotype. However, a secondary infection with a different serotype will result in a detrimental immune response and cause life threatening Dengue hemorrhagic fever [14,18]. In a similar way, it is hypothesized that ADE can occur when an individual contracts ZIKV following DENV infection, or even WNV infection [14].

Recent studies show strong similarity between the envelop protein and non-structural proteins of ZIKV and other flaviviruses [13,19,20]. Envelop proteins play a role in viral tropism, mediate viral fusion and are typically targeted by neutralizing enzymes [13]. Non-structural proteins are produced by the infected cell and function in immune evasion [19]. Settler and colleagues showed that the immune response of envelop proteins from ZIKV infection contributed to ADE of DENV infection. Specifically, the cross-reactive EDI/II monoclonal antibody generated by ZIKV infection resulted in a lethal DENV infection in vivo [13]. In vitro, they also observed that DENV infection produced ADE of ZIKV infection via cross reactivity of envelop proteins [13]. These findings suggest that flavivirus envelop proteins play a critical role in ADE. Interestingly, the non-structural proteins of both ZIKV and DENV are about 50% homologous. However, despite this shared homology, ZIKV did not cross react with antibodies against DENV non-structural proteins, but DENV did react with antibodies from ZIKV non-structural proteins [13]. Furthermore, Bardina and colleagues recently showed that WNV and DENV enhanced ZIKV infection in vitro and in vivo through Fcy Rs as in most cases of ADE [12]. Furthermore, in a STAT2 murine knock-out model, mice treated with DENV and WNV plasma had significantly worse outcomes following ZIKV infection [12]. This is a key finding given that ZIKV has been shown to antagonize innate immunity via STAT2 [21,22].

In contrast to the studies just discussed, Swanstrom and colleagues isolated a class of monoclonal antibodies against the envelop dimer epitope-1 from human sera of patients with DENV infection, and demonstrated its protective nature in neutralizing ZIKV infection in vitro and in vivo [15]. The monoclonal antibodies were isolated from patients several days after recovery from DENV infection. One explanation for the discrepancy seen between Swanstrom’s study and previous studies could be due to the fact that Swanstrom isolated a specific monoclonal antibody as opposed to polyclonal antibodies in sera or monoclonal antibodies against different viral protein epitopes [15,23]. This study, combined with the previous studies, exemplify the complexity of the immune system and the various challenges associated with identifying and implementing a therapeutic solution.

CONCLUSION

As ZIKV continues to pose a public health threat, the need for identifying virus-host interactions is increasingly significant [24]. Use of a human NSC culture can provide mechanistic insight into viral mediation of innate immunity, as well as serve as an easily controlled model system for screening various treatments [17,25]. Additionally, the role of ADE in ZIKV infections following previous exposure to other flaviviruses needs to be better understood in order to implement effective therapies to reduce ZIKV pathogenesis [26]. Previous studies have provided excellent targets such as viral envelope proteins and STAT2 signaling [12,22]. Emerging literature suggests that the most promising methods for attenuating ZIKV neuropathologies may rest in mediation of host immune responses.

ACKNOWLEDGEMENTS

E.L.M. drafted the manuscript and P.W. edited the manuscript. This work was supported by funds from the John S. Dunn Foundation (P.W.), R21AI115950-01 (P.W. and N.V.), 4T32DA007287 (E.L.M.), the Pilot Research Grant of the Institute for Human Infections and Immunity (P.W.), and the Chief Research Office at the University of Texas Medical Branch (P.W.).

REFERENCES


