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Pathogenesis And Consequences Of Zika Virus Infection

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Abstract

Following the 2015 outbreak in Brazil, the Zika virus—a member of the Flaviviridae family that causes a disease spread by mosquitoes—became more well-known globally. There have been concerning indications during this outbreak that Zika infection may have contributed to fetal microcephaly and other neurodevelopmental disorders. The virus also results in thrombocytopenia, multi-organ failure, and uveitis, an inflammatory condition that can cause blindness in adults. It may spread through sexual contact and the placenta, a mode of transmission uncommon in other flaviviruses. The fetus eventually develops microcephaly and neurological abnormalities as a result of the virus infection. Despite its severity, no particular medication or vaccine is currently available to treat it. In conclusion, knowledge of ZIKV pathogenesis may aid in the fight against its worldwide outbreak.

keywords: Brain, Microcephaly, Neuroinflammation, Trans-Placental Transmission, Zika Virus

1. INTRODUCTION

The Ades mosquito, which is a member of the flaviviridae family and is categorized as a flavivirus, is the primary mosquito responsible for spreading the Zika virus [1]. The virus has positive RNA strands. It shares a close relationship with other well-known flaviviruses, including the viruses that cause yellow fever and dengue [2]. The virus was initially discovered in 1947 in a sentinel Rhesus monkey from Uganda's Zika Forest, but it didn't become widely known until a significant outbreak happened in Brazil in 2015 [3]. The pathogenesis linked to the Zika virus during the outbreak is significant in terms of intracranial calcification and fetal microcephaly, among other things [4]. In addition, this virus can result in thrombocytopenia, thrombocytopenic purpura, and multi-organ failure. Moreover, adult cases of uvetis, an inflammatory disease that can cause blindness, are brought on by Zika virus infection of the eyes [5]. Here, we concentrate on learning about the pathophysiology of ZIKV infection in order to stop its spread.

2. VIRAL ENTRY AND TRANSMISSION

Like other flaviviruses, the Zika virus replicates by attaching itself to the cell surface and then entering the host cell through Clathrin-mediated endocytosis, particularly when the virus uses an E-dependent viral

glycoprotein. The typical protein secretory pathway is followed by mature viruses released into the extracellular space, however the exact mechanisms of viral exit are still unknown [6]. The Zika virus is distinct from other flaviviruses in that it can spread through sexual contact and transplacental transmission [7]. Once the placental barrier is breached, it multiplies in a variety of cell types, including fetal macrophages and endothelial cells, and it infects the Hofbauer cells found in the fetal capillary villi. These infected cells can serve as a breeding ground for the Zika virus, which then spreads to the brain parenchyma and kills developing neurons, especially in the cortex region, resulting in microcephaly and neurological dysfunctions [8].
ZIKV is sexually transmitted much more frequently between men and women than between women and men. The median serial interval or the interval between the onsets of symptoms in two sexual partners, for ZIKV sexual transmission is 12 days. ZIKV RNA persistence in semen has a longer median duration (34 days) than it does in the female genital tract (12 days). Reverse transcription polymerase chain reaction allows for longer-term detection of ZIKV than viral culture. There isn't any proof that any other vector-borne flaviviruses can be spread sexually [9].

3. ZIKA VIRUS PATHOGENESIS

In a study funded by the Rockefeller Foundation, the Zika virus (ZIKV) was initially isolated in 1947 from a sentinel rhesus monkey from Uganda's Zika forest. It is known that ZIKV can cause microcephaly in newborns and Guillain-Barre syndrome in adults. It results in massive brain cell death in the developing neonate, which causes a variety of motor and cognitive disabilities. In order to replicate, the virus alters the cell's machinery on multiple levels, suppresses the signaling of toll-like receptors-3, and deregulates microRNA. Three structural and seven non-structural proteins are present in ZIKV. Precursor membrane (prM), envelope protein (E), and capsid (C) are the three structural proteins; the remaining seven non-structural proteins (NS) are NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [10]. The seven non-structural proteins are essential for vital viral functions during genome replication, while the structural proteins PrM, C, and E form the viral particle. The Zika virus (ZIKV) can spread vertically when it enters a developing fetus through the mother during pregnancy or childbirth. Congenital Zika syndrome, a disorder linked to a number of neurological defects and developmental problems, may arise from this transmission. Multiple processes were involved in the mechanism by which ZIKV caused developmental abnormalities in the brain [3].

4. CONGENITAL ZIKA SYNDROME AND VERTICAL TRANSMISSION

Although mosquito bites are the main way that ZIKV is transmitted, it may also enter the fetus through the placental barrier and infect its developing brain cells. Brain microvascular endothelial cells (BMECs), which form the blood-brain barrier, are the virus's primary target once it enters the brain. When BMECs are infected with ZIKV, interferon β (IFN β), interferon λ, and other interferon-stimulated genes are released, which compromises the integrity of the blood-brain barrier [11].
Neural stem cells (NSCs) are the principal cell type in the developing brain. ZIKV infects NSCs and causes apoptosis, or cell death, as well as the unfolded protein response (UPR), a reaction indicative of cellular stress. ZIKV also modifies NSCs' process of self-renewal, which impacts how normally they function [12].
ZIKV affects neurogenesis, which is the production of new neurons in the growing brain. When ZIKV or its proteins are present, differentiating NSCs are stimulated to go through apoptosis, which impairs brain development.
Moreover, although less frequently than NSCs, the Zika virus can infect mature neurons and oligodendrocytes, which are cells that produce myelin. Another kind of brain cell called anastrocytes reacts to ZIKV infection by releasing MCP1 and IFN α, triggering the unfolded protein response, and initiating autophagy, which is a kind of cellular self-destruction. Last but not least, ZIKV infection of microglial cells results in the release of a variety of cytokines and chemokines, such as IFN-α, IL-6, MCP1, TNFα, IL-1β, IL-8, and inducible nitric oxide synthase (iNOS), which exacerbates the inflammatory situation in the developing brain [13]. Congenital Zika syndrome has devastating effects on the developing brain of the affected person due to a combination of factors including disrupted blood-brain barrier, altered neural stem cells, impaired neurogenesis, and the inflammatory response caused by ZIKV infection [14, 15].

5. SERIOUS ILLNESSES BROUGHT ON BY ZIKV

5.1. Guillain-Barré syndrome: GBS is a rapidly progressive, self-limited polyneuropathy. Acute inflammatory demyelinating polyneuropathy, another name for GBS, is a demyelinating disease of the peripheral nervous

system. It can cause anything from a very mild case with a brief weakness to devastating paralysis that prevents the person from breathing on their own [16].

5.2. Congenital Zika Syndrome (CZS): Abnormally high rates of early miscarriages and intrauterine foetal death were observed in a study of pregnant women infected with ZIKV. Approximately 20% of pregnancies infected with ZIKV result in compromised foetal growth and placental dysfunction. Congenital Zika syndrome (CZS) is the condition that affects fetuses infected with ZIKV [6].

During their blood meal, infected vectors (Aedes aegypti and Aedes albopictus) transfer the Zika virus to the host. Viral particles containing E glycoprotein can be incorporated into receptor-mediated endocytosis to infect a range of cell types, including fibroblasts, keratinocytes, and immature dendritic cells. A number of receptors, including DC-SIGN (CD209), TIM-1, 4 (T-cell immunoglobulin and mucin domain-1, 4), AXL, and Tyro3 (cell surface receptor tyrosine kinases, a member of the TAM family), mediate Zika virus entry into these cells [17]. The two primary processes of neuronal cell death have been determined to be apoptosis and necrosis. The function of the inflammasome in the ZIKV-induced host immune response has been validated by recent investigations. The study conducted immunohistochemistry analysis on brain tissues and found that there was a significant increase in the expression of NLRP1, NLRP3, and AIM2, as well as cytokines IL-1β, IL-18, IL-33, and caspase 1. This suggests that IL-33 is one of the cytokines that has multiple functions related to necroptosis, pyroptosis, and inflammasome activation [18]. Experiments verifying that Zika virus infection hinders downstream interferon gene induction as well as type-I interferon induction confirm this. These processes are impacted by several viral proteins. Interferon-mediated signaling of type I and type III is inhibited by the degradation of STAT2 caused by viruses. According to recent research using mouse models, ZIKV infection and related pathogenesis can be controlled by the effector phase of the IFN response [19].

6. MECHANISM OF NEUROPATHOGENESIS

The main way that the Zika virus (ZIKV) spreads is through the bite of an infected Aedes mosquito. When the virus infects the growing fetus during pregnancy, it can cause serious neuropathogenesis and developmental problems [20]. Multiple strategies are involved in ZIKV infection mechanisms, such as

(A) ZIKV infection can affect dermal fibroblasts and epidermal keratinocytes. This facilitates the virus's potential spread by enabling it to attach itself to dermal dendritic cells, also known as Langerhans cells.

(B) The placenta has the ability to transmit ZIKV to the developing foetus. This can happen through the transmigration of infected primary human placental macrophages known as Hofbauer cells, or through infection of cytotrophoblasts, a type of placental cell. This indicates a brand-new intrauterine transmission mechanism. Hofbauer placental macrophages infected with ZIKV continue to be permissive to ZIKV replication despite secreting type I interferon (IFN) and up regulating interferon-stimulated genes (ISGs) [21].

(C) Placental syncytiotrophoblasts produce IFNλ1 and ISGs later in pregnancy, which may have a protective effect by preventing ZIKV infection.

(D) ZIKV specifically targets neural progenitor cells during the initial trimester of fetal brain development. An important factor in ZIKV entry into neural cells is the TAM receptor AXL. ZIKV causes dysregulation of genes involved in neuronal development and apoptosis by activating TLR3-mediated immune responses. A condition known as microcephaly is caused by this severe disruption, which seriously damages the developing brain [22, 23, 24].

7. CONCLUSION

Intensive research efforts have been focused on identifying potential solutions following the World Health Organization's declaration on February 1, 2016, of a Public Health Emergency of International Concern [25]. We can comprehend the mechanistic elements of ZIKV pathogenesis, with a focus on neuropathologies, from this review. The Zika virus may require these details in order to be effectively treated. Further research should be necessary to identify these particular cellular targets in order to improve resolution and recovery from ZIKV-induced neurological dysfunction, as ZIKV has some distinct cellular targets and signaling pathways.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Data availability statement

No data was used for the research described in the article.

Author's contribution

Rajen Dey (RD) participated in the conception of the study. RD and Manojit Bysack (MB) participated in literature searches and extraction. Subhrajyoti Paul (SP1), Sudipta Patra (SP2), Ayan Mondal (AM), Gungun Sharma Adhikari (GSA), Piu Ghosh (PG), MB, and RD wrote the manuscript and approved the article for submission to this journal.

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