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Viral and immunological characteristics of Zika virus and its impact on pregnancy

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Abstract

Zika virus (ZIKV) is a newly emerging flavivirus primarily transmitted by Aedes mosquitoes, but also via sexual contact, maternal-fetal transmission, and bloodborne routes. Congenital Zika syndrome (CZS) is a spectrum of severe birth defects including microcephaly, cortical malformations in the brain, ocular defects and growth restrictions that are caused by infection during pregnancy. The severity of the outcomes depends on what point the infection occurs in pregnancy, the immunological status of mother and relative viral load — with first-trimester infections considered the most dangerous.

Endogenous immune pathogen defense mechanisms, namely basic innate, interferon mediated pathways as well as adaptive B and T cell directed responses are required for host suppression of infection; however cross reactivity with pathogenic strains of flavivirus may contribute to antibody dependent enhancement (ADE). The structure, neurotropism and multiple routes of transmission of ZIKV present challenges to public health.

Prevention efforts focus on vector control, safe sex practices, maternal care and the development of a vaccine. Understanding both viral biology as well as its interplay with the immune system is key to preventing congenital sequelae and for optimal management of maternal-fetal outcomes.

Keywords: Zika Virus; Congenital Zika Syndrome; Pregnancy; Flavivirus

1. Introduction

The emergence of Zika virus (ZIKV) as a causative agent of severe neurological complications and poor pregnancy outcomes has raised great global public health concern. Zika virus is a mosquito-borne flavivirus of the family Flaviviridae, a group that comprises several chemically similar but distinct medically important viruses such as dengue virus, yellow fever virus and West Nile virus. Although historically the infection was classified as mild and self-limiting, introduced outbreaks since the last decade have shown that ZIKV infection can cause severe neurological and congenital effects [1,2].

The Zika virus was first isolated, in 1947, from a rhesus macaque in the Zika forest of Uganda during surveillance studies for yellow fever. The virus was isolated from mosquitoes shortly thereafter and confirmed in humans in the early 1950s [3,4]. For decades after it was discovered, ZIKV infections were only infrequently reported in Africa and parts of Asia, and the disease was considered to be rare and clinically mild [3]. CHIK has long been characterized as a benign, self-limited illness but this perception changed dramatically with the major outbreak that occurred in Yap Island in Micronesia 2007, its first significant epidemic beyond Africa and subsequent rapid spread north to islands in the Pacific region and later into the Americas [3,5].

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The worldwide attention towards Zika virus reached its max during the large-scale outbreak of this disease in Brazil, on 2015. During this outbreak an unexpected increase was observed in congenital malformations, especially microcephaly, among newborns born to mothers infected by Zika virus (ZIKV) during pregnancy [6]. The, and extra epidemiological and experimental information clearer the association between maternal ZIKV an infection and fetal abnormalities (congenital start defects as properly as neurological deficits), which resulted in a 2016 declaration by the World Health Group that Recommend reported cluster circumstances of microcephaly as being related to Zika virus transmission represented a Public Wellbeing Emergency of Worldwide Concern [1,6]. Besides congenital malformations, ZIKV infection shows several neurological manifestations in adults such as Guillain–Barré syndrome and other types of neuropathies [1, 2].

Another reason is that Zika virus represents a significant public health threat because of its routes of infection. The virus is mainly transmitted by the bite of an infected Aedes mosquito, but other routes such as sexual [6], blood-borne [7] and vertical transmission [2] have also been reported. This transmission via vector-borne and convector routes are intertwined, adding complexity to control as they increase epizootics risk.

Because Zika virus infection can have extremely serious effects on both pregnant women and their fetuses, extensive virological studies have been conducted to characterize the virus, with concurrent efforts to elucidate the immunological implications that may contribute to understanding the underlying mechanistic properties involved in its pathogenesis. In particular, understanding how the virus interacts with the host immune system and its ability to cross the placental barrier is crucial for understanding congenital Zika syndrome (CZS) and other pregnancy-related complications [6, 8]. Hence, this review focuses on details of viral and immunological features of Zika virus and discusses their contribution to adverse pregnancy outcomes.

2. Overview of Zika Virus

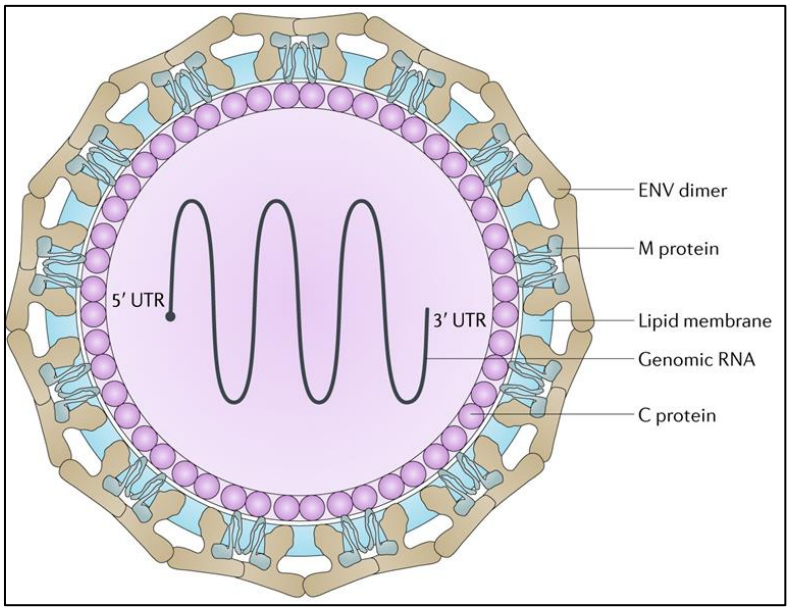

Figure 1 Schematic Outline of the Zika Virus Virion Structure, displaying a lipid envelope with surface glycoproteins as well as the internal RNA genome and capsid proteins [15]

Zika virus (ZIKV) is a single-stranded positive-sense RNA virus in the genus Flavivirus, family Flaviviridae [1,2]. ZIKV, like other flaviviruses, is an enveloped virus with a icosahedral capsid which encloses its ~10.7 kb RNA genome [8]. The virus particle is about 40–50 nm in size and comprises three structural proteins, including the capsid (C) protein, the envelope (E) protein, and a membrane (M/prM) protein [9]. These include structural proteins essential for assembly of the virus and its attachment to host cells. The viral genome encodes one polyprotein, which is processed by viral and host proteases into three structural proteins and seven non-structural proteins (NS1–NS5). Non-structural proteins are important for viral replication, evasion of host immune response and modulation of host responses [10]. These include NS5, which acts as the viral RNA-dependent RNA polymerase and methyltransferase, thus involved in genome replication, and capping [12]; and NS1 that is secreted and modulates immunity/pathogenesis [11]. ZIKV is mainly transmitted by Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus, which are most prevalent in tropical

and subtropical areas. But other routes have been reported, including sexual transmission, vertical transmission (mother-fetus), and transfusion of infected blood [2,13]. The egg-transmission route is also hapless for these methods, as previously mentioned, which lead to sporadic outbreaks outside of the infection/endemic regions. More than any other arboviral disease, ZIKV is known for fluoroquinolone pxl hcl its transplacental transmission and congenital infections. Such tropism in kind is limited to fetal neural progenitor cells, and correlates with the presentation of congenital Zika syndrome (CZS) defined by microcephaly, ocular malformations and other neurological damages [6,14]. The Zika virus particle, schematically illustrated in Figure 1.

Deciphering the protein structure of these viruses is crucial to inform vaccine design and antiviral approaches, since the E protein is the main target for neutralizing antibodies while other structural or non-structural proteins are explored as possible therapeutic targets [14, 16]. Cryo-electron microscopy and molecular modeling studies have provided high-resolution details of the virion and its protein components leading to improved understanding of viral entry, replication, and assembly mechanisms [9,16].

3. Viral Structure and Genome

Like other flaviviruses, the Zika virus (ZIKV) has a structure composed of a lipid envelope derived from the host cell membrane with a outer layer of surface glycoproteins and an icosahedral capsid that contains the viral RNA genome (fig: 1) [17]. The envelope consists of two principal structural proteins, the envelope (E) protein that mediates receptor binding and membrane fusion, and the membrane [M/prM] protein which stabilizes the immature virion and helps in viral assembly [17,18]. The capsid (C) protein binds to and protects the single-stranded, positive-sense RNA genome (~10.7 kb), which encodes a single polyprotein whose products are cleaved into structural and non-structural proteins [19].

Three structural proteins (C, prM/M, E) and seven non-structural proteins (NS1–NS5) are encoded within the viral genome. The proteins encoded are non-structural proteins that play a role in the viral replication cycle, assembly of viral genetic material and immune system evasion as well as modulation of host cell pathways [11,20]. NS3 and NS5 (with the first one acting as viral protease and helicase whereas the second is an RNA dependent RNA polymerase and methyltransferase responsible for genome replication and capping [12]). These proteins are thought to be potential targets of antiviral therapy and for vaccine development.

The structure of the Zika virus is critical to its infectivity, stability, and ability to elicit an immune response. Neutralizing antibodies bind to three structural proteins: the E protein binds to the receptor [15] and facilitates viral fusion with host cell membranes. The PrM protein functions similarly as a companion protein during viral maturation, preventing premature fusion [18]. Mutations in these proteins can affect the virus's ability to survive, its transmission efficiency, and its ability to cause disease [21].

Table 1 Zika virion structural proteins, their localization and primary functions Table summarizes the viral structure and functional components for the appropriate propagation of a virus and its interactions with hosts that are important targets for intervention.

Table 1 Structural Components of Zika Virus

Component	Location in Virion	Function
Capsid (C) protein	Inside capsid	Encapsulates viral RNA; forms nucleocapsid
Envelope (E) protein	Virus surface	Mediates receptor binding and membrane fusion; target of neutralizing antibodies
Membrane (M/prM) protein	Virus surface (immature: prM)	Stabilizes immature virion; assists in viral assembly and maturation
RNA genome	Inside nucleocapsid	Encodes structural and non-structural proteins for replication

The architecture of the E protein and other proteins in this and adjacent regions of the polyprotein, are relevant for vaccine development, antiviral strategies since the E protein is believed to be a principal immunogenic target while other proteins may represent opportunities for based interference with specific aspects of viral biology [15,17,20]. All of these have been complemented by state-of-the art imaging techniques, especially cryo-electron microscopy (cryo-

EM) which has had tremendous impact in elucidating the architecture of viral protein arrangements and glycoprotein rich 3D structures [17,22] a major source of rational drug and vaccine design.

4. Transmission and Epidemiology

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus), with Aedes species as the primary vectors, particularly Aedes aegypti and Aedes albopictus [23]. These mosquitoes are widespread in the tropics and subtropics, typically developing around urban environments and stagnant pools. These or other mosquito vectors examples demonstrated the wide geographical distribution of Aedes mosquitoes, which was an important factor that enabled ZIKV to invade avirulent regions like parts of Americas, southeast Asia and Pacific Islands [24].

The most widespread way of ZIKV transmission is through the bite of infected mosquitoes, but maternal-fetal (vertical) transmission, sexual transmission and blood transfusion have been also reported as ways in which virus spreads [25]. Vertical transmission concerns are primarily based on the potential risk for congenital Zika syndrome (CZS), a phenotype that includes microcephaly, ocular findings and other neurologic deficits [6,14]. In fact, documented sexual transmission occurs with some frequency in both male-to-female and male-to-male partners several weeks after the primary infection [26], emphasizing that this virus does exist despite being undetectable and it can have a long half-life even in colo-genital tissues and seminal fluid. Transmission by blood transfusion has been reported during an epidemic only infrequently [25].

Its mappings are highly connected to environmental conditions and human traffic. They are also rapidly undergoing spread between continents through urbanization, global travel and climate change. Dissemination may be rapid, as observed in the 2015—16 outbreak in Brazil with over 400,000 suspected cases and emergence of congenital disabilities in otherwise immunologically naive populations exposed to ZIKV [6,27]. Furthermore, sporadic outbreaks remain endemic through some regions [27] such as picks of American countries in central and southern areas, Southeast Asia nations and African continents. Table 2 lists the main routes, mechanisms and cases reported for ZIKV transmission.

Table 2 Modes of Zika Virus Transmission

Transmission Route	Mechanism	Example / Notes
Mosquito-borne	Bite from infected Aedes mosquitoes	Primary route; responsible for most outbreaks
Maternal-fetal (vertical)	Transplacental infection during pregnancy	Leads to congenital Zika syndrome
Sexual transmission	Virus present in semen or genital secretions	Male-to-female and male-to-male documented cases
Blood transfusion	Transfusion of infected blood	Rare; reported during epidemics
Laboratory exposure	Accidental exposure in research labs	Extremely rare; biosafety level 2 precautions recommended

Zika virus is highly adaptable to multiple transmission routes, which complicates control strategies. Therefore, integrated vector management, public awareness, and monitoring of non-vector transmission are essential for controlling it. Epidemiological modeling studies have indicated that low levels of sexual transmission are sufficient to sustain outbreaks in certain areas with high mosquito density, highlighting the need for integrated approaches [29, 30].

5. The Immune Response to Zika Virus Infection

The host immune response to Zika virus (ZIKV) infection, encompassing both innate and adaptive immunity, is critical for controlling viral clearance and disease outcome [31]. Viral RNA is recognized by pattern recognition receptors (PRRs) in host cells, such as Toll receptors (TLRs) and RIG-I-like receptors (RLRs), which promote the release of type I interferons (IFNs). This very early innate immune response restricts viral replication and triggers downstream antiviral mechanisms [32, 33].

The second component of immunity is adaptive immunity, which is crucial for long-term immunological protection. CD8+ T cells kill infected cells, and CD4+ helper T cells stimulate proliferation of B lymphocytes to generate neutralizing

antibodies [34]. The envelope protein (E) is the main target of these antibodies besides neutralizing antibody response, preventing viral entry to a host cell and providing protective immunity [15]. Though, cross-reactivity with other flaviviruses (e.g., dengue virus) might sometimes create an antibody dependent infection (ADE), aggravate the infection and/or modulating clinical symptoms [35, 36].

Pregnant women are considered an island of immunity. The mother's immune system must balance protection against the viral pathogen with the acceptance of developing fetal tissues to allow the Zika virus to temporarily pass between mother and fetus [6, 37]. Zika virus can infect various placental cells, including trophoblasts and Hofbauer cells (placental phagocytes), all of which respond with localized immune responses that may affect pregnancy outcomes [38]. This study introduces novel mechanisms by which Zika virus induces congenital anomalies and represents an important discovery for designing therapeutic strategies to prevent congenital Zika syndrome. Table 3: Overview of the components of the immune response to Zika virus, major components, category and function, outcome.

Table 3 Immune Responses to Zika Virus Infection

Immune Component	Role in Infection	Outcome
Innate immunity (IFNs, macrophages, NK cells)	Early detection of viral RNA, antiviral response	Limits viral replication and spread
Adaptive immunity (T cells, B cells)	Clearance of infected cells, production of neutralizing antibodies	Viral elimination and long-term protection
Neutralizing antibodies	Target E protein	Block viral entry into host cells
Antibody-dependent enhancement (ADE)	Cross-reactive antibodies from prior flavivirus infection	May increase infection severity
Placental immune response	Local antiviral response in trophoblasts and Hofbauer cells	May affect fetal infection risk

Therefore, protective immunity and immunopathology both drive clinical outcomes. A vigorous type I interferon response may restrict early viral dissemination, but if unchecked inflammation causes tissue injury [39]. Adaptive immunity is critical for viral clearance, however immune responses need to be tightly regulated during pregnancy in order to protect the fetus [37]. How these complex interactions are so far not yet fully understood and is an active area of research holding significance towards vaccination efforts, vaccines and therapeutic strategies [12; 40].

6. Effect of Zika Virus on Pregnancy

Infection of a fetus with the Zika virus (ZIKV) during early pregnancy can lead to fetal complications that are collectively termed congenital Zika syndrome (CZS) 1–4. This form of transmission is termed vertical transmission and happens in utero, when the virus penetrates the placental barrier during organogenesis period and populates maternal tissues from which it makes path to fetal tissue [42]. This viral orientation is in accordance with neurological defects found in infected babies including microcephaly, cortical malformations and windows [6, 14, 43].

The fate of the fetus is highly dependent on the timing of infection. Infections in the first trimester are historically associated with more severe forms of congenital malformations whereas infection during the sec ond and third trimesters are associated with less severe or sub clinical manifestations [44]. Active detection of maternal infection in the early stage becomes labor-intensive; it would be very likely that any active maternal infection may remain symptomless, therefore with endemic population, routine monitoring might be essential [45].

The pathogenesis of ZIKV during pregnancy likely involves both direct viral cytopathic effect and immune-mediated mechanisms. Proinflammatory cytokines secreted from infected placental cells (i.e., cytotrophoblast and Hofbauer/placental macrophage cells) in the yolk sac will cross into the interstitial compartment, affecting apoptosis processes that are related to tissue damage or negative regulation of fetal development [38,46]. Moreover, maternal immune elements such as type I interferons have been shown to reduce the virus replication potential but may have adverse effects on fetal nervous system maturation [39]. Table 4 summarizes fetal and maternal complications of ZIKV infection during pregnancy.

Table 4 Maternal and Fetal Complications of Zika Virus Infection During Pregnancy

Complication	Description	Risk Factors
Microcephaly	Abnormally small head due to impaired brain development	Highest risk in first trimester infection
Cortical malformations	Lissencephaly, ventriculomegaly, or calcifications	Detected via prenatal ultrasound or MRI
Ocular abnormalities	Retinal lesions, optic nerve hypoplasia	May co-occur with microcephaly
Intrauterine growth restriction (IUGR)	Reduced fetal growth	Can occur even without overt microcephaly
Pregnancy loss	Miscarriage or stillbirth	Rare but documented in severe infections

Epidemiological studies have linked ZIKV outbreaks to increased rates of congenital malformations, the most prominent association being in Brazil from 2015–2016 when a sudden rise in reports of microcephaly occurred following widespread transmission of ZIKV [27,41]. Preventive Action for Pregnant Woman (e.g., mosquito bite prevention, protected sexual relations, planning travels in endemic regions [23,24].

7. Zika Virus Infection Congenital Complications

Zika virus (ZIKV) infection during pregnancy has been linked to a spectrum of congenital disorders that constitute the so-called congenital Zika syndrome (CZS). Predominantly these complications involve the central nervous system and can also effect the ocular, auditory and musculoskeletal systems [47 48].

A bygone feature of CZS has been microcephaly caused by neural progenitor cell defective proliferation and increased apoptosis during fetal brain development in utero. [43,49]. Neuroimaging typically reveals features of cortical thinning, ventriculomegaly, and calcifications. Common ocular syndromes include macular scarring, optic nerve hypoplasia and retinal pigment epithelium defect which can be present in isolation along with microcephaly [50].

IUGR, hearing deficits, and arthrogryposis were the other recorded complication and reflected systemic effects of congenital infection [51]. Maternal immunity and viral load [44,52] and gestational age at infection determine the risk and severity of these outcomes.

New data emphasize that fetal disease can occur even following subclinical infections in mothers and prenatal screening can provide tremendous value in endemic settings [45,47]. Ultrasound and MRI imaging studies play important role in early diagnosis that can assist for timely intervention and counseling of the parents [44].

In experimental systems, ZIKV selectively infects placental macrophages (Hofbauer cells) [46,49] as well as neural progenitor [47] and downstream neurons causing cell death and impaired neurodevelopment. Because I did not find a highly risk factor about congenital infection from my readings on immune develop utero, so the finding indicates the potential role of vaccination and antiviral activity on prevention of those infections.

8. Conclusions

The risks of ZIKV infection on the mother and fetus, especially when acquired in early pregnancy (the first trimester), still remain a threat. Its several modes of transmission and immune evasion mechanisms make it difficult to control an outbreak. Studies of effective vaccines, antiviral therapies and early diagnostics to prevent any congenital implications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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