Zika Virus Pathogenesis

Subjects: Virology

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ZIKV (Zika virus) is a mosquito-borne, positive-sense single-stranded RNA virus belonging to the family *Flaviviridae* (genus *Flavivirus*). ZIKV is further classified by homology to the Spondweni virus (SPONV) in the Spondweni viral clade or serogroup, both viruses were first characterized in Africa in 1947 and 1952, respectively.

Keywords: Zika virus (ZIKV) ; immune evasion ; infection ; tissue propagation ; congenital and neurological disorders

1. Introduction

Apart from the congenital Zika syndrome (CZS) that covers the pathogenic events associated with maternal-fetal ZIKV transmission and the Guillain-Barré syndrome (GBS) [1], primary ZIKV infection is generally asymptomatic or mild in adults [2][3][4][5][6]. Factors determining asymptomatic or mild ZIKV infection, and severe manifestations, as well as chronic sequelae, are still to be determined. Understanding the importance of being infected by a particular ZIKV lineage, the influence of comorbidities and previous flavivirus infections (i.e., Dengue virus (DENV)), as well as viral load and the molecular mechanisms underlying severe infection, such as host genetic susceptibility to infection, immunosuppression and/or failure of the innate immunity are key to improving the overall knowledge of the complex ZIKV disease, diagnosis, prophylaxis and treatment [7][8][9][10][11][12][13][14][15][16][17][18].

The interplay between ZIKV and immune responses is initiated once the virus invades different cells, tissues and organs from the early infection. In infected individuals and non-human primates, the virus is fast cleared from blood, but persisting in saliva, urine, semen, breast milk and the central nervous system (CNS) for months [19][20][21][22][23]. Several *in vitro* and *ex vivo* studies indicate that ZIKV replicates in human endothelial and epithelial cells [24], peripheral blood mononuclear cells (PBMCs) [24], astrocyte and microglial cells [25][26], different placenta cells, such as trophoblasts [27], Hofbauer cells in chorionic villi and amniotic epithelial cells [28], as well as fibroblasts (placental, uterine, pulmonary) [29]. Moreover, ZIKV has a broad cell tropism in vitro, infecting human skin cells (i.e., dermal fibroblasts and epidermal keratinocytes), human myeloid cells (i.e., dendritic cells (DCs) and macrophages), and human progenitor cells of neuronal, placental and testicular origin (reviewed in [30][31]).

It is important to understand how ZIKV interacts with these cells and tissues, as well as with the host immune system to cause severe disease. The following sections describe the mechanisms underlying interferon (IFN) immune response against flavivirus, and the available knowledge concerning the events triggered by the ZIKV genome and proteins to escape or neutralize the antiviral IFN functions to infect and induce pathogenesis in immune privileged organs such as the brain and eye [11][32][33][34].

2. Mechanisms of ZIKV Immune Evasion

ZIKV persistence and pathogenesis involve a complex immune-evasion strategy to facilitate ZIKV trafficking, infection and spread through different cell types and tissues to finally cross protective barriers to the immune-privileged fetus, affecting the development of the fetal brain and eyes.

ZIKV uses its own viral proteins, gRNA and sfRNA elements to evade antiviral immunity, particularly the anti-ZIKV IFN response and associated signals and factors, as mentioned above. Hence, multiple NS proteins of ZIKV negatively modulate the antiviral response at various levels by inhibiting type I IFN production and the expression of downstream ISGs, acting on the IFN-associated cGAS-STING pathway, targeting with TBK1 and therefore impairing IRF3 promoters, or modulating RIG-I- and MDA5-directed type I IFN induction, as well as different steps of the antiviral type I IFN system against RNA viruses such as ZIKV. The NS proteins could cooperate to overcome the INF antiviral functions, limiting immune-protection and the understanding of ZIKV immune-evasion and pathogenesis. Moreover, gRNA-associated modifications that function as an antagonist of the innate type-I IFN response, and sfRNA stability against XRN-1, 5′-3′ exoribonuclease, which help to efficiently suppress RIG-I- and MDA-5-mediated IFN have been identified as an important

proviral pathway, abrogating IFN neutralization of ZIKV infection during the early-phase of the viral life cycle. Moreover, ZIKV infection modifies the miRNA landscape of host cells in order to evade innate and adaptive immune responses and promote viral replication and survive. Although the involvement of viral antigen specific $CD4^+$ T cells in the control of ZIKV infection and disease is still controversial, the $CD8^+$ T cell response is associated with the control of the ZIKV infection and pathogenesis. This protective action has been more clearly demonstrated by cross-immune reactions of human DENV-elicited $CD8^+$ T cells [35] which react against ZIKV-NS (i.e., mainly recognizing NS3 protein [36][37]). Anti-ZIKV vaccines are therefore focused on generating protective $CD8^+$ and $CD4^+$ T cells in order to control ZIKV infection and promote virus clearance, thereby avoiding harmful ADE effects with potential reinfection events by ZIKV or other flaviviruses [38][39][40][41][42].

In order to reach the human fetus, ZIKV must cross the placenta barrier which develops within days of conception and is indispensable for pregnancy [43][44]. Furthermore, fetal damage by ZIKV infection can be observed after the first trimester, and persistence infection, late during pregnancy, results in fetal disease or adverse pregnancy outcomes [45][46].

Recently, as a result of the global impact of ZIKV and its teratogen effects, such as microcephaly in newborns to infected mothers along with neurological abnormalities and GBS, and comparison with previous congenital pathogens such as *Toxoplasma gondii*, other (e.g., syphilis, human immunodeficiency virus (HIV) or parvovirus B19), rubella virus, cytomegalovirus (CMV) and herpes simplex virus (HSV) (i.e., all of which are grouped under the term of TORCH pathogens) [47]. ZIKV has been proposed as a new TORCH pathogen but more complex in the associated pathogenesis [47]. ZIKV-induced congenital microcephaly abnormality alarmed the whole of the planet [48] together with other developmental abnormalities that determine the CZS (i.e., severe microcephaly with partially collapsed skull, thin cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures and marked early hypertonia) [49][50], and placental insufficiency and fetal loss [51]. ZIKV is able to infect, traffic and spread through several cells and tissues during fetal differentiation, just after overcoming/crossing several protective barriers such as those mentioned above. ZIKV is able to infect eye and brain immune-privileged organs, avoiding innate IFN defenses and provoking neuroinflammation and cytokine release that halt neurogenesis [52], thereby favoring viral spread and tissue damage.

Therefore, understanding how ZIKV interacts with the INF system and influences the outcome of infection in barrier tissues such as the placenta, eyes and brain during pregnancy may help in the development of therapeutic strategies to clear ZIKV from the organism, based on the action mechanism of the IFN system, and keeping immune-privileged organs safe during both fetal development and in adults.

Moreover, determining the molecular interplay between the ZIKV genome and viral proteins with the IFN and T cell responses and antiviral signals is also crucial to improving vaccine strategies based on mutant live-attenuated viral candidates that need to induce adaptive cellular and humoral immune protective responses, also helping type-I IFN antiviral responses [39][53][54][55].

References

1. Liang, B.; Guida, J.P.; Costa Do Nascimento, M.L.; Mysorekar, I.U. Host and viral mechanisms of congenital zika syndrome. Virulence 2019, 10, 768–775.
2. Musso, D.; Nhan, T.; Robin, E.; Roche, C.; Bierlaire, D.; Zisou, K.; Shan Yan, A.; Cao-Lormeau, V.M.; Broult, J. Potential for zika virus transmission through blood transfusion demonstrated during an outbreak in french polynesia, november 2013 to february 2014. Eur. Surveill. Bull. Eur. Sur Les Mal. Transm. Eur. Commun. Dis. Bull. 2014, 19, 20761.
3. Wiwanitkit, S.; Wiwanitkit, V. Afebrile, asymptomatic and non-thrombocytopenic zika virus infection: Don’t miss it! Asian Pac. J. Trop. Med. 2016, 9, 513.
4. Wikan, N.; Suputtamongkol, Y.; Yoksan, S.; Smith, D.R.; Auewarakul, P. Immunological evidence of zika virus transmission in thailand. Asian Pac. J. Trop. Med. 2016, 9, 141–144.
5. Oduyebo, T.; Petersen, E.E.; Rasmussen, S.A.; Mead, P.S.; Meaney-Delman, D.; Renquist, C.M.; Ellington, S.R.; Fischer, M.; Staples, J.E.; Powers, A.M.; et al. Update: Interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible zika virus exposure—United states, 2016. MMWR Morb. Mortal. Wkly. Rep. 2016, 65, 122–127.
6. Haby, M.M.; Pinart, M.; Elias, V.; Reveiz, L. Prevalence of asymptomatic zika virus infection: A systematic review. Bull. World Health Organ. 2018, 96, 402–413.

7. Grossi-Soyster, E.N.; LaBeaud, A.D. Clinical aspects of zika virus. Curr. Opin. Pediatr. 2017, 29, 102–106.
8. Plourde, A.R.; Bloch, E.M. A literature review of zika virus. Emerg. Infect. Dis. 2016, 22, 1185–1192.
9. Mercado-Reyes, M.; Acosta-Reyes, J.; Navarro-Lechuga, E.; Corchuelo, S.; Rico, A.; Parra, E.; Tolosa, N.; Pardo, L.; González, M.; Martìn-Rodriguez-Hernández, J.; et al. Dengue, chikungunya and zika virus coinfection: Results of the national surveillance during the zika epidemic in colombia. Epidemiol. Infect. 2019, 147, e77.
10. Chaves, B.A.; Orfano, A.S.; Nogueira, P.M.; Rodrigues, N.B.; Campolina, T.B.; Nacif-Pimenta, R.; Pires, A.; Júnior, A.B.V.; Paz, A.D.C.; Vaz, E.; et al. Coinfection with zika virus (zikv) and dengue virus results in preferential zikv transmission by vector bite to vertebrate host. J. Infect. Dis. 2018, 218, 563–571.
11. Cugola, F.R.; Fernandes, I.R.; Russo, F.B.; Freitas, B.C.; Dias, J.L.; Guimarães, K.P.; Benazzato, C.; Almeida, N.; Pignatari, G.C.; Romero, S.; et al. The brazilian zika virus strain causes birth defects in experimental models. Nature 2016, 534, 267–271.
12. Halai, U.A.; Nielsen-Saines, K.; Moreira, M.L.; de Sequeira, P.C.; Junior, J.P.P.; de Araujo Zin, A.; Cherry, J.; Gabaglia, C.R.; Gaw, S.L.; Adachi, K.; et al. Maternal zika virus disease severity, virus load, prior dengue antibodies, and their relationship to birth outcomes. Clin. Infect. Dis. 2017, 65, 877–883.
13. Shao, Q.; Herrlinger, S.; Zhu, Y.N.; Yang, M.; Goodfellow, F.; Stice, S.L.; Qi, X.P.; Brindley, M.A.; Chen, J.F. The african zika virus mr-766 is more virulent and causes more severe brain damage than current asian lineage and dengue virus. Development 2017, 144, 4114–4124.
14. Esser-Nobis, K.; Aarreberg, L.D.; Roby, J.A.; Fairgrieve, M.R.; Green, R.; Gale, M., Jr. Comparative analysis of african and asian lineage-derived zika virus strains reveals differences in activation of and sensitivity to antiviral innate immunity. J. Virol. 2019, 93.
15. Dowall, S.D.; Graham, V.A.; Hewson, R. Lineage-dependent differences of zika virus infection in a susceptible mouse model are associated with different profiles of cytokines, chemokines, growth factors and acute phase proteins. Cytokine 2020, 125, 154864.
16. Avilés-Vergara, P.A.; Trujillo-Correa, A.; Gómez-Suárez, L.A.; Ricardo-Caldera, D.; Soto-De León, S.C.; Brango, H.; Tovar Acero, C. Denv and zikv detection in patients with acute febrile syndrome in córdoba, colombia. Int. J. Infect. Dis. 2020, 99, 458–465.
17. Bourdon, M.; Manet, C.; Montagutelli, X. Host genetic susceptibility to viral infections: The role of type i interferon induction. Genes Immun. 2020, 21, 365–379.
18. Sultan, N.; Bukhari, S.A.; Ali, I.; Asif, M.; Umar, Z.; Akash, M.S.H. Zika virus: A critical analysis and pharmaceutical perspectives. Crit. Rev. Eukaryot. Gene Expr. 2018, 28, 357–371.
19. Petersen, L.R.; Jamieson, D.J.; Powers, A.M.; Honein, M.A. Zika virus. N. Engl. J. Med. 2016, 374, 1552–1563.
20. Osuna, C.E.; Lim, S.Y.; Deleage, C.; Griffin, B.D.; Stein, D.; Schroeder, L.T.; Omange, R.W.; Best, K.; Luo, M.; Hraber, P.T.; et al. Zika viral dynamics and shedding in rhesus and cynomolgus macaques. Nat. Med. 2016, 22, 1448–1455.
21. Bonaldo, M.C.; Ribeiro, I.P.; Lima, N.S.; Dos Santos, A.A.; Menezes, L.S.; da Cruz, S.O.; de Mello, I.S.; Furtado, N.D.; de Moura, E.E.; Damasceno, L.; et al. Isolation of infective zika virus from urine and saliva of patients in brazil. PLoS Negl. Trop. Dis. 2016, 10, e0004816.
22. Sotelo, J.R.; Sotelo, A.B.; Sotelo, F.J.B.; Doi, A.M.; Pinho, J.R.R.; Oliveira, R.C.; Bezerra, A.; Deutsch, A.D.; Villas-Boas, L.S.; Felix, A.C.; et al. Persistence of zika virus in breast milk after infection in late stage of pregnancy. Emerg. Infect. Dis. 2017, 23, 856–857.
23. Aid, M.; Abbink, P.; Larocca, R.A.; Boyd, M.; Nityanandam, R.; Nanayakkara, O.; Martinot, A.J.; Moseley, E.T.; Blass, E.; Borducchi, E.N.; et al. Zika virus persistence in the central nervous system and lymph nodes of rhesus monkeys. Cell 2017, 169, 610–620.e614.
24. Hou, W.; Armstrong, N.; Obwolo, L.A.; Thomas, M.; Pang, X.; Jones, K.S.; Tang, Q. Determination of the cell permissiveness spectrum, mode of rna replication, and rna-protein interaction of zika virus. BMC Infect. Dis. 2017, 17, 239.
25. Retallack, H.; Di Lullo, E.; Arias, C.; Knopp, K.A.; Laurie, M.T.; Sandoval-Espinosa, C.; Mancia Leon, W.R.; Krencik, R.; Ullian, E.M.; Spatazza, J.; et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc. Natl. Acad. Sci. USA 2016, 113, 14408–14413.
26. Meertens, L.; Labeau, A.; Dejarnac, O.; Cipriani, S.; Sinigaglia, L.; Bonnet-Madin, L.; Le Charpentier, T.; Hafirassou, M.L.; Zamborlini, A.; Cao-Lormeau, V.M.; et al. Axl mediates zika virus entry in human glial cells and modulates innate immune responses. Cell Rep. 2017, 18, 324–333.

27. Aagaard, K.M.; Lahon, A.; Suter, M.A.; Arya, R.P.; Seferovic, M.D.; Vogt, M.B.; Hu, M.; Stossi, F.; Mancini, M.A.; Harris, R.A.; et al. Primary human placental trophoblasts are permissive for zika virus (zikv) replication. Sci. Rep. 2017, 7, 41389.

28. Tabata, T.; Petitt, M.; Puerta-Guardo, H.; Michlmayr, D.; Wang, C.; Fang-Hoover, J.; Harris, E.; Pereira, L. Zika virus targets different primary human placental cells, suggesting two routes for vertical transmission. Cell Host Microbe 2016, 20, 155–166.

29. Chen, J.C.; Wang, Z.; Huang, H.; Weitz, S.H.; Wang, A.; Qiu, X.; Baumeister, M.A.; Uzgiris, A. Infection of human uterine fibroblasts by zika virus in vitro: Implications for viral transmission in women. Int. J. Infect. Dis. 2016, 51, 139–140.

30. Miner, J.J.; Diamond, M.S. Zika virus pathogenesis and tissue tropism. Cell Host Microbe 2017, 21, 134–142.

31. Ngono, A.E.; Shresta, S. Immune response to dengue and zika. Annu. Rev. Immunol. 2018, 36, 279–308.

32. Wiwanitkit, V. Eye problem in zika virus infection. Eur. J. Intern. Med. 2018, 47, e17.

33. Carson, M.J.; Doose, J.M.; Melchior, B.; Schmid, C.D.; Ploix, C.C. Cns immune privilege: Hiding in plain sight. Immunol. Rev. 2006, 213, 48–65.

34. Russo, F.B.; Jungmann, P.; Beltrão-Braga, P.C.B. Zika infection and the development of neurological defects. Cell. Microbiol. 2017, 19, e12744.

35. Wen, J.; Tang, W.W.; Sheets, N.; Ellison, J.; Sette, A.; Kim, K.; Shresta, S. Identification of zika virus epitopes reveals immunodominant and protective roles for dengue virus cross-reactive cd8(+) t cells. Nat. Microbiol. 2017, 2, 17036.

36. Herrera, B.B.; Tsai, W.Y.; Chang, C.A.; Hamel, D.J.; Wang, W.K.; Lu, Y.; Mboup, S.; Kanki, P.J. Sustained specific and cross-reactive t cell responses to zika and dengue virus ns3 in west africa. J. Virol. 2018, 92.

37. Lim, M.Q.; Kumaran, E.A.P.; Tan, H.C.; Lye, D.C.; Leo, Y.S.; Ooi, E.E.; MacAry, P.A.; Bertoletti, A.; Rivino, L. Cross-reactivity and anti-viral function of dengue capsid and ns3-specific memory t cells toward zika virus. Front. Immunol. 2018, 9, 2225.

38. Terzian, A.C.B.; Schanoski, A.S.; Mota, M.T.O.; da Silva, R.A.; Estofolete, C.F.; Colombo, T.E.; Rahal, P.; Hanley, K.A.; Vasilakis, N.; Kalil, J.; et al. Viral load and cytokine response profile does not support antibody-dependent enhancement in dengue-primed zika virus-infected patients. Clin. Infect. Dis. 2017, 65, 1260–1265.

39. Lin, H.H.; Yip, B.S.; Huang, L.M.; Wu, S.C. Zika virus structural biology and progress in vaccine development. Biotechnol. Adv. 2018, 36, 47–53.

40. Hurtado-Monzón, A.M.; Cordero-Rivera, C.D.; Farfan-Morales, C.N.; Osuna-Ramos, J.F.; De Jesús-González, L.A.; Reyes-Ruiz, J.M.; Del Ángel, R.M. The role of anti-flavivirus humoral immune response in protection and pathogenesis. Rev. Med. Virol. 2020, 30, e2100.

41. Pattnaik, A.; Sahoo, B.R.; Pattnaik, A.K. Current status of zika virus vaccines: Successes and challenges. Vaccines 2020, 8, 266.

42. Martín-Acebes, M.A.; Saiz, J.C.; Jiménez de Oya, N. Antibody-dependent enhancement and zika: Real threat or phantom menace? Front. Cell. Infect. Microbiol. 2018, 8, 44.

43. Turco, M.Y.; Moffett, A. Development of the human placenta. Development 2019, 146, dev163428.

44. Rossant, J.; Cross, J.C. Placental development: Lessons from mouse mutants. Nat. Rev. Genet. 2001, 2, 538–548.

45. Brasil, P.; Pereira, J.P., Jr.; Moreira, M.E.; Ribeiro Nogueira, R.M.; Damasceno, L.; Wakimoto, M.; Rabello, R.S.; Valderramos, S.G.; Halai, U.A.; Salles, T.S.; et al. Zika virus infection in pregnant women in rio de janeiro. N. Engl. J. Med. 2016, 375, 2321–2334.

46. França, G.V.; Schuler-Faccini, L.; Oliveira, W.K.; Henriques, C.M.; Carmo, E.H.; Pedi, V.D.; Nunes, M.L.; Castro, M.C.; Serruya, S.; Silveira, M.F.; et al. Congenital zika virus syndrome in brazil: A case series of the first 1501 livebirths with complete investigation. Lancet 2016, 388, 891–897.

47. Coyne, C.B.; Lazear, H.M. Zika virus—Reigniting the torch. Nat. Rev. Microbiol. 2016, 14, 707–715.

48. Schuler-Faccini, L.; Ribeiro, E.M.; Feitosa, I.M.; Horovitz, D.D.; Cavalcanti, D.P.; Pessoa, A.; Doriqui, M.J.; Neri, J.I.; Neto, J.M.; Wanderley, H.Y.; et al. Possible association between zika virus infection and microcephaly—Brazil, 2015. MMWR Morb. Mortal. Wkly. Rep. 2016, 65, 59–62.

49. Moore, C.A.; Staples, J.E.; Dobyns, W.B.; Pessoa, A.; Ventura, C.V.; Fonseca, E.B.; Ribeiro, E.M.; Ventura, L.O.; Neto, N.N.; Arena, J.F.; et al. Characterizing the pattern of anomalies in congenital zika syndrome for pediatric clinicians. JAMA Pediatr. 2017, 171, 288–295.

50. Vhp, L.; Aragão, M.M.; Pinho, R.S.; Hazin, A.N.; Paciorkowski, A.R.; Penalva de Oliveira, A.C.; Masruha, M.R. Congenital zika virus infection: A review with emphasis on the spectrum of brain abnormalities. Curr. Neurol. Neurosci. Rep. 2020, 20, 49.
51. Martines, R.B.; Bhatnagar, J.; de Oliveira Ramos, A.M.; Davi, H.P.; Iglezias, S.D.; Kanamura, C.T.; Keating, M.K.; Hale, G.; Silva-Flannery, L.; Muehlenbachs, A.; et al. Pathology of congenital zika syndrome in brazil: A case series. Lancet 2016, 388, 898–904.
52. Nelson, B.R.; Roby, J.A.; Dobyns, W.B.; Rajagopal, L.; Gale, M., Jr.; Adams Waldorf, K.M. Immune evasion strategies used by zika virus to infect the fetal eye and brain. Viral Immunol. 2020, 33, 22–37.
53. Morabito, K.M.; Graham, B.S. Zika virus vaccine development. J. Infect. Dis. 2017, 216, S957–S963.
54. Valente, A.P.; Moraes, A.H. Zika virus proteins at an atomic scale: How does structural biology help us to understand and develop vaccines and drugs against zika virus infection? J. Venom. Anim. Toxins Incl. Trop. Dis. 2019, 25, e20190013.
55. Abbink, P.; Stephenson, K.E.; Barouch, D.H. Zika virus vaccines. Nat. Rev. Microbiol. 2018, 16, 594–600.