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Zika Virus, A Tool to Fight Against Glioblastoma

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ABSTRACT

Glioblastoma multiforme (GBM) is a deadly human cancer. It occurs in the brain cells or in spinal cord. GBM stem cells are reported to be resistant to treatment and reappearance is unpreventable. GBM stem cells are the target of Zika virus (ZIKV) which is known to cause impaired brain development leading to microcephaly in human embryos. The virus ensures the survival of mice having gliomas. ZIKV has been reported as an oncolytic virus targeting GBM cells selectively. Here, we will discuss the immunological aspect of protection against GBM mediated by ZIKV. When ZIKV was introduced into the brain, the recruitment of CD8+ T and myeloid cells to the tumor microenvironment was augmented. CD8+ T cells were needed for ZIKV-mediated tumor clearance. Here we will also discuss the role of cellular gasdermin D (GSDMD) in efficient killing of a human GBM cell line that was promoted by ZIKV infection. The ZIKV protease cleaves specifically human GSDMD for activating caspase-independent pyroptosis thus damaging, both the naive neighboring as well as viral protease-harboring cells.

Keywords: Glioblastoma multiforme (GBM); Glioblastoma Stem Cells (GSC); Zika virus (ZIKV); Gasdermin D (GSDMD); SRY (sex determining region Y)-box 2 (SOX2).

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INTRODUCTION

GBM is the most invasive primary brain tumor. Almost all patients succumb to death within two years of detection [1]. Surgery, temozolomide chemotherapy, radiation therapy and use of adjuvants more recently comprise standard treatment [2]. In spite of maximal treatment, the recurrence of most GBMs within 6 months was reported at that time when no curative or standard treatment persists. The outcomes of poor patients from GBM are multifaceted that included the existence of GBM stem cells (GSCs), which are reported to be resistant to chemotherapy as well as radiation therapy [3-5] and feeble antitumor immunological responses [6-11]. Cancer is reported to be one of the major causes of death in this world. The World Health Organization categorized GBM as a grade IV glioma among different brain tumors due to its malignant nature [12]. This invasive tumor sustains cell proliferation, escapes from immune system, and shows resistance to drugs because GBM stem cells are reported to be self-renewing, multipotent, and resistant to apoptosis [13, 14].

ZIKV is reported to be transmitted by Aedes mosquitoes primarily. These mosquitoes usually bite during day time. Most people infected with ZIKV hardly develop symptoms. Those who develop symptoms typically suffer from rash, conjunctivitis, fever, joint and muscle pain, headache and malaise that continues for 2–7 days. If ZIKV infection occurs during pregnancy, it leads to the birth of infants with microcephaly and other inherited malformations in addition to miscarriage and premature birth. Myelitis, neuropathy and Guillain-Barre syndrome in adults and children are reported to be associated with ZIKV infection. Although from 2017 onwards the cases of ZIKV disease declined globally. The transmission is still prevalent at low levels in some American countries [15, 16].

For ZIKV infection no specific treatment is available. People having symptoms of rash, joint pain or fever should drink plenty of fluids, take sufficient rest and can be treated with analgesics or antipyretics. Pregnant women infected with ZIKV should immediately seek medical treatment [17].

ZIKV Genetic Material & Oncolysis:

In 2007 for the first time the whole genome of MR 766, the African prototype ZIKV strain, was sequenced. The ZIKV arbovirus belongs to the Flavivirus genus of the Flaviviridae family [18]. The ZIKV genome contains a 10.8-kb positive-sense, single-stranded RNA molecule, which consists of a 5′ untranslated region (UTR) of around 100 nt length, one single open reading frame (ORF) of around 10 kb, and 3′ UTR of around 420 nt. A single polyprotein encoded by the ORF is processed further into the capsid C, the precursor membrane prM, the envelope protein E and seven nonstructural proteins viz., NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 (Figure 1) [19].

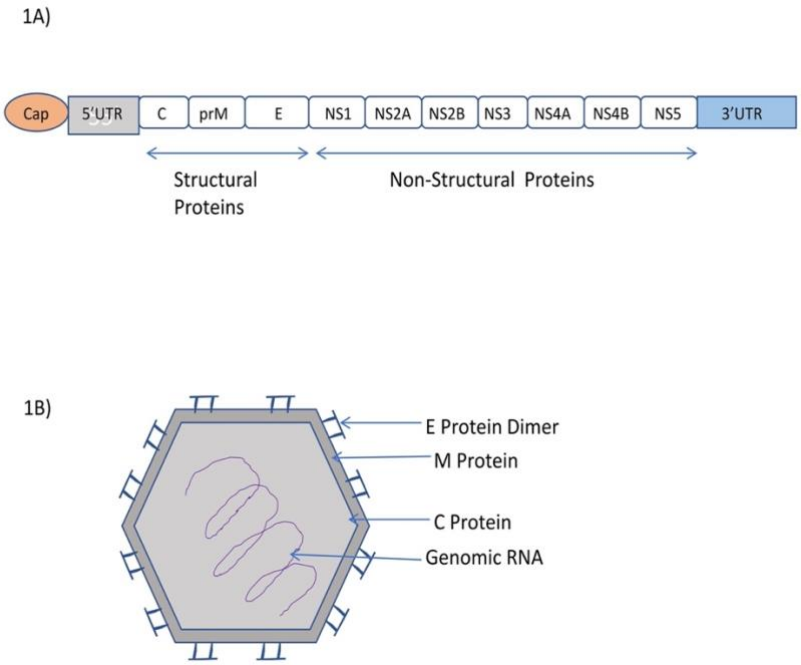


Figure 1: Zika Virus. (A) Zika Virus Genome. A single 10 kb ORF codes for a polyprotein which undergoes post-translational processing to yield the three structural and seven non-structural proteins. (B) Zika Virus Structure [19].

The evolution of the ZIKV genome in a rapid manner was reported to account for the current ZIKV pandemic with unique Zika disease. The immune system activated by ZIKV promotes the activation and proliferation of glial cells and induces apoptotic cell death. The development of inflammation has critical contribution to Zika disease [20].

An oncolytic virus would be considered as a desirable candidate for cancer treatment if the virus destroys the cancer cells selectively without harming the normal healthy cells [21, 22]. Irrespective of the genetic material, DNA or RNA, several viruses were categorized as oncolytic viruses. This includes Newcastle disease virus, adenovirus, herpes simplex virus 1, poliovirus, vaccinia virus, parvovirus and reovirus [23-25]. Recently, the causative agent of microcephaly in the fetus, ZIKV was categorized as an oncolytic virus as it infects and destroys the GBM stem cells preferentially and probably does not injure adult neurons [26, 27].

Viral Neurotropism:

Although ZIKV was reported to kill both the pediatric and adult brain cancer cells, adult GBMs were studied with preference for illustrating the oncolytic mechanisms requiring T cells for increasing the efficacy [28-30]. The ZIKV neurotropism was possibly due to the specific expression of αvβ5 and SOX2 on the surface of GBM stem cells [31]. The ZIKV receptor tyrosine kinase AXL expression makes GBM cells greatly permissive to ZIKV that

enters and kills the cells. Nonetheless the viral receptor expression is a necessity for virus infection but this hardly guarantees the killing [32].

Integrin αvβ5 is reported to be proangiogenic member of broader RGD-binding integrin family. They are the primary receptors utilized by animal cells for binding to the extracellular matrix. The heterodimers work as transmembrane proteins [33]. The screening of the distribution of integrins in human cancers is of huge interest. At present there is little knowledge regarding the αvβ5 expression in gastric cancers, mainly due to dearth of antibodies appropriate for utilization on formalin-fixed and paraffin-embedded (FFPE) tissues [34].

SRY (sex determining region Y)-box 2 is termed as SOX2, a transcription factor, essential for maintenance of pluripotency or self-renewal of embryonic stem cells that are undifferentiated. Sox2 plays a critical function for maintaining neural and embryonic stem cells [31].

An in-depth examination is needed to know how ZIKV destroys GBM cells after infection in order to develop a safe and accurate virotherapy. Among several kinds of virus-mediated cell death, recently pyroptosis was interpreted as protein-mediated cellular destruction of gasdermin family accompanied by inflammatory responses distinguishable mechanistically from apoptosis [35, 36].

Mode of Replication:

Virions docking on the receptors on cell surfaces enter the cells by receptor-driven endocytosis and are taken into the vesicles coated with clathrin inside the cells. Conformational changes are triggered by endosome acidification, viral membrane getting fused with endosome membrane, followed by particle disassembly and release of viral genomic RNA into the cytoplasm from viral nucleocapsid [37-39].

After the release of positive-stranded genomic RNA from nucleocapsid into cytoplasm, it undergoes translation into a single polyprotein, which is processed further co-translationally as well as post-translationally by cellular and viral proteases. This cleavage is reported to produce three structural proteins (C, prM and E) as well as seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) [40]. NS-5 has the RNA-dependent RNA polymerase (RdRp) activity and synthesizes the negative-strand antigenomic RNA using the positive-strand genome as template [39]. On the endoplasmic reticulum surface, new viral positive-strand genomes are synthesized using the negative-strand RNA. The newly synthesized genomes are translated further into viral polyproteins by host cell machinery.

As reported earlier the viral genome replication starts with the synthesis of negative-strand RNA, and serves further as a template for the positive-strand genomic RNA synthesis. The

assembly of virus occurs in the surface of endoplasmic reticulum (ER) by the process of budding. The virus particles, yet to be matured, traverse through the trans-Golgi system along the host secretory pathway. The virion maturation takes place at trans-Golgi system and subsequently released by the process of exocytosis from the cell [41, 42].

The replication process of ZIKV is depicted in the Figure 2.

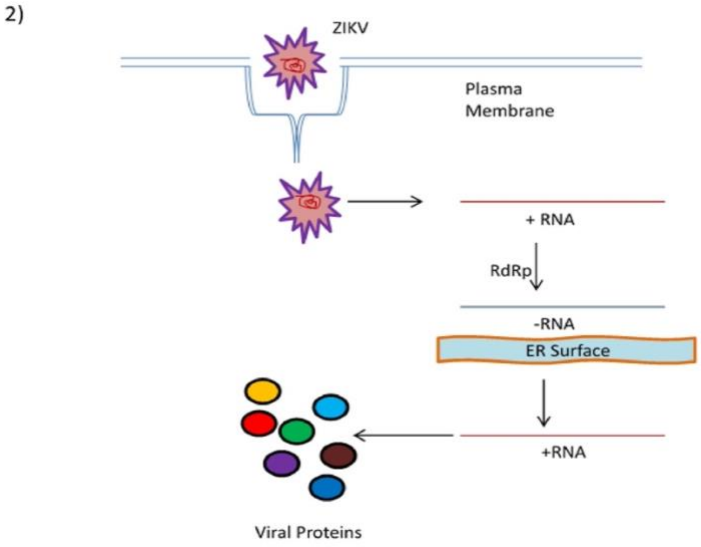


Figure 2: A schematic representation of ZIKV replication. Positive stranded RNA is copied into a negative strand, followed by a positive strand before encoding proteins [40].

Immunology of Oncolytic ZIKV:

ZIKV is reported to augment the infiltration of CD8+ T cells into the tumor site. Solid tumors with little quantity of T cell infiltration normally do not get any benefit from immune checkpoint blockade treatment [43, 44]. Immune checkpoint blockade treatments fail in induction of responses almost in all cancer affected patients, so that the procedure for increasing the objective response rate is a serious challenge. It was demonstrated that abundant infiltration of T cells in tumour tissues is a precondition to respond to PD-L1 blockade (Figure 3) [45, 46].

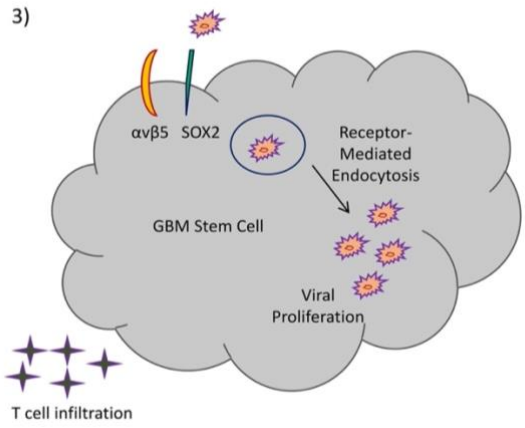


Figure 3: T cell infiltration at GBM tumor site after ZIKV infection [45].

In this context oncolytic virotherapy is a fruitful treatment option. This is because the inflammation induced by the virus is able to increase the effectiveness of checkpoint blockade treatment. While monotherapy using anti–PD-1 antibody, improved tumor survival to a limited degree, when administered together with ZIKV, tumor survival is enhanced. PD-1 is a checkpoint protein on T cells. A vivid study in humans revealed that Talimogene laherparepvec, T-VEC together with anti–PD-1 immunotherapy had a bearable safety profile in melanoma treatment, and the combination was reported to have greater effectiveness against melanoma as compared to checkpoint blockade anti–PD-1 antibody monotherapy or T-VEC treatment [47]. Because of success of the inhibitors of immune checkpoints in other types of cancers and their probable supplementary effects with several oncolytic viruses, many combinations of virus/antibody are recently being probed in clinical trials. This includes an ongoing phase II clinical trial with pembrolizumab (anti–PD-1) combined with an oncolytic adenovirus (DNX-2401) for patients suffering from recurrent GBM (ClinicalTrials.gov NCT02798406) [48, 49].

An analogous conjugation with ZIKV will be worth following. In addition to this, future studies should be conducted in nonresponders to PD-1 blockade and ZIKV combination therapy. This may point out the mechanisms of resistance, as for example immune infiltration reduction surrounding the tumor, depletion of tumor antigens, or other processes leading to T cell exhaustion or anergy [29].

ZIKV treatment also enhanced the response of myeloid cells that are associated with tumors in the tumor site, particularly the microglia and monocyte populations. Macrophage subsets associated to tumors may contribute to presentation of antigens as well as the anticancer immune cycle. They may boost up growth of tumor cells and arrest an immune response [50-52]. Further studies will make it clear what rebalancing and skewing of myeloid cells ZIKV treatment ushers in.

GSDMD-mediated cell death by ZIKV protease:

ZIKV is reported to be an oncolytic virus as it destroys human GBM by GSDMD activation mediated by viral protease. This cleavage is species-specific. This suggests that human GSDMD transgenic mice models, i.e., humanized animals, never a simple GBM mice model would provide assuring experimental outcomes of preclinical trials on ZIKV oncotherapy [53].

GSDMD, is a novel biomarker to evaluate the progression of cancer due to an elevated level of protein expression in glioma and it is reported to be connected with significant longevity of GBM patients [54]. Pyroptosis mediated by GSDMD accompanies the pro-inflammatory cytokine, IL-1β release that helps in supporting immune response against carcinoma mediated by the T helper 1 cells specific to the particular tumor [55, 56]. The mature IL-1β release by conventional pyroptosis is due to caspase-4/5/11 or caspase-1- mediated cleavage of GSDMD that in turn ensures the release of GSDMD-N to perforate the plasma membrane [57]. Because caspase-3-mediated GSDMD-N cleavage negatively regulates the process, infection-elicited caspases may manipulate the pyroptosis activated by ZIKV protease [58].

Overexpression of E protein of ZIKV alone is adequate for suppressing proliferation of cells as well as in inducing caspase-mediated programmed cell death [59]. In the 3' untranslated region of viral genome deletion of 10-nt generates a live-attenuated strain of ZIKV both in vivo and in vitro. This strain was suggested as a vaccine candidate for treatment against ZIKV as well as to treat malignant GBM [60, 61].

Among several cytokines and proteins that are secreted following ZIKV infection, the release of GSDMD-N is a matter of interest. Upon release GSDMD-N may cause harm to the uninfected cancer cells for expanding the therapeutic effects as well as to the normal healthy tissues for generating side effects. Taking into consideration that GBM is not a liquid tumor but a solid one, with secretion of GSDMD-N locally and capability of ZIKV replication, a little dosage of ZIKV would be enough for the treatment. The extracellular GSDMD-N is reported to aid patients having brain tumor and are vulnerable to bacterial infection as GSDMD peptide is antibacterial [62, 63].

Oncolytic Activity against Glioblastoma Stem Cells

ZIKV infects and kills glioblastoma stem cells (GSCs) preferentially compared to normal neuronal cells or differentiated tumor progeny. This effect of ZIKV against GSCs is not a common property of neurotropic flaviviruses. West Nile Virus kills both normal and tumor neural cells indiscriminately. ZIKV depletes patient-derived GSCs potently that are grown in culture or in organoids. Moreover, mice having glioblastoma survive considerably longer and at higher rates up on inoculation of the tumor with a mouse-adapted strain of ZIKV [64, 65].

ZIKV, an oncolytic virus, targets GSCs preferentially, so genetically engineered strains can further optimize safety, thereby increasing the therapeutic efficacy for glioblastoma patients.

ZIKV is reported to target GSCs via a SOX2-Integrin αvβ5 Axis. Integrin αvβ5 is a marker of GSC, so it promotes infection of GSCs by ZIKV. SOX2 ascertains vulnerability to ZIKV infection having reduced antiviral responses [66].

ZIKV, having increased cytosine phosphate–guanine (CpG) recoding in viral genome, shows higher infectivity as well as oncolytic activity in GSCs that was recorded by reduction in cell proliferation; whereas nonmalignant brain cells have reduction in infection kinetics [67].

Future Perspectives:

Whether the caspase profiles induced by ZIKV or particular caspase inhibitors have any effect on the therapeutic outcomes of anti-tumor treatment using ZIKV is to be investigated further. Virulence factors that contribute to cell death induced by ZIKV must be detected for providing the basis of applying ZIKV. Therefore, to do away with any unpredictability regarding other ZIKV constituents, attenuated single-round infectious particles or nanoparticles harboring GSDMD-N or the ZIKV protease should be safe and sound in comparison to the live virus to treat cancer [52, 68, 69].

To date, clinical trials based on ZIKV virotherapy have not yet been conducted for cancer treatment. Coexistence of pros and cons can cause complications in the virotherapy. An appropriate animal model to study ZIKV therapy for treating human GBM is yet to be developed. It was demonstrated that activation of GSDMD by ZIKV protease is associated with the prognosis as well as management of ZIKV virotherapy. The genetic background of GSDMD could be utilized for screening positive responders to conduct virotherapy. When ZIKV infection is out-of-control, for stopping the therapy our target should be ZIKV protease. Nonetheless, the small molecules that are reported to regulate the activation of GSDMD might terminate the virotherapy that is not dependent on the activity of ZIKV protease. Until a profound understanding regarding the mechanisms underlying cell lysis induced by ZIKV is obtained, this study will provide a base of reference for preclinical assessment to predict therapeutic outcomes as well as the probable influence of effects of treatment that are combined with medicines targeting oligomerization of GSDMD or activity of caspases [52, 70, 71].

Limitations:

It was demonstrated in the previous work that the replication of ZIKV is hugely self-limited to Glioblastoma Stem Cells, partly due to their intrinsically enervated innate immune response as well as important integrin signaling molecules expression that ensure infection, the most important concern is safety [72, 73].

It was reported that the protease 3C of the enterovirus stops pyroptosis by cleaving GSDMD-N further, so oncotherapy using ZIKV would prove to be complicated if the coinfecting microbes are able to antagonize activation of GSDMD [72].

CONCLUSION:

In a nutshell we can comment that ZIKV is potentially an emerging tool for the treatment of Glioblastoma. Natural property of ZIKV will be exploited to destroy the unnatural outcomes of Glioblastoma [74, 75].

REFERENCES:

1. Stupp R, Hegi ME, Mason WP, Van Den Bent MJ, Taphoorn MJB, Janzer RC. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459–466.
2. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA. 2017;318(23):2306–2316.
3. Lathia JD, Mack SC, Mulkearns-Hubert EE, Valentim CL, Rich JN. Cancer stem cells in glioblastoma. Genes Dev. 2015;29(12):1203–1217.
4. Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science. 2014;344(6190):1396–1401.
5. Bao S, Wu Q, McLendon R, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006;444(7120):756–760.
6. El Andaloussi A, Lesniak MS. An increase in CD4+CD25+FOXP3+ regulatory T cells in tumor-infiltrating lymphocytes of human glioblastoma multiforme. J Neurooncol. 2006;8(3):234–243.
7. Han S, Zhang C, Li Q, Dong J, Liu Y, Huang Y, et al. Tumour-infiltrating CD4(+) and CD8(+) lymphocytes as predictors of clinical outcome in glioma. Br J Cancer. 2014;110(10):2560–2568.
8. Raychaudhuri B, Rayman P, Huang P, Grabowski M, Hambardzumyan D, Finke JH, et al. Myeloid derived suppressor cell infiltration of murine and human gliomas is associated with reduction of tumor infiltrating lymphocytes. J Neurooncol. 2015;122(2):293–301.

9. Raychaudhuri B, Rayman P, Ireland J, Ko J, Rini B, Borden EC, et al. Myeloid-derived suppressor cell accumulation and function in patients with newly diagnosed glioblastoma. Neuro Oncol. 2011;13(6):591–599.
10. Gielen PR, Schulte BM, Kers-Rebel ED, Verrijp K, Bossman SAJFH, Laan MT, et al. Elevated levels of polymorphonuclear myeloid-derived suppressor cells in patients with glioblastoma highly express S100A8/9 and arginase and suppress T cell function. Neuro Oncol. 2016;18(9):1253–1264.
11. Woroniecka KI, Rhodin KE, Chongsathidkiet P, Keith KA, Fecci PE. T-cell dysfunction in glioblastoma: applying a new framework. Clin Cancer Res. 2018;24(16):3792–3802.
12. Stoyanov GS, Lyutfi E, Georgieva R, Georgiev R, Dzhenkov DL, Petkova L, et al. Reclassification of glioblastoma multiforme according to the 2021 World health organization classification of central nervous system tumors: a single Institution report and practical significance. Cureus. 2022;14(2):e21822.
13. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance bypreferential activation of the DNA damage response. Nature. 2006;444:756–760.
14. Alvarado AG, Thiagarajan PS, Mulkearns-Hubert EE, Silver DJ, Hale JS, Alban TJ, et al. Glioblastoma cancer stem cells evade innate immune suppression of self-renewal through reduced TLR4 expression. Cell Stem Cell. 2017;20(4):450–461.e4.
15. de Araújo TVB, Ximenes RA de A, Miranda-Filho D de B, Souza WV, Montarroyos UR, Melo d APL, et al. Association between microcephaly, Zika virus infection, and other risk factors in Brazil: Final report of a case-control study. Lancet Infect Dis. 2017;18(3):328–336.
16. Krauer F, Riesen M, Reveiz L, Oladapo OT, Martínez-Vega R, Porgo TV, et al. Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain–Barré Syndrome: Systematic Review. PLoS Med. 2017; 14(1):e1002203.
17. Musso D, Ko AI, Baud D. Zika Virus Infection – After the Pandemic. N Engl J Med. 2019;381(15): 1444-1457
18. Huang Y-JS, Higgs S, Horne KM, Vanlandingham DL. Flavivirus-mosquito interactions. Viruses. 2014; 6(11): 4703–4730.
19. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016;374(16):1552–1563.
20. Wang A, Thurmond S, Islas L, Hui K, Hai R. Zika virus genome biology and molecular pathogenesis. Emerg Microbes Infect. 2017;6(1):1-6.

21. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat. Rev. Drug Discov. 2015;14:642–662.
22. Peruzzi P and Chiocca EA. Viruses in cancer therapy - from benchwarmers to quarterbacks. Nat Rev Clin Oncol. 2018;15(11):657-658.
23. Choudhury SR, Hudry E, Maguire CA, Sena-Esteves M, Breakefield XO, Grandi P. Viral vectors for therapy of neurologic diseases. Neuropharmacology. 2017;120:63–80.
24. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: a new era of cancer treatment at dawn. Cancer Sci. 2016;107(10):1373-1379.
25. Foreman PM, Friedman GK, Cassady KA, Markert JM. Oncolytic virotherapy for the treatment of malignant glioma. Neurotherapeutics. 2017;14(2):333–344.
26. Araujo AQC, Silva MTT, Araujo APQC. Zika virus-associated neurological disorders: a review. Brain. 2016;139(8):2122–2130.
27. Parra B, Lizarazo J, Jiménez-Arango JA, Zea-Vera AF, González-Manrique G, Vargas J, et al. Guillain-barre syndrome associated with Zika virus infection in Colombia. N Engl J Med. 2016;375:1513-1523.
28. Kaid C, Goulart E, Caires-Júnior LC, Araujo BHS, Soares-Schanoski A, Bueno HMS, et al. Zika virus selectively kills aggressive human embryonal CNS tumor cells in vitro and in vivo. Cancer Res. 2018;78(12):3363–3374.
29. Nair S, Mazzoccoli L, Jash A, Govero J, Bais SS, Hu T, et al. Zika virus oncolytic activity requires CD8+ T cells and is boosted by immune checkpoint blockade. JCI Insight. 2021;6(1):e144619.
30. Chen L, Zhou C, Chen Q, Shang J, Liu Z, Guo Y, et al. Oncolytic Zika virus promotes intratumoral T cell infiltration and improves immunotherapy efficacy in glioblastoma. Mol. Ther. Oncolytics. 2022;24:522–534.
31. Zhu Z, Mesci P, Bernatchez JA, Gimple RC, Wang X, Schafer ST, et al. Zika virus targets glioblastoma stem cells through a SOX2-Integrin alphavbeta5 Axis. Cell Stem Cell. 2020;26(2):187-204.
32. Zwernik SD, Adams BH, Raymond DA, Warner CM, Kassam AB, Rovin RA, et al. AXL receptor is required for Zika virus strain MR-766 infection in human glioblastoma cell lines. Mol. Ther. Oncolytics. 2021;23:447–457.
33. Lippa RA, Barrett J, Pal S, Rowedder JE, Murphy JA, Barrett TN. Discovery of the first potent and selective αvβ5 integrin inhibitor based on an amide-containing core. Eur. J. Med. Chem. 2020;208:112719.

34. Goodman SL, Grote HJ, Wilm C. Matched rabbit monoclonal antibodies against αv-series integrins reveal a novel αvβ3-LIBS epitope, and permit routine staining of archival paraffin samples of human tumors. Biol. Open. 2012;1(4):329–340.
35. Aglietti RA and Dueber EC. Recent insights into the molecular mechanisms underlying pyroptosis and gasdermin family functions. Trends Immunol. 2017;38(4):261–271.
36. Broz P, Pelegrín P and Shao F. The gasdermins, a protein family executing cell death and inflammation. Nat. Rev. Immunol. 2020;20:143–157.
37. Shi Y, Dai L, Song H, Gao GF. Structures of Zika Virus E & NS1: Relations with Virus Infection and Host Immune Responses. Adv Exp Med Biol. 2018;1062:77-87.
38. Chambers TJ, Hahn CS, Galler R, Rice CM. Flavivirus genome organization, expression, and replication. Annu Rev Microbiol. 1990;44:649–688.
39. Bernatchez JA, Tran LT, Li J, Luan Y, Siqueira-Neto JL, Li R. Drugs for the Treatment of Zika Virus Infection. J Med Chem. 2020;63(2):470–489.
40. Ngono AE and Shresta S. Immune Response to Dengue and Zika. Annu. Rev. Immunol. 2018;36:279–308.
41. Cox BD, Stanton RA, Schinazi RF. Predicting Zika virus structural biology: Challenges and opportunities for intervention. Antivir Chem Chemother. 2015;24(3-4):118–126.
42. Van Leur SW, Heunis T, Munnur D, Sanyal S. Pathogenesis and virulence of flavivirus infections. Virulence. 2021;12(1):2814–2838.
43. Peng D, Kryczek I, Nagarsheth N, Zhao L, Wei S, Wang W, et al. Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy. Nature. 2015;527(7577):249–253.
44. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signaling prevents anti-tumour immunity. Nature. 2015;523(7559):231–235.
45. Tang H, Wang Y, Chlewicki LK, Zhang Y, Guo J, Liang W, et al. Facilitating T cell infiltration in tumor microenvironment overcomes resistance to PD-L1 blockade. Cancer Cell. 2016;29(3):285-296.
46. Wang C, Xie Y, Li W, Ong CP, Ding H, Yuan S, et al. Activation of PD-1/PD-L1 immune checkpoint by Zika virus. PLoS Pathog. 2025;21(9):e1013457.
47. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell. 2018;174(4):1031-1032.

48. LaRocca CJ and Warner SG. Oncolytic viruses and checkpoint inhibitors: combination therapy in clinical trials. Clin Transl Med. 2018;7(1):35.
49. Chen C-Y, Hutzen B, Wedekind MF, Cripe TP. Oncolytic virus and PD-1/PD-L1 blockade combination therapy. Oncolytic Virother. 2018;7:65–77.
50. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel). 2014;6(3):1670–1690.
51. Komohara Y, Ohnishi K, Kuratsu J, Takeya M. Possible involvement of the M2 anti-inflammatory macrophage phenotype in growth of human gliomas. J Pathol. 2008;216(1):15–24.
52. Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat Med. 2013;19(10):1264–1272.
53. Kao Y-T, Wang H-I, Shie C-T, Lin C-F, Lai MMC, Yu C-Y. Zika virus cleaves GSDMD to disseminate prognosticable and controllable oncolysis in a human glioblastoma cell model. Mol. Ther. Oncolytics. 2023;28:104–117.
54. Liu J, Gao L, Zhu X, Geng R, Tao X, Xu H, et al. Gasdermin Dis a novel prognostic biomarker and relates to TMZ response in glioblastoma. Cancers (Basel). 2021;13(22):5620.
55. He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, et al. Gasdermin D is an executor of pyroptosis and required for interleukin-1beta secretion. Cell Res. 2015;25(12):1285-1298.
56. Haabeth OAW, Lorvik KB, Yagita H, Bogen B, Corthay A. Interleukin-1 is required for cancer eradication mediated by tumor-specific Th1 cells. Oncoimmunology. 2015;5(1):e1039763.
57. Qiu S, Liu J, Xing F. 'Hints' in the killer protein gasdermin D: unveiling the secrets of gasdermins driving cell death. Cell Death Differ. 2017;24(4):588–596.
58. Taabazuing CY, Okondo MC and Bachovchin DA. Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. Cell Chem Biol. 2017;24(4):507–514.
59. Liu J, Li Q, Li X, Qiu Z, Li A, Liang W, et al. Zika virus envelope protein induces G2/M cell cycle arrest and apoptosis via an Intrinsic cell death signaling pathway in neuroendocrine PC12 cells. Int J Biol Sci. 2018;14(9):1099-1108.
60. Shan C, Muruato AE, Nunes BTD, Luo H, Xie X, Medeiros DBA, et al. A live-attenuated Zika virus vaccine candidate induces sterilizing immunity in mouse models. Nat Med. 2017;23(6):763-767.

61. Chen Q, Wu J, Ye Q, Ma F, Zhu Q, Wu Y, et al. Treatment of human glioblastoma with a live attenuated Zika virus vaccine candidate. mBio. 2018;9(5):e01683-18.
62. Kuang S, Zheng J, Yang H, Li S, Duan S, Shen Y, et al. Structure insight of GSDMD reveals the basis of GSDMD autoinhibition in cell pyroptosis. Biophys. Comput. Biol. 2017;114(40):10642-10647.
63. Cashman KS, Mistry AM, Kesarwani A, De Andrade Costa A, Daneshmand J, Rehman HU, et al. Oncolytic zika virus therapy leverages CCR2+ monocytes to boost anti-glioblastoma T cell responses. Neuro Oncol. 2026;28(6):1410-1425.
64. Zhu Z, Gorman MJ, McKenzie LD, Chai JN, Hubert CJ, Prager BC, et al. Zika virus has oncolytic activity against glioblastoma stem cells. J Exp Med. 2017;214(10):2843–2857.
65. Tinnirello R, Chinnici CM, Miceli V, Busà R, Bulati M, Gallo A, et al. Two Sides of The Same Coin: Normal and Tumoral Stem Cells, The Relevance of In Vitro Models and Therapeutic Approaches: The Experience with Zika Virus in Nervous System Development and Glioblastoma Treatment. Int J Mol Sci. 2023;24(17):13550.
66. Zhu Z, Mesci P, Bernatchez JA, Gimple RC, Wang X, Schafer ST, et al. Zika virus targets glioblastoma stem cells through a SOX2-integrin αvβ5 axis. Cell Stem Cell. 2020;26(2):187–204.e10.
67. Trus I, Berube N, Jiang P, Rak J, Gerdts V, Karniychuk U. Zika Virus with Increased CpG Dinucleotide Frequencies Shows Oncolytic Activity in Glioblastoma Stem Cells. Viruses. 2020;12(5):579.
68. Menezes D, Reis CR, Mamede I, Geddes VEV, de Souza RP, Aguiar RS. Transcriptomic Profile of Glioblastoma Cells Infected with Zika Virus: A Systematic Review and Pathway Analysis. Viruses. 2026;18(2):249.
69. Tinnirello R, Chinnici CM, Miceli V, Busà R, Bulati M, Gallo A, et al. Two Sides of The Same Coin: Normal and Tumoral Stem Cells, The Relevance of In Vitro Models and Therapeutic Approaches: The Experience with Zika Virus in Nervous System Development and Glioblastoma Treatment. Int J Mol Sci. 2023;24(17):13550.
70. Francipane MG, Douradinha B, Chinnici CM, Russelli G, Conaldi PG, Iannolo G. Zika Virus: A New Therapeutic Candidate for Glioblastoma Treatment. Int J Mol Sci. 2021;22(20):10996.
71. Han X, Du J, Li W, Yang S, Sun H, Wang G, et al. Zika virus and host protein interactions for understanding molecular mechanisms of pathogenesis and therapeutic development. Front. Cell. Infect. Microbiol. 2026;16:1754465.

72. Lubin JA, Zhang RR, Kuo JS. Zika virus has oncolytic activity against glioblastoma stem cells. Neurosurgery. 2018;82(5):E113–E114.
73. Lei X, Zhang Z, Xiao X, Qi J, He B and Wang J. Enterovirus 71 inhibits pyroptosis through cleavage of gasdermin D. J Virol. 2017;91(18):e01069-17.
74. de Sena Barbosa MG, Messias BR, Tatit RT, de Paula MCG, Júnior VBS, Braga MGB, et al. Zika virus and brain cancer: Can Zika be an effective treatment for brain cancer? A systematic review. Oncotarget. 2024;15:662-673.
75. Calderón-Peláez MA, Maradei Anaya SJ, Bedoya-Rodríguez IJ, González-Ipuz KG, Vera-Palacios D, Buitrago IV, et al. Zika Virus: A Neurotropic Warrior against High-Grade Gliomas-Unveiling Its Potential for Oncolytic Virotherapy. Viruses. 2024;16(4):561.

