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Chapter

Zika Virus for Brain Cancer Treatment?

Mateus Gonçalves de Sena Barbosa and Nicollas Nunes Rabelo

Abstract

Malignant brain tumors are among the most aggressive cancers with poor prognosis and no effective treatment despite all available therapies and technologies. The search for treatments for gliomas allowed the discovery that the Zika virus (ZIKV), a flavivirus, has a tropism for brain tumor cells and acts with an oncolytic effect, reaching brain tumors, in addition to stimulating the antitumor immunity of the host. Thus, it provides long-term immunity against cancer remission, reduces tumor burden, less metastasis and complete remission in some animals, consequently increases survival. There has been support that treatment with ZIKV against glioblastoma can be effective, suggesting a new future therapy that could revolutionize the prognosis of patients with brain tumors.

Keywords: Zika, neurotropism, glioblastoma, MSI1, AXL, oncolytic, brain cancer, brain tumor

1. Introduction

Central nervous system (CNS) tumors are pathologies that occur due to an exacerbated and disorganized cell proliferation. According to GLOBOCAN 2020, more than 300,000 new cases were recorded in 2020, with a mortality rate of 2.5%. The available treatments are neurosurgery, radiotherapy and chemotherapy [1, 2].

Glioblastomas (GBS) are considered the most aggressive and common primary brain tumor, with rapid progression and poor prognosis. Usual treatment includes neurosurgery, chemotherapy, radiation therapy, and alternative therapies that reduce neurological effects. In this case, there is no cure, so the treatment aims to increase survival with as much quality of life as possible [2–4].

Many recent studies present possible options for biochemical and intracellular pathways, therefore, the use of ZIKV is being suggested to reduce and/or inhibit the proliferation of tumor cells and induce apoptosis. Specific viral proteins and molecules have been observed in controlled and oriented studies to obtain stem cells, using attenuated vaccines, encapsulated viral fragments and viral therapy [2, 5, 6].

2. Methodology

A systematic and comprehensive literature review was performed from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science...
and SciELO, using the following keywords: “brain tumor”, “brain cancer”, “brain neoplasm”, “glioma”, “glioblastoma”, “neuroblastoma”, “stem cells”, “oncology”, “zika virus”, “oncolytic”, “oncolysis”, “treatment”, “therapy”, “immunotherapy”, “immunology”, “approach”, “outcome”, “outcome”, “vaccine” and “anticancer”. These are in combination with the Boolean operators: “AND” and “OR”. The keywords were searched in the “all fields” modality. Each article and its respective references were obtained in full and carefully analyzed.

The articles were included based on presenting scientific evidence from studies demonstrating the presence or absence of the oncolytic capacity of the zika virus against brain tumors and/or presenting the efficacy or inefficacy of this virus in the fight against brain tumors. Only articles in English, Spanish or Portuguese, without data restrictions (Figure 1).

3. Results/discussion

Table 1 contains the main objective aspects of each article selected for the qualitative synthesis. There are in vitro, in vivo and in vitro/in vivo studies. In the articles they have different signaling pathways and different biomarkers.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Title of the study</th>
<th>ZIKV strain</th>
<th>Cell lineage</th>
<th>Biomarker</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen Qi, Wu Jin, Ye Qing, et al. 2018 [7]</td>
<td>Treatment of Human Glioblastoma with a Live Attenuated Zika Virus Vaccine Candidate</td>
<td>FSS 13025/GZ01</td>
<td>GSCs specimens 387 and 4121</td>
<td>—</td>
<td>ZIKV-LAV was shown to be safe and significantly intracerebral tumor growth and reduced animal survival by selectively killing GSCs within the tumor</td>
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<tr>
<td>Crane AT, Chrostek MR, Krishna VD, et al. 2020 [8]</td>
<td>Zika virus-based immunotherapy enhances long-term survival of rodents with brain tumors through upregulation of memory T-cells</td>
<td>ZIKV H/ PF/2013</td>
<td>GL261 GBM cells; GS-9 L glioma cell line</td>
<td>—</td>
<td>ZIKV immunotherapy could be an adjuvant to tumor vaccines to intensify long-term survival, through enhanced T-cell response</td>
</tr>
<tr>
<td>Dabaja MZ, Lima EO, Oliveira DN, et al. 2018 [5]</td>
<td>Metabolic alterations induced by attenuated Zika virus in glioblastoma cells</td>
<td>ZIKVpr</td>
<td>U-251 GBM cells</td>
<td>Phospholipids², chlorinated metabolite², phosphatidylinositol-3-phosphate</td>
<td>ZVp might be an alternative treatment for GBM, given the cytopathic effects and cell damage induced on neural tumor cells</td>
</tr>
<tr>
<td>Iannolo G, Sciuto MR, Cuscino N, et al. 2019 [9]</td>
<td>Zika virus infection induces MiR34c expression in glioblastoma stem cells: new perspectives for brain tumor treatments</td>
<td>ZIKV H/ PF/2013</td>
<td>GSCs U87MG and T98G</td>
<td>CD133, SOX-2, Musashi-1, and nestin</td>
<td>ZIKV infection induced MiR34c expression and its overexpression reproduced an effect equivalent to that of infection. MiR34c can inhibit GSCs and reduce Bcl2, which could potentially enhance the effect of chemotherapy/radiotherapy.</td>
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<tr>
<td>Li M, Zhang D, Li C, et al. 2020 [10]</td>
<td>Characterization of Zika Virus Endocytic Pathways in Human Glioblastoma Cells</td>
<td>kv963796</td>
<td>Glioblastoma T98G cells</td>
<td>clathrin heavy chain</td>
<td>Viruses penetrate cells by various mechanisms, including fusion with the cell membrane or entering by receptor-mediated endocytosis. Clathrin-mediated endocytosis is the most frequently used pathway. ZIKV can enter T98G cells through not only clathrin-dependent but also clathrin-independent pathways</td>
</tr>
<tr>
<td>Luplertlop N, Suwanmanee S, Muangkaew W, et al. 2017 [12]</td>
<td>The impact of Zika virus infection on human neuroblastoma cell line (SH-SYSY)</td>
<td>SV0127/14 and SV0010/15</td>
<td>human neuroblastoma cell line (SH-SYSY)</td>
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<td>Mazar J, Li Y, Rosado A, et al. 2018 [13]</td>
<td>Zika virus as an oncolytic treatment of human neuroblastoma cells requires CD24</td>
<td>PRVABC39</td>
<td>Neuroblastoma MYCN and non-MYCN</td>
<td>NS1</td>
<td>ZIKV infection reduces cell viability. However, the permissiveness to zika virus depends on CD24 expression. It occurs mainly on high metabolic activity progenitors, not having this effect on differentiated cells</td>
</tr>
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<td>Nair S, Mazzoccoli L, Jash A, et al. 2021 [3]</td>
<td>Zika virus oncolytic activity requires CD8+ T cells and is boosted by immune checkpoint blockade</td>
<td>ZIKV-Dakar GL261 and CT2A GBM cells</td>
<td>CD8-depleting antibodies, isotype control IgG2b, antibodies against PD-1, IgG2a control</td>
<td>Histological analysis revealed comparable tumor sizes between the ZIKV and PBS groups at day 14 after tumor implantation (7 days after ZIKV treatment) but a decrease in tumor size 1 week later at day 21 after tumor implantation (14 days after ZIKV treatment) in response to ZIKV treatment. It was observed infiltration of immune cells in the tumor microenvironment at days 14 and 21 after tumor implantation in animals treated with ZIKV treatment; also increased the tumor-associated myeloid cell response in the tumor bed, particularly the monocyte and microglia populations.</td>
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<tr>
<td>Zhu Z, Mesci P, Bernatchez J, et al. 2020 [15]</td>
<td>Zika Virus Targets Glioblastoma Stem Cells through a SOX2-Integrin avb5 Axis</td>
<td>H/PAN/2016/BEI-259634 and PRVABC59 293FT Cell Line, ENSA (ENS-tem-A), NSC11, NM53, NM55, NM177, NPC C4-7, hNP1 (STEMEZ hNP1) and H1 ESC</td>
<td>avb5 integrin was shown to be a functional marker of cancer stem cells essential for maintenance of GBM and ZIKV infection</td>
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<td></td>
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</table>

Abbreviations: CNS (central nervous system), GBM (glioblastoma), MALDI (matrix laser desorption/ionization mass spectrometry imaging), ZVp (attenuated ZIKV prototype).

1Lysophosphatidic acid, oxidized phosphatidylserine and simple phosphatidylserine.

25-methyltetrahydrooptroptoyl-L-glutamate.

Table 1.
Summary of the main in vitro/in vivo studies (2017–2021) investigating the oncolytic effects of Zika virus (ZIKV) in CNS tumors.
A research carried out with the aim of understanding how human embryonic CNS tumor stem cells behave in the face of ZIKV infection. Therefore, the study focused on analyzing three embryonic CNS tumor cell lines (DAOY, USP13-MED and USP7-ATRT), as well as three non-CNS tumor cell lines from breast, colorectal and prostate cancer. All six cell lines were infected with ZIKV to assess the in vitro oncolytic effects of ZIKV infection. Seventy two hours after infection, researchers observed cell death and/or reduced growth in all CNS tumor lineages, although DAOY infection was less pronounced when compared to USP13-MED and USP7-ATRT. Flow cytometry analysis was performed and showed an increase in the population of PI-positive CNS tumor lines as a consequence of ZIKV infection, suggesting cell death by rupture of the plasma membrane. It was also stated that ZIKV infection interfered with CNS tumor spheres, mainly in CNS embryonic tumor spheres. However, a slight or no effect on oncolytic properties and tumor sphere disruption was observed in non-CNS tumor cell lines. Based on these findings, the authors proposed a selective ZIKV infection and cell death of CNS tumor cells when compared to normal CNS stem cells and other tumor cell lines (prostate, breast, colorectal). Two years later, the same author showed for the first significant remission of the CNS tumor after intrathecal injections of ZIKV BR in two dogs bearing spontaneous intracranial tumors with no clinical side effects associated with ZIKV infection [2, 6].

Then, an in vivo study was performed with intracerebroventricular injection of ZIKV in BALB/c nude mice after a period of tumor establishment in the CNS (1 to 2 weeks for DAOY, USP13-MED and USP7-ATRT cell lines). In this study, ZIKV was shown to induce remission in 20 of the 29 animals in the experimental group, with complete remission in seven mice. When compared to the sham group, the OS of USP7-ATRT tumor-bearing mice treated with ZIKV infection was statistically increased (P = 0.0046) and 60% of the group had complete metastatic remission (n = 3). Reduction of tumor growth rate in USP7-ATRT and USP13-MED was also observed, although the DAOY cell line had a poor response to ZIKV infection, which fits the in vitro findings. In addition, the study suggests that the Wnt/β-catenin pathway may be involved in cell death associated with ZIKV infection, since USP7-ATRT, the cell line with the best results, showed hyperactivity of this specific pathway [7].

It was found that ZIKV interfered in cells infected with glioblastomas, through metabolic alterations. This happened, primarily, due to the non-structural protein of the virus (NS5), which considerably inhibits tumorigenicity due to the lesion of glioma stem cells, reducing their proliferation [4]. Moreover, cardiac glycoside molecules, such as digoxin, observed early in ZIKV infection, have already shown good results in patients with neuroblastoma, melanoma and breast cancer [11]. It has also been shown to increase p536 activity.

It was evidenced that the virus could act positively on other types of cancer, such as medulloblastoma, prostate, breast and rhabdoid teratoid tumor, however, they obtained good specific results for the central nervous system, especially the rhabdoid teratoid tumor, since they originate from cells -stem and neuroprogenitors, which are parts of greater tropism for the virus [6]. In another study, significant efficacy was observed for the treatment of neuroblastoma, in which the virus dominated most tumor cells in a few days [13].

Furthermore, tumor remission was observed in mice that survived glioblastoma by vaccination with cells previously infected with ZIKV and by intracranial injections of live attenuated virus or by previously infected cells. In this group, they obtained the possibility of long-term immunization from the generation of memory T cells, with significant survival. Therefore, ZIKV can contribute to the development of vaccines [8]. Another study showed that just one intracerebroventricular injection in
mice was enough to reduce viral load, increase survival and reduce the incidence of remission and metastasis [6].

GBM has the characteristic of suppressing apoptosis pathways mediated by caspase activation, it was denoted that ZIKV infection induced the inhibition of the development of genes responsible for the maintenance and proliferation of tumor cells, such as NOTCH and NUMB. In addition, it decreased the expression of Bcl2, which may be responsible for the apoptotic response, with a reduction in NUMB, reducing AKT phosphorylation in glioblastoma cell lines. Down-modulation of NUMB induces p73 degradation in a proteasome-dependent manner. P73 has been found to confer an invasive phenotype on glioblastoma cells, and its deletion impairs invasion and chemoresistance in animal models and glioblastoma patients, with prolonged survival [9].

One study presented the analysis in GSCs and showed that there was an induction of miR34c production, consequently reducing the growth of these cells and regulating the expression of Bcl2 and NUMB, mimicking the same effect perceived in ZIKV infection. The answer obtained was that there is a reduction in tumor growth, promoting oncolytic activity in the treatment of GBM [9]. However, the ability of GBM to resist ZIKV activity in vivo still needs to be studied [14], it was noticed that some strains of GSC in vitro derived from CpG recoding in a ZIKV viral genome, using dinucleotide implementation technology CpG for candidate development may have different results for the oncolytic response. This dissonance of different recoded CpG variants demonstrates that the oncolytic activity of a virus can be modulated by adjusting the number of CpG dinucleotides introduced de novo into a viral genome. Thus, oncolytic therapy still needs to understand the behavior between the CpG-encoded viruses, the tumor, the tumor environment and the host responses for this oncolytic therapy to be more effective [9, 14].

4. Conclusion

ZIKV can be highly efficient and viable for brain cancer therapy, with safety, high T cell activity and can be used in conjunction with surgery/radiotherapy to improve survival. Despite the low number of studies and quality information to support the diligence and safety of ZIKV for the treatment of CNS studies, the results demonstrate efficacy and possibility of using this treatment in the future.

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Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

Nil.
Ethical approval

The local IRB waived the need for ethical approval due to the retrospective nature of the study.

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