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POTENTIAL THERAPEUTIC EFFECT OF ZIKA VIRUS IN GLIOBLASTOMA TREATMENT

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Abstract: Since the twentieth century, humanity has been experiencing a public health reality marked by numerous mosquito-borne diseases (belonging to the arthropod class), known as arboviruses. The Zika virus has become in recent years a risk to Brazilian and international public health due to its devastating effect due to its pathogenesis but also to fetal neurological development, causing serious health problems such as microcephaly and Guillain-Barré Syndrome, but also myelitis and meningoencephalitis. However, scientists studying the Zika virus have been trying to use the agent's ability to cause infections in healthy cells to attack and destroy cancer cells, such as the case of grade IV astrocytoma known as Gliobastoma Multiforme (GBM), which is a tumor of the very aggressive central nervous system and worse prognosis among primary cancers. As a result of effective therapy for GBM and the tropism of this etiological agent for brain cells, the hypothesis is that this virus would cause cell death in glioblastomas through metabolic alterations induced by the induced viral infection, but further studies must be carried out to demonstrate this therapeutic advantage in using the virus for the treatment of this malignant disease.

Keywords: Zika virus; Gliobastoma Multiforme; Tumor of the Central Nervous System.

Introduction

The Zika virus is a mosquito-borne flavivirus and was first identified in monkeys in Uganda in 1947.[1,2] The virus subsequently spread to Asia and from there to the Americas.[3] The first major outbreak of the disease caused by the Zika infection was reported on the island of Yap (Federated States of Micronesia) in 2007.[1] It is an arbovirus (arthropod virus) belonging to the Flaviviridae family and to the genus Flavivirus.[4]

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The majority of human infections by Zika are transmitted by the vector, however, it can also be transmitted directly through sexual contact and vertically from the mother to the fetus, in addition to body fluids.[2,4]

The Zika virus has recently emerged as a major public health risk because of its devastating effect on fetal neurological development.[3] In July 2015, Brazil reported an association between the virus infection and Guillain-Barré syndrome, in addition to the notification of the association between infection by this agent and microcephaly.[1,2,5] Infection by this agent was correlated with myelitis and meningoencephalitis.[2,5]

Scientists studying the virus have long sought to harness the agent's power to cause diseases in healthy cells and engineering to attack and destroy cancer cells, such as grade IV astrocytoma known as GBM (glioblastoma multiforme) .[5] The potential therapeutic application of virus for the treatment of cancer is a mature concept and the aim is to induce the preferential viral infection in tumor cells and to minimize immunosuppressive responses in normal cells.[6,7]

Glioblastoma has an annual incidence rate of 6 per 100,000 and accounts for about 27.5% of all primary brain tumors and 80% of all primary malignant brain tumors.8 Glioblastoma (GBM), the most common malignant glioma, is an aggressive brain cancer with a poor prognosis, presenting an unfavorable natural history.[9,10] Characteristics that contribute to its reserved prognosis include its relative resistance to traditional therapy; physiological isolation of the tumor due to the blood-brain barrier; the infiltrative nature of these tumors; and identification of cancer stem cells with the ability to self-renew.[11]

Since the first study on the possibility of using oncolytic viruses to treat glioma published 25 years ago, the number of researches with the virus and the groups studying this approach have grown.[11] Malignant gliomas may be particularly suitable for oncolytic virotherapy due to its isolated location surrounded by neurons with silent mitosis rates.[7]

Researchers at the University of Washington have shown that the Zika virus can kill stem cells in brain tumors in laboratory tests, from theorizing that as the virus affects brain stem cells from fetuses, it could also induce the death of stem cells in brain tumors.[5] Zika-infected human neural progenitor cells (NSCLCs) have increased rates of cell death and deregulation of cell cycle progression, in addition to the transcriptional deregulation associated with induction of apoptosis.[12,13] The virus efficiently targets human neural

progenitor cells (HCNPs) and attenuates their growth.[2] The Zika virus, because of its high destructiveness, was injected into the cancer cells, and twenty-four hours later the virus had already eliminated half of the tumor cells and after 48 hours, more cancer cells died, while healthy cells were not affected by the virus.

Zika's glioblastoma cell infection induces the endogenous synthesis of a molecule capable of inducing cell death by disrupting neuronal excitability, which is restricted to tumor cells.[13,14] This molecule is a cardiac glycoside, called digoxin, which induces apoptosis via the activation of Caspase-3 and ends with the generation of reactive oxygen species (ROS), and therefore all these signaling cascades together will affect DNA translation and consequently alter the synthesis of proteins that are involved with the growth, survival and control of the cell cycle.[13,14]

Given the absence of an effective treatment for GBM and the Zika tropism for brain cells along with their ability to induce neural cell death, the hypothesis formulated by the current contribution was that this agent would cause cell death in glioblastomas through metabolic changes induced by viral infection.[12]

Zika's infection

Zika's infection in skin cells in vitro is mediated by the AXL, DC-SIGN, TIM1 and TYRO3 receptors, of which TIM1 is expressed by neuronal and astrocytic progenitor cells, showing similarities between them.[12] The binding of neural RNA and Musashi-1 protein (MSI1) interacts with the viral genome and allows replication, so this interaction explains the vulnerability of nervous system cells to virus infection.[7] Brain tumor rats receiving intra-tumor injections of Zika showed prolonged survival in comparison to untreated mice.[12] As a result of an effective treatment for GBM and the tropism of this agent for brain cells, the hypothesis formulated by the current contribution was that this virus would cause cell death in glioblastomas through metabolic changes induced by viral infection.[13]

Therefore, the next step is to find out whether the virus would be able to kill human tumor cells in mice, and after a successful outcome, a clinical trial with people could be designed.[5] With the recent onset of immunotherapies in glioma, the research community is

rapidly gaining a better understanding of the composition and mechanisms of action of glioma immune fauna.[7] Together, these results suggest that Zika may have the potential as an oncolytic virus to focus on brain malignant tumors and, moreover, that the use of oncolytic viruses is a promising strategy. Therefore, additional studies should be carried out to verify the link between digoxin synthesis and Zika virus infection.[12,13] Studies aimed at establishing a better understanding of immune responses to oncolytic viruses will be required to optimize the anti-glioma effects of oncolytic viruses.

Despite the current standard of treatment, including maximal surgery resection, followed by radiotherapy and temozolomide, chemotherapy, the GBM remains with high lethality, with a median survival of only 14.6 months. It is pointed out as main responsible for this reserved prognosis the nature of the refractory GBM, characterized by its inevitable recurrence after intensive multimodality therapy. In addition, the modest improvement in survival achieved with currently approved therapies is plagued by systemic toxicities and poor health-related quality of life. It should be reported that once recurrent, the median survival is only 4-7 months.[15,16]

As cancer cells evolve to a totally malignant pattern and metastatic phenotype, they acquire multiple mutations and epigenetic modifications, creating a heterogeneous environment, resistant to standard treatment and frequently induce development in treatment refractory disease. Therefore, one of the challenges facing the cancer research community is to develop strategies that can combine and overcome the resistance mechanisms of the tumor.[17] Over the past 20 years, research has begun to identify and characterize viruses with a potential oncolytic effect for the treatment of astrocytoma grade IV.[18]

Conclusions

After the identification of stem cells for glioblastoma (GSCs) responsible for tumor renewal, it was possible to encourage research that targets these cells and is fundamental for the development of new treatments that prevent local recurrence and, at the same time, reduce neural damage adjacent. The researchers hypothesized that the virus would preferentially target GSCs rather than differentiated tumor cells and normal neuronal cells. In this way, it

would provide the selective action of zika on these target cells. Consequently, patient-derived GSCs infected with this virus would lose their ability to self-renew, decrease proliferation, and increase apoptosis when compared to differentiated glioma cells after 7 days.[15,18]

Therefore, the next step is to find out if the virus would be able to kill human tumor cells in mice, and after a successful outcome, a clinical trial with people could be designed.[5] With the recent emergence of glioma immunotherapies, the research community is rapidly gaining a better understanding of the composition and mechanisms of action of glioma immune fauna.[7] Together, these results suggest that Zika may have potential as an oncolytic virus to target tumors malignancies and, moreover, that the use of oncolytic viruses is a promising strategy. Therefore, additional studies should be carried out to verify the link between digoxin synthesis and Zika virus infection.[12,13] Studies aimed at establishing a better understanding of immune responses to oncolytic viruses will be necessary to optimize the anti-glioma effects of oncolytic viruses[6].

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