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Short Communication

The Oncolytic Effect of Zika Virus Against Glioma Stem Cells: A Promise for Treating Brain Tumors

Osama Atif*

Faculty of Science, Mansoura University, Dakahlia, Egypt

***Corresponding Author:** Osama Atif, Faculty of Science, Mansoura University, Dakahlia, Egypt.

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Glioblastoma is the most malignant primary brain tumor. Due to rapid tumor growth and invasiveness, the recurrence rate after routine surgery, radiotherapy, chemotherapy and other treatments is extremely high, and the prognosis is poor. The median survival of most patients is less than two years [1]. The cause of glioblastoma is complex, and recent research suggests that glioma blast stem cells (GSCs) may play a key role. Glioma stem cells are a group of cells with the potential of infinite proliferation, self-renewal and multi-directional differentiation, which not only participate in promoting tumor angiogenesis, but also resist the tumoricidal effect of radiotherapy and chemotherapy [2]. The new therapy with glioma stem cells as the target has become one of the most hotspots of current research.

Zika virus (ZIKV) is a new arbovirus that spread to more than 70 countries around the world after a pandemic in Brazil in 2015. Zika virus infection in adults is mild, but pregnant women infected with Zika virus can cause neonatal microcephaly, abortion, stillbirth and other serious diseases. The study found that Zika virus can penetrate the blood-fetal barrier, specifically infect and kill neural progenitor cells (NPCs), leading to abnormal development of the fetal central nervous system [3,4]. At present, the research on Zika vaccine and antiviral drugs has made significant progress, and several candidate vaccines have entered the clinical research stage [5].

Glioma stem cells have many features in common with neural precursor cells [6]. Recently, the Jeremy Rich team at the University of California collaborated with the University of Washington's Michael Diamond and the Milan Chheda team [7] to find that Zika virus can specifically infect and kill glioma stem cells, and is expected to develop into a new oncolytic virus.

First, in order to determine whether Zika virus can effectively infect glioma stem cells, the researchers compared the infectivity of two strains of Zika virus (Dakar 1984 and Brazil 2015) to human glioma stem cells from different sources. It was found that both Zika virus can effectively infect glioma stem cells and inhibit their ability to form spheroids. Zika virus infection can significantly down-regulate the glioma stem cell dry marker molecule SOX2 and the cell proliferation marker molecule Ki-67, and lead to the upregulation of the apoptosis marker molecule Caspase-3. For differentiated glioma cells (DGCs) differentiated from glioma stem cells, the infection rate of Zika virus is very low, and the effect on cell proliferation is very limited, indicating that Zika virus has obvious tropism on glioma stem cells, and poor ability to differentiate into differentiated glioma stem cells. In addition, the researchers also found that West Nile virus (WNV), a member of the Flavivirus family, is effective against both glioma stem cells and differentiated glioma cells, and infection rates and viruses. Both tumor stem cells and differentiated glioma cells can be effectively infected, and there is no difference in infection rate and virus replication level [7]. This indicates that the specific tropism of glioma stem cells is characteristic of Zika virus.

After confirming that Zika virus can specifically infect glioma stem cells at the cellular level in vitro, the researchers further validated the glioblastoma organoid model and the tumor sample of patients with glioblastoma, which are more representative of tumor cell heterogeneity. It was found that Zika virus can effectively infect SOX2-positive glioma stem cells in organs and human glioblastoma samples, and reduce glioma in glioblastoma-like organs. The proportion of stem cells leads to massive death of glioma stem cells in glioblastoma sections. In addition, the researchers also found that Zika virus is very limited in the isolation of neuronal cells and differentiated neural stem cells from the brains of patients with epilepsy; NeuN-positive neuronal cells and GFAP-positive glial cells in the brain tissue of patients with epilepsy have almost no infection ability.

On this basis, the researchers further explored the anti-tumor effect of Zika virus in mice (*Mus musculus*). They first transplanted mouse glioma cell lines (GL261 and CT-2A) into the brain of C57BL/6 mice, and after two weeks, different doses of Zika virus were used for intracerebral injection. The results showed that compared with the control group, Zika virus treatment significantly prolonged the survival time of mice and the prolonged time was positively correlated with the amount of virus. The histological examination found that Zika virus mainly infected SOX2-positive glioma stem cells in glioma, but less infection of GFAP-positive differentiated glioma cells and resulted in higher levels of apoptosis inside the tumor.

Finally, in order to clarify the molecular mechanism of Zika virus-specific for the killing of glioma stem cells, the researchers found that there are differences in the expression of a series of immune genes between glioma stem cells and differentiated glioma cells by RNA sequencing.

The expression levels of multiple type I interferon-stimulated genes (ISGs) in differentiated glioma cells were significantly higher than those in glioma stem cells. More importantly, the infection rate and killing effect of Zika virus were significantly improved after treatment of differentiated glioma cells with type I interferon antibody. The researchers speculated that Zika virus can specifically infect and kill glioma stem cells, mainly due to the lack of effective interferon signal response in glioma stem cells; Due to the strong ISGs-mediated interferon response in glioma cells, neuronal cells and glial cells, Zika virus cannot be effectively infected and replicated.

Zika virus as a pathogen that can cause serious diseases in humans, the scientific community has carried out in-depth research on its pathogenic mechanism and prevention methods. This research has taken a unique approach and skillfully utilized the specific tropism of Zika virus on glioma stem cells. It is expected to develop into a new oncolytic virus, providing a new idea for the treatment of glioblastoma. Unfortunately, the in vivo oncolytic efficacy of this study was evaluated using a mouse in situ glioma model, which failed to confirm its anti-tumor effect in animal models of patient-derived glioma stem cell transplantation. At the same time, in view of the extensive organizational tropism of Zika virus, how to develop a safer Zika virus attenuated strain by genetic engineering will become the focus of future research.

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