Oncolytic herpes simplex virus for glioblastoma

Oncolytic herpes simplex virus is one of the new promising strategy for human glioblastoma treatment. Oncolytic herpes simplex virus stimulate immune cells to release cytokines such as Interferon gamma (IFN-γ) during oncolysis, further improve tumor microenvironment (TME) and enhance therapeutic efficacy. IFN-γ plays vital role in the apoptosis of tumor cells and recruitment of tumor-infiltrating T cells. Zhu et al. hypothesized that oncolytic herpes simplex virus-1 (oHSV-1) enhanced the antitumor efficacy of novel CD70-specific chimeric antigen receptor (CAR) T cells by T cell infiltration and IFN-γ release. In this study, oHSV-1 has the potential to stimulate IFN-γ secretion of tumor cells rather than T cell secretion and lead to an increase of T cell activity, as well as CD70-specific CAR T cells can specifically recognize and kill tumor cells in vitro. Specifically, combinational therapy with CD70-specific CAR T and oHSV-1 promotes tumor degradation by enhancing pro-inflammatory circumstances and reducing anti-inflammatory factors in vitro. More importantly, combined therapy generated potent antitumor efficacy, increased the proportion of T cells and natural killer cells in TME, and reduced regulatory T cells and transformed growth factor-β1 expression in orthotopic xenotransplanted animal model of Glioblastoma. In summary, they revealed that oHSV-1 enhance the therapeutic efficacy of CD70-spefific CAR T cells by intratumoral T cell infiltration and IFN-γ release, supporting the use of CAR T therapy in Glioblastoma therapeutic strategies [1)].

Oncolytic viruses show specific targeting and killing of tumor cells and therefore provide attractive assets for cancer immunotherapy. In parallel to oncolytic viral vectors based on adenoviruses and herpes simplex viruses, oncolytic RNA viruses and particularly alphaviruses have been evaluated as delivery vehicles. Immunization studies in experimental rodent models for various cancers including glioblastoma, hematologic, hepatocellular, colon, cervix, and lung cancer as well as melanoma have been conducted with naturally occurring oncolytic alphavirus strains such as M1 and Sindbis AR339. Moreover, animals were vaccinated with engineered oncolytic replication-deficient and -competent Semliki Forest virus, Sindbis virus and Venezuelan equine encephalitis virus vectors expressing various antigens. Vaccinations elicited strong antibody responses and resulted in tumor growth inhibition, tumor regression and even complete tumor eradication. Vaccination also led to prolonged survival in several animal models. Furthermore, preclinical evaluation demonstrated both prophylactic and therapeutic efficacy of oncolytic alphavirus administration. Clinical trials in humans have mainly been limited to safety studies so far [2)].

The unique oncolytic herpes simplex virus (oHSV) property to target multiple components of DNA damage response (DDR) generates cancer selective sensitivity to PARP inhibitor . This combination of oHSV with PARP i is a new anticancer strategy that overcomes the clinical barriers of PARP i resistance and DNA repair proficiency and is applicable not only to glioblastoma, an invariably lethal tumor, but also to other tumor types [3)].

Esaki et al. hypothesized that oHSV and TGF-β inhibitors would synergistically exert anti-tumor effects for recurrent Glioblastoma.

They established a panel of patient-derived recurrent tumor models from Glioblastomas that relapsed

after post-surgical radiation and chemotherapy, based on GSC-enriched tumor sphere cultures. These GSCs are resistant to the standard-of-care temozolomide but susceptible to oHSVs G47Δ and MG18L. Inhibition of TGF-β receptor kinase with selective targeted small molecules reduced clonogenic sphere formation in all tested recurrent GSCs. The combination of oHSV and TGF-βR inhibitor was synergistic in killing recurrent GSCs through, in part, an inhibitor-induced JNK-MAPK blockade and increase in oHSV replication. In vivo, systemic treatment with TGF-βR inhibitor greatly enhanced the anti-tumor effects of single intratumoral oHSV injections, resulting in cures in 60% of mice bearing orthotopic recurrent Glioblastoma. These results reveal a novel synergistic interaction of oHSV therapy and TGF-β signaling blockade, and warrant further investigations aimed at clinical translation of this combination strategy for Glioblastoma patients [4].

We show that oHSV-TRAIL modulates cell survival and MAP Kinase proliferation signaling pathways as well as DNA damage response pathways in both primary and recurrent TMZ-resistant GSC. Utilizing real-time in vivo imaging and correlative immunohistochemistry, we show that oHSV-TRAIL potently inhibits tumor growth and extends survival of mice bearing TMZ-insensitive recurrent intracerebral GSC tumors via robust and selective induction of apoptosis-mediated death in tumor cells, resulting in cures in 40% of the treated mice. In comparison, the anti-tumor effects in a primary chemoresistant GSC Glioblastoma model exhibiting a highly invasive phenotype were significant but less prominent. This work thus demonstrates the ability of oHSV-TRAIL to overcome the therapeutic resistance and recurrence of Glioblastoma, and provides a basis for its testing in a Glioblastoma clinical trial [5]

1)
Zhu G, Zhang J, Zhang Q, Jin G, Su X, Liu S, Liu F. Enhancement of CD70-specific CAR T treatment by IFN-γ released from oHSV-1-infected glioblastoma. Cancer Immunol Immunother. 2022 Mar 6. doi: 10.1007/s00262-022-03172-x. Epub ahead of print. PMID: 35249119.
2)
Lundstrom K. Oncolytic Alphaviruses in Cancer Immunotherapy. Vaccines (Basel). 2017 Apr 12;5(2). pii: E9. doi: 10.3390/vaccines5020009. Review. PubMed PMID: 28417936; PubMed Central PMCID: PMC5492006.
3)
Ning J, Wakimoto H, Peters C, Martuza RL, Rabkin SD. Rad51 Degradation: Role in Oncolytic Virus-Poly(ADP-Ribose) Polymerase Inhibitor Combination Therapy in Glioblastoma. J Natl Cancer Inst. 2017 Mar 1;109(3):1-13. doi: 10.1093/jnci/djw229. PubMed PMID: 28376211.
4)
Esaki S, Nigim F, Moon E, Luk S, Kiyokawa J, Curry W, Cahill DP, Chi AS, Iafrate AJ, Martuza RL, Rabkin SD, Wakimoto H. Blockade of transforming growth factor-β signaling enhances oncolytic herpes simplex virus efficacy in patient-derived Glioblastoma recurrence models. Int J Cancer. 2017 Aug 12. doi: 10.1002/ijc.30929. [Epub ahead of print] PubMed PMID: 28801914.
5)
Jahan N, Lee JM, Shah K, Wakimoto H. Therapeutic targeting of chemoresistant and Glioblastoma recurrence stem cells with a proapoptotic variant of oncolytic herpes simplex virus. Int J Cancer. 2017 May 31. doi: 10.1002/ijc.30811. [Epub ahead of print] PubMed PMID: 28567859.