Vasculostatin-armed oncolytic herpes virus decreased bevacizumab-induced glioma invasion by regulating CCN1 and AKT signaling pathway

Yusuke Tomita M.D.[1], Kazuhiko Kurozumi M.D., Ph.D.[1], Ji Young Yoo Ph.D.[2], Kentaro Fujii M.D., Ph.D.[1], Tomotsugu Ichikawa M.D., Ph.D.[3], Yuji Matsumoto M.D.[1], Atsuhito Uneda M.D.[1], Yasuhiko Hattori M.D.[1], Yoshihiro Otani M.D., Ph.D.[2], Balveen Kaur Ph.D.[2], Isao Date M.D., Ph.D.[1]

[1]Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[2]Department of Neurosurgery, University of Texas Health Science Center at Houston, Houston, Texas, USA

[3] Department of Neurosurgery, Kagawa Prefectural Central Hospital, Kagawa, Japan

[Introduction]The molecular-targeting therapeutic agent taking vascular endothelial growth factor (VEGF) as a target has demonstrated convincing therapeutic benefit in glioblastoma patients, whereas anti-VEGF therapy has also been reported to induce glioma invasion. Oncolytic viral therapy with herpes virus is an emerging biological treatment modality, and the effectiveness of combination therapy with oncolytic virus and molecular targeting drugs has been reported. In this study, we evaluated the effects of a oncolytic herpes simplex virus on the glioma invasion induced by anti-VEGF therapy. [Methods] Rapid Antiangiogenesis Mediated By Oncolytic virus (RAMBO) is used as oncolytic virus, which is composed of the cDNA encoding for human vasculostatin (Vstat120), driven by the HSV-1 IE4/5 promoter, within the backbone of an attenuated HSV-1 virus (HSVQ). We used bevacizumab as an anti-VEGF therapeutic agent. The effect of the combination of RAMBO with bevacizumab *in vitro* was assessed by cytotoxicity, migration, and invasion assays. For *in vivo* experiments, glioma cells were stereotactically injected into the brain of nude mice. Seven days after tumor implantation, RAMBO was injected into the tumor and then bevacizumab was administered intraperitoneally twice per week. [Results] RAMBO significantly reduced both the migration and invasion of glioma cells induced by bevacizumab. In mice treated with a combination of bevacizumab and RAMBO, the survival time was significantly longer and the depth of tumor invasion was significantly smaller than those treated with bevacizumab as monotherapy. Bevacizumab increased the expressions of cysteine-rich protein 61 (CCN1) and phosphorylation of AKT that were decreased by combination therapy. [Conclusion] RAMBO suppressed bevacizumab-induced glioma invasion *in vitro* and *in vivo*. RAMBO and bevacizumab combination increased anti-tumor effect. These results may lead to a promising treatment strategy of malignant glioma.