Innovative Combination Therapy for Treating Brain Tumors: Using Avatar Models to Help Improve Patient Outcomes

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Glioblastoma (GBM), the most malignant brain tumor, remains nearly universally fatal despite aggressive cancer treatment involving surgery, radiation and temozolomide (TMZ) chemotherapy. TMZ rapidly loses efficacy due to acquired chemoresistance; tumors stop responding to TMZ, typically leading to death within two years. An animal avatar model of human GBM was created to test my hypothesis that specially engineered microRNA in transport vesicles, called exosomes, and focused ultrasound (FUS), could enhance TMZ's efficacy by preventing chemoresistance. Beginning with in vitro proof of concept experiments, I tested whether these genetically engineered exosomes, CEC-m214-exos, plus TMZ, could more effectively fight human GBM cell lines compared to TMZ alone. Next, avatars mimicking actual GBM patients were created by neurosurgically implanting human GBM cells into nude rat brains and then measuring tumor response. I then used FUS to open the blood-brain barrier (BBB) to allow a higher concentration of drug and microRNA exosomes to reach targets inside the brain. The treatment procedures in this project were designed by the principal investigator of the lab, and I independently conducted the experiments. In vitro combination therapy demonstrated enhanced TMZ efficacy. In my in vivo avatar animal model, TMZ + CEC-m214-exos + FUS combination therapy led to a dramatic 77x tumor volume reduction and more than doubled survival compared to controls, with 28% longer survival compared to standard TMZ treatment alone. A combination of TMZ, microRNA-exosomes, and FUS can more effectively treat GBMs in an avatar animal model, providing credible scientific evidence to launch clinical trials and potentially translate these findings to the clinic, offering more hope to patients.

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