Glioblastoma (GBM) is the most common malignant primary brain tumor and one of the most lethal human cancers, with a median survival of less than 16 months for treated patients (1). Various biological properties of GBMs contribute to the failure of current treatments, including the relative radiation/drug resistance of the glioma stem cell (GSC) subpopulation, intratumoral clonal heterogeneity, extreme sensitivity of the normal brain tissue to toxicities of various therapeutic modalities, and the presence of the blood–brain barrier, limiting systemic delivery of antitumor agents (2–4).

Perhaps the most vexing and deadly property of GBMs, however, is their ability to diffusely and extensively infiltrate into surrounding normal cerebrum from the onset of the disease. Unlike systemic malignancies, GBMs rarely metastasize but rather kill patients by extensive tumor invasion. This diffuse tumor invasion into normal cerebrum limits the extent of surgical resection and other focally based therapies without causing unacceptable neurological morbidity.

Given the lack of effective GBM therapies, investigators have looked to many novel strategic approaches, including viral-based gene transfer. The earliest of such approaches used murine retroviruses, with the first human gene therapy trials for cancer conducted in patients with recurrent GBM (5). The results of the trial were disappointing: minimal retroviral transduction of GBM cells occurred immediately adjacent to the implanted, immobile retroviral packaging cell lines. This limited transduction efficiency led to a decade of developing cell-free–based viral and nonviral gene delivery vectors with the hope that these small vectors would more widely distribute throughout the brain and brain tumor. Unfortunately, subsequent clinical trials of various viral vectors (eg, adenoviral, adeno-associated, lentiviral based vectors) and nonviral-based vectors (eg liposomes) delivered by several direct intracerebral delivery techniques (eg, direct injection, diffusion, convection enhanced delivery) resulted in the same problem of limited distribution vector-mediated gene transduction (6).

The low-efficiency vector transduction led to the development of conditional replication competent cytotoxic viral vectors that could preferentially replicate in and kill glioma tumor cells but not normal cells. Although various viruses have been used (eg adenoviral, polio-virus), herpes simplex–based vectors have generated the greatest amount of attention given their natural neurotropism, cytotoxicity in replication-competent cells and the relative ease of constructing vector mutants that replicate selectively in tumor cells. Unfortunately, the early results from clinical trials of replication conditional herpes simplex–based viral vectors have been similarly disappointing (7).

Attempts to find a more efficient strategy for vector distribution within the brain led to the preclinical observation that both neural and mesenchymal stem cells (MSC) could preferentially migrate to areas of glioma when injected at distant sites within the brains of experimental animals. Various investigators have published data demonstrating the ability of these “cellular stem cell vectors” to deliver antitumor therapeutic genes to GBM cells in preclinical models (8,9).

The article in this issue of the Journal by Duebgen and colleagues describes a strategy for combining replication conditional viral vectors and cellular stem cell vectors for the purpose of increasing the efficiency of viral transduction of target cells (10). These investigators demonstrate that human MSCs preloaded with an oncolytic herpes simplex virus (MSC-oHSV) more efficiently killed cocultured GBM cell lines in vitro compared with oHSV placed directly on tumor cells. They further demonstrated how filling a postsurgical cavity with MSC-oHSV encapsulated in a biocompatible synthetic extracellular matrix allows greater vector efflux into the wall of the cavity compared with direct vector injection. Finally, Duebgen and colleagues demonstrate that MSCs preloaded with both oHSV and a herpes simplex virus vector that expresses the death receptor ligand TRAIL can overcome herpes simplex virus resistance in vitro.

The clever strategies used by Duebgen and colleagues may bring us closer to successful use of vector-based therapies of malignant gliomas; however, outstanding questions and challenges remain. First, despite these and other authors having demonstrated the ability of stem cell–based vectors to move toward intracerebral implanted bulk xenograft tumors in vivo, they have yet to use a glioma model that recapitulates the highly invasive biology found in human GBMs in situ. Therefore, it is important for investigators to use a more invasive glioma model system, such as those based on primary human GBM-derived GSCs, to evaluate the ability of their MSC-oHSV vectors to reach infiltrative glioma cells at a distance from the initial injection. Once that is shown, it will be necessary to see if the cellular vectors can effectively transduce replicating herpes simplex virus into these singular glioma cells when surrounded by hundreds to thousands of vector replication resistance postmitotic normal host cells.

The clinical application of Duebgen and colleagues’ strategy represents greater challenges. For instance, the authors only demonstrated a survival advantage of mice in a post-resection model in which 200,000 MSC-oHSV cells were used to treat only tens to hundreds of thousands residual glioma cells. By contrast, the number of GBM cells at the time of recurrence in a human brain is probably two to three orders of magnitude greater than the animal model. Does this imply that tens to hundreds of millions of MSC-oHSV cells will need to be injected into human brains to achieve
a similar antitumor effect? Additionally, would the MSV-oHSV cells survive long enough with their replicating herpes simplex virus load to reach the relatively long distances the cellular vectors would need to travel in the human brain to reach the extensively infiltrating glioma cells? Finally, even if enough MSC-oHSV cellular vectors could be produced, safely injected into the human brain, and survive long enough in a human brain to reach the GBM cells, there is concern for how the immune system might react to a process whereby millions of MSC cells are carrying millions to billions of herpes viral particles diffusely spread throughout the brain (eg, a clinical scenario analogous to a viral encephalitis).

In conclusion, Duebgen and colleagues have helped push the field of viral- and cellular-based vector delivery for malignant gliomas forward with their novel strategic approach as outlined in this issue of the Journal. Nevertheless, their strategy requires further preclinical testing in a more clinically relevant and challenging model of GBM. Even if such hurdles are overcome, the scale-up to the clinical use of such a therapeutic strategy will face a number of pragmatic, logistical, and safety issues that will need to be addressed. Thus, although cellular- and vector-based therapy of malignant gliomas remains a hopeful prospect, there is still work to be done.

References

Notes
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