

NEURO-ONCOLOGY

EDITORIAL

Stem Cells for Treating Glioblastoma: How Close to Reality?

It is widely acknowledged that the incurable nature of glioblastoma (GBM) is primarily attributable to the infiltrative growth of the cancer. This makes *complete* surgical resection at best unlikely and necessitates that adjunctive therapies must eradicate all residual tumor cells in the brains of affected patients to prevent tumor recurrence. Moreover, this should ideally be accomplished while causing as little damage to the normal brain as possible. The history of translational research toward this end now spans more than 50 years, with only incremental improvements in extending glioblastoma patients' lives.

This slow progress has not been due to a lack of creative approaches for treating GBM. To the contrary, innovative therapeutic approaches have proliferated in recent years. Nonetheless, results from the clinical trials associated with these approaches have proven GBM to be a formidable and therapy-resistant foe. We are currently testing targeted therapies, and it is teaching us about the importance of tailoring therapies to individuals. Perhaps in the not-too-distant future, the ability to obtain comprehensive tumor molecular profiles in a clinically meaningful time frame will coalesce with a sufficiently large body of knowledge regarding the relationships between these molecular characteristics and responses to specific therapeutic regimens. Until, and if, such a time is reached, the search for broadly applicable therapies continues. The newest entrant in the field of promising approaches is the subject of this editorial.

Potential Therapeutic Applications of Stem Cells

In the current issue of *Neuro-Oncology*, Uzzaman et al. (starting on p. 102) demonstrate the potential utility of stem cells as sources for cellular-based therapy for GBM. To an extent, cellular-based therapy for cancer can be viewed as the next generation of a treatment concept involving the application of self-renewing therapeutic agents. For brain tumors, the first approach of this therapeutic strategy involves the use of replication-restricted viruses for delivering pro-drug converting enzymatic activity to tumor cells, combined with subsequent administration of pro-drug to patients. The field of viral delivery for cancer therapy remains highly active, and has seen an elaboration of viral types and viral "payloads" to achieve improved outcomes for individuals

with GBM. Nonetheless, even taking into consideration the ongoing evolution of approaches for optimizing viral therapy, numerous barriers have thus far prevented the attainment of the ultimate objective of total and specific tumor cell eradication.

Is there reason to believe that the use of stem cells and their derivatives will prove more efficacious for treating cancer than viruses? Some would say "yes" and for reasons that include the following: stem cells and their derivatives have shown extensive tropism for experimental cancers; in the case of gliomas, they have shown the ability to migrate toward outgrowing microsatellites; and stem cells can be genetically modified *in vitro* and rapidly increased.

Here, Uzzaman et al. used stem cells as producers of therapeutic astrocytes. This was accomplished by modifying the stem cell precursors so that expression of the *tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)* was under the control of a doxycycline-regulated cassette, ensuring that their astrocytic progeny would be capable of conditional expression of *TRAIL*. The key experiment in this study involved the injection of subcutaneous glioblastoma xenografts together with the stem cell-derived astrocytes; in the treatment group that was allowed to ingest doxycycline, this led to significant reductions in tumor volume, thereby inducing *TRAIL* expression in the therapeutic astrocytes.

While these are impressive results indeed, it is important to note that, just as with viruses, there are many options for the type of stem cell or stem cell derivatives to test in experimental cancer therapeutic paradigms, as well as many options to consider for cellular therapy payload. Undoubtedly it will require a substantial effort to first assess whether stem cell therapy should be used to treat GBM and, in the event of favorable indicators, to optimize this therapeutic approach. Nevertheless, the door is now cracked open and the present work has allowed a glimpse of what might be possible.

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