OXFORD

JNCI J Natl Cancer Inst, 2015, 1–2

doi:10.1093/jnci/dju368
First published online XXXX XX, XXXX
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RE: Stem Cells Loaded with Multimechanistic Oncolytic Herpes Simplex Virus Variants for Brain Tumor Therapy

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Glioblastoma multiforme (GBM) remains the most aggressive brain tumor, fatal within two years from diagnosis in most patients. Oncolytic viruses, such as oncolytic herpes simplex viruses (oHSVs), constitute a promising therapeutic approach in cancer (1). Yet, direct delivery of oHSV has shown clinical limitations in terms of efficacy. Duebgen et al. analyzed the role of oHSVs for the treatment of GBM by employing cell delivery systems based on the use of mesenchymal stem cells (MSCs) encapsulated in synthetic extracellular matrices (sECMs). Loading of MSCs with oHSVs demonstrated statistically significant advantages over direct delivery of oHSVs, in terms of efficacy, in clinical animal models of GBM (2). Engineering of oHSVs with tumor necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) molecules further enhanced antitumoral responses and led to increased survival. While the study by Duebgen et al. represents a substantial advancement on the development of therapies against GBM, we also find issues that require further consideration.

First, MSCs have demonstrated immunomodulatory roles affecting T-cells, B-cells, and dendritic cells (DCs) (3), as well as brain immunity through regulation of microglia (4). Immune cells synthesize cytokines mediating tissue inflammation, and inflammation has been linked to immune evasion, migration, and growth of several cancer types, including brain tumors (5). Therefore, the immunodeficient xenograft models used in this study might not fully recapitulate human physiology and, accordingly, the responses that MSCs might elicit in human patients. Indeed, it is widely accepted that inflammation should be considered when aiming at developing novel anticancer therapies. As MSCs can be readily isolated from rodents, autologous immunocompetent models might provide important information parallel to the use of xenograft heterologous transplantation experiments. Therefore, evaluating the role of inflammation remains critical for the future development of autologous therapies in humans, as suggested by the authors.

Second, we also wondered whether the use of oHSVs-MSCs might provide additional beneficial effects in combination with standard strategies. MSCs are sensitive to various types of anticancer drugs (6) that could provoke changes in their behavior (eg, differentiation), or even induce apoptosis. An alternative possibility is that radio and chemotherapy effectively target the differentiated tumoral mass, whereas oHSVs-MSCs might provide a beneficial effect against glioma stem cells, populations presumably resistant to conventional therapies and responsible for tumor relapse, as well as patient death upon migration into the contralateral hemisphere.

Last, TNF family members have demonstrated to drive basal glioma migration in syngeneic animal models (7). However, the study by Duebgen et al. (2) relies on the use of human cancer lines that hardly recapitulate the infiltrative properties of GBM. Therefore, it would be of interest to evaluate the antitumoral responses elicited upon TRAIL-loaded oHSVs in models more faithfully recapitulating human GBM infiltrative behavior.

Funding

Work in the laboratory of JCIB was supported by grants from the National Institutes of Health (5U01HL107442), California Institute for Regenerative Medicine, the G. Harold and Leila Y. Mathers Charitable Foundation, and The Leona M. and Harry B. Helmsley Charitable Trust 2012PG-MED002. ISM was partially supported by a Nomis Foundation postdoctoral fellowship.

Notes

The sponsors/funders had no role in the writing of this correspondence or the decision to submit it to the journal for publication.
We thank M. Schwarz for administrative support.

Received: June 21, 2014; **Accepted:** September 17, 2014

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