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NEURAL STEM/PROGENITORS AND GLIOMA STEM-LIKE CELLS HAVE DIFFERENTIAL SENSITIVITY TO CHEMOTHERAPY

To the Editor: Gong et al.¹ compared the sensitivity of embryonic neural stem cells (NSC) and adult glioma stem cells (GSC) to chemotherapy. Temozolomide (TMZ)—the most common treatment of adult gliomas—and the rarely used cisplatin (CDDP) were studied. Erlotinib and bortezomib were also included.

The clinical relevance of the particular agents selected is unclear given the lack of single agent activity in recurrent adult gliomas with the exception of TMZ. GSC are relatively quiescent, radiation and chemotherapy resistant, multipotent, and able to self-renew.^{2–5} GSC exists in brain tumors although their relative abundance and relationship with normal NSC is unclear.^{2–5} GSC are genomically unstable and the acquisition of stemness does not imply a relationship with normal NSC. The authors should have described the relationship between NSC and GSC. In addition, Gong et al. should have explained if GSC exist as a rare subpopulation within a glioma and if the cell of origin for different types of glioma affects response.

The role of NSC in adults is controversial. Gong et al.¹ reported TMZ and CDDP injure NSC while minimally affecting GSC and postulate that TMZ may result in cognitive injury and specifically memory loss. There are no current data to support this hypothesis in adults treated only with TMZ. GSC have a number of mechanisms by which resistance to therapy is manifested, including active and upregulated DNA damage repair systems; upregulated anti-apoptotic pathways; increased expression of multidrug transporters; and residence in microvascular niches.^{2–5} It is unclear whether NSC have similar therapy-resistant mechanisms.

It is also uncertain whether the NSC sensitivity to DNA-damaging agents reflects a paucity of DNA repair following genotoxic injury. The lack of correlation with MGMT and mismatch repair system seems counterintuitive as TMZ cytotoxicity is a function of cellular MGMT activity as well as proficient mismatch repair. The correlation of NSC drug sensitivity with low expression of the drug transporter system (multidrug resistance gene) is also unclear be-

cause neither TMZ nor CDDP are exported by this system.

Regarding targeted therapy, GSC showed increased drug sensitivity compared to NSC. A variety of cell signaling pathways have been characterized for GSC (Notch, ErbB1 and 2, hedgehog, Wnt/B-catenin, IL6/STAT3, and CXCR1/2) although less is known regarding NSC.⁵ Erlotinib, an ErbB1 inhibitor, preferentially affected GSC with relative sparing of NSC presumably due to overexpression of ErbB1 on GSC. In lieu of the lack of single agent activity for ErbB1 inhibitors in adult glioma is the relevance of this finding that may reflect the failure of in vitro chemosensitivity assays to predict in vivo responses in cancer and specifically glioma. The increased sensitivity of GSC to the bortezomib was postulated to reflect a paucity of proteasomes in GSC.

Peripheral nerve injury is dose limiting. This suggests that if proteasome inhibitors easily entered the CNS—none do at present—CNS-related drug injury would likely manifest. Finally, does embryonic NSC as used by Gong et al. reflect adult NSC behavior with respect to function as well as treatment sensitivity?

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Disclosure: The author reports no disclosures.

Reply from the Authors: We proposed an in vitro approach to evaluate chemotherapeutics as potential treatments for glioblastomas. We also attempted to investigate potential causes of damage to endogenous NSCs, which are responsible for maintaining active neurogenesis in the adult brain.¹

The choice of chemotherapeutics for our initial studies was based on drugs most commonly used in neuro-oncology and also those used in general oncology. This is because drugs used for non-nervous system tumors may still have significant nervous system effects. For example, although the platinum adduct agents are widely used for treatment in a variety of cancers, a current search of the clinicaltrials.gov database identifies more than 100 studies using cisplatin or carboplatin for the treatment of CNS malignancies. Moreover, the proteasome inhibitors are now integral to multiple myeloma treatment, while the epidermal growth factor receptor tyrosine kinase

inhibitors are widely used in the treatment of lung cancer.

Since the established treatment for malignant gliomas includes radiation and chemotherapy with temozolomide, it is hard to ascribe the cognitive damage our patients experienced to just one of these modalities. This underscores the need to model treatment toxicity in both in vivo and in vitro models.

Although the lack of correlation between MGMT levels, the mismatch repair system, and the NSC response to temozolomide may seem counterintuitive, there are other, multiple genes involved in TMZ resistances including several genes involved in differentiation.⁶ These complexities aside, *Abcg2*—a multidrug resistance gene which we found to have a lower expression in NSCs than in glioma stem-like cells (GSCs)—has been shown to be involved in cisplatin resistance in other cancers,⁷ and higher *Abcg2* expression was reported in TMZ-resistant GSCs.⁸

Although none of the chemotherapeutics we tested, with the exception of temozolomide, has single activity in malignant gliomas, our data suggest that erlotinib and bortezomib have the ability to preferentially target GSCs, even though a subpopulation of GSCs displayed resistance to even high doses of these targeted drugs. This is not a “failure of in vitro chemosensitivity assays to predict in vivo responses,” but rather points to a need to intelligently design a treatment cocktail for the malignant gliomas that target cells in different stages of differentiation.

The differential toxicity of chemotherapy for different neural cell populations at various stages of development still warrants investigation. Although adult NSCs can be harvested and cultured, they are usually generated from anterior temporal lobe resections taken from epilepsy patients who received multiple drug treatments known to affect neurogenesis.⁹

The NSCs we used, although neither embryonic nor adult but preserved from newborns,¹⁰ have been established as the most reliable source of normal NSCs.

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Disclosure: See original article for full disclosure list.

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