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Targeted Cancer Stem Cell Therapies Start with Proper Identification of the Target - Letter

We read with great interest the article by Monticone and colleagues in the November 2009 issue (1). Evidence is accumulating that tumor-initiating cells (TIC) contribute to glioma initiation and to resistance against current therapies. Therefore, as the authors point out, specific elimination of this population holds great promise in improving glioma therapies. In this article the authors report that the NOTCH pathway inhibitor LLNle specifically eliminates glioma TICs. Interestingly, they make the observation that this cytotoxic effect is due to the inhibition of the 26S proteasome by LLNle. Although intriguing, we believe these results need to be interpreted with caution. We have previously shown that glioma TICs are characterized by low proteasome activity and that glioma cells grown under "proliferation" conditions, which enrich for glioma TICs, were resistant to the proteasome inhibitor Velcade, compared with glioma cells grown under differentiation conditions (2). Therefore, it came as a surprise to us that glioma TICs in this study by Monticone and colleagues were sensitive to the proteasome-inhibiting effect of LLNle. We believe that the authors' conclusion that the effect of the LLNle inhibitor on the freshly isolated glioma cultures is specific to TICs is premature. Freshly isolated glioma samples were treated with LLNle immediately after glioma tissue digestion and the drug effect was assessed 24 to 48 hours later. However, the culture conditions used by the authors take time to enrich for TICs *in vitro* and, therefore, the bulk of glioma cells obtained after tumor digestion in their study is most likely comprised of a large number of progenitors or fully differentiated glioma cells. Both cell populations are prone to die under these culture conditions and the addition of any cytotoxic drug will enhance this effect. Because no attempt was made to show the TIC phenotype of the targeted cells by operational means (3), more rigorous and direct experimental comparisons (i.e., effect of the drug on TICs versus non-TICs) are needed to answer the question whether the LLNle dual-inhibition effect is indeed targeting the glioma TIC population. Given the notorious resistant phenotype of glioma TIC, it is likely that the effect of most drugs on the glioma TIC population will be distinct from its effect on the rest of the glioma cells, and careful definition and identifications of TICs will be crucial in designing successful targeted therapies in an effort to improve glioma therapy.

Erina Vlashi
Frank Pajonk
Division of Molecular and Cellular Oncology, Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Monticone M, Biollo E, Fabiano A, et al. z-Leucinyl-leucinyl-norleucinal induces apoptosis of human glioblastoma tumor-initiating cells by proteasome inhibition and mitotic arrest response. Mol Cancer Res 2009;7:1822–34.
2. Vlashi E, Kim K, Lagadec C, et al. *In vivo* imaging, tracking, and targeting of cancer stem cells. J Natl Cancer Inst 2009;101:350–9.
3. Fan X, Khaki L, Zhu TS, et al. Notch pathway blockade depletes CD133-positive glioblastoma cells and inhibits growth of tumor neurospheres and xenografts. Stem Cells 2009. Epub 2009 Nov 10.

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Erina Vlashi and Frank Pajonk

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