Response to “Tumor cells in search for glutamate: an alternative explanation for increased invasiveness of IDH1 mutant gliomas”

We thank the authors for a very thoughtful letter and agree that there are a number of different mechanisms through which isocitrate dehydrogenase (IDH) mutation, the downstream 2-hydroxylglutarate (2HG), can lead to a number of different state changes within tumor cells. The acidification of the tumor microenvironment was solely an interpretation of our Fig. 1. Schematic overview of the proposed effects of mutated IDH1 on cellular metabolism. α-KG is reduced to 2-HG, which when exported out of the cell could lead to acidification of tumor microenvironment. This may promote local invasive growth of tumor cells. We postulate the hypothesis that, because of depletion of cytosolic α-KG, glutamate is imported via EAAT2 and converted to α-KG by GDH (thick arrows). In this way glutamate could act as a chemotactic source that also promotes invasive tumor cell growth.

mathematical model. It is much more likely that the effects are multifactorial, as mentioned by the authors, and the potential for a glutamate gradient resulting in diffusion behavior is an intriguing possibility that can easily be experimentally validated in vitro, though a more mechanistic explanation would be favored. It is possible that 2HG, and specifically the enantiomer R-2-hydroxyglutarate, which is formed by the conserved mutation at R132, may in fact inhibit 2-oxoglutarate-dependent dioxygenase activity, which in turn alters the stability of hypoxia-inducible factor alpha, leading to many larger downstream effects. We also agree that the authors’ suggestion of a means of testing the hypothesis of glutamate depletion by using glutamate dehydrogenase inhibitors is a good one, and one that they are clearly well prepared to carry out.

The scope of our manuscript was to focus on the very evident difference in measurable tumor behavior in vivo for patients with IDH1 mutation, though we believe that the discussions about the molecular mechanism underlying this gross behavior is incredibly important to gain further understanding of the tumorigenicity of both low- and high-grade gliomas. We look forward to further discussion and data regarding the underlying mechanisms related to IDH mutation.

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