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LETTER TO THE EDITOR

Production of 2-hydroxyglutarate by isocitrate dehydrogenase 1–mutated gliomas: an evolutionary alternative to the Warburg shift?

Dear Editor:

The past 2 years have seen a flurry of activity surrounding the 2008 discovery of a conserved mutation in isocitrate dehydrogenase 1 (IDH1) in ~75% of grade II and III gliomas and a small fraction (~12%) of grade IV glioblastomas that putatively arose from lower-grade precursors.[1] It was found also that the secondary glioblastomas carrying this mutation had a very different natural history, typically being found in younger patients and carrying a much better prognosis.[2,3] Follow-up studies have reproduced these findings, and this mutation is quickly coming to represent a new subtype of this devastating disease. The recent work on this mutation has been thoroughly and beautifully reviewed by Kloosterhof et al.[4]

Although the prognostic implications of this mutation are clear, there is not yet a consensus as to the underlying biological mechanism of progression in tumors harboring this mutation. A first hint at its significance in glioma progression came from a study by Zhao et al.[5] that showed mutated IDH1 correlated with decreased levels of α-KG in vitro. Furthermore, subsequent activation of the cellular hypoxia–induced stress response was observed in IDHmut cells through stabilization of hypoxia inducible factor–1α and up-regulation of downstream proteins.[5] The authors concluded that wild-type IDH1 functioned as a tumor suppressor that, when mutated, led to progression.

In contrast, Dang et al.[6] found that tumors with the IDH1 mutation actually had a gain of function—the mutated enzyme specifically catalyzed the NADPH dependent conversion of α-KG to 2-hydroxyglutarate (2-HG)—and reported that α-KG levels were unaffected in whole-tumor cell lysates. The significance of this gain of function mutation is not yet clear, although metabolic disorders have been well described that lead to build-up of 2-HG and are associated with both demyelinating processes and early brain tumor formation.[7]

Structurally, 2-HG is very similar to α-KG, sharing the same carbon backbone and only differing by a single moiety: an α-keto-acid replaces an α-hydroxy-acid. A major difference is that, although α-KG is a normal inhabitant of the cell, 2-HG apparently is not, and it builds up to extremely high (~100-fold) levels in IDHmut gliomas.[6,8] Although 2-HG cannot passively cross the cell membrane, the cell can actively transport the molecule out, which could acidify the extracellular microenvironment.

The Warburg shift—the metabolic shift to aerobic glycolysis—has long been considered a hallmark of cancer; however, its specific role in tumorigenesis remains unclear. Gatenby and Gillies[9] suggested that cancer cells increase their fitness by utilizing aerobic glycolysis, cycling through glucose at an accelerated rate and producing acidic byproducts (lactate). They propose that this advantage is gained through Darwinian mechanisms: in response to hypoxic conditions, cells switch to glycolysis through physiologic mechanisms and subsequently produce an acidic environment that, in turn, produces evolutionary pressure in the form of a microenvironmental change. "Cell populations that emerge from this evolutionary sequence have a powerful growth advantage, as they alter their environment through increased glycolysis in a way that is toxic to other phenotypes, but harmless to themselves. The environmental acidosis also facilitates invasion through destruction of adjacent normal populations, degradation of the extracellular matrix and promotion of angiogenesis (p. 892)." Furthermore, the byproduct, lactate, is a useful building block of many products that are needed for replication.[9]

The evolutionary shift to a Warburg-driven metabolism does not come without an initial energy penalty. Both Gatenby and Gillies[9] and other groups[10,11] have hypothesized that the existence of a basement membrane acting as a spatial constraint—an evolutionary crucible, as it were—is a necessary condition to drive the Warburg shift. This condition is not met in glioma, however, where movement is less constrained and there is no ductal architecture. Intriguingly, the only other tumors in which this mutation has been found (acute myeloid leukemia,[12] melanoma[13] and, recently, chondrosarcoma[14]) share the lack of constraint of motion with glioma, suggesting a common evolutionary pathway for the IDH mutation.

The importance of an acidic environment has been tested theoretically in glioma progression and invasion by Basanta et al.[15] with the help of a game theory model.[15] Basanta and colleagues found that acid production favored the emergence of invasive phenotypes. In this work, the acid was assumed to have come from the byproducts of glycolytic metabolism, putatively from glial cells that had undergone the Warburg shift; however, this assumption is not central to their results. A second game theoretical work taking into consideration the effects of an IDH-1–mutated tumor cell suggested a dependence of speed of progression on this metabolic dysregulation.[16]

There is also experimental work that has shown that acidic environments can increase the motility of glioma cells[17] and can increase the background mutation rate in normal diploid cells.[18] Although investigators have found that the IDH1 mutation itself is stable,[6] an increased background mutation rate would not preferentially effect IDH1, but instead would speed genetic drift from the new baseline of the mutated tumor. This coupled with the putatively increased levels of HIF-1α could provide the benefit that these otherwise indolent low grade gliomas would need to progress toward a secondary glioblastoma.

Although the production of 2-HG could be equivalent to excess lactate when it comes to acidity (they have a very similar pKa), it would provide a somewhat lesser benefit to the cells because it is not able to be used for anabolic purposes. If this hypothesis involving IDH1 and acidosis is valid, it could explain the slower natural history of IDH1mut tumors: they have enough of an advantage to grow and outcompete their neighbors, but not enough to do so at the speed of a typical glioblastoma. This "lesser evolutionary advantage" argument also helps to explain the growing body of data showing that IDHmut glioblastomas (World Health Organization [WHO] grade IV) have a better prognosis than even their WHO grade III IDHwt counterparts,[19] because the IDHmut are not truly grade IV in a prognostic sense.

We hypothesize that the mechanism behind IDHmut glioma progression is an alternative (non-Warburg) pathway by which the tumor can produce an acid to outcompete its neighbors and promote itself. Having the IDH1 mutation does not obviate the possibility of also undergoing the Warburg shift, but we hypothesize that in general, this early mutation would function in place of the Warburg shift to promote tumor invasion and progression. This makes even more tantalizing the possibility of metabolic modulation in the therapy of these tumors—a reality that has been suggested in several recent works,[20,21] but not one that has yet been widely translated to the clinic. As a result of our hypothesis, we suggest 3 testable results:

1. IDH1-mutated gliomas will have, on average, a lower metabolic rate, as measured by (18)F-Fluorodeoxyglucose Positron emission tomography, because they would not have necessarily undergone the Warburg shift responsible for the lion's share of a tumor's PET avidity.
2. Magnetic Resonance Spectroscopy measures of lactate and 2-HG would reveal that acid production in IDH-mutated tumors can come from the buildup of 2-HG in the absence of lactate.
3. Sampling tissue in the peri-tumoral area of IDH1-mutated low grade gliomas and secondary glioblastomas will reveal acidic microenvironments similar to those of their primary glioblastoma cousins.

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