Towards personalised medicine for cancer

From initial therapy to follow-up

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Chapter 6: Tumour cells in search for glutamate: an alternative explanation for increased invasiveness of IDH1-mutated glioma

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With great interest we read the article "Invasion and proliferation kinetics in enhancing gliomas predict IDH1 mutation status" by Baldock et al.187 They describe a mathematical model of tumour growth based on MR imaging, which can determine proliferation and invasion of gliomas. In their study, they compared model-predicted growth profiles of a large series of contrast-enhancing gliomas with and without *IDH1* mutation. A strong correlation between *IDH1* mutational status and invasion profile was found, the *IDH1*-mutated gliomas being more invasive and less proliferative than their *IDH1* wild-type counterparts.

To explain increased invasion, the authors suggest modulation of the tumour microenvironment by D-2-hydroxyglutarate (D2HG), the oncometabolite that is a product from the acquired neo-activity of mutant IDH1.13 The authors propose that extracellular depositions of high concentrations of D2HG acidify the tumour microenvironment to an extent that is toxic to normal cells, resulting in degradation of tissue and generating space for glioma cell migration.245 Acidosis of the tumour microenvironment has been proposed as a general form of niche engineering by tumour cells that enables their invasion in extracellular matrix, but so far acidosis has mainly been regarded to result from lactate produced by the glycolytic pathway in cells where the Warburg effect is active. Baldock *et al.* assume that D2HG does likewise because it has a pKa similar to that of lactate.

Although this may be an appropriate explanation, there are also arguments against this hypothesis. D2HG production is a common phenomenon in the majority of grade II and grade III gliomas, in which normally no evidence of extensive acidosis and tissue damage is observed. This is exemplified by the fact that low-grade gliomas do not enhance in contrast-enhanced MRI, suggesting an intact blood-brain barrier and arguing against destruction of the glioma microenvironment.

Besides the production of D2HG, *IDH1* mutations have important consequences for cellular metabolism. Since the mutant IDH1 enzyme converts αKG to D2HG while consuming NADPH, steady-state levels of NADPH and αKG are both expected to be reduced. Both are important for lipid synthesis, and reduced levels thereof will therefore affect biochemical processes that are fundamental for tumour progression. It is therefore envisioned that reduced αKG and NADPH levels in cells carrying the *IDH1* mutation impose metabolic stress that affects cell proliferation.15 This phenomenon may explain the lower proliferation rates of *IDH1*-mutated gliomas that Baldock *et al.* observed and contribute to better prognosis for these patients.

The predicted large impact of the mutation on fundamental biological processes also predicts that tumour cells need anaplerotic pathways in order to keep proliferating. One such pathway has been suggested to involve glutamine metabolism because *IDH1*-mutated cells are more sensitive to glutaminolysis inhibition than *IDH1* wild-type cells.135 Glutaminolysis is a two-step reaction in which glutaminase converts glutamine to glutamate, which can subsequently be converted to αKG by glutamate dehydrogenase (GDH). Therefore, we have postulated that glioma cells import glutamate from the tumour microenvironment.16 This would be quite easy since glutamate is a neurotransmitter that is present in both synaptic clefts and white matter,136 predominant sites of glioma invasion. Increased glutamate import in *IDH1*-mutated cells is supported by the finding that especially World Health Organisation (WHO) grade II-III gliomas, of which >80% are *IDH1*-mutated, express the glutamate importer excitatory amino-acid transporter 2 (EAAT2).137
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We therefore propose that the neurotransmitter glutamate in the brain acts as a chemotactic compound, specifically for $IDH1$-mutated glioma cells, as an alternative and/or additional explanation for the increased invasion profiles in IDH-mutated gliomas that Baldock et al. observed in their study (Figure 1). As Baldock et al. already suggested, $IDH1$-mutated gliomas could be candidates for therapies directed against tumour-specific metabolic pathways (e.g. using inhibitors of the glutamate-dependent anaplerotic pathway) using GDH inhibitors such as green tea extract epigallocatechin gallate (EGCG), and the malaria medicine chloroquine.

Figure 1. Schematic overview of $IDH1$ mutant-associated metabolism.

Schematic overview of the proposed effects of mutated $IDH1$ on cellular metabolism. $\alpha$KG is reduced to $D2HG$, which when exported out of the cell could lead to acidification of tumour microenvironment. This may promote local invasive growth of tumour cells. We postulate the hypothesis that, because of depletion of cytosolic $\alpha$KG, glutamate is imported via EAAT2 and converted to $\alpha$KG by GDH (thick arrows). In this way glutamate could act as a chemotactic source that also promotes invasive tumour cell growth. Abbreviations: $\alpha$KG, alpha-ketoglutarate; BCAT, branched-chain amino acid transferase; $D2HG$, D-2-hydroxyglutarate; EGCG, epigallocatechin gallate; GDH, glutamate dehydrogenase; Gln, glutamine.