Magnetic resonance spectroscopy of isocitrate dehydrogenase mutated gliomas: current knowledge on the neurochemical profile

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Purpose of review
Magnetic resonance spectroscopy (MRS) may play a key role for the management of patients with glioma. We highlighted the utility of MRS in the noninvasive diagnosis of gliomas with mutations in isocitrate dehydrogenase (*IDH*) genes, by providing an overview of the neurochemical alterations observed in different glioma subtypes, as well as during treatment and progression, both in vivo and ex vivo.

Recent findings
D-2-hydroxyglutarate (2HG) decrease during anticancer treatments was recently shown to be associated with altered levels of other metabolites, including lactate, glutamate and glutathione, suggesting that tumour treatment leads to a metabolic reprogramming beyond 2HG depletion. In combination with 2HG quantification, cystathionine and glycine seem to be the most promising candidates for higher specific identification of glioma subtypes and follow-up of disease progression and response to treatment.

Summary
The implementation of advanced MRS methods in the routine clinical practice will allow the quantification of metabolites that are not detectable with conventional methods and may enable immediate, accurate diagnosis of gliomas, which is crucial for planning optimal therapeutic strategies and follow-up examinations. The role of different metabolites as predictors of patient outcome still needs to be elucidated.

Keywords
brain metabolites, glioma, *IDH* mutation, progression, treatment effect

INTRODUCTION

In 2009, mutations of the genes encoding the enzymes isocitrate dehydrogenase 1 and 2 (*IDH*1/2) were discovered in gliomas [1]. *IDH* mutations are found in nearly 90% of diffuse grade II and 60% of diffuse grade III gliomas, 5% of primary glioblastomas (GBMs) and are absent in other brain tumours [2]. *IDH*-mutated gliomas form a biologically independent subset of tumours associated with a two to four-fold longer median survival compared with wild-type tumours [3]. Own to its high diagnostic and prognostic value, *IDH* mutational status was integrated into the 2016 WHO classification of gliomas [4]. Diffuse glioma classification requires histologic evaluation and assessment of the *IDH* mutational status and codeletion status of chromosomal arms 1p and 19q (1p/19q codeletion) [5]. 1p/19q codeletion is found only in *IDH*-mutated gliomas, is linked with the oligodendroglial histologic subtype, and is associated with the best prognosis. *IDH*-mutated 1p/19q-noncodeleted gliomas are classified as diffuse astrocytomas and are associated with intermediate outcome, while *IDH*-wild-type have the poorest prognosis [2].

MRI plays a vital role in the diagnosis and management of patients with brain tumours [6▪▪]. Among different MRI modalities, in vivo ^{1}H MR spectroscopy (MRS) provides unique metabolic information through the measurement of the neurochemical concentrations in tissue.

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Curr Opin Neurol 2020, 33:413–421
DOI:10.1097/WCO.0000000000000833

KEY POINTS

- Reliable 2HG quantification for clinical examinations requires implementation of advanced MRS methods.
- *IDH* mutation leads to tumour metabolic reprogramming beyond 2HG overproduction.
- Cystathionine and glycine may play a crucial role for glioma subtype identification and follow-up of glioma progression.
- The evaluation of the full neurochemical profile may help achieving higher specificity in glioma subtype identification and prediction of patient outcome.

The aim of this review is to provide an overview of the metabolic alterations observed in different glioma subtypes both in vivo and ex vivo, and to highlight the possible role of ^{1}H MRS in the noninvasive diagnosis of *IDH*-mutated gliomas, as well as in monitoring the effect of tumour progression and anticancer treatments on the neurochemical profile.

D-2-HYDROXYGLUTARATE

IDH mutations result in the overproduction of D-2-hydroxyglutarate (2HG) (Fig. 1) and have been suggested to cause changes in global cellular metabolism, either in consequence of increased 2HG or through inhibition of isocitrate metabolism [7]. In vivo MRS enables the noninvasive detection of 2HG, potentially providing a great impact on patient management.

Clinical relevance

Noninvasive 2HG detection by MRS is a powerful tool for immediate, presurgical diagnosis of *IDH*-mutated gliomas. Indeed, 2HG MRS allows in first place to differentiate noninvasively gliomas from metastases, primary brain lymphomas or other non-neoplastic lesions. In vivo assessment of *IDH* status is highly beneficial for neurosurgical planning, as maximal surgical resection has been shown to confer a better prognosis in *IDH*-mutated gliomas compared with wild-type [8]. Thus, although in vivo MRS is not meant to replace surgery or biopsy, which are needed for histological confirmation of the *IDH* status and assessment of the tumour genetic profile, preoperative MRS would be extremely useful as part of the clinical routine practice as noninvasive identification of *IDH* mutation may influence surgical decision-making regarding the extent of the resection. Moreover, 2HG quantification may be useful for the identification of minor *IDH* mutations undetectable by immunohistochemistry, given that DNA sequencing is not available in all

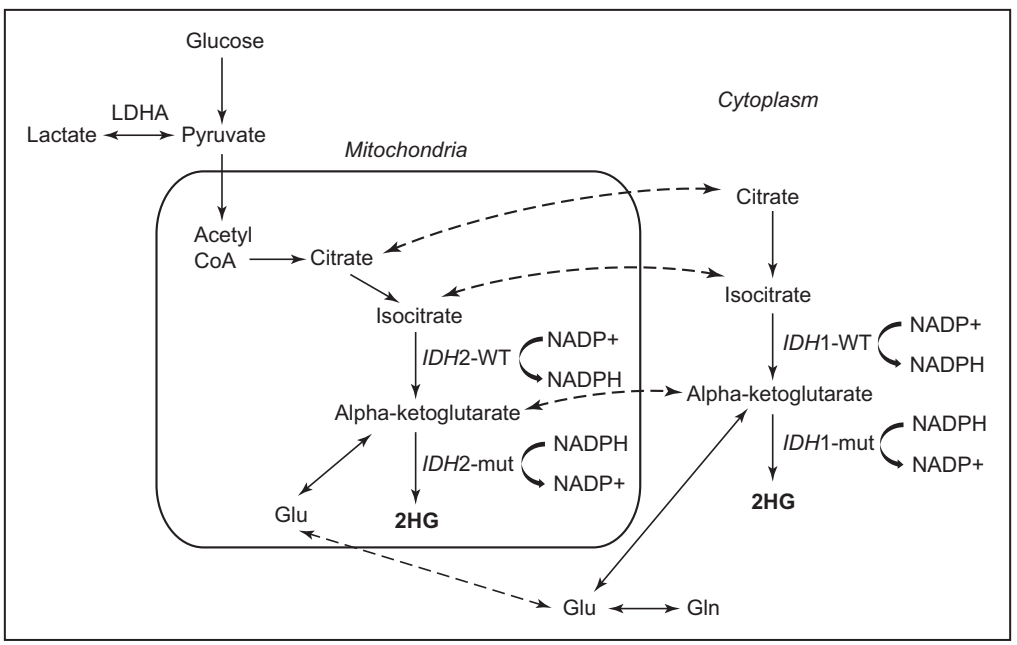

FIGURE 1. Schematic diagram of the D-2-hydroxyglutarate metabolic pathway. Illustration of *IDH* function change with cytosolic *IDH*1 and mitochondrial *IDH*2 mutations. Dashed arrows indicate exchange of a metabolite between the mitochondria and the cytosol. Schematic based on previous publication [7]. 2HG, D-2-hydroxyglutarate; Gln, glutamine; Glu, glutamate; LDHA, lactate dehydrogenase A; mut, mutated; NADP+, nicotinamide adenine dinucleotide phosphate; WT, wild-type.

clinical centres. 2HG may also serve as a biomarker of *IDH* mutation if surgery is not feasible or associated with high risk, and as a marker of treatment efficacy, treatment response and tumour progression, especially when evaluation based on other imaging methods is inconclusive, assisting clinicians in the choice of the best therapeutic strategy.

In vivo magnetic resonance spectroscopy methods

Since 2012, several in vivo ^{1}H MRS methods have been proposed for 2HG detection [9,10,11▪▪]. These can be grouped into three types: short echo-time (T_E) MRS [12]; long-T_E MRS optimized for 2HG detection [13,14]; edited MRS [15,16▪]. Examples of spectra acquired with these three methods have been shown previously [9].

Short-T_E ($T_E = 30$ ms) MRS is typically performed using the point resolved spectroscopy (PRESS) sequence, available on clinical scanners. This method has been shown to produce the highest rate of false-positives, which is the worst outcome for clinical evaluation [11▪▪]. This is because the quantification of the 2HG signal at 2.25 ppm is complicated by the presence of other signals, including metabolites, macromolecules and baseline.

Long-T_E MRS optimized for 2HG detection partially removes the overlap of 2HG at 2.25 ppm with other resonances, by employing the T_E that provides minimal contribution of other signals. These methods require modified sequences and are rarely available in the clinic. Optimized PRESS uses $T_E = 97$ ms and has been shown to better quantify 2HG and reduce false-positive results compared with short-T_E MRS [17]. Nevertheless, a recent study suggested that necrosis and treatment status were associated with false-positive 2HG measurements using optimized PRESS in GBM [18]. A semi-localization by adiabatic selective refocusing pulse sequence with $T_E = 110$ ms was also proposed as alternative approach for 2HG detection at 7 T [14].

Finally, edited MRS measures the 2HG signal at 4.02 ppm by completely removing the signals from other metabolites (Fig. 2) and provided no false positives in a recent prospective 3 T study [16▪]. These results point towards the need of implementation of advanced MRS methods for clinical examinations.

Both single-voxel MRS and MRS imaging (MRSI) have been employed for the detection of 2HG, yet the majority of the studies employed single-voxel MRS, own to the shorter acquisition times and the higher reproducibility of the results with respect to MRSI.

Regardless the method employed, a few studies have reported lower sensitivity and specificity in

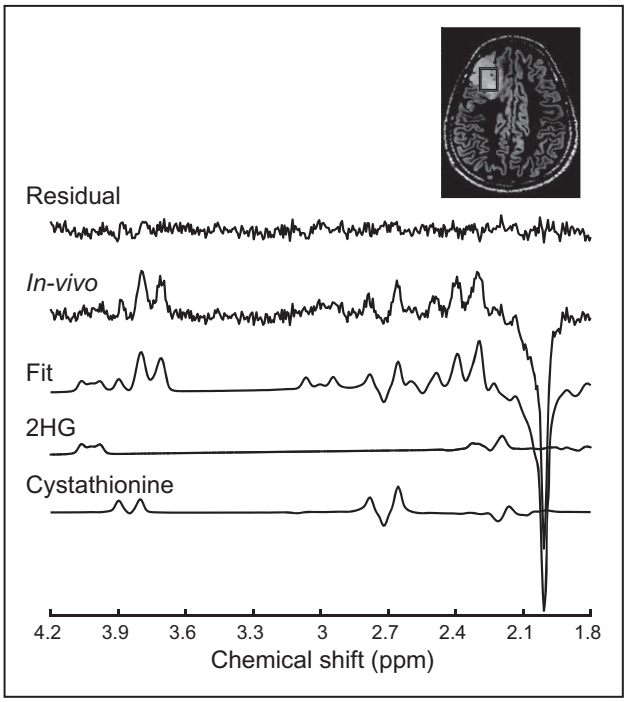

FIGURE 2. In vivo detection of D-2-hydroxyglutarate and cystathionine. An in vivo spectrum acquired in an *IDH*1-mutated, 1p/19q-codeleted glioma is shown together with the LCModel fit, the 2HG and cystathionine contributions, and residuals. No line broadening was applied. The location and size of the VOI is shown on a FLAIR image. 2HG, D-2-hydroxyglutarate.

postoperative compared to preoperative cohorts [19,20]. This could be due to technical challenges related to the presence of postsurgical cavities, size of the residual tumour or effect of previous treatments. The evaluation of the full metabolic profile may thus become crucial for follow-up examinations and evaluation of tumour progression.

Correlation with cellularity and grade

Previous reports showed that 2HG concentrations detected by MRS were positively correlated with tumour cellularity [19,21]. 2HG concentrations were also found to be significantly different between low and high-grade, consistent with differences in tumour cellularity in different grades [21] and confirming ex vivo findings obtained using ^{1}H high-resolution magic angle spinning (HR-MAS) spectroscopy [22]: mean ex vivo 2HG levels were shown to be significantly higher in grade IV than in grade II gliomas. When normalized by average cellularity, 2HG levels did not differ significantly between grades II and IV, suggesting that 2HG differences between glioma grades reflect differences in

cellularity [22]. Conversely, another short-T_E MRS 3 T study suggested that tumour grade had a significant influence on glutamate (Glu), but not on 2HG concentration [23]. This negative result could be due to the technical challenges associated with 2HG quantification using short-T_E MRS, as discussed above.

In line with these findings, a recent study reported increased ex vivo 2HG levels in gliomas undergoing malignant progression from grade III to grade IV [24]. In addition, 2HG levels were correlated with increased mitotic activity, axonal disruption, vascular neoplasia and with several metabolites (see section 'Correlation with other metabolites') [24]. Although in vivo studies did not report significant differences in 2HG levels between different histological subtypes [21,25], elevated ex vivo 2HG levels were reported in oligodendrogliomas undergoing progression to grade III and IV compared with astrocytomas [24].

Longitudinal changes

A 2HG concentration decrease during treatment has been shown previously [21,26,27▪▪]. A prospective longitudinal study employing single-voxel optimized PRESS at 3 T reported stable absolute 2HG levels in untreated patients with indolent disease, while 2HG showed a marked increase at progression. In contrast, 2HG levels decreased during radiotherapy and chemotherapy in most patients under investigation, and the decrease during treatment was accompanied by a measurable decrease in tumour volume in almost all gliomas. 2HG concentration decreased more rapidly in oligodendrogliomas than astrocytomas or mixed gliomas, consistent with a better response to treatment of the first subtype. In patients included up to 24 months after treatment, 2HG levels were very close to the detectability threshold set to 1 mmol/l [21].

An edited 3D MRSI sequence was employed at 3 T to evaluate the effect of both standard treatments and a novel *IDH*1 inhibitor on 2HG levels [26,27▪▪]. 2HG levels measured relative to total creatine (creatine and phosphocreatine, tCr) were found to decrease significantly in patients receiving adjuvant radiation and chemotherapy and correlated with clinical status. Results from a phase 1 clinical trial indicated a rapid 2HG/tCr decrease by 70% after only 1 week of treatment with a novel *IDH*1 inhibitor [27▪▪].

Correlation with other metabolites

The median value of 2HG/tCr was found positively correlated with that of lactate(Lac)/tCr in pretreatment scans, possibly resulting from the Warburg effect due to silencing of lactate dehydrogenase A (LDHA) in *IDH*-mutated gliomas, while it was negatively correlated with that of Glu and glutamine (Glx)/tCr in posttreatment scans, as a possible direct consequence of 2HG depletion during treatment [26]. These findings require further corroboration from larger patient cohorts. Similarly, the inhibition of *IDH*1 activity through a novel anti-*IDH*1 treatment was suggested to induce a reprogramming of tumour metabolism, showing decreased 2HG levels, reported relative to tCr quantified in healthy tissue ($tCr_{healthy}$), associated with increased Glx/$tCr_{healthy}$, glutathione (GSH)/$tCr_{healthy}$ and Lac/$tCr_{healthy}$ levels. [27▪▪] The trend to an inverse correlation between 2HG/$tCr_{healthy}$ and Glx/$tCr_{healthy}$ in *IDH*-mutated gliomas after treatment suggested the 2HG/Glx ratio as a more sensitive biomarker of *IDH* mutation, given that Glu levels were found to be lower in *IDH*1-mutated than in wild-type gliomas, as measured by the mass spectrometry in tumour biopsies [23]. However, the inverse correlation between 2HG and Glx in mutated gliomas has not yet been shown in vivo at baseline. Increased GSH levels after anti-*IDH*1 treatment may lead to a reduced sensitivity of *IDH*-mutated gliomas to radiotherapy, providing evidence against a benefit of simultaneous administration of *IDH*1 inhibitors and radiotherapy [27▪▪]. The increase in Lac levels posttreatment was suggested to be linked with reversible downregulation of LDHA activity associated with inhibition of mutant *IDH*1.

A previous ^{1}H HR-MAS experiments also reported a positive correlation between 2HG and Lac levels in *IDH*-mutated recurrent glioma biopsies, as well as correlations of 2HG with several other metabolites commonly associated with tumour, such as free choline (Cho), phosphocholine (PCho), glycerophosphocholine (GPC), tCho, aspartate (Asp), gamma-aminobutyric acid (GABA), threonine (Thr), hypotaurine (hTau), creatine and phosphocreatine (Cr, PCr), betaine (Bet), glycine (Gly), GSH, phosphoethanolamine, Glu and Gln. Conversely, 2HG was negatively correlated with the *myo*-inositol (mIns)/tCho ratio, an index associated with the relative contribution of tumour cells and treatment-induced gliosis [22]. However, these correlations have not been yet corroborated by other ex vivo or in vivo studies. Correlations between 2HG and other metabolites observed both in vivo and ex vivo are summarized in Table 1.

OTHER METABOLITES

Differences in several other metabolites have been reported in *IDH*-mutated vs. wild-type gliomas, as well as across different glioma genetic subtypes and tumour grades, using in vivo and ex vivo MRS. Main

Table 1. Correlations of D-2-hydroxyglutarate with other metabolites

	In vivo ^{1}H MRS			Ex vivo ^{1}H MAS
		Treatment		
	Pretreatment	RT + CT	Anti-*IDH*1	Recurrent tumours
Positive correlations	Lac/tCr [26]			Asp, Bet, Cho, PCho, GPC, tCho, Cr, PCr, GABA, Gln, Glu, GSH, Gly, Lac, PE, Thr, hTau [22]
Negative correlations		Glx/tCr [26]	Glx/$tCr_{healthy}$, Lac/$tCr_{healthy}$, GSH/$tCr_{healthy}$ [27▪▪]	mIns/tCho [22]

Asp, aspartate; Bet, betaine; Cho, free choline; CT, chemotheraphy; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; Glx, glutamate + glutamine; Gly, glycine; GPC, glicerophosphocholine; GSH, glutathione; hTau, hypotaurine; Lac, lactate; PCho, phosphocholine; PCr, phosphocreatine; PE, phosphoethanolamine; RT, radiotheraphy; tCho, total choline; tCr, total creatine; $tCr_{healthy}$, tCr measured in the contralateral healthy tissue; Thr, threonine.

findings are summarized in Table 2 [7,11▪▪,14,23,24,28,29,30▪▪,31,32,33▪].

IDH vs. wild-type

IDH-mutated tumours exhibited a significantly lower Glu/tCr than wild-type gliomas from ultra-high-field short-T_E MRS experiments [28]. The same study also reported a significantly lower GSH/tCr and significantly elevated tCho/tCr in mutated gliomas with respect to wild-type. However, a small cohort of patients was investigated and the basis set for metabolic quantification did not include the experimentally measured macromolecular spectrum, which may bias the results. Decreased Glu, Gln and GSH levels in *IDH*-mutated vs. wild-type gliomas were also reported from Short-T_E 3-T experiments [23]. However, the experimentally measured macromolecular spectrum was not used for the quantification, and Glu, Gln and GSH levels associated with a CRLB larger than 30% were excluded, possibly introducing a bias [34]. Significantly lower Glx levels and a trend to lower GSH levels were observed in a small cohort of *IDH*-mutated vs. wild-type GBM at 3 T [29]. Despite technical limitations, these results are in line with the reported lower Glu, Gln and GSH levels measured in mutant vs. wild-type *IDH* cell cultures [7]. Lower GSH levels in mutant *IDH* vs. wild-type may be explained by the selective depletion in these gliomas of NADPH, which is used by *IDH* for 2HG production and is thus less available for GSH recycling. However, lower total GSH levels in mutated gliomas were not observed by liquid chromatography-mass spectrometry (LC-MS) in a recent study [30▪▪].

Other more recent studies reported decreased Glu, but not Gln, levels in *IDH*-mutated glioma cells compared with wild-type, as well as in *IDH*-mutated vs. wild-type glioma tissue samples using gas chromatography-mass spectrometry [23] and ^{1}H HR-MAS [24]. Lower GABA concentration was also observed in the *IDH*-mutated group in one of these studies [24].

Table 2. Currently known effects of *IDH* mutations and 1p/19q codeletion on the neurochemical profile

	In vivo ^{1}H MRS	Ex vivo tissue
IDH vs. WT	2HG ↑ [11▪▪] tCho/tCr ↑ [28,32] Glu/tCr ↓, GSH/tCr ↓ [28] Glu ↓, Gln ↓, GSH ↓ [23] Glx ↓ [29]	2HG ↑ GPC ↑, PCho ↑, Cho ↑ [24] PE ↓ [35] Glu ↓ [23,24,31] Gln ↓ [31] GABA ↓ [24] NAA ↓, NAAG ↓ [7]
*IDH*2 vs. *IDH*1	2HG/tCho ↑ [14] mIns/tCho ↑ [33▪]	
1p/19q-codeleted vs. noncodeleted	Cystathionine ↑ [30▪▪]	Cystathionine ↑ [30▪▪] Ser ↓, Gly ↓, Thr ↓, Orn ↓ [30▪▪]

2HG, D-2-hydroxyglutarate; Cho, free choline; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; Glx, Glu + Gln; Gly: glycine; GPC, glicerophosphocholine; GSH, glutathione; mIns, *myo*-inositol; NAA, *N*-acetylaspartate; NAAG, *N*-acetyl-aspartyl-glutamate; Orn, Ornitine; PCho, phosphocholine; PE, phosphoethanolamine; Ser, serine; tCho, total choline; tCr, total creatine; Thr, threonine.

Depletion of Glu levels was suggested to compensate for the altered flux of alpha-ketoglutarate to 2HG in *IDH*-mutated gliomas [23]. Significant differences in both Glu and Gln levels between *IDH*-mutated and wild-type glioma biopsies were observed in another study and were both linked to replenishment of alpha-ketoglutarate by glutaminolysis [31].

NAA and *N*-acetyl-aspartyl-glutamate (NAAG) levels were also found to be significantly lower in *IDH*-mutated vs. wild-type human glioma tissues; yet, the biological mechanism for NAA and NAAG depletion and whether it contributes to tumour pathogenesis remains unclear [7].

Very recently, maximum tCho/*N*-acetylaspartate (NAA) and tCho/tCr values measured using short-T_E MRSI in lesions were shown to be significantly higher in *IDH*-mutated tumours than in wild-type, whereas mean tCho/NAA and tCho/tCr were not significantly different between the two groups. In addition, maximum tCho/NAA was significantly higher in grade IV gliomas than in lower grade gliomas. In contrast, in the peritumoral area, the mean tCho/tCr was found to be significantly elevated in *IDH*-mutated vs. wild-type gliomas [32]. These results are in line with the elevated tCho/tCr measured in vivo in human mutated gliomas at 9.4 T [28], and with the observed higher levels of free Cho, GPC and PCho in *IDH*-mutated vs. wild-type gliomas measured ex vivo using ^{1}H HR-MAS [24]. Given the very low concentration of free Cho in the brain, elevated tCho levels are very likely dominated by increased GPC and PCho. Lower phosphoethanolamine and higher GPC levels in *IDH*-mutated vs. wild-type gliomas were reported in a study combining in vivo ^{31}P MRSI in mouse xenograft models, ex vivo ^{31}P HR-MAS measurements in human biopsies of *IDH*-mutated tumours and cell line ^{31}P MRS experiments, suggesting altered phospholipid metabolism caused by *IDH* mutation [35].

*IDH*1 vs. *IDH*2

Higher 2HG levels in gliomas harbouring mitochondrial *IDH*2 R172K mutations with respect to cytosolic *IDH*1 R132H mutations were measured at 7 T [14], confirming previous cell culture findings [36]. The same group also reported higher 2HG/tCho and mIns/tCho, and a trend to increase in citrate/tCho and tCr/tCho, in *IDH*2 vs. *IDH*1-mutated gliomas [33▪]. However, given the variable tCho levels associated with *IDH* mutation, normalization of metabolic concentrations over tCho may represent a possible source of bias.

1p/19q codeletion

Higher cystathionine levels in brain tumours compared with normal tissue were previously reported from ex vivo tissue analysis [37,38]. A recent in vivo study reported significantly elevated cystathionine in patients with *IDH*-mutated 1p/19q-codeleted gliomas compared with their noncodeleted counterparts [30▪▪]. In vivo results obtained using single-voxel edited MRS (Fig. 2) were corroborated by ex vivo LC-MS analysis in tumour samples. Ex vivo experiments showed significantly decreased levels of serine (Ser), Gly, Thr and ornithine (Orn), and a trend for lower GSH in 1p/19q-codeleted vs. noncodeleted tumours. Interestingly, cystathionine, Gly and serine are involved in the glutathione biosynthesis pathways and their altered levels were specifically attributed to the deletion of two serine and cystathionine-pathway genes located on chromosome 1p – phosphoglycerate dehydrogenase (PHGDH) and cystathionine gamma-lyase (CTH) – possibly leading to a compensatory antioxidant mechanism in gliomas with 1p/19q codeletion (Fig. 3) [30▪▪]. Although cystathionine can be reliably detected using the same edited MRS protocol used for 2HG, possible further acquisition improvements have been reported [39▪].

Grade and progression

Elevated in vivo tCho concentration was reported in high-grade compared with lower-grade gliomas [40,41], suggesting that tCho could be used as a marker of cellularity. However, as tCho is not a specific tumour cell marker, and its levels may change due to other pathological processes such as inflammation or gliosis, these results need to be taken with caution.

Choline containing compounds as measured using ^{1}H HR-MAS were found to be significantly higher in tumours that had undergone malignant progression [24]. Interestingly, oligodendrogliomas showed higher levels of GPC and tCho, while astrocytomas had higher levels of PCho and Cho. The associations of oligodendrogliomas with elevated GPC and astrocytomas with elevated PCho and Cho were suggested to reflect differences in the phospholipid metabolism found in the choline kinase pathway between these tumour subtypes. In the same study, positive correlations of 2HG levels with all choline-containing compounds were reported, corroborating previous findings suggesting that both 2HG and choline compounds levels are linked to cellularity. Given the reported differences of choline compounds between different tumour grades and histological subtypes, care must

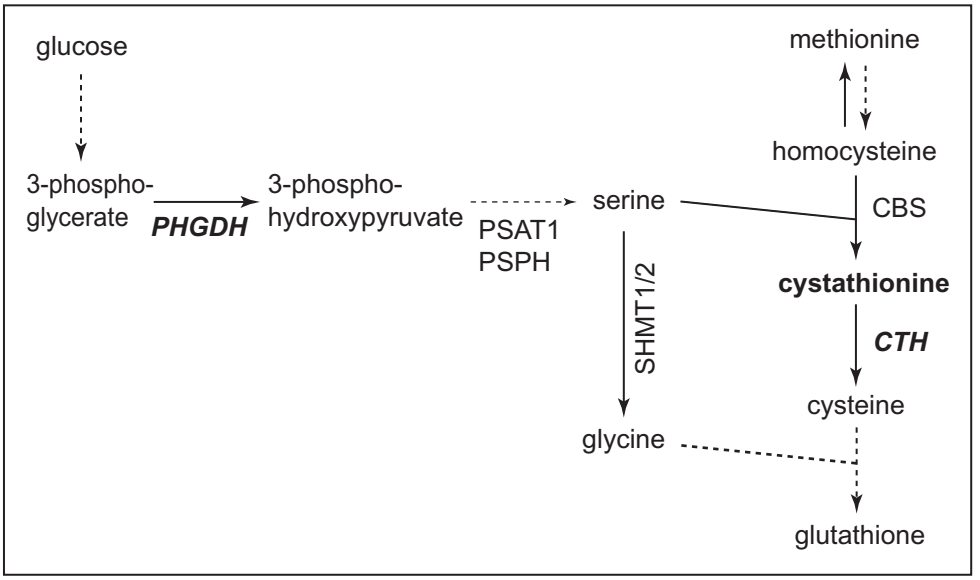

FIGURE 3. Schematic diagram of the cystathionine metabolic pathway. Solid arrows = single metabolic step, dash arrows = multiple (not drawn) metabolic steps. CBS, cystathionine-β-synthase; CTH, cystathionine gamma-lyase; PHGDH, phosphoglycerate dehydrogenase; PSAT, phosphoserine amino transferase; PSPH, phosphoserine phosphatase; SHMT1/2, serine hydroxy methyl transferase 1/2.

be taken when reporting metabolic levels as ratios over tCho.

Several other metabolites measured using ^{1}H HR-MAS were found to be significantly elevated in gliomas undergoing malignant progression [24]. These included taurine (Tau), hTau, Gly, Glu, GSH, alanine (Ala), Asp and Bet, Gln and glucose. 2HG was positively correlated with PE, GSH, Tau, Glu, Gln, Asp, myo-I, SI, GABA, PCr/Cr, Gly, Bet and Thr. Among these metabolites, increases in PE, Glu and Gln were specifically associated with anaplastic astrocytomas, while Tau, Gly, Gln and Bet were increased in anaplastic oligodendrogliomas.

Gln and Gly, which can be quantified using in vivo MRS, may be useful markers of tumour malignant progression. A very recent study reported a strong association between Gly levels measured by 3 T MRS and the presence of gadolinium enhancement. In addition, Gly levels, but not 2HG levels, were positively correlated with tumour cell proliferation as quantified by MIB-1 labelling index and high Gly/2HG was strongly associated with shorter survival [42▪▪]. The correlation between Gly/2HG and patient outcome observed in this study may reflect the better outcome of *IDH* vs. wild-type gliomas (higher 2HG) combined with the better outcome of 1p/19q codeleted vs. noncodeleted gliomas (lower Gly [30▪▪]). However, no information on the codeletion status was reported.

CONCLUSION

Noninvasive 2HG detection has a strong clinical utility due to its high diagnostic and prognostic power. While conventional in vivo MRS methods available in clinical settings have shown low specificity to *IDH* mutation, the implementation of advanced in vivo MRS methods enabling reliable 2HG quantification is highly desirable for routine clinical examinations and follow-up of treatment response. Lower Glu, Gln and GSH levels seem to be associated with *IDH* mutation and abnormal production of 2HG, while elevated tCho suggests altered phospholipid metabolism, which may depend on tumour subtype, grade and cellularity. Anticancer treatments have been suggested to affect tumour metabolism beyond 2HG production, yet the role of different metabolites in predicting patient outcome requires further elucidation. The recent discovery of cystathionine detectability in glioma using in vivo MRS opens up the possibility to exploit a potential novel biomarker of tumour response to treatment and progression. Although at the moment the quantification of the full metabolic profile does not have a direct implication for clinical evaluation, we believe that it provides a better understanding of the tumour pathophysiology and, in the future, it may be crucial for achieving higher specificity in glioma subtype identification and for evaluation of tumour response to treatment and patient outcome.

Acknowledgements

Francesca Branzoli acknowledges the support from the programmes 'Institut des neurosciences translationnelles' ANR-10-IAIHU-06 and 'Infrastructure d'avenir en Biologie Santé' ANR-11-INBS-0006.
Małgorzata Marjańska acknowledges the support of the following NIH grants: BTRC P41 EB027061 and P30 NS076408.

Financial support and sponsorship

Support was received from the programmes 'Institut des neurosciences translationnelles' ANR-10-IAIHU-06 and 'Infrastructure d'avenir en Biologie Santé' ANR-11-INBS-0006 and NIH grants: BTRC P41 EB027061 and P30 NS076408.

Conflicts of interest

There are no conflicts of interest.

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