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Is there a prominent role for MR spectroscopy in the clinical management of brain tumors?

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See article by Tiwari et al in this issue, pp. 1018–1029.

Metabolic profiling of cancer has received increased attention in the research community, spurred by technological advances in mass spectrometry and nuclear MR spectroscopy. The ability of these technologies to uncover underlying phenotypic and functional effectors of disease provides great opportunities for the discovery of biomarkers. The identification of a mutation in the enzyme isocitrate dehydrogenase (IDH) further triggered interest for metabolic reprogramming in gliomas and the search for therapeutic interventions targeting metabolism.[1]

The changing metabolic landscape of tumors has long been used for diagnostic imaging in the management of cancer patients. ^{18}F-FDG is the most widely used PET tracer in oncology, while amino acid tracers such as ^{11}C-MET and ^{18}F-FET are preferable in brain tumors because of the high background signal generated by glucose consumption in neurons. While PET is valued for its high sensitivity, the logistical constraints associated with the provision and handling of radioactive tracers limit its availability to larger clinical centers. Instead, proton magnetic resonance spectroscopy (^{1}H-MRS) is a metabolic imaging method that combines the advantages of not using ionizing radiations with a wider clinical availability. By sweeping through a range of resonance frequencies beyond that of water protons, ^{1}H-MRS provides a simultaneous quantitative assessment of several abundant metabolites. In brain tumors, changes in N-acetyl-aspartate, lactate, creatine, and choline levels have proven useful markers for prognostication, delineation of tumors for local therapy, and assessment of response to treatment.[2]

Several studies have also shown that key molecular features of gliomas can be measured by ^{1}H-MRS, allowing glioma subtyping. The most prominent is the IDH mutation detected through the accumulation of the oncometabolite 2-hydroxyglutarate (2HG), showing excellent diagnostic performance to distinguish IDH mutant from IDH wildtype gliomas.[3] Recently, a ^{1}H-MRS study reported cystathionine accumulation specifically in the 1p/19q codeleted glioma subtype.[4] In the present issue of *Neuro-Oncology*, Tiwari et al report on the detection of the amino acid glycine by ^{1}H-MRS, which the authors propose as a marker of glioma aggressiveness.[5] Using a long echo time point-resolved spectroscopy sequence, the study shows that glycine and 2HG can be detected simultaneously and that tumors with high levels of glycine proliferate and progress more rapidly. Glycine levels correlated with contrast enhancement and with a high proliferation index. Increased glycine was also associated with shorter patient survival, and this association was considerably improved when applying the glycine/2HG ratio. The work proposes a promising approach to assess tumor aggressiveness non-invasively using a protocol that can easily be implemented on clinical MRI systems. Availability of such metabolic imaging information prior to surgery would provide neurosurgeons upfront knowledge on tumor type and/or aggressiveness, aiding in surgical decision making. Metabolic imaging may also be the only option available to guide diagnosis and treatment in elderly patients and in those suffering from comorbidities or brainstem gliomas, for which biopsies can hardly be considered.

While this is undoubtedly an appealing and likely future reality, several questions remain to be addressed. The study was conducted on a relatively low number of patients (n = 35) encompassing an unusually high proportion of IDH mutated gliomas (n = 22). Larger cohort studies with an unbiased representation of glioma subtypes are needed to confirm the potential of this method. Such studies should also incorporate state-of-the-art molecular neuropathology for glioma classification, as well as an assessment of tumor grade. Indeed, a correlation between the glycine/2HG ratio and tumor grade may be even more relevant and predictive than a correlation with contrast enhancement. This would also clarify the relationship between glycine and 2HG levels, IDH mutation, and aggressiveness.

The positioning of single voxels in enhancing and non-enhancing regions of the tumors is key to obtain reliable and

reproducible measures. Gliomas are known to be heterogeneous, and studies have shown glycine levels to vary significantly across tumor regions.[6] This suggests that relying on single voxel spectroscopy, as done by Tiwari et al, might introduce a risk of sampling bias. Improving the sensitivity of detection in methods of true metabolic imaging (multivoxels) would help here, and such techniques may include advanced analytical approaches based on deep learning.[7]

An intriguing question is the underlying mechanism resulting in high glycine levels in aggressive tumors. Glycine, which, next to serine, fuels one-carbon (1C) metabolism, has previously been associated with high proliferation rates.[8] One carbon metabolism, encompassing the folate and methionine cycles, provides cells with metabolic intermediates for nucleotide biosynthesis, and targeting the folate cycle is a mainstay in cancer treatment (eg, with the antifolates methotrexate and pemetrexed, as well as 5-fluorouracil). The biological explanation for high glycine in aggressive tumors may thus be linked to a highly active 1C metabolism, necessary to maintain proliferation rates. It is therefore somewhat surprising that expression of major enzymes of this pathway were not found to correlate with glycine levels.[5] Serine hydroxymethyltransferase 2 (SHMT2) is the key mitochondrial enzyme fueling 1C metabolism by generating a 1C unit and glycine from serine, while glycine decarboxylase is part of the glycine cleavage system. SHMT2 mRNA is upregulated in gliomas compared with normal brain tissue, without difference of tumor grade or IDH mutation status,[9] although this may not directly extrapolate to enzyme activity. To address the origin of glycine from 1C metabolism or alternative pathways, it is worthwhile to determine serine levels and related downstream metabolites of the folate cycle such as formate. Of note, increased formate release was recently reported as a hallmark of oxidative cancers and was found to increase cancer cell invasion, including a glioblastoma.[10] Isotopic labeling of precursors of the metabolic pathways involved, to trace their downstream metabolites by metabolomics analysis or by MR spectroscopy of hyperpolarized compounds in vivo, could provide valuable insight into associated metabolic fluxes and enzymatic activity.

In conclusion, the perspective of novel imaging biomarkers of tumor aggressiveness opens exciting new opportunities to extend the role of MR spectroscopy in standard clinical practice and to improve our understanding of underlying metabolic aberrations specific to various brain tumor subtypes.

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