Molecular Imaging toward Precision Medicine

SY16-1

Brain Tumor MRS Imaging at 3T and 7T: 2-Hydroxyglutarate and Glycine

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Cancers reprogram metabolism, resulting in alterations in metabolite concentrations. Accumulation of 2-hydroxyglutarate (2HG) is a direct consequence of specific mutations in isocitrate dehydrogenase (IDH) 1 and 2 in gliomas. The incidence of IDH mutation is high (> 70%) in WHO grade-2 and grade-3 gliomas and secondary glioblastomas. The mutations are associated with 2 - 3 fold longer patient survival compared to IDH wild-type tumors. Glycine (Gly) is markedly elevated in malignant brain tumors and thus may be a biomarker of tumor aggressiveness. Noninvasive and precise analyses of 2HG and Gly in brain tumors may therefore have significant clinical utility in patient care.

We developed a 1H MRS method at 3T for in vivo detection of 2HG in patients with IDH mutant gliomas and published preliminary patient data (Choi et al. Nat Med 2012). The 2HG level was estimated to be 2 - 10 mM with precision in 15 IDH mutant gliomas and undetectable in 15 IDH wild type tumors, indicating that the 2HG-optimized long echo time (TE) PRESS method can be used as a triaging tool for IDH mutant gliomas for an undiagnosed neurological lesion in the workup. After this, we extended our 2HG MRS study to investigate the correlation of 2HG with clinical interventions (Choi et al. J Clin Oncol 2016). The data showed that 2HG MRS can be used for monitoring tumor stableness, progression, and response to treatment. Some data indicated high correlation of 2HG with tumor cellularity. It has become apparent that 2HG MRS imaging provides an unprecedented opportunity to study the biological behavior of the tumors, including issues related to the heterogeneity of cellularity, tumor growth, and transformation to higher grade. The long-TE PRESS is also capable of measuring other tumor-related metabolites with precision, which include Gly. Similarly to 2HG, Gly was increased with progression and decreased with treatment.

We disseminate our long-TE 2HG MRS protocol to other institutions worldwide (currently ~19 hospitals). 2HG-optimal scan parameters were developed for the PRESS sequences of three major vendors (Philips, Siemens, and GE). Metabolite quantification was also developed in parallel. Data from multiple sites will be presented together with some discussion of protocol differences between the vendors.

To improve detection of 2HG and Gly, we continued to develop MRS techniques at 3T and 7T in the past 2-3 years. The strongly-coupled spin signals can be effectively manipulated with triple refocusing. We designed a 2HG triple-refocusing method at 3T that offers improved 2HG detectability compared to long-TE PRESS (An et al. Magn Reson Med, Published online). Also, we achieved markedly improved Gly detection using triple refocusing compared to previously-reported approaches (manuscript under review). High-field MRS benefits from signal gain and enhanced spectral resolution. We reported in-vivo detection of 2HG using long-TE PRESS at 7T (Ganji et al. Magn Reson Med, Published online). Brain tumors are highly heterogeneous. Our on-going development of 2HG echo-planar spectroscopic imaging (EPSI) at 3T and 7T will also be presented.
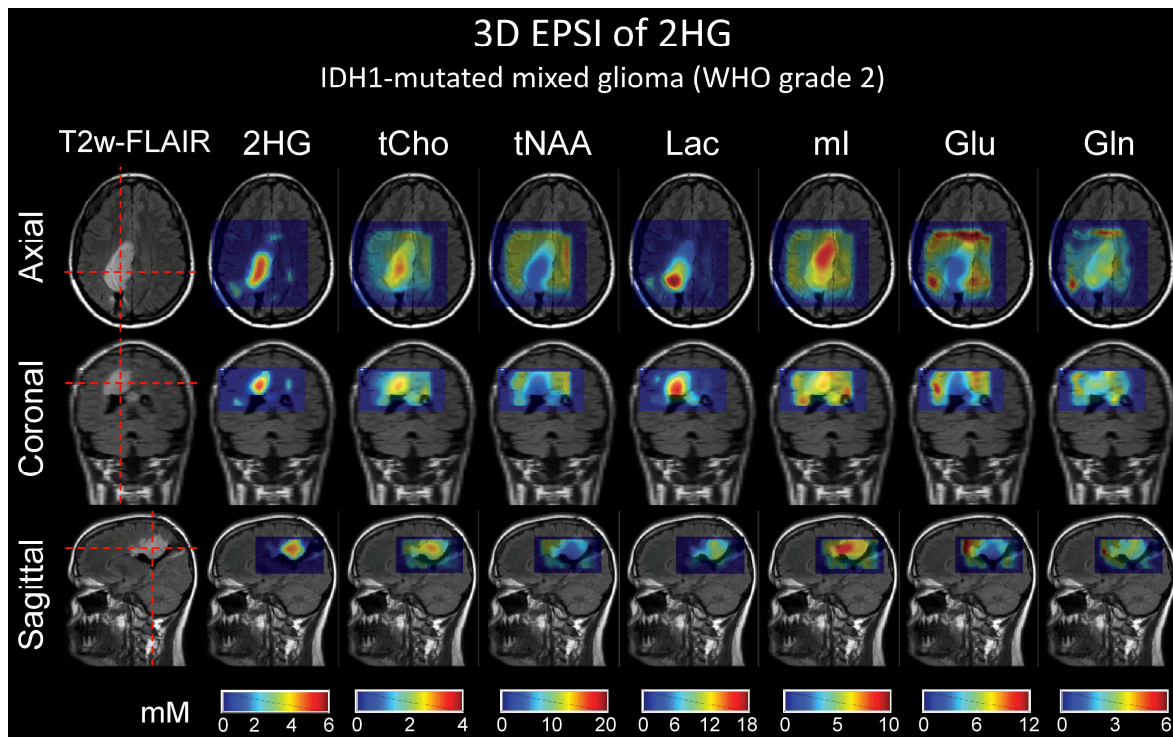
Fig 1. 3D-EPSI-of-2HG

Legend : 3D EPSI of a brain tumor at 3T. The concentrations of 2HG and other metabolites in an IDH mutant glioma patient are color mapped on top of axial, coronal, and sagittal T2-FLAIR images. In the experiment, echo-planar readouts followed PRESS TE 97 ms.

Keywords : MRS, Brain, Glioma, 2-Hydroxyglutarate, Glycine

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Nanomedical Technology in Precision Medicine

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In vivo understanding of target molecules via molecular imaging with nanoprobe is crucial to assess indication of targeted drug and to monitor its efficacy in patients, which are the key factors in planning personalized cancer therapies. In the smart contrast agent, target contents is the cornerstone to cataloguing patient subgroups and evaluating targeted anticancer drug efficacy as well as its resistance. Further, the ultrasensitivity from high crystallized monodiverse metal oxide nanoparticle enables us to image very small sized tumor via MRI. On the other hand, *in vitro* measurement of target contents has a critical role to optimize personalized cancer medicine. These contents promise various nanoplatforms and nanodevices to translate precise and sensitive nanobiosensor into personalized clinical settings. Thus it is necessary to develop *in vivo* and *in vitro* diagnostic tools to measure multiple targets and/or signaling pathways of cancer toward personalized medicine.

Keywords : Molecular MR

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Molecular fMRI of neurochemical dynamics

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Reuptake of neurotransmitters from the brain interstitium shapes chemical signaling processes and is disrupted in several pathologies. Serotonin reuptake in particular is important for mood regulation and is inhibited by first-line drugs for treatment of depression. Here we introduce a molecular-level fMRI technique for micron-scale mapping of serotonin transport in live animals. Intracranial injection of an MRI-detectable serotonin sensor complexed with serotonin, together with serial imaging and compartmental analysis, permits neurotransmitter transport to be quantified as serotonin dissociates from the probe. Application of this strategy to much of the striatum and surrounding areas reveals widespread nonsaturating serotonin removal with maximal rates in the lateral septum. The serotonin reuptake inhibitor fluoxetine selectively suppresses serotonin removal in septal subregions, whereas both fluoxetine and a dopamine transporter blocker depress reuptake in striatum. These results highlight promiscuous pharmacological influences on the serotonergic system and demonstrate the utility of molecular fMRI for characterization of neurochemical dynamics.

Keywords : FMRI, Neurotransmitter, Serotonin

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SY16-4

Translational research in neuro-oncologic imaging

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In the past 10 years there have been a number of scientific discoveries that have dramatically influenced the diagnosis and treatment of malignant gliomas. These discoveries have given crucial information about the cellular origin of gliomas and how we can use molecular defects in these tumors to predict their prognosis and generate more accurate and effective therapeutic regimens. To link between bench work and clinical application in the filed of translational research in neuro-oncologic imaging, there should be several efforts in several aspects. First, understanding molecular biology including genomic alterations is necessary. For example, new WHO classification suggests that genetic information should be integrated for the diagnosis of gliomas, which includes IDH mutation and 1p/19q co-deletion. Second, appropriate animal models for brain tumors should be available for the translational research in neuro-oncologic imaging. There have been developments of brain tumor animal models such as patient-derived xenograft models. To test new strategies for brain tumor diagnosis and treatment, these models help researches to widen investigation scopes. Third, clinical support for potential application of research ideas is necessary, which includes neurosurgery, neuro-oncology, radiation oncology, neuropathology and neuroimaging.

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Keywords : Translational research, Neurooncology, Neuroimaging