Title
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Abstracts

TM-07. ^{13}C MRS DETECTS METABOLIC FLUX ADAPTATION IN IDH MUTANT GLIOMA CELLS

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The isocitrate dehydrogenase (IDH)1 mutation is associated with accumulation of 2-hydroxyglutarate (2-HG), but the metabolic fluxes associated with 2-HG production and cellular reprogramming of mutant IDH1 cells are not fully understood. The objective of this study was to use ^{13}C magnetic resonance spectroscopy (MRS) to probe the fate of ^{13}C-labeled metabolites (at thermal polarization and hyperpolarized by dynamic nuclear polarization) and to monitor the glycolytic pathway, the TCA cycle, and glutamine metabolism in wild-type and mutant IDH1 glioma cells. To achieve this goal, U87 cells expressing mutant IDH1 and wild-type IDH1 were generated by transduction with a lentiviral vector coding for mutant or wild-type IDH1 respectively. MRS studies were performed using a cell perfusion (bioreactor) system. Live cells were exposed to hyperpolarized 1-^{13}C or 2-^{13}C-labeled pyruvic acid, 1-^{13}C glucose or 3-^{13}C glutamine and cell metabolism was probed using ^{13}C MRS. We found that in mutant IDH1 cells pyruvate flux to lactate was increased relative to wild-type cells, and pyruvate flux to glutamate and 2-HG was decreased compared to pyruvate flux to glutamate in wild-type IDH1 cell. Glutamine flux to glutamate in wild-type cells, or to glutamate and 2-HG in mutant IDH1 cells was comparable. Accordingly, the total intracellular glutamate pool was reduced in mutant IDH1 cells. The drop in pyruvate flux to the TCA cycle was mediated by a significant drop in pyruvate dehydrogenase (PDH) activity, which was due to significantly increased inhibitory PDH phosphorylation. When considering 2-HG synthesis, our data also indicate that, consistent with previous work, the majority of 2-HG is produced from glutamine (82%). However in our cells a significant portion (18%) was also derived from glucose. Our findings thus point to metabolic reprogramming in IDH1 mutant cells beyond 2-HG production and highlight the value of MRS for characterizing the metabolic changes associated with the IDH1 mutation.