O4.09. IN SITU METABOLIC PROFILING SHEDS LIGHT ON OXIDATIVE STRESS PATHWAYS IN IDH1 MUTANT OLIGODENDROGLIOMA
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BACKGROUND: The oncometabolite D-2-hydroxyglutarate (2-HG) is strongly increased in glial tumors presenting a heterozygous point mutation in isocitrate dehydrogenase (IDH) and is a key indicator of aberrant metabolic circuitries in these tumors. IDH1 is a dimeric enzyme converting isocitrate to α-ketoglutarate (α-KG), a metabolite involved in energy production, macromolecule biosynthesis and an important enzyme co-factor. In IDH1-mutated tumors, α-KG is processed to 2-HG in a NADPH consuming reaction, leading to a hypermethylation phenotype through inhibition of α-KG-dependent demethylases. However the direct effect of the IDH mutation on metabolic dysregulation remains poorly understood. A limitation in the analysis of IDH mutated tumors is the lack of appropriate pre-clinical models. Indeed glioma cells carrying the IDH mutation are notoriously difficult to grow in vitro and only a handful of laboratories, including ours, have been able to generate patient derived orthotopic xenograft models. Thus, current studies addressing the role of 2-HG are mostly based on cell lines overexpressing mutant IDH1 in a wildtype background, with unknown consequences for the function of the oncogenic enzyme. Here we aimed to get insight into the major metabolic aberrations observed in human IDH mutant gliomas with a special emphasis on oxidative stress and glutamine/glutamate pathways.

METHODS: In situ high resolution mass spectrometric imaging (MSI) was performed on IDH1 mutant xenografts derived from human oligodendrogial tumors with 1p19q deletion. This allows a detailed metabolic profiling with anatomical localization in tumor sections. Key enzymes of the perturbed metabolic pathways were monitored by Western blot and immunohistochemistry. Liquid chromatography mass spectrometry (LC-MS) was applied to validate our findings in fresh clinical specimen.

RESULTS: 2-HG was specifically localized in the tumor bed but not in the surrounding brain parenchyma, while α-KG levels were not significantly altered in IDH1 mutated tumors. We identified a large set of differentially present metabolites in IDH1-mutant tumors, including the anti-oxidant glutathione. Importantly we reveal significant differences in metabolite levels between human glioma samples with an endogenous IDH mutation compared to previously reported data on mutant IDH1 overexpressing cell lines.

CONCLUSIONS: We provide for the first time a detailed metabolic profiling of human IDH mutant gliomas with high anatomical resolution in situ. Our data point to the importance of oxidative stress regulation and its possible link to epigenetic dysregulation in IDH mutant oligodendrogliomas.