Title: Hyperpolarized Imaging of BCAT1 for Targeted Hepatocellular Carcinoma Therapy

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Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality worldwide, with most patients presenting with advanced disease and a median survival of less than two years. Despite expanding therapeutic options, HCC remains one of the few malignancies where molecular profiling does not inform clinical decision-making, limiting our ability to stratify risk and tailor therapies based on tumor biology. Emerging evidence demonstrates that distinct molecular and metabolic profiles correlate with therapeutic responses in HCC. Branched-chain amino acid transaminase 1 (BCAT1) expression identifies an aggressive HCC subtype associated with poor prognosis and hyperactivated mTOR signaling. BCAT1 catalyzes the reversible transamination of branched chain amino acids (leucine, isoleucine, valine) to their corresponding α-ketoacids (KIC, KMV, KIV) while simultaneously converting alpha-ketoglutarate (αKG) to glutamate. Our research demonstrates that BCAT1 activity can be non-invasively detected using Dynamic Nuclear Polarization-^{13}Carbon-Magnetic Resonance Spectroscopic Imaging (DNP-13C-MRSI). By administering hyperpolarized ^{13}C-labeled α-ketoisocaproate (KIC), BCAT1 expression can be visualized through the in vivo conversion of 1-^{13}C-KIC into 1-^{13}C-leucine, providing a promising imaging biomarker for identifying BCAT1-expressing HCC tumors. Using patient-derived and established cell lines, we have shown that BCAT1 expression correlates with intracellular αKG levels, a crucial metabolite that regulates gene expression and HIF1α signaling through αKG-dependent enzymes. BCAT1 overexpression in some, but not all, HCC cell lines dramatically alters cellular phenotype, enhancing cellular proliferation and metabolic activity. Furthermore, through BCAT1's relationship with mTOR signaling and αKG metabolism, we have demonstrated that BCAT1 expression predicts sensitivity to mTOR inhibitors and to combination therapy with cell-permeable dimethyl-αKG plus BCAT1/2 inhibitors. Together, this work establishes hyperpolarized MRI of 1-^{13}C-KIC as a critically needed dual biomarker for HCC—providing both prognostic information and predicting response to targeted metabolic therapies.