Background: With growing therapeutic options for patients with hepatocellular carcinoma (HCC), identifying predictors of response to therapies has become increasingly important. We investigated the impact of β-catenin mutations on response to transarterial chemoembolization (TACE) in unresectable HCC.

Methods: HCC patients undergoing TACE were enrolled in a prospective cohort study at two academic medical centers from 2016-2021. Mutational profiles were determined by next generation sequencing of HCC biopsies. Tumor response was measured by modified Response Evaluation Criteria in Solid Tumors. Four established cell lines (Huh7, SNU-447, SNU-398, HepG2) and one primary cell line were used for *in vitro* studies. Dynamic Nuclear Polarization Carbon-13 Magnetic Resonance Imaging Spectroscopy was performed to measure in vivo metabolism

Results: 53 HCCs from 50 patients were biopsied, including 22/53 tumors with β-catenin pathway mutations. Tumors with these mutations demonstrated higher rates of complete response after TACE (12/22, 54.5% vs 7/31, 22.6%, p=0.02) and a longer time-to-progression (median not reached vs 8.3 months, p=0.02). Similarly, β-catenin mutant HCC cell lines showed reduced viability (21.4% vs 59.9%, p<0.01) and ATP levels (8.47 vs 4.26 pM/cell, p<0.001) under ischemic conditions compared to β-catenin wildtype HCC lines. β-catenin mutant HCC cells also demonstrated greater sensitivity to inhibition of the electron transport chain (43.9% vs 59.5%, p=0.02,) and higher basal oxygen consumption (0.74 vs 0.39 pM/min, p=0.04), maximal respiratory capacity (1.46 vs 0.51 pM/min, p=0.01) and ATP-linked respiration (0.58 vs 0.29 pM/min, p=0.04). Consistent with these findings, HCC patient-derived xenografts with β-catenin pathway mutations demonstrated reduced levels of conversion of pyruvate to lactate *in vivo.*

Conclusions: HCC tumors with β-catenin mutations are more susceptible to treatment-induced ischemia due to greater dependence on oxidative phosphorylation for bioenergetic homeostasis, providing a molecular basis for treatment selection in patients with HCC.