Hexokinase Domain Containing 1 (Hkdc1): A Metabolic Regulator of Nonalcoholic Fatty Liver Disease (NAFLD)

Yu, Caroline (School: Jericho High School)

Nonalcoholic fatty liver disease (NAFLD) is a major health concern in western countries as the most common contributor to chronic liver disease. Left untreated, NAFLD can develop into chronic nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma, leading to liver failure which necessitates costly transplants. NAFLD's undetermined molecular origin is highly associated with limitations of treatment outcomes, but targeting key regulators of hepatic energy metabolism, such as hexokinases, may reveal new targets. In NAFLD, hexokinase domain containing 1 (Hkdc1) is overexpressed, and here the role of Hkdc1 in in-vitro NAFLD progression was explored. Gifted murine Hkdc1 liver-specific knockouts (Hkdc1-LKO) post 10 weeks NASH inducing diet showed significant increases of lipid accumulation with advanced steatosis (27.5% triglyceride increase over control). Furthermore, microvesicular lipid accumulation in Hkdc1-LKO hepatic tissue suggested cellular stress associated with mitochondrial dysregulation in NAFLD. Bioinformatics (PHYRE Protein Fold Recognition Server and PyMOL) and confocal imaging indicated previously undocumented Hkdc1 binding with the mitochondrial membrane ($p<0.001$) while qualitative analysis suggested altered hepatic mitochondrial morphology with Hkdc1 binding. Western blot analysis showed Hkdc1 overexpression targeted Mitofusin-2 to stimulate mitochondrial fusion and function ($p<0.05$). This study elucidated the role of Hkdc1 overexpression as a primary inhibitor of mitochondrial dysfunction in NAFLD progression. Interestingly, Hkdc1 may serve as a biomarker to distinguish early NAFLD from other hepatic disorders. Subsequent investigation of Hkdc1 transduction in NAFLD progression may unveil a novel target for early NAFLD treatment.

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