

# **Translational Approach to Examine the Importance of Aerobic Fitness on Nonalcoholic Fatty Liver Disease**

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Low cardiorespiratory fitness, independent of physical activity levels, is the best predictor of early mortality and is linked to type 2 diabetes and CVD. In the absence of exercise training, it is believed that genetic inheritance accounts for up to 70% of the variation in intrinsic aerobic fitness. Recent cross-sectional reports in humans also have linked low aerobic fitness with nonalcoholic fatty liver disease (NAFLD). NAFLD, fatty liver not due to alcohol consumption, encompasses a gamut of liver maladaptations and is a primary cause of chronic liver disease and liver-related morbidity and mortality. NAFLD occurs in ~30% of US adults, 75-100% of obese and extremely obese individuals, and is considered the hepatic component of the metabolic syndrome. Despite the recent observations in humans between low fitness and NAFLD, there is a paucity of mechanistic information detailing this link. In order to address this important clinical problem, we have developed an interdisciplinary team across multiple institutions and fields of study and have taken a translational approach, employing both novel whole animal model studies and isolated primary hepatocyte cell culture experiments, to gain mechanistic insight into the human observational studies. We have utilized a novel rat model in which rats are artificially selected over several generations for high and low intrinsic endurance capacity, resulting in high capacity runners (HCR) with high aerobic fitness and low capacity runners (LCR) with significantly lower aerobic fitness (Science, 307:418-20, 2005). These rats display contrasting phenotypes without the influence of exercise training, making them an excellent model to mechanistically assess the role of aerobic fitness on NAFLD. Utilizing this model, we have provided the first mechanistic evidence that the LCR rats have reduced hepatic

mitochondrial content and oxidative capacity, increased hepatic de novo lipogenic profiles, and develop hepatic steatosis with progression to greater fibrosis and apoptosis compared to the HCR rats. The LCR rats also are unable to maintain systemic insulin sensitivity following exposure to high-fat feeding. However, since it is impossible to completely eliminate the influence of peripheral factors on liver metabolism, we have subsequently isolated primary hepatocytes from HCR and LCR rats. We have observed a similar phenotype in the primary hepatocytes from LCR animals, with significant reductions in fatty acid oxidation and the inability to maintain insulin signaling in response to lipid exposure compared with HCR hepatocytes. These findings have important clinical implications, as low aerobic fitness due to physical inactivity and/or genetic inheritability may lead to increased susceptibility to NAFLD, and suggest that the clinical measurement of aerobic fitness may serve as a valuable prognostic tool. We are currently conducting a human clinical trial to assess the efficacy of exercise in improving aerobic fitness and reducing NAFLD, and because exercise is the proven method to increase aerobic fitness, it should remain the cornerstone therapy for fatty liver disease.