Not just fat: proteotoxicity in non-alcoholic fatty liver disease (NAFLD)

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Abstract: Escalating prevalence of metabolic syndrome and its skewed systemic and/or tissue-specific manifestation in the form of type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases etc. have become major public health problem across India. NAFLD is characterized by ER stress, hepatocellular death and accumulation of ubiquitinylated inclusion bodies. Thus hepatic proteasomal dysfunction in the background of steatosis underscores the importance of proteotoxicity in the pathogenesis of NAFLD. Impact, outcome and molecular basis of proteasomal inhibition on hepatocellular health and in the pathogenesis of NAFLD remained unexplored. We demonstrate that acute inhibition of proteasomal activity leads to profound hepatic injury and dysfunction, effects that are associated with ROS accumulation that in turn promotes ASK1-JNK dependent hepatocellular death with concomitant failure in surmounting an effective anti-oxidant response through PEDF-PPARg-NRF2 pathway. Utilizing the two druggable candidates in these pathways we show that co-treatment with ASK1 inhibitor and PPARg activator potently reverse hepatic proteotoxicity, improve insulin resistance in a murine model of NAFLD.