The fat that feeds the fire: Understanding the pathogenesis of NASH and how it progresses to hepatocellular carcinoma

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Although discussion of the obesity epidemic spreading around the developed world had become a cocktail party cliché, the impact of obesity on public health and the economy of healthcare is profound and long-lasting. In the past decade, cancer had joined the long list of chronic debilitating diseases whose risk is greatly increased by obesity and hypernutrition. The impact of obesity on cancer risk is most striking in the liver and pancreas, two organs that are directly engaged in lipid metabolism. To better understand how obesity leads to non-alcoholic steatohepatitis (NASH), a chronic fat-induced liver inflammation that progresses to liver fibrosis and then to cancer, we had developed a new mouse model that develops NASH-like disease in response to ingestion of high fat diet. Using this model, we found that endoplasmic reticulum (ER) stress and TNF-driven inflammation play key roles in the development of NASH and its progression to hepatocellular carcinoma (HCC). We also found that interference with TNF signaling or administration of compounds that relieve ER stress can be used to prevent NASH development and may be effective in reducing HCC risk. In addition, we have identified inflammatory mechanisms that interfere with the acquisition of an anti-HCC immune response. Interference with these immunosuppressive mechanisms represents an effective strategy for the treatment of NASH-induced HCC, a heretofore incurable malignancy.