



LIVER CENTER SEMINAR SERIES

Unraveling the Mechanisms of Steatohepatitis: Roles of too Much JNK and Not Enough Autophagy

SPEAKER:

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TIME & PLACE

9:00 AM. ROOM S-214

(Second floor, Medical Sciences, Parnassus Campus)

The mechanisms by which fatty liver (hepatic steatosis) develops and progresses to liver injury (steatohepatitis) are largely unknown. Human and experimental steatohepatitis are associated with oxidative stress and overexpression of the cytochrome P450 isoform 2E1 (CYP2E1). Studies in cultured hepatocytes overexpressing CYP2E1 revealed that the chronic oxidant stress induced by this enzyme sensitized cells to death from TNF and impaired their insulin signaling. Both effects were mediated by oxidant-induced overactivation of c-Jun N-terminal kinase (JNK). High fat diet-induced steatohepatitis in mice was associated with JNK overactivation and a genetic knockout or knockdown of the JNK1 isoform blocked the development of steatosis and liver injury and reversed established disease. In contrast, loss of JNK2 worsened liver injury, delineating critical but distinct functions of the two JNK isoforms in the pathogenesis of steatohepatitis.

In other studies the function of the lysosomal degradative pathway of macroautophagy in the regulation of intracellular lipid stores was examined. Genetic or pharmacological inhibition of macroautophagy increased hepatocyte triglyceride (TG) accumulation in lipid droplets as the result of a decrease in lipolysis. Consistent with the breakdown of stored TG by macroautophagy, lipid and lipid droplet components were found to traffic through the autophagic pathway. Studies in fasted mice and mice with a hepatocyte specific knockout of the macroautophagy gene *atg7* confirmed that autophagy functioned to limit hepatic lipid content in vivo. These investigations demonstrate that lipids are a substrate for macroautophagy and that this degradative pathway regulates hepatic lipid stores.

References

Singh, R., Wang, Y., Xiang, Y., Tanaka, K.E., Gaarde, W.A. and Czaja, M.J. Differential effects of JNK1 and JNK2 inhibition on murine steatohepatitis and insulin resistance. *Hepatology* 2009; 49:87-96.

Singh, R., Kaushik, S., Wang, Y., Xiang, Y., Novak, I., Komatsu, M., Tanaka, K., Cuervo, A.M., and Czaja, M.J. Autophagy regulates lipid metabolism. *Nature* 2009; 458:1131-1135.

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