Title: How Diet regulates NASH progression.
Casp2PIDDosome: A New Regulator of Hepatic Lipid Metabolism

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Obesity is pandemic, affecting approximately 40% population across the world, and its associated complications are prevalent. Of these, non-alcoholic fatty liver diseases (NAFLD) is becoming the most serious liver complication that causes a heavy social burden and demands high medical costs. Epidemiology indicates that a change in lifestyle and dietary patterns significantly affect the incidence of obesity. Indeed, consumption of western diet (WD), of which the ingredients contain a high portion of processed meat, saturated fats, and refined sweeteners, is steeply increasing and closely correlated with the prevalence of obesity and metabolic syndrome (MS). However, the pathogenic mechanism linking obesogenic diet to NASH is far from clear.

Sterol regulated element binding protein (SREBP) is the master regulator of hepatic lipid synthesis: SREBP1c mainly regulates triglyceride synthesis and SREBP2 synthesizes cholesterol. Sterol deficiency triggers SCAP-mediated SREBP activation, whereas hypernutrition together with ER-stress activate SREBP1/2 via caspase-2 (Casp2), the most conserved cysteine protease, promoting lipid synthesis in response to ER stress by leading non-canonical activation and secretion of site-1 protease (S1P). Hence, we proposed serum S1P as an early detection marker and inhibition of Casp2 as a therapeutic approach for patients with NASH (Kim et al., ***Cell*** 2018). However, whether these pathways interact and how they are selectively activated by different dietary cues is unknown. In recent study, we reveal regulatory crosstalk between the two pathways that controls the transition from hepatosteatosis to steatohepatitis. Hepatic ER-stress elicited by NASH-inducing diets activates IRE1 and induces expression of the PIDDosome subunits caspase-2, RAIDD and PIDD1, along with INSIG2, an inhibitor of SCAP-dependent SREBP activation. PIDDosome assembly activates caspase-2 and sustains IRE1 activation. PIDDosome ablation or IRE1 inhibition blunt steatohepatitis and diminish INSIG2 expression. Conversely, while inhibiting simple steatosis, SCAP ablation amplifies IRE1 and PIDDosome activation and liver damage in NASH-diet fed animals, effects linked to ER disruption and preventable by IRE1 inhibition. Thus, the PIDDosome and SCAP pathways antagonistically modulate nutrient-induced hepatic ER-stress to control non-linear transition from simple steatosis to hepatitis, a key step in NASH pathogenesis (Kim, et al., ***Cell Metabolism*** 2022)