OS42-2 **Chemical-induced abnormal lipid metabolism and multiple metabolic toxicities**

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AMP-activated protein kinase (AMPK) is a key regulator of energy metabolism. Inactivation of AMPK results in the repression of cellular catabolism and activation of several anabolic processes leading to the negative metabolic adjustment. Suppression of AMPK by chemicals induces multiple metabolic toxicities in various tissues. Inactivation of AMPK by orotic acid induces hepatic lipogenesis by activating mTOR-LXRα-SREBP-1 pathway in hepatocytes. In the vasculature, suppression of AMPK induces endothelial dysfunction. Metformin- or insulin-induced activation of Akt and eNOS is compromised by orotic acid or uric acid in HUVEC cells as well as in rat aortic ring resulting in the endothelial dysfunction and hypertension. AMPK activation, although generally regarded as a positive regulator of various metabolic syndromes, can also increase the risk of the metabolic syndrome. We found that activation of AMPK by metformin or berberine induces the phosphorylation of CCAAT/enhancer-binding protein β (C/EBPβ) and the expression of fatty acid translocase/CD36 in the liver. Upregulation of CD36 facilitates the uptake of fatty acid in the liver and induces hepatic steatosis. Autophagy, a lysosome-mediated intracellular bulk degradation process, is promoted by AMPK and inhibited by mTOR. Blockage of autophagy by some non-steroidal anti-inflammatory drugs inhibited breakdown of lipid droplet and induced cellular lipid accumulation. Taken together, chemical-induced impairment of lipid metabolism disrupts cellular energy homeostasis and induces diverse metabolic toxicities.