

## SUMMARY

Non-alcoholic fatty liver and subsequent insulin resistency are important complications of obesity. NAFLD is vulnerable to conditions that compromise hepatocellular energy homeostasis. Lipid-laden hepatocytes highly express uncoupling protein-2, which – by mediating the proton leak – competes with the cells' ATP synthesis and modulates the generation of reactive oxygen species. However, the link between UCP2 expression and susceptibility of fatty liver to acute injury is still unclear. We asked whether absence of UCP2 is beneficial for leptin deficient *ob/ob* mice when challenged with Fas-mediated cell destruction and subsequent acute liver injury. *Ob/ob* mice deficient for UCP2 (*ob/ob:ucp2<sup>-/-</sup>*) and UCP2-competent littermates (*ob/ob:ucp2<sup>+/+</sup>*) received a single dose of agonistic anti-Fas antibody (Jo2) intraperitoneally. Low-dose Jo2 (0,15 mg/ttkg) caused less ALT elevation and lower apoptosis rates in *ob/ob:ucp2<sup>-/-</sup>* mice. High-dose Jo2 (0,4 mg/ttkg) proved uniformly fatal in 24 hours; however, *ob/ob:ucp2<sup>-/-</sup>* mice survived longer with less depletion of hepatic ATP stores, indicating that fatty hepatocytes may benefit from ablation of UCP2 during Fas-mediated acute liver injury. Although UCP2 reportedly controls mitochondrial generation of ROS, we could not detect significant difference in MDA levels of tissue lysates from the different genotypes. This finding prompted us to determine UCP2 expression in Kupffer cells, a major source of intrahepatic oxidative stress. UCP2 expression was found diminished in Kupffer cells of untreated *ob/ob:ucp2<sup>+/+</sup>* mice, contributing to increased oxidative stress and limiting the impact of UCP2 ablation. Therefore, UCP2 abundance in fatty liver exacerbates Fas-mediated cell destruction by compromising ATP stores and diminished expression of UCP2 found in Kupffer cells results in persistent oxidative stress. Our data emphasize the cell-specific therapeutic approach when considering the enhancement of mitochondrial uncoupling in fatty liver disease.

Fluvastatin is a widely used drug in treatment of hyperlipidemia which is commonly associated with obesity. However, its chemopreventive effect on *in vivo* tumor development has not been studied yet. Using Gelaspon sponge discs we implanted hepatocellular cancer cells under the renal capsules of rats. The animals received different doses of fluvastatin orally, either started simultaneously with the implantation or were pretreated only before the surgical procedure. Also, fluvastatin was administered before and continued after the tumor implantation in a third group of animals. The drug showed no significant impact on cancer development when given only before implantation; while the anticancer effect was detectable in higher doses of simultaneous administration. Additionally, chemopreventive fluvastatin treatment continued after tumor implantation demonstrated the most intense anticancer effect. Our results draw the attention to the beneficial effect of fluvastatin inhibiting *in vivo* hepatocellular cancer development.