Abstract

Under normal conditions, fasting results in decreased protein disulfide isomerase (PDI) activity and accumulation of unfolded proteins, leading to the subsequent activation of the unfolded protein response (UPR)/autophagy signaling pathway to eliminate damaged mitochondria. Fasting also induces upregulation of thioredoxin-interacting protein (TXNIP) expression and mice deficient of this protein (TXNIP-KO mice) was shown to develop severe hypoglycemia, hyperlipidemia and liver steatosis (LS). In the present study, we aimed to determine the role of TXNIP in fasting-induced LS by using male TXNIP-KO mice that developed LS without severe hypoglycemia. In TXNIP-KO mice, fasting induced severe microvesicular LS. Examinations by transmission electron microscopy revealed mitochondria with smaller size and deformities and the presence of few autophagosomes. The expression of β-oxidation-associated genes remained at the same level and the level of LC3-II was low. PDI activity level stayed at the original level and the levels of p-IRE1 and X-box binding protein 1 spliced form (sXBP1) were lower. Interestingly, treatment of TXNIP-KO mice with bacitracin, a PDI inhibitor, restored the level of LC3-II after fasting. These results suggest that TXNIP regulates PDI activity and subsequent activation of the UPR/autophagy pathway and plays a protective role in fasting-induced LS.