Mitophagy in steatotic hepatocytes of ethanol-treated wild-type and Parkin knockout mice

Nabil Eid, Yuko Ito, and Yoshinori Otsuki
Department of Anatomy and Cell Biology, Division of Life Sciences, Osaka Medical College, Daigaku machi, Takatsuki, Osaka, Japan
Submitted 28 July 2015; accepted in final form 5 August 2015

TO THE EDITOR: In a recent paper in the American Journal of Physiology Gastrointestinal and Liver Physiology, Williams et al. (21) investigated the role of Parkin against alcohol-induced liver injury in wild-type (WT) and Parkin knockout (KO) mice using two methods of alcohol administration: acute-binge and Gao-binge. They found that Parkin protects against alcohol-induced liver injury and steatosis in treated WT mice via activation of mitophagy (autophagic clearance of proapoptotic mitochondria) (5, 6, 9, 16, 19, 20, 22), reduction of steatosis, and enhancement of mitochondrial adaptation to ethanol toxicity. In ethanol-treated Parkin KO mice, there was a reduction of mitophagy resulting in an increase of hepatic damage and steatosis in addition to suppression of mitochondrial adaptation.

Seeing is believing, and transmission electron microscopy (TEM) is still the golden tool for analysis of autophagy (13). A few years ago, we were the first to show pieces of evidence for involvement of PINK1-Parkin pathway in activation of mitophagy in hepatocytes of chronic ethanol-treated rats (ETRs) (2, 4). Using immunoelectron microscopy, we found that PINK1 (stimulator of Parkin translocation to damaged mitochondria and specific marker of mitophagy) was overexpressed in damaged mitochondria and mitophagosomes (autophagosomes engulfing mitochondria) in hepatocytes of ETRs. This was supported by localization of LC3 (a specific marker of autophagy) to mitophagosomes (2, 16, 20, 22). Moreover, TEM revealed perinuclear aggregations of damaged mitochondria and mitophagosomes in hepatocytes of ETRs, an additional evidence of PINK1-Parkin regulation of mitophagy in alcoholic liver (2, 3, 20, 22). Activation of mitophagy in hepatocytes of ETRs was confirmed by immunohistochemical detection of LC3 puncta and colocalization of LC3 and lysosomal cathepsins, indicating the formation of autolysosomes (2, 15, 23, 24).

Four important issues regarding Parkin-mediated mitophagy in ethanol-treated animals (2, 3, 11, 21) are worthy to be addressed. The first issue is related to ring-shaped mitochondria or spheroids, observed in livers of ETRs 50 years ago (8) and recently reported to be negatively regulated by Parkin (12). Actually, we detected a few ring-shaped mitochondria in hepatocytes of ETRs (2), as shown in Fig. 1 and also in Sertoli cells (3, 7). We wonder whether Williams et al. (21) observed mitochondrial spheroids in hepatocytes of WT and Parkin KO mice. The second issue is related to the PINK1-Parkin-mediated formation of mitochondrial-derived vesicles under oxidative stress in some cell lines for avoiding the sequestration of the whole mitochondrion as in canonical mitophagy (10, 14). We speculate that there is a possibility of formation of these vesicles in hepatocytes of alcohol-exposed animals based on oxidative damage of ethanol (5, 17, 19). The third issue is concerned with the selective escape of antiapoptotic proteins from the mitochondria to endoplasmic reticulum during mitophagy in stressed cells (18). Is there a role for selective preservation of antiapoptotic proteins in ethanol-induced hepatocyte mitophagy?

The fourth issue is related to the reduction of hepatic steatosis by Parkin (21). Mitochondria may directly donate their membrane to form autophagosomes during Parkin-associated mitophagy (1); thus there is a possibility of Parkin-mediated autolipophagosome formation in hepatocytes of ethanol-treated WT mice by providing the autolipophagosomal membrane and subsequent reduction of steatosis via lipophagy (autophagy of lipid droplets) (2, 5, 11, 15).

REFERENCES


