

The regulation of autophagy and ROS axis in fatty liver disease

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Nonalcoholic fatty liver disease are caused by dysregulation of lipid metabolism and are associated with oxidative stress, a condition resulted from an imbalance between the production and elimination of reactive oxygen species (ROS). Accumulation of ROS induces the expression of antioxidative genes through activation of Nrf2-Keap1 pathway. The activity of Nrf2 is negatively regulated by Keap1, a substrate adaptor for the ubiquitination of Nrf2 by the Cul3-Rbx1 E3 ubiquitin ligase complex. Keap1 targets Nrf2 for proteasomal degradation in normal condition. Upon oxidative stress, Keap1 is modified and disrupts its interaction with Nrf2 and perturbs its ability to direct Nrf2 ubiquitination. Accordingly, Nrf2-Keap1 pathway plays an essential protective role from oxidative stress in metabolic liver diseases. In addition to this canonical pathway, p62 activates Nrf2 by disrupting the Keap1-Nrf2 interaction in autophagy-deficient cells. Nonalcoholic fatty liver diseases are also associated with hyperactivation of mTORC1 signaling pathway or insufficient autophagic activity. Activated mTORC1 attenuates autophagy, resulting in the accumulation of p62. However, the regulation of p62-dependent Nrf2-Keap1 pathway has not been clearly understood in the contexts of metabolic liver diseases. Therefore, we investigate that the regulatory mechanisms for p62-Nrf2-Keap1 axis in dysregulation of lipid metabolism.