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Role of mitochondrial dysfunction in primary graft non-function after transplantation of marginal liver grafts: Study with novel intra vital confocal/multi-photon microscopy

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Background & Aim: The mitochondrial permeability transition (MPT) has been implicated in liver injury in vivo after ischemia/reperfusion (I/R). Reactive oxygen and nitrogen species (ROS & RNS) can trigger onset of the MPT. Hepatic I/R occur in organ harvesting, cold storage, and implantation surgery during liver transplantation. This abstract describes studies investigating mitochondrial depolarization caused by the MPT in vivo and its relationship to occurrence of primary non-function after transplantation of marginal liver grafts.

Methods: Fatty liver transplantation was performed in rats and non-heart-beating liver transplantation was performed in mice. Mitochondrial depolarization was monitored using intra vital confocal/multi-photon microscopy, a novel technology that allows direct visualization of mitochondria in living animals.

Findings: Inducible nitric oxide synthase (iNOS) expression, alanine aminotransferase release, total bilirubin, hepatic necrosis, TUNEL-positive cells and cleaved caspase-3 were higher in fatty liver grafts (FG) induced by ethanol treatment than in lean grafts (LG). After implantation, viable cells with depolarized mitochondria were 3-fold higher in FG than in LG. 1400W, a specific iNOS inhibitor, prevented mitochondrial depolarization, decreased graft injury and improved graft survival 3.5-fold. In another study, iNOS expression, mitochondrial depolarization and liver injury and dysfunction were substantially higher in grafts from cardiac-death donors (CDD) than in grafts from non-cardiac death donors. Mitochondrial depolarization and graft injury in CDD grafts were markedly attenuated by iNOS-deficiency.

Conclusion & Significance: Mitochondrial dysfunction occurs in marginal liver grafts, leading to graft failure after transplantation. Mitochondrial dysfunction in marginal grafts is, at least in part, due to increased iNOS expression and excessive RNS formation. Prevention of mitochondrial dysfunction and inhibition of RNS formation are promising strategies to improve the outcomes of marginal liver transplantation.

Biography

Zhi Zhong is an Associate Professor in College of Pharmacy, Medical University of South Carolina, SC, USA. Her expertise is in hepatic ischemia/reperfusion injury and experimental liver transplantation. She obtained her Doctoral degree at University of North Carolina, Chapel Hill. She has been conducting basic and translational research on the role of reactive oxygen and nitrogen species in mitochondrial dysfunction in various liver injury/diseases and published ~100 papers in the field. She is also a Reviewer and Editorial Board Member of many scientific journals.

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