Small-For-Size Liver Transplantation Increases Pulmonary Injury in Rats: Prevention by NIM811

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Introduction: Pulmonary complications occurring after liver transplantation frequently lead to mortality. Transplantation of small-for-size liver grafts increases the risk of graft failure. Accordingly, the aim of this study was to investigate whether acute pulmonary injury occurs after small-for-size liver transplantation. Moreover, we reported that NIM811, an inhibitor of the mitochondrial permeability transition (MPT), prevents dysfunction of small-for-size liver grafts. Here, we investigated whether protection of liver grafts by NIM811 also attenuated acute pulmonary injury after small-for-size liver transplantation.

Methods: Livers were reduced to 50% of original size, stored in cold UW solution for 6 h and then implanted into recipients of the same or about twice the donor body weight, resulting in half-size and quarter-size liver grafts, respectively. NIM811 (5 µM) was added to the storage solution. Lungs and livers were harvested at 5, 18 and 38 h after implantation.

Results: Hepatic necrosis and alanine aminotransferase release were higher after transplantation of quarter-size than full-size and half-size grafts, indicating more severe liver injury. Liver regeneration increased in half-size grafts but was suppressed in quarter-size grafts. NIM811 blocked liver injury and promoted regeneration of quarter-size grafts, as observed previously. Pulmonary histological alterations were minimal at 5-18 h after liver transplantation. After 38 h, infiltration of neutrophils and monocytes/macrophages to pulmonary alveoli occurred with sepsis thickening and increased cellularity in quarter-size graft recipients. These changes were mild in lungs of full-size and half-size graft recipients. NIM811 decreased alveolar septal thickening, monocytes/macrophage infiltration and neutrophil infiltration by 52, 44 and 51%, respectively. Infiltrating leukocytes can produce reactive oxygen and nitrogen species, leading to cell death. 4-Hydroxynonenal and 3-nitrotyrosine adducts increased markedly in pulmonary leukocytes, vascular endothelial cells and alveolar epithelial cells in quarter-size graft recipients, indicating oxidative/nitrosative stresses. TUNEL-positive vascular endothelial/ alveolar epithelial cells were 12- and 8-fold higher in lungs of quarter-size compared to full-size and half-size graft recipients, indicating apoptosis. NIM811 blunted 4-hydroxynonenal and 3-nitrotyrosine adduct formation and attenuated apoptosis by >80% after quarter-size liver transplantation. After transplantation, hepatic IL-1β and TNFα mRNA were 3.3 and 2.5-fold higher in quarter-size than full-size grafts. Pulmonary ICAM-1 expression was also markedly higher in quarter-size graft recipients. NIM811 decreased hepatic IL-1β and TNFα as well as pulmonary ICAM-1 expression.

Conclusion: Together, failing small-for-size grafts produce toxic cytokines, leading to pulmonary inflammation and injury. NIM811 decreased hepatic injury and toxic cytokine formation, thus attenuating acute pulmonary injury after small-for-size liver transplantation (NIDDK).