Virginia Commonwealth University
School of Medicine

PHYSIOLOGY & BIOPHYSICS
Defense

"Novel Molecular Mechanisms of Liver Preservation Injury: a Complication Preceding Organ Transplantation"

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ABSTRACT: Of the over 108,000 Americans awaiting a life-saving organ transplant today, over 12,000 (11%) of those need a new liver (OPTN, 2020). Last year, only 35% of patients on the waiting list for an organ were transplanted. Improving the quality of marginal organs by preventing preservation injury could vastly increase the number of transplants performed. Preservation injury refers to the injury that occurs in an organ graft during cold storage (hypothermic ischemia), and it is proportional to graft dysfunction in the recipient. Many of the intracellular molecular mechanisms of this injury remain elusive and are not mitigated by current preservation methods. During procurement, liver grafts are flushed with cold preservation solution *in situ*, which washes away blood and any circulating, endogenous molecules that may promote survival. Circulating lysophospholipids (LPLs), such as lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) are attractive targets due to their terminal downstream effectors (namely the cytoskeleton and mitochondrial activity). Using an *in vitro* model of organ preservation, we found that biologically-relevant concentrations of LPA did not prevent preservation injury in hepatocytes (though higher concentrations did show a protective effect). Inhibiting RhoA and Rho kinase (which are downstream of LPL surface receptors) during cold storage worsens the preservation injury phenotype. Albumin, which carries and sequesters lipids in aqueous solution, is dose-dependently cytotoxic during cold storage; this supports the idea that growth and survival factors are important in dampening preservation injury. The ratio of intracellular S1P:ceramide, a barometer for cell health, was shifted in favor of cell death following cold storage, implicating that sphingolipid signaling is disrupted. Pharmacologically inhibiting sphingosine kinase-2 (SK2), the enzyme likely responsible for producing most of the intracellularly-acting S1P, proved devastating in rodent liver transplant, *ex vivo* perfusion, and *in vitro* models. Upon further investigation, the mechanism of ABC294640 (the selective SK2 inhibitor) toxicity is, in fact, two-fold: ABC294640 directly inhibits complex I of the electron transport chain (ETC) in the mitochondria, independent of its effects on SK2 (clarifying its vastly devastating effects on liver grafts following transplantation in rodents). These results indicate that LPLs, such as LPA and S1P, may be relevant signaling pathways to target for improved liver graft function following cold storage. Determining how to modulate these pathways in favor of maintaining hepatocyte survival, and thus liver graft viability, is on the horizon, with the ultimate goal of improving liver preservation methods.

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Via Zoom

Mentor: Dr. Martin Mangino