Abstract:
Background: Delayed graft function (DGF) independently predicts reduced 5 yr kidney transplant survival. Cold ischemia (CI) contributes to the development of DGF and results in renal tubular cell (RTEC) apoptosis. RTEC apoptosis of donor kidneys predicts the development of DGF. Our published data demonstrates that mouse kidneys subjected to CI have significantly increased RTEC apoptosis and cleaved caspase-3 (CC3). X-linked inhibitor of apoptosis (XIAP) is the most potent, naturally occurring inhibitor of CC3. UCF-101 is a chemical inhibitor of XIAP degradation. We hypothesized that: (a) CI leads to decreased XIAP expression resulting in increased CC3 and RTEC apoptosis; (b) Treatment of donor kidneys with UCF-101 will prevent activation of CC3 and RTEC apoptosis.

Methods: RTEC apoptosis, XIAP, and caspase-3 protein and activity were examined a) in vivo in C57BL/6 mice kidneys exposed to 24 hours of CI with and without 100 uM UCF-101. (b) in vitro in LLC-PK1 cells subjected to CI in UW (University of Wisconsin) solution with and without 50 uM UCF-101. Apoptosis in vivo was quantified by a nephropathologist in a blinded fashion. Annexin V and PI staining was used to evaluate apoptosis in vitro by flow cytometry.

Results: Kidneys exposed to CI in vivo, and RTEC exposed to CI in vitro had significantly decreased XIAP expression and increased CC3 protein, caspase-3 activity and apoptosis. UCF-101 treatment during CI: a) increased XIAP expression; (b) decreased CC3 protein, caspase-3 activity and apoptosis.

Conclusions: CI injury results in degradation of XIAP and subsequent RTEC apoptosis. Prevention of XIAP degradation by UCF-101 results in decreased CC3, caspase-3 activity and prevention of apoptosis during both in-vitro and in vivo CI. UCF-101 may be an important therapy to prevent apoptosis during CI of donor organs and potentially improve DGF.

Research Category: Basic Science