Regulatory role of JNK1 in apoptosis of tubule cells following renal ischemia-reperfusion injury

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Background : Renal ischemia-reperfusion injury (IRI) has been found as the major cause of acute renal failure, partly due to apoptosis leading to early tubule cell death. Although there are many pathways which contribute to IRI, the Daxx/ASK1/JNK signal transduction pathway has recently been identified as potentially pro- or anti-apoptotic in this process and yet to be fully explored.

Hypotheses: The purpose of this study was to determine the role of the JNK1 isoform as part of the Daxx/ASK1/JNK signal transduction pathway to prevent apoptotic activation, and therefore tubule cell death following renal ischemia-reperfusion injury.

Methods: Wild-type (n=10) and JNK1-disrupted (n=9) mice underwent bilateral renal artery clamping for 30 minutes and kidneys/blood were harvested 24 hours after reperfusion. Paraffin embedded sections were stained with H&E (histologic evaluation) and TUNEL Assay (apoptotic evaluation). Serum creatinine was determined to assess kidney function.

Results: JNK1-disrupted mice subjected to IRI showed an amelioration in functional injury (serum creatinine 2.48±0.81 mg/dl versus 3.36±0.45 in wild-type mice; p=0.002), and a reduction in number of apoptotic cells (9±2.6% versus 13±3.1% in wild-type mice; p=0.04). Parallel evaluation of JNK2 knockout mice (n=9) by other lab members revealed a more robust improvement in kidney function (serum creatinine 2.10±0.74) and a more dramatic reduction in apoptotic cells (5.6±2.2; p=0.04 versus JNK1 knockout mice).

Conclusion: Both the JNK1 and JNK2 knockout mice displayed partial protection of structural and functional kidney damage following IRI. It is likely that the two isoforms act in synergy, and pharmaceutical interruption of both isoforms may be required to abrogate the renal failure caused by IRI. Additionally, the considerable improvement in relation to apoptosis with only a partial decrease of serum creatinine may illustrate that apoptosis is only partly responsible for acute renal failure following IRI.