

EFFECT OF NOTCH ACTIVATION ON THE REGENERATIVE RESPONSE TO ACUTE KIDNEY INJURY (AKI)

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There is growing evidence that episodes of AKI are not fully reversible, and may lead to the development of CKD, that may be due to an inadequate regeneration. The Notch signaling pathway is an evolutionary conserved intercellular signaling pathway responsible for the control of cell fate and tissue morphogenesis. In adult tissue the Notch pathway is involved in tissue maintenance and repair. The purpose of this study was to examine the role of the Notch pathway in the regenerative response following AKI. The adult kidney expresses components of the Notch pathway with the Notch ligand Dll4 being expressed in peritubular capillary endothelial cells, and Notch1 receptor in tubular epithelial cells. Ischemia-reperfusion injury (I/R) in the rat resulted in activation of the Notch pathway as evidenced by increased expression of the Notch intracellular domain (NICD) which peaked at 1h following injury when examined by Western blot and immunohistochemistry. Other Notch components were also induced in the ischemic kidney when examined by qRT-PCR including Notch1, Notch2 and the Notch ligands Dll4 and Dll3 all peaking at 1h post I/R. We next studied the effects of Notch activation on recovery from AKI. Male rats were pretreated for 2 days with Dll4 (25 µg ip tid) or vehicle followed by bilateral renal artery clamping for 45 minutes. A similar degree of injury was induced in Dll4 and Control rats as evidenced by the peak serum creatinine on Day 1, but recovery was faster in the Dll4 treated rats. More severe histologic injury was seen at 5 days in Control compared to Dll4 treated rats. Increased expression of NICD, examined by Western blot, and in the expression of the Notch target genes Hes-1 and Hey-2, examined by qRT-PCR, was seen in Dll4 treated rats, confirming Dll4 treatment resulted in Notch activation. In conclusion, activation of the Notch pathway enhances recovery from AKI and represents a novel therapeutic option for regenerating the injured kidney.