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ACE2 overexpression mediates spatial distribution of pathologic features in acute kidney injury

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Abstract

Background

Acute kidney injury (AKI) is a widespread health problem, with increased incidence among hospitalized patients. The most common cause of AKI is ischemic injury, which targets the proximal tubule causing damage to kidney structure and function. Within ischemic AKI, overactivation of the renin angiotensin system (RAS) can drive pathologic changes. Angiotensin converting enzyme 2 (ACE2) is an integral part of the RAS and is highly expressed along the brush border of the proximal tubule (PT), where it acts to enzymatically degrade angiotensin II (AngII) and extinguish its effects. While several studies have examined the protective role ACE2 plays within chronic kidney disease and hypertension, less is known about ACE2 in acute injury.

Here, we hypothesize that ACE2 overexpression is protective against AKI through local AngII metabolism and promotes recovery of renal function after AKI.

Methods

To investigate whether ACE2 can mediate renal protection, we use K18-hACE2 (hACE2) mice which overexpress human ACE2 in epithelial tissue. Renal ischemia reperfusion (unilateral nephrectomy combined with 25-minute clamping of renal pedicle) was performed on age-matched hACE2 and wildtype (WT) littermates. Blood urea nitrogen (BUN), serum creatinine (SCr), albuminuria, and histologic staining were performed to evaluate injury.

Results

Renal human ACE2 expression is increased (mRNA) 53.49 ± 1.318 fold in hACE2 compared to WT mice (p=0.0159). At baseline, there is a trend towards lower AngII levels in K18-mice levels (428.4 ± 307.0 fmol/g vs 246.6 ± 122.8 fmol/g, ns), while no

difference is seen in Ang1-7 levels between groups, indicating that RAS balance is not changed at baseline.

24 hours after injury, renal function was similarly decreased in WT and hACE2 mice, as evident in the rise in SCr, BUN, and proteinuria. Characteristics of acute tubular necrosis were quantified and revealed lower levels of brush border loss and hyaline casts in the corticomedullary junction of hACE2 mice (13.37 ± 2.902 in WT vs 4.312 ± 1.172, p=0.004). In the cortex, levels of brush border loss and epithelial attenuation were prominent in hACE2 and WT mice, however the hACE2 mice had reduced levels of complete necrosis in this region (23.21 ± 14.04 vs 10.93 ± 11.12, p=0.006). (In addition, early analysis shows a trend of lower KIM-1 staining in hACE2 kidneys compared to WT following IRI (15.39 ± 6.84% area vs 9.59 ±0.88%, ns).

Conclusions

Our results demonstrate that hACE2 mice can serve as a valuable tool for understanding ACE2 in the context of kidney injury. Reduced KIM-1 and brush border injury scores in K18-hACE2 mice following IRI suggests that ACE2 appears to mediate regional differences in pathologic injury, with protection against brush border loss in the corticomedullary junction and protection against necrosis within the cortex. Further examination of the injury and repair processes will elucidate the impact of ACE2 overexpression on injury mechanisms.