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ACUTE KIDNEY INJURY. EXPERIMENTAL - 1

SP181 PAX2+ PROGENITOR CELLS PLAY A KEY ROLE IN TUBULAR REGENERATION AFTER ACUTE KIDNEY INJURY

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Introduction and Aims: Traditionally, AKI was considered as reversible because of the high regenerative capacity of the tubule. Despite this, AKI is associated with an increased risk to develop CKD suggesting an incomplete repair of the tubules. Since, it is debated whether regeneration is mediated by differentiated tubular cells or a population of tubular progenitors, we aimed to analyze the tubular response to injury to understand if regeneration is mediated by differentiated tubular cells or by tubular progenitors.
Methods: We developed inducible transgenic Pax8-rtTA/tetO-cre/ROSA26-Confetti (Pax8/Confetti) mice to track all tubular cells and the PAX2.rtTA;tetO.cre;R26.Confetti mouse model (Pax2/Confetti) to track putative tubular progenitors. Administration of doxycyline at the 5th week of age drove the stochastic expression at single cell level of CFP, GFP, RFP, YFP, allowing to track Pax2+ or Pax8+ cells and their progeny. After 1 week of washout, mice underwent 30 min of unilateral ischemia followed by a 30 day reperfusion period.
Results: Clonal analysis in Confetti mice demonstrated that Pax2+ cells is a definite subpopulation of tubular progenitors that is enriched with high survival and clonogenic capacity and that is responsible for most of the regenerative potential of tubular cells after injury, excluding involvement of other tubular cells. However, regeneration was limited, and the majority of lost tubular cells was not replaced. These results argue against the current knowledge about AKI, that suggests that tubular epithelial cells massively divide to replace lost cells and heal the injured nephrons.
Conclusions: In summary: 1. The tubule displays limited regenerative capacity; 2. Only tubular progenitors undergo cell division providing regeneration after injury. Taken together, these results suggest an innovative explanation of the mechanisms of tubular repair and a suggestive hypothesis to explain the occurrence of CKD after AKI.