ABSTRACT

Tissue resident stem cells are known to play a major role in the repair and regeneration of post natal organs. Despite advances in stem cell research, no definitive clues lead to a complete understanding on the regenerative potential of resident stem cells in vital organs like kidney. In case of complex tissues like the kidney, it would be imperative to consider that organ repair would follow a more pragmatic way; where-in somatic cells would acquire phenotypic flexibility rather than activating the quiescent resident stem cell population.

Glomerular parietal epithelial cells (GPECs) are known to revert to embryonic phenotype in response to renal injury. However, the mechanism of de-differentiation in GPECs and the underlying cellular processes are not fully understood. In the present study, we show that cultured GPECs of adult murine kidney undergo epithelial-mesenchymal transition (EMT) to generate cells, which express CD24, CD44 and CD29 surface antigens. Characterization by qRT-PCR and immunostaining of these clonogenic cells demonstrate that they exhibit metastable phenotype with co-expression of both epithelial (cytokeratin-18) and mesenchymal (vimentin) markers. Transcript analysis by qRT-PCR revealed high expression of metanephric mesenchymal (Pax2, WT-1, SIX-1, EYA-1, GDNF) and uterinc bud (Hoxb-7, C-RET) genes in these cells, indicating their bipotent progenitor status. Incubation of GECs with EMT blocker Prostaglandin-E2 resulted in low expression of renal progenitor markers reflecting the correlation between EMT and acquired stemness in these cells. Additional in vitro renal commitment assays confirmed their functional staminality. When injected into E13.5 kidney rudiments, the cells incorporated into the developing kidney primordia and co-culture with E13.5 spinal-cord resulted in branching and tubulogenesis in these cells. When implanted under renal capsule of unilaterally nephrectomised mice, the cells differentiated into immature glomeruli and vascular ducts. This study demonstrates that EMT plays a major role in imparting plasticity to terminally differentiated GPECs by producing metastable cells with traits of kidney progenitors. The present study would improve our understanding on epithelial cell plasticity, furthering our knowledge of its role in renal repair and regeneration.

Once the kidney reaches adult size, further proliferation of the glomerular and tubular cells dramatically slows, with less than 0.5% of tubular cells proliferating at any given time under baseline conditions. However, kidney shows good regenerative potential in response to ischemia/reperfusion or toxic injury. An ultimate manifestation of renal regeneration is the compensatory renal growth in response to unilateral nephrectomy. After unilateral nephrectomy, the remaining kidney increases in size and restores normal kidney function within short time period. Although compensatory renal growth is largely referred to as compensatory hypertrophy, the exact mechanism by which this multi step adaptive process takes place is not known. The present study was undertaken to understand the cellular and molecular stimuli and events that occur during the early phase of compensatory renal growth. We report here that in Swiss Albino mice, the early phase of compensatory renal growth (CRG) after unilateral nephrectomy is associated with an active phase of renal hyperplasia and neo-glomerular formation and most importantly, involves increased transcript abundance of specific progenitor genes that mediate early kidney organogenesis. Using several cell proliferation analyses like BrdU incorporation studies, Hoechst intensity analysis, Ki-67 transcript studies we demonstrate that CRG is commenced with an active period of renal hyperplasia. Transcript analysis by qRT PCR for kidney development markers during CRG showed significant up-regulation in the expression of Pax2 and Lim-1 as well as Wnt 6 and Wnt 7b transcripts. Interestingly we also observed EMT like changes within glomerular and tubular cells during CRG, which was confirmed by transcript abundance of major regulators of EMT. The study demonstrates active phase of renal hyperplasia coupled with up regulation in the expression of markers of early kidney development and EMT like changes during initial phase of compensatory renal growth. These results indicate that renal hyperplasia is active during early phase of CRG and the adaptive growth shares some parallelism with metanephric kidney development.