ABSTRACT
Chronic Kidney Disease (CKD) often develops in patients with co-morbidities such as obesity, chronic hypertension, and metabolic disorders and is characterized by severely impaired renal filtration (uremia) and impaired erythropoiesis (anemia). The combination of a rising cost burden of dialysis on the healthcare system, a limited number of donor kidneys suitable for transplant, and the side effects associated with Erythropoiesis Stimulating Agents (ESAs) provide impetus for developing new treatment paradigms for CKD.

Alphawet et al. (2008) showed that ex vivo cell cultures established from mouse whole kidney tissue contain highly-specialized cells that express erythropoietin (Epo) in addition to other kidney cell types. Similar methods were used to establish cultures from rat kidney. Epo-producing cells, as well as tubular, ductal, vascular, interstitial, and glomerular cells were found in the rat cultures by immunofluorescence and qRT-PCR. A pilot study was conducted whereby intrarenal transplantation of the ex vivo-cultured rat cells in an established rodent model of progressive renal failure stabilized renal filtration and tubular function, restored erythropoiesis homeostasis, and prolonged survival versus untreated rats. These systemic observations were confirmed histologically, with clear demonstration of tubular and glomerular repair and regeneration, reduction of glomerular and tubulointerstitial fibrosis, stabilization of erythropoietin function, and reduction of bone catabolism. These results demonstrated that this heterogeneous culture contained therapeutically relevant cells.

Cell isolation was extended successfully to swine and human kidney tissue; with starting material isolated from CKD and non-CKD kidneys. All cell compartments identified in the rodent cultures were identified in swine and human cell cultures. Retention of functional proximal tubular cell cultures in propagated from both CKD and non-CKD kidney was demonstrated by receptor mediated albumin uptake. Epo-expressing cells were also present in both CKD and non-CKD kidney-derived cultures and retained oxygen-responsive, HIF-1α-driven EPO expression during expansion. Taken together, these results suggest that autologous sourcing of therapeutically-relevant cell populations is feasible in advanced CKD. Experiments are ongoing to identify the bioactive cellular component(s) responsible for the observed therapeutic benefits and establish potential mechanisms of action.

RESULTS

Figure 1. Cell cultures established from rat kidneys contain all the major renal cell types: tubular, ductal vascular, interstitial, and glomerular.

Figure 2. Systemic assessment indicated that NK Cell treatment prevented CKD disease progression in an established rodent model.

Figure 3. Histopathological assessment of bone and kidney revealed that treatment with NK Cell prevented disease progression.

Figure 4. Human and porcine kidneys with CKD-associated structural abnormalities remain sources for isolation and expansion of therapeutically active cell populations.

Figure 5. Ex-vivo tubular cell function confirmed in cultured rat, swine, and human kidney cell cultures.

Figure 6. Growth kinetics of cells isolated and expanded from CKD tissue mimic those isolated from non-CKD tissue.

Figure 7. Oxygen-Regulated expression of EPO mRNA levels in cultured rat, swine, and human cells.

CONCLUSIONS

- Ex vivo cell cultures established from rodent are therapeutically active:
  - Functional renal tubular cells
  - Stabilized renal filtration and tubular functions
  - Blorepressing Epo-producing cells
  - Restored erythropoiesis homeostasis
  - Prolonged survival

- Despite clear differences in tissue architecture between non-CKD and CKD specimens, cultures established are remarkably similar:
  - Morphology & growth kinetics
  - Marker expression patterns
  - Functional attributes

- These results suggest that autologous sourcing of therapeutically active cell populations is feasible in advanced CKD.

References cited: