Mouse kidney progenitor cells accelerate renal regeneration and prolong survival after ischemic injury

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In Taiwan, the incidence of end-stage renal disease ranked first and the prevalence ranked second in the world. Patients with end-stage renal disease need hemodialysis, peritoneal dialysis or kidney transplant to maintain their life. For the shortage of available organ, most of the patients are under regular dialysis. To accelerate renal repair or even make a functioning kidney is the emergent issue to be solved and interesting topic for research. Following the discovery of tissue-specific progenitor cells in other organs and their ability to improve regeneration after injury, progenitor cell-based therapy is new strategy in the treatment of acute kidney injury and has potentially more value than single-agent drug therapy due to the highly versatile response of cells to their environment. These cells may not only secrete cytokines within the injured kidney, but also participate in tubular cell proliferation or angiogenesis to facilitate renal regeneration. Based our previous studies that interstitial cells might be engaged in the process of tubular regeneration after acute renal failure, we hypothesized that renal interstitial may serve as a better niche for adult renal stem cells. The purpose of our study was to isolate and characterize a population of renal progenitor cells from adult mouse kidney and to test whether these cells could participate in renal repair after acute kidney injury. A unique population of cells exhibiting characteristic consistent with renal stem cells, mouse kidney progenitor cells (MKPC), was isolated from Myh9 targeted mutant mice. Features of these cell include: (1) spindle-shaped morphology, (2) self-renewal of more than 100 passages without evidence of senescence, (3) expression of Oct-4, Pax2, Wnt-4, WT-1, vimentin, alpha-smooth muscle actin, CD29, and S100A4 but not SSEA-1, c-kit, or other markers of more differentiated cells. MKPC exhibit plasticity as demonstrated by the ability to differentiate into endothelial cells and osteoblasts in vitro (Fig. 1) and endothelial cells and tubular epithelial in vivo. The origin of the isolated MKPC was from the interstitium of medullar and papilla. Importantly, intra-renal injection of MKPC in mice with ischemic injury rescued renal damage, as manifested by decreases in peal serum urea nitrogen, the infarct zone and the necrotic injury (Fig. 2). Seven days after the injury, some MKPC formed vessels with red blood cells inside and some incorporated into renal tubules. In addition MKPC treatment reduces the mortality in mice after ischemic injury. Our results indicate that MKPC represent a multipotent adult progenitor cells population, which may contribute to the renal repair and prolong survival after ischemic injury.
Figure 1. In vitro differentiation. Phase contrast microscopy and immunofluorescence of mouse kidney progenitor cells (MKPC) that were incubated under culture conditions that promoted differentiation into other cell types. (A) MKPC that was cultured for 42 days in the presence of osteogenic differentiation medium developed osteoblastic morphology and were detected by positive staining for calcium deposits using Alizarin red. (B) MKPC that was cultured in collagen gel for 4 days developed endothelial morphology and stained for von Willebrand factor.
Figure 7. MKPC, but not fibroblasts, protect ischemia reperfusion-injured mice from renal function and structure deterioration. (A) Serial blood urea nitrogen levels as measured in ischemia reperfusion-injured mice that received 3T3 fibroblasts (▲), PBS (◆) or MKPC (■). MKPC administration immediately after reflow to mice with acute ischemic injury significantly improves renal function on 2 days after clamping, whereas PBS- and fibroblast-treated mice show no such response. Data are expressed as mean values ± SD. * P < 0.02 MKPC- versus PBS- and 3T3-treated mice at the same time. (B) Representative gross morphologies of hemisected kidneys that were not treated (normal), treated with fibroblasts (3T3, upper panel), with PBS (middle panel) or with MKPC (lower panel) 2, 4 and 7 days after ischemia reperfusion injury in SCID mice. The infarct zones (dark red areas) are similar in 3T3- and PBS- treated mice but decrease in MKPC-treated mice at each time point. Scale bar: 10 mm.