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Could tubular interstitium be a source of adult epithelial stem cells?

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To the Editor: Although it is admitted that kidney is a restoring organ, to date adult renal stem cells are far to be identified. Two recent reports on this Journal reported that after an ischemic injury, tubular epithelium may be recovered by bone marrow derived cells¹ or mesenchymal stem cells.² In particular, Duffield and Bonventre¹ showed an increase in the number of peritubular endothelial cells after ischemia/reperfusion experiments, whereas Lange *et al.*² showed absence of labeled mesenchymal stem cells in tubules.

These results, in our opinion, are also in agreement with other recent experiments, conducted by Bussolati *et al.*³ that isolated a clone of CD133+ cells able to differentiate in both endothelial and epithelial tubular cells.

The presence of 'multipotent' undifferentiated cells in kidney may suggest an intriguing hypothesis. Indeed, in our experience, it is very uncommon to observe by light and electron microscopy elements with morphologic features of undifferentiated/stem/germinal/precursor/basal cells within renal tubules, as terminally differentiated cellular elements are commonly present above the basal membrane throughout all the tubules. By contrast, a number of cells with large nucleus and a light narrow of cytoplasm all around, with sporadic immunohistochemical positivity for epithelial markers, are present in the interstitium. We would introduce a new paradigm: could interstitium be a source of epithelial-oriented stem cells in adult kidney, as well as in other organs? If not disproved, this suggestion could unlock a new scenario also on kidney carcinogenesis and stem-cell transplantation.

1. Duffield JS, Bonventre JV. Kidney tubular epithelium is restored without replacement with bone marrow-derived cells during repair after ischemic injury. *Kidney Int* 2005; **68**: 1956–1961.
2. Lange C, Togel F, Ilttrich H *et al.* Administered mesenchymal stem cells enhance recovery from ischemia/reperfusion-induced acute renal failure in rats. *Kidney Int* 2005; **68**: 1613–1617.
3. Bussolati B, Bruno S, Grange C *et al.* Isolation of renal progenitor cells from adult human kidney. *Am J Pathol* 2005; **166**: 545–555.

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Response to 'Could tubular interstitium be a source of adult epithelial stem cells?'

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Cappello and Zummo¹ suggest that interstitial cells could be a source of stem cells that are 'epithelial oriented'. This is not a new concept. Although interstitial cells can derive from bone marrow, contrary to their interpretation of our studies, our work indicates that few if any epithelial cells derive from bone marrow, and only a minority of endothelial cells derive from bone marrow cells after injury.^{2,3} It is possible that a sub-population of surviving intratubular cells possess multi-potentiality and selectively proliferates after damage to neighboring cells. To date, however, studies have not unequivocally identified cells expressing 'stem cell' markers in the tubule. Our studies have supported a model whereby many surviving renal epithelial cells after injury become dedifferentiated, take on mesenchymal characteristics, proliferate, and subsequently redifferentiate into functional epithelial cells restoring the integrity of the epithelium.⁴

Populations of cells have been isolated from the human and rodent kidney that express stem cell antigens *in vitro* and under certain conditions express epithelial markers.⁵ Oliver *et al.*⁶ reported a stem cell niche in the papillary interstitium based on 5-bromo-2'-deoxyuridine retention, although thymidine analogs may not be ideal for tracking cell fate due to potential leakage from the cells and uptake by others. If interstitial cells are precursors to epithelial cells in the adult mammalian kidney, they would have to cross the basement membrane. Interstitial multipotent mesenchymal cells have been demonstrated to generate new tubules in adult fish following partial nephrectomy;⁷ however, unlike fish, mammalian kidneys do not regenerate new nephrons.

Interstitial cells with mesenchymal stem cell characteristics can also have a significant role in repair through processes that do not involve differentiation into epithelial cells. We and others have shown that systemic infusion of bone marrow-derived mesenchymal cells can result in functional improvement in the kidney after an ischemic insult. This effect may be due to paracrine effect on the repair process due to potentiation of proliferation of surviving renal epithelial cells. In addition, the interstitial cells may decrease inflammation, which is an important contributor to the pathophysiology of many form of renal injury. Another possibility is that the interstitial cells may play a trophic role in mesenchymal to epithelial conversion and differentiation of cells into endothelial structures.^{1,2}