The emerging concept of a fibrotic microenvironment in CKD

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To the Editor: The elegant paper by Udo *et al.*,[1] published in the last issue of *Kidney International*, adds another relevant piece of information to support the concept of the existence of a fibrotic microenvironment in chronic kidney disease (CKD). A disease-perpetuating microenvironment is rather an established concept in oncology, regarding which several studies have shown that a tissue surrounding a carcinoma is more than merely a scaffold on which the malignant cells rest, but in fact plays an important interactive role with growth-enhancing properties for the tumor.[2,3] After overemphasis on epithelial–mesenchymal transition, renal epithelial cells emerge as phenotypes able to direct the biology, in an open cross-talk through still unknown mediators, of the surrounding resident fibroblasts and myofibroblasts. Similarly to carcinomas, wherein cancer cells can selectively induce expression of alpha smooth muscle actin (α-SMA) in surrounding stromal fibroblasts, injured tubular epithelial cells have been recently demonstrated[4] to behave as a major source of pro-inflammatory cytokines in experimental induced kidney fibrosis. Bonventre's group[4] showed that unilateral ischemia induces G2/M arrest in proximal tubule cells, resulting in abnormal amplification of profibrogenic factors. In *in vitro* experiments, the same group showed that enriched fractions of HK-2 cells in G2/M phase have specifically higher mRNA levels of *COL4A1* and *ACTA2*, the latter gene encoding α-SMA, the hallmark of myofibroblast activation. Thus, the *in vitro* study by Udo *et al.*, demonstrating that MDCK cells, but not 3T3 fibroblasts, inhibit regeneration of mesenchymal stem cells from adipose tissue fragments, confirms that renal tubular cells are able to contribute to the general maintenance of the static state of mesenchymal cells. These findings further corroborate the relevance of deepening the scientific knowledge of regeneration process mechanisms normally taking place in the kidney after injury. Microarray, proteomics, and phosphoromic applied to this specific question may open new possibilities to design and create innovative drugs for CKD patients preserving or inducing tubular epithelial cells toward a healthy phenotype.

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The Authors Reply: We thank Drs Prunotto and Moll[1] for their remarks and for giving us the opportunity to describe our comments. In our study,[2] tubular cells inhibited the regeneration of mesenchymal stem cells (MSCs) and preadipocytes from adipose tissue (AT), while AT suppressed and promoted the growth/apoptosis and differentiation of tubular cells, respectively. Thus, tubular cells and AT mutually regulate their homeostasis. As pointed out by Drs Prunotto and Moll, the determination of the mediators for their interaction would lead to the discovery of new molecules that convert the abnormal phenotypes of tubular cells and mesenchymal cell types to the normal phenotypes. This may open up a new approach for CKD treatment. In general, myofibroblast phenotype seems to be critical for epithelial–mesenchymal interaction that occurs in the organogenesis, tissue repair, and cancer. For example, cancer-associated stromal cells such as fibroblasts and MSCs gain myofibroblast phenotype.[3] In our study (in submission), isolated AT stromal cells (ATSCs) express myofibroblast phenotype under the interactions between ATSCs and epithelial cell types such as tubular cells and cancer cells. Interestingly, ATSCs localized within AT never express the myofibroblast phenotype under the interactions. This suggests that the biological behaviors of cell types isolated from the tissue are different from those of the cell types localized within the tissue regulated by the tissue microenvironment even *in vitro*.

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