Mechanisms of Epithelial Repair and Regeneration After Acute Kidney Injury

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Summary: Acute kidney injury (AKI) is a common clinical problem and is associated with high mortality rates. It is accepted that after AKI cellular regeneration of the proximal tubule occurs from intrinsic tubule cells. Recently, scattered tubular cells (STCs) were discovered as a novel subpopulation of tubule cells involved in regeneration. STCs have a distinct morphology, unique protein expression profile resembling that of parietal epithelial cells, proliferate more than the remaining proximal tubule cells, and are less susceptible to injuries. In response to AKI, STCs become more numerous, independent of the primary insult (ischemic, acute obstruction, and so forth). STCs can be detected with the highest sensitivity and manipulated by the parietal epithelial cell–specific, doxycycline inducible transgenic mouse line PEC-rtTA. In cell fate tracing experiments it was shown that STCs are not a fixed progenitor population. Rather, STCs arise from any surviving proximal tubule cell. Thus, the STC phenotype is a transient, graded, and specific transcriptional program facilitating tubular regeneration. Understanding this program my open new approaches to prevent and/or treat AKI.
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Acute renal failure can be defined as an abrupt decrease in glomerular filtration with resultant azotemia, in most cases caused by acute ischemic and/or toxic insults.[1] In both cases, the proximal tubule is the main site of injury, therefore the term *acute tubular necrosis* often is used synonymously. The mammalian kidney is particularly susceptible to these two kinds of acute kidney injuries (AKIs) for several reasons. First, the mammalian kidney has no portal blood supply (unlike the mesonephros in fish, amphibians, or reptile-like animals). Because all blood first has to pass through the glomeruli in mammals, glomerular vasoconstriction may decrease the blood supply of the entire kidney (eg, in hypovolemia). The proximal tubule is particularly sensitive to ischemia[2] because it relies predominantly on aerobic adenosine triphosphate production (mitochondrial Krebs cycle) and it cannot use the ischemic salvage pathway of glycolysis efficiently.[3]

Furthermore, the proximal tubule reabsorbs most of the filtered substances including toxins, in part by endocytosis. For example, gentamycin is taken up by the cubilin-megalin complex and gentamycin toxicity is increased in a water-retaining kidney (induced by withholding liquids, salt, or volume depletion).[4–6]

The subsequent mechanisms for AKI still are controversial. Besides a reduction in glomerular filtration rate, tubular obstruction likely represents a major factor.[7–9] In brief, after AKI, cellular debris and protein casts obstruct individual nephrons transiently. Depending on the severity of AKI, many or just a few tubules are obstructed, resulting in the transient loss of renal function. Tubular obstruction may last long enough to drive the affected nephron into reversible or irreversible degeneration—similar to tubular degeneration after unilateral ureteral obstruction. In addition, complex interactions with cells of the immune system and release of inflammatory mediators likely play a role during the course of AKI (reviewed by Cantaluppi et al[10]).

Nevertheless, tubules have a remarkable capacity to regenerate lost cells, usually within less than a week. The present article focuses on recent insights into the mechanisms of epithelial repair and regeneration. In particular, the role of a recently discovered subpopulation of tubule cells is discussed: scattered tubular cells (STCs). These cells become abundant in response to AKI and likely play a major role in the regenerative process.

UNIFORM RESPONSE TO AKI: TRANSITION INTO THE STC PHENOTYPE

In 2011, a novel subpopulation of proximal tubular cells was described.[11] Because these cells showed a distinct morphology and were scattered as single cells among fully differentiated inconspicuous tubular cells

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throughout the entire proximal tubule, these cells were termed *scattered tubular cells*.

STCs show very characteristic morphologic and ultrastructural features[12,13] (Fig. 1A). They generally are smaller than fully differentiated tubular cells and may have different shapes.[12] In the normal kidney, they occur as single cells or, less often, as doublets or triplets. They are surrounded by fully differentiated tubular cells, mostly with an abrupt transition. In this setting, STCs often show a narrow flask-like shape. Importantly, STCs show a dramatic decrease in mitochondria compared with neighboring proximal tubule cells.[12,13]

In the normal human kidney, STCs can be detected, preferentially at the inner turn or along infoldings of the tubule (eg, along the tubular plicae where the tubule makes a hairpin turn).[11–13] The reason for this preferential location is controversial. Increased mechanical forces could push the cells into the STC phenotype, or a hairpin turn could represent a microniche for a fixed progenitor population. However, this would imply that no STCs should be expected along the pars recta of the proximal tubule (ie, the S2 and S3 segment), however, this is not the case.

In contrast to differentiated tubule cells, STCs do not have a pronounced apical brush border. STCs also express only very low levels of the classic multitarget protein endocytic transporter megalin. STCs also lack the basolateral labyrinth of extensive membrane infoldings, which is characteristic for differentiated proximal tubular cells.[13] We have shown previously that the infoldings of the basolateral membrane extend almost up to the apical aspect of proximal tubule cells. Filtered albumin is taken up by differentiated proximal tubular cells from the primary filtrate and released into the apical aspects of the basolateral labyrinth from where it diffuses back into the tubulointerstitial capillaries or lymphatics.[14] Absence of an apical brush border and a basolateral labyrinth strongly suggests that STCs are less active endocytically compared with differentiated proximal tubule cells.

In the regenerative phase after AKI, STCs may become rather abundant and also mostly acquire shapes similar to the surrounding tubular cells.[13,15]

To date, it has not been investigated systematically which stimuli can push tubule cells into the STC transcriptional program. We have shown previously that proteinuria or transient ischemia-reperfusion injury

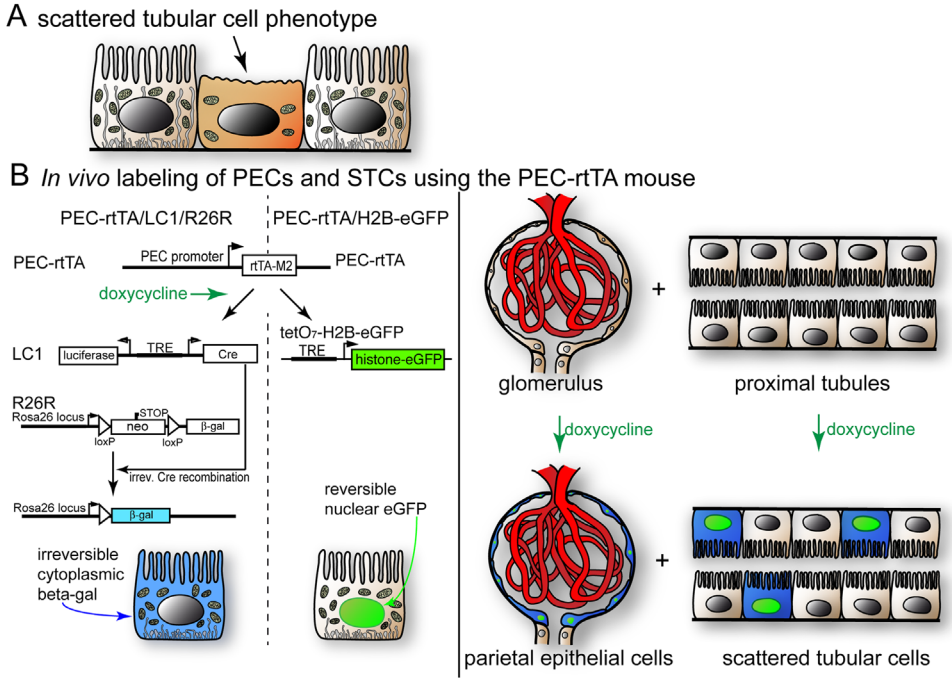

Figure 1. STCs. (A) STCs (arrow) lack a brush border and a basolateral labyrinth and contain fewer mitochondria. STCs express a distinct panel of marker proteins (indicated by the orange color), similar to PECs. (B) The doxycycline-inducible transgenic PEC-rtTA mouse is currently the most sensitive method to mark and/or manipulate proximal tubule cells with the STC phenotype. The transgenic map is shown in the left panel. The PEC-rtTA/LC1/R26R triple transgenic mouse expresses β-galactosidase (β-gal) (blue) irreversibly upon Cre recombination induced by transient administration of doxycycline. The PEC-rtTA/H2B-eGFP mouse loads nuclei with histone-enhanced green fluorescent protein during administration of doxycycline (green). The labeling pattern is shown in the right panel. In the glomerulus, PECs are marked. In the proximal tubule, scattered tubular cells are marked. TRE, tet-responsive element; neo, neomycin resistance cassette; rtTA-M2, improved reverse tetracycline-controlled transactivator. Schematic on the left is modified with permission from Berger et al.[50]