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Tubular recovery after acute kidney injury

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Abstract

Background: A significant portion of patients who suffer from acute kidney injury (AKI) do not fully recover due to largely unclear reasons. Restoration of tubular function has been proposed to be a prerequisite for GFR recovery.

Summary: Proximal tubular cells dedifferentiate during the tubular injury phase, which is required for subsequent cell proliferation and replacement of lost epithelial cells. Experimental studies indicate that some cells fail to redifferentiate and continue to produce growth factors (e.g. transforming growth factor β) that can induce fibrosis. Preclinical studies provide first evidence for beneficial effects of inhibiting glucose transport in the proximal tubule in models of ischemia-reperfusion injury (IRI). Comparing renal RNA sequencing data with kidney function during recovery from varying levels of AKI may provide new cues with regard to the sequence of events and help identify key determinants of recovery from AKI.

Key Messages: Tubular recovery after acute kidney injury is vital for recovery of kidney function including improvement of GFR, and likely determines which patients fully recover from AKI or progress to CKD. There is a need to better understand the sequence of events and the processes of tubular cell proliferation and repair, including safe strategies to intervene. The temporary inhibition of selected tubular transport processes, possibly in selected nephron regions, may provide an opportunity to improve tubular cell energetics and facilitate tubular cell recovery with consequences for kidney outcome.

Keywords

tubular transport; acute kidney injury; glucose transport

Acute kidney injury (AKI) is associated with an acute decrease in renal function. Some patients with AKI have full resolution of their injury but in a subset of patients chronic kidney disease (CKD) develops. It is poorly understood how and why this transition occurs in these patients and what factors determine recovery. In the clinical setting, AKI and its recovery are primarily defined by changes in glomerular filtration rate (GFR) which is

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Disclosure

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usually estimated from changes in serum creatinine. However, there is mounting evidence that suggests the tubular system, specifically the proximal tubules (PT) and the thick ascending limb (TAL), could play a major role not only in the development of AKI but also in the subsequent recovery of kidney function, including GFR. Here we will briefly discuss functional and morphological aspects of tubular epithelial cells which could have a role in AKI recovery. Moreover, we outline potential tubular proteins the therapeutic targeting of which may improve or hasten recovery of tubular and subsequently glomerular function after AKI.

Tubular recovery as a prerequisite for GFR recovery

Tubular injury is an early and decisive step in many cases of AKI [1;2]. In this setting, tubular injury-induced impairment in tubular reabsorption of NaCl and fluid lowers the GFR to limit urinary NaCl and fluid loss. This is achieved through the physiology of the tubuloglomerular feedback (TGF) system and an increase in tubular back pressure. Restoration of the tubular integrity and of the tubular NaCl and fluid reabsorption capacity is likely to be a prerequisite for GFR recovery [3].

An important aspect of tubular recovery is the morphological and functional restoration of the tubular epithelial cell lining and barrier. Tubular epithelial cells are highly differentiated, polarized cells. Proximal tubular cells dedifferentiate during the tubular injury phase, which is required for subsequent cell proliferation and replacement of lost epithelial cells, but some cells fail to redifferentiate during the recovery process. Venkatachalam and colleagues have hypothesized that the cells that fail to redifferentiate continue to produce factors that stimulate proliferation. In the context of cells that cannot redifferentiate, these signaling pathways, which include transforming growth factor (TGF-β), may lead to fibrosis [4]. Further investigation is needed into the failed redifferentiation of these tubular cells during the recovery process and the possibility of rescuing or eliminating these cells. Experimental studies in the diabetic kidney suggest that maneuvers that overcome cell cycle arrest can lead to apoptosis in the short-term but may be beneficial for the integrity of the renal epithelial system in the long-term [5]. A recent study analyzed kidney biopsies of renal transplant recipients at 6 wks, 3 months and 6 months after transplantation in order to investigate which morphological features of acute tubular injury correspond to worse outcomes. The degree of epithelial cell pyknosis, flattening and brush border loss correlated best with the severity of renal allograft dysfunction. Vice versa, the degree of expression of the proliferation marker Ki67 correlated with stable or improved renal function [6]. It remains to be determined if these results are also applicable to the transition to CKD for other causes of AKI and whether these changes can be modified and if modification affects outcome.

Tubular transport as a potential target for AKI recovery

The GFR determines the subsequent tubular reabsorption work, which determines the oxygen requirement and consumption of the kidney. Little is known about the priorities of a recovering tubular epithelial cell with regard to initiating transport work as soon as possible versus using limited available energy supplies first to assure a sustained restoration of cellular integrity. Nevertheless, inhibition of transport in vulnerable tubular segments during

the AKI phase may improve recovery in the long-term. Of particular interest may be the transport systems in the renal outer medulla, including the medullary TAL (MTAL) and the late PT, which due to the physiology of low oxygen delivery in the face of high oxygen consuming active transport seem specifically vulnerable. Inhibition of Na-2Cl-K cotransport via NKCC2 by furosemide in the TAL was previously shown to decrease tubular damage in the isolated perfused kidney [7] but systemic long term studies are lacking and excessive NaCI and fluid loss due to the dominant role of the transporter in the kidney are a concern.

Renal sodium-glucose cotransport (SGLT) has recently obtained a lot of attention due to the blood glucose lowering and renal and cardio-protective effects of inhibitors of SGLT2 in patients with type 2 diabetes and high cardiovascular risk, with the potential for similar positive effects in patients with type 1 diabetes [8]. The main role of this transporter is tubular glucose reabsorption with SGLT2 being responsible for 97% of the reabsorption in the early PT (S1/S2 segment) in normoglycemia. SGLT1 reabsorbs the remaining glucose in the downstream late PT (S2/S3 segment), which enters the outer medulla. Tubular injury enhances glucose delivery to the late proximal tubule, and thereby potentially glucose reabsorption via SGLT1. Preliminary data by Nespoux and colleagues showed that in a mouse model with gene-knockout of SGLT1, tubular injury in response to ischemia reperfusion (IR)(bilateral renal artery clamping) was reduced as indicated by lesser urine excretion and renal mRNA expression of kidney injury molecule KIM-1. This was associated with lesser kidney inflammation and better recovery of GFR and urine concentrating ability compared to wild type after 2 weeks [9]. Limiting transport particularly in the vulnerable OM might improve renal recovery by not only restoring the metabolic homeostasis of the cells involved but by decreasing the spread of inflammation from the OM to the neighboring cortical and medullary segments. Notably, Chang and colleagues determined whether pretreatment with the SGLT2 inhibitor dapagliflozin has beneficial effects in a mouse model of IR. Dapagliflozin reduced kidney injury as indicated by better renal function and tubular structure as assessed by plasma creatinine and renal cortical vacuolization, peritubular/proximal tubule leukocyte infiltration, proximal tubule simplification, loss of PT brush border, blebbing of apical membranes and intraluminal aggregation of cells and proteins at 24 hours after IR. This was proposed to be in part due to increased hypoxia-inducible factor HIF-α signaling [10]. Unfortunately, no longer term assessment of kidney function recovery was performed. Nevertheless, the studies indicate the possibility that inhibition of SGLT2 in kidney cortex may have beneficial effects in AKI.

Need to better understand the sequents of events in tubular recovery

Little is still known about the sequence of events following AKI and the relationship between GFR and tubular alterations. Fattah and colleagues performed preliminary studies using RNA sequencing (RNA-seq) in the transition from AKI to CKD in a murine model of IR [11]. C57BL6J mice were subjected to bilateral renal artery clamping with varying degrees of ischemia, namely 10 and 15 minutes and compared with sham. On days 1, 3 and weeks 2 and 14 after reperfusion, GFR was assayed and whole kidney tissue was harvested for RNA-seq. On day 1 after IR, the preliminary data showed an ischemia time dependent rise in the mRNA expression of tubule-derived AKI biomarkers such as kidney injury marker 1 (KIM1), neutrophil gelatinase associated lipocalin (NGAL) and clusterin. In the 10

min IR group, the renal expression of thousands of genes was altered on day 1 while GFR was not changed. Vice versa, the tubule-derived AKI biomarkers and most other genes normalized close to sham levels by 14 weeks, while in the 15 minute IR group GFR had recovered from day 1 but still remained ~30% below normal, associated with prominent fibrosis. With few exceptions, the renal expression profile of tubular transport genes in the solute carrier (SLC) family showed an initial fall followed by an eventual rise close to normalization by 14 weeks [11].This re-emphasizes the hypothesis that during initial AKI, tubular transport is compromised either by cell death or to conserve energy, and that both the tubular transporter expression and GFR increase during recovery. An important question to ask with regard to these transporters is which ones do not show this typical pattern and actually initially rise with AKI as they may have a different role in the pathogenesis of AKI or eventual recovery. Which transporters recover first as these transporters could be potential targets for hastening or facilitating AKI recovery? The preliminary studies by Nespoux and colleagues showed that at 14 days after IR the renal mRNA expression of SGLT2 was still strongly suppressed whereas SGLT1 appeared normal [9]. Little is known about which tubular functions recover earlier or later (e.g. NaCl or K transport, acid base transport, phosphate and Ca transport, secretion of organic anions and cations, urine concentration and dilution) and whether this has implications for recovery or therapeutic intervention.

In summary, tubular recovery after acute kidney injury is vital for recovery of kidney function including improvement of GFR, and likely determines which patients fully recover from AKI or progress to CKD. There is a need to better understand the processes of tubular cell proliferation and repair, including strategies to intervene. The temporary inhibition of selected tubular transport processes, possibly in selected nephron regions, may provide an opportunity to improve tubular cell energetics and facilitate tubular cell recovery with consequences for kidney outcome.

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