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Proximal convoluted tubule cells in ischemia and post-injury regeneration

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ABSTRACT

Proximal convoluted tubule (PCT) cells are more sensitive than other nephron tubular cells to injury induced by ischemia and nephrotoxins. After injury, some PCT cells die and disconnect from basal lamina and finally shed in tubular lumen. In this article, we reviewed effect of ischemia on PCT cells, regeneration and origin of newly formed PCT cells and then tight junction assembly between regenerating cells. PCT cells originate from any tubular differentiated cells that survived after injury. Survived cells dedifferentiate to scatter tubular cells (STCs) that proliferate and renew epithelial tubule. STCs are present in human PCT in normal healthy condition but do not exist in normal rodents. A question has remained unclear, if the STCs are transient cells in regenerating PCT, why these cells are present in normal human PCT.

Review

Core tip: Proximal convoluted tubule (PCT) cells are more sensitive than other nephron tubular cells to injury induced by ischemia and nephrotoxins. After injury, some PCT cells die and disconnect from basal lamina and finally shed in tubular lumen.

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Introduction

Proximal convoluted tubules (PCTs) are functionally the masterpiece of reabsorption from glomerular filtrate. PCTs cells carry out the reabsorptive role for NaCl, NaHCO3, completes the reabsorption of glucose, amino acids, and important anions, including phosphate and citrate, because it is the exclusive site of transport of these filtered solutes (1). PCTs are responsible for reabsorbing about 65% of filtered load and most, if not all, of filtered amino acids, glucose, solutes, and low molecular weight proteins. Proximal tubules also play a key role in regulating acid-base balance by reabsorbing about 80% of filtered bicarbonate (1,2). PCT is also a metabolic organ. For example, within the proximal tubule, 25-hydroxy-vitamin D convert to 1,25-dihydroxy-vitamin D and convert 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D to their inactive forms (3). In addition, the proximal tubule is an important site of gluconeogenesis (4). Unfortunately, many harmful factors induce PCT cells injury that maybe leads to acute renal failure (ARF).

Materials and Methods

This review article discusses mechanisms by which ischemia (ATP depletion) leads to renal PCT cells injury, and then explains origins of regenerated tubular cells after ischemia and finally tight junction formation between these cells. For this review, we used a variety of sources by searching through PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was conducted using combinations of the following key words and or their equivalents; PCT, regeneration, ischemia, tight junction, scatter tubular cells.

Discussion

Acute kidney injury (AKI) is the leading cause of PCTs injury and is associated with high mortality rates. Acute tubular necrosis (ATN) is the term used to assign AKI consequential from damage especially to the PCTs. The primary and important causes of AKI are ischemia (hypoxia) and nephrotoxins.

Sensitivity of PCTs to pathogens

In the most animal models of AKI, the proximal tubule is considered the most sensitive renal tubular cells to ischemic, hypoxic or nephrotoxins (5,6). Proximal tubule cell is particularly sensitive to injury specially ischemia because it relies mostly on aerobic ATP production from mitochondria via Krebs cycle and it cannot use

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the ischemic rescue pathway of glycolysis efficiently (7). Furthermore, the proximal tubule reabsorbs most of the filtered substances including toxins, in part by endocytosis. For example, gentamycin is taken up by the cubilinmegalin complex and gentamycin toxicity is increased in a water-retaining kidney induced by preservation liquids, salt or volume depletion (8-10). Proximal tubule cells within the S1 and S2 segment manifest a largely reversible injury; if cell death occurs, it localized primarily in the S3 segment (11). Proximal tubule sensitivity relates largely to high metabolic rate and a strong dependence on oxidative phosphorylation. The intact mammalian kidney reabsorbs nearly 80-meq Na/g kidney/day across the renal tubules and accounts for nearly 70% of oxygen consumption by the kidney (12). To meet this demand, tubule cells generate a significant amount of ATP. The preferential energy substrate are non-esterified free fatty acids, primarily palmitate, and to a lesser degree, lactate, citrate and pyruvate. Proximal tubules do not use glucose, but rather are gluconeogenic (12).

PCT cells in ischemic condition

Renal ischemia occurs in kidney surgeries such as partial nephrectomy, renal artery angioplasty, transplantation and elective urological operations. Because of renal vessels ligation during the procedures, ischemia (tissue hypoxia) occurs and leads to renal damages specially PCTs injuries (13-15).

PCTs cells are affected by ATP depletion especially in renal ischemia. ATP depletion leads to Rho GTPase inactivation that makes activation of ADF (actin depolymerizing factor) or cofilin in the apical brush border of proximal tubules (16-18). Activated cofilin (ADF) rapidly depolymerizes apical actin cytoskeleton and redistribution. Deterioration of microvillar structure leads to formation of membrane blebs, which maybe either internalized or shed into the tubular lumen. Brush border membrane components that release into the lumen give to cast formation and tubular occlusion (19). oteins such as tropomyosin and ezrin (20), permitting the activated cofilin to bind and then depolymerize actin, which finally leads to microvillar breakdown.

Activation of cofilin also can induce apoptosis in PCT cells by inducing release of cytochrome C from mitochondria to cytoplasm (21). PCT cells death occurs from at least two cell death mechanisms, necrosis and apoptosis. ATP depletion activates cofilin that induce apoptosis by activating intrinsic and extrinsic pathways (22). Deterioration of the apical cytoskeleton via ATP depletion also results in loss of tight junctions and adherents junctions between tubular cells and leads to tubular cells separation (23).

Ischemia leads to disruption of at least two important proteins, Na, K-ATPase and integrins. Deterioration of basolateral Na, K-ATPase in PCTs is the major cause of increasing in excretion of sodium in tubular lumen (10). Integrins are in basal region of PCTs and mediate cell connection to basal lamina. Ischemia leads to relocalization of integrins to the apical membrane, and then makes detachment of PCT cells from the basement membrane (24).

Ischemic proximal tubule cells also produce mediators such as proinflammatory cytokines (e.g., TNF-α, IL- 6, IL-1β, and TGF-β) and chemotactic cytokines such as monocyte chemo attractant protein-1 (MCP-1) and IL-8 (25).

Nephrotoxins are a variety of exogenous compounds (e.g. aminoglycosides, amphotericin B, cis-platinum, cadmium, radio contrast media) and endogenous compounds (e.g. hemoglobin in hemolysis, myoglobin in rhabdomyolysis) that are toxic or potentially toxic to the kidney (26-29).

Briefly, after ischemia and nephrotoxic agents PCT cells show necrosis, apotosis, adhering junction changes, loss of brush border and finally epithelial cell disjunction or tubular basement membrane denudation (30). Because the proximal tubule is the main site of injury, therefore the term "acute tubular necrosis" is often used synonymously (31).

After PCT cells desquamation, based on injury tention denuded basement membrane gradually recovered by new cells and after differentiation and junctional complex reformation, PCT function may be return. The nature of recovery response mediates by the degree to which sub lethal cells can restore normal function and promote regeneration (32).

Although cell division is uncommon in the adult kidney, this organ has the capability to regenerate and repair by its cellular proliferation and functional recovery after tubular necrosis. After kidney ischemia, there is a marked increase in proliferation of tubular cells. Differentiated tubular cells thought to dedifferentiate and proliferate after injury. After cell proliferation, undifferentiated regenerating cells seems to repopulate the injured area and then redifferentiate into mature epithelial cells to rebuild the functional integrity of nephron. Through these steps, most damaged tubules regain their essential functions and recover from injury (5). During the repair process, surviving tubular cells actively proliferate and differentiate into new mature tubular cells to rebuild their functional structures (33).

PCT regeneration and origin of regenerating tubular cells

The renal tubule has a strange capacity to start regeneration within a few days after AKI. The origin of the regenerating cells is not completely clear and different origins have been proposed relating to the regenerating cellular resource (34).

In 2003, Bonventre announced that after renal injury, surviving tubular cells rapidly lose epithelial cell properties and acquire a more mesenchymal phenotype. The dedifferentiated cells migrate into the regions where cell necrosis, apoptosis, or detachment has resulted in denudation of the tubular basement membrane. They proliferate and finally differentiate into mature epithelial cells with polarized lumen, completing the

repair process (35).

Morigi et al reported that bone marrow mesenchymal stem cells (MSCs) could differentiate into renal tubular epithelial cells and improve renal function (36).

After Morigi et al, some researchers reported that bone marrow derived cells (BMDCs) significantly take part in regeneration of the renal tubular epithelium, differentiate into renal cells tubules (37-39), or promote proliferation of both endothelial and epithelial cells after injury (40). Nevertheless, the relative contribution of extra renal cells to kidney regeneration has not been established. There are several reports in combat with the potential of BMDCs to trans- differentiate into tubular cells after injury. Lin showed that intrarenal cells, not bone marrow–derived cells, are the major source for regeneration in post-ischemic kidney (41).

Transgenic mice that express glial fibrillary protein in BMDCs (42) and in mature renal tubular epithelial cells (41), or in all mesenchyme derived renal epithelial cells (43) revealed that, while BMDC recruitment occurs, tubular recovery after renal ischemia is mainly elicited via proliferation of endogenous renal tubular cells (41-43).

MSCs derived from bone marrow also have reported to enhance the intrinsic tubular recovery in several AKI models in a paracrine signaling. Treatment with MSCs promoted proximal tubular cell proliferation, reduced apoptosis, and preserved microvascular integrity, leading to the amelioration of renal tissue oxygenation (36,44-46). It is considered that MSCs interact with tubular resident cells in endocrine and paracrine manners through the secretion of growth factors or cytokines (47,48). Medium with MSC-derived, which contains renotrophic factors and anti-inflammatory factors improved kidney repair after injury (47,48-50). BMDCs including MSCs are now considered to responsible for the regenerative process by producing protective and regenerative factors, rather than by differentiating to directly replace damaged cells.

In early descriptive investigate, it has been proposed that regeneration of PCT cells occurred from any surviving tubular cell subsequent mild to moderate injury (51,52). In addition, staining for cyclin D1, Ki-67, and bromodeoxyuridine recommended that fully differentiated tubular cells were either growth arrested or had progressed to the G1 phase, potentially acting as a reserve cells and rapidly re-enter the cell cycle in injury (52).

At present only two major hypotheses remain for origin of PCT regenerating cells: One, any differentiated tubular cells that existing after injury and two, specific tubular cell subpopulation with high regenerative potential that called scattered tubular cells (STCs) or both. An STC population has suggested as a candidate for a progenitor cell population within the PCT epithelium (53,54). STCs find in all the way through the mammalian renal tubule in a scattered style. Phenotypically, these cells show signs of dedifferentiation and express marker proteins, which express by other stem or progenitor cells or cells in metanephric blastema development (54).

For the first time in year 2011, Lindgren et al described scattered tubular cells as a new subpopulation of proximal tubular cells. Because these cells showed a different morphology and were scattered as single cells between fully differentiated tubular cells throughout the entire PCTs, these cells named scattered tubular cells. STCs show very distinctive morphology in electron microscopic images. They are generally smaller than fully differentiated tubular cells and may have different shapes (54,55). In the normal human kidney, STCs occur as single cells or seldom as doublets or triplets. STCs surround by fully differentiated tubular cells and show a narrow flask-like shape. Significantly, STCs have small number of mitochondria in comparison with full-differentiated neighboring PCT cells (54,55).

In the normal human kidney, STCs were detected at the inner turn or along infoldings of the tubule (e.g. along the tubular plicae where the tubule makes a hairpin turn) probably because of mechanical forces of adjacent cells (34,54). In contrast to differentiated tubule cells, STCs do not have a prominent apical brush border. STCs also express only very low levels of protein endocytic transporter megalin. STCs lack the basolateral membrane infoldings, in contrast to fully differentiated proximal tubular cells (54). Lack of an apical brush border and a basolateral infoldings are signs of low endocytosis activity of STCs in comparison with differentiated PCT cells. In the regenerative phase after AKI, STCs may become rather abundant and mostly get shapes similar to the surrounding tubular cells (34,54).

In addition, STCs and parietal epithelial cells (PECs) of bowman capsule express similar markers (53). There are higher levels of CD133 and CD24 in isolated STCs from human kidney cortex. In the human kidney, both of these markers express by PECs (56).

Houghton et al also had described two different types of tubular cell morphologies in more detail after AKI using transmission electron-microscope. First, there were "apparently residual cells" with preserved microvilli, mitochondria, and prominent endoplasmic reticulum. Cells of the second type were "apparently regenerating cells" (putative STCs). The latter cells were wider with a more loosely arranged cytoplasm. There were fewer mitochondria, only rudimentary or absent microvilli and no basal infoldings in these cells (57).

Proteinuria or transient ischemia (IRI) induces the STC phenotype in mice and unilateral urethral obstruction induces the STC phenotype in mice and rats (34,54).

To treat or even prevent AKI, a pharmacological agent will be required, which propel tubule cells into the STC phenotype. In the renal corpuscle, such an agent may activate PECs, and this may be Sufficient to induce crescentic nephritis (58). In one study, induction of the STC phenotype in small but significant numbers of PCTs cells in the contra lateral kidney were observed during the recovery phase after unilateral ischemic AKI. It is speculate that unidentified soluble factor induces the PCTs cells to acquire the STC phenotype that rendering

the kidney more resistant to injury (34).
STC observe in normal human kidney but are absent in normal mouse or rat kidney and originates from any surviving proximal tubule cell after AKI (35). If STCs were a fixed progenitor population, they should always be detectable in minimal numbers in healthy rat or mice kidneys. Taken together, the results show that STCs are not a fixed progenitor population and those STCs can arise from any surviving proximal tubular cell (34).
Some believed that terminally differentiated PCTs cells undergo dedifferentiation upon injury to replace lost neighboring tubular epithelial cells through proliferative self-duplication. This new evidence includes data clearly indicating that STCs are not committed tubular stem cells but instead represent individual dedifferentiated tubular epithelial cells that transiently express putative stem cell markers (35,59,60). Nevertheless, it remains unclear, if the STCs are dedifferentiated transitional tubular cell during tubular regeneration, why STCs are present in normal human PCT.

Tight junction formation between regenerated cells

ATP depletion in ischemic condition leads to formation of large insoluble complexes from tight junction proteins (zonula occludens 1 (ZO-1) and ZO-2), probably in association with the cytoskeletal protein fodrin. Furthermore, in ischemic condition occludin, the transmembrane protein of the tight junction localized to the cell interior, probably in membrane vesicles (61).
After ischemia and cells regeneration, tight junction assembly between new cells needs to form apical-basolateral polarity and functional tubules with special permeability. Tight junction the most important junction for maintaining the permeability and barrier in Para cellular region forms by assembly of special cludins, occludin and ZO molecules (62). Thus, it is necessary to understand how new renal epithelial cells forms the junctions to restore proper function to the tubules.
Tight junction assembly under normal physiological conditions remains ill understood. Although is not yet completely clear how the kidney restores tight junction structure after ischemic injury, but some information discusses in bellow.
Ayyappan and co-workers proposed a two-step model for the formation of tight junctions in epithelial cells (63). Step 1 is dependent on the cell-cell adhesion function of E-cadherin. On E-cadherin-mediated cell-cell interactions, tight junction proteins are translocated from the cytoplasm to the plasma membrane and circumferential actin ring and the adherence junctions are established. The translocation of ZO-1 might be due to its association with catenins that, in turn, are associated with E-cadherins containing transport vesicles (64). In addition, during this initial step of tight junction assembly, ZO-1 association with the actin cytoskeleton as well as with occludin and claudin might take place to form the discontinuous tight junction strands. Step 2 of tight junction assembly is dependent on active actin polymerization that probably regulated by RhoA GTPase. Active polymerization of actin filaments associated with ZO-1, ZO-2, ZO-3, or occludin might provide the propulsive force to mobilize discontinuous tight junction strands in the plane of the membrane and facilitate maintenance of tight junction strands at the apicolateral region to establish functional tight junctions (65).
According to some report, the initial phase of tight junction biogenesis is characterized by interactions of ZO-1 with cadherins at the primordial adherens junction that gradually fuse to form belt-like tight junctions. At this stage, claudins, occludins, and junctional adhesion molecules are recruited and polymerize to form the tight junction strands that eventually segregate from the adherens junction (66). In the mature tight junction, ZO-1 is completely excluded from the adhering junction and found exclusively at the tight junction (67). Phosphorylation of occludin regulates tight junction permeability through c-Src, PKC, and protein phosphatases (68).
Multiple signaling pathways regulate tight junction reassembly. Heterotrimeric G proteins control cellular responses through G and G subunits, and several G subunits that localize in the tight junction. G o, G i2, and G s stimulate tight junction assembly (69). Rho GTPases are also major regulators of the tight junction and the actin cytoskeleton (70). PKC has multiple effects on the phosphorylation of tight junction proteins and diverse roles in tight junction assembly. Protein phosphatase 2A is a serine-threonine phosphatase that localizes to the tight junction and regulates the phosphorylation of ZO-1 and occludin, antagonizing PKC phosphorylation of these proteins (71). Various additional studies implicate other tyrosine kinases, phosphatases, and signaling proteins in the regulation of tight junction assembly. Some studies showed that PKC isoforms such as PKCη, PKCλ and PKCζ are involved in the assembly of tight junctions (70,72,73).

Conclusion

Ischemia leads to PCT cells necrosis. New cells originate from any tubular differentiated cells that survived after injury. Survived cells dedifferentiate to STCs that proliferate and renew epithelial tubule. STCs are detectable in human PCT in normal condition but do not exist in normal rat. A question has remained unknown, if the STCs are transient cells in regenerating PCT, why these cells are present in normal human PCT.

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Authors' contribution

AH and HA wrote the primary draft. MT edited the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by authors.

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References

1. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. Clin J Am Soc Nephrol. 2014;9:1627-38.
2. Zhuo JL, Li XC. Proximal nephron. Compr Physiol. 2013;3:1079-123.
3. Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch Biochem Biophys. 2012;523:9-18.
4. Meyer C, Dostou JM, Gerich JE. Role of the human kidney in glucose counter regulation. Diabetes. 1999;48:943-48.
5. Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. J Am Soc Nephrol. 2003;14:2199-210.
6. Wei Q, Dong Z. Mouse model of ischemic acute kidney injury: technical notes and tricks. Am J Physiol Renal Physiol. 2012;303:F1487-F94.
7. Uchida S, Endou H. Substrate specificity to maintain cellular ATP along the mouse nephron. Am J Physiol. 1988;255:F977-83.
8. Porter GA. Risk factors for toxic nephropathies. Toxicology letters. 1989;46:269-79.
9. Bennett WM. Drug interactions and consequences of sodium restriction. Am J Clin Nutr. 1997;65:678-81.
10. Bennett WM, Hartnett MN, Gilbert D, Houghton D, Porter GA. Effect of sodium intake on gentamicin nephrotoxicity in the rat. Proc Soc Exp Biol Med. 1976;151:736-38.
11. Venkatachalam MA, Bernard DB, Donohoe JF, Levinsky N. Ischemic damage and repair in the rat proximal tubule: differences among S1, S2 and S3 segments. Kidney Inter. 1978;14:31-49.
12. Lewy PR, Quintanilla A, Levin NW, Kessler RH. Renal Energy Metabolism and Sodium Reabsorption. Annual Review of Medicine. 1973;24:365-84.
13. Dorai T, Fishman A, Ding C, Batinic-Haberle I, David S. Amelioration of renal ischemia-reperfusion injury with a novel protective cocktail. J Urol. 2011;186:2448-54.
14. Koga H, Hagiwara S, Kusaka J, Goto K, Uchino T, Shingu C, et al. New α-lipoic acid derivative, DHL-HisZn, ameliorates renal ischemia-reperfusion injury in rats. J Surg Res. 2012; 174(2):352-8.
15. Koga H, Hagiwara S, Mei H, Hiraoka N, Kusaka J, Goto K, et al. The vitamin E derivative, ESeroS-GS, attenuates renal ischemia-reperfusion injury in rats. J Surg Res. 2012;176(1):220-5.
16. Singh P, Ricksten SE, Bragadottir G, Redfors B, Nordquist L. Renal oxygenation and haemodynamics in acute kidney injury and chronic kidney disease. Clin Exp Pharmacol Physiol. 2013;40:138-47.
17. Ashworth SL, Sandoval RM, Horsford M, Bamburg JR, Molitoris BA. Ischemic injury induces ADF relocalization to the apical domain of rat proximal tubule cells. Am J Physiol Renal Physiol. 2001;280:F886-94.
18. Ashworth SL, Southgate EL, Sandoval RM, Meberg PJ, Bamburg JR, Molitoris BA. ADF/cofilin mediates actin cytoskeletal alterations in LLC-PK cells during ATP depletion. Am J Physiol Renal Physiol. 2003;284:F852-62.
19. Molitoris BA. Actin cytoskeleton in ischemic acute renal failure. Kidney Int. 2004;66:871-83.
20. Ashworth SL, Wean SE, Campos SB, Temm-Grove CJ, Southgate EL, Vrhovski B, et al. Renal ischemia induces tropomyosin dissociation- destabilizing microvilli microfilaments. Am J Physiol Renal Physiol. 2004;286:F988-96.
21. Huang TY, Dermardirossian C, Bokoch GM. Cofilin phosphatases and regulation of actin dynamics. Curr Opin Cell Biol. 2006;18:26-31.
22. Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol. 2006;17:1503-20.
23. Lee DB, Huang E, Ward HJ. Tight junction biology and kidney dysfunction. Am J Physiol Renal Physiol. 2006;290:F20-34.
24. Molina A, Ubeda M, Escribese MM, Garcia-Bermejo L, Sancho D, de Lema GP. Renal ischemia/reperfusion injury: Functional tissue preservation by anti-activated beta1 integrin therapy. J Am Soc Nephrol. 2005;16:374-82.
25. Simmons EM, Himmelfarb J, Sezer MT, Chertow GM, Mehta RL, Paganini EP. PICARD Study Group: Plasma cytokine levels predict mortality in patients with acute renal failure. Kidney Int. 2004;65:1357-65.
26. Tavafi M, Ahmadvand H, Toolabi P. Inhibitory effect of olive leaf extract on gentamicin-induced nephrotoxicity in rats. Iran J Kidney Dis. 2012;6:25-32.
27. Tavafi M, Ahmadvand H, Tamjidipour A, Rasolian B. Effect of normobaric hyperoxia on gentamicin-induced nephrotoxicity in rats. Iran J Basic Med Sci. 2014;17:287-93.
28. Tavafi M, Ahmadvand H. Effect of rosmarinic acid on inhibition of gentamicin induced nephrotoxicity in rats. Tissue Cell. 2011;43:392-7.
29. Tavafi M. Antioxidants against contrast media induced nephrotoxicity. J Renal Inj Prev. 2014;3:55-56.
30. Tavafi M. Suggestions for attenuation of renal ischemia reperfusion injury based on mechanisms involved in epithelial cells damages. J Nephropharmacol. 2015;4:1-3.
31. Berger K, Moeller MJ. Mechanisms of epithelial repair and regeneration after acute kidney injury. Semin Nephrol. 2014;34:394–403.
32. Basile DP., Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2:1303–53.
33. Maeshima A, Takahashi S, Nakasatomi M, Nojima Y. Diverse cell populations involved in regeneration of renal tubular epithelium following acute kidney injury. Corporation Stem Cells International. 2015;2015:964849.
34. Berger K, Bangen JM, Hammerich L, Liedtke C, Floege J, Smeets, et al. Origin of regenerating tubular cells after acute kidney injury. Proc Natl Acad Sci USA. 2014;111: 1533-38.
35. Bonventre JV. Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. J Am Soc Nephrol. 2003;14:S55-S61.
36. Morigi M, Imberti B, Zoja C, Corna D, Tomasoni S, et al. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol. 2004;15:1794-804.
37. Poulsom R, Forbes SJ, Hodivala-Dilke K, Ryan E, Wyles

S, et al. Bone marrow contributes to renal parenchymal turnover and regeneration. J Pathol. 2001;195(2):229-35.
38. Kale S, Karihaloo A, Clark PR, Kashgarian M, Krause DS, et al. Bone marrow stem cells contribute to repair of the ischemically injured renal tubule. J Clin Invest. 2003;112:42-49.
39. Lin F, Cordes K, Li L, Hood L, Couser WG, et al. Hematopoietic stem cells contribute to the regeneration of renal tubules after renal ischemiareperfusion injury in mice. J Am Soc Nephrol. 2003;14:1188-99.
40. Li B, Cohen A, Hudson TE, Motlagh D, Amrani DL, et al. Mobilized human hematopoietic stem/progenitor cells promote kidney repair after ischemia/reperfusion injury. Circulation. 2010;121:2211–20.
41. Lin F, Moran A, Igarashi P. Intrarenal cells, not bone marrow-derived cells, are the major source for regeneration in postischemic kidney. J Clin Invest. 2005;115:1756-64.
42. Duffield JS, Park KM, Hsiao LL, Kelley VR, Scadden DT, et al. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. J Clin Invest. 2005;115:1743-55.
43. Humphreys BD, Valerius MT, Kobayashi A, Mugford JW, Soeung S, et al. Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell. 2008;2:284-91.
44. Herrera MB, Bussolati B, Bruno S, Fonsato V, Romanazzi GM, et al. Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. Int J Mol Medicine. 2004;14:1035-41.
45. Morigi M, Introna M, Imberti B, Corna D, Abbate M, Rota C, et al. Human bone marrow mesenchymal stem cells accelerate recovery of acute renal injury and prolong survival in mice. Stem Cells. 2008;26:2075-82.
46. Lange C, Tögel F, Ittrich H, Clayton F, Nolte-Ernsting C, et al. Administered mesenchymal stem cells enhance recovery from ischemia/reperfusioninduced acute renal failure in rats. Kidney Int. 2005;68:1613-17.
47. Imberti B, Morigi M, Tomasoni S, Rota C, Corna D, Longaretti L, et al. Insulin-like growth factor-1 sustains stem cell-mediated renal repair. J Am Soc Nephrol. 2007;18:2921-28.
48. Bi B, Schmitt R, Israilova M, Nishio H, Cantley LG. Stromal cells protect against acute tubular injury via an endocrine effect. J Am Soc Nephrol. 2007;18:2486-96.
49. Eliopoulos N, Zhao J, Bouchentouf M, Forner K, Birman E, et al. Human marrow derived mesenchymal stromal cells decrease cisplatin renotoxicity in vitro and in vivo and enhance survival of mice post-intraperitoneal injection. Am J Physiol Renal Physiol. 2010;299:F1288-98.
50. Tögel F, Zhang P, Hu Z, Westenfelder C. VEGF is a mediator of the renoprotective effects of multipotent marrow stromal cells in acute kidney injury. J Cell and Mol Med. 2009;13:2109-14.
51. Glaumann B, Glaumann H, Trump BF. Studies of cellular recovery from injury. III. Ultrastructural studies on the recovery of the pars recta of the proximal tubule (P3 segment) of the rat kidney from temporary ischemia. Virchows Arch B Cell Pathol Incl Mol Pathol. 1977; 25:281-308.
52. Vogetseder A, Picard N, Gaspert A, Walch M, Kaissling B, et al. Proliferation capacity of the renal proximal tubule involves the bulk of differentiated epithelial cells. Am J Physiol Cell Physiol. 2008;294:C22-8.
53. Lindgren D, Bostrom AK, Nilsson K, Hansson J, Sjolund J, Möller C, et al. Isolation and characterization of progenitor-like cells from human renal proximal tubules. Am J Pathol. 2011;178:828-37.
54. Smeets B, Boor P, Dijkman H, Sharma SV, Jirak P, Mooren F, et al. Proximal tubular cells contain a phenotypically distinct, scattered cell population involved in tubular regeneration. J Pathol. 2013;229:645-59.
55. Hansson J, Hultenby K, Cramnert C, Ponten F, Jansson H, Lindgren D, et al. Evidence for a morphologically distinct and functionally robust cell type in the proximal tubules of human kidney. Hum Pathol. 2014;45:382-93,.
56. Sagrinati C, Netti GS, Mazzinghi B, Lazzeri E, Liotta F, et al. Isolation and characterization of multipotent progenitor cells from the Bowman's capsule of adult human kidneys. J Am Soc Nephrol. 2006;17:2443-56.
57. Houghton DC, Hartnett M, Campbell-Boswell M, Porter G, Bennett W. A light and electron microscopic analysis of gentamicin nephrotoxicity in rats. Am J Pathol. 1976;82:589-612.
58. Sicking EM, Fuss A, Uhlig S, Jirak P, Dijkman H, Wetzels J, et al. Subtotal ablation of parietal epithelial cells induces crescent formation. J Am Soc Nephrol. 2012;23:629-40.
59. Kramann R, Kusaba T, Humphreys BD. Who regenerates the kidney tubule? Nephrol Dial Transplant. 2015;30:903-10.
60. Kusaba T, Lalli M, Kramann R, Kobayashi A, Humphreys BD. Differentiated kidney epithelial cells repair injured proximal tubule. PNAS. 2014;111:1527–32.
61. Tsukamoto T, Nigam SK. Tight junction proteins become insoluble, form large complexes and associate with fodrin in an ATP depletion model for reversible junction disassembly. J Biol Chem. 1997;272:16133-39.
62. Trujillo J, Molina-Jijón E, Medina-Campos ON, Rodríguez-Muñoz R, Reyes JL, Loredo ML, et al. Renal tight junction proteins are decreased in cisplatin-induced nephrotoxicity in rats. Toxicol Mech Methods. 2014;24:520-28.
63. Rajasekaran AK, Rajasekaran SA. Role of Na-K-ATPase in the assembly of tight junctions. Am J Physiol Renal Physiol. 2003;285:F388-96.
64. Rajasekaran AK, Hojo M, Huima T, Rodriguez-Boulan E. Catenins and zonula occludens-1 form a complex during early stages in the assembly of tight junctions. J Cell Biol. 1996;132:451-63.
65. Wittchen ES, Haskins J, Stevenson BR. Protein interactions at the tight junction. Actin has multiple binding partners, and ZO-1 forms independent complexes with ZO-2 and ZO-3. J Biol Chem. 1999;274:35179-85.
66. Bradley DM, Sabath E. The Biology of Epithelial Cell Tight Junctions in the Kidney. J Am Soc Nephrol. 2011;22:622-5.
67. Ikenouchi J, Umeda K, Tsukita S, Furuse M. Requirement of ZO-1 for the formation of belt-like adherens junctions during epithelial cell polarization. J Cell Biol. 2007;176: 779-86.
68. Dörfel MJ, Huber O. Modulation of tight junction structure and function by kinases and phosphatases targeting occludin. J Biomed Biotechnol. 2012;2012:807356.
69. Sabath E, Negoro H, Beaudry S, Paniagua M, Angelow S, et al. G{alpha}12 regulates protein interactions within the MDCK cell tight junction and inhibits tight-junction

assembly. J Cell Sci. 2008;121:814-24.
70. Suzuki T, Elias BC, Seth A, Shen L, Turner JR, et al. PKCeta regulates occludin phosphorylation and epithelial tight junction integrity. Proc Natl Acad Sci USA. 2009;106:61-6.
71. Nunbhakdi-Craig V, Machleidt T, Ogris E, Bellotto D, White CL, et al. Protein phosphatase 2A associates with and regulates atypical PKC and the epithelial tight junction complex. J Cell Biol. 2002;158:967-78.
72. Zyrek AA, Cichon C, Helms S, Enders C, Sonnenborn U, et al. Molecular mechanisms underlying the probiotic effects of Escherichia coli Nissle 1917 involve ZO-2 and PKCzeta redistribution resulting in tight junction and epithelial barrier repair. Cell Microbiol. 2007;9:804-16.
73. Cichon C, Sabharwal H,R€uter C, Schmidt MA. MicroRNAs regulate tight junction proteins and modulate epithelial/endothelial barrier functions. Tissue Barriers. 2014;2:e944446.