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EDITORIAL

Different modes of renal proximal tubule regeneration in health and disease

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Abstract

Tissues are equipped with reasonable strategies for repair and regeneration and the renal proximal tubule (PT) is no exception. New information has become available on the mode of PT regeneration in mammals. Unlike the intestinal epithelium with a high rate of turnover maintained by the stem cell system, the kidney has low turnover under normal physiological conditions. The PT seems to be maintained physiologically by hyperplasia, a regenerating system with self-renewal of mature tubular cells. This mode of regeneration is advantageous for effective replenishment of randomly isolated and eliminated tubular cells by self-renewal of adjacent cells. On the other hand, it has been suggested that dedifferentiation of mature tubular cells plays a role in regeneration after acute kidney injury. Recent studies employing genetic labeling and DNA-labeling techniques have confirmed that the proliferation of preexisting injured mature tubular cells contributes mainly to PT regeneration in ischemic reperfusion injury. This mode of regeneration is beneficial with regard to the rapid reparation of focally injured tubules often induced by ischemic reperfusion injury. What happens, however, when the PT is homogeneously injured with almost no remaining surviving cells? Is the PT equipped with another backup regeneration system, e.g., the stem cell system? Is it possible that certain types of renal injuries evoke a stem cell response whereas others do not? This review focuses on all three possible modes of tissue regeneration (compensatory hyperplasia, dedifferentiation and stem cell system) in mammals and their involvement in PT regeneration in health and disease.

Key words: Proximal tubule; Regeneration; Compensatory hyperplasia; Dedifferentiation; Stem cell; Progenitor cell

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MECHANISMS OF RENAL TUBULE REGENERATION

There are three mechanisms of tissue regeneration in vertebrates[1], as illustrated in Figure 1: (1) compensatory hyperplasia, where mitosis of cells occurs during the differentiation state (e.g., liver, pancreas[2,3]); (2) dedifferentiation of mature cells where stem-like cells are raised by the dedifferentiation of differentiated cells (e.g., myofibers, lens[4-6]); and (3) activation of undifferentiated adult stem cells sequestered during tissue development, where the stem cell divides to produce one daughter cell committed to specific lineage differentiation, while another daughter cell is renewed as a stem cell (e.g., skin epidermis, hair follicles, epithelium of the digestive tract[7-9]). In general,

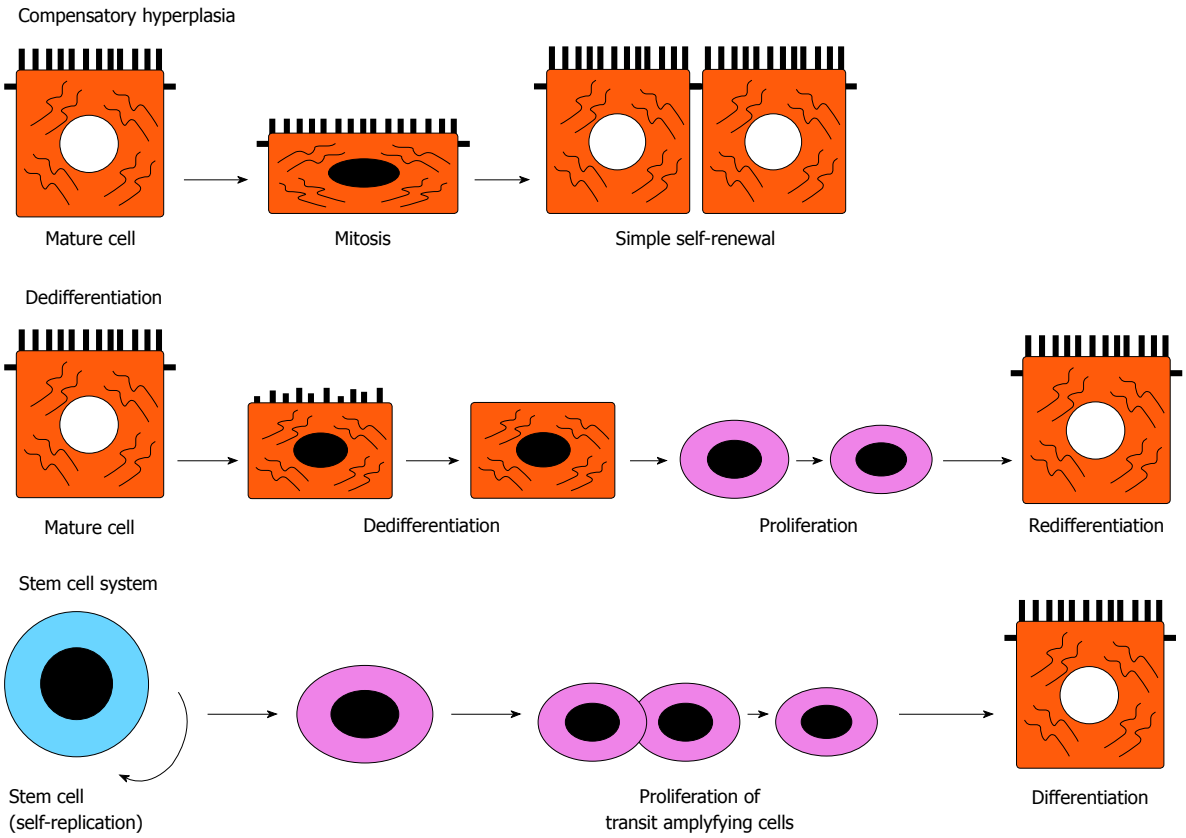

Figure 1 Three mechanisms of tissue regeneration in vertebrates.

epithelial tissues equipped with a stem cell system may use such a system to maintain cell turnover under both physiological and pathological conditions.

Like other organs, the kidney is also known to regenerate completely in lower vertebrates, such as teleost fish, the skate, elasmobranch fish and zebrafish, during which the entire nephron regenerates following injury or partial removal of the kidney[10-13]. The source of the new nephrons is a population of stem cells that exist in the special nephrogenic zone[14]. On the other hand, the regenerative capacity of the mammalian kidney is limited compared to that of lower vertebrates. However, it is well known that even in mammalian kidney, renal tubules have regenerative capacity, especially after acute kidney injury such as acute tubular necrosis[15], through yet unknown regeneration mechanisms.

Recent interest in stem cell-based therapy led many investigators to study the source of regenerating tubular cells and the role of stem cells after acute kidney injury in mammalian kidneys[16-33]. However, accumulating evidence indicated that the main source of regenerating cells is resident kidney cells, not bone marrow-derived cells (e.g., hematopoietic stem cells, mesenchymal stromal cells and endothelial progenitor cells)[34,35]. Moreover, resident kidney cells, rather than bone marrow-derived cells, were the main contributors to the tubular repair in the ischemic reperfusion injury model[34,35]. However, recent reports have demonstrated that the bone marrow-derived mesenchymal stromal cells play renoprotective roles in tubular repair and/or recovery by producing various humoral factors not at a cell basis[36-41]. More recent studies of rats with ischemic reperfusion injury indicated that the source of tubular regenerating cells that contribute to the repair of renal tubules is limited to resident (pre-existing) tubular cells[42] and that the intratubular stem cell system is not involved in tubular regeneration[43]. However, it is too early to conclude that there is no intratubular stem cell system in mammalian kidneys.

In this review, we discuss the modes of regeneration of proximal tubules (PTs) and their implication in health and disease.

REGENERATION OF PT CELL UNDER PHYSIOLOGICAL CONDITIONS

The physiological processes of renal tubular cell turnover play an important role in the maintenance of normal tissue function and architecture, which is achieved by a dynamic balance between the rate of cell elimination and the rate of cell proliferation. In 1959, McCreight and Sulkin counted the number of mitotic figures and calculated the proliferation index of PT cells to be 0.1% in the normal rat kidney, and hence concluded that the kidney has a low cell turnover under physiological conditions[44]. In another study, the estimated proliferation indexes of PT cells stained for S-phase markers in paraffin sections (percentages of cells positive for the proliferation

cell nuclear antigen and Ki67 antibodies) were 0.22 and 0.24, respectively[45]. In a study from our laboratory[46], about 40% of S3 segment of PT cells were labeled by the S-phase marker, bromodeoxyuridine (BrdU), when adult normal rats were treated with BrdU by osmotic mini-pump for 2 wk. Since the number of eliminated cells should be substituted by the same number of newly regenerating tubular cells to maintain normal tissue function and architecture, at most about 20% of tubular cells in the S3 segment should divide into two cells during a 2-wk period if they divided only once during the period. This suggests that the proliferation index 1 h after BrdU administration may be about 0.06% in the S3 segment in adult rats. Considered together, the above studies indicate that PT cell proliferation or turnover is slow in adults.

Recently, Vogetseder *et al*[47,48] concluded that the S3 segment of PT is maintained by a physiological regenerating system with self-renewal of mature tubular cells. Their conclusion was based on the finding of numerous cells with proliferative potency (retaining positivity for the proliferation marker, BrdU). Both cycling and non-cycling cells remained morphologically and phenotypically fully differentiated PT cells and cycling cells did not show the characteristics of transit amplifying cells[47,48], which can expand the number of cells by rapid cycling after division from stem cell[49]. This does not support the notion that stem cell system ensures turnover of tubular cells under physiological conditions.

In our study, we also found that BrdU+ proliferating PT cells in the S3 segment of normal rat nephron exhibited a mature PT phenotype, such as staining for megalin, aquaporin 1 and Na^+K^+-ATPase, and also maintained a mature PT ultrastructure[50]. However, these cells did not express vimentin, a marker of mesenchyme or dedifferentiated PT cells[51]. These findings suggest that normal PT cells can undergo cell division without dedifferentiation.

In the liver, cell marking studies indicated that during normal liver turnover and after partial hepatectomy, hepatocytes are replaced by compensatory hyperplasia of existing hepatocytes[52]. Interestingly, mature hepatocytes can replicate during normal liver growth, but the newly formed cells do not migrate[53]. Since cells generated by simple self-renewal through compensatory hyperplasia cannot migrate, it is unlikely that these newly regenerating cells can repair largely damaged areas in a mode of simple self-renewal. This may also be the case in renal PT cells. Thus, compensatory hyperplasia provides effective replenishment of randomly eliminated tubular cells by self-renewal of adjacent cells under physiological conditions. However, other modes of regeneration are required under pathological conditions.

REPAIR AFTER ACUTE TUBULAR INJURY

The mammalian kidney is classically regarded as an organ that cannot truly regenerate. In the past, it was thought that acutely injured tubular cells slough off the tubular basement membrane and that the surviving tubular cells undergo migration, dedifferentiation, proliferation and re-differentiation to reline the injured tubules[54,55]. Vogetseder *et al*[48] reported that in rats treated with potent proliferative agents (lead acetate injection[56]), PT proliferation did not require stem cells but involved proliferation of preexisting differentiated tubular cells. Interestingly, they concluded that PT cells were probably not quiescent but resting in G1-phase of the cell cycle, i.e., they could divide rapidly in response to injury. Recently, Humphreys *et al*[42] used sophisticated technology to demonstrate that tubular cells *per se* are the source of regenerating tubular cells. They prepared transgenic mouse strains in which all cells involved in nephrogenesis were lineage labeled. Using these mice, they tested whether any endogenous cell type entered the tubules and contributed in the repair process of tubules after ischemic reperfusion injury. Their data showed a lack of non-tubular cells in renal tubules before as well as after ischemic reperfusion injury. However, this finding neither excludes the possibility of the existence of intratubular stem cells/progenitor cells nor the proliferation of preexisting differentiated cells within the tubules.

More recently, Humphreys *et al*[43] used a DNA analog-labeled approach to chase multiple rounds of cell divisions in mice after ischemic reperfusion injury and demonstrated that PT cell division in the cortex and outer medulla occurred predominantly in injured and dedifferentiated PT cells. PT cell injury was confirmed by Kim-1 expression[57] and dedifferentiated cells by both PAX-2 expression[58] and reduction in Na^+K^+-ATPase expression in proliferating cells labeled with DNA analog. A stochastic kinetics of proliferation was identified, probably reflecting simple self-duplication rather than selective activation of an intratubular progenitor population. The findings of Humphreys *et al*[43] strongly suggest that proliferation of preexisting differentiated cells within the tubules is the main event in PT regeneration in ischemic reperfusion injury.

We also examined the importance of dedifferentiation in the initiation of cell division of PT cells after acute PT injury induced by uranyl acetate (UA), a nephrotoxic agent[50]. High-dose UA induced severe PT injury of the S3 segment and the first proliferating PT cells showed loss of PT cell protein phenotype (megalin, aquaporin 1 and Na^+K^+-ATPase) but became positively stained for vimentin. In comparison, low-dose UA induced focal PT injury of the S3 segment, with the first proliferating PT cells still exhibiting the PT phenotype and not staining for vimentin. Subsequently, the proliferating PT cells showed loss of PT cell phenotype and expressed vimentin. Thus, similar to the changes seen under physiological conditions, the PT cells can enter the cell cycle without apparent dedifferentiation after low-dose UA-induced focal PT injury. However, dedifferentiation with vimentin expression may follow after initial cell division. Interestingly, continuously proliferating tubular cells tend to express vimentin unlike regenerating cells under physiologi-

cal conditions[54,55]. Since vimentin is a major intermediate filament protein and is associated with the development of migratory capacity[59,60], it is conceivable that proliferating PT cells can acquire vimentin expression to undergo cell division more than once and to migrate to cover the denuded tubular basement membrane. This may not be the case in regenerating PT cells under physiological conditions.

Thus, dedifferentiation must be a beneficial mode of regeneration for rapid reparation of focal areas following focal injury of the tubule, such as after ischemic reperfusion injury[61]. However, questions remain on whether all PT cells possess the ability to enter the cell cycle and acquire dedifferentiation property (i.e., is a stem-like cell) and whether the insult of ischemic reperfusion injury is adequate to activate intratubular progenitor cells, if they do exist. It is also possible that certain forms of renal damage can evoke a stem cell response whereas others do not.

DIFFERENT REPAIR PROCESSES OF PT AFTER ACUTE TUBULAR INJURY

The study of Oliver and colleagues[61] indicated that the main site of tubular injury following traumatic and toxic insults is PTs, based on histopathological examinations of cadaver kidneys in patients with severe fatal acute renal failure. They also found two types of tubular injuries. The first was nephrotoxic necrosis limited to that part of the nephron in the PT that is functionally concerned with the handling of poisons; the necrosis was homogeneous in that part of the nephron. The second type of lesion was disruption of the renal tubule due to focal cortical ischemia. It occurs at random among nephrons. The authors suggested that, in the kidney of any case of fatal acute renal failure arising under various clinical circumstances, these two types of lesions appear in varying proportions depending on the nature of the renal insult, whether toxic or circulatory or both. Thus, the number and distribution of surviving tubular cells after acute tubular injury must be highly variable among the different causes of acute tubular injury. It is also conceivable that different repair processes of tubules also occur under different pathological conditions.

In fact, we found two different modes of repair processes of PT after acute tubular injury induced even by the same nephrotoxic agent, low- or high-dose of UA in rats using the ^{3}H-thymidine pulse/chase approach[62] for the detection of early regenerating PT cells[63]. In these studies, low-dose UA (0.25 or 0.5 mg/kg) induced mild and focal PT depletion in S3 segment without significant increase in serum creatinine. Some of the surviving PT cells scattered in the proximal three quarters of the S3 segment became thymidine-incorporating (detected by grain on sections) early regenerating PT cells. They were increasingly found in the proximal three quarters of S3 and to a lesser extent in the distal S3 at day 7, and decreased in number by day 42. The number of label-retaining PT cells increased in the entire S3 and the number of label-diluted PT cells was significantly increased, mainly in the proximal three quarters of S3, and both were decreased in parallel at day 42. Early regenerating cells maintained the differentiated phenotype initially then loss of the phenotype was noted shortly after the initial regeneration[50,63]. Taken together, the surviving PT cells contributed to the repair of focal PT injury, suggesting that dedifferentiated PT cells, derived from preexisting mature PT cells are responsible for focal repair of the S3 segment.

On the other hand, high-dose UA (1 or 5 mg/kg) induced a significant increase in serum creatinine and necrotic PT started to appear at the corticomedullary junction as early as day 2 after injection of UA, and then maximally spread in the entire S3 segment with almost complete PT depletion in three-quarters of the S3 segment with less PT depletion in the distal quarter of S3 by day 5[63,64]. The BrdU or thymidine-incorporating early regenerating cells were limited to the distal area of the S3 segment from days 2 to 3, remote from the initial site of damage, then upstream proliferation of PT cells occurred along the denuded tubular basement membrane, which was almost completed by day 7[63,64]. Thymidine-labeled PT cells were increasingly found in the entire S3 at day 7 during the repair phase. Label retaining PT cells were increased in the entire S3 and to a significantly greater extent in the distal S3. They were rapidly decreased in number in the proximal three quarters of S3 by day 21, but their number remained constant in the distal S3 until day 42. In contrast, the label-diluted PT cell population increased in the entire S3, although to a significantly lesser extent in the distal S3 at day 7, and their numbers decreased markedly in the entire S3 by day 42[63]. Early regenerating cells after high-dose UA insult seem to be the cellular source of regenerating tubules with high proliferative properties to repair the entire S3 segment with infrequent cycling after completion of the repair process of PT. Thus, we hypothesized that these cells might be slow cycling cells responsible for the repair of the entire S3. Next, we examined whether they could be designated the "target cells" and have intratubular progenitor-like properties.

POSSIBLE EXISTENCE OF RENAL TUBULAR PROGENITOR-LIKE CELLS

No specific renal tubular stem/progenitor cell markers are currently available. Therefore, indirect markers of slow cell cycling properties (label retention) have so far been used to search for potential population of intratubular progenitor cells. These include transcription factors and cell surface expression markers. However, once the PT cells are injured *in vivo* or isolated into a culture system, they also express genes and proteins of earlier stages of development[65], which makes it difficult to distinguish dedifferentiated tubular cells from mature differentiated tubular cells and intratubular progenitor cells. Therefore,

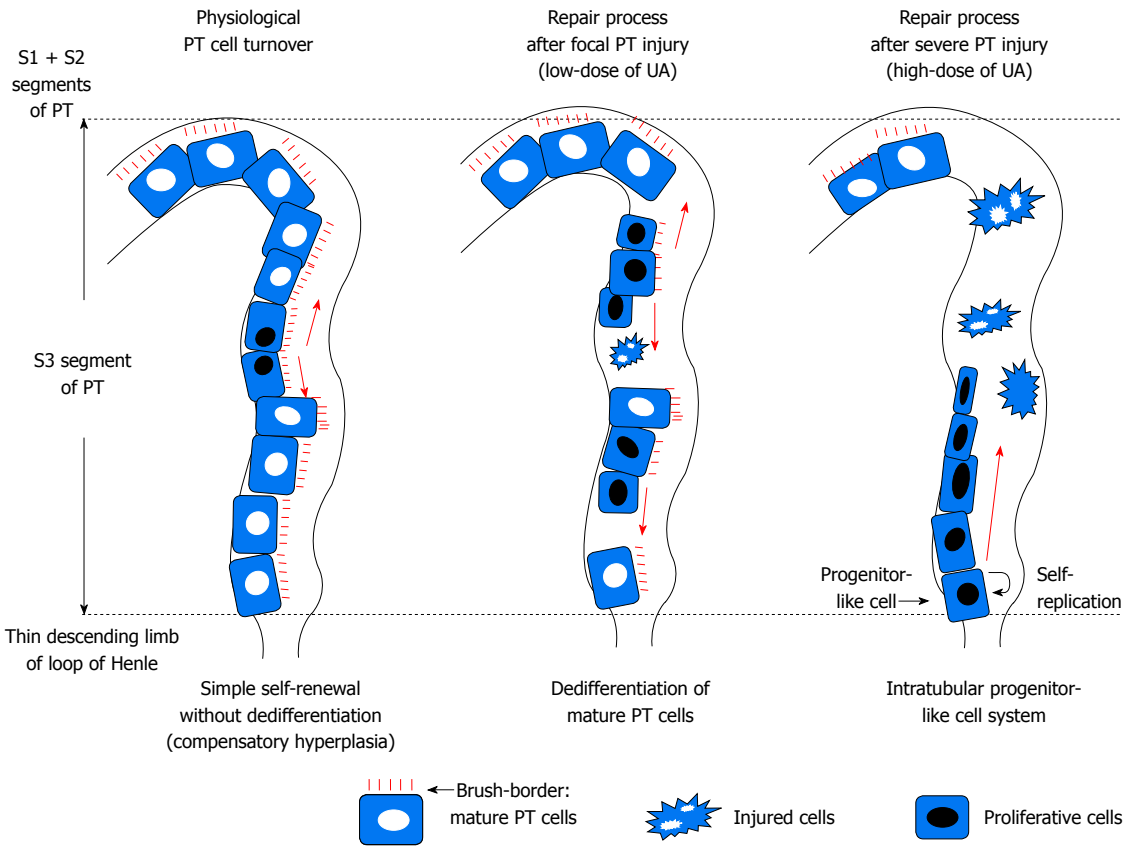

Figure 2 Three modes of regeneration of tubular cells in S3 segment of proximal tubule. PT: Proximal tubule.

at present there seems to be no reliable method to prove the existence of intratubular stem cells, both *in vivo* and *in vitro*.

To examine the specific properties of the early regenerating cells (designated as "target cells") in the S3 segment of rats with high-dose UA-induced acute tubular injury, we searched for possible cell features that could define progenitor-like cells *in vivo* among the different tubular cells in the S3 segment. Our studies yielded the following conclusions regarding target cell characteristics: (1) The target cells (i.e., thymidine-labeled cells) were persistently present in the distal area of the S3 up to and including week 40[66], further suggesting slow-cycling cells; (2) About 60% of PT cells in the S3 segment were "thymidine-labeled cells" at day 7 after high-dose UA-induced acute renal failure[66], suggesting that the majority of the regenerating cells in the S3 were newly synthesized following injury and originated from the target cells in the distal area of S3; (3) Some target cells reproliferated after a second high-dose UA insult[66]; (4) The target cells were resistant to 5-fluorouracil (5-FU) *in vivo* and showed restoration of regenerative property after withdrawal of 5-FU and were also reactivated by the second UA insult[66]. Whereas there is substantial information on the response of hematopoietic stem cells to 5-FU[67], there is little information on the response of epithelial stem/progenitor cells to 5-FU. Previous studies reported that 5-FU is cytotoxic to proliferating epithelial cells such as retinal pigment epithelial cells[68] and lens epithelial cells[69]. Thus, the findings suggest that the target cells may be in some way unique with possible progenitor-like cell properties; (5) The target cells showed weak or no staining for all three markers of mature PT phenotype (megalin, aquaporin1 and Na^+K^+-ATPase) but became positive for a mesenchymal marker (vimentin)[50]. On the other hand, following acute tubular injury induced by low-dose UA, the initial proliferating PT cells divided while keeping the mature PT phenotype, but subsequently showed regression of this phenotype[50]. Unlike other PT cells, the target cells could undergo cell cycle progression without accumulation of heat shock protein 27[70], which is thought to provide partial protection for PT cells against injury or death by acting as a molecular chaperone and thus promotes the stabilization, repair and/or disposal of denatured proteins[71]. The data showed that the PT cell phenotype at the time of initial cell division was different between the target cell and other tubular cells, suggesting that the target cells are probably unique; (6) The target cells exhibited morphological features of dedifferentiated/undifferentiated cells, such as smaller brush-border, large nuclei, fewer cytoplasmic organelles and spindle-like morphology[66], compatible with the features of progenitor cells[72]. At present, there are no reports on the existence of morphologically and phenotypically unique cells (e.g., cells lacking brush-border or cells negative for markers of mature PT) among PTs based on histological examination under physiological conditions. However, progenitor cells usually exhibit spindle-like morphology

with small length; thus, it is difficult to detect them when they are sequestered and/or buried among other PT cells without proper labeling such as BrdU; (7) A proportion of the target cells were localized at the transition zone between PT and the thin descending limb of Henle[66]. The target cells might have a bipotential differentiation because they exist at a unique location where cells can differentiate into both PT cells and thin descending limb of Henle; and (8) Under physiological conditions, most target cells did not enter the cell cycle based on BrdU-labeling[66], probably being different from the previously reported progenitor-like cells, which can be labeled with BrdU, during a 2 wk observation under physiological conditions[22,23]. This also suggests that the target cells do not contribute to the maintenance of cell turnover under physiological conditions but may be activated after severe PT injury in the S3 segment.

As mentioned earlier, we cannot confirm the existence of intratubular progenitor cells due to the lack of definitive markers for these cells, although some recent reports have provided some evidence for the existence of intratubular progenitor-like cells[22-30,33]. Therefore, it is not clear at this stage whether our "target cells" are truly progenitor-like cells or merely dedifferentiated PT cells that can acquire progenitor-like properties. However, our findings suggest the presence of a distinct population of tubular cells in the distal area of the S3 segment or at the transition zone between PT and thin descending limb of Henle. This cell population can be activated and stimulated to proliferate for adequate repair of PTs after severe impairment of the replicative capacity of PT cells in S3 segment or upon depletion of surviving PT following acute tubular injury.

PERSPECTIVES

Based on our data, we conclude that the three modes of regeneration, compensatory hyperplasia, dedifferentiation of mature tubular cells and intratubular progenitor-like cell system, as illustrated in Figure 2, may be involved in PT repair. Compensatory hyperplasia provides effective PT cell turnover by self-renewal of adjacent cells without dedifferentiation under physiological conditions. However, PT cells are vulnerable because they are exposed to a variety of toxins and are susceptible to ischemic injury. This might explain why PT cells can regenerate through dedifferentiation of mature tubular cells, which can result in effective and rapid repair of focal PT lesions. Intratubular progenitor-like cells can play a role as a backup system to repair severely injured PTs. This does not exclude the possibility that both dedifferentiation and intratubular progenitor-like cells also contribute together to repair PTs in certain types of tubular injury. Interestingly, evidence points to the presence of stem cells in the liver of several rat models of liver injury, which promote tissue regeneration as a second backup system for liver regeneration when the proliferative capacity of hepatocytes *via* compensatory hyperplasia is compromised[52]. The PTs also seem to be equipped with the same backup system for PT regeneration, including intratubular progenitor-like cells at different locations. For instance, severe injury in S1 and S2, but not S3 segment, of PT induced by gentamicin[73] might evoke different progenitor-like cells than in other intratubular locations.

Unfortunately, there is only a limited knowledge about the modes of regeneration of tubular cells and the factors that induce regeneration. Understanding tubular regeneration in health and disease can potentially allow the design of new therapeutic strategies against various tubular diseases.

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