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• Review

Role of adult resident renal progenitor cells in tubular repair after acute kidney injury

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ABSTRACT: Acute kidney injury is a serious global health problem and determinant of morbidity and mortality. Recent advancements in the field of stem cell research raise hopes for stem cell-based regenerative approaches to treat acute kidney diseases. In this review, the authors summarized the latest research advances of the adult resident renal progenitor cells (ARPCs) on kidney repair, the role of ARPCs on tubular regeneration after acute kidney injury, the current understanding of the mechanisms related to ARPC activation and modulation, as well as the challenges that remain to be faced.
KEYWORDS: acute kidney injury; stem cell; regeneration; adult renal progenitor cells; reviews

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1 Introduction

Acute kidney injury (AKI) arises in a variety of clinic situations and is a critical public health problem worldwide. It affects 7%–10% of all hospitalized patients and is associated with a mortality rate of 35%–40% in intensive care units[1]. Although clinical management of AKI has improved over the last decades, there are still few preventative or therapeutic interventions, and AKI-associated mortality is still unacceptably high[2]. AKI occurs in response to a variety of renal insults, most commonly, transient ischemia and/or exposure to nephro-toxicants[3]. It is clear that renal tubular epithelial cells (TECs) are the primary target of injury. The renal tubule has an extraordinary capacity to regenerate and restore function within a few days after AKI. According to the observation of injury pathology, some renal tubular cells are lost through apoptosis and necrosis; some injured cells may detached from the tubular basement membrane, which results in denuded areas. Over time, injured tubules are repaired by repopulation of the lost TECs through regeneration[4]. Renal tubules are believed to be made of highly differentiated epithelial cells. Recovery of renal function after AKI may be partially or completely depend on the regeneration capacity of injured tubules. It is currently thought that epithelial cell repair in response to AKI is accomplished through the differentiation, migration, and proliferation of surviving cells, ultimately resulting in restoration of tissue integrity[5,6]. However, the source of newly formed TECs that replace injured tubular epithelia is still not exactly known. Different hypotheses have been proposed regarding the cellular source. In early descriptive studies, someone proposed that the surviving proximal tubular cells retain the ability to repopulate the tubule[7]. Others suggested that the adult stem cells contribute to epithelial renewal after injury[8]. In addition, the bone marrow-derived stem cells (BMSCs) may play a role in stimulating epithelial regeneration[9].

Recently, the finding by genetic fate-mapping techniques demonstrated that tubule regeneration from ischemic/reperfusion injury was accomplished by the surviving tubular cells or a specific tubular cell subpopulation with high regenerative potential[10]. With the resident renal progenitor/stem cells identified, it was believed that the

intrinsic "seeding" cells might be the main source of kidney regeneration[11,12]. In this review, we summarized recent research developments in acute renal tubular injury and new research progress in tubule regeneration.

2 Cells contribute to tubule regeneration after AKI

TECs of the kidney are susceptible to injury from many causes, such as ischemia, reperfusion and associated oxidative stress, nephrotoxins, and inflammatory and immune disorders. Intriguingly, under some situation, the injured tubules can regenerate and renal functions can recover over time. But the origin of tubular cells that replenish the epithelial population is controversial. Several studies showed that tubular cell regeneration after an ischaemia/reperfusion injury is predominantly accomplished by surviving tubular cells, without the contribution of extra-renal and extra-tubular cells[13]. Accordingly, some studies support the hypothesis that surviving TECs dedifferentiate, proliferate, and migrate into the affected regions, then redifferentiate into an epithelial phenotype, eventually replacing the lost TECs and restoring tubular integrity[14]. Some studies demonstrated that surviving epithelial cells might dedifferentiate into the mesenchyme state (epithelial-mesenchymal transition), and then re-enter the cell cycle to repair tubular damage[15]. Sakakima *et al*[16] found that segment S3 of the proximal tubule showed a high susceptibility to acute tubular necrosis; injury to this region was followed by high proliferative activity. Initially regenerating cells in S3 were dedifferentiated into proximal tubular cells, which could scatter throughout S3 and replace lost cells. Vogetseder *et al*[7] also confirmed that the S3 segment of the proximal tubule was maintained by a physiological regenerating system that involved self-renewal of mature tubular cells with proliferative potency. Recently, Kusaba *et al*[17] analyzed the lineage and clonal behavior of fully differentiated proximal TECs after injury. They found that fully differentiated proximal tubule cells not only proliferate after injury, but also up-regulate apparent stem-cell markers. In a study using genetic fate-mapping techniques, Humphreys *et al*[18] showed that after kidney tissue suffered from transient ischemic injury, most if not all of the newly generated TECs were derived from surviving differentiated epithelial cells. In addition, they further found that the new epithelial cells arose from replication of the surviving cells, which were often injured and dedifferentiated; no nontubular cells contributed to the process of repair. Consequently, they concluded that epithelial dedifferentiation was responsible for repair of mouse proximal tubule, rather than an adult stem-cell population.

The source of cells for tubule regeneration still needs to be clarified. Some research implies the possibility that adult stem cells contribute to organ repair after kidney injury. Kim *et al*[19] labeled slow cell-cycle cells with 5-bromo-2′-deoxyuridine (BrdU) and investigated their location in tubules damaged by ischemia/reperfusion in mice. They found that some intrarenal slow cell-cycle cells contributed to the restoration of kidney tubules. However, these studies could not distinguish whether regeneration relies on intratubular progenitor/stem cells or on any surviving tubular cell. Until now, there has been no strong evidence to exclude the possibility of pre-existing intratubular stem cells or progenitor cells re-entering the cell cycle after injury, generating new proximal tubule cells through self-duplication[20]. More recently, Smeets *et al*[21] reported that proximal tubular cells contained a phenotypically distinct, scattered cell population, which showed characteristics of $CD24^+/CD133^+$ and were vimentin-positive. In acute tubular necrosis (ATN) biopsies, as well as in normal kidneys, approximately 85% of proliferating cells were CD24-positive. This finding suggests that there is an existing intratubular progenitor-like cell, or stem cell, which could be activated by renal injuries, and participate in tubular regeneration.

It has long been known that BMSCs have the potential to repair organs. Several studies have shown that BMSCs can migrate and engraft into the kidney, participate in normal TEC turnover and repair tissue after AKI[22]. Other investigators[10] have demonstrated elegantly that there is no evidence of BMSCs differentiating into renal TECs, even though post-ischemic functional impairment of kidney can be reduced by intravenous injection of BMSCs. The genetic cell fate tracing is a unique method that gives definitive experimental evidence. Using this method, studies have found no evidence that BMSCs contribute to tubular regeneration after injury, either by differentiation or fusion[23]. The major contribution of BMSCs in renal repair is dependent on their ability to inhibit apoptosis by preventing inflammation and enhancing renal cell proliferation through paracrine actions[24]. So far, the only cells found to differentiate to another cellular lineage and display a limited self-renewal potential in the adult kidney are the renal stem/progenitor cells[25].

3 Adult resident renal progenitor cells

Many adult organs contain stem cells. They reside in adult tissues and are able to differentiate into any cells of the organ of origin. In contrast to embryonic stem cells, they are considered multipotent rather than pluripotent. Progenitor cells are considered to have more limited differentiation capacity than stem cells, can differentiate into one or multiple cell types of the original tissue, but are only able to replicate a limited number of times. In the kidney, the progenitor cells usually stay in a quiescent state, and, when activated by stimulus, proliferate, eventually