Kidney regeneration and repair after transplantation

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Purpose of review
To briefly show which are the mechanisms and cell types involved in kidney regeneration and describe some of the therapies currently under study in regenerative medicine for kidney transplantation.

Recent findings
The kidney contains cell progenitors that under specific circumstances have the ability to regenerate specific structures. Apart from the knowledge gained in the self-regenerative properties of the kidney, new concepts in regenerative medicine such as organ engineering and the use of mesenchymal stem cell-based therapies are currently the focus of attention in the field.

Summary
Overall, kidney regeneration is a reality and the knowledge on how to control it will be one of the main scopes in the present and future.

Keywords
hepatocyte growth factor, kidney, regenerative medicine, stem cells, transplantation

INTRODUCTION

Kidney transplantation is the best option for end-stage renal disease patients. However, this is only a temporary solution and most of the patients develop interstitial fibrosis and tubular atrophy and eventually lose their grafts. A better knowledge on endogenous healing mechanisms for nonfibrotic wound healing and new therapies designed to increase the regenerative potential of the kidney might mean in a near future a longer graft survival or even no need for transplantation because of regeneration of native kidney.

In the context of kidney transplantation, the possibility to obtain biopsies regularly could provide a window of opportunity to detect stable grafts with initial signs of fibrosis, which could be used to foster regeneration before the onset of complete damage.

Until now, transplantation research has focused on the impact of the immunosuppressive drugs on the graft survival; however, these drugs might have a negative impact on the potential regeneration ability of the graft [1–3].

ENDOGENOUS MECHANISMS OF RENAL REGENERATION

The kidney has been classically considered unable to regenerate, in comparison with other organs such as the liver. Advances in developmental biology and in the knowledge of the balance between regeneration and fibrosis have brought major advances in the last years.

Adult kidney stem cell niches

When an adult tissue is damaged, the cell renewal process is crucial for its maintenance and, in certain organs, this is achieved by the presence of stem cells. These stem cell populations are housed in an in-vivo milieu, named a *niche*, which regulates stem cell survival, self-renewal, and differentiation. Stem cell niches are present in many adult organs and tissues [4]. In a normal environment, stem cells remain quiescent into the niche during long periods of time until they are activated by the requirement of new cells to maintain the tissue or because of tissue damage. When an insult happens, stem cells might be activated, exit the niche, proliferate, and

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KEY POINTS

- The kidney has intrinsic ability to regenerate after an injury.
- Several populations of stem cells with regenerative potential have been identified in the renal parenchyma.
- Regenerative medicine and organ engineering hold the potential to be the best alternatives to current treatments in transplantation.
- Mesenchymal stem cells and their derived microvesicles have been shown to protect from developing chronic injury.
- Other therapies such as hepatocyte growth factor or microvasculature regeneration enhances have already proven the regenerative potential in animal models.

differentiate into the needed cell types to replace the cell lost.

The kidney has a very complex structure and is composed of more than 20 cell types that function as a tissue unit rather than as individual cells, making harder its regeneration. These factors make it difficult to find a single renal stem cell able to differentiate into each renal cell type. Overcoming all these complications, some stem cell niches have been proposed in different renal compartments: the renal corpuscle, the nephron tubule, and the renal papilla.

Glomerular populations (the renal corpuscle)

Sagrinati *et al.* [5] identified, in human adult kidneys, a subset of parietal epithelial cells (PECs) in the Bowman's capsule that exhibit coexpression of the stem cell markers ($CD24^+CD133^+$). CD24 is a surface molecule expressed in the developing human fetal kidneys [6] and it has been used to identify different types of human stem cells [7]. CD133 is also expressed in human fetal kidney (by around 50% of the cells) and only in 0.5–3% of the adult human kidney [8].

This $CD24^+CD133^+$ PEC population reveals self-renewal potential and a high cloning efficiency. The localization of this $CD24^+CD133^+$ population is suitable for both podocyte and tubule regeneration. The infusion of $CD24^+$ and $CD133^+$ cells in SCID mice with acute renal failure resulted in the regeneration of tubular structures ameliorating the morphologic and functional kidney damage. A transitional cell population ($CD24^+CD133^+PDX^+$) shares the features of either renal progenitors or podocytes and localizes between the urinary pole and the vascular pole [7]. More recently, Angelotti *et al.* [9▪▪] have demonstrated that this $CD24^+CD133^+$ progenitor population can be distinguished in distinct subpopulations from normal human kidneys based on the surface expression of vascular cell adhesion molecule 1 (CD106). Thus, it has been described in two subpopulations: $CD24^+CD133^+CD106^+$ which is localized at the urinary pole and $CD24^+CD133^+CD106^-$ localized in the proximal tubule as well as in the distal convoluted tubule. The $CD24^+CD133^+CD106^+$ subpopulation exhibits a high proliferative rate and can differentiate toward the podocyte as well as the tubular lineage. By contrast, the $CD24^+CD133^+CD106^-$ subpopulation shows a lower proliferative capacity and solely differentiates into the tubular lineage. Both subpopulations, when injected into SCID mice with acute tubular injury, were able to engraft within the kidney, generate tubular cells, and improve renal function.

Bruno *et al.* [10▪▪] identified another glomerular population with stem cell features. They found that human glomeruli deprived of the Bowman's capsule contain a population of $CD133^-CD146^+$ cells that coexpress the typical mesenchymal stem cell markers (such as CD29, CD105, and CD73) and renal-specific stem cell markers (such as CD24 and Pax2). This population exhibits in-vitro self-renewal capability, clonogenicity, and multipotency. Moreover, when these cells are cultured in the appropriate culture conditions, they are able to differentiate into endothelial cells, epithelial cells expressing podocyte markers, and mesangial cells.

Tubular populations

The tubules of the kidney display a remarkable capacity for self-renewal on damage. Whether this regeneration is mediated by dedifferentiating surviving cells or stem cells has not been completely settled. On one hand, Humphreys *et al.* [11] described that nonlethally injured cells repopulate the kidney epithelium after injury in the absence of any specialized progenitor cell population. On the other hand, Lindgren *et al.* [12] detected a progenitor cell population in human kidney scattered through the proximal tubules which expressed the markers previously described for PECs, CD24 and CD133, and displays mixed features of renal progenitors and tubular cells. These tubular progenitors may proliferate and differentiate after tubular injury to replace dead cells. Moreover, it is well known that $CD24^+CD133^+$ (either PECs or tubular populations) express cytokeratin 7, cytokeratin 19, BLC2 (antiapoptotic gene), MYOF (regeneration-promoting molecule), and vimentin. Although this

tubular population has been identified, the identification of novel markers that may allow distinction between $CD24^+CD133^+$ renal progenitors of Bowman's capsule and $CD24^+CD133^+$ tubular cells is still required, as has been performed for podocytes ($CD24^+CD133^+$ PDX^- vs. $CD24^+CD133^+PDX^+$).

Otherwise, according to findings by Patschan and Oliver, in which they described the migration of nestin-positive cells following acute kidney injury [13,14], an overexpression of nestin in proximal tubules that may participate in the cell migration during renal repair has been recently observed [15].

The renal papilla

Oliver *et al.* determined, some years ago, another niche for adult kidney stem cells [14]. These authors detected a cell population in the renal papilla, which had a slow cycling rate. It was observed that during the repair phase of transient renal ischemia, these cells entered the cell cycle. More recently, these authors described that the SDF-1/CXCR4 axis is a critical regulator of papillary label-retaining cells activation following transient kidney injury and during organ repair [16].

REGENERATIVE MEDICINE

Cell therapies and organ engineering are two major lines of research in kidney regenerative medicine (Fig. 1). Advances in the field are fast growing and changing concepts.

Organ engineering

One of the research lines that has attracted much of the attention in the last years in kidney regeneration is the use of decellularized organs. Bioengineering custom-made organs, in which the cellular component is autologous and has an internal vascular network, will theoretically overcome the two major hurdles in transplantation: the shortage of organs and the toxicity deriving from lifelong immunosuppression.

This procedure is based on ex-vivo tissue regeneration using a donor scaffold by repopulating it with recipient-induced pluripotent stem cells (iPSCs) or embryonic stem cells. Although a few groups have been able to obtain a decellularized kidney scaffold [17], the success in recellularizing it has been rather scarce and limited to small vessels, arterioles, and glomeruli being repopulated by endothelial cells [18] and some tubular repopulation [19]. The structural complexity of the kidney, composed of more than 20 cell types, converts this into a difficult endeavor compared with the partial success obtained in heart, lung and liver [20,21].

Mesenchymal stem cells

Mesenchymal stem cells are stromal cells that can be found and isolated from virtually every tissue. Because of interesting multilineage differentiation potential and their ability to migrate to the site of injury, they have been studied in the last 10 years as a therapeutic agent in kidney injury. Although initial studies observed migration of the injected cells to injured kidney and even tubular replacement [22], there is no solid evidence that those cells can regenerate damaged tissue (by differentiation or fusion) and truly give rise to kidney-specific cell populations [23].

Although some studies have suggested that about 2% of the injected MSCs engraft the injured kidney [24], a recent study proved rapid clearance

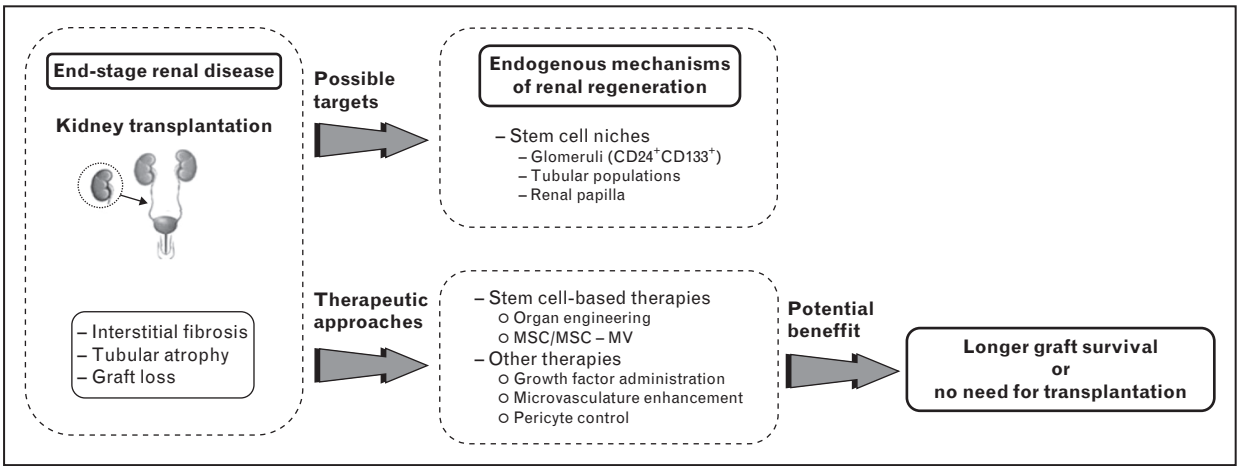

FIGURE 1. Scheme of the targets and therapeutic approaches in regenerative medicine.

of the injected cells that get trapped in the lungs making impossible to detect any live injected cell after 24 h [25▪▪]. In that respect, to overcome the fast clearance other injection routes (renal artery or femoral artery) have been developed to increase the chances of MSCs to get in touch with the kidney [23,26]. However, even when MSCs are injected systemically they exert a clear immunosuppressive effect that can lead to long-term reduction of interstitial fibrosis and tubular atrophy signs of chronic kidney damage [27▪]. This effect is partially explained by the reduction in inflammatory infiltrate that mediates tissue scarring, and also by the ability of MSCs to shift the immunologic balance toward a more anti-inflammatory milieu (M2 macrophages, regulatory T cells, tolerogenic dendritic cells) [28]. However, the anti-inflammatory actions *per se* are generally not sufficient to protect renal function and repair the damaged organ.

Overall, the consensus about the regenerative potential of MSCs is that they do not differentiate or fuse into any kidney cell type, MSCs will only reach the renal parenchyma when injected bypassing the lungs, and that their mechanism of action is through paracrine release of factors. Those factors are also found in the conditioned media, which when injected exert similar protective functions as MSCs, and one of the most plausible mechanism might be through released microvesicles.

Microvesicles

The use of MSC-derived microvesicles as a therapeutic agent to induce regeneration or at least to reduce kidney rejection is a new approach that evolved from the inconvenience of using whole replicating cells and might be the mechanistic explanation to solve the differential clearance/effect observed with MSCs. Microvesicles are spontaneously released by many cell types including MSCs, and they can present surface receptors and contain biologically active proteins and lipids as well as mRNA or microRNA. Therefore, they have a potential role in the exchange of genetic material between cells [29▪▪].

In addition to their immunomodulatory properties (same as MSCs), they showed potential to activate proliferation in tubular epithelial cells in glycerol-induced acute kidney injury combined with severe combined immunodeficiency (SCID) mice model [30]. This effect was comparable with the one obtained with MSCs and was RNA dependent. Similar effect was observed in a model of renal ischemia/reperfusion injury, not only inhibiting acute injury but also preventing the development of chronic kidney disease [31].

Other therapeutic approaches

As research in the field is growing, other therapies and molecular mechanisms have been described (Fig. 1).

Hepatocyte growth factor

Hepatocyte growth factor (HGF) has been broadly studied because of its antifibrotic and pro-regenerative properties in kidney damage models. This short-lived growth factor presented some issues in the administration as a protein and it soon moved forward to an experimental gene therapy application to provide sustained expression. This has proved effective in acute ischemia/ reperfussion injury [32] and in chronic kidney damage after kidney transplantation [33]. One of the main mechanisms of action was the shift in the balance with TGFβ inhibiting pro-scarring factors, and it has been recently shown that when this therapy is applied together with a hematopoietic stem cell (HSC) mobilization factor (G-CSF), regeneration of the injured kidney is enhanced by the migration of bone-marrow-derived M2 macrophages to the site of injury [34▪].

This regenerative effect induced by the migration of macrophages is in line with the effect observed by Jung *et al.* [35▪] of acute kidney injury repair after injecting M2 macrophages over-expressing IL-10.

Microvasculature and pericytes

Chronic kidney disease is characterized by progressive loss of the renal microvasculature. Hence, it is proposed that revascularization might be a key process to restore kidney function and regenerate the damaged structure. There are many therapeutic approaches proposed to regenerate the microvasculature, such as vascular endothelial growth factor, angiopoietin-1 and endothelial progenitor cells (reviewed in [36]), HSC [37], MSCs [38], and the preservation of the pericytes.

Pericytes are cells of mesenchymal origin that manage and coordinate endothelial action and are also able to coordinate between endothelium and epithelium [39]. In response to injury, pericytes detach from the capillary walls and migrate into the interstitium, where they are activated contributing to fibrosis [40▪]. This detachment evidences the role of pericytes with regard to microvasculature. In contrary, blocking pericyte detachment not only results in a reduction in interstitial fibrosis but also prevents capillary rarefaction. Thus, strategies to modulate pericyte function in these fibrotic processes are therefore therapeutically attractive [41].

CONCLUSION

The kidney is a complex organ with a complex structure that, in contrast with what was believed, has the intrinsic capacity to regenerate. New knowledge on progenitor cells within the kidney, which in a steady state are responsible for correct kidney repair, and on their use as a therapeutic targets might be a key in the near future to reduce fibrotic scarring or even induce regeneration. However, future research will tell us whether these newly discovered progenitors are responsible for the regeneration mediated by endogenous signals or if they need external signaling (from infiltrating cells) to start the regenerative process. Regardless of the initial level of function, all transplanted kidneys suffer some ischemia and reperfusion injury followed by intrinsic regeneration. As biopsies are commonly obtained, the kidney transplant could provide valuable information about the regeneration of the human kidney.

Cell-based therapies are now being developed with promising results. MSCs seem to play a role in the reduction of damage, but their regenerative role still needs to be proved whether it is only a secondary effect to their immunoregulatory properties. However, their regenerative potential might be reduced because of their size after culturing. This problem might be bypassed by local injection of MSCs, the use of microvesicles, or new strategies to come. Organ engineering of the kidney is also moving fast and a full success in this field could be the final solution to all the problems related to organ transplantation. However, because of the complexity of the kidney in structure and cell types, a lot of research has to be done before we reach that point.

Other therapies are also currently studied among which we emphasize the use of HGF and microvasculature repairing mechanisms. Both represent important therapeutic approaches that have shown interesting outcomes, although their use might be in combination with other therapies.

Overall, kidney regeneration is a reality and the knowledge of how to control it will be one of the main scopes in the present and future.

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Conflicts of interest

There are no conflicts of interest.

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