Growth factors and renal regeneration

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ABSTRACT

Cell replenishment is critical for adult tissue repair after damage. In some organs this process is facilitated by stem cells. In contrast to the liver, the kidney has limited regeneration capacity and has even been considered over several years as not being able to regenerate itself. Nevertheless, there are several recent studies suggesting the presence of stem cells in the adult kidney. Stem cell renal niches have been identified in the renal papillae in animals as well as in the urinary pole of the Bowman's capsule in humans (CD24+CD133+ stem cells). Although these cells may contribute to organ regeneration, how these cells exert this effect and their role after kidney injury is not known. Nevertheless, renal stem cells may be therapeutic targets for treatment of renal diseases. On the other hand, bone-marrow-derived stem cells may also contribute to renal repair, particularly mesenchymal stem cells. However, the mechanism for producing such effect has not been elucidated. Some studies suggest there is cell fusion between bone marrow and resident tubular cells; others suggest that bone marrow cells are able to differentiate in resident cells, while some authors propose bone marrow cells facilitate organ regeneration by a paracrine action; that is by secreting growth factors such as HGF, VEGF and IGF1. All these secreted molecules would provide a regenerative milieu able to constrain renal damage and to amplify stem cells migration to the damaged organ.

Key words: Renal regeneration, Stem cells, Hepatocyte growth factor, Bone marrow.

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Factores de crecimiento y regeneración renal

RESUMEN

Cuando se produce un daño en un tejido adulto, el proceso de renovación celular continuada es crítico y crucial para la reparación del mismo y, en determinados órganos, se facilita por la presencia de células madre o progenitoras. El riñón, a diferencia de otros órganos como el hígado, es de regeneración lenta. Incluso ha sido considerado durante años como incapaz de regenerarse. Sin embargo, varios estudios han demostrado que existen posibles nichos de células madre renales en la papila renal, progenitores tubulares o progenitores renales CD24+CD133+ localizados en el polo urinario de la cápsula de Bowman. Estas células podrían participar teóricamente en la reparación de la lesión renal. Sin embargo, todavía no se ha demostrado de forma precisa cuál sería su papel ni cómo actuarían después del daño. Aún así, estas células madre renales podrían ser dianas terapéuticas para el remodelado del tejido renal dañado. Por otro lado, se ha postulado que las células madre derivadas de la médula ósea podrían participar en la regeneración renal, especialmente las de estirpe mesenquimal. Sin embargo, tampoco se conoce con exactitud el modo en que actuarían. Hay estudios que sugieren la existencia de fusión celular entre estas células y células residentes, otros apuntan a su diferenciación en células renales, mientras que otros sugieren una acción paracrina responsable del efecto reparador a través de la secreción de factores de crecimiento como HGF, VEGF y IGF-1. Todas estas moléculas secretadas proporcionarían un entorno regenerativo que limitaría el área del daño y que facilitaría la migración de las células madre.

Palabras clave: *Regeneración renal, Células madre, Factor de crecimiento de los hepatocitos, Médula ósea.*

INTRODUCTION

The incidence and prevalence of chronic kidney disease (CKD) continue to rise in such a way that it is considered a worldwide public health threat.[1,2] Many patients with chronic

nephropathy go on to develop terminal chronic kidney failure (TCKF), with diabetes being the most common cause both in Spain and in most western countries. The progression of chronic kidney disease towards loss of function and renal sclerosis also appears in many glomerular, interstitial and vascular chronic nephropathies. Essentially, it is thought that, once enough renal mass is lost, the residual nephrons suffer from intraglomerular hypertension, a phenomenon which produces local activation of, among others, the renin-angiotensin-aldosterone system (RAAS), inducing TGF-beta 1 and the production of extracellular matrix which finally accelerates the loss of renal mass. This physiopathological concept, known as the hyperfiltration theory,[3] is the base of clinical testing of the usefulness of the blockade of RAAS, both in diabetic nephropathy and other chronic nephropathies. However, despite the significant advances that these treatments have brought about (they are able to reduce or stabilise the rate of the loss of renal function), the number of incident patients requiring kidney replacement treatment, whether peritoneal dialysis, haemodialysis or kidney transplants, continues to rise. Within this context of a shortage of treatments or strategies able to induce a decline in chronic nephropathy, the study of renal regeneration mechanisms acquires a great deal of interest.[4,5]

KIDNEY REGENERATION

When adult tissue is damaged, the continuous cell renewal process is crucial for its maintenance and, in certain organs, this is achieved by the presence of stem cells. Stem cells enable periodic cell renewal or regeneration when tissue is damaged, and they have the capacity for cell renewal through mitotic divisions or for differentiation into the cell lines of the corresponding organ. Furthermore, some adult stem cells from bone marrow are able to differentiate into more than one type of cell (mesenchymal and hematopoietic). In general, adult stem cells are a self-renewing cell population: they are quiescent cells that divide asymmetrically during tissue regeneration, on the one hand, into stem cells and, on the other, into transit-amplifying cells which proliferate, differentiate and lastly, reconstruct damaged tissue.[6] One of the ways to identify stem cells in solid organs is to stain them with bromodeoxyuridine (BrdU). Quiescent cells, which do not divide, maintain the high levels of BrdU deposited in their genome, whereas the dividing, more mature stem cells steadily dilute the BrdU incorporated into their genomes as they proliferate.

The kidneys are traditionally considered organs which are unable to regenerate. Yet, they possess a certain degree of regeneration which varies according to the species. Some cartilaginous fish form nephrons during adulthood, while mammals have lost this capacity. In fact, humans do not form new nephrons after 36 weeks of gestation.[7] The kidneys are one of the few organs to undergo mesenchymal-epithelial transition (MET) during their development.[8] This process is controlled by growth factors such as hepatocyte growth factor (HGF) and bone morphogenetic protein-7 (BMP-7), amongst many others. Therefore, kidney development in mammals requires a conversion process of the metanephric mesenchymal cells into polarised epithelial cells.[9] As mentioned above, when sufficiently extensive chronic renal injury occurs, whatever the cause, kidney function worsens inexorably until reaching TCKF, with no treatment available to reverse this process.[10] One of the processes taking place in the progression of nephropathies is epithelial-mesenchymal transition capable of producing extracellular matrix. To be precise, this is the inverse process to that taking place during foetal development of the kidney.

Renal regeneration could be approached using different strategies, such as the administration of growth factors capable of reversing epithelial-mesenchyma transition, and even by the mobilisation or infusion of endogenous (from the kidney itself) or exogenous (from bone marrow) stem cells. However, this is an extremely difficult challenge. Kidneys have a very complex architecture, great cellular heterogeneity and their cell renewal is slow. They have over 24 types of mature stem cell distributed in vascular, interstitial, glomerular and tubular compartments.[8] All of this complicates the search for adult stem cells[11] capable of repairing the kidney by replacing damaged cells. In any case, renal regeneration requires very precise mechanisms capable of directing the repair of each of the damaged renal compartments. Studies have been performed supporting the presence of stem cells in adult kidneys, showing that these cells have an intrinsic function. However, the participation of stem cells derived from bone marrow is not so clear (Table 1).[12-17]

STEM CELLS AND RENAL REGENERATION

Renal stem cells

Kidneys have a very complex structure and a very low degree of regeneration compared with other organs. This makes it difficult to study the existence of renal stem cell niches and to investigate how they participate in organ repair. Overcoming these difficulties with different strategies, some stem cell niches have been proposed in different renal compartments. Maeshima et al.[12] described a population of tubular progenitors with regenerative properties which proliferate and differentiate in epithelial cells during tubular regeneration. In fact, the origin of the cells that replace the damaged tubular epithelial cells

Table 1. Participation of endogenous (renal) and exogenous (derived from bone marrow) stem cells in the regeneration of kidney tissue

Damaged Cell	Stem Cell	Repair mechanism	Author and reference
Tubular cells	Renal	Proliferation and differentiation in epithelial cells	Maeshima, et al.[12]
			Duffield, et al.[13]
			Lin, et al.[14]
			Humpphreys, et al.[17]
Papilla cells	Renal	Cellular niche	Oliver, et al.[15]
Bowman's capsule cells	Renal	Cellular niche	Sagrinati, et al.[16]
Tubular cells	BMDC	Cellular fusion	Held, et al.[33]
Mesangial cells	BMDC	Cellular differentiation	Imasawa, et al.[71]
Mesangial cells	BMDC (HSC)	Formation of mesangial cells	Masuya, et al.[72]
Glomerular endothelial cells	BMDC	Glomerular integration and microvascular repair	Rookmaaker, et al.[73]

Several authors describe the different types of renal cell that participate in kidney regeneration. They also mention the existence of a niche of stem cells in the renal papillae and in the Bowman's capsule. Besides, other studies show that BMDC play a role in mesangial, renal endothelial and tubular mantenaince and repair, by means of cell fusion and differentiation.

is not known, but some studies suggest that they are from the kidneys and not from bone marrow.[13,14] Oliver et al[15] identified the renal papillae as a stem cell niche in the adult kidney. They observed a group of cells in this area that retained BrdU. After ischemic damage, they found that these cells entered a cell cycle, and thus the BrdU stains disappeared. Furthermore, these cells were able to form spheres *in vitro*. However, these cells being located in the renal papillae creates doubts about how they are able to repopulate the most proximal segments of the nephron. Recent studies in humans have identified a subset of renal progenitors CD24+CD133+ in the Bowman's capsule,[16] near to the tubular pole. This location would allow them to repair tubular and glomerular epithelial cells. It has been described that the progenitor cells CD24+CD133+ have the capacity to differentiate, providing a regenerative mechanism for damaged epithelial cells in the kidneys.[18,19] The existence of these kidney epithelial progenitor cells provides a possible explanation for the regression of kidney lesions. The damage repair process probably requires the capacity to slow the fibrotic response, so progenitor cells should be able to regenerate tissue and, at the same time, prevent extracellular matrix accumulation[18] by means of their capacity to secrete growth factors, as will be detailed below. In another study, Appel et al[20] postulated that, as podocytes have no self-renewal capacity, the glomerular parietal epithelial cells (which proliferate and are adjacent to the podocytes) might migrate to the glomerular capillary and differentiate into podocytes. Although several niches of renal stem cells have been identified, it is still not known what their role is and how they behave in repairs after a kidney injury. Still, renal stem cells could be therapeutic targets for remodelling damaged kidney tissue.[21]

Bone marrow stem cells

Bone marrow contains different types of stem cells, including haematopoietic (HSCs) and mesenchymal (MSCs) stem cells and endothelial progenitor cells. HSCs express surface markers such as Sca-1, c-kit, CD90 in mice, and CD34, CD133, CXCR4 and CD150 in humans, and can differentiate into any type of adult blood cell. Besides creating a support environment for HSCs, MSCs are able to differentiate into various types of mesenchymal cells such as bone, cartilage, muscle, neurons, hepatocytes and adipose tissue.[22-25] They can adhere to plastic and express surface markers such as CD90, CD73, CD105, CD44 and CD29. MSCs also express growth factors such as VEGF, HGF and IGF-1, as well as antiapoptotic cytokines. At present the role of marrow bone stem cells in the kidney regeneration after damage is being investigated. Cell therapy is one of the fields of greatest interest in biomedicine at this time, so much so that the use of these multipotent cells to re-establish damage organ function has generated remarkable expectation.

The most common technique for studying the plasticity of bone marrow cells is bone marrow transplantation (BMT). The receptor's bone marrow cells are replaced by those of the donor and, once chimerism is established, the donor cells can be identified by different strategies. Among these we can highlight the identification of the Y chromosome in a female receptor, the expression of molecules such as beta-galactosidase, luciferase or enhanced green fluorescent protein (EGFP), or a function being re-established in knockout animal model.[26] To check the cell type (tubular, mesangial, etc.) that the marrow bone cells have given rise to, the use of specific protein staining with immunohistochemistry, immunofluorescence and analysis with a confocal microscope are common.

A significant number of glomerulopathies begin with podocyte injury or loss. Podocytes are cells with complex interdigitations which participate in the synthesis of components of the glomerular basement membrane (GBM), collagen IV being one of the most important. Several studies have suggested the integration of cells derived from bone marrow as functional podocytes. Studies have been performed with mice models of Alport syndrome. The mice had mutations in the gene which codifies for the alpha chain of the collagen IV, bringing about defects in the GBM, proteinuria and kidney failure. Prodromidi et al.[27] and Sugimoto et al.[28] observed that bone marrow cells contribute to the regeneration of podocytes in damaged glomeruli, leading to the expression of the collagen IV alpha-3 chain being re-established and a decrease in proteinuria. In a study with mice published a few years ago, the BMT from obese diabetic db/db mice in healthy non-diabetic mice transferred diabetic nephropathy to the receptor mice without them becoming hyperglycaemic. The authors postulated that the glomerulus was probably repopulated by mesangial and endothelial cells from the db/db donor mice and that these were responsible for the albuminuria and glomerulosclerosis that the receptor mice developed.[29]

On the other hand, there are authors who suggest that bone marrow cells participate in renal regeneration by fusing with the renal cells themselves. In fact, studies in livers have shown that hepatocytes generated after liver damage are formed by cellular fusion, and not by differentiation of hematopoietic stem cells.[30-32] Therefore, a possible fusion between bone marrow stem cells and epithelial tubular cells is postulated. Held et al.[33] observed that, after injury, tubular epithelial cells are generated by the fusion of hematopoietic cells and existing proximal tubular cells, and not by transdifferentiation. However, this is still a very controversial matter since several studies suggest a paracrine/endocrine action of endogenous stem cells instead of direct repopulation of the damaged nephrons.[34] In short, besides the possible role of endogenous stem cells (renal), other studies support the idea of differentiation and/or fusion of cells from bone marrow into precursor cells of damaged kidney cells (figure 1).

GROWTH FACTORS

Tubular epithelial cells which survive damage secrete growth factors which could interact with resident cells and renal and extrarenal stem cells, accelerating tubular repair mechanisms. The tubular epithelium exists in a relatively quiescent to slowly replicating state (also a characteristic of stem cells), but, on the other hand, it has a remarkable morphogenic regeneration capacity after severe toxic or ischemic aggression.[35] Although some studies show how stem cells migrate to damaged tissue,[36,37] most authors do not support the idea of the integration of these cells into injured organs. In this respect, Duffield et al.[13,38] showed that kidney repair is independent of the participation of cells derived from bone marrow, something also observed by Lin et al.[14] On the other hand, Morigi et al[39] showed how the infusion of human mesenchymal cells from bone marrow led to a decrease in proximal tubular damage and improved kidney function in mice. Several studies have been performed which have not been able to verify the differentiation of stem cells into epithelial cells, but others have described how stem cells contribute to renal recovery. Thus, it was proposed that cell migration only facilitates regeneration because of an endocrine/paracrine effect[40,41] and it is the kidney cells themselves that re-establish the tubular epithelium.[13,14,38,42]

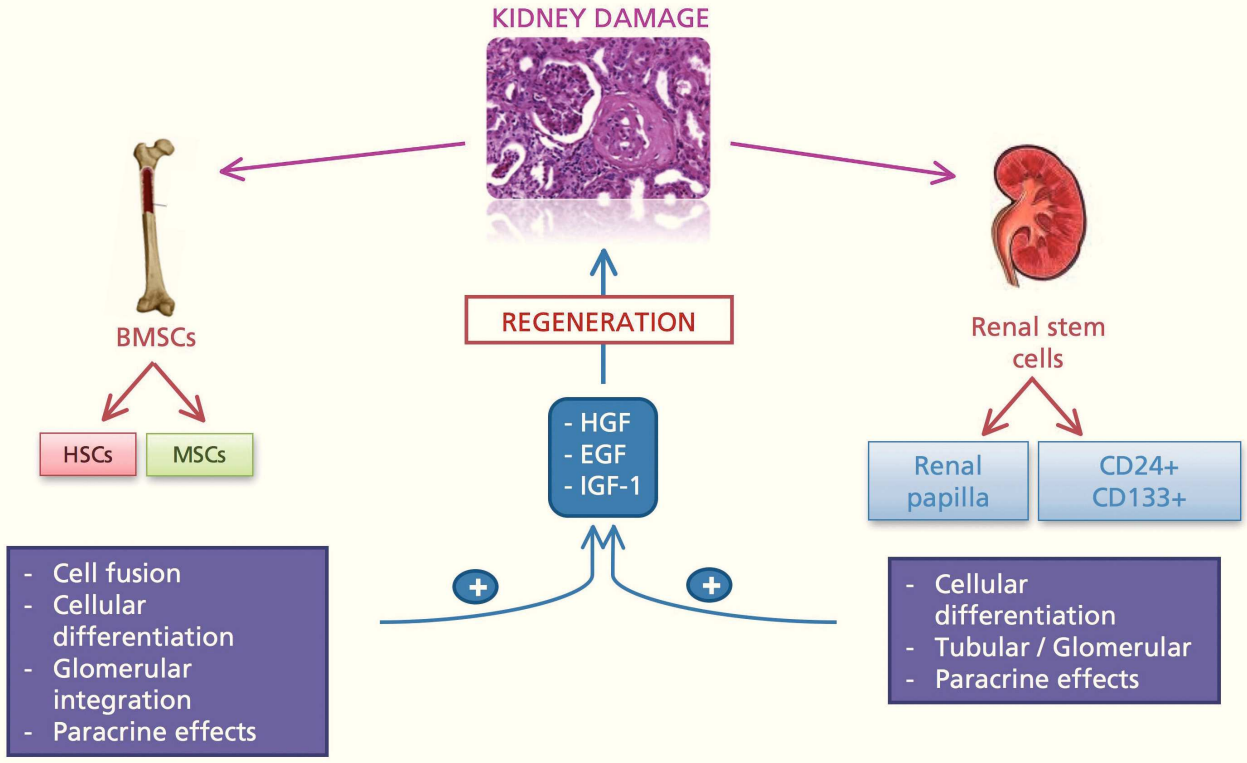
Interaction between stem cells, resident kidney cells and growth factors

The interaction between mesenchymal and epithelial cells and growth factors is fundamental for nephrogenesis and for maintaining the integrity of adult organs.[43,44] This reciprocated interaction between mesenchymal-epithelial cells is a key factor in renal regeneration after damage.

Studies using animal models of acute kidney injury have been performed administering growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) or insulin-like growth factor 1 (IGF-1). They observed a decrease in mortality due to kidney function being restored and normalised.[45] In fact, it is well known that tubular epithelial cells that survive damage secrete growth factors and cytokines involved in kidney repair mechanisms. On the other hand, it seems to have been proven that MSC have a protective effect, especially in acute kidney injury models, thanks to their ability to express growth factors such as VEGF, HGF and IGF-1, which facilitate recovery from kidney injury.[46,47] The mechanism of action of this system could have several modes: autocrine (the kidney cells themselves secrete growth factors), paracrine (renal and bone marrow stem cells) and endocrine (soluble circulating factors). A brief review of some of these factors is given below.

Glial cell line-derived neurotrophic growth factor (GDNF). This factor is involved in renal organogenesis. The exogenous administration of GDNF protects against ischemic kidney injury in a mouse and accelerates repair mechanisms. *In vitro*, GDNF induces MSC migration and inhibits MSC apoptosis.[48]

Epidermal growth factor (EGF). This factor is synthesised in the renal epithelium and increases after



Cell therapy, or stem cell mobilization, could revert chronic kidney damage. Bone marrow stem cells (BMSCs), whether haematopoietic (HSCs) or mesenchymal (MSCs), could regenerate the kidney by different mechanisms, but above all due to the local release of certain growth factors. Renal stem cells, whether from the renal papilla or the CD24+CD133+ cell niche of the Bowman's capsule could differentiate into adult epithelial cells or tubular cells such as podocytes. They could also facilitate kidney regeneration by other mechanisms.

Figure 1. Stem cells and renal renegeneration.

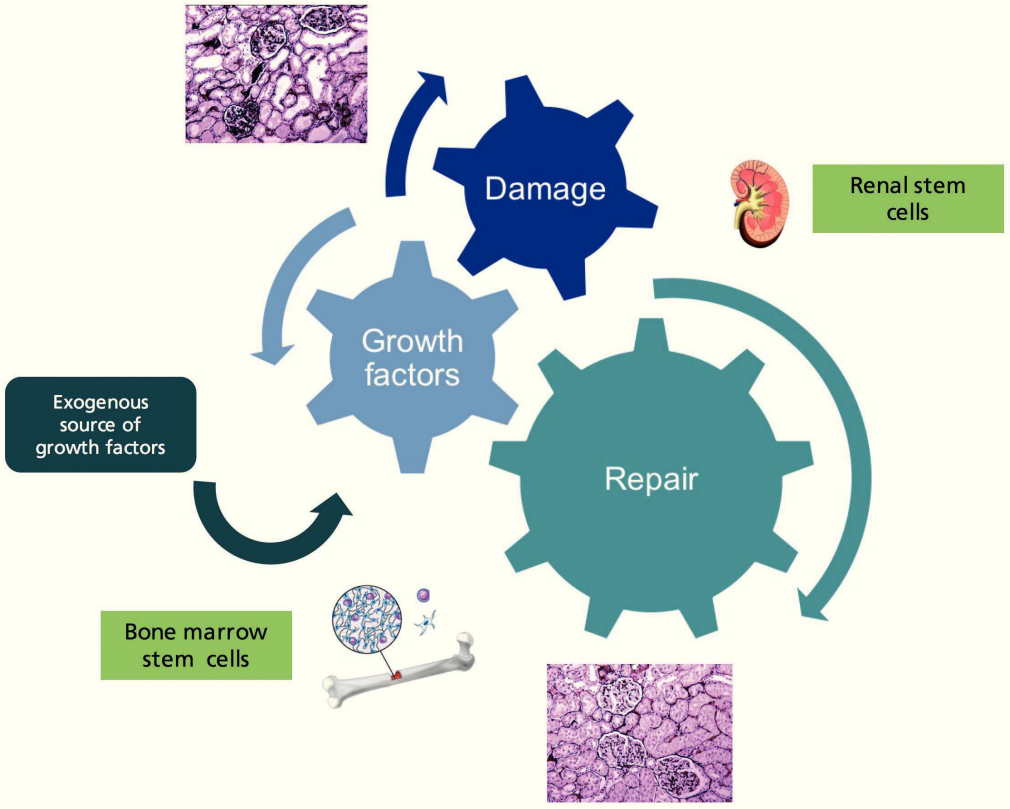
kidney damage.[49] It exerts different actions on several types of cells, such as migration and proliferation.[50,51] EGF has been shown to induce cellular proliferation and MSC migration *in vitro*.[52]

Hepatocyte growth factor (HGF). It is a heterodimer consisting of 60-kDa alpha-chain and a 34-kDa beta-chain. The interaction of HGF and its c-Met receptor leads to the activation of the tyrosine kinase pathway, giving rise to mitogenic and angiogenic activity in several types of cells, particularly in epithelial and endothelial cells.[55] Furthermore, HGF has anti-apoptotic and antifibrotic effects. The anti-apoptotic effect is directly related to the phosphatidylinositol-3 kinase-Akt signal pathway,[56] while the antifibrotic effect is linked to its antagonist action on TGF beta-1.[57] HGF modulates the balance between extracellular matrix synthesis and degradation, increasing expression from matrix metalloproteases (MMP) and reducing production of MMP inhibitors (TIMP). Furthermore, HGF suppresses the effect of TGF beta-1 by blocking the TGF beta/Smad pathway.[58] HGF is able to counteract the profibrotic action of TGF beta-1 in different renal cells through different mechanisms of action, amongst which the inhibition of epithelium-mesenchyma transition stands out. It is also known that TGF beta-1 and HGF inhibit each other's synthesis in a reciprocal fashion[59] and that HGF also down-regulates the expression of TGF beta-1 receptors *in vivo*. Some authors described a decrease in TGF beta-1 using an exogenous HGF supplement in several chronic damage models.[60-62] It is worth pointing out that HGF also has an effect on bone marrow cells, attracting stem cells to the site of the damage. It is not known if HGF has a cellular mobilisation and/or localisation effect on these cells. In a study performed using a model of liver damage, Kollet et al[64] showed the effect of HGF on the recruitment of hematopoietic cells in liver damage. When the liver is damaged (by irradiation or inflammation) there is an increase in the expression of SDF-1 and MMP-9 activity, giving rise to the recruitment of hematopoietic progenitor cells mediated by SDF-1. In another study performed using a mouse model of CCl_4-induced hepatic fibrosis,[65] it was

observed that HGF per se did not increase the expression of MMP-9. Treatment with G-CSF is used to promote the recruitment of cells from bone marrow. Overexpression of HGF together with treatment with G-CSF synergistically increased MMP-9 in fibrotic liver while increasing the number of cells from bone marrow and liver cells expressing MMP-9. In addition, it is known that the inhibition of HGF activity leads to impaired tissue repair.[57,66]

Vascular endothelial growth factor (VEGF). This is a factor which regulates vascular growth both in normal and damaged tissue. Mesenchymal cells can secrete this factor.[67-69] Renal ischemia inhibits the expression of VEGF through diverse mechanisms, shifting the balance from a proangiogenic to an antiangiogenic environment, thus inhibiting kidney repair. MSCs express VEGF and could exert a renoprotective, paracrine action which facilitates recovery from acute kidney injury. It has even been postulated that giving high doses of erythropoietin in a model of endothelial lesion attenuates the damage by liberating VEGF.[70]

In short, certain growth factors, many of which are involved in renal embryogenesis, are able to directly induce a certain degree of tissue repair, while possibly acting on resident stem cells, facilitating their



When acute or chronic renal damage occurs, repair mechanisms are activated such as the release of growth factors. In certain circumstances, this is sufficient. However, when the effect of repair factors destined for the synthesis of extracellular matrices predominates, the process can only be reversed with the addition of exogenous growth factors such as HGF. This factor is capable of inhibiting the synthesis of the extracellular matrix, activating metaloproteases, and favouring angiogenesis. Additionally, HGF facilitates the recruitment of bone marrow stem cells to the damaged organ. These cells, through a paracrine mechanism, liberate other factors that facilitate repair. It is unknown whether or not these growth factors could also favour differentiation of stem cells (circulating or renal) into mature resident cells.

Figure 2. Growth factors and renal renegeneration.

differentiation and even contributing to the recruitment in the kidneys of stem cells from bone marrow which, directly or through the secretion of growth factors, play a part in renal regeneration (figure 2).

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KEY CONCEPTS

1. The incidence of CKD continues to increase and many patients go on to develop TCKF despite the advances in renoprotection. Because of this, there is a huge interest in the study of renal regeneration mechanisms, looking for future clinical applications.
2. Possible renal stem cell niches have been described in the renal papillae and the urinary pole of the Bowman's capsule, and tubular progenitor cells have also been observed. It has not been proven irrefutably that stem cells from bone marrow differentiate and integrate in vivo like adult renal cells.
3. The niche of renal stem cells CD24+CD133+ located in the urinary pole of the Bowman's capsule in humans could contribute to tubular and podocyte regeneration. Stem cells from bone marrow could theoretically differentiate into endothelial and mesangial cells.
4. The injury repair process is achieved by slowing the fibrotic response first, and then restoring the tissue architecture of the organ. Administering certain growth factors, at the same time as acting as an antifibrotic, could mobilise stem cells from the kidney and bone marrow. These cells facilitate renal regeneration by fusing with resident renal cells directly, or through paracrine mechanisms.

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