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From stem cells to the pathogenesis and treatment of renal disease

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INTRODUCTION

The recent and remarkable interest in stem cell research is the result of high expectations that it will contribute to advances in the treatment of a variety of pathologies, and to a deeper understanding of the pathophysiological complexity of the wide range of diseases affecting mankind.

This is the context in which we are conducting our brief review of the significance of this topic for the field of nephrology, particularly for the pathogenesis and treatment of renal disease. Our review sketches an introduction to this amazing field of science and establishes a link between the renal cell's capacity for differentiation, the diversity and multipotential functionality of stem cells according to their origin, and the morphological changes that characterize acute and chronic renal disease. The importance of genetics, the cell phenotype transformation and their multifactorial effects on renal pathogenesis are threads that run throughout this extraordinary field of research. In addition, the direct or indirect intervention of stem cells in the phenomena of repair and regeneration of renal tissue is the basic foundation for the application of bioengineering techniques, and these areas are sure to provide, clearer answers to our questions about cellular and molecular biology, hopefully in the near future.

STEM CELLS: A MULTIFORM AND MULTIPOTENTIAL WORLD

Stem cells are undifferentiated cells capable of both self-renewal, assuring a permanent sup-

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ply in the body, and differentiation into cells with specific functions, such as red blood cells, white blood cells, hepatocytes, and muscle cells[1].

Our knowledge about stem cells has its beginnings in the sixties with the first research studies on hematopoietic stem cells[2,3]. Stem cells can be classified by their potential for differentiation and by whether they are adult or embryonic in origin.

More recent studies allow us to describe three major type of stem cells: 1 – totipotent (or embryonic) stem cells, capable of generating any of the two hundred different types of cells that make up the adult organism, the three germ layers, or the extraembryonic membrane cells (placenta), found only in the fertilized egg and only until when the first four cells appear; 2 – pluripotent (or somatic) stem cells, capable of generating any differentiated cell in the body, but unable to form extraembryonic membranes, and which are derived from the trophoblast; 3 – multipotent (or adult somatic) stem cells, capable of differentiating into a limited number of cell types, such as the blood precursors, and which preserve the ability to differentiate that mature cells lose[4].

Pluripotent stem cells can be further broken down into three types: a-embryonic, isolated from the inner cell mass of the blastocyst; b-embryonic germ cells, which can be isolated from the gonad precursor cells; and c-embryonal carcinoma cells, isolated from teratocarcinomas. These three types of pluripotent stem cells can only be isolated from fetal or embryonic tissue, and they may be grown in cultures using special methods to impede their differentiation[4,7].

The cells thus evolve from an immature state, typical of the stem cell, to a specialized state, losing their ability to divide.

According to the published work, it is important to introduce the concept of progenitor stem cells here [5], as they have been the most thoroughly studied, due to the greater ease with which they can be isolated. These are intermediate cells, derived from the primitive stem cell, that demonstrate more limited differentiation capacity while maintaining the proliferative potential that adult cells lack. Progenitor cells can be found in the circulation or already embedded in the deepest layers of adult tissues, where they remain in an immature state with their ability to multiply intact. They thus serve as reserve cells, waiting for an opportunity to replace aging cells and preserving tissue integrity. Once differentiation is triggered, they can exhibit all the characteristics of mature tissue cells, but they are only capable of differentiating into one type of cell. According to these authors, the most primitive stem cell is, in other words, the multipotent ancestor cell of the unipotent progenitor cell[2,5].

It must be stressed, however, that a certain number of somatic (multipotent) stem cells always remain in the tissue and never mature. This phenomenon has been demonstrated to varying degrees in tissues with high regenerative potential, such as the blood, epidermis, intestine and liver, and, surprisingly, it has also been discovered in the brain, a tissue that was previously thought to have no regenerative ability[6]. The discovery of stem cells in the brains of adult mice and later in humans, where germinative regions with life-long new cell production were identified, has debunked the neurobiological preconception that nervous cells have no other fate but to mature, age and die. It has also been observed that somatic neural stem cells can differentiate into various cell types of different tissues, although it is not clear whether this is true for all cell types that exist in the adult organism. Indeed, the brain stem cells of mice have been shown to exhibit extraordinary potential for growth and differentiation into blood cells, which means that the multipotent stem cell is

programmed during development to produce specific cells that can acquire the characteristics of the mature cells at the homing site[7]. Other work has shown that the somatic stem cells of the blood, the medullary stroma and the epidermis can also switch identities and transdifferentiate, creating other types of cells from different original tissues[8].

STEM CELLS AND TISSUE REPAIR/REGENERATION

When we try to establish a relationship between stem cells and the concepts of repair and regeneration, these must be understood as complete recovery of the morphofunctional characteristics of the original mature tissue.

Tissue regeneration takes place by means of three fundamental cellular and molecular mechanisms: a – proliferation of mature cells; b – differentiation of immature cells (somatic stem cells); and c – mobilization, with subsequent homing and differentiation of circulating stem cells[9].

A number of studies carried out on different types of tissues have shown that underlying the process of cell repair and regeneration is the intervention of circulating stem cells (multipotent or adult somatic) and progenitors, which act as repair "emissaries", similar to other types of stem cells and progenitors of the same nature but located in the tissue itself. Four types of multipotent stem cells have been shown to function in this manner: hematopoietic stem cells (in the bone marrow and peripheral blood); mesenchymal stem cells (present in the bone marrow and peripheral blood); monocytoid cells of the neural crest; and circulating fibrocytes[10].

One of the most important features to emphasize about these cells is the phenomenal characteristic of transdifferentiation, or plasticity, which makes it possible for them to transform themselves into completely unexpected types of cells. The hematopoietic stem cells are a good example of this. In addition to constituting the blood cells lines, they are capable of forming cells of other organs, such as the kidney, heart, liver, lung, gastrointestinal tract, skin, brain and blood vessels[10]. The mesenchymal cells are another class of multipotent stem cells, located in the bone marrow, which demonstrate the ability to form tissues such as bone, cartilage and fat, and whose plasticity enables them to be incorporated into many organs [11,12]. As a whole, these observations have strengthened the argument that incorporation of these cells into other organs is part of the repair process.

Progenitor cells, are further downstream in the germinative line and their capacity for differentiation is, as mentioned above, much more limited. Nevertheless, these cells, located in the peripheral blood or in the tissues, also demonstrate a relative capacity for transdifferentiation and plasticity, similar to that of the multipotent (or adult somatic) stem cells.

STEM CELLS AND RENAL PATHOGENESIS – HOW ARE THEY RELATED?

The principal pathogenic mechanisms involved in the majority of renal diseases, acute and chronic, can be summarized as follows: genetic anomalies, immuno-inflammation, cell tension, hypoxia, chemical breakdown of the cell membrane, necrosis, apoptosis and fibrogenesis. Each mechanism assumes a varying degree of importance depending on the trigger stimulus, but it is not unlikely that nearly all these mechanisms may be found in many, if not all, nephropathies.

In essence, these phenomena can be found in varying degrees in the evolution of glomeru-

lar, tubular-interstitial and vascular diseases, all depending on the type, intensity and duration of the triggering stimulus. The end result, reflected as change in the tissue structure and more or less characteristic of the disease, is a product of the nature of the native cell response and whether it is more or less adaptive, in the phylogenetic sense of defense and preservation of the tissue. It is precisely from this point, the way that the cells react to aggression, that we are able to extrapolate much of our knowledge about the biological behavior of stem cells. In reality, and contrary to what was believed for many years, the cells of mature tissue still also retain a significant potential for differentiation that allows them to develop the neo-expression of phenotypes characteristic of their embryonic phase, or to assume the identities of the distinct phenotypes of other cell types of the organism; a process that has also been ascribed to stem cells. This cell response involves the triggering of transcription of a vast quantity of molecules, implicated in multiple cellular phenomena that affect cell infiltration of tissue, and the anomalous synthesis and disorganization of the extracellular matrix generically known as fibrosis.

We know today that it is in this seemingly regressive way that the native cell tries to respond to the harmful environment, mobilizing the machinery embedded in the deepest recesses of the genome.

From this perspective, we can go as far as to conceptualize a certain parallel between the potential and diverse capability of the cells, which vacillates between the tissue repair or regeneration response, and the unregulated cell division that characterizes oncogenesis, or even the terminal option of irreversible annihilation through necrosis or apoptosis.

Another way of approaching this subject, one which sparks the central interest of this topic, lies in investigating the origin and processes of possible regenerative or repair mechanisms in the kidney, relating to the existence of stem cells from the bone marrow and/or resident (progenitor cells), elements that together might be referred to as repair agents, with an eye towards complete morphofunctional reconstruction.

If the problem could be expressed succinctly, we would place on one side of a scale the transformations occurring in the renal tissue that characterize the disease, as evidenced by the scarring process, and on the other side all the mechanisms involved in stem cell mobilization, proliferation and differentiation, whatever their origin, to protect the integrity of the tissue, which make repair, or even regeneration possible.

WHICH STEM CELLS ARE INVOLVED IN RENAL DISEASE AND HOW DO THEY ACT?

In the last five years, just as we have seen with regard to other tissues, there has been a notable effort on the part of researchers to try to identify the type of stem cells involved in renal pathogenesis, especially in the repair/regeneration mechanisms.

During this time, a few studies have noted the existence of adult somatic (multipotent) stem cells with the ability to differentiate into renal tissue cells. In one of these studies[13], researchers were able to isolate an adult multipotent cell from the bone marrow of the murine mouse that had the ability to form virtually all the structures that make up the kidney, including the renal endothelial and tubular cells. The molecular and cellular mechanisms studied in tubular regeneration of acute tubular necrosis also suggest the possibility that there are also adult somatic stem cells in the kidney with the same potential. This hypothesis, still somewhat controversial, has

gained strength with the work of Oliver *et al.*[14], who observed cells with these characteristics in the deepest portion of the medullary inner papilla in mouse and rat kidneys. Their presence at this site could be explained by the fact that this zone is ontogenically the earliest and the most hypoxic, making it a favorable environment for stem "behavior".

Later, the majority of studies of the kidney focused on the role of progenitor stem cells in basal renovation and repair of tissue in reversible renal lesion models, such as acute tubular necrosis, while the role of adult somatic (multipotent) stem cells has been studied more in kidney transplant and bone marrow transplant models. In these studies, stem cells derived from the bone marrow have been isolated in the vessels and renal interstitium[15], in the glomerula[16], and in the renal tubules[17], where they showed positivity for typical epithelial markers, suggesting adaptation to a tubular phenotype. Other animal studies have also demonstrated differentiation of bone marrow derived stem cells into proximal tubule epithelium[18], mesangial cells[19], endothelial cells and interstitial cells[20].

Transdifferentiation and fusion

As mentioned above, the transdifferentiation process consists of conversion of the phenotype of one cell into that of a different cell. Through this mechanism the stem cell can contribute to tissue repair, from the starting point of cells with different lines[21]. This concept was initially described for native renal cells when glomerular and tubular cells changed phenotypes during the complex process of remodeling[22]. This cell plasticity has come to be known as epithelial-mesenchymal transition, and also as "reverse embryogenesis". It is due to this phenomenon that the glomerular and tubular cells lose their epithelial phenotype and undergo mesenchymal transformation[23]. By undergoing this transformation, the cell's new identity carries with it the potential to produce large quantities of the molecules that form the extracellular matrix as well as growth factors, which converge in order to repair the tissue. Based on our current knowledge, the transdifferentiation capacity of the stem cell is a pivotal feature of its biology.

Meanwhile, some doubts have been raised that the transformation of stem cells may not result from transdifferentiation, but rather from their merging with native tissue cells[24]. This question has been raised primarily in studies showing that stem cells derived from bone marrow can fuse with hepatocytes, cardiomyocytes and Purkinje cells, forming products with mixed genotypes and phenotypes[25]. Other experimental studies have demonstrated the ability of bone marrow cells to merge with cells from the liver[26], brain[27], heart[28] and skeletal muscle[29]. With regard to the kidney, the hypothesis of fusion of stem cells with native renal tissue cells has not yet been confirmed, but the topic continues to be the target of research[29].

The role of progenitor cells in the kidneys

The presence of progenitor cells, circulating and/or residing in the tissues, and the quest to understand their function, has met with technical difficulties relating to the problem of distinguishing these cells from the more immature elements derived from the bone marrow. Nevertheless, there is already evidence for the involvement of renal and extra-renal progenitor cells in the maintenance and repair of adult kidney tissue, as well as the existence of progenitors for the principal types of renal cells – endothelial, mesangial, tubular and fibroblasts.

Endothelial Cells

There are several types of endothelial cells in the kidney, depending on whether we are looking at the large vessels, the peritubular capillaries or the glomerular capillaries. The first big question lies in knowing whether endothelial progenitor cells capable of regenerating mature cells exist. Answers began to appear in studies on ischemia and angiogenesis in cardiovascular disease, where circulating endothelial progenitor cells were discovered[30]. These observations have been confirmed by other authors, who have demonstrated that these cells are different from mature circulating endothelial cells. The endothelial progenitor cell is involved in the formation of new vessels by means of the secretion of pro-angiogenic factors, such as VEGF and bFGF, which stimulate proliferation and migration of resident cells[31]. Other studies have observed the capacity to maintain and regenerate glomerular capillaries, with normal mice showing a glomerular cell renovation rate of around 1% per day, and in which the endothelial fraction is predominant[32]. In an experimental model of glomerular nephritis induced by anti-Thy1.1 antibody, Iruela-Arispe *et al.*[33] showed that the repair phase is accompanied by an increase in proliferation and migration of the endothelial and mesangial cells, which play a role in the partial restoration of glomerular structure and function. In the same study, the authors observed that the number of bone marrow derived endothelial cells in the glomerules quadrupled, confirming that the repair phase is due, not only to the participation of resident endothelial progenitor cells, but also to the involvement of bone marrow derived cells. The regenerative role of endothelial progenitor cells in the human kidney has also been demonstrated in renal transplantation, where the presence of recipient endothelial cells in the graft has been confirmed[34].

Mesangial Cells

The mesangium plays a pivotal role in the pathogenesis of human and experimental glomerular disease. In the beginning it was thought that maintenance and repair of the mesangium was solely dependent on the proliferation of resident mesangial cells[35]. Hugo *et al.*[36] demonstrated that, during recovery from anti-Thy 1.1 antibody-induced glomerular nephritis, there are immature mesangial cells that migrate from the juxtaglomerular apparatus and the hilar region to the glomerula.

As mentioned earlier, researchers have demonstrated involvement of bone marrow derived cells in the normal renewal of mesangial cells[19,20]. In the work of Ito *et al.*[37] in animal bone marrow transplant models, an increase in bone marrow derived mesangial cells was also demonstrated during recovery from post anti-Thy 1.1 antibody-induced mesangiolysis. Other studies have supported these experimental results by demonstrating that glomerular sclerosis can be transmitted in mice through bone marrow transplantation[38].

These observations reinforce the role that bone marrow derived cells play in glomerular maintenance and repair, but they also suggest the possibility that sick or dysfunctional progenitor cells may carry disease to the kidney.

Tubular Cells

The tubular epithelium has a huge regenerative capacity in acute tubular necrosis caused by ischemia or toxic insult, which is characterized by an intense cell activity of a migratory and proliferative nature, contributing to restore the morphological and functional structure of the tissue. Studies that have been carried out to date suggest different origins and a high degree of

adaptation for the epithelial progenitor cells[39]. As an example, tubular epithelial cells of the adult rabbit kidney show a great potential *in vitro* for self-regeneration and differentiation into three-dimensional tubular structures[40]. Along with the existence of progenitor cells in the renal tissue, Poulsom *et al.*[16] demonstrated the presence of bone marrow derived tubular progenitor cells, while the intervention of these in the phenomena of tubule repair were demonstrated in the work of Kale *et al.*[41]. In humans, progenitor stem cell intervention was demonstrated in tubular repair after acute tubular necrosis, when a Y-chromosome was observed in the regenerated epithelium of a female donor kidney, transplanted into a male recipient[42].

Fibroblasts

Fibrosis is a histopathological characteristic common to all chronic renal diseases. Some authors have put forth the hypotheses that the increased interstitium, resulting from the disorganized accumulation of extracellular matrix, may be a way of recreating the embryonic environment, thereby providing favorable conditions for tubular lesion repair[43]. This viewpoint leads us to the problematic questions surrounding the cell responsible – the fibroblast – and the nature of its origins. Several studies have appeared proposing the phenomenon of epithelial-mesenchymous transition as an explanation for the formation of fibroblasts originating from tubular epithelium[44]. In the work of Strutz *et al*.[45], *de novo* expression of a fibroblast-specific marker (FSP-1) was demonstrated in tubular epithelial cells in the late stages of renal fibrogenesis, and other authors have advanced the possibility of a relationship between progressive renal failure and the transdifferentiation of tubular cells into myofibroblasts[46].

Another hypothesis on the origin of fibroblasts proposes that bone marrow stromal cells may be their progenitors. In support of this hypothesis, in the work of Bucala *et al.*[47], a distinct population of human leukocytes capable of differentiating into fibroblasts was identified. Iwano *et al.*[48], on their part, concluded that in a kidney with fibrosis induced by unilateral ureteral obstruction, around 15% of fibroblasts come from the bone marrow, 49% are resident, while the remaining 36% are the result of epithelial-mesenchymal transdifferentiation.

THE FUTURE OF STEM CELLS IN TREATING RENAL DISEASE

Progenitor cells

The application of stem cells has an important place in the treatment of diseases in general pathology, including nephrology. Circulating kidney progenitor cells are an excellent target for application, and much less difficult to access than are the resident progenitor cells. The endothelial repair potential of circulating progenitor cells can be strengthened by expanding them through *in vivo* and *ex vivo* techniques, using VEGF or erythropoietin; molecules that stimulate cellular mobilization and pro-angiogenic activity[49,50]. Another approach consists of enhancing the function of the progenitor cell, as was demonstrated in an experimental model demonstrating restoration of angiogenic capacity in diabetic mice after they were infused with progenitor cells from non-diabetic mice[51]. Progenitor cells can also serve as vectors for local gene transport, as was demonstrated in transfection of skeletal muscle with the gene inhibitor TGF-β1, leading to a decrease in glomerular sclerosis in an experimental model of nephritis[52].

Bioengineering techniques

The great advances in our knowledge of the functional mechanisms of stem cells will be able to be applied in bioengineering to help us overcome current limitations in the field of therapeutics. Some examples include *in vitro* manipulation of stem cells and their inclusion in biomaterials, either biodegradable or permanent, to produce devices for implantation or incorporation into extracorporeal circuits. Saito *et al*.[53] demonstrated the usefulness of a cellular implant for continuous degradation of low molecular weight molecules, such as B2µ. Based on this concept, it may be possible in the future to implant a type of differentiated cell to replace a metabolic or catabolic function. For example, it has already be shown that it is possible to break down urea by administering microcapsules containing a bacteria that has been genetically modified to express urease activity[54], or by encapsulating these cells in the capillary fibers of implantable devices[55].

Increasing renal mass is another goal, and this has already been demonstrated in the works of Woolf *et al.*[56] and Rogers *et al.*[57] who, upon carrying out experiments with subcapsular transplant of metanephros in mouse and rat kidneys, confirmed the development of nephrons with vascularized glomerules and mature tubules.

At the other end of the spectrum of expectations is the development of a device to replace the entire kidney. The groundwork of this exciting area of research, the quest for the much desired bio-artificial kidney, began with the expansion of renal cells in culture and the later seeding of these cells in collagen-coated polycarbonate membranes, where it was possible to reconstruct functioning nephronal units[58].

Although science has already made remarkable strides toward understanding the biology of stem cells there are still many unanswered questions and expectations. Throughout these pages, we will endeavor to touch on some of the more significant aspects of this amazing world of Biology – a world that, though still in its embryonic phase, will certainly come to signify, for the future of mankind, one of the most extraordinary steps in the quest for scientific knowledge in pathophysiology and the treatment of disease in general.

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