



Stem cells and stem cell-derived extracellular vesicles in acute and chronic kidney diseases: mechanisms of repair

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Abstract: Acute and chronic renal failure have long been described and now renamed as acute kidney injury (AKI) and chronic kidney disease (CKD). New concepts are emerging in the pathophysiology of kidney diseases. AKI is often caused by triggering factors (e.g., toxic, ischemic, immunologic) either individually or combined such as in sepsis (inflammation and hypoxia), and it is initiated at a defined time. Several experimental models of AKI have provided deep insight and have convincingly shown important proof-of-concepts of therapeutic relevance over the years. CKD is now considered a slowly developing disease with often an insidious course, lasting many years whereby co-morbidities (e.g., diabetes, hypertension, dysmetabolic syndrome) may act as worsening factors. It has become increasingly evident that even a single event of AKI may lead to a higher predisposition to develop a progressive CKD. In the present review, we will report studies on the renal protection by adult stem cells in different experimental models and clinical trials. The emerging role of extracellular vesicles (EVs) in cell-to-cell communication and their predominant effect in the paracrine mechanisms of stem cell-dependent actions have prompted several studies on their ability to attenuate both AKI and fibrosis occurring in CKD. We discuss several critical issues that need to be addressed before EVs may have a therapeutic application in humans.

Keywords: Stem cells; extracellular vesicles (EVs); exosomes; acute kidney injury (AKI); chronic kidney disease (CKD)

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Introduction

The kidney has a very complex structure represented by several, highly specialized cells composed in an interwoven architecture. The different microscopic structures composing the nephron include the glomerulus acting as filtrating unit and the tubules involved in active release and absorption of molecules. The kidney far from being a simply “filtering device” is capable of sensing variations in plasma osmosis and volume by correctly interpreting sensor-guided signals. Glomeruli and tubules play in a harmonized vascularized environment embedded in the interstitium.

The kidney is composed by a large vascular bed represented by a unique fenestrated endothelial lining in the glomerulus and an extensive peritubular capillary network. Epithelial cells differentiated into several types with specialized functions line the walls of glomerular capillaries (podocytes) and the wall of membranes of the proximal and distal tubules. Finally, the kidney is a relevant endocrine organ in the regulation of fluid volume, blood pressure, calcium-phosphate metabolism, and erythropoiesis. It is evident that for its central role in the maintenance of the body's interne milieu, the failing kidney induces important repercussions for many other vital organs of the body. Likewise, its

central role in receiving at least 1/4th of the cardiac output is subjected to many types of insults that may markedly reduce or even stop the function of the kidneys.

Classically, acute and chronic renal failure have long been described and now renamed as acute kidney injury (AKI) and chronic kidney disease (CKD). New concepts are emerging in the pathophysiology of kidney diseases. AKI is often caused by triggering factors (e.g., toxic, ischemic, immunologic) either individually or combined such as in sepsis (inflammation and hypoxia) and it is initiated at a defined time. Several experimental models of AKI have provided deep insight and have convincingly shown important proof-of-concepts of therapeutic relevance over the years. CKD is now considered a slowly developing disease with often an insidious course, lasting many years whereby co-morbidities (e.g., diabetes, hypertension, dysmetabolic syndrome) may act as worsening factors. However, although AKI and CKD initially have been described as different entities, it has become increasingly evident that even a single event of AKI may lead to a higher predisposition to develop a progressive CKD:

AKI: epidemiology and economic burden

AKI is still one of the most puzzling renal syndromes, with incidence rates fluctuating from 0.9% to 20% and the whole mortality between 25% and 80% (1). These divergences are most probably due to large differences in AKI designation, case-mix, and experience with AKI therapy and its associate pathology [as reviewed by the Acute Dialysis Initiative in (2)]. Nonetheless, we still face a large uncertainty in the early diagnosis of AKI due to the lack of specificity of diagnostic markers and late intervention [reviewed in (3)]. The need of biomarkers has led to the search for novel biomolecules for early detection of AKI. AKI is also frequently associated with the heart, liver, lung and cardiovascular disease based on organ cross-talk (4). Selected urine biomarkers of kidney injury were independently related with higher incidence of heart failure, cardiovascular disease events, and death in the CRIC study (5). Among the biomarkers examined, only KIM-1/Cr was associated with each outcome (5).

An important percentage of patients with AKI needs dialysis (6). The incidence of mortality in patients who necessitate dialysis for AKI in the intensive care units (ICU) is of 50–60%, approximately twofold that of equivalent patients without AKI (7,8). Care is increased several-fold, resource intense, and technically involved. Patients

with AKI necessitating dialysis therapy need to be treated competently and effectively. A recent cost analysis of the different renal replacement therapies has been published (9).

Pathophysiology of AKI

The glomerular cells are composed of mesangial, endothelial and epithelial cells (podocytes). Podocytes allow the glomerular filtration barrier to be stably maintained thanks to their highly differentiated post mitotic phenotype. Originally, cells in the adult kidney were considered to be unable to proliferate after full completion of the development. However, recently kidney cells have been shown to be able to regenerate and to repair themselves throughout life (10). Podocytes may undergo various kinds of stress, mechanical, oxidative or immunologic. Podocytes have a relevant ability to strain stress. For a long time, our knowledge on podocyte-associated injury has been only related to the presence of foot effacement by electron microscopy. However, it has nowadays become increasingly clear that the application of gene profiling and single cell analysis (11) will help in the recognition of certain gene dysregulation and molecule expression. The latter may be not only paradigmatic signs of the disease but also potential targets of therapeutic intervention (12). Glomerular podocytes, endothelial and mesangial cells and tubular epithelial cells are particularly vulnerable when exposed to antibodies, cytokines such as in sepsis, to exogenous radiocontrast agents and aminoglycosides or to endogenous toxins such as myoglobin and activated complement, or to ischemia (13). AKI recovery depends on the capacity of renal tubules to regenerate and recuperate normal function and on the entity of the injury. In parallel, patient age may lead to requirement for long-term dialysis and to increased mortality (14). Widespread necrosis and exfoliation of tubular epithelial cells are commonly seen in AKI (15). Replacement of necrotic tubular cells with functional tubular epithelium is observed during recovery (16). Failure of replacing injured epithelial and endothelial cells may lead to tubule-interstitial fibrosis and CKD (16). After injury, tubular cells, may acquire a mesenchymal phenotype after de-differentiation thus becoming capable of replacing necrotic or apoptotic cells and of repopulating areas of denuded tubular basement membrane. Subsequent differentiation into mature epithelial cells will lead to recovering tissue integrity. The process of repair is based on local paracrine mechanisms including the release of growth factors such as insulin-like growth factor-1,

epidermal growth factor and hepatocyte growth factor (17). Furthermore, several G protein-coupled receptors are critical in both renal physiology and pathophysiology. Upregulation of Gpr97 occurs in experimental AKI and in AKI patients. Deficiency of Gpr97 was shown to reduce the expression of semaphorin 3A, which in AKI is considered a biomarker of renal injury (18).

Finally, a relevant role in coordination of renal repair has been also ascribed to bone marrow-derived and resident stem/progenitor cells (19).

Pathophysiology of CKD

CKD has a prevalence of approximately 15% in the general population and it is frequently associated with cardiovascular disease and/or diabetes (20). Currently, the expenditure has raised up to \$35 billion annually for CKD care (21). The better understanding of the risk factors associated to progression of CKD from type 2 to type 4 is an area of recent, great interest especially in the light of the fact that these patients are still too often lost to follow-up by nephrologists. More advances in this area of pathophysiology, novel biomarkers and overall a higher clinical readiness are expected to reduce consistently the incidence of CKD. Today, the development of CKD is mainly associated to comorbidities such as hypertension, cardiovascular disease, diabetes mellitus, pre-existing renal dysfunction or glomerular and/or tubular diseases. These co-morbid factors, alone or in association with AKI or even AKI alone may lead to structural damage depending on a series of concurrent, multiple pathophysiological alterations including glomerular hyper-filtration, proteinuria, glomerular- and tubular-sclerosis, interstitial inflammation leading to progressive decline of the renal function. Moreover, it has been shown that tubular/interstitial complement activation has a critical role in CKD progression (22). The tubular/interstitial injury is considered an independent factor of CKD progression also for glomerular diseases (23,24).

The pattern of morbidity and mortality is changing worldwide. Before and through the 20th century, infectious diseases or heavy exposure to toxic agents were among the first causes of both morbidity and mortality and still are in the undeveloped countries. The era of non-communicable, noninfectious affections is now appearing as the new challenge. Diabetes is the single principal cause of CKD (25). Treatments that may delay progression of CKD in diabetes will greatly impact on clinical outcomes and will

reduce the cost of CKD care. Even if the diet may partially slow down CKD, until now only therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may moderately decrease CKD progression in diabetes (26). An improved glycemic control by the sodium-glucose transport protein-2 inhibitors (27) may give even more hope that in the future the decline in renal function may be kept under a tighter control leaving more space for innovative cell therapies.

Experimental models of acute and chronic kidney injury

Adequate animal models are needed to discover new biomarkers for disease staging and therapy individualization as well as dosing and route of administration. Experimental models of renal injury hardly resemble the human setting as many factors may interfere with the renal response including toxins, intrinsic vaso-constrictive renal response, aging etc., that are difficult to reproduce in a single experimental model. In this review, we will refer only to the models that have been used to prove a potential role of stem cells and stem cell-derived extracellular vesicles (EVs) (*Table 1*). To the interested reader, excellent reviews offer a clear picture on the experimental models of renal disease (50,51).

In *Table 1* we summarized the different experimental models, their categorization (whether acute or chronic or both), and their mechanisms of action. The use of immunodeficient mice as well as strain-dependent variation in sensitivity need to receive full awareness.

Stem cells: novel insights in the mechanisms of renal repair

Important progress has been made in recent years on the identification of embryonic precursor cells and adult progenitor cells of the kidney. Due to ethical concerns related to the utilization of embryonic cells and the difficulty to access embryonic tissues, researchers focused on adult stem cells such as bone marrow- and adipose-tissue derived mesenchymal stem cells, endothelial progenitor cells and human liver-derived stem cells.

Self-renewing and differentiation into multiple cell types are features of all stem cells. Stem cells present in the bone marrow are capable to generate the cellular components of various tissues (52-54). In fact, while blood cells originate from the hematopoietic stem cell compartment, osteoblasts, chondrocytes, adipocytes and myocytes originate from mesenchymal stem cells (MSC) (55). Resident stem cells

Table 1 The different experimental models and the mechanisms of action

Model	Species	Intervention	Mechanism of action	Main histology	Increased creatinine	With/out CKD	In vivo effects of EVs	Refs
Anti-Thy 1.1	Mice	EPC	Complement-mediated glomerular injury	Endothelial and mesangial loss followed by mesangial proliferation	Yes	Yes	decreased intra-glomerular deposition of the MAC or C5b-9 and expression of smooth muscle cell actin; preserved RECA-1 and the podocyte marker synaptopodin	(28,29)
Glycerol-induced AKI	Mice	BM-MSC, HLSC, and related EVs, FB-EVs (as controls)	Toxic and ischemic injury due to extensive myolysis and hemolysis	Tubular protein casts with tubular epithelial exfoliation, tubular interstitial inflammatory cell accumulation	Yes (transient)	No	Single administration ameliorated renal function and morphology	(30-34)
Cisplatin induced AKI	Mice	BM-MSC	Toxic	Tubular and interstitial injury	Yes	Yes	BM-MSC improved repair	(35-37)
Ischemia/reperfusion injury	Rats, mice	MSC and EVs from BM-MSC, WJ-MSC, Renal-MSC, EPC	Oxidative stress	Tubular necrosis and apoptosis	Yes	With CKD	Improved renal function, reduced cytokines & apoptosis, increased proliferation of TEC, reduced macrophage infiltration, interstitial fibrosis, decreased oxidant stress	(28,38-43)
Diabetic nephropathy	Mice	Urine-MSC; EV from BM-MSC & HLSC	Oxidative stress with endothelial injury, activation of mesangial cells and glomerular fibrosis	Foot effacement, glomerulosclerosis, tubular interstitial atrophy	Yes	With CKD	Type 1 diabetes; type 2 diabetes	(44-48)
Aristolochic acid nephropathy	Mice	HLSC-EV		Diffuse, severe fibrosis and inflammatory infiltration	Yes	With CKD	AA intoxication, Balkan syndrome	(49)

CKD, chronic kidney disease; EVs, extracellular vesicles; EPC, endothelial progenitor cells; MAC, membrane attack complex; RECA-1, rat endothelial cell antigen-1; AKI, acute kidney injury; BM-MSC, bone marrow-mesenchymal stem cells; HLSC, human liver stem cells; FB-EVs, fibroblast-extracellular vesicles; BUN, blood urea nitrogen; ADMSC, adipose derived mesenchymal stem cells; CB-MSC, cord blood-mesenchymal stem cells; WJ-MSC, Wharton's jelly-mesenchymal stem cells; TEC, tubular epithelial cells; AA, aristolochic acid.

have been found in different tissues such as the central nervous system (56), the retina (57), the skeletal muscle (58), the liver (59) and the kidney (60). Tissue stem cells may differentiate into cells of the same tissue, but also into cells of diverse embryonic lineages (55). Resident stem cells cooperate to the growth of organs after birth and to the tissue cell turnover mostly in skin, intestine and kidney, all these organs sharing a high level of cell turnover. Adult stem cells could be critical also for tissue repair following damage (61).

Even if new nephron genesis does not occur after birth, it has been demonstrated that during life, kidneys may renew the cellular compartments and, to a certain extent, undergo repair (10). In the presence of an insult, however, the regenerative potential may be overcome. Adult stem cells are regarded as a promising alternative in the field of kidney regeneration following AKI.

Many studies in the literature have shown that MSC exert beneficial effects at least partly through a paracrine action as opposed to engraftment within damage tissue (62). An important prerequisite for the homing of stem cells to a specific site is the presence of injury in order to exert their regenerative effects (30).

Several experimental studies described renal improvement by MSC administration both in AKI and CKD conditions (31,35,38,63). Systemically injected MSC were able to reach the damaged tissues and act within the microenvironment. The homing of MSC into the site of injury was triggered by stromal derived factor with the activation of the CXCR4 chemokine receptor (64,65). Additionally, the interaction between CD44 and glycosaminoglycan hyaluronan correlated with the ability of MSC to migrate in the extracellular matrix (30) as demonstrated by a decrease in homing of MSC within the damaged kidney when the loss of CD44 function was induced by mutant MSC (30). Only a small number of systemically injected MSC engrafted within the injured tubules (30,31,35). In a rat experimental model of IRI, Toegel *et al.* (39) showed a differentiation independent mechanism of protection by MSC. In fact, MSC first concentrated in the peritubular capillaries, localized in the interstitium 24h after injection. No MSC trans-differentiation into tubular epithelial cells was present 3 days later. In another study performed in the glycerol-induced AKI model, Hauser *et al.* (32) demonstrated the vanishing of MSC from the renal tissues 5 days post injection pointing toward a paracrine action exerted by MSC in the improvement of the renal function. In effect, Bi *et al.* (66)

could prove that in a murine AKI model induced by cisplatin, the intraperitoneal injection of MSC conditioned medium was capable to reproducing the positive effects exerted on the kidney by the cells with enhanced tubular cell survival and reduced apoptosis. Notably, it has been shown that insulin-like growth factor-1 and vascular endothelial growth factor were considered mediators of kidney repair (67,68). Indeed, it has been demonstrated that insulin-like growth factor-1 gene silencing in MSC in the cisplatin AKI model and the vascular endothelial growth factor knockdown by small interfering RNA in IRI model decreased the positive effects of MSC on renal repair (67,68). Moreover, MSC allowed to ameliorate kidney function in a model of renal failure induced in Sprague-Dawley rats by 5/6 nephrectomy (63).

Of interest, Baban *et al.* (69) showed the influence of the diabetic microenvironment on circulating and kidney stem cells leaving space to the concern on how it could also influence paracrine mechanisms of repair. Collectively, their results propose that the diabetic environment negatively influences the survival of stem cell subsets ensuing in increased apoptosis. For stem cell-based therapies, it remains to be established how the environment may hamper allogeneic stem cells and their paracrine function.

The favorable properties of MSC in preclinical studies performed in animal models both in acute and chronic renal injuries encouraged the performance of phase I and II clinical trials to study safety and efficacy of MSC therapy for kidney disease (70). One phase I trial in 2013 (NCT00733876) evaluating safety and efficacy of bone marrow-derived MSC injection in 16 patients submitted to on-pump cardiac surgery characterized by high risk of AKI, showed that therapy with MSC was safe and protective for the kidney (71). However, these results were not confirmed by a subsequent phase II study (NCT01602328) performed on 156 patients who developed AKI 48 hours after surgery. The intra-aortic administration of allogeneic MSC was shown to be safe and well tolerated but did not improve kidney function and mortality (72). Other clinical studies evaluated safety and efficacy of therapies with MSC for CKD. The NCT02166489 phase I trial in 2014 aimed at testing the safety and tolerability of autologous bone marrow-derived MSC treatment in 6 CKD patients, revealed the absence of adverse effects over 1-year follow-up but without exerting beneficial effects on kidney function (73). Characterization of clinical grade homogeneous populations of adipose tissue-derived MSC has been done (74). Adipose tissue derived MSC have

been used in a phase I trial in 2013 (NCT01840540) with the purpose to assess the safety and toxicity of these cells in CKD patients suggesting the possibility for using this source of MSC for clinical therapy. For other clinical trials including CKD patients using autologous bone marrow-derived MSC (NCT02195323) and adipose tissue derived MSC (NCT02266394) the results are not yet published (75). Finally, a phase I/II clinical trial designed to develop new treatments for diabetic nephropathy using MSC therapies (NCT02585622) is still ongoing. This trial is evaluating safety and efficacy of therapy with bone marrow-derived MSC in diabetic nephropathy.

EVs: an alternative to stem cells

EVs collectively including exosomes, ectosomes and microvesicles, are produced by all living cells and have attracted the interest of many investigators for their role in affecting recipient cells through their complex cargoes of biological molecules such as lipids, proteins and nucleic acids. Many studies show that transitory cell localization in the damaged tissues may be sufficient to support functional and regenerative actions suggesting the involvement of paracrine mediators. Beside secretion of growth factors, also EVs actively released from cells may represent a mechanism of cross talk between cells (76-78).

The vesicles originated from the endosomal membrane compartment after fusion with the cell membrane are named exosomes, whereas EVs released from the surface of activated cells are named ectosomes or microvesicles (79-81). EVs may influence target cells directly or by conveying their cargo (77-79).

Embryonic stem cells are an abundant source of EVs that may sustain stem cell self-renewal and expansion (82). In addition, Ratajczak *et al.* (83) showed that a horizontal transfer of mRNA and proteins mediated by embryonic stem cell EVs can reprogram the haematopoietic progenitors. Deregibus *et al.* (84) showed that the horizontal transfer of mRNA mediated by EVs released from endothelial progenitor cells is associated with the activation of the regenerative programs. Valadi *et al.* (85) have shown that beside mRNA, functional miRNA can be transferred through EVs and represent a more general mechanism of interchange of genetic material among cells.

The content of the EV cargo is also dependent on the state of the releasing cell (whether in physiologic or stressed conditions). *In vitro* the production of EVs from adipose tissue-derived MSC may lead to different composition

of miRNAs and soluble factors that may induce opposite biological effects (pro- *vs.* anti-angiogenetic) (86). EVs carry the hallmarks of the secreting cell type. In the kidney, EVs have a role in renal physiology including development, control of ion transport, removal of bio-waste, proximal-to-distal communication, regulation of inflammation and immune reaction in renal diseases (87,88). Different renal cells release EVs, which may be recovered in the urines leading to new perspectives in the field of biomarkers for diagnosis and severity assessment in renal diseases (89). Due to their potential as mediators of cellular signaling, their regenerative activity has emerged. The commonest experimental models used in pre-clinical studies reproduce glomerular immunologic damage, mixed toxic-ischemia, and ischemia reperfusion injury (IRI). Recently, EVs derived from different adult stem and progenitor cells were able to support tissue regeneration in a variety of experimental models by favoring a transient dedifferentiation and proliferation of tissue resident cells survived to tissue injury (*Table 1*). For instance, it has been shown that EVs induce AKI recovery by reducing tubular apoptosis and promoting tubular cell proliferation (90). IRI is a frequent pathophysiological condition of AKI. In the clinical setting, hypotension, acute hypovolemia, hypoxia frequently seen in septic shock, abdominal surgery and severe bleeding are associated with AKI. IRI represents a very important condition as it also frequently occurs during kidney, lung and liver transplantation. *Ex vivo* experiments have shown that EVs exhibit a protective effect on organ oxidative stress and promote tissue integrity in liver and lung perfusion models (91). Several *in vivo* models of IRI have been used to show the protective effect of EVs derived from different cell sources (bone marrow-derived MSC (40,41), umbilical cord blood-MSC (92), Wharton's jelly-MSCs (42), renal-cells (43) and endothelial progenitor cells (28). In all these models, EVs seem to act poly-functionally by reducing inflammation and by increasing tubular epithelial cell proliferation. In an IRI model, MSC-EVs also preserved against CKD progression by reducing vascular rarefaction, glomerular and interstitial fibrosis (40). Several papers have consolidated the notion that EVs released from MSC can exert a therapeutic effect in AKI and other renal diseases by transferring their miRNA content (33,88). AKI protection by EVs derived from endothelial progenitor cells was mediated by the transfer of pro-angiogenic miRNAs (28). In fact, the curative and protective effects of EVs were mainly ascribed to the transfer of pro-angiogenic miR-126 and miR-296 to hypoxic resident renal cells. Of interest, Dicer

knock-down or specific antagomirs in endothelial progenitor cells (28) as well as Droscha knock-down in MSC (33) blunted the EV biological activities. Moreover, MSC were shown to accelerate recovery and enhance survival in cisplatin-induced AKI (36,37). Likewise, EVs derived from human liver stem cells were shown to favor recovery in a murine model of AKI (34).

In the Thy1.1 glomerulonephritis featuring complement-mediated mesangial cell injury and endothelial cell loss (93), Cantaluppi *et al.* (29) demonstrated that EVs derived from endothelial progenitor cells inhibit complement-mediated injury. Concerning the translation of EVs into the clinics, in 2014, Kordelas *et al.* (94) described the use of MSC-derived EVs to treat a patient with conventional therapy-refractory acute graft-versus-host disease. The authors reported no side effect, decrease of symptomatology, and the possibility to reduce steroids. The treatment allowed the patient to remain stable for several months. More recently, Nassar *et al.* (95) reported the safety of administration of two doses of umbilical cord-blood MSC-EVs, one dose intravenously and one dose intra renal artery, in 20 patients with stage III and IV CKD. No side effects were linked to EV administration. The EV treatment transiently ameliorated the disease progression and improved the renal function and the inflammatory immune reaction.

Fibrosis

The hallmark of CKD is interstitial fibrosis that can be considered a possible target for therapy, since it has been recognized as an independent contributor or predictor of CKD evolution (3). The release of inflammatory mediators, the activation and proliferation of resident fibroblasts, the infiltration of inflammatory/immune cells, the dysregulation of extracellular matrix deposition, and the epithelial to mesenchymal transition are all peculiar features of fibrosis (4).

Kholia *et al.* (49) studied the role of human liver stem cell-derived EVs in a model of aristolochic acid-induced nephropathy and showed that EVs can prevent interstitial fibrosis by down regulating renal pro-fibrotic genes.

Using a streptozocin-induced type 1 diabetes model, Grange *et al.* (44) investigated the potential curative effect of repeated *i.v.* injections of EVs derived from human bone marrow-derived MSC and human liver stem cells. Both the renal function and the glomerular and interstitial fibrosis were significantly improved in stem cell EV-treated animals. Down regulation of several pro-fibrotic genes in renal

tissues was correlated with the anti-fibrotic effect of human bone marrow-derived MSC and human liver stem cells. The analysis of the miRNA content of human bone marrow-derived MSC and human liver stem cells showed the presence of some common and specific patterns of miRNAs targeting genes related to fibrosis. Despite some differences, both human bone marrow-derived MSC and human liver stem cells targeted genes coding for well-known mediators of tissue fibrosis such as insulin-like growth factor-1, transforming growth factor- β , platelet derived growth factor receptor and epidermal growth factor receptor. Furthermore, both human bone marrow-derived MSC and human liver stem cells contained miRNAs triggering Collagen I, Snail, and FAS ligand such as miRNA-29a, let-7 family, miRNA-30a, miRNA-24 and miRNA-21. Of interest, human liver stem cell-derived EVs contained high amounts of miR-146a, that inhibits inflammation and fibrosis in CKD and is a potential therapeutic tool for renal fibrosis in a unilateral ureter obstruction model (96,97). MSC-EVs were enriched in let-7 and miR-30 family members that favor renal regeneration (41,98). Urine-purified EVs (45) and MSC-EVs (46) were also shown to have a preventive effect on diabetic nephropathy. Despite the encouraging results indicating that stem cell-derived EVs may attenuate and antagonize the progression of the functional and morphological abnormalities in the streptozotocin-induced model of diabetes, there remains a need for robust mouse models of diabetic nephropathy that mimic key features of advanced human pathology. Nevertheless, preliminary data indicate that MSC-derived EVs may have a role in attenuating type 2 diabetes by reversing peripheral insulin resistance and by reducing beta cell loss (47,48).

EVs as therapeutics: hurdles and perspectives

Several critical issues need to be addressed before EVs may be applied to study protocols in humans. (I) EVs need a classification by the Regulatory Authorities being borderline between advanced therapy medicinal products (ATMPs) and biologics. The classification will relevantly affect the future of EVs as a pharmaceutical product. In favor of the ATMPs is the complex nature of EVs that are small pieces of cells reproducing in a nanoscale magnitude the complexity of the cell of origin. In fact, stem cell derived EVs express surface membranes and intra-cytoplasmic molecules characteristic of the cell of origin including biologically active proteins, lipids, and nucleic acids. Since

EVs are a heterogeneous population, the identification of a single biologically relevant component as in biologics would create a major hurdle in the clinical advance of EV-based therapies. (II) Phase 1 studies have to define safety of EV therapy. More specifically, in study protocols with repeated injections of EVs, there will be the need to exclude an antibody response to HLA antigens. (III) In clinical studies based on the pre-clinical models, the amount of EVs to be injected needs a large-scale production. Possible strategies of EV isolation such as standard ultracentrifugation, continuous flow ultracentrifugation or tangential flow filtration need appropriate setups and acceptable recovery as well as maintenance of EV integrity, phenotype characterization and biological potency. (IV) Validated potency assays coherent with the therapeutic application have to be established to evaluate efficacy of produced EVs. (V) Cryopreservation or lyophilization as strategies for storage and related definition of shelf life should be verified. (VI) Finally, the pharmacodynamics, pharmacokinetics and bio-distribution of EVs should be studied after different administration routes (intravenous, intra-arterial, intra-parenchyma injection).

Conclusions

In a time of steep cost increase and with the need to insuring health care for acute and chronic renal disease patients, therapies addressing renal protection need to incorporate several challenging concepts including predictive, preventive and personalized medicine. The crucial role of kidney diseases in affecting whole body balance and other organs' physiopathology along with the fact that the kidney is the target for immunologic, metabolic and toxic as well as toxic-ischemic causative factors call for a strong commitment of basic science and clinical researchers alike to shape innovative therapies. Type 2 diabetes is a good example on how much would be important to select patients with a higher propensity to develop the disease and progress to CKD. As described, the diabetic microenvironment and even more so the uremic state would be detrimental to the repairing and homeostatic mechanisms. The ability to insure a better glycemic control is very important and may indeed reduce progression to late stages of CKD. Notwithstanding, diabetes may slowly have a negative impact on the kidneys. Stem cells and more specifically their derived EVs hold a promise today. However, we are still far away from solving several fundamental questions related to their final classification by official regulatory agencies, the best choice

of the cell origin, the mass production, and their safety and toxicity. As it is usual and right to be so, while basic science is revolutionary in concepts and in suggesting new attractive hypothesis, we are all demanded to seriously accept the task to insure the patients with a truly safe, highly efficient therapy at the timely window of their disease. Based on the increasing evidence of stem cells and their derived EVs in experimental models of renal diseases, new clinical studies will have to confirm the potential of regenerative medicine to enter the therapeutic armamentarium.

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