HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Kidney Int. 2016 April ; 89(4): 767–778. doi:10.1016/j.kint.2015.11.023.

Challenges and opportunities for stem cell therapy in patients with chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a global healthcare burden affecting billions of individuals worldwide. The kidney has limited regenerative capacity from chronic insults, and for the most common causes of CKD, no effective treatment exists to prevent progression to end-stage kidney failure. Therefore, novel interventions, such as regenerative cell-based therapies, need to be developed for CKD. Given the risk of allosensitization, autologous transplantation of cells to boost regenerative potential is preferred. Therefore, verification of cell function and vitality in CKD patients is imperative. Two cell types have been most commonly applied in regenerative medicine. Endothelial progenitor cells contribute to neovasculogenesis primarily through paracrine angiogenic activity and partly by differentiation into mature endothelial cells in situ. Mesenchymal stem cells also exert paracrine effects, including pro-angiogenic, anti-inflammatory, and anti-fibrotic activity. However, in CKD, multiple factors may contribute to reduced cell function, including older age, coexisting cardiovascular disease, diabetes, chronic inflammatory states, and uremia, which may limit the effectiveness of an autologous cell-based therapy approach. This review highlights current knowledge on stem and progenitor cell function and vitality, aspects of the uremic milieu that may serve as a barrier to therapy, and novel methods to improve stem cell function for potential transplantation.

Keywords

stem cells; end-stage renal disease; senescence; uremia

INTRODUCTION

Chronic kidney disease (CKD), affecting 8–16% of the population worldwide, is now viewed as part of the rising global non-communicable disease burden[1, 2]. Given the growing

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DISCLOSURE

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aging population, CKD growth rate is expected to increase exponentially, particularly in the United States and other developed countries. Beyond primary prevention measures, the most common causes of CKD, including diabetes and hypertension, have no effective intervention to stop progression to end-stage kidney failure. The increased morbidity, mortality, and costs of healthcare utilization inherent with initiation of renal replacement therapy thereafter serve as substantial motivation for pursuit of novel therapeutic interventions to prevent or delay progression to end stage renal disease (ESRD)[3–8].

Cell-based regenerative therapy is being extensively evaluated as an alternative treatment modality for many with no other treatment options[9]. Targeting the underlying disease process and boosting the endogenous reparative capacity may reset the clock at least temporarily, allowing structural and functional restoration of the diseased kidney (Figure 1). To achieve this, the chief cell types under investigation are stem and progenitor cells. Endothelial progenitor cells (EPCs), which are derived from the bone-marrow and circulate in the peripheral blood, contribute to neovasculogenesis primarily through the secretion of paracrine angiogenic cytokines, and possibly partly by differentiation into mature endothelial cells in situ. Mesenchymal stem cells (MSCs), isolated from a variety of tissues, are non-embryonic stem cells that possess the ability to differentiate along three main cell lineages. Nevertheless, through paracrine activity on other cell types, MSCs maintain anti-fibrotic, anti-inflammatory, and pro-angiogenic properties, which modulate inflammation, immune activation, and neovasculogenesis. Clinical trials using MSCs have been initiated for acute kidney injury, polycystic kidney disease, and kidney transplantation, but only one trial has been registered for the indication of CKD [Clinicaltrials.gov][10–14]. Notably, a recent randomized, multicenter, double-blind, placebo-controlled study applying allogenic MSC for treatment of acute kidney injury in cardiac surgery patients was terminated early due to lack of benefit[15, 16].

Preclinical studies provide ample support for use of EPC and MSC in CKD[17–23]. In a systematic review and meta-analysis of 71 articles in animal models, Papazova et al[20] found that cell-based therapy reduced development and progression of CKD. This was evidenced by decreases in urinary protein and urea, which structurally associated with glomerulosclerosis and interstitial fibrosis. However, direct evidence from glomerulosclerosis and interstitial fibrosis analyses was incomplete. Additionally, Li et al[24] found that human MSCs prevented hyperglycemia-induced podocyte apoptosis and injury, and other investigations have shown that in animal models of diabetic nephropathy, MSCs reduced glomerulosclerosis and oxidative stress[18, 20, 25, 26]. We also previously demonstrated the beneficial effect of EPC and MSC transplantation in a porcine model of renovascular hypertension, wherein intrarenal delivery of cells attenuated renovascular hypertension-induced myocardial injury and decreased renal injury[19, 27, 28]

Adequate cell functionality and vitality is critical for the success of autotransplantation, Autotransplantation is preferred over allogeneic transplantation, to decrease the risk of allosensitization, particularly in patients that may eventually require kidney transplantation. However, while EPCs and MSCs were identified as the most effective cell types for CKD therapy[20], these cells themselves are not impervious to damage and wear. Cell loss and dysfunction may manifest by impaired circulating cell count and pro-angiogenic or anti-

inflammatory functionality. Reduced vitality is characterized by premature senescence and increased apoptosis. Cellular senescence is an age-related decline in response to stress and damage originating from exogenous (e.g., disease or oxidative stress) and endogenous (e.g., DNA damage) sources, leading to an irreversible proliferation arrest[29–32]. Senescence is characterized by cell cycle arrest, telomere shortening, and altered cellular morphology, and is most apparent in disease states and advanced aging, wherein environmental stressors reduce cellular vitality and functionality. Affected cells develop a senescence-associated secretory phenotype, producing excessive inflammatory cytokines, extracellular matrix-modifying proteases, and reactive oxygen species, which impair neighboring cell function and alter tissue structure that may contribute to chronic injury.[31, 33–35] Apoptosis, programmed death of damaged cells, aims to minimize necrosis-induced damage, yet nonetheless leads to cellular loss. Notably, CKD may increase cellular propensity for senescence and death. Characterized by a high prevalence of older age, multiple morbidities such as diabetes, hypertension and other cardiovascular diseases, and a uremic milieu, CKD encompasses a poor microenvironment for both harvesting and transplantation of cells, thereby potentially limiting their overall effectiveness in cell-based therapy for CKD.

This review summarizes the relevant evidence regarding EPC and MSC functionality and vitality in the setting of CKD, as well as the associated mechanisms, which may serve as a barrier to therapy. We further provide an overview of promising future strategies to optimize cell function for autotransplantation in cell-based treatments.

Endothelial progenitor cells

Asahara et al[36] first isolated endothelial progenitor cells in 1997, and illustrated that these circulating CD34+ cells contributed to angiogenesis. EPCs primarily originate from the bone marrow, and upon expansion in an endothelial-permissive milieu, can adopt an endothelial-like phenotype. They circulate in and patrol the peripheral blood, and home to injured tissues, where they release angiogenic factors and extracellular vesicles that stimulate the local endothelium, promoting angiogenesis and contributing to vascular repair and regeneration[37]. A small fraction of EPCs may differentiate into mature endothelial cells and incorporate into the damaged endothelium to replace or support existing endothelial cells in forming new blood vessels.

Although the validity of specific EPC surface markers or means to reliably measure EPC levels have been debated, circulating bone marrow-derived cells positive for the surface markers CD34, vascular endothelial growth factor receptor-2 (VEGFR2, or kinase insert domain receptor), and negative for the inflammatory cell marker CD45, are often considered as EPC. Cells with both CD34 and CD133 positivity represent an early (“immature”) circulating EPC population with a potential to develop into mature endothelial cells in-vivo[38, 39]. The divergent phenotypes of EPC subpopulations applied over the years makes comparison of EPC studies somewhat challenging, given the important prognostic significance associated with these cells for cardiovascular events among patients with cardiovascular disease (CVD)[40–42]. Nevertheless, low EPC subpopulation numbers or impairment of EPC function consistently associates with the presence of CVD and risk factors[43–47].

The primary functional feature of EPC consists of angiogenic potency to induce vascular repair. Angiogenic functionality is demonstrated through secretion of growth factors, as well as their proliferation, migration, and tube formation in in-vitro assays or when injected to murine models. In addition, their ability to home to sites of vascular or tissue injury allowing for both re-endothelization and neovascularization is an important functional feature that can be assessed in-vitro by their migration capacity (in response to VEGF or other chemotactic molecules) and cell-cell or cell-matrix adhesion[39, 48]. Finally, these cells possess anti-inflammatory capacity, and we have shown their ability to suppress the prevalence of pro-inflammatory macrophages[19, 49].

Over the past decade, exogenous administration of EPC has been successfully used in experimental models of CKD. Previous studies have shown that mobilization of EPC contributes to endothelial repair in the kidney immediately after ischemia-reperfusion[50, 51]. In agreement, we have found in swine renovascular disease that a single intrarenal delivery of autologous EPC improves the renal microvasculature, protecting the stenotic kidney[17, 19, 52]. Furthermore, intrarenal delivery of autologous EPC in conjunction to renal revascularization restores the hemodynamics, function, and oxygenation of the stenotic swine kidney[49, 53], suggesting a therapeutic potential for EPC in preserving the kidney in chronic experimental renovascular disease.

Mesenchymal stem cells

First isolated and characterized by Friedenstein and colleagues in 1974[54, 55], MSCs have emerged as ideal candidates for cell-based therapies for preservation of the human kidney. Unlike EPCs that are isolated from the bone marrow or peripheral mononuclear cells and cultured for several weeks before transplantation, MSCs can be harvested from a variety of tissues including adipose tissue, bone marrow, skin, and skeletal muscle, and are easily expanded in-vitro within a relatively short period of time[56]. Minimal criteria for defining MSCs include trilineage differentiation potential (adipocytes, chondrocytes, and osteocytes), plastic-adherence under standard culture conditions, expression of CD29, CD44, CD73, CD90, CD105, and CD166, and no expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules [57].

Importantly, MSCs secrete several growth factors and cytokines that modulate adjacent parenchymal cells, triggering tissue regeneration. Like EPC, MSCs release extracellular vesicles that contain a combination of mRNA and miRNA capable of regulating transcription of genetic information and modulating angiogenesis, inflammation, and other pathways in recipient cells[58, 59]. Although slightly less potent than EPC, swine adipose tissue-derived MSCs have pro-angiogenic properties, supporting their ability to preserve the renal microvasculature[19]. Moreover, MSCs possess pronounced immunomodulatory properties that promote tissue repair and decrease inflammation. We have shown that cultured MSCs induce a shift in macrophage phenotype from inflammatory (M1) to reparative (M2), underpinning their anti-inflammatory properties[60]. Likewise, MSCs inhibit lymphocyte proliferation via the secretion of interleukin (IL)-10 and Fas ligand[61]. Finally, MSCs lack co-stimulatory molecules such as CD40, CD80, and CD86, which evoke an allogeneic T-cell immune response [62]. Therefore, the lower risk of rejection of

immunoprivileged MSCs promoted development of off-the-shelf products with the hope for feasible allogeneic administration, although this application remains limited.

The ability of MSCs to preserve renal structure and function has been demonstrated in experimental CKD[20, 63], as their administration preserved renal function and attenuated renal injury in several rodent models of diabetic nephropathy [64], partial nephrectomy [65], and chronic allograft nephropathy[66]. We have shown that intrarenal delivery of adipose tissue-derived MSCs attenuated in swine renovascular disease stenotic kidney injury and dysfunction despite sustained hypertension[19, 60]. Intrarenal delivery of MSCs in conjunction with renal revascularization also restores renal hemodynamics and function and decreases hypoxia, inflammation, apoptosis, oxidative stress, microvascular loss, and fibrosis [28, 67]. Notably, intrarenal delivery of MSCs during reversal of experimental renovascular hypertension subsequently improves cardiac function, uncovering their therapeutic potential to preserve the heart[68]. Finally, MSCs excellent safety record [65, 69], and their unique immunomodulatory properties and promising results from experimental studies eventually led to their approval by the U.S. Food and Drug Administration for treatment of steroid-resistant graft-versus-host disease, the only stem cell-based drug approval.

EPC and MSC function and vitality in CKD: Human studies

EPC have been thoroughly evaluated in CKD patients, whereas similar studies assessing MSC in this population are lacking (Table). With the exception of one early study[70], a large body of evidence shows that EPC number is impaired in patients with CKD[45, 47, 48, 71–85]. Although different subpopulations have been studied, primarily in patients receiving dialysis, decreased EPC numbers (30–50% lower than in healthy controls) were consistently demonstrated in both CKD and dialysis-dependent states of ESRD[40, 86]. In addition, EPC function (tube formation, cellular adhesion, and migratory capacity in-vitro) is generally decreased in comparison to healthy controls. Some studies explored the differing effects of renal replacement therapy through dialysis modality (conventional hemodialysis, peritoneal dialysis, nocturnal dialysis) or kidney transplantation on EPC number and function[48, 73, 81, 84, 87, 88]. Interestingly, augmented efficiency of clearance of uremia appears to restore EPC number and functionality. Fewer studies investigated EPC number and function in patients with CKD[45, 71, 73, 74, 77, 80, 84, 89], and reported that even small reductions in glomerular filtration rate (GFR) led to significantly lower EPC numbers compared to healthy controls. In the largest cohort of patients with CKD, Chen et al[45] supported earlier findings by Jie et al[77], arguing against correlation of the stage of non-dialysis CKD with EPC number. Interestingly, a sharp fall in EPC number was observed at the transition from normal GFR (in healthy controls) to early CKD, providing the impetus to intervene with cell-based therapy even at the early stage of CKD.

Alterations in EPC vitality in CKD, such as the frequency of senescent or apoptotic cells relative to normal or viable cells, have not been fully established. A pattern of increased apoptosis has been identified in dialysis patients, but is yet to be confirmed in subsets of non-dialysis CKD patients[81, 85]. Overall, the vast body of evidence suggests that EPC number and function are impaired in CKD patients, whereas cellular senescence and apoptosis in this patient population require further studies.

In comparison to EPC, substantially fewer studies have assessed MSC function in human subjects with CKD or ESRD (Table 1). Roemeling-van Rhijn et al[90] showed in 16 ESRD patients that adipose-derived MSC proliferative rates were similar to healthy controls, but their vitality was not fully evaluated. Similarly, Reinders et al[91] demonstrated that bone marrow-derived MSC from 10 ESRD patients were phenotypically and functionally similar to healthy controls, supporting the feasibility of autologous clinical application. Yamanaka et al[92] determined that long-term uremic conditions in 9 ESRD patients led to persistent and systematic downregulation of gene and protein expression of p300/CBP-associated factor, which regulates differentiation, angiogenesis, and gluconeogenesis, as well as poor *in-vivo* angiogenic potency of adipose-derived MSCs. Given the paucity of human studies of MSC function, much extrapolation on cellular function in CKD is derived from animal models. In bone marrow-derived MSCs harvested from CKD rats, Klinkhammer et al[93] found increased senescence, reduced proliferation capacity, accumulation of actin, and a modulated secretion profile. Noh et al[94] induced uremia in a CKD mouse model and demonstrated decreased expression of VEGFs its receptor-1, and stromal cell-derived factor-1α, as well as increased cellular senescence, decreased proliferation, and impaired in-vitro tube formation of bone marrow-derived MSC. Taken together, there is conflicting evidence regarding MSC functionality and vitality in CKD states. However, there is a clear need for additional investigations in human subjects to determine whether MSC function and vitality are altered in the noxious milieu that characterizes CKD.

Barriers to therapy: Mechanisms underlying impaired EPC and MSC function and vitality in CKD

Mechanisms by which CKD impairs EPC and MSC function could involve factors common to many pathogenic mechanisms activated by CVD risk factors. In particular in CKD, important roles are ascribed to factors such as inflammation, activation of the renin-angiotensin-aldosterone system, increased oxidative stress, endothelial dysfunction, atherosclerosis, and other CKD-associated conditions (e.g., erythropoietin deficiency, metabolic acidemia, hyperhomocysteinemia, uremic toxins) (Figure 2). Levels of EPCs are believed to be a surrogate marker for vascular function and cumulative CVD risk. A low number of EPCs may reflect a depletion of EPC supply due to either increased demand (e.g., persistent, ongoing endothelial damage), kidney sequestration in the setting of vascular injury[95], or impaired EPC mobilization[44, 48, 96]. EPC supply/demand disparity and endothelial dysfunction, which is common in CKD[97, 98], might both contribute to CKD-induced CVD risk[99], and vice versa. In the largest study of dialysis patients to date, low circulating EPC was an independent and significant predictor for cardiovascular events and all-cause mortality[82]. Moreover, emerging evidence suggests that cardiovascular risk factors may in fact elicit a preponderance of EPC capable of contributing to the complications of CVD. For example, EPC bearing osteogenic markers (OCN) have been identified in patients with early CVD, and postulated to contribute to vascular calcifications[100–102]. Whether a similar population of calcifying EPC might be involved in the increased propensity for calcification observed in patients with CKD is yet to be determined.

Uremic toxins may also contribute to EPC or MSC depletion and malfunction via endothelial dysfunction observed in CKD. For example, a decrease in bioavailability of

nitric oxide (NO), which participates in release of EPC from the bone marrow[103], can decrease EPC mobilization in CVD and CKD. Increased reactive oxygen species (ROS) and chronic inflammation secondary to CKD[104, 105], dialysis[106], or comorbidities[107–112] also impair EPC function. Moreover, uremic toxins and aging may exert epigenetic and transcriptional modulation and thereby contribute to pathogenesis in CKD[113–117]. Finally, co-existing diabetes mellitus in patients with CKD may substantially reduce autologous treatment efficacy using MSC[118, 119].

Toxicity of the uremic milieu—Several uremic toxins have been implicated as contributors to endothelial dysfunction, including homocysteine[120], advanced glycation end products[121], p-cresylsulfate, and indoxyl sulfate[122, 123], all of which may indirectly contribute to depletion of EPCs allotted to repair the abnormal endothelium in CKD[104]. A progressive decline in kidney function leads to progressive accumulation of compounds of differing chemical and physical composition, which are normally efficiently excreted by healthy kidneys. Prominent among the uremic toxins are urea, guanidines, p-cresol, indoles, homocysteine, and advanced glycosylation end (AGE) products. Many of these toxins promote oxidative stress and reduced availability of NO, thereby promoting vascular damage and excess CVD found in patients with CKD[124, 125]. Urea, a small water-soluble uremic compound, is linked to survival among dialysis-dependent patients [126]. Its biochemical effect has not been well demonstrated, but may include increased ROS production[127]. Guanidines, p-cresols, and indoxylsulfate are among the most frequently studied protein-bound toxins in patients with ESRD. Guanidines are small water-soluble compounds, which are metabolites of L-arginine, the substrate for NO synthesis. Guanidine compounds include creatinine, creatine, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). Various guanidines are shown to have pro-inflammatory activities by leukocyte proliferation stimulation[128, 129]. ADMA, often elevated in ESRD, is an inhibitor of NO synthase, marker of endothelial dysfunction, and associated with several adverse vascular outcomes[130–133]. Although previously considered biologically inactive, recent studies illustrated a role of SDMA in the inflammatory process of CKD, wherein monocytes incubated with SDMA showed increased IL-6 and tumor necrosis factor-α expression[134], a rise in active nuclear factor-κB, and inhibition of endothelial NO synthase[135]. P-cresols are protein-bound, intestinally-derived end-products of tyrosine and phenylalanine catabolism. Their main in-vivo metabolite p-cresylsulfate, exerts pro-inflammatory activity exhibited by increased proportion of leukocytes displaying oxidative burst activity, and has been identified as a predictor of survival in CKD[136, 137]. Indols, also protein-bound compounds, are produced by intestinal flora as metabolites of tryptophan. Indoxyl sulfate and p-cresol inhibit endothelial proliferation and wound repair contributing to endothelial dysfunction in CKD[122]. Moreover, indoxyl sulfate induces ROS production by endothelial cells[123], and microparticle release, and is associated with vascular disease and mortality in CKD patients[104, 123, 136]. The amino acid homocysteine associates with CV events in both the CKD and the general population[138], with pathogenic mechanisms including up-regulation of multiple genes associated with atherogenesis, increased vascular smooth muscle cell proliferation, C-reactive protein production, endothelial dysfunction, and oxidative damage[139]. Finally, AGE's, the products of a non-enzymatic reaction between reducing sugars and amino groups of proteins, lipids, and nucleic acids, accelerate aging of

macromolecules and also contribute to endothelial dysfunction[140]. In the setting of hyperglycemic (diabetes) or oxidative stress (kidney failure) conditions, production and/or accumulation of AGE rise. AGEs stimulate leukocyte activation, inhibit NO synthase, form cross-links between molecules in the basement membrane of the extracellular matrix, and engage the receptor for AGE, resulting in ROS generation and invoking an inflammatory response thereby contributing to the endothelial dysfunction and vascular damage provoked by other uremic toxins[140–143]. Each of these uremic retention substances, individually or cumulatively, contribute to ongoing endothelial dysfunction through alteration of NO availability and increased ROS production, which may deplete EPC number and impair function of both EPC and MSC. Moreover, direct effects of uremic toxins likely play a major role in their deleterious effect on EPC and MSC.

Effect of uremic toxins on EPCs and MSCs—In-vitro studies have greatly increased our understanding of the effect of uremic toxins on EPC and MSC. de Groot et al[74] demonstrated decreased number of circulating EPC in patients with advanced CKD, and their uremic sera inhibited differentiation and migration of healthy EPC. Yet, Jourde-Chiche et al[78] found that uremic toxic substances (p-cresylsulfate, indoxylsulfate, indole-3 acetic acid, β-2 microglobulin, and homocysteine) did not induce apoptosis of myeloid EPC from healthy controls, whereas, Wu et al[144] determined that indoxyl sulfate inhibited angiogenic function and increased senescence and autophagy of EPC collected from patients with acute kidney injury. Taken together, these data suggest that EPC from patients with kidney disease might be more susceptible to the deleterious effect of uremic toxins. In non-CKD models, homocysteine impairs the homing to injured vasculature, proliferative, migratory, adhesive and in-vitro vasculogenesis capacity of EPC[145, 146], and both p-cresol[147] and ADMA[148, 149] attenuate angiogenic function and proliferation of EPC.

Fewer recent studies assessed the in-vitro effect of uremia or uremic toxins in CKD on MSCs. Kramann et al[150, 151] found that uremic serum induced an osteoblast-like phenotype and enhanced MSC proliferation and vascular wall remodeling, but not apoptosis. Lanza et al[114] also found a propensity towards osteogenic differentiation of human bone marrow-derived MSC when exposed to either uremic sera or multiple uremic toxins, which likely contributes to bone modification in patients with CKD. Izdiak et al[152] showed that p-cresol and indoxyl sulfate decreased human bone marrow-MSC functionality and vitality in vitro, but despite cell membrane damage, apoptosis was not increased. Contrarily, homocysteine-treated MSC manifest increased apoptosis[153]. Noh et al[154] showed that p-cresol induced MSC dysfunction by impairing insulin-induced elevation of hypoxia-inducible factor-1α. These studies demonstrated the potential inhibitory effect of uremia on adequate MSC function in the setting of uremia, which does not necessarily lead to apoptosis. However, more studies are needed to identify specific treatment targets to improve MSC and EPC function.

Strategies to improve EPC and MSC function in CKD

Given that EPC become dysfunctional during the course of a number of prevalent diseases, means for optimization of EPC number and function have been actively sought[155]. Among the best-documented drugs are 3-hydroxy-3-methylglutaryl-coenzyme-A reductase

inhibitors, which increase EPC mobilization and function and reduce apoptosis[44, 156–158]. Vasa et al[44] reported a three-fold increase in circulating progenitor cells after patients with CAD were treated with statins for four weeks, and several randomized trials[159] showed a statin-induced increase in EPC number ranging from 25.8% to 223.5%. Similarly, Wu et al[144], using a NO-releasing statin, reversed the NO-dependent negative effects of indoxyl sulfate on EPCs in-vitro. Other drugs commonly used in CVD and CKD, such as angiotensin-converting enzyme inhibitors, also lead to mobilization of EPCs, possibly through stimulation of NO activity and a reduction in oxidative stress. Similarly, angiotensin-2 receptor blockers may directly affect EPCs through peroxisome proliferator-activated receptor-γ receptor activity. Figure 3 outlines several drugs shown to affect EPC[155], including erythropoietin stimulating agents[71, 89], calcium channel blockers[160], biguanides (metformin) without or with thiazolidinedione (pioglitazone)[161, 162], and dipeptidyl peptidase-4 inhibitors (sitagliptin)[163]. However, some interventions aimed at improving EPC function in dialysis patients, like green tea consumption[164], exercise[165], or differing middle molecule removal[81], had no discernible effect. Finally, as previously mentioned, optimal clearance of uremic toxins through effective renal replacement therapy, such as kidney transplantation or nocturnal hemodialysis[48, 73], is associated with EPC mobilization and improved function, yet is not a uniformly viable option for all ESRD patients.

Drugs or interventions that may improve function and reduce senescence or apoptosis in MSC include hypoxic and other preconditioning measures[166–168], pravastatin[169], rosiglitazone[170, 171] or coenzyme Q10[172] therapies, and epigenetic regulation[173, 174]. Both preconditioned MSC and EPC have shown improved cell survival, homing to injured sites, and paracrine activities. Finally, given the toxicity of cells acquiring senescence-associated secretory phenotype, their removal with senolytic agents could optimize function and structure of neighboring cells[175]. To our knowledge, the potential effect of senolytics on MSC or EPC function is yet to be fully explored.

Future directions

Greater investment is needed for better understanding of EPC and MSC function in a diverse group of individuals with varying CKD etiology, race/ethnic, gender, or age groups. For example, African-American hypertensive patients manifest elevated number of circulating pro-inflammatory endothelial cells positive for the inflammatory marker, vascular adhesion-protein-1[176]. Studies are needed to determine whether comparable phenotypic changes are observed in MSC or EPC of specific population sub-groups. Identification of such harmful cells may facilitate development of targeted treatment modalities to eliminate or improve their function. Furthermore, EPC or MSC function might hypothetically be differently affected in patients with differing CKD etiologies, such as renal-limited IgA nephropathy relative to systemic disease like diabetic nephropathy, despite comparable changes in GFR. This would imply that therapeutic approach cannot be decided based on GFR alone. Additionally, preconditioning protocols may need to be implemented not only on cells in-vitro, but also in-vivo, as a means to optimize the microenvironment in which they will ultimately be implanted.

Several issues in stem cell dysfunction remain unresolved. A documented fall in MSC number and/or function would likely substantiate the motivation to apply their replenishment in CKD. While a decrease in EPC number and function has been well recognized in CKD (Table), the fate of MSC remains to be defined. In as much as MSC derived from different sources (e.g., skin, fat, bone marrow, etc.) are representative of the ubiquitous MSC population[177], their availability and functionality might reflect on the endogenous reparative capacity of kidney resident MSC. However, given that MSC are often expanded prior to evaluation, their enumeration is less straightforward than that of circulating EPC. Furthermore, while cell-based therapy has been shown to attenuate tubular and vascular injury, its ability to reverse established glomerulosclerosis remains to be shown. Lastly, some of the paracrine activity of both EPC and MSC is mediated by release of membrane microparticles, which carry genetic and protein cargo derived from their parent cells. Being non-replicating, microparticles are not subject to apoptosis and senescence, and might therefore prove to have a longer lasting impact, as long as local proliferation of delivered vectors is not mandatory for tissue repair. Nonetheless, studies are needed to determine the required residence time of cellular or non-cellular elements, and whether cells derived from subjects with CKD pack harmful (e.g., pro-inflammatory) cargo within the microparticles that they release.

The choice between EPC vs. MSC might be considered based on disease etiology. Kidney diseases associated with predominant microvascular loss would likely benefit from the prominent pro-angiogenic properties of EPC, whereas those characterized by a strong inflammatory or immune components might gain from MSC therapy. Hopefully, future studies will outline specific recommendations for delivery regimens.

CONCLUSION

Regenerative medicine provides new hope for a means to change the trajectory of CKD. In planning for cell-based therapy for CKD, special considerations should be given to patient-related factors that may limit the efficacy of MSC and EPC. Clearly, more studies in humans, particularly of MSC from patients with CKD, are needed to assess the feasibility and efficacy of this approach, as well as the window of opportunity to intervene, prevent, or reverse kidney damage. Advancement in the field is somewhat burdened by expense and expertise of the research laboratories, need for standardization of methodology for cell characterization and cell growth medium, and heterogeneity of the CKD patient population. Nevertheless, identification of means to optimize cell function and/or the microenvironment in which the cells will be transplanted, are of utmost importance as we move into this burgeoning era of treatment.

Acknowledgments

Partly supported by NIH grants DK73608, HL123160, DK102325, DK106427, and DK106427, the Mayo Clinic Center for Regenerative Medicine, and the Satellite Healthcare Foundation.

L.J.H. was supported by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery.

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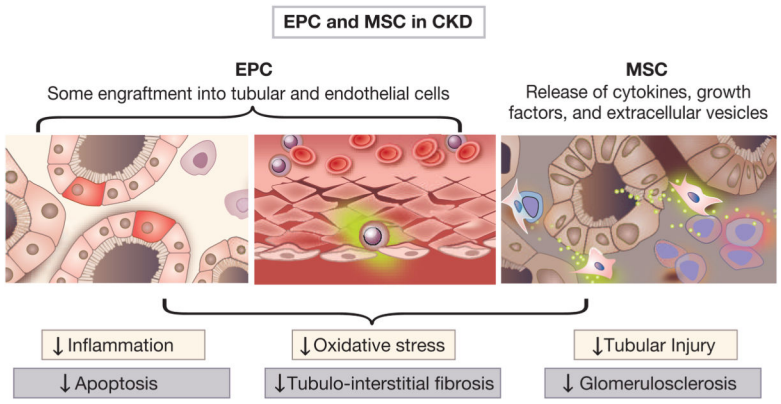

Figure 1.

Endothelial progenitor cell (EPC) and mesenchymal stem cell (MSC) reparative functions in chronic kidney disease. Both cell types possess the capacity to release a variety of cytokines, growth factors, and extracellular vesicles. Cells home to the injured tissue, engraft (although incorporation in kidney structures is often modest), and promote neoangiogenesis. Cumulative effects of the EPC and MSC result in multiple beneficial effects including decreased inflammation, oxidative stress, and apoptosis. Structural effects include minimization of tubular injury, tubulointerstitial fibrosis, and potentially glomerulosclerosis.

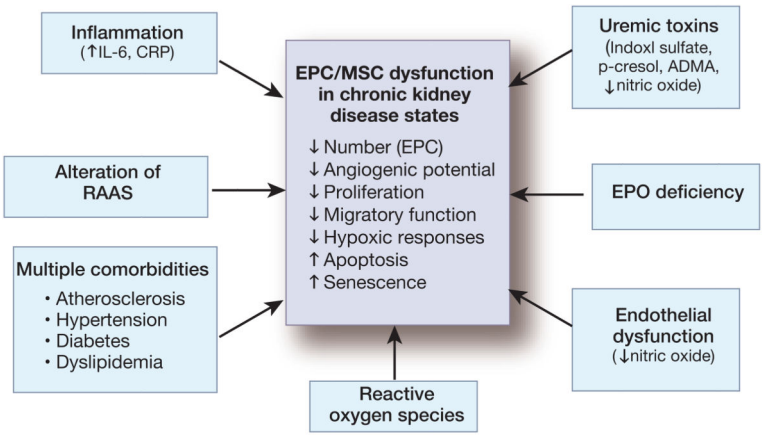

Figure 2.

Causative factors for endothelial progenitor (EPC) and mesenchymal stem cell (MSC) dysfunction in chronic kidney disease (CKD). In the setting of CKD, EPC and MSC become functionally impaired, and EPC demonstrate a reduction in the number of circulating cells. Moreover, the cell vitality might decrease, demonstrated by apoptosis and cellular senescence. A variety of factors shown to contribute to these findings are listed above. IL-6: interleukin-6, CRP: C-reactive protein, RAAS: renin-angiotensin-aldosterone system, EPO: erythropoietin, ADMA: asymmetric dimethylarginine.

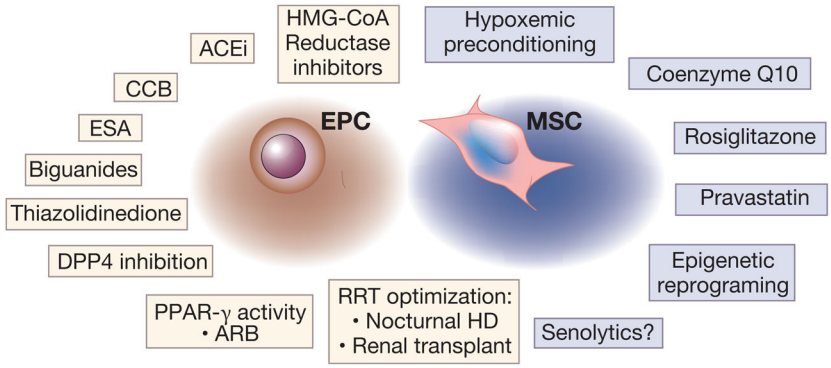

Figure 3.

Preconditioning treatments, pharmacological agents, and other interventions with potential to improve endothelial progenitor (EPC, highlighted in tan boxes) and mesenchymal stem cell (MSC, highlighted in blue boxes) function for stem cell transplantation in chronic kidney disease. Given the EPC and MSC dysfunction in varying disease states, several studies have examined the beneficial effects of drugs and interventions that increase their function and number.

HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme-A, ACEi: angiotensin-converting enzyme inhibitors, CCB: calcium channel blockers, ESA: erythropoietin stimulating agent, DPP4: dipeptidyl peptidase-4 inhibitors, PPAR: peroxisome proliferator-activated-receptor, ARB: angiotensin-2 receptor blockers. RRT: renal replacement therapy

Table

Endothelial progenitor (EPC) and mesenchymal stem cell (MSC) studies in human subjects with chronic kidney disease (CKD)

Reference	Publication year	Primary aim	CKD-Dialysis Group	Demographics	Age group
Bahlmann et al.[71]	2003	Effect of darbepoetin alfa on EPC differentiation, proliferation, and tube formation.	CKD	8 (5M, 3F)	Adult
Bahlmann et al.[89]	2004	Effect of erythropoietin on EPC mobilization and tube formation.	CKD	11 (6M, 5F)	Adult
Chan et al. (a)[48]	2005	Effect of uremic clearance by NHD on EPC number and migratory function vs. CHD.	Dialysis-CHD	12 (8M, 4F)	Adult
Chan et al. (b)	2005	Effect of uremic clearance by NHD on EPC number and migratory function vs. CHD	Dialysis-NHD	10 (7M, 3F)	Adult
Chen et al. (a)[45]	2013	Relationship between CKD severity and EPC number.	CKD	121 (combined:100M, 66F)	Adult
Chen et al. (b)	2013	Relationship between CKD severity and EPC number.	Dialysis-?	45 (combined:100M, 66F)	Adult
Choi et al.[72]	2004	Relationship between CHD and EPC number, migratory function, tube formation.	Dialysis-CHD	44 (44M,0F)	Adult
deGroot et al. (a)[74]	2004	Relationship of uremia and EPC number, differentiation, tube formation, migration.	CKD	46 (29M, 17F)	Adult
deGroot et al (b)	2004	Relationship of uremia and EPC number, differentiation, tube formation, migration.	Dialysis-CHD	6 (5M, 1F)	Adult
de Groot et al. (a)[73]	2005	Relationship between kidney transplant function, and EPC number and differentiation.	Kidney Transplant	74 (46M, 28F)	Adult
de Groot et al. (b)	2005	Relationship between kidney transplant function, and EPC number and differentiation.	CKD	29 (19M, 10F)	Adult
Eizawa et al.[75]	2003	Relationship between CHD and EPC number.	Dialysis CHD	50 (35M, 15F)	Adult
Herbrig et al.[70]	2004	Relationship between CHD and EPC number and migratory function.	Dialysis-CHD	20 (14M, 6F)	Adult
Herbrig et al.[88]	2006	Effect of uremic clearance after KTx on EPC number and migratory function.	Dialysis-CHD and PD transition to KTx	20 (10M, 10F)	Adult
Jie et al.[77]	2010	Relationship between CKD and EPC number and migratory function.	CKD	49 (22M, 27F)	Adult
Jie et al. (a)[76]	2010	Relationship between CKD, CHD and EPC number and migratory function.	Dialysis Peds	13 (9M, 3F)	Pediatric
Jie et al. (b)	2010	Relationship between CKD, CHD and EPC number and migratory function.	CKD Peds	15 (9M, 6F)	Pediatric
Jourde-Chiche et al.[78]	2009	Relationship between CHD and EPC number.	Dialysis-CHD	38 (20M, 18F)	Adult

Reference	Publication year	Primary aim	CKD-Dialysis Group	Demographics	Age group
Kohagura K. et al.[79]	2008	Relationship of recombinant human erythropoietin dose in CHD and EPC number.	Dialysis CHD	35 (18M, 17F)	Adult
Krenning et. al. (a)[80]	2009	Relationship between CKD, CHD and EPC number and proliferation.	CKD	30 (22M, 8F)	Adult
Krenning et. al. (b)	2009	Relationship between CKD, CHD and EPC number and proliferation.	Dialysis-CHD and PD	20 (16M, 4F)	Adult
Krieter et. al.[81]	2010	Effect of differing middle molecule removal in CHD on EPC number.	Dialysis-Low/high flux, HDF	18 (15M, 3F)	Adult
Manfredini et al.[165]	2009	Effect of exercise in CHD patients on EPC number.	Dialysis-CHD	30 (20M, 10F)	Adult
Maruyama et al.[82]	2008	Relationship between EPC number in CHD with cardiovascular events and mortality.	Dialysis-CHD	216 (122M, 94F)	Adult
Park et al.[164]	2010	Effect of green tea consumption in CKD patients on EPC number.	Dialysis-?	40 (?M,?F)	Adult
Schlieper G et al.[83]	2008	Relationship between cardiovascular disease, CHD and EPC number and migration.	Dialysis CHD	65 (32M, 33F)	Adult
Steiner et al.[87]	2005	Relationship between PD and EPC number.	Dialysis-PD	38 (28M, 10F)	Adult
Ueno et al. (a)[84]	2010	Relationship between PD, HD and EPC number.	Dialysis-PD	67 (45M, 22F)	Adult
Ueno et al. (b)	2010	Relationship between PD, HD and EPC number.	Dialysis-HD	142 (104M, 38F)	Adult
Ueno et al.[46]	2011	Relationship between CHD and EPC number.	Dialysis-CHD	212 (127M, 85F)	Adult
Westerweel et al.[85]	2007	Relationship between CHD and EPC number and tube formation.	Dialysis CHD	45 (30M, 15F)	Adult
Zhao et al.[47]	2014	Relationship between CHD and EPC proliferation, migratory function, tube formation.	Dialysis-CHD	15 (9M, 6F)	Adult
Reinders et al.[91]	2013	Relationship between CKD5 and dialysis and MSC differentiation, proliferation, gene expression, cytokine and angiogenic factors, and immune suppression capacity.	Dialysis-PD, HD and CKD5	10 (7M, 3F)	Adult
Roemeling-van Rhijn et. al.[90]	2012	Relationship between PD, HD, CKD and MSC differentiation, proliferation, and immunomodulatory function.	Dialysis-PD, HD and CKD	16 (10M, 6F)	Adult
Yamanaka et. al.[92]	2014	Relationship between dialysis and MSC differentiation, proliferation, function, hypoxic response, angiogenesis activation, gene expression, and senescence.	Dialysis-?	9 (7M, 2F)	Adult

To illustrate varying subject enrollment, some references were divided into (a) and (b) groupings.

Abbreviations: CHD: conventional hemodialysis, NHD: nocturnal hemodialysis, PD: peritoneal dialysis, HDF: hemodiafiltration, KTx: Kidney transplantation; ?: unknown data (not provided by authors).

EPC number: generally refers to the circulating number of EPC