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Review

Endothelial progenitor cells participation in cardiovascular and kidney diseases: a systematic review

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Endothelial progenitor cells (EPCs) represent a small population of blood cells (5–40 cells/mm³), with an ability to differentiate into endothelial cells that form the lining of the blood vessels and contribute to postnatal angiogenesis. Abundant evidence shows that recruitment of EPCs from the bone marrow, the monocyte/macrophage lineage and the organs facilitate the endothelial regeneration and repair. Changes in the number of EPCs were observed in both, chronic kidney and cardiovascular diseases. Thus, these cells were tested for usage in diagnosis and therapy. In this paper, we review the current knowledge on the EPC biology and contribution of these cells to the kidney and cardiovascular diseases.

Key words: endothelial progenitor cells, chronic kidney diseases, cardiovascular diseases.

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INTRODUCTION

A single layer of squamous cells lining blood vessels, described as the endothelium, forms a natural barrier which separates blood and the connective tissue. Endothelial cells which build this layer are highly metabolically active, and play a critical role in many physiological processes, including the angiogenesis, hemodynamics, immunological reactions, control of the vasomotor tone, membrane permeability and trafficking of blood cells between blood and the underlying tissue (Aird *et al.,* 2012; Fig. 1A). Endothelial cells also form a selective barrier in the kidney. Capillaries of the glomerulus are highly fenestrated, with 50- to 80-nm pores (Maezawa *et al.,* 2015). These small blood vessels contribute to formation of the glomerular filtration barrier (Maezawa *et al.*, 2015); a functional integrity of the glomerular endothelium is needed to protect against vascular diseases. Endothelial exposure to destructive factors progresses towards reduction of renal glomerular endothelial barrier, a pro-inflammatory pattern, senescence, and apoptosis of the endothelial cells (Jourde-Chiche *et al.,* 2009). Moreover, the chronic kidney disease (CKD) increases endothelial activation and lesion, and decreases endothelial repair, leading to endothelial dysfunction (Jourde-Chiche *et al.,* 2009; Fig. 1B). However, repair processes can be conducted by circulating or resident progenitor cells (Hillebrands *et al.,* 2002) which may include endothelial progenitor cells (EPCs).

The EPCs represent a small population of blood cells with an ability to differentiate into endothelial cells and participate in the postnatal angiogenesis. They also contribute to the regeneration of endothelium in different diseases, including those with advanced kidney and cardiovascular disorders. CKD, defined as gradual loss of renal function, is highly proatherogenic and results in exposing patients to a very high cardiovascular morbidity. This in turn results in markedly increased cardiovascular (CVS) mortality, which is elevated from 30–60% in the early stages of CKD. In the end-stage renal disease (ESRD; patients that need dialysis or kidney transplantation), it may exceed by 10- to 80- fold the mortality observed in the general population (O'Hare *et al.,* 2007; Rifkin *et al.,* 2010; Dalrymple *et al.,* 2011). In this paper, we review recent data from experimental and clinical studies, investigating the potential of EPCs in the endothelial repair and contribution to cardiovascular disease (CVD), with special attention to patients with CKD.

EPCS BIOLOGY

Isolation, characterization, quantification

Low oxygen level and the presence of chemoattractant-like stromal cell-derived factor (SDF-1/CXCL12) present an excellent environment for EPCs in bone marrow (BM). EPCs dwell in stem cell niches and may be released into the circulation upon certain stimuli (Lin *et al.,* 2000). In the blood, the number of circulating EPCs

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Abbreviations: CKD, chronic kidney disease; EPCs, endothelial progenitor cells; CVS, cardiovascular; ESRD, end-stage renal disease; CVD, cardiovascular disease; SDF-1/CXCL12, chemoattractant-like stromal cell-derived factor; BM, bone marrow; vWF, von Willebrand factor; PBMCs, peripheral blood mononuclear cells; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor; *KDR,* kinase insert domain *receptor;* HUVEC, umbilical vascular endothelial cells; Dil-Ac-LDL, fluorescently-labeled low-density lipoprotein; UEA-1, *Ulex eurapaeus* agglutinin-1; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ADMA, asymmetric dimethyl-arginine; EPO, erythropoietin; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocking; GM-CSF, granulocyte/macrophage colony stimulating factor; SPC, smooth muscle progenitor cells; GFR, glomerular filtration rate; PLGF, placental growth factor; MCP-1, monocyte chemoattractant protein-1; IL1β, interleukin 1β; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; IAA, indole-3-acetic acid; β2m, β2-microglobulin; IL 8, interleukin 8; RAAS, renin-angiotensin-aldosterone system; CCA-IMT, common carotid artery intima-media thickness; CFU, colony forming units; IL 6, interleukin 6, hsCRP, high-sensitive C-reactive protein; PAI-1, plasminogen activator inhibitor; TNFα, tumor necrosis factor alpha; EMP, endothelial microparticles; AKI, acute kidney injury.

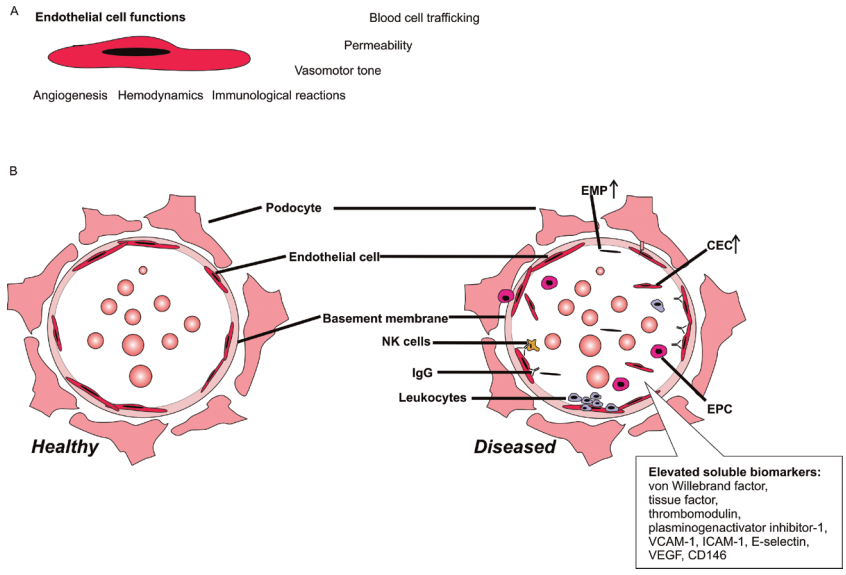

Figure 1. Endothelial cell functions (A) and endothelial glomerular barrier in a healthy and dysfunctional state (B).
Antibody-dependent cellular cytotoxicity and aggregates of leukocytes in the capillary lumen indicate microvascular inflammation (Sis *et al.,* 2012). Increased (↑) number of circulating endothelial microparticles (EMP), circulating endothelial cells (CEC) and soluble biomarkers secreted by activated endothelial cells are depicted (Jourde-Chiche *et al.,* 2011). Endothelial progenitor cells (EPC) were marked.

ranges between 5 and 40 cells/mm^3 (Vasa *et al.,* 2001). However, they can be also derived from the monocyte/macrophage lineage and migrate from the walls of aorta, arteries and veins of liver, prostate, heart, kidney, testes and lungs (Caplice & Doyle, 2005). They were detected in all tunica's of vascular wall (Goligorsky *et al.,* 2014).

In the first report, published in 1997, Asahara and coworkers (1997) had described BM-derived CD34$^+$/VEGFR-2$^+$ monocyte cell population collected from peripheral blood.

EPCs are distinguished based on the identification of CD34, VEGFR2 and CD133 surface markers (Urbich & Dimmeler, 2004; Fig. 2). The CD34 antigen is used to identify hematopoietic progenitors, while KDR/VEGFR2 expression on the EPCs surface suggests their ability to differentiate into endothelium (Urbich & Dimmeler, 2004). The CD133 antigen is typical for less matured EPCs (Urbich & Dimmeler, 2004). Other markers co-expressed on the EPCs surface that characterize their 'endothelial' potential include the von Willebrand factor (vWF), CD31 and CD144 (Urbich & Dimmeler, 2004). CD34$^-$/CD133$^+$/VEGFR-2$^+$, CD34$^+$/CD133$^+$/VEGFR-2$^+$ and CD34$^+$/CD133$^-$/VEGFR-2$^+$ cells represent defined subpopulations of EPCs (Friedrich *et al.,* 2006). Moreover, the CD34$^-$/CD133$^+$/VEGFR-2$^+$ cells are considered to be precursors of CD34$^+$/CD133$^+$/VEGFR-2$^+$ cells. The CD34$^-$/CD133$^+$ subpopulation has a much greater potential for regeneration than their mature form, and the cells representing this subpopulation are preferably recruited in such processes as ischemia and vascular injury in the unstable human coronary artery disease and experimental limb ischemia model (Friedrich *et al.,* 2006).

The differences in the EPCs number can clearly be noticed between men and women throughout different

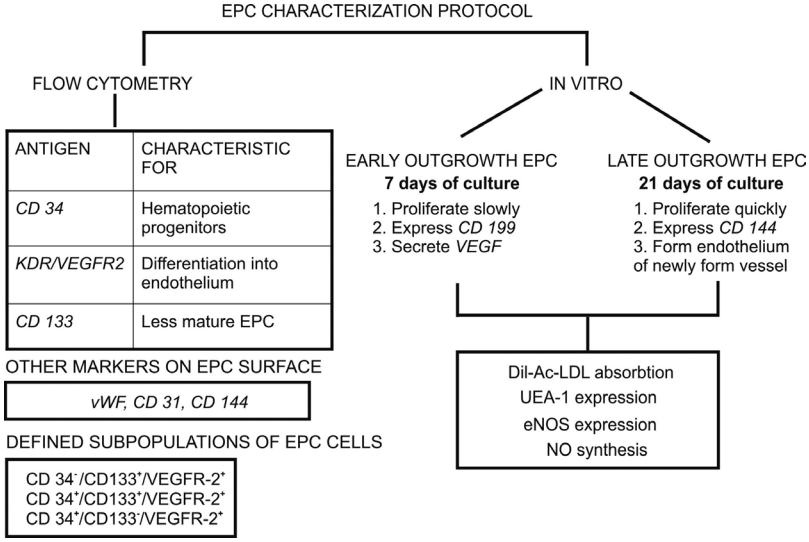

Figure 2. Scheme presenting methods of EPC isolation and characterization.
VEGFR, vascular endothelial growth factor receptor; Dil-Ac-LDL, fluorescently-labeled low-density lipoprotein; UEA-1, *Ulex eurapaeus* agglutinin-1 antigen; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

Table 1. Potential agents affecting EPCs recruitment and mobilization

	Factors	References
Activators		
Intrinsic factor/condition	Low oxygen level	Hoffmann *et al.,* 2013
	Mechanical endothelial damage	Werner *et al.,* 2003
	Ischemia	Takahashi *et al.,* 1999
	Physical exercise	Laufs *et al.,* 2004
	Cytokine release	Takahashi *et al.,* 1999
	VEGF	Xiao *et al.,* 2007
	Stromal-derived growth factor 1	Xiao *et al.,* 2007
	Granulocyte/macrophage colony stimulating factor	Xiao *et al.,* 2007
	Uric acid	Westerweel *et al.,* 2007
Drug	Angiotensin converting enzyme (ACE) inhibitors	Xiao *et al.,* 2007
	Angiotensin II receptor blocking agents (ARBs)	Yu *et al.,* 2008
	Erythropoietin	Bahlman *et al.,* 2004
	Insulin	Dong *et al.,* 2011
	Glitazones	Pistrosch *et al.,* 2005
	Statins	Dimmeler *et al.,* 2001; Xiao *et al.,* 2007
	Hormone replacement therapy	Xiao *et al.,* 2007
Inhibitors		
Intrinsic factor/condition	Age	Park *et al.,* 2014
	Reduced levels of high-density lipoprotein cholesterol	Park *et al.,* 2014
	Higher bone erosion scores	Park *et al.,* 2014
	Angiotensin II	Endtmann *et al.,* 2011
Drugs	Sirolimus	Banerjee *et al.,* 2012
	Paclitaxel	Banerjee *et al.,* 2012
	Cyclosporine A	Wang *et al.,* 2008
	Steroids	Bahlman *et al.,* 2010

periods of life (Fadini *et al.,* 2008). Xiao and coworkers (2007) demonstrated a significantly lower number of circulating EPCs in females, as compared to males at a corresponding age. Higher numbers of circulating EPCs were detected in fertile women as compared to men, however, no sex differences could be detected after menopause (Fadini *et al.,* 2008). As EPCs display alpha and beta forms of estrogen receptors, the numbers of EPCs change in the menstrual cycle phase- and estrogen-dependent manner. Moreover, it was shown that the EPCs participated more effectively in compensatory angiogenesis in women than in men (Fadini *et al.,* 2008).

Populations of EPCs can be also identified in *in vitro* cultures (Fig. 2). *Early-outgrowth* EPCs obtained from a fraction of peripheral blood mononuclear cells (PBMCs), separated from the whole blood with the Ficoll gradient method, appear after 7 days of culture (Ingram *et al.,* 2004). The cells proliferate slowly, express CD133 antigen and may secrete chemotactic, growth factor substances known to stimulate angiogenesis (vascular endothelial growth factor; VEGF; Ingram *et al.,* 2004). The EPCs that appear in the culture on about the 21st day (called the *late-outgrowth* EPCs) have a high proliferative potential, express CD144 antigen, can directly incorporate into endothelia of newly formed vessels and form tube-like structures when merged in culture with human umbilical vascular endothelial cells (HUVEC; Laschke *et al.,* 2011). Both, late- and early-outgrowth EPCs, absorb the modified, fluorescently-labeled low-density lipoprotein (Dil-Ac-LDL) and display the UEA-1 (*Ulex eurapaeus* agglutinin-1) antigen on their surfaces (Asahara *et al.,* 1997). Moreover, EPCs express endothelial nitric oxide synthase (eNOS) gene and protein, and synthesize nitric oxide (NO) upon *in vitro* stimulation with VEGF (Bahlman *et al.,* 2010). Asymmetric dimethyl-arginine (ADMA) significantly suppresses eNOS activity in cultured EPCs and this effect is abolished by statin (Thum *et al.,* 2005). Moreover, rosuvastatin, the statin with the highest potential to reduce LDL-cholesterol serum level, decreases ADMA levels in a culture and this effect is accompanied by enhanced colony forming potential of EPCs (Thum *et al.,* 2005). EPCs with impaired ability to form 'tube-like structures', when co-cultured with HUVEC, restore this function after addition of rosuvastatin (Thum *et al.,* 2005).

Mobilization, inflammation, recruitment

Several factors that mobilize the EPCs from bone marrow and/or vascular niches have been identified. Decrease in the level of oxygen (Hoffmann *et al.,* 2013), mechanical damage of endothelia (Werner *et al.,* 2003), ischemia (Takahashi *et al.,* 1999), physical exercise (Laufs *et al.,* 2004), cytokine release (Takahashi *et al.,* 1999), VEGF (Xiao *et al.,* 2007), erythropoietin (Epo; Bahlmann *et al.,* 2004), stromal derived growth factor 1 (SDF-1; Xiao *et al.,* 2007), granulocyte/macrophage colony stimulating factor (GM-CSF) (Xiao *et al.,* 2007) and variations in uric acid serum concentration (Westerweel *et al.,* 2007) are among the most important stimuli. Moreover, a potential to activate or suppress the mobilization and activation of EPCs has been also identified for several drugs (Table 1).

A normal number of circulating EPCs is considered as a marker of 'endothelial health' and regenerative potential of the endothelium. A high number of EPCs in peripheral blood may also indicate ongoing endothelial damage, transient restricted inflammatory response or persistent/excessive inflammatory stimulation. EPCs exposed to oxidative stress pass through mitochondrial disintegration, which results in DNA destabilization and telomeres' shortening (Satoh *et al.,* 2009; Giannotti *et al.,* 2010; Carracedo *et al.,* 2011). Upon challenge with the above mentioned initiators, EPCs move into the sites of inflammation and injury where they roll, adhere to the endothelial damaged area and contribute to endothelial repair (Vajkoczy *et al.,* 2003). It seems that no more than 1% to 20% of circulating EPCs has the potential to directly incorporate into an injured vascular wall (Urbich *et al.,* 2003). Fusion of EPCs with damaged, although still viable endothelial cells, has been also postulated but this mechanism appears unlikely to significantly contribute to the endothelial repair (Goligorsky *et al.,* 2010). Most probably, EPCs attracted to the neighborhood of a damaged epithelium exert their regenerative effect in a paracrine way, i.e. releasing substances that promote and enhance the repair processes (Goligorsky *et al.,* 2010).

EPCS IN THE CHRONIC KIDNEY DISEASE

In general, in many clinical studies, a decreased number of circulating EPCs was observed in patients with CKD. A marked reduction in the number of circulating $CD34^+$ EPCs in the blood, when compared to healthy controls, was observed in stages 1 and 2 of CKD (Krenning *et al.,* 2009). Moreover, the number of $CD34^+$ decreased with the disease progression (Krenning *et al.,* 2009). However, Jie and coworkers (2010) did not observed a correlation between the degree of kidney dysfunction, the cause of disease and the CKD stage. A significantly lower number of EPCs ($CD34^+/VEGFR\text{-}2^+$ cells), but not smooth muscle progenitor cells (SPC), was demonstrated in CKD patients, as compared with healthy controls (which was the lowest among patients with GFR < 30 mL/min/1.73m^2 and cardiovascular co-morbidity (Jie *et al.,* 2010)). A strong, inverse relationship between GFR and the number of circulating SPC was observed (Jie *et al.,* 2010).

ESRD and low serum albumin were the predictors for lower number of EPCs (Chen *et al.,* 2013). Patients with ESRD had higher number of late outgrowth EPCs which could directly participate in re-endothelialisation and new vessel formation (Zhao *et al.,* 2014). However, impairment of EPCs function in the course of CKD progression was observed *in vitro* with an increased thrombin production (Krenning *et al.,* 2009). In ESRD patients, the late outgrowth EPCs had higher proliferative potential in comparison to early outgrowth EPCs (Zhao *et al.,* 2014), and this correlated with angiogenesis factor like placental growth factor (PLGF), monocyte chemoattractant protein-1 (MCP-1) and interleukin 1β levels (IL1β; Zhao *et al.,* 2014).

Dialysis

Most of the studies on the role of EPCs in a renal disease were performed in patients with advanced CKD, i.e. in the pre-dialysis period and in those on dialysis. The number of EPCs was significantly lower among patients with ESRD on maintenance hemodialysis (HD), when compared to healthy controls (Jourde-Chiche *et al.,* 2011). HD patients were also characterized by a significantly lower number of EPCs in the blood that were CD34/VEGFR-2 double-positive and that had a potential to incorporate into endothelia (type 1 EPCs) under *in vitro* conditions. Type 2 EPCs derived from the HD subjects were characterized by a reduced potential to form cultures *in vitro* and had a decreased ability to produce angiogenic factors (VEGF) facilitating endothelial regeneration, than type 2 EPC derived from healthy control (Westerweel *et al.,* 2007).

Dialysis modality (continuous ambulatory peritoneal dialysis – CAPD and HD) also influences the number of circulating EPCs in patients with ESRD (Ueno *et al.,* 2010). CAPD patients were characterized with higher numbers of circulating EPCs when compared to subjects on HD, after gender adjustment (Ueno *et al.,* 2010). Associations were also found between the number of EPCs and dialysis adequacy, as well as erythropoietin administration. The higher the dose of dialysis (extended or daily HD) or EPO, the higher the level of EPCs was observed (Krenning *et al.,* 2009; Jourde-Chiche *et al.,* 2011). In HD patients, a lower number of EPCs could also be associated with accelerated atherosclerosis (Ueno *et al.,* 2010). Analysis of the association between EPCs and survival in the ESRD patients treated with HD revealed that CVS event-free survival and all-cause survival were prolonged in patients with a higher level of circulating progenitor cells ($CD34^+$; Maruyama *et al.,* 2008).

Uremic toxins are responsible for alterations in vascular progenitor cell differentiation, impaired endothelial regeneration and susceptibility to atherosclerosis (Westerweel *et al.,* 2007). Uremic toxicity adversely affected progenitor cells in the early stages of kidney dysfunction and in ESRD (Jie *et al.,* 2010). However, dialysis assisted removal of uremic toxins did not affect the EPCs number (Krieter *et al.,* 2010). In patients with sepsis and elevated serum creatinine, increased uric acid serum level had been identified as a strong stimulus of EPCs mobilization (Patschan *et al.,* 2011). However, the proliferative potential of EPCs was reduced in this disease setting independently from the creatinine level (Patschan *et al.,* 2011).

The number of $CD34^+/CD133^+$ progenitor cells negatively correlated with serum indole-3-acetic acid (IAA) and β2-microglobulin (β2m) levels (Jourde-Chiche *et al.,* 2011). Uremic serum containing IAA blocked the EPCs differentiation and functional activity *in vitro*, leading simultaneously to an increased apoptosis of cultured EPCs (de Groot *et al.,* 2004; Jourde-Chiche *et al.,* 2011). In HD patients who developed ESRD as the result of chronic glomerulonephritis, hypertensive nephropathy or diabetic kidney disease, the serum levels of IL-8 and SDF-1 were increased when compared to healthy volunteers (Ribeiro

et al., 2014). After an *in vitro* exposure of endothelial cells harvested from the HD patients to uremic toxins, the cellular expression of SDF-1 decreased, while the expression of IL-8 was increased (Ribeiro *et al.,* 2014).

Kidney transplantation

Successful kidney transplantation leads to an increase in $CD34^+/VEGFR2^+$ and $CD133^+/VEGFR2^+$ cell numbers in the blood (Herbrig *et al.,* 2006; Di Marco *et al.,* 2011), and renal graft functions positively correlated with the number of circulating EPCs (de Groot *et al.,* 2005). Kidney transplant recipients were characterized with a higher number of circulating EPCs, when compared to the gender and aged-matched hypertensive subjects with preserved renal function. In renal transplant patients, no correlations were observed between the EPCs number and the use of statins or renin-angiotensin-aldosterone system (RAAS) blocking agents. Plasma SDF-1 level in patients with functioning renal graft was increased when compared to patients with an essential hypertension and normal kidney function (Di Marco *et al.,* 2011). Indices of endothelial dysfunction related to hyperemia were associated with a reduced EPCs number and an increased serum parathyroid hormone concentration (Fatini *et al.,* 2012).

EPCS IN CARDIOVASCULAR DISEASE

EPCs are considered to be promising biomarkers of cardiovascular health (Fadini *et al.,* 2008). However, some authors postulated that no correlation exists between EPCs subpopulations and remodeling of the arterial vessel wall (Sibal *et al.,* 2009), and that no direct link can be documented between changes in the EPCs number and development of CVD (Xiao *et al.,* 2007).

EPCs may protect against atherogenesis and their importance is greater when the process of vascular damage is ongoing (Xiao *et al.,* 2007; Fadini *et al.,* 2008). The number of EPCs was a strong and independent negative predictor of the presence of atherosclerotic plaque in the common carotid artery (Lau *et al.,* 2007; Fadini *et al.,* 2008). The number of $CD34^+/KDR^+$ cells was diminished with the presence and advancement of preclinical atherosclerosis and the risk factors constituted a reduction in aortic and femoral sites, but not in carotid circulation (Friedrich *et al.,* 2006).

A higher common carotid artery intima-media thickness (CCA-IMT), a higher ADMA level and a lower percentage of EPCs within the total peripheral blood monocyte population, when compared with healthy controls, were observed in patients with rheumatoid arthritis, the disease considered as highly proatherogenic (Surdacki *et al.,* 2007). Moreover, a low number of circulating $CD34^+/KDR^+$ cells and an increase in serum ADMA were predictors of the GFR loss in patients with a coronary artery disease (Surdacki *et al.,* 2010). The EPCs number was lower in patients on HD than in healthy controls, or in patients with coronary artery disease with preserved renal function (Schlieper *et al.,* 2008). There was no association between the EPCs number, and such parameters of vascular damage as an increased pulse wave velocity or advancement of coronary calcification (Schlieper *et al.,* 2008).

Men with a certain cardiovascular risk, but without clinically overt CVD, were characterized with inversed correlation between the number of EPCs colony forming units (CFU) in culture and the Framingham Risk Score, a well-documented clinical scale to assess the risk for development of the CVS disease (Hill *et al.,* 2003). The number of EPC-CFU was in turn positively associated with a change in the brachial artery reactivity in response to an increased blood flow, a parameter reflecting the function of endothelium (Hill *et al.,* 2003). When comparing patients with low, intermediate and high number of EPCs, those with the highest number of the mentioned cells were the healthiest (being younger, having lower total- and LDL- cholesterol, and lower prevalence of hypertension or diabetes; Hill *et al.,* 2003).

Hypertensive patients are at a higher risk for development of CKD (Hsu *et al.,* 2013). In patients with hypertension who developed microalbuminuria or macroalbuminuria, a decreased circulating EPCs number could be found; this finding may be associated with progression of atherosclerosis and a higher cardio-vascular risk (Huang *et al.,* 2010). In patients with atherosclerotic renal artery stenosis, who were on a limited sodium intake and were using an appropriate antihypertensive regimen, function of the circulating EPCs, sampled from the renal vein, was well preserved (Chen *et al.,* 2014). A unilateral renal artery stenosis which induced renovascular hypertension in the pig model, increased the EPCs migration, proliferation, potential for tube formation, and VEGF and eNOS expression *in vitro* (Zhu *et al.,* 2011). SDF-1 was demonstrated to attract EPCs to the sites of injury in the porcine model of renovascular hypertension (Zhu *et al.,* 2011). An increased expression of SDF-1, angiopoietin-1, Tie-2 and c-kit was detected in EPCs isolated from animals with experimental atherosclerotic renal artery stenosis (Chade *et al.,* 2010).

Diabetes still remains one of the most important risk factors for development of atherosclerosis. Patients with type 1 diabetes are characterized with a significantly elevated markers of chronic inflammation (i.e. interleukin 6 [IL 6], high-sensitive C-reactive protein [hsCRP], plasminogen activator inhibitor [PAI-1], and tumor necrosis factor alpha (TNFα; Lau *et al.,* 2007). This proinflammatory cytokine profile was shown to be associated with a significantly reduced number of the following EPCs: $CD133^+/VEGFR2^+$, $CD133^+/VE\text{-}cadherin^+$, $CD34^+$ and $CD133^+$ cells. The number of EPCs was also significantly decreased in patients with the history of stroke, when compared to healthy controls (Lau *et al.,* 2007). Post-ischemic brachial flow-mediated dilation, a measure of the preserved endothelial function, inversely correlated with the number of several subpopulations of EPCs, namely $CD34^+/VE\text{-}cadherin^+$, $CD133^+/VEGFR2^+$ and $CD34^+$ cells (Sibal *et al.,* 2009).

EPCS IN DIAGNOSIS AND THERAPY

The number of EPCs in the blood can be used as a factor for predicting the patients' outcome. It can be considered as a marker of active non-specific inflammation, corresponding to endogenous vascular repair capacity in the presence of an endothelial injury (Schmidt-Lucke *et al.,* 2005). Dysfunctional EPCs may result in an impaired ability to repair the endothelial damage (Schmidt-Lucke *et al.,* 2005). Association between "endothelial health", as reflected by the circulating EPCs and CCA-IMT, may illustrate the usefulness of the EPCs assessment in diagnosis and monitoring of atherosclerosis (Fadini *et al.,* 2006; Friedrich *et al.,* 2006; Lau *et al.,* 2007; Xiao *et al.,* 2007).

Reduction of $CD34^+/KDR^+$ cells to below 0.0038% of the total circulating peripheral blood mononuclear cells (PBMC) was associated with a 6-fold higher

risk for development of CVS, event over a 20-month follow-up period (Schmidt-Lucke *et al.,* 2005). In the group of 587 patients with angiography-proven coronary artery disease, those with the highest likelihood to remain event-free (mortality and combined endpoint comprising of myocardial infarction, hospitalization, a need for coronary revascularization procedure) were characterized with the highest level of EPCs (Werner *et al.,* 2005). However, assessment of the circulating EPCs number failed to predict death caused by an acute myocardial infarction or stroke (Werner *et al.,* 2005).

Vesiculation of the membrane of endothelial cells that are damaged or undergo apoptosis, leads to the formation of endothelial microparticles (EMP), which have an important modulatory role in inflammation, coagulation, and vascular function. The higher EMP/EPC ratio in patients with hypertension was related to the risk of GFR loss (Hsu *et al.,* 2013). Thus, therapies aimed at increasing the circulating EPCs number may have potential usefulness in preventing progression of the hypertensive kidney disease (Hsu *et al.,* 2013). Moreover, assessing longitudinal changes in the EMP/EPC ratio may become a biomarker allowing prediction of the CKD progression.

The improvement of 'local' and 'systemic' parameters reflecting the kidney function were observed during sepsis and adriamycin-induced acute kidney injury (AKI) following intrarenal transplantation of the EPCs embedded within hyaluronic acid hydrogels (Ratliff & Goligorsky, 2013). Such a procedure improved cortical and medullary microcirculation, reduced proteinuria, decreased serum creatinine and ameliorated interstitial fibrosis (Ratliff & Goligorsky, 2013). In addition, blood pressure was stabilized and hepatic release of aminotransferases was reduced, while the release of anti-inflammatory and pro-angiogenic molecules was enhanced (Ratliff & Goligorsky, 2013).

It seems likely that the fate of different progenitor cells is not fully determined even after releasing from the bone marrow, and under certain conditions these cells can change their phenotype into 'regenerative' or may alternatively contribute to the further damage of the vascular wall (Westerweel *et al.,* 2007). Intrarenal infusion of autologous EPCs led to a new vessel formation, mainly in the outer renal cortex (Chade *et al.,* 2010). Liang and coworkers found that injection of EPCs derived from a human Wharton's jelly, into the renal sub-capsular region, resulted in improvement in renal microcirculation, reduced the number of apoptotic cells and decreased expression of certain inflammatory cytokines (macrophage inflammatory protein-2 and keratinocyte-derived cytokine; Liang *et al.,* 2014). Acute kidney injury was characterized with a reduction in renal capillary density which may lead to the development of renal fibrosis (Liang *et al.,* 2014). Thus, transplantation of human Wharton's jelly-derived EPCs into renal sub-capsular space may be considered as a powerful therapeutic method for recovery of microvascular function which was shown in mice (Liang *et al.,* 2014). However, establishing of an effective route of cell delivery into the diseased kidney in humans still remains a challenge (Liang *et al.,* 2014).

The bulk of data clearly shows that measuring the circulating EPCs level may provide a clinically useful insight into the present status of endothelia, although the interpretation and real clinical significance of these findings still remain the matters of debate.

SUMMARY

Taken together, EPCs participate and play an important role in both, cardiovascular and kidney disease. However, the question about their structural and functional homogeneity, regenerative potential, significance, and therapeutic use still remains opened. Larger clinical studies with long-term follow-up and with implementation of objective methods of EPC effect quantification are needed to confirm significance of the EPCs in therapy.

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Conflict of interest

All of the authors have declared no competing interests.

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