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Review article: Endothelial progenitor cells in renal disease

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Summary

This brief overview is intended to provide basic information about endothelial progenitors, their definition and consensus markers used for their detection, describe the pathways of their mobilization and homing and highlight the mechanisms and manifestations of their incompetence that occurs in some chronic kidney diseases. Discussion is geared towards the potential role of endothelial progenitor cells in organ regeneration, in particular, in kidney regeneration. The concept we attempted to promote attributes to the incompetence of endothelial progenitor cells in failed regeneration and ensuing progression of chronic kidney disease. This field of inquiry remains insufficiently explored, especially in renal diseases. Promising areas for future exploration are emphasized.

Keywords

stem cell mobilization; engraftment; tissue regeneration

The concept of restoration of vascular supply to damaged or ischaemic organs for accelerating their regeneration is well-established. One therapeutic strategy based on this concept is the delivery of angiogenic factors. This has not resulted so far in substantial improvement of regeneration.[1] Therapeutic transplantation of stem and progenitor cells has become an important alternative strategy aiming at organ revascularization and regeneration.[2] There is controversial evidence in support of transplantation of bone marrow-derived stem cells (BMDC) for regenerative medicine both in heart,[3] peripheral vascular[4] and kidney disease.[5] It has been reported that in kidney disease in animals and in humans with gender-mismatched bone marrow or kidney transplants, circulating stem cells had frequently engrafted the kidney.[6–9] Hematopoietic stem cells isolated from male Rosa26 mice (expressing β-galactosidase) and transplanted into female wild-type animals subjected to renal ischaemia were detected in renal tubules of recipients 4 weeks after the transplantation y.[10] Yet, the cyclophosphamide and granulocyte colony-stimulating factor (G-CSF)-induced mobilization of endogenous hematopoietic stem cells (HSC) in the mouse renal ischaemia model resulted in the worsening of renal failure, allegedly because of the induction of granulocytosis.[11] Direct regenerative role of BMDC was seriously questioned in two publications finding negligible if any engraftment of these cells to the damaged kidney,[12,13] in fact echoing previously published similar studies in the heart. Moreover, most clinical studies performed by cardiologists using BMDC have shown at best a modest improvement of myocardial function attributable to the paracrine secretion of cytokines and growth factors, as well as improved micro-circulation.[3] There is,

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therefore, growing tendency to reconsider the strategy and use certain subpopulations of stem cells, especially endothelial progenitor cells (EPC) for the purposes of transplantation in myocardial infarction, limb ischaemia and for endothelialization of vascular grafts. This is also the case with some kidney diseases, as demonstrated in our previous studies for acute kidney injury.[5,14] This brief review will focus on EPC in renal disease.

Definition and Consensus Markers

The exact nature of EPC still needs to be elucidated, and there is an ongoing debate whether these cells represent a structurally and functionally homogeneous population.[15] Although the bone marrow has been shown to be a principal source of EPC, it is probably not the only one, as stem/progenitor cells with endothelial cell-like properties have been isolated from different tissues including peripheral blood, adipose and cardiac muscle tissue.[16] The sources of EPC are many, including, in addition to Sca^+ bone marrow hemangioblasts and side-population $CD34^-$ cells, many tissue-resident (e.g. adventitial, skeletal muscle, adipose tissue, spleen and so on) progenitors and circulating peripheral blood vascular endothelial growth factor (VEGF)-$R2^+$, $CD34^+$-mononuclear cells (review in[17]). Hence, the current view is that EPC are a heterogeneous group, which by latest count originates from HSC or their angioblastic subpopulation and mesenchymal stem cells (MSC). By convention, in the bone marrow these cells are characterized by the combination of surface markers such as CD34, VEGF-R2 (Flk-1) and an early marker CD133; moreover, in the blood they may express markers of HSC, c-kit and Sca-1. Upon further differentiation, these cells loose CD133 and acquire VE cadherin and von Willebrand factor.[18]

Mobilization

Mobilization of EPC from their respective niches can be triggered by mechanical injury and ischaemic stress through generation of hypoxia-inducible factor-1-regulated release of VEGF, erythropoietin and stromal cell-derived factor-1 (SDF-1), as well as by placental growth factor (PlGF), granulocyte- and granulocyte-macrophage colony-stimulating factors.[19–23] A number of investigators have addressed the question whether EPC can be efficiently delivered to areas of tissue ischaemia to preserve or restore end-organ function by participating in vasculogenesis. In a model of myocardial infarction in bone marrow-transplanted mice, histological analysis showed donor-derived endothelial cells in areas of neovascularization at the border zone of the infarct or reduced neointimal formation after vascular injury.[24,25] These experimental data have been strongly supported by clinical observations. Adams *et al.* found increased levels of circulating EPC in patients with coronary artery disease after exercise-induced myocardial ischaemia.[26] Lambiase *et al.* showed an inverse correlation between the density of coronary collaterals and numbers of peripheral EPC in coronary artery disease.[27]

Pharmacological mobilization of EPC can be achieved by using statins, VEGF, erythropoietin, angiotensin-converting enzyme inhibitors and oestrogens.[28–32] Each of these medications has side-effects; therefore, the search for endogenous signalling pathways leading to mobilization of EPC is so critically important.

Ischaemia is one of the potent signals to mobilize EPC; this has been unequivocally documented in humans and in experimental animals with myocardial ischaemia, ischaemic stroke and renal ischaemia.[26,33–37] Despite the apparent universality of this response to ischaemic insult, the precise molecular mechanisms responsible for it remain uncertain.

Mobilization of stem and progenitor cells from the bone marrow depends on the local bone marrow microenvironment or stem cell niche, consisting of endothelial cells and fibroblasts osteoblasts. Mobilizing factors interfere with the interaction between hematopoietic and bone marrow stromal cells through release of proteinases such as elastase, cathepsin G and matrix

metalloproteinases (MMP). EPC mobilization by VEGF, SDF-1 and PlGF has been shown to be dependent of MMP-9-mediated Kit ligand (stem cell factor) processing.[22,38] Endothelial nitric oxide synthase (eNOS) has also been shown to be essential for EPC mobilization in response to VEGF, statins, exercise and oestrogen.[39,40]

What are stress (SOS) signalling molecules discharged from the ischaemic tissue that are capable of downstream mobilization and recruitment of stem and EPC? Uric acid, one of the prototypical alarm signals activating the innate immune system, exhibits a short-lived surge after ischaemia/reperfusion injury. Previous studies demonstrated that exogenous uric acid leads to a rapid mobilization of EPC and HSC and protection of the kidney against ischaemic injury. We have recently demonstrated[41] that monosodium urate (MSU) *in vitro* and *in vivo* resulted in exocytosis of Weibel-Palade bodies with the release of interleukin-8, von Willebrand factor and angiopoietin-2 into the culture medium and circulation, respectively. Confocal and immunoelectron microscopy of mouse aortic endothelial cells demonstrated depletion of immunodetectable von Willebrand factor after injection of MSU, thus confirming the exocytosis of Weibel-Palade bodies. Angiopoietin-2 alone partially reproduced the action of MSU in that it mobilized HSC and depleted splenic EPC niche. In addition, angiopoietin-2 afforded functional nephroprotection from ischaemia. In Toll-like receptor-4 deficient mice, acute elevation of uric acid level by injection of MSU did not result in the release of von Willebrand factor and angiopoietin-2 to the circulation, suggesting that the effect of uric acid on exocytosis of Weibel-Palade bodies was mediated via this receptor. The release of interleukin-8 in response to elevated uric acid level required both Toll-like receptors-2 and 4. These findings outline a novel paradigm linking post-ischaemic repair and inflammation via the release of the constituents of Weibel-Palade bodies and further broaden the spectrum of alarm signalling to establish constituents of Weibel-Palade bodies as potential second messengers not only for pro-inflammatory responses but also for mobilization of stem cells.

Interactions between HSC and stromal cells (aka MSC) are mediated in part through α4β1 (VLA4)/vascular cell adhesion molecule-1 (VCAM-1) interaction.[42,43] Inducible ablation of α4β1(VLA4) or conditional ablation of VCAM-1 are both associated with the enhancement of G-CSF-induced mobilization of HSC.[44–46] In our previous studies of monocyte-to-endothelial cell adhesion using atomic force microscopy we demonstrated the potency of cyclic arginine-glycine-aspartic acid (cRGD) peptide in inhibiting monocyte-endothelial cell interaction.[47] These data demonstrated that the target of this inhibition is interaction between α4β1(VLA4) and VCAM-1. Our most recent unpublished data (D Patschan *et al.*, 2009) demonstrate high potency of RGD peptide in mobilizing HSC. Its effect is comparable to that of stem cell factor.

Homing

Recruitment and engraftment of vascular progenitor cells to injured or ischaemic tissue is a multi-step process that includes adhesion of the bone marrow-derived cells to the endothelium, transendothelial migration, chemotaxis, matrix degradation and invasion and *in situ* differentiation.[48] Ability of circulating progenitors to differentiate towards endothelial or smooth muscle cell lineages has been furthered by studies of a parabiotic model in which a wild-type mouse and a transgenic mouse expressing green fluorescent protein (GFP) are conjoined subcutaneously via anastamosing circulations. Tanaka *et al.*[49] demonstrated that mechanical injury to femoral arteries of wild-type mice resulted within 4 weeks in a chimerism of cells comprising developing neointima: 15% and 31% of parabiotic partner-derived GFP-positive cells were detected in the intimal and medial layers, with some cells expressing α-smooth muscle actin, others CD31.

Tissue Regeneration

A landmark study on EPC and new vessel formation has provided an impetus for stem cell transplantation.[50] Human circulating $CD34^+$ cells were demonstrated to differentiate *in vitro* into cells with endothelial-like properties. Moreover, administration of the cells to athymic nude mice with hind limb ischaemia resulted in the integration of transplanted cells into capillary vessels and improved collateral circulation. The idea that such cells derive from the HSC in the bone marrow has been strongly supported in the murine system where transplantation of a single HSC repopulated the bone marrow and the endothelium of retinal blood vessels following experimental retinal ischaemia.[51] Comparable results have been published by others.[52]

Comparatively less published information exists on EPC and endothelial regeneration in the kidney.[53] We observed a more than fourfold increase in the number of bone marrow-derived glomerular endothelial cells by day 7 after anti-Thy-1.1 injection to bone marrow-transplanted rats.[54] The participation of donor-derived cells in glomerular endothelial cell turnover has also been shown in bone marrow-transplanted rats with unilateral nephrectomy and anti-Thy-1.1 injection.[55]

Intrarenal administration of bone marrow-derived EPC reduced endothelial injury and mesangial activation in anti-Thy-1.1 glomerulonephritis.[56] Unselected BMDC infusion also ameliorated progressive glomerulosclerosis in an experimental rat model.[57] Both studies reported increased incorporation of BMDC in the glomerular microvasculature. In ischaemic or toxic acute renal failure, beneficial effects of bone marrow-derived HSC and of bone marrow-derived MSC infusion have been reported.[12,13,58–60] It was suggested that the paracrine capabilities of BMDC and their ability to differentiate into cells of endothelial phenotype rather than transdifferentiation into tubular cells may play a major role.[12,13,60–62]

Endothelial cell transplantation experiments were performed in our laboratory.[63] Injections of human umbilical vein endothelial cells to athymic nude rats subjected to renal artery clamping dramatically improved renal function. Chimeric cells expressing eNOS, thus mimicking one of the functions of endothelial cells, were also partially protective, although less than the mature endothelial cells. These studies were extended to stem cells derived from skeletal muscle of Tie-2/GFP mice, *ex vivo* expanded and differentiated to EPC, and injected to mice with acute renal ischaemia. This procedure was associated with a significant functional and structural preservation.[14]

The presence of regenerating stem and progenitor cells in the kidney itself was demonstrated in the renal papilla[64] and in the cortex.[65] We have recently identified a previously unknown putative stem/progenitor cell niche in the renal capsule.[66] Nestin-positive cells were immunodetected in the renal capsule, and FACS analysis of capsule-derived cells showed that they were $CD29^+$ (99%), $vimentin^+$ (97%), Sca-1 (86%) and $nestin^+$ (87%), but $CD31^-$, $CD34^-$, $Flk\text{-}1^-$, $CD150^-$ and $CD117^-$, identifying these cells as MSC. Long-term culture of capsular stem cells showed the capacity for self-renewal, and clonogenicity and ability to differentiate into different lineages. The population of renal capsular cells labelled *in situ* with CellTracker was monitored in time. In control kidneys, labelled cells were confined to the renal capsule and showed no migratory patterns. In contrast, acute renal ischaemia resulted in a time-dependent migration of capsular cells into the renal parenchyma. This migration reached the peak on day 3 after ischaemia. Migration distance in ischaemic kidneys ranged 81–4560 μm, and the capsular cells were preferentially homing to post-ischaemic perivascular space. Ki68 staining of the renal capsule obtained from mice pulse-chased with BrdU showed steady level of co-staining with anti-BrdU (ca 1.5%) with no increase in proliferation of BrdU-retaining cells after acute ischaemia. Using *in vitro* adhesion assay, we presented MSC to control and

post-ischaemic kidney sections. Results demonstrated increased binding of these cells to the renal capsule of ischaemic kidneys. In conclusion, these findings identify a novel niche for MSC, the renal capsule, and demonstrate that the capsular cells are migrating towards the sites of renal injury. Their functional contribution to tissue repair and regeneration remains unknown.

There is growing, albeit a somewhat conflicting, evidence that transplantation of stem and progenitor cells may substitute for the injured cells and improve regeneration of different injured organs, such as the myocardium, arterial wall, kidney, to name a few.[58,59,67] Alternatively, different investigators employed maneuvers to mobilize endogenous stem/(endothelial)progenitor cells – G-CSF, SDF-1, VEGF, PlGF, erythropoietin and others – for improved organ regeneration.[11] There is strong evidence demonstrating the presence of stem and progenitor cells at sites of injury even in the absence of any pharmacological stimulation of their mobilization suggesting that some intrinsic factors generated during organ damage may be responsible for their mobilization. Our studies provided evidence for ischaemia-induced mobilization of EPC.[5] In fact, there may even exist a 'dose–response' relation between the severity of injury and stem cell mobilization: increasing duration of renal ischaemia resulting in an increased mobilization of stem cells.[68]

EPC Incompetence In Chronic Kidney Disease (CKD)

Recent data indicate that BMDC may become incompetent in their ability to regenerate various tissues and organs.[69] Patients with cardiovascular risk factors such as essential hypertension, preeclampsia, smoking, aging, metabolic syndrome and type I and type II diabetes exhibit lower numbers of circulating EPC. Moreover, these EPC are dysfunctional, showing reduced migratory capacity in response to SDF-1, an impaired angiogenic function and enhanced cell senescence.[70–76] The reduced circulating EPC levels may be because of a negative effect of cardiovascular risk factors on mobilization. Diabetes has been shown to result in impaired bone marrow eNOS activation and hence reduced mobilization of EPC from bone marrow into circulation.[77] Our recent studies showed that BMDC in db/db mice are functionally incompetent, whereas BMDC from syngenic dbm mice significantly improved vasculopathy and insulin sensitivity in db/db recipients.[78] In patients with chronic renal insufficiency numbers of circulating EPC are almost 30% lower than in healthy controls.[79] EPC in CKD have also been shown to be dysfunctional.[80,81]

In human blood outgrowth of cells with a vascular smooth muscle/myofibroblast phenotype may occur, named circulating smooth muscle/myofibroblast progenitor cells (SPC).[82,83] We[84] and others[85] have shown that disease conditions such as diabetes or reduced NO activity may favour differentiation towards SPC over EPC, causing EPC/SPC imbalance and possibly altering the SPC towards a more profibrotic phenotype. In patients with end-stage renal disease we also observed EPC/SPC imbalance, compatible with impaired endogenous vascular repair but retained potential of progenitor cells to contribute to adverse remodelling.[86] Importantly, altered SPC function may induce adverse effects. For example, transplantation of bone marrow-derived mesangial cell progenitors obtained from a donor mouse with glomerulosclerosis caused the induction of glomerulosclerosis in the recipient.[87] Bone marrow-derived MSC transmitted diabetic nephropathy from diabetic donors to naïve recipients.[88] On the other hand, glomerulosclerotic lesions in aged mice were reversible by BMDC transplantation from young donors,[89] and in a mouse model of chronic, progressive renal fibrosis manipulation of BMDC by inhibition of the p38 mitogen-activated protein kinase and transforming growth factor β1/Smad signalling pathways led to structural and functional renal recovery and the attenuation of renal interstitial fibrosis.[90] These observations identify improving EPC/SPC balance and maintenance of their function as potential therapeutic goals.

In addition to the reduction in EPC numbers, the EPC/SPC imbalance and EPC dysfunction, impaired progenitor cell homing may occur in cardiovascular disease conditions. In aging and diabetes, impaired recruitment of normal stem and progenitor cells to injured tissue has been demonstrated, related to a diminished hypoxia response and reduced SDF-1 tissue levels.[77,91,92] In patients with coronary artery disease impaired interaction of SDF-1 with its receptor CXCR-4 on EPC has been reported to occur. Whether recruitment and homing of stem and progenitor cells is affected in CKD has not been reported.

Future Perspective: EPC-Based Therapy In CKD?

The importance of the renal microvasculature as a defence mechanism against progressive renal damage[93] and the recent observations that EPC may function as endogenous regenerating system of the (micro)vasculature suggest that EPC-based therapy represents a potential therapeutic option in renal disease. Such therapeutic strategies may include administration of autologous EPC after expansion or preconditioning but may also aim at enhancement of EPC mobilization, recruitment and homing as well as improving EPC/SPC balance and function. Ultimately this may lead to novel strategies enhancing the regenerative capacity of the kidney.

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