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Forum Review

Endothelial Progenitor Cell Dysfunction in Type 1 Diabetes: Another Consequence of Oxidative Stress?

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ABSTRACT

Endothelial progenitor cells (EPC) have been shown to contribute to neovascularization and vascular maintenance and repair in adults. Recently, the concept has evolved that EPC dysfunction, in patients at risk for cardiovascular disease, may contribute to the development of atherosclerosis and ischemic vascular disease. Particularly, patients with diabetes mellitus are likely to be affected by EPC dysfunction as several studies have shown a reduced number and function of EPC in patients, as well as in preclinical models for type 1 diabetes. Here, we review our current understanding of EPC (dys)function in diabetes and discuss some potential mechanisms underlying their altered properties. Moreover, we provide circumstantial evidence indicating that increased oxidative stress could play a role in the development of EPC dysfunction in type 1 diabetes. Finally, we discuss the potential implication of our findings for EPC-based therapies and the potential impact of pharmacological interventions on the vascular regenerative capacity of EPC. *Antioxid. Redox Signal.* 7, 1468–1475.

INTRODUCTION

TYPE 1 DIABETES is associated not only with microvascular complications (47), but also with premature atherosclerosis and a reduced capacity to form collateral vessels after an ischemic insult (37, 59). Likewise, patients with type 1 diabetes have an increased risk for the clinical consequences of these macrovascular manifestations, including myocardial infarction and peripheral vascular disease (28). Numerous studies have shown that dysfunction of the vascular endothelium plays a central role in the pathophysiology of these diseases (11). The metabolic abnormalities that characterize diabetes, particularly hyperglycemia, provoke molecular mechanisms that have a major impact on endothelial cell function and survival. Especially, activation of protein kinase C (PKC) and increased oxidative stress can lead to endothelial cell dysfunction. Moreover, prolonged exposure of endothelial cells to these adverse conditions increases endothelial cell apoptosis and turnover. Although adjacent mature endothelial cells have the capacity to proliferate and replace these dying cells, chronic exposure to oxidative stress has been shown to lead to premature replicative senescence and limit this form of endothelial repair (29, 46). Eventually, endothelial cell death and shedding may lead to disturbances of the endothelial monolayer, leaving a highly proatherogenic luminal surface (13, 62). Hence, the integrity of the endothelium and thus the atherogenicity of the vasculature are likely to be determined by the balance between endothelial turnover and repair (13). In recent years, it has become clear that bone marrow-derived endothelial progenitor cells (EPC) represent an additional cellular source of rejuvenation of the damaged endothelium. EPC have been shown in both animal models and humans to contribute to neovascularization and reendothelialization, indicating an essential role of these progenitor cells in the maintenance of endothelial integrity (56). Recently, a number of studies have suggested that the classical risk factors for atherosclerosis not only affect the mature endothelium, but also lead to EPC dysfunction (25, 58). This notion may not

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only contribute to our insight into the pathophysiology of atherosclerosis, but also have consequences for the use of progenitor cells in clinical protocols that use progenitor cell transplantation for the treatment of ischemic vascular disease. Here, we will review our current understanding of EPC dysfunction in type 1 diabetes. In particular, we will discuss the potential role of oxidative stress as an underlying cause of the dysfunction of these progenitors. Finally, we will address some potential approaches that may counteract EPC dysfunction in the clinical setting.

EPC: ORIGINS AND SPECIES

It is important to appreciate that the nature of the "true" circulating EPC is poorly defined. Different populations of EPC have been studied, each of which may have unique properties (40). In general, two types of EPC can be distinguished. First, circulating EPC (CEP), which can be recruited from the bone marrow, are characterized by the expression of the early hematopoietic stem cell markers CD34, CD133, and the vascular endothelial-cell growth factor receptor-2 (VEGFR2) (3, 38, 48). The EPC share these characteristics with hematopoietic stem cells, and CEP may function analogous to the embryonic hemangioblast, which can give rise to both circulating blood cell lineages and vascular cells (3, 15). Cultured with endothelial cell growth factors, purified CEP can differentiate into endothelial-like cells that display a classical endothelial cell morphology and characteristics like the expression of von Willebrand factor (vWF), vascular endothelial (VE) cadherin, and the capacity to take up acetylated low-density lipoprotein (acLDL). Although normally the number of CEP are limited, their levels can be markedly elevated within days after the administration of CEP-mobilizing agents (39) or secondary to vascular trauma (18) or tissue ischemia induced by myocardial infarction (33, 49).

Early support for a role of bone marrow-derived CEP in vascular repair in humans stems from the observation that the neointima formed on the surface of a left ventricular assist device accumulates a $CD133^+$ hematopoietic stem cell population that also expresses the endothelial cell marker VEGFR2 (38). In a mouse model, it was shown that bone marrow-derived CEP can home to denuded arterial vessels and contribute to reendothelialization. Interestingly, statin-induced mobilization of CEP was associated with an increased rate of reendothelialization and reduced neointimal thickening (60).

A second cell type that has been shown to be involved in vascular healing can be obtained by culturing peripheral blood mononuclear cells (PB-MNC) on gelatin or fibronectin for 4 days in endothelial cell differentiation medium. These attaching cells, which are also referred to as EPC, display a spindle-like morphology and also express endothelial cell markers like vWF, VEGFR2, and VE-cadherin and are usually characterized by the binding of endothelial specific lectins and the uptake of acLDL (40, 56) The large number of attaching cells that can be obtained from the PB-MNC cultures make it unlikely that all these cells are derived from the low number of circulating $CD34^+$ cells. Most likely, these EPC are derived from more abundant subpopulations present in the mononuclear cell (MNC) fraction like monocytes (16, 22, 41, 44). When human bone marrow-derived monocyte-lineage attaching cells were intraarterially transplanted into denuded arteries of athymic nude rats, they adhered to the injured endothelium, differentiated into endothelial-like cells, and inhibited neointimal hyperplasia (17). Likewise, transplantation of EPC cultured from PB-MNC in rabbits led to a rapid reendothelialization of balloon-injured carotid arteries and graft segments and, again, reduced neointima deposition (20). It is currently unclear whether the two types of EPC are related through shared developmental stages, *i.e.,* whether a monocyte-related intermediate is a required step in the differentiation of $CD34^+$ cells into EPC.

EPC DYSFUNCTION IN TYPE 1 DIABETES

From the above, it can be concluded that EPC of different hematopoietic lineages appear to play a crucial role in the maintenance of endothelial cell integrity in injured vessels and therefore may serve an important atheroprotective function. Following these insights, it was hypothesized that impaired EPC function would predispose to endothelial cell dysfunction and its clinical manifestations, including premature atherosclerosis and ischemic vascular disease. Seminal observations supporting this concept were reported by Vasa *et al.,* who demonstrated that the number and function of circulating EPC inversely correlated with risk factors for coronary artery disease (58). It was shown that this concept holds true both for CD34 and VEGFR2 double positive CEP and for PB-MNC-derived attaching EPC. Hill *et al.* extended this observation showing that, for patients at risk for cardiovascular disease, there was a strong inverse correlation between the number of endothelial cell colonies that could be grown out from PB-MNC cultures and the subjects' combined Framingham risk factor score (25). Moreover, measurements of flow-mediated brachial-artery reactivity revealed a significant relation between endothelial function and the number of progenitor cells. These reports again suggest that the quality of the endothelium may well be related to the endothelium-regenerative potential of circulating EPC.

Schatteman and colleagues were the first to report data supporting the concept of EPC dysfunction in streptozotocin-induced diabetic nude mice (43). Using an established model for neovascularization of the ischemic hindlimb, they demonstrated that, like shown before in nonobese diabetic mice (42), restoration of blood flow was significantly impaired in the diabetic mice. Whereas injection of human $CD34^+$ cells, purified from the PB-MNC fraction, did not accelerate the rate of neovascularization in the healthy controls, it markedly enhanced blood-flow restoration in the diabetic mice (53). When labeled, the $CD34^+$ cells were found to incorporate in the vasculature of the previously ischemic tissue. It was concluded that in the diabetic mice the EPC function was deficient and that this could be corrected by transplantation of exogenous human $CD34^+$ cells. These data indirectly provided evidence for deficient EPC function in experimentally diabetic mice and initiated subsequent studies to investigate the nature of the EPC dysfunction.

Diabetes-associated metabolic factors may affect EPC function at several levels, including the number of available

progenitor cells with capacity to differentiate into cells of the endothelial cell lineage, their capability to adhere and migrate to sites of reendothelialization and neovascularization, and their proangiogenic (paracrine) potential.

Effect on the number of EPC

In the study by Schatteman *et al.,* it was shown that, although the absolute numbers of $CD34^+$ cells isolated from peripheral blood from control subjects and type 1 diabetes patients did not differ significantly, the number of endothelial-like cells that formed *in vitro* from the patient $CD34^+$ cell fraction was reduced over threefold compared with that from the nondiabetic controls (43). In this study, a similar analysis for type 2 diabetic patients failed to show different yields in $CD34^+$ derived EPC. However, Tepper *et al.* reported that when attaching cells were cultured from PB-MNC from human type 2 diabetics and age-matched control subjects, the number of cells obtained from the patients was 48% percent lower than from healthy volunteers (55). Likewise, we demonstrated that the number of attaching cells cultured from type 1 diabetic patients was reduced almost twofold compared with that from age and gender-matched control subjects (31). In both studies, this reduction was inversely related to the levels of HbA_{1C}, demonstrating that the degree of glycemic dysregulation is associated with EPC phenotype or differentiation. The most pronounced reduction of EPC numbers also was observed in a study using streptozotocin-induced diabetic mice (53). It was found that the number of attaching cells cultured on vitronectin from bone marrow mononuclear cells (BM-MNC) of diabetic mice with femoral artery ligatures was fivefold lower than that of control mice.

Hence, in diabetes there appears to be a reduced number of cells in mononuclear cell (MNC) fractions that can differentiate into EPC *in vitro*.

Effect on the function of EPC

EPC from a diabetic background have been studied for properties that are thought to be required for proper EPC function. *In vitro,* functions like adhesion to endothelial cells (55), incorporation into endothelial tubular structures (55), and paracrine release of proangiogenic factors (31) were assessed, and in each reported study these functions appeared significantly impaired in cells obtained from a diabetic background. As attaching EPC may be closely related to monocytes or macrophages, these results may not come as a surprise as the response of monocytes to growth factors is also impaired in diabetic patients (59).

Two reports directly assessed the function of "diabetic" progenitor cells in neovascularization in an *in vivo* model. One study investigated the effect of type 2 diabetes on the potential of exogenous stem cells to promote skin wound vascularization and healing (51). Bone marrow stem cells from nondiabetic and diabetic $Lepr^{db}$ mice were injected underneath experimentally induced skin wounds. It was shown that, in contrast to nondiabetic stem cells, diabetic stem cell-containing fractions not only failed to enhance, but also even inhibited, wound vascularization. A second study reported that transplanted diabetic EPC, obtained from BM-MNC fractions of streptozotocin-induced mice, were markedly impaired in their capacity to enhance ischemia-induced neovascularization assessed by the ischemic/nonischemic angiographic score, capillary number, and blood flow recovery. Taken together, evidence is accumulating that, in diabetes, the number and function of EPC pools are reduced and therefore may be involved in the pathogenesis of both vascular complications.

POTENTIAL ROLE OF OXIDATIVE STRESS IN EPC DYSFUNCTION IN DIABETES

Then what molecular mechanisms may cause this reduction in EPC capacity in diabetes? It is clear that the answer to this simple question will be complex and dependent on the particular risk factors present and type of diabetes that affects individual patients. In type 1 diabetes, chronic hyperglycemia appears to be the major initiator of vascular complications through the increased production of reactive oxygen species (ROS) by the vascular endothelium (6, 11). Endothelial cells are particularly sensitive to hyperglycemia as they, unlike most cell types, are not capable of down-regulating glucose uptake in high ambient glucose concentrations (26). Hyperglycemia can lead to elevated ROS production in the endothelial cells via a number of enzymatic systems, including the mitochondrial electron transport chain, activation of NADPH oxidase, and uncoupling of endothelial nitric oxide synthase (eNOS) (21). Although the endothelial cells are equipped with potent antioxidant systems, sustained production of ROS in chronic hyperglycemia can exhaust these protective mechanisms and lead to a state of "oxidative stress" (4). This condition is associated with endothelial cell dysfunction, a proinflammatory endothelial phenotype that is characterized by a reduced bioavailability of nitric oxide (NO).

Oxidative stress and EPC mobilization

Another landmark study performed in the laboratory of Stephanie Dimmeler provided a possible explanation for the reduced mobilization of EPC in patients with cardiovascular disease (1). Using eNOS knockout mice, they demonstated that NO expressed by bone marrow stromal cells plays an essential role in vascular endothelial growth factor (VEGF)-induced mobilization of CEP ($CD34^+/VEGFR2^+$) from the bone marrow stroma to the vascular compartment. As endothelial cell dysfunction and impaired NO bioavailability are the hallmark of most cardiovascular risk factors, these data support the hypothesis that CEP mobilization is impaired secondary to oxidative stress. Hyperglycemia also decreases endothelium-derived NO both *in vitro* (11) and during hyperglycemic clamping in healthy subjects (61). It therefore seems likely that also in diabetes a reduced bioavailability of NO in the bone marrow stroma is involved in the reduced mobilization of EPC.

Oxidative stress and EPC function

Given the central role of oxidative stress in type 1 diabetes, oxidative stress or altered redox signaling may also directly affect the survival, differentiation, and function of EPC. Although little data on CEP function have been re-

ported, a number of articles may provide indirect evidence for a role of redox signaling in the fate and function of MNC-derived EPC (attaching cells). Given the fact that these cells are thought to function in sites of ischemia or reperfused tissue that can be characterized as an inflammatory, high oxidative stress environment (40), Dernberg *et al.* investigated the antioxidative systems of cultured EPC (12). They demonstrated that, compared with mature human umbilical vein endothelial cells (HUVEC), EPC exhibited a significantly lower basal ROS concentration and a relative high expression of the intracellular antioxidative enzymes catalase, glutathione peroxidase, and manganese superoxide dismutase (MnSOD). Incubation of HUVEC with hydrogen peroxide (H_2O_2) increased ROS production up to fourfold and induced apoptosis. In contrast, H_2O_2 hardly affected ROS production and apoptosis in the EPC, demonstrating that EPC display a reduced sensitivity toward ROS-induced cell death. Combined inhibition of the antioxidant enzymes increased ROS levels in the EPC and impaired EPC survival and migration. He *et al.* demonstrated a critical role for MnSOD in protecting EPC from cytotoxicity induced by the naphthoquinolinedione LY83583, a generator of intracellular superoxide (23). LY83583 inhibited *in vitro* tube formation by mature endothelial cells, but not by EPC. These data suggest that although EPC are relatively resistant to oxidant stress, elevation of ROS production *can* affect survival and function, most likely by affecting redox-sensitive signaling pathways, such as the nuclear factor-κB (NF-κB) pathway (50).

Potential mechanisms of diabetes-associated ROS production by EPC

The question remains how in a diabetic environment oxidative stress would be elevated in these EPC. It is unclear to what extent mechanisms that are known to function in mature endothelial cells can be translated to EPC. For instance, can cultured EPC take up glucose in the same apparently "uncontrolled" way as mature endothelial cells (26)? Nevertheless, hyperglycemia induced activation of PKC, and its downstream effects on, *e.g.,* activation of NADPH oxidase, could be a potential mechanism for elevation of ROS in EPC. Also, hyperglycemia-associated formation of extracellular and intracellular advanced glycation end products (AGE) may affect the redox state of the cells. AGE are the products of nonenzymatic glycation/oxidation of proteins and lipids and have been regarded as one of the main mechanisms responsible for vascular damage in patients with diabetes (5). It was shown that, in streptozotocin-treated diabetic mice, blockade of AGE formation restores ischemia-induced angiogenesis (52). AGE are signal transduction ligands for receptor for AGE (RAGE) that, upon AGE binding, trigger the generation of ROS and the proinflammatory NF-κB pathway via activation of NADPH oxidase (63). RAGE is present on monocytes (45) and also EPC cultures from PB-MNC (unpublished data from our laboratory).

As hyperglycemia in type 1 diabetes is associated with activation of the renin–angiotensin system (35), angiotensin II signaling could comprise a third route to ROS production in EPC. Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that is used to reduce renin–angiotensin–aldosterone system activation in patients with stable coronary artery disease. A recent study showed that increased numbers of EPC could be cultured from ramipril-treated patients with stable coronary artery disease and that the ACE inhibition resulted in improved functional properties like adhesion, proliferation, migration, and an *in vitro* vasculogenesis assay (36). These results show that EPC are sensitive to angiotensin II signaling and that this could indeed impact on number and function.

EPC from type 1 diabetes patients up-regulate genes associated with oxidative stress

To investigate further whether EPC in type 1 diabetes are altered in function due to the adverse metabolic environment, we analyzed whether changes in gene expression could be observed between the patient and control EPC. Therefore, we compared the gene expression profiles of pooled RNA isolated from cultured EPC obtained from five type 1 diabetes patients (age 34.2 ± 10 years) and five age- and gender-matched controls (age 33.9 ± 7.7 years) using Affymetrix high-density oligonucleotide microarray analysis. In the diabetic EPC, out of 12,600 gene transcripts tested, we observed significant up- and down-regulation of 472 and 360 genes, respectively. Among the major differentially expressed genes, we observed a striking number of genes that have been reported to be associated with diabetes mellitus in general, with hyperglycemia, oxidative stress, or AGEs, both in a clinical setting [*e.g.,* osteopontin (9), plasminogen activator inhibitor 1 (32), thrombomodulin (7), and type IV collagen (19)] and in animal models [matrix metalloproteinase 1 (54), lectin-like oxidized LDL receptor (8), fructose-1,6,-biphosphatase (2), and GTP cyclohydrolase I (34)] (Table 1). Our data demonstrate that EPC function as "biosensors," translating metabolic cues into altered gene expression, and support the hypothesis that dysfunction of the EPC in type 1 diabetes may be secondary to elevated oxidative stress.

CONCLUSIONS AND IMPLICATIONS

Recent data show that the vascular regenerative potential of patients with diabetes may be impaired as a consequence of reduced number and function of circulating progenitor cells that can support endothelial maintenance and ischemia-induced neovascularization. Although direct evidence is lacking, indirect evidence supports a role for oxidative stress in the diabetes-associated EPC dysfunction. Notably, our DNA microarray analysis suggests that EPC cultured from the PB-MNC fraction from type 1 diabetes patients display a proinflammatory phenotype. The implication of these findings is that autologous transplantation of progenitor cells that are affected by risk factors, such as high glucose, may not only be hampered by a dysfunctional nature of these cells (24) but in fact may stimulate proatherogenic mechanisms, such as monocyte recruitment or vascular smooth muscle cell proliferation. Interestingly, a recent study, in which granulocyte colony-stimulating factor-mobilized vascular progenitor cells were infused into patients with myocardial infarction to

Table 1. Differential Expression of Diabetes-Associated Genes in Cultured EPC from Type 1 Diabetes Patients

Protein name	*Gene name*	*Genbank*	*Fold change**	p *value†*	*Category‡*
Osteopontin	SPP1	J04765	19.7	<0.00001	D
Plasminogen activator inhibitor 1	PAI1	J03764	17.1	<0.00001	D
α-2 type IV collagen	COL4A2	M33653	11.3	0.0002	D
Lectin-like oxidized LDL receptor	LOX1	AF079167	8.0	<0.00001	D
Fructose-1,6-biphosphatase	FBP1	U21931	3.7	<0.00001	D
Thrombomodulin	THBD	J02973	3.5	<0.00001	D
Cystatin A	CSTA	AA570193	2.3	0.00005	D
Heat shock protein	HSP27	Z23090	1.9	0.0004	D/O
CD11b, complement receptor 3	MAC1	J03925	1.3	0.0010	D
Matrix metalloproteinase 1	MMP1	Z48481	−1.9	<0.00001	D
VEGF	VEGF	M97863	−2.5	0.0006	D
MHC class II HLA-DR2-Dw12	MHC2	M16276	−2.8	<0.00001	D
GTP cyclohydrolase I	GCH1	U19523	−4.3	0.00001	D
Macrophage scavenger receptor 1	MSR1	D13264	19.7	0.00001	O
Hepatic dihydrodiol dehydrogenase	AKRC1	U05861	13.9	<0.00001	O
Glutathione *S*-transferase A4-4	GSTA4	AF025887	8.6	0.0002	O
Peroxiredoxin 2	PRDX2	L19185	2.5	0.00003	O
A2b adenosine receptor	ADORA2B	X68487	2.5	<0.00001	O
P8 protein	P8	W47047	2.3	0.0002	O
Superoxide dismutase 1	SOD1	X02317	1.3	0.0008	O

*Fold changes were calculated with control values as baseline comparison file.

†*p* values express the significance of the fold changes as calculated by Affymetrix Microarray Suite 5.0 software.

‡Categories represent genes whose products were reported to be induced or repressed in hyperglycemia or type 1 diabetes (D) or as a consequence of increased oxidative stress (O).

improve cardiac function, showed enhanced in-stent restenosis, which led to a premature termination of the trial (27).

A current concept is therefore that autologous progenitor cell therapy, in patients with cardiovascular risk factors, probably should be accompanied by drug therapy that modulates the dysfunctional and adverse phenotype of these cells. First, the particular risk factor should be carefully treated through conventional approaches. In diabetes, this would mean that an optimal control of hyperglycemia should be pursued for some time in advance of the isolation of progenitor cell fractions. Second, an adjunctive therapy could be used to improve EPC function. For instance, HMG-CoA reductase inhibitors have been shown to increase the number of circulating EPC both in animal models (14, 30) and in patients with stable coronary artery disease (57). In these studies, statins were also shown to improve functional aspects of the studied EPC populations *in vitro,* like proliferation, migration (30, 57), chemotaxis (30), and adhesion (60). Statin treatment also augmented corneal neovascularization in mice (30) and reendothelialization after vascular injury in rats (60), and in both models the contribution of bone marrow-derived EPC to these effects was increased. In coronary artery sections, it was shown that statins can reduce glucose-induced ROS production by the endothelium through the inhibition of GTPase-mediated activation of the NADPH subunit $p22^{Phox}$ (10). This observation together with the fact that EPC can respond to statins would suggest that inhibition of HMG-CoA reductase may also counteract the adverse EPC phenotype observed in EPC cultured from the PB-MNC of type 1 diabetes patients or *in vivo*. Likewise, pharmacologic intervention in angiotensin II signaling by ACE inhibitors or angiotensin receptor 1 antagonist may also prove beneficial to EPC number and function. Whatever future therapeutic strategy will prove effective, it seems most likely that redox signaling will be one of its targets.

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ABBREVIATIONS

ACE, angiotensin-converting enzyme; acLDL, acetylated low-density lipoprotein; AGE, advanced glycation end products; BM-MNC, bone marrow mononuclear cells; CEP, circulating endothelial progenitor cells; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; H_2O_2, hydrogen peroxide; HUVEC, human umbilical vein endothelial cells; LDL, low-density lipoprotein; MNC, mononuclear cells; MnSOD, manganese superoxide dismutase; NF-κB, nuclear factor-κB; PB-MNC, peripheral blood mononuclear cells; PKC, protein kinase C; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; VE-cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial-cell growth factor receptor-2; vWF, von Willebrand factor.

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