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Endothelial Loss and Repair in the Vascular Complications of Diabetes
– Pathogenetic Mechanisms and Therapeutic Implications –
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Although seemingly diverse, the tissue injury at sites of diabetic complications, whether in the heart, kidneys or eyes, shares the common histopathological feature of endothelial cell loss, a consequence of both increased cell death and deficient regeneration. In medium-sized and larger arteries the loss of the protective lining contributes to the atherosclerotic process, while at sites of microvascular disease endothelial cell loss leads to capillary rarefaction and ischemia. The pathophysiology of these changes and their consequences on organ structure and function in diabetics are reviewed, and the potential for endothelial regenerative strategies to enhance repair and ameliorate the long-term complications of diabetes is explored. (Circ J 2013; 77: 849–856)

Key Words: Diabetes mellitus; Endothelium; Kidney

Endothelial Cell (EC) Loss in Diabetes

Though anchored to the vascular basement membrane, ECs, albeit few in number, can still be detected in the peripheral blood of healthy individuals. Whether their presence in the circulation reflects apoptosis and subsequent detachment or vice versa is, however, uncertain. Marked increases are nevertheless evident in the setting of the EC injury that occurs in conditions such as autoimmune vasculitis, cardiovascular disease, sepsis, cancer and sickle cell crisis. Consistent with diabetes (DM) as a cause of endothelial damage, the number of circulating ECs, identified by the cell surface marker CD146, is substantially (~7-fold) elevated in subjects with type 2 DM (Figure 1).

EC microparticles or microsomes can also be detected in higher numbers in the circulation of patients with DM when compared with healthy controls. These microparticles, measuring 100–500 nm in diameter, arise from the plasma membrane in the setting of cell stress or apoptosis. Microparticles are not inert but rather vehicles of intercellular communication, serving as biomarkers of cell injury, as well as agents of both tissue injury and repair.

In the setting of coronary artery disease (CAD), elevated levels of EC-derived microparticles have been documented in patients with acute coronary syndromes, correlating with high-risk features on angiography and providing a potential prognostic marker for atherosclerotic vascular disease. In patients with DM, the abundance of CD144-expressing endothelial microparticles is not only elevated when compared with non-diabetic subjects but correlates with endothelial dysfunction and denotes a high likelihood of CAD, particularly among those without typical anginal symptoms (Figure 2).

Consequences of EC Loss in DM

Atherosclerosis

The arterial endothelium provides a continuous barrier between the elements of blood and the arterial wall. As such, disruption or dysfunction of the endothelium, as in DM, can be viewed as a pivotal event in the initiation of the atherosclerotic process, as first suggested by Virchow in 1856. By permitting high concentrations of lipoproteins and other injurious factors to permeate in the vicinity of medial smooth muscle cells, endothelial injury allows these cells to migrate into the intima, proliferate and undergo phenotypic change that, together with an associated inflammatory response, leads to the formation of an atherosclerotic plaque. Moreover, while thrombus formation is often the result of fracture of the fibrous cap of an atherosclerotic plaque, approximately 25% are the consequence of EC denudation that exposes the procoagulant surface of the subendothelium.

Cardiac Microvasculature in CAD

Among patients with documented CAD, the presence of DM confers a 50–100% increase in mortality and hospitalization because of heart failure (HF) when compared with non-diabetic subjects. Importantly, the poor prognosis among diabetic patients persists even after adjusting for angiographic differences between the 2 groups, suggesting that factors beyond the traditional focus on the epicardial coronary arteries may contribute.

In the setting of myocardial infarction (MI), restoration of

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TIMI flow grade 3 in the culprit coronary artery, regarded as an angiographic success, typically occurs in approximately 90% of both diabetic and non-diabetic subjects. TIMI-3 flow, however, does not necessarily denote effective myocardial reperfusion. Indeed, attention has recently focused on the potential contribution of the microvasculature, for which a number of imaging modalities, including angiographic, Doppler, PET and MRI-based methods, have been used to assess microvascular structure and function. When assessed angiographically, impaired microvasculature perfusion after TIMI-3 flow denotes a particularly grave outcome. Indeed, when microvascular perfusion is quantified by myocardial blush grade (MBG), patients with poor perfusion (MBG: 0/1) have a 4.7 and 1.8 higher likelihood of death and major adverse cardiac events, respectively, when compared with subjects whose MBG is 2 or 3.7

The Enhanced Myocardial Efficacy and Removal of Liberated Debris (EMERALD) trial examined the effects of adjunctive microvascular protection in patients with acute ST-elevation MI undergoing emergency percutaneous coronary intervention (PCI). Although distal embolic protection was not effective, the EMERALD trial provides insight into the contribution of microvascular disease in the 62 patients with and without DM and 439 patients without DM. Following PCI, TIMI-3 flow was restored in approximately 90% of patients in both the diabetic and non-diabetic groups. Despite this, twice as many patients with DM recorded a MBG of 0/1 when compared with those without (P=0.0017). Moreover, these differences were associated with significant increases in infarct size and 6-month mortality among patients with DM. Although the poor MBG in diabetic patients may be in part functional, autopsy studies show that structure is also affected, with a reduction in capillary density in the hearts of diabetic patients with CAD when compared with their non-diabetic counterparts. These findings suggest that microvascular augmentation in response to CAD is impaired in the DM context. Indeed, this phenomenon has been clearly shown in the experimental setting where amerosed constriction of the left circumflex coronary artery of mini-pigs was followed by restoration of perfusion in non-diabetic animals contrasting the persistent reductions in flow and reduced EC density among those with DM.9

Cardiomyopathy
Clinical, histopathological and experimental data all support the existence of diabetic cardiomyopathy as a cause of systolic and diastolic dysfunction in the absence of significant CAD.10

Cardiac myocytes are critically dependent on a robust capillary network to maintain a constant supply of oxygen and nutrients. This functional interdependency is evident at the cellular level, where myocytes and ECs are present in a 1:1 ratio. Several experimental studies have documented a reduction in cardiac capillary density in DM in association with reduced perfusion, myocyte loss and fibrosis along with both systolic and diastolic dysfunction. Similar findings have also been noted in humans. In a pivotal study of human diabetic cardiomyopathy, Frustaci et al examined biopsied left ventricular tissue from patients with DM and HF in the absence of angiographically significant CAD. When compared with cardiac muscle obtained from patients undergoing mitral valve replacement or from non-diseased hearts obtained at autopsy, tissue from patients with DM displayed a greatly increased rate of EC apoptosis in conjunction with myocyte death, hypertrophy and interstitial fibrosis (Figure 3). Reduced capillary density in the setting of HF is, however, not unique to the diabetic heart, but is also seen in pressure overload and uremic cardiomypathy, suggesting that capillary loss might be a common initiating and progression factor in the pathogenesis of HF.

Nephropathy
Glomerular filtration, the principal function of the glomerular capillaries, is directly related to the capillary filtration surface of the glomerulus. In DM, progressive expansion of the mesangium restricts the capillary surface available for filtration and, as a consequence, the glomerular filtration rate (GFR) falls. However, whether the mesangial expansion is the cause of the capillary loss or vice versa is unclear and a combination of the 2 seems likely.

Following its sojourn through the glomerulus, blood then flows to the tubulointerstitium. Deriving its entire oxygen supply from post-glomerular capillary perfusion, this region of the kidney, which constitutes 90% of its volume, is rendered highly vulnerable. The DM-induced reduction in glomerular
capillary perfusion will accordingly lead to sluggish post-glomerular blood flow and hypoperfusion in the remainder of the nephron. Indeed, as glomerulosclerosis continues, worsening post-glomerular perfusion exacerbates tubular ischemia and a vicious cycle ensues between ischemia and fibrosis, whereby excessive scar tissue compresses local capillaries and reduces oxygen delivery, which in turn exacerbates the fibrogenic response. As might be predicted from this scenario, there is a close relationship between post-glomerular capillary density, interstitial fibrosis, tubular atrophy and GFR in a range of glomerular diseases, including diabetic nephropathy.

Pathogenesis of EC Loss in DM
The EC loss in DM results from the dual insults of accelerated death and impaired regeneration.

EC Death
ECs replicate very slowly. In the aorta, for instance, approximately 0.4% of ECs take up 3H-thymidine and although this doubles in areas exposed to hemodynamically-induced injury, presumably in response to cell loss, it remains low. Similarly infrequent replication has also been reported in capillaries, where it is notably reduced in the retinae of diabetic mice.

Unlike hepatocytes, adipocytes or skeletal myocytes, ECs do not require insulin for glucose entry and are, accordingly, a target for glucose-dependent activation of intracellular signalling pathways, several of which have been implicated in the pathogenesis of EC apoptosis in DM. Reactive oxygen species, for instance, produced in excess as a consequence of increased metabolic flux, lead to caspase-3-induced EC apoptosis through a range of intermediaries that include activation of nuclear factor κB, c-Jun NH2 terminal kinase and p38 MAP kinase, as well as translocation of Bax and downregulation of Bcl-2.

In addition to causing abrupt cell death, high glucose may also be viewed as an inducer of premature senescence. This is seen in cell culture where increasing concentrations of glucose shortens the lifespan of ECs in a dose-dependent manner. The intracellular signalling mechanisms responsible for this effect center on the activity of the enzyme, silent information regulator protein 1 (SIRT1). This NAD+-dependent lysine deacetylase is considered a key factor in mediating the life-shortening effects of glucose and SIRT1 activity increases intracellular glucose denotes energy excess, leading to the downregulation of endothelial SIRT1 in both the cell culture and in vivo settings. Consistent with the fundamental importance of this pathway, forced overexpression of SIRT1 or disruption of p53 attenuates high-glucose-induced EC senescence and in mice protects from DM-related vascular dysfunction.

In addition to hyperglycaemia per se, other attributes of the diabetic state such as hemodynamic injury, low-density lipoprotein and vasoactive hormones, such as angiotensin II, may also contribute to EC apoptosis. These pathophysiological changes, commonly seen in DM, may account in part, not only for the cardiac protective effects of antiangiotensiv therapy, lipid-lowering treatment and blockade of the renin–angiotensin system, but may also contribute to the beneficial effects of such therapies in the diabetic retina and kidney.

Impaired Endothelial Regeneration: Role of Bone Marrow-Derived Angiogenic Cells
Until recently, it had been assumed that endothelial renewal was primarily the result of proliferation and migration of neighbouring ECs. However, following the seminal studies of Asahara et al in 1997, it has now become apparent that in addition to this in situ repair, certain circulating bone marrow-derived cells also contribute to this process. Multiple defects in these cells have been identified in the setting of DM, which are thought to contribute to the pathogenesis of both micro- and macrovascular disease. These include not only reductions in cell number but also impaired function with impaired mobilization, migration and angiogenic activity (Figure 4).

Nomenclature
In contrast to the deluge of publications on the role of bone marrow-derived angiogenic cells, mostly referred to as endothelial progenitor cells (EPCs), comparatively little attention has been paid to their precise nature. Importantly, no unique cell surface marker(s) have been shown to specifically identify the cell types responsible for the angiogenic activity of bone marrow-derived cells. Instead, a panel of cell surface markers is most used to identify them, whereby cells expressing CD34, VEGFR2±CD133 are commonly labelled as EPCs. It has, however, become apparent that similar antigen profiles are exhibited by hematopoietic cells and that angiogenic activity is not confined to the CD34 subpopulation, but is also exhibited by circulating mononuclear and bone marrow stromal cells.

As an alternative to cell surface markers, several investiga-
tors have described the cells that they are studying by the culture techniques used to produce them. Within this system of classification, adherent bone marrow cells maintained in endothelial media are referred to as either early or late outgrowth cells.23 Whereas late outgrowth cells are highly proliferative and can integrate into endothelial structures, early outgrowth cells are secretory, tend not to integrate and exhibit a phenotype that seems most closely related to immature monocytes while still expressing markers such as CD34 and VEGFR-2. Accordingly, the acronym EPC may also now be used to denote these early pro-angiogenic cells,24 and in accordance with the prevailing utilitarian approach, I will continue using the term “EPC” in the present review, though with the understanding of its inherent simplification. Those interested, however, in a more detailed exploration of the controversies and complexities of the nomenclature are referred to a recent, outstanding review on the subject.25

Mechanisms of Action
Akin to the multiple cell types with angiogenic activity, the processes by which these cells initiate and support angiogenesis are also varied. For instance, EPCs may directly incorporate into vascular structures, though the secretion of paracrine factors is currently viewed as the major mechanism that accounts for their angiogenic effects.26 Intriguingly, the absence of significant cell retention in target organs, despite the long-term benefits of cell therapy, has been noted by several investigators,27,28 leading some to postulate that at least some of the administered cells may exert their effects by a systemic or “endocrine” mode of action.29

Circulating EPC Number
Although much of the biology underlying the nature and identity of EPCs remains unknown, it is abundantly evident that these cells, albeit broadly and variably defined, have a major role in cardiovascular repair and homeostasis. Indeed, the number and function of circulating EPCs serves a biomarker for cardiovascular health, correlating inversely with cardiovascular risk factors. For instance, in subjects with various degrees of cardiovascular risk, but no history of cardiovascular disease, the number of circulating EPCs correlates closely with the Framingham risk factor score.30 Indeed, in these subjects the circulating EPC count served as a better predictor of vascular reactivity than the conventional risk factors, leading the study’s authors to conclude that endothelial injury in the setting of insufficient circulating EPCs may adversely affect the progression of cardiovascular disease.30 As may have been predicted from the latter statement, the number of circulating EPCs was subsequently shown to predict the occurrence of cardiovascular events and death in subjects with angiographically confirmed CAD.31

Unsurprisingly, given its relationship with cardiovascular risk factors, the number of circulating EPCs has been shown in numerous studies to be reduced in type 2 DM (T2DM).32,33 However, the finding that the count is similarly reduced in type 1 DM (T1DM)34 suggests that hyperglycaemia per se, as well as the attributes of the metabolic syndrome may contribute to the observed changes. Moreover, in both T1 and T2 DM, the number of circulating EPCs correlates inversely with glycaemic control.32,34 Consistent with this, treatment of hyperglycaemia is associated with an increase in the circulating EPC number.35

Not only is the basal number of EPCs reduced in DM, but the response to bone marrow stimulation with mobilizing agents such as granulocyte colony stimulating factor (G-CSF) is also impaired.36 Although the pathophysiological basis for these findings is incompletely understood, the defect appears to reflect impaired egress, possibly as a consequence of autonomic neuropathy, rather than reduced stem cell numbers within the bone marrow.37

In addition to agents that are used clinically to mobilize cells from the bone marrow, such as G-CSF and plerixafor, several studies have shown that exercise training and statins, albeit less powerfully, are also able to do so.38,39 Importantly, the lat-
versed by culturing the EPCs in normal (5.5 mmol/L) glucose for 7 days.

45 EPCs in Diabetic Retinopathy

Unlike other sites of DM complications, the retina is subject to both capillary loss and neovascularization. In a case-control study, Brunner et al counted circulating angiogenic cells in 90 patients with T1DM and varying stages of retinopathy. A step-wise reduction in EPC count was noted among patients with no, mild and moderately-severe non-proliferative diabetic retinopathy. These findings suggest that the bone marrow fails to respond to retinal capillary loss, permitting the progression of non-proliferative diabetic retinopathy. Accordingly, angiogenic cell therapy may restore vascular integrity and potentially reverse the natural history of the disease. However, in contrast to non-proliferative disease, proliferative diabetic retinopathy is characterized by an increase in circulating angiogenic cells that rises further as patients evolve from low- and high-risk proliferative diabetic retinopathy.

46 The pathophysiological basis for this angiogenic switch is incompletely understood, but is likely to follow the local elaboration of angiogenic factors such as VEGF and SDF-1 that stimulate not only EC proliferation in situ but also enhance the mobilization and chemotaxis of angiogenic cells from the bone marrow.

Mobilization and Trafficking

Under basal conditions, EPCs mostly remain in the bone marrow, but are released in the setting of tissue ischemia when they migrate in response to HIF-dependent chemokines. Current understanding of EPC egress from the bone marrow and their homing to areas of ischemia pivots around the role of various growth factors and chemokines, focusing in particular on the C-X-C chemokine, stromal cell-derived factor-1 (SDF-1 also known as CXCL12) and its cognate receptor CXCR4. This signaling pathway keeps EPCs within the bone marrow where SDF-1 produced by marrow stromal cells anchors CXCR4-bearing EPCs and hematopoietic stem cells. In the setting of tissue hypoxia, however, HIF activation augments local SDF-1 expression and drives EPCs from the bone marrow to the area of ischemia.

Importantly, SDF-1 is degraded by dipeptidyl peptidase-4 (DPP-4), a near-ubiquitous enzyme that cleaves its 2 N-terminal amino acids and renders it chemotactically inactive. In DM, both soluble and cell surface (CD26) DPP-4 activity is increased, providing a plausible explanation for the relatively poor prognosis for patients with DM and ischemic heart disease.

Angiogenic Activity

In addition to their impaired mobilization and homing to target tissues, EPCs from diabetic patients and experimental animals are less angiogenic. Because EPCs are now thought to induce angiogenesis through paracrine mechanisms rather than by being incorporated into new blood vessels, their angiogenic activity may be assessed by examining the conditioned medium obtained from culturing EPCs. Using this assay system, EPC-conditioned medium induces human umbilical vein ECs to form tubular, capillary-like structures in the in vitro setting. When compared with the angiogenic activity of EPCs obtained from healthy donors, those from individuals with T1DM are substantially impaired. Similar findings have also been reported in animal studies where, akin to the concept of metabolic memory, the DM-related defect could not be reversed by culturing the EPCs in normal (5.5 mmol/L) glucose for 7 days.

EPCs in Diabetic Retinopathy

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Therapeutic Strategies

Preventing EC loss is within the spectrum of action of many of the therapies currently used to lessen cardiovascular risk in patients with DM, as well as being a target for ongoing drug discovery and the subject of a recent excellent review. Accordingly, the present review focuses more on strategies to improve EC regeneration by increasing the number and function of bone marrow-derived angiogenic cells.

EPC Administration

Given the reduction in circulating EPCs in DM, a simple strategy might be to increase their number by autologous administration. With this in mind, Boyle et al were among the first to show the effects of cell therapy in patients with intractable angina, despite maximal medical therapy and previous revas-
in which, although statistically significant, the benefit in terms significantly improved. Importantly, no proliferative retinopathy 

symptoms was seen in all patients following infusion of cells such cells. Sustained and significant reduction in anginal row, enabling the intracoronary infusion of large numbers of tan substantially increased the number of circulating CD34 + showing that the administration of both olmesartan and irbesartan, a receptor blocker, telmisartan, increases the number of circulat-

ing CD34 + /VEGFR2 + cells in the setting of stable CAD. 

SDF-1 is a chemokine for EPCs 


cellularization. In this small study of 5 patients, 4 of whom had DM, G-CSF was used to mobilize CD34+ cells from bone mar-
erow, enabling the intracoronary infusion of large numbers of such cells. Sustained and significant reduction in anginal symptoms was seen in all patients following infusion of cells (Figure 5). Moreover, mean collateral flow grade, assessed angiographically after 12 months of follow-up, was also significantly improved. Importantly, no proliferative retinopathy was induced and no in-stent restenosis was seen. Numerous other studies have examined patients with CAD, in which, although statistically significant, the benefit in terms of improvement in left ventricular ejection fraction (LVEF) has been relatively modest, in the order of 4%. However, a recent meta-analysis with longer follow-up has now shown that the small, early changes in LVEF are accompanied later by far more robust improvements in all-cause mortality (odds ratio: 0.39 [0.27–0.55]), cardiac mortality (0.41 [0.22–0.79]) and MI (0.25 [0.11–0.57]). Although not specifically targeting patients with DM, there are as yet no data, to suggest a different response in the DM setting. Unfortunately, microvascular complications of DM such as retinopathy, nephropathy and neuropathy have been little investigated. In addition, the optimal angiogenic cell type also remains to be defined and may be mesenchymal, rather than endothelial, in origin. 

Indirect Strategies to Augment EPC Number 

Renin-Angiotensin System In early outgrowth human EPCs, angiotensin II, acting via its type 1 receptor (AT1) adversely affects their function with impaired migration, colony unit formation and increased apoptosis. Consistent with these in vitro findings, angiotensin II infusion reduces EPC number, as well as their function, and impairs recovery following carotid artery denudation in mice. In humans, treatment with the AT1 receptor blocker, telmisartan, increases the number of circulating CD34+/VEGFR2+ cells in the setting of stable CAD. Similar findings have also been reported in T2DM where a range of DPP-4 inhibitors are currently in progress and are expected to be completed in 2013–18 (NCTs 01107886, 00790205, 01243424 and 00968708).

Other Modalities A number of other cardioprotective ther-
apies have a salutary effect on circulating EPC number and function and those that have been studied in patients with DM include inhibitors of hydroxy-methyl-glutaryl CoA (HMGCoA) reductase (statins) and exercise. 

Augmenting Mobilization and Migration: Role of Stromal Derived Factor-1 (SDF-1) SDF-1 is a chemokine for EPCs that, while constitutively expressed in the bone marrow, is also induced in peripheral tissues in the setting of ischemia by HIF-1 dependent mechanisms. EPCs express the cell surface receptor for SDF-1, CXCR4, allowing these cells to egress from the bone marrow and migrate along an SDF-1 gradient to initiate and support angiogenesis in areas of ischemia. In addition to supporting the migration of these cells, SDF-1 also promotes angiogenic sprouting in situ, by stimulating tip and stalk cells of the neovascular front. The response to SDF-1 is, however, diminished in DM, caused at least in part by the increased activity of the enzyme responsible for its degrada-
tion, DPP-4, in the periphery. Given its role in augmenting angiogenesis and protecting the myocardium, a number of strategies have been developed to enhance SDF-1 availability, including local admin-

istration of unmodified recombinant SDF-1, polypeptide analogs and protease-resistant SDF-1, as well as forced expression of SDF-1 by adenoviral gene delivery. Indeed, a clinical trial examining the effects of myocardial delivery of a non-viral DNA-plasmid, encoding for SDF-1, is currently in early phase clinical trials for ischemic heart disease, HF and critical limb ischaemia (http://www.juventasinc.com/trials/index.html, accessed January 28, 2013).

An alternate strategy to enhance the local concentration of SDF-1 is to prevent its degradation by inhibiting DPP-4. Studies, initially in non-diabetic mice, have shown improvements in several parameters of cardiac injury post-MI. Notably, the enzymatic activity of DPP-4 can be inhibited by a relatively new class of antihyperglycemic agents, the DPP-4 inhibitors or “gliptins”, that lower blood glucose by preventing the deg-
radiation of glucagon-like peptide-1. In recent studies, rats with streptozotocin-induced DM were administered the DPP4 in-
hibitor, sitagliptin. Consistent with its presumed effects on increasing the bioavailability of cardiac SDF-1, these studies showed that DPP4 inhibition increased capillary density, re-
duced adverse remodeling and attenuated diastolic dysfunc-
tion following MI. Similar findings have also been reported in experimental diabetic cardiomyopathy and hindlimb ischemia. The effects of DPP4 inhibition have also been examined in patients with T2DM in whom 4 weeks of treatment increased both plasma SDF-1 level and the circulating EPC (CD34+/VEGFR2+) count. However, whether these SDF-1-related mechanisms may also account for the diminution in cardiovascular events observed in meta-analyses of DPP-4 treatment in diabetic patients remains speculative. Indeed, caution is needed to avoid over-interpreting these data, which are based predomi-
nantly on adverse events. Fortunately, a series of large, prospective, randomized controlled cardiovascular studies using a range of DPP-4 inhibitors are currently in progress and are expected to be completed in 2013–18 (NCTs 01107886, 00790205, 01243424 and 00968708).

Preventing Premature Senescence: Role of Silent Information Regulator Protein 1 

As discussed earlier, SIRT1 has been implicated in the early death of mature ECs in DM. Recent studies show that SIRT1 is additionally involved in the regulation of EPC function. This NAD+-dependent lysine deacetylase catalyzes substrate-spe-
cific de-acetylation from the ε-amino group of lysine, modu-
lating a myriad of cell functions that include the lifespan-ex-
tending properties of caloric restriction in mammalian systems. Notably, prolonged (10 day) culture in normoglycemic me-
dium failed to restore the angiogenicity of diabetic donor-de-

rived EPCs or the reduction in SIRT1 expression and pro-angiogenic factor secretion. Using an ex vivo approach, Yuen et al recently showed that SIRT1 activation, using a small-
molecule SIRT1 activator, not only restored the secretion of pro-angiogenic ELR+ CXC chemokines, CXCL1, CXCL3, and CXCL5, in EPCs from diabetic animals, but also increased their in vitro and in vivo angiogenic activity to levels similar to EPCs derived from control animals. These findings sug-
gest a pivotal role for SIRT1 in DM-induced EPC dysfunction and that its pharmacologic activation may provide a mechanism whereby EPC-mediated repair mechanisms might be restored.

Conclusions 

EC loss in DM is the consequence of increased cell death and
impaired regeneration, for which multiple defects have been identified, including impaired mobilization from the bone marrow, reduced chemotaxis to areas of ischemia and impaired angiogenic function. Recent insights into the pathogenesis of these phenomena and the development of therapeutic strategies that address them will hopefully give rise to new therapies that prevent, arrest or even possibly reverse, the endothelial loss that underlies the development and progression of both the micro- and macrovascular complications of DM.

Addendum

The author regrets, owing to space limitations, that much of the excellent work of others in the field has not been included in this review.

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