Introduction

The critical role of the vascular endothelium in cardiovascular health and disease is increasingly recognized [1]. Over the last decades, the endothelium has emerged as the key regulator of vascular homeostasis, acting not merely as a barrier, but also as an active sensor and signal transducer that regulates dynamic changes in vascular biology. The importance of the endothelium was first recognized by its effect on vascular tone, which operates by producing and releasing several vasoactive molecules as well as by response to and modification of circulating vasoactive mediators [2]. However, this simple cell monolayer is able to respond to physical and chemical signals releasing a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance/fibrinolysis, vascular smooth muscle cell proliferation and vessel wall inflammation, and plays a key role in angiogenesis [2, 3].

Cardiovascular risk factors switch endothelial cell phenotype, thus triggering an inflammatory process associated with a profound alteration of endothelial cell function. Specifically, chronic exposure to a harmful stimulus such as hypercholesterolemia could lead to severe endothelial injury and increased endothelial cell apoptosis, a threatening condition for endothelium integrity [4, 5]. Under these conditions, endothelial cells replicate, but because of their limited regenerative capacity, they require the assistance of endothelial progenitor cells (EPCs), which have recently emerged as key contributors to the maintenance of endothelial cell monolayer integrity [6] (fig. 1). Growing evidence indicates that hypercholesterolemia reduces EPC availability and functionality [7], thus limiting vascular reparative potential of EPCs. In this context, the preservation of EPC number and function is regarded as a critical intervention to limit atherosclerosis progression and improve blood flow in ischemic tissues.

This review focusses on the mechanisms involved in the dysfunction of endothelium and EPCs triggered by hypercholesterolemia, with special emphasis on their implications in vascular repair, angiogenesis and vasculogenesis in cardiovascular diseases.

Hypercholesterolemia-Induced Endothelial Dysfunction: Impairment of Nitric-Oxide-Mediated Vascular Protection

Low-density lipoproteins (LDLs) play an active role in the onset and progression of atherosclerosis and elicit an early modulation of endothelial gene expression responsible for the structural and functional changes characteristic of endothelial dysfunction [5]. Elucidation of the mechanisms by which LDLs modulate endothelial function is fundamental to improve therapeutic strategies in cardiovascular diseases and identify novel pharmacological targets. In the last years, a growing number of genes regulated by LDLs/hyperlipidemia in endothelial cells have been identified applying techniques for differential gene expression analysis [8–10]. For instance, we have recently shown that atherogenic concentrations of native LDLs downregulate lysyl oxidase (LOX) expression and activity in endothelial cells and in the vascular wall of hypercholesterolemic animals [9]. LOX is a copper-dependent enzyme involved in extracellular matrix maturation, which has been associated with hypoxia-mediated cell invasiveness [11]. Downregulation by LDLs of heparan sulfate proteoglycan synthesis [12] and extracellular matrix processing could alter vascular endothelial integrity/permeability as well as impair extracellular matrix remodeling associated with the angiogenic processes. Table 1 summa-
rizes some of the effects exerted by LDLs on adult endothelial cells.

The impairment of endothelium-dependent vascular relaxation secondary to a decrease in nitric oxide (NO) bioavailability is characteristic of endothelial dysfunction and is one of the early deleterious effects produced by high plasma levels of LDLs. In hypercholesterolemic patients, NO-mediated flow-mediated dilatation, a surrogate indicator of endothelial function that has recently been shown to predict cardiovascular events [20], is dramatically improved after a single session of LDL apheresis [21]. Moreover, supplementation with l-arginine, the precursor of NO, reverses endothelial dysfunction in otherwise healthy young humans with hypercholesterolemia [22]. The reduction in NO bioavailability observed in hypercholesterolemic patients [23, 24] could be related to various mechanisms, among them: (1) a decrease in endothelial NO synthase (eNOS) expression (mRNA and protein levels) in response to oxidized LDLs (oxLDLs) and atherogenic concentrations of native LDLs (nLDLs) has been described in vivo [25] and in vitro [13, 14, 17]; (2) an increase in caveolin-1 and the inactive complex caveolin-1/eNOS, has been reported in endothelial cells treated with sera from hypercholesterolemic patients [26]; (3) an increase in the degradation of NO mediated by superoxide anion (O$_2^-$), has been observed ex vivo in vessels from hypercholesterolemic animals [27]; (4) the uncoupling of eNOS activity produced by oxLDL and atherogenic concentrations of nLDLs that reduce the association between eNOS and hsp90 and increases the generation of O$_2^-$ have been reported [28, 29]; (5) the reduction of eNOS activity as a consequence of the inhibitory effect of asymmetric dimethylarginine (ADMA), whose levels are increased in hypercholesterolemic patients [30] or (6) the impairment of l-arginine uptake by endothelial cells produced by both nLDLs and oxLDLs [29].

NO is a highly versatile molecule that effects a variety of actions in the vasculature and plays a central role in vascular biology [31]. Originally identified as a principal determinant of vascular tone, NO has since been recognized to exert antithrombotic, antiproliferative, and anti-inflammatory effects and it seems to play a key role in angiogenesis. The loss of NO may impact on multiple steps in the atherogenic process. Therefore, it is conceivable that the well-established downregulation of NO by LDLs may account not only for the deleterious effects of hypercholesterolemia on endothelium-dependent NO-mediated flow-mediated dilatation, but also for the lipoprotein-induced alteration of endothelial cell adherence, thromboreactivity and angiogenic properties. Indeed, NO is a critical regulator of the neovascularization response triggered by proangiogenic factors such as vascular endothelial growth factor or basic fibroblast growth factor [32, 33]; consequently, prevention of eNOS activity using specific eNOS inhibitors (i.e. nitro-L-arginine-methyl ester) reduce angiogenesis in different experimental settings both in vitro and in vivo [34, 35]. It is likely that the disturbance of NO bioavailability by atherogenic concentrations of LDLs accounts for the antiangiogenic effects and the impairment in collateral vessel formation in response to ischemia observed in animal models of hypercholesterolemia and in hypercholesterolemic patients [19, 18, 36]. In apolipoprotein-E-deficient (ApoE−/−) subjects, the increased ADMA levels and the consequent disturbance of NO synthesis have been related to the reduced angiogenesis observed in this hypercholesterolemic model [37]. Conversely, transgenic mice that overexpress dimethylarginine dimethylaminohydrolase, the enzyme that degrades ADMA, show reduced plasma and tissue ADMA levels and increased angiogenesis [38]. Taken together, these results support the potential role of ADMA and NO in the antiangiogenic effects induced by hypercholesterolemia, and have led to propose dimethylarginine dimethylaminohydrolase as novel therapeutic target to enhance angiogenesis [39].

**Modulation of the Angiogenic/Apoptotic Balance by Lipoproteins**

A disturbed lipid metabolism impairs angiogenesis. A mechanism that could explain the reduced angiogenesis in the setting of hypercholesterolemia could be the decreased vascular endothelial growth factor expression in the ischemic tissues as has been shown in the ischemic limbs of ApoE−/− mice [40] and in tumors from hyper-

<table>
<thead>
<tr>
<th>Table 1. Effect of LDLs on endothelial cell function</th>
</tr>
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<tbody>
<tr>
<td>↓ NO availability [13, 14]</td>
</tr>
<tr>
<td>↑ Apoptosis [15, 16]</td>
</tr>
<tr>
<td>↑ Adhesiveness [17]</td>
</tr>
<tr>
<td>↓ Angiogenesis [18, 19]</td>
</tr>
<tr>
<td>↓ ECM components (HSPG) [12]</td>
</tr>
<tr>
<td>↓ ECM processing (LOX) [9]</td>
</tr>
</tbody>
</table>

ECM = Extracellular matrix; HSPG = heparan sulfate proteoglycan.
cholesterolemic patients [36]. However, most evidence suggests that hypercholesterolemia causes an imbalance of the angiogenic/apoptotic rate favoring endothelial cell apoptosis, which becomes evident in advanced stages of atherosclerosis [41]. The mechanism(s) and intracellular signaling that regulate the onset and execution of endothelial cell apoptosis have been elucidated only in part.

Apoptosis or programmed cell death is an active process of cell death that contributes to pathophysiological processes such as atherosclerosis, inflammation and wound healing [42]. Countering proliferation, excessive apoptosis may limit angiogenesis and may actively lead to vessel regression; conversely, prevention of endothelial cell apoptosis may improve angiogenesis and vasculogenesis [43]. Although it has not been established to what extent endothelial cell death occurs in vivo, there is increasing evidence that chronic hypercholesterolemia favors a proapoptotic stage of vascular endothelial cells. In minipigs fed a cholesterol-rich diet for 34 weeks, in the absence of coronary stenosis, hypercholesterolemia reduced endomyocardial coronary flow reserve and capillary density and induced capillary endothelial cell apoptosis [44]. Moreover, in the rabbit model of hypercholesterolemia, apoptotic endothelial cells were detected in areas of lipid accumulation colocalizing with oxLDL epitopes [45]. Further evidence comes from a number of in vitro studies showing that cultured endothelial cells undergo apoptosis upon exposure to modified LDLs (i.e. oxLDLs, glycated LDLs) [15, 46–48]. The mechanism responsible for this effect has been extensively analyzed and involves multiple stages of the apoptotic cascade. Endothelial cell apoptosis induced by oxLDLs is mediated by the lectin-like oxLDL receptor-1 (LOX-1) [49] and is associated with increased activity of CPP32-like protease [46], the major enzyme that initiates the proteolytic cascade leading to cell death, and with the activation of caspase-9 and -3 [49]. Moreover, oxLDLs decreased the expression of anti-apoptotic proteins Bcl-2 and c-inhibitory apoptotic protein-1, which are involved in the release of cytochrome c and Smac and the activation of caspase-9 [50]. Furthermore, oxLDLs sensitize endothelial cells to Fas-mediated cell apoptosis by downregulating the caspase inhibitor FLIP [51] and increasing the proapoptotic protein p53 [16]. Interestingly, most of these effects caused by oxLDLs are mediated by reactive oxygen species [15, 16, 46, 47, 52]. The complexity of the apoptotic response triggered by mildly oxidized LDLs was demonstrated by Napoli et al. [16] in an extensive study that linked this proapoptotic effect to the activation of the class I and II cascade, mitogen-activated protein kinase and Jun kinase signaling pathways together with the increase in p53 and several transcription factors including activating transcription factor-2, E-26 like protein-1, cAMP response element binding protein and activator protein-1. Electron-negative LDLs, a subtraction of mildly oxidized LDLs, which are increased in plasma of hypercholesterolemic patients, also exhibit proapoptotic properties related to the ability to suppress transcription of the angiogenic factor fibroblast growth factor-2 [53]. Regarding the lipoprotein component responsible for the apoptotic effect, Kontush et al. [54] showed that the content of lipid hydroperoxides determines the proapoptotic potential of lipoprotein particles.

More recently, it has been shown that the induction of endothelial apoptosis by oxLDLs is accompanied by a release of endothelial microparticles [55]. Interestingly, this is in accordance with the enhanced level of plasma-endothelial-cell-derived microparticles reported in hypercholesterolemic and coronary artery disease (CAD) patients [56–58]. Indeed, the number of circulating microparticles correlates with coronary endothelial function in patients with CAD [57, 58] and could be predictive of cardiovascular risk [57]. The central role of the endothelium in vascular homeostasis has led to the development of a range of methods to test different aspects of its function. In this regard, microparticles derived from adult endothelial cells undergoing apoptosis have emerged as a promising novel biomarker of endothelial function.

**EPCs and Endothelial Function: Modulation by Hypercholesterolemia**

When endothelial integrity is severely disturbed, physiological mechanisms activate replication of surrounding endothelial cells; however, mature human endothelial cells possess limited regenerative capacity [2]. Since the discovery of EPCs and their role in vasculogenesis in an animal model of hind-limb ischemia [59], research has been focussed on the potential of EPCs to revascularize ischemic tissues and to improve blood flow [60]. However, EPCs by nature not only have the potential to form new vessels, but also to home at sites of endothelial damage and thus to contribute to endothelial repair. Current evidence suggests that endothelial repair does not exclusively rely on preexisting endothelial cells, but also involves the contribution of bone-marrow-derived circulating EPCs. In fact, in humans, mobilization of EPCs is enhanced after vascular injury secondary to coronary artery bypass grafting or myocardial infarction.
[61,62], and EPC-mediated neovascularization has been involved in the formation of collateral vessels in patients with CAD [63]. This has allowed building up the EPC-mediated repair-to-injury hypothesis. Indeed, this was clearly demonstrated when labeled-marrow transplanted cells were found to line implanted vascular grafts [64]. More recent evidence supports an active role of EPCs in endothelial repair, limiting atherosclerosis and restenosis, and in neovascularization, limiting injury to the ischemic myocardium [63, 65–68]. In animal models, transfused EPCs home to sites of endothelial injury, enhance reendothelialization, impair neointimal growth and limit atherosclerotic lesion progression [66, 69]. Moreover, infusion of spleen-derived mononuclear cells or differentiated EPCs in atherosclerotic ApoE–/–, an animal model of early atherosclerosis, promote EPC incorporation in atherosclerotic plaque areas and cause prolonged improvement of endothelium-dependent vasodilation associated with an increase in eNOS activity and NO production [70]. Accordingly, in patients with limb ischemia, bone-marrow mononuclear cell implantation improves endothelium-dependent vasodilation [71]. The critical role of EPCs in endothelial function was supported by studies demonstrating that EPC levels are a better prognostic factor of vascular reactivity than conventional risk factors in healthy men [72] and predict severe endothelial dysfunction independently of classical cardiovascular risk factors [73].

In hypercholesterolemic patients, endothelial dysfunction is a chronic condition, and the balance between endothelial injury and endothelial regeneration is critical for reducing cardiovascular events [1]. Unfortunately, in these patients, hypercholesterolemia not only exerts a direct harmful effect on the endothelium but also indirectly aggravates endothelial dysfunction, reducing EPC number and impairing EPC-mediated endothelial repair. Indeed, hypercholesterolemia [7, 58] and other atherosclerotic risk factors, including diabetes [74–78], hypertension [79], aging [80] and smoking [81], alter EPC function and inversely correlate with the number of circulating EPCs (table 2). As a result, patients with CAD exhibit low levels of circulating EPCs and an impaired EPC number [82], which are associated with stenosis severity [83] and increased cardiovascular mortality [84].

Hypercholesterolemia reduces proliferative, migratory, adhesive and tubulogenic activities of EPCs [7, 58, 88]. The mechanisms underlying these effects of hypercholesterolemia on EPC function are only partially understood. oxLDLs seem to play a key role in the hypercholesterolemia-mediated effect on EPCs. In fact, therapeutic neovascularization is impaired by the administration of oxLDL-treated EPCs in the hindlimb ischemia model [89]. This intervention reduces EPC homing and migration in the neovascularization of ischemic tissues [89]. Moreover, oxLDL-treated EPCs show an attenuated adhesion to fibronectin or to endothelial monolayers, and reduced

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Risk factor</th>
<th>EPC bioactivity</th>
<th>EPC number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>hypercholesterolemia</td>
<td>↓ migration</td>
<td>↓ circulating EPC</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>smoking</td>
<td>↔ migration</td>
<td>↓ circulating EPC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypertension</td>
<td>↓ migration</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>diabetes</td>
<td>↔ migration</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypercholesterolemia</td>
<td>↓ migration, adhesion, proliferation, tubulogenesis</td>
<td>↓ (cell culture)</td>
<td>[7]</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>diabetes</td>
<td>↓ tubulogenesis</td>
<td>↓ (cell culture)</td>
<td>[75]</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>diabetes</td>
<td>↓ tubulogenesis</td>
<td>↓ (cell culture)</td>
<td>[76]</td>
</tr>
<tr>
<td>Health</td>
<td>hypercholesterolemia</td>
<td>NE</td>
<td>CFUs</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>smoking</td>
<td>NE</td>
<td>circulating EPC</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>homocysteine</td>
<td>↓ migration, adhesion, proliferation, tubulogenesis</td>
<td>↓ (cell culture)</td>
<td>[7]</td>
</tr>
</tbody>
</table>

CFUs = Colony forming units; DM = diabetes mellitus; NE = not evaluated; NS = not significant.
Multiple in vitro studies have shown that oxLDLs alter EPC adhesive, migratory and tube formation capacities, impair EPC differentiation and increase EPC senescence [90–94]. These deleterious effects of oxLDLs have been related to a dose-dependent inhibition of Akt activation (phosphorylation) mediated by the LOX-1 receptor, that among other downstream effects leads to a decrease in eNOS and telomerase activities [90, 91, 93, 95]. Finally, in differentiated EPCs, oxLDLs also increase the transfer of mitochondria-derived superoxide anion to p53, which in turn induces a conformational change in Bax that enables its translocation to mitochondria-promoting apoptosis [94].

Concerning lipid lowering by pharmacological treatment, multiple studies have shown the effectiveness of different 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) to reduce cholesterol and prevent cardiovascular morbidity and mortality. A schematic representation of the cholesterol biosynthesis pathway and the mechanism of cellular uptake of LDL-cholesterol via the LDL receptor (LDL-R) is shown in figure 2. The clinical benefit of statins has been related to the ability of these drugs to improve endothelial function both through cholesterol-dependent and...
LDLs Modulate Endothelial and EPC Function

It is widely recognized that statins increase NO production by several mechanisms, including upregulation of eNOS mRNA and protein levels and restoring eNOS activity reduced by oxLDLs [103] or atherogenic nLDL concentrations [104]. However, recent studies have shown that statins also exert beneficial effect on angiogenesis and EPC number and function, both in vivo and in vitro, mechanisms that could also be associated with the significant improvement of endothelial function produced by these drugs (fig. 3). Indeed, statin treatment increases the number of circulating EPCs in animals [105, 106] and in patients with stable CAD [107]. In several animal models, statins increase mobilization of bone marrow-derived EPCs and promote vasculogenesis [105] and re-endothelialization [67, 68]. Early EPC mobilization and incorporation into denuded areas induced by statins result in accelerated reendothelialization and decreased neointimal growth after balloon injury, a matter of special interest to prevent postangioplasty restenosis [67]. Interestingly, EPC treated with statins in vitro show an increased ability to form colonies, increased proliferation [105, 108] increased migration kinetics [105, 107, 109], better survival rates [105, 108] and a reduction in senescence characteristics [108] (table 4). These in vitro effects of statins have been used to increase the number and viability of autologous EPCs during ex vivo expansion prior to their administration to patients in cell therapy approaches [110]. Furthermore, it has recently been shown that statin therapy also enhances endothelial differentiation of peripheral blood mononuclear cells in hypercholesterolemic patients [111].

NO and eNOS seem to be essential for statin-promoted effects on neovascularization processes. Accordingly, simvastatin enhanced phosphorylation of the endogenous Akt substrate eNOS, inhibited apoptosis and accelerated vascular structure formation in vitro in an Akt-dependent manner [112]. Furthermore, inhibition of eNOS by nitro-L-arginine-methyl ester prevents the formation of angiotubes in cell cultures [113], and collateral growth in response to ischemia is observed in wild-type animals treated with cerivastatin but not in eNOS-deficient (eNOS−/−) mice [114]. Similarly, atorvastatin-induced improvement of EPC mobilization and neovascularization after myocardial infarction requires eNOS, thus it was not observed in eNOS−/− mice [115]. The PI3K/Akt signaling pathway plays a critical role in statin-induced neovascularization and in the improvement of EPC viability. Indeed, overexpression of a dominant-negative Akt blocks the positive effects of simvastatin on EPC bioactivity [105, 106]; and the anti-apoptotic effects of statins on EPCs are dependent on PI3K/Akt activation that lead to inactivation of forkhead transcription factor-4) and the subsequent downregulation of Bcl-2-interacting mediator of cell death [116]. Regarding the statin-mediated delay of EPC senescence, it has been related to the modulation of cell-cycle-promoting proteins [108] as well as to the upregulation of the telomere-capping protein telomere repeat-binding factor-2 that prevents telomerase dysfunction [109]. The beneficial effect of statins on

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**Fig. 3.** The bone marrow transplantation (BMT) model has been successfully used to demonstrate the role of EPCs in adult vasculogenesis. Transgenic animals constitutively expressing β-galactosidase (encoded by lacZ) under the transcriptional control of the endothelium-specific Tie-2 promoter were chosen as donors. Irradiated recipient animals become Tie-2/LacZ/BMT mice in which lacZ expression is restricted to Tie-2-expressing bone marrow-derived cells. These animals are useful tools to prove the role of EPCs in postnatal vasculogenesis and demonstrate the ability of statins to improve neovascularization through an enhanced mobilization and homing of EPCs.
telomere function has also been related to the enhanced migratory ability of EPCs observed after statin treatment [109]. Finally, the increased adhesiveness reported in statin-treated EPCs [67, 68], that could increase EPC homing at sites of vascular injury, seems to rely on the upregulation of integrin \( \alpha_5 \), \( \beta_1 \), \( \alpha(v) \), and \( \beta_5 \) [68].

Therefore, multiple studies support the opinion that the improvement of EPC function and neovascularization promoted by statins could contribute to the clinical benefit of these drugs. The effect of statins on EPC function and vascularization seems to be the result of the combination of their lipid-lowering effects, mainly exerted at the hepatic level, which led to a reduction on plasma circulating LDLs thereby decreasing the harmful effect of these lipoproteins on NO/eNOS and vascularization, and the ability of these drugs to improve endothelial function and EPC activity through a PI3K/Akt-dependent mechanism in a lipid-lowering independent manner. This later mechanism seems to involve proteins that require isoprenylation, a process that is dependent on isoprenoid derivatives generated from the cholesterol pathway (fig. 2). Indeed, the dramatic improvement in EPC number and function produced by nonpharmacological strategies for lipid lowering suggest that in hypercholesterolemic patients both lipid-lowering-dependent and -independent mechanisms could contribute to the beneficial effect of statins on EPC.

### Conclusions and Perspectives

Multiple studies have consistently reported an association between hypercholesterolemia and the biology of endothelium and EPC. Hypercholesterolemia induces endothelial dysfunction and accelerates a natural age-dependent process of deterioration of EPC quantity and function. Indeed, chronic exposure to hypercholesterolemia could affect EPC mobilization, homing and angiogenic capacity as well as promote senescence and apoptosis. Nowadays, the mechanisms underlying such effects are partially understood. Besides the potential use of EPC to revascularize ischemic tissues, EPC-mediated endothelial repair may also have important therapeutic implications. Many studies exploring the potential use of EPC in the clinical setting are being undertaken and they will provide valuable data to improve cell-therapy-based approaches. Alternatively, pharmacological strategies aimed to specifically preserve endothelial function and potentiate endothelial repair could also allow to limit restenosis and atherosclerosis progression and improve neovascularization after ischemia. In this regard, lipid-lowering drugs (statins) have been shown to increase NO bioavailability and prevent hypercholesterolemia-induced dysfunction of endothelium and EPC better than other current pharmacological interventions. Future pharmacological strategies could take into account the possibility of increasing this aspect of the pharmacological action of statins.

### Table 4. Studies with statins and peroxisome proliferator-activated receptor-\( \gamma \) agonists targeting EPC number or function

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Treatment</th>
<th>EPC bioactivity</th>
<th>EPC number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>atorvastatin</td>
<td>↑ migration</td>
<td>↑ circulating EPCs</td>
<td>[107]</td>
</tr>
<tr>
<td>Health</td>
<td>atorvastatin, simvastatin, mevastatin</td>
<td>NE</td>
<td>↑ proliferation</td>
<td>[106]</td>
</tr>
<tr>
<td>Health</td>
<td>simvastatin</td>
<td>↓ apoptosis</td>
<td>↑ proliferation</td>
<td>[105]</td>
</tr>
<tr>
<td>Health</td>
<td>atorvastatin</td>
<td>↓ senescence</td>
<td>↑ proliferation</td>
<td>[108]</td>
</tr>
<tr>
<td>Health</td>
<td>simvastatin</td>
<td>↑ adhesion</td>
<td>NE</td>
<td>[68]</td>
</tr>
<tr>
<td>Health</td>
<td>atorvastatin, mevastatin</td>
<td>↑ migration</td>
<td>NE</td>
<td>[109]</td>
</tr>
<tr>
<td>Heart failure</td>
<td>atorvastatin, ezetimibe</td>
<td>NE</td>
<td>↑ cell culture</td>
<td>[115]</td>
</tr>
<tr>
<td>CAD</td>
<td>pioglitazone</td>
<td>↑ migration</td>
<td>↑ circulating EPCs</td>
<td>[86]</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>pioglitazone</td>
<td>↑ migration</td>
<td>↑ circulating EPCs</td>
<td>[78]</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>rosiglitazone</td>
<td>↑ migration</td>
<td>↑ cell culture</td>
<td>[77]</td>
</tr>
</tbody>
</table>

CFUs = Colony-forming units; DM = diabetes mellitus; NE = not evaluated.
deed, in a model of limb ischemia in type-1 diabetic mice, an NO-releasing pravastatin derivative (NCX 6550), a compound that incorporates a bioactive NO moiety into the pravastatin molecule, recently induced greater reparative neovascularization as well as higher increase of circulating ECP number and EPC migratory capacity than pravastatin [117]. Further studies and large clinical interventions trials are required to clearly establish which patients are elective for cellular therapy and/or pharmacological treatment with emerging compounds able to control cardiovascular risk and potentiate endogenous endothelium-regenerative processes.

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