Endothelial mitochondria and heart disease

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The endothelium is vital to the proper functioning in the heart, in particular due to its production of nitric oxide (NO) which regulates vascular tone. Damage to the endothelium contributes to the development of atherosclerosis, and hence to possible myocardial infarction and subsequent heart failure. Like most cells, endothelial cells contain mitochondria, despite their having relatively little dependence on oxidative phosphorylation for ATP production. However, endothelial mitochondria are centrally involved in maintaining the fine regulatory balance between mitochondrial calcium concentration, reactive oxygen species (ROS) production, and NO. This raises the question of whether damage to endothelial mitochondria would have repercussions in terms of the development of heart disease. In fact, increasingly nuanced techniques enabling restricted transgenic expression of antioxidant proteins in mice has demonstrated that mitochondrial ROS do contribute to endothelial damage. New pharmaceutical approaches designed to target protective molecules such as ROS scavengers to the mitochondria promise to be effective in preventing heart disease. As well as protecting cardiomyocytes, these drugs may have the added benefit of preventing damage to the endothelial mitochondria. However, much remains to be done in understanding the contribution that mitochondria make to endothelial function.

Keywords Mitochondria • Heart • Endothelial cells • Heart disease • ROS • Calcium • Nitric oxide

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1. Introduction

The endothelium lines the entire inner surface of the myocardial vasculature down to the level of the capillaries. Here, in the heart, perhaps more than in any other organ apart from the brain, the endothelium plays a vital role. This is evident from the fact that some of the most life-threatening consequences of injury to the cardiovascular endothelium are observed in the brain, manifest as stroke, and in the heart, manifest as ischaemic heart disease/atherosclerosis, which leads inexorably to increased probability of myocardial infarction and subsequent heart failure. Outnumbering cardiomyocytes by at least three to one (Figure 1), endothelial cells (EC) are evidently more than just ‘wall paper’ for the vessels, and the mitochondria they contain are likely to be more than merely decoration. This review article examines the role of endothelial mitochondria and their potential contribution to heart disease.

2. The normal role of the endothelium

The major functions of the endothelium may be categorized as: trophic, tonic, and trafficking (Figure 2). A ‘trophic’ role is performed by controlling access of overlying cells to glucose, fatty acids, and other metabolites, while also exerting a negative influence on smooth muscle proliferation. The endothelium controls vascular tone by acting as the primary source of nitric oxide (NO), vascular-derived hyperpolarizing factor, and other secreted hormones and molecules that control vascular smooth muscle contraction and, consequently, the extent of vasodilation or vasoconstriction (‘tonic’ role). And it controls ‘traffic’ of macrophages and leucocytes that require passage through the endothelial layer to perform their functions in the interstitium in addition to exerting antiplatelet, anticoagulant, and fibrinolytic actions on the luminal side of the vessel.

NO mediates many of the most well-studied aspects of endothelial function—particularly vascular relaxation—and has wide-spread effects in the myocardial cells and the blood. It is produced mainly at the plasma membrane by endothelial NO synthase (eNOS), but is able to diffuse distances of several microns as far as the cardiomyocytes, where it has been shown to modulate cardiac contraction, oxygen consumption, substrate utilization, apoptosis, and hypertrophy (reviewed in Davidson and Duchen2), and also into the vessel lumen where it modulates platelet adhesion. There is also evidence for a mitochondrial isoform of NOS which in EC is activated by mitochondrial Ca2+ uptake, although its existence remains controversial.3,4 Irrespective of their ability to produce NO, as a source of reactive oxygen species (ROS) and sink for Ca2+, mitochondria form an important part of an integrated homeostatic regulatory system

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The endothelium should not be considered simply as an agglomeration of individual cells acting independently to regulate solely their own local environment, but as an organ in which the performance depends upon its functional intactness. For example, the ability to alter vascular permeability by retraction of EC edges forming junctions between cells might suggest a measure of co-operation, since the segments of a sieve must act homogeneously to function. This implies a level of communication between the cells. Indeed, a considerable level of Ca\textsuperscript{2+} activity has been observed in the endothelium of some vascular beds including propagating waves and oscillations passing from cell to cell\textsuperscript{6–8}.

3. The contribution of the endothelium to heart disease

Damage to the cardiovascular endothelium not only develops with heart disease, but is one of the first steps on the path to heart disease, detectable even before structural changes to the vessel wall are apparent.\textsuperscript{9} The endothelium is a direct target of all of the major risk factors for heart disease: diabetes, hyperlipidaemia and hyperglycaemia, oxidized low-density lipoprotein (oxLDL), inflammation, smoking, ageing, and hypertension—the common element in these being ROS.\textsuperscript{10} For example, ageing increases endothelial oxidative...
4. The normal role of mitochondria in the endothelium

Mitochondria are estimated to occupy on the order of 5% of EC volume (Figure 1). This, and evidence suggesting that EC preferentially utilize non-mitochondrial pathways to generate ATP, has led to the perception that mitochondria play no significant role in the endothelium. However, some recent observations challenge this view (reviewed in Davidson and Duchen15) and suggest that mitochondria can not only contribute to ATP generation but also play a role in regulating the homeostatic triangle of NO, ROS, and Ca$^{2+}$.5

Previous metabolic experiments have indicated that mitochondria do not represent a major source of ATP in primary EC, with respiration being inhibited in the presence of glucose (Crabtree effect).34–37 More recently, however, highly sensitive measurements of mitochondrial respiratory flux in primary bovine aortic EC indicate that mitochondrial respiration is highly coupled to ATP production.38 One might speculate that under certain conditions, the reliance of EC upon oxidative phosphorylation might be increased, implying a significant 'mitochondrial reserve capacity' or 'spare electron transport chain capacity'. This recently developed concept is defined as the ability to elevate metabolic rate from baseline in order to accommodate rapid rises in metabolic demand39 and promises to resolve some paradoxical observations of mitochondrial metabolism. For example, in the brain, tissue with the lowest metabolic resting rate is often the most sensitive to mitochondrial poisons perhaps, it is suggested, because it has a low mitochondrial reserve capacity.39 Mitochondrial reserve capacity can be determined by comparing the level of basal mitochondrial respiration to maximal respiration when uncoupled (Figure 3A). Neonatal cardiomyocytes have been shown to possess a significant 'mitochondrial reserve capacity', with a basal level of mitochondrial respiration that is less than half of the maximal, uncoupled respiratory rate (Figure 3B), and which becomes severely depleted by exposure to oxidized lipids.40 Mitochondrial reserve capacity may be even higher in (non-contracting) primary adult cardiomyocytes.41 Interestingly, bovine aortic EC do appear to have a certain reserve capacity (Figure 3B), although exposure to sublethal oxidative stress diminishes this reserve capacity, and higher levels irreversibly deplete it, suggesting that mitochondrial reserve capacity is involved in the protective response of EC to oxidative stress.42 This new concept of mitochondrial function promises to be a rich area for future study. For example, it would be interesting to determine whether the reserve capacity of endothelial mitochondria is called upon under certain physiological conditions such as those activating the 'energy-sensing' protein kinase, AMP-activated protein kinase (AMPK), known to switch endothelial ATP generation between non-oxidative and oxidative (mitochondrial) pathways.42

One factor known to modulate mitochondrial respiration is NO, which competes with oxygen at cytochrome oxidase, the terminal acceptor in the mitochondrial electron transport chain.63 The majority of eNOS in the heart resides, as its name suggests, in the EC. Endothelial NO from the microvascular endothelium can therefore inhibit mitochondrial respiration in the myocardium.44,45 It is an interesting conundrum, therefore, that the high local concentrations of NO generated by EC might be expected to inhibit their own mitochondria, decreasing oxidative production of ATP, but also potentially increasing production of ROS.46 Indeed, after inflammation increased inducible NOS expression in aortic EC, sufficient NO was generated...
to inhibit respiration, not only in EC but also in the neighbouring cells. It has even been suggested that EC exist in a state of ‘metabolic hypoxia’ due to this NO-mediated respiratory inhibition. If this is so, NO may mask potential, additional reserve mitochondria capacity in these cells.

Whether or not mitochondria are required for endothelial ATP generation, mitochondrial activity may be important in modulating signalling via Ca\(^{2+}\) and/or ROS. In most cells, mitochondrial respiration accounts for a substantial proportion of the ROS produced, with up to 1% of the electrons traversing the electron transport chain transferred to molecular oxygen. As with most cells, ROS are produced in EC as a by-product of mitochondrial respiration. ROS from various sources are important in modulating endothelial function including proliferation, apoptosis, barrier function, inflammatory response, vasorelaxation, and vascular remodelling. This may be partly via the destructive interaction of ROS with NO, but could also indicate a role for mitochondrial ROS in signal transduction in EC.

A general principle appears to be emerging in which mitochondrial ROS signals to and triggers ROS production from other cellular sources. For example, angiotensin-II, hyperglycaemia, or hypoxia increase mitochondrial ROS production in EC, which then stimulate the NADPH oxidase via activation of MAPK. Components of oxLDL can also activate MAPK in EC by increasing mitochondrial ROS production. Hypoxia also increases mitochondrial production of ROS in human umbilical vein endothelial cells, which then activates AMPK, which can alter fuel selectivity and also protects EC from apoptosis during anoxia. These data suggest that mitochondria, while perhaps not a major source of ROS on their own, can stimulate overall cellular ROS production. Furthermore, a ‘reverse’ pathway, in which ROS produced by the NADPH oxidase leads to increased mitochondrial ROS production (via activation of mitochondrial K\(_{ATP}\) channels and matrix swelling and alkalization) may also exist, suggesting a feedback amplification system. As pointed out by Daiber, many ROS sources are themselves redox-activated, e.g. xanthine oxidoreductase is converted by oxidation and proteolytic modifications from xanthine dehydrogenase, and NOS can be uncoupled to produce ROS. How the lid is ever put back on such an explosive keg of ROS production is an intriguing question.

In certain circumstances, mitochondrial ROS may also be involved in transcriptional activation. For example, a highly conserved family of proteins called hypoxia-inducible factors (HIFs) form a central part of the hypoxia response pathway, and emerging evidence suggest that mitochondria regulate HIF-1α and HIF-2α stabilization by releasing ROS to the cytosol. HIF-2α is actually identical to EPAS1, an endothelial transcription factor that transactivates expression of target genes including those involved in angiogenesis and those encoding primary antioxidant proteins including mitochondrial antioxidants MnSOD and frataxin. This strongly suggests an important role for endothelial mitochondria in hypoxic sensing and also appears to indicate that HIF-2α is involved in endothelial mitochondrial homeostasis. This sensing function may come into play under certain pathological situations.

Mitochondrial ROS, by causing an increase in mitochondrial Ca\(^{2+}\), can also activate NF-κB in EC treated with thrombin. In many cell types, mitochondria influence the entire cellular network of cellular Ca\(^{2+}\) signalling. For example, in rat tail artery, mitochondria can influence Ca\(^{2+}\) signalling by buffering cytosolic Ca\(^{2+}\) in smooth muscle cells and funnelling Ca\(^{2+}\) into the sarcoplasmic reticulum. Increases in mitochondrial ROS can also affect Ca\(^{2+}\) signalling. Hyperglycaemia, which increases mitochondrial ROS production in cultured EC, also alters the response of mitochondrial Ca\(^{2+}\) to histamine. Examples of the influence of mitochondria on Ca\(^{2+}\) signalling continue to accumulate in many and varied cell types, raising the possibility that despite their relatively low mitochondrial volume, this also occurs in EC.

5. The mechanism by which mitochondrial damage leads to heart disease

Mitochondria are a potential target of classical risk factors (diabetes, oxLDL, ageing, smoking, and shear stress) and damage to mitochondria affects endothelial function. For example, the normal age-related decline in endothelial function is exacerbated in animals with genetic depletion of (mitochondrial) MnSOD, in parallel with an increase in ROS. The relationship between mitochondrial dysfunction, mitochondrial ROS production, and endothelial dysfunction is illustrated by the example of prohibitin, a mitochondrial protein highly expressed in the vasculature. Although the exact role of this protein is not known, it appears to be involved in the maintenance of mitochondrial organization. When prohibitin expression is prevented in EC, complex I is inhibited, mitochondrial ROS production increases, and EC migration and in vivo capability for angiogenesis is impaired.
Damage to endothelial mitochondria may conceivably contribute to heart disease in three ways:

(i) by impairing the normal function of mitochondria described above,
(ii) by aggravating mitochondrial dysfunction (e.g. causing excessive mitochondrial ROS production), and, in extreme situations, 
(iii) by leading to the activation of defensive pathways including mitochondrial fragmentation, autophagy/mitophagy, and apoptosis.

Given that the understanding of normal function of endothelial mitochondria is still somewhat rudimentary, it is difficult to assess whether heart disease is influenced by impairment of the normal function of endothelial mitochondria. However, there is substantial evidence for mitochondrial dysfunction culminating in mitochondrial damage and apoptosis in heart disease, points that will be elaborated below.

As discussed, ROS underlie much of the endothelial damage related to heart disease. Lipid oxidation products such as oxLDL may even interact directly with EC mitochondria to increase ROS production. In dogs with pacing-induced heart failure, superoxide production from mitochondria and NADPH oxidase is detectable in genetically obese and hyperglycaemic rat hearts before they undergo elimination by autophagy (i.e. ‘mitophagy’). This chain of events has been observed in EC after exposure to hyperglycaemia, to ROS generated by activated macrophages, or after ischaemia and reperfusion injury. There is still some debate as to the extent that these mechanisms are protective, clearing faulty mitochondria and cells, or might themselves contribute to the damage of the original stimulus.

### 6. Novel therapeutic approaches targeting mitochondria

With the emerging realization that mitochondria play a central role in the development of many important degenerative diseases, there are a number of interesting novel pharmacological therapeutic approaches being developed. Unlike transgenic approaches, these are usually not cell-type-specific and will therefore affect mitochondrial ROS production in aortic EC resulting in eNOS inhibition. ROS production from mitochondria and NADPH oxidase is detectable in genetically obese and hyperglycaemic rat hearts before they develop cardiac dysfunction and endothelial dysfunction, suggesting a causative role. The contribution of inflammation must also be considered, as macrophages can generate NO that interacts with ROS from the mitochondria of EC and lead to an inflammatory mode of cell death called necroptosis. Inhibition of this pathway with necrostatin-1 prevents EC death and also protects against cardiac ischaemia and reperfusion injury both in vitro and in vivo.

Some of the most compelling evidence that mitochondrial ROS is a causative agent in the development of heart disease comes from experiments using transgenic mice to alter expression of mitochondrial antioxidant proteins. Initial experiments using genetic knockouts showed that mice lacking MnSOD produce huge amounts of mitochondrial ROS and develop cardiomyopathy within the first weeks of birth. Transgenic overexpression of the mitochondrial ROS scavenger, thioredoxin (Trx2), however prevents mitochondria oxidative stress in hypertensive mice, preserving endothelial function.

Significantly, even when overexpression of thioredoxin is restricted to the endothelial mitochondria, it is still able to decrease oxidative stress, improve aortic EC function, and prevent atherosclerotic lesions in the ApoE−/− mouse model. Arteriogenesis, angiogenesis, and endothelial function are also enhanced in these mice after limb ischaemia, due to increased NO bioavailability and prevention of apoptosis. These data demonstrate that ROS production by endothelial mitochondria contribute to heart disease, and therefore that targeted scavenging of ROS in the endothelial mitochondria may have various protective and beneficial effects on the heart.

The mitochondria of primary EC are typically elongated, with membrane potential of approximately −140 mV, as can be demonstrated with the aid of a lipophilic potentiometric fluorescent dye such as tetramethyl rhodamine methyl ester (TMRM; Figure 1F and H). Damage to mitochondria causes them to depolarize, as the electron transport chain and/or F0F1ATPase cease to function. Depolarization of mitochondria often precedes mitochondrial fragmentation (Figure 1G) and also increases the likelihood of opening of the mPTP. With the emerging realization that mitochondria play a central role in the development of many important degenerative diseases, there are a number of interesting novel pharmacological therapeutic approaches being developed. Unlike transgenic approaches, these are usually not cell-type-specific and will therefore affect mitochondrial ROS production.

#### 6.1 Mitochondrially targeted ROS scavengers

After generally disappointing results using ROS scavengers to treat heart disease, research interest has moved on to what might be called ‘second generation’ ROS scavengers, designed to target specific intracellular sources of ROS. These are based on the hypothesis that it is possible to deplete ‘detrimental’ ROS, while leaving beneficial, ‘signalling’ ROS pathways intact, supported by early observations that mice lacking manganese (mitochondrial) superoxide dismutase develop dilated cardiomyopathy, and more recently, that overexpression of catalase in the mitochondria decreases oxidative damage, decreases mtDNA damage, delays cardiac pathology, and extends lifespan of mice. Overexpression of another mitochondrial antioxidant, peroxiredoxin-3, prevents left ventricular remodelling and failure after myocardial infarction in mice. Although some of the benefit is undoubtedly due to scavenging of mitochondrial ROS in cardiomyocytes, as suggested by the fact that cardiomyocyte-specific knockouts of MnSOD develop heart failure, the recent demonstration that overexpression of mitochondrial Trx2 in the
endothelium protects from atherosclerosis strongly suggests that endothelial mitochondria are a valid therapeutic target.

One of the first targeted ROS scavengers to be developed was MitoVit-E, in which vitamin E is covalently attached to a triphenylphosphonium cation (Figure 4). MitoVit-E successfully decreased ROS production and apoptosis in bovine aortic EC exposed to oxidative stress but was ineffective against hypoxic–ischaemic striatal injury in neonatal rats. One disadvantage of vitamin E is that it is not a catalytic antioxidant and its scavenging activity is not regenerated. In contrast, MitoQ10 consists of a lipophilic triphenylphosphonium cation covalently attached via an aliphatic linker to a ubiquinone derivative (Figure 4), which, after detoxifying an oxidant species, is regenerated by the respiratory chain. MitoQ10 concentrates several hundred-fold within the mitochondria, is orally bioavailable, distributes in various organ including the heart without adverse effects in rats or humans, and decreases mitochondrial oxidative damage in rodent models of cardiac ischaemia and reperfusion injury. Importantly, no effect is observed when using the lipophilic cation lacking ubiquinone.

MitoQ was not designed specifically to target endothelium, but the biophysical mechanism that produces ROS during EC respiration appears to be much the same as in other cell types. A careful examination of ROS generation in mitochondria isolated from bovine aortic EC determined that superoxide production results largely from reverse electron transport to complex I, but concern has been expressed that mitoQ might actually enhance superoxide production derived by forward transport, and rather than scavenging ROS, in some situations, it seems that mitoQ can actually ‘increase’ mitochondrial ROS production via redox cycling. This is suggested by increased oxygen consumption in mitoQ-treated EC. In contrast, there was no evidence of pro-oxidant effect in mice administered mitoQ orally for 28 weeks.

Administration of MitoQ10 to stroke-prone hypertensive rats improves endothelial function and attenuates cardiac hypertrophy, suggesting that endothelial ROS production contributes to the pathology in this model. However, other sources of ROS appear to be involved since inhibition of NADPH oxidase has a similar effect.

Although these experiments implicate ROS in the development of cardiac hypertrophy, they do not distinguish whether it is the prevention of damaging ROS or ‘signalling’ ROS that is important. Furthermore, it will be important to verify that the effects are really via inhibition of mitochondrial ROS, and not increase in ROS production and consequent alteration of metabolism.

Despite the concern raised above that mitochondrial targeted ROS scavengers would scavenge both ‘detrimental’ and ‘beneficial’ ROS indiscriminately, the results of animal studies using MitoQ10 or an alternative compound called SkQ1 (Figure 4) have certainly been impressive. Indeed, when perfused through isolated heart preparations or fed to rats, SkQ1 was able to reduced ischaemia-induced arrhythmia and infarct size when used at a concentration that was an astounding six orders of magnitude lower than that of mitoQ. The results of planned clinical studies are awaited with great interest.

6.2 Compounds affecting mitochondrial shape or quantity

Mitochondrial fragmentation is considered to be an obligatory step in the pathway towards apoptosis. Fragmentation and fusion are processes mediated by a number of GTPases. By altering expression or activity of these proteins, it is possible to tip the balance towards a more elongated mitochondrial morphology, which also increases resistance of cells to oxidative and other types of injury. mDivi-1 is a small molecule that inhibits fragmentation, thereby increasing the extent of mitochondrial elongation. Treatment of cells or mice with mDivi-1 confers cardioprotection against ischaemia and reperfusion. Interestingly, SkQ1 also prevents fragmentation of mitochondria in kidney epithelial cells exposed to ischaemia and reperfusion.

However, this is a new and rapidly evolving field of mitochondrial research, and the long-term effects of stimulating mitochondrial fusion are not known. The importance of clearing damaged mitochondria by autophagy or mitophagy is emerging, and as the tools for examining and inhibiting these processes are refined, there will no doubt be a great deal of interest in their role in the endothelium.

Mitochondrial mass is altered in heart disease, leading to the hypothesis that increasing mitochondrial biogenesis may protect the diseased heart. Cardiomyocyte-specific overexpression of master mitochondrial transcription factor A in mouse myocardium prevented the development of heart failure. In contrast, however, cardiac-specific overexpression of another master mitochondrial gene regulator, PGC1-α, led to development of cardiomyopathy. The effect of such manipulations in EC on development of cardiac disease has not yet been investigated.

Figure 4 Chemical structure of some mitochondrially targeted ROS scavengers and their parent molecules.
6.3 Compounds targeting sirtuins

There is great interest currently in the Class III (NAD+-dependent) deacetylases called sirtuins, not least because of their demonstrated involvement in ageing. Recently, sirtuins family members SIRT3, SIRT4, and SIRT5 have been shown to be mitochondrial (reviewed in Gertz and Steegborn1). Endothelial overexpression of SIRT1 has been shown to suppress atherogenesis and preserve endothelial function in mice fed a high-fat diet and may protect against hyperglycaemia-induced vascular cell senescence. The clinical potential of these observations is suggested by the fact that resveratrol (believed to be one of the protective components of red wine) attenuates mitochondrial ROS production in EC and induces mitochondrial biogenesis in the aortas of type 2 diabetic mice, suggesting the potential for new treatment approaches targeting endothelial mitochondria in metabolic diseases. However, this story is somewhat clouded, since recent data suggests that resveratrol does not actually inhibit sirtuins.

6.4 Indirect approaches to mitochondrial protection

Of the many and varied approaches being taken to prevent heart disease, a significant number are intended to protect the cardiovascular endothelium, and many of these are likely to influence mitochondrial function, even if indirectly. These include drugs targeting the eNOS pathway such as tetrahydrobiopterin, which has also been shown to restore endothelial function after reperfusion injury. A number of known cardioprotective drugs have been shown to affect mitochondrial activity. Even statins, widely used to reduce levels of circulating cholesterol, have recognized beneficial effects on the endothelium that may be partly mediated by enhanced mitochondrial ROS scavenging by thioredoxin. Other cardioprotective drugs such as the KATP channel opener, diazoxide, have been proposed to act selectively on mitochondrial channels; however, given the incomplete specificity of this and other typically used reagents, rigorous evaluation of the role of the mitochondrial KATP channel awaits its unambiguous molecular identification, as has been recently reviewed.

Ischaemic preconditioning is a well-studied method of protecting the myocardial mitochondria from ischaemia and reperfusion injury. Measuring endothelial function by flow-mediated dilatation, it has been shown that the human endothelial function can be preconditioned (reviewed in Davidson and Duchen). Even more dramatically, ischaemic preconditioning of the limb has been shown to decrease the cardiac injury associated with a coronary bypass operation. Although it is difficult to determine what proportion of this protection is arrived at via the cardiac endothelium, it does give further support to the idea that EC and their mitochondria represent a relevant target for future therapies.

7. Conclusion

No doubt part of the reason that mitochondria of the cardiovascular endothelium have been somewhat ignored has been the difficulty of studying their function in the intact heart. However, this is changing with the development of novel transgenic tools such as the EC-Trx2 mice, which have already been used to demonstrate the importance of endothelial mitochondria in heart disease. An imbalance in NO, ROS, or Ca²⁺ signalling can result in: loss of normal mitochondrial function; perturbation of a mitochondrial signalling mechanism; or damage to the vascular endothelium. Therefore, in disease conditions, re-establishment of this balance of NO, ROS, and Ca²⁺ signalling is essential to restore normal mitochondrial functioning. Newly developed drugs that targeting mitochondria are opening up exciting clinical possibilities. The actual cellular destination of these drugs in the intact heart or animal needs to be clarified, but evidence is accumulating that at least part of their beneficial effect may be exerted in the endothelium.

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