Translating the effects of statins: From redox regulation to suppression of vascular wall inflammation

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Summary
Vascular oxidative stress is a key feature of atherogenesis, and targeting vascular redox signalling is a rational therapeutic goal in vascular disease pathogenesis. 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors or statins are potent lipid-lowering drugs that improve cardiovascular outcomes. It is now widely accepted that cardiovascular disease prevention by statins is dependent not only on their lipid lowering effects, but also on their beneficial effects on vascular redox signalling. Cell culture and animal models have provided important findings on the effects of statins on vascular redox and nitric oxide bioavailability. Recent evidence from studies on human vessels has further enhanced our understanding of the “pleiotropic” effects of statins on vascular wall. Reversal of endothelial dysfunction in human vessels by statins is dependent on the mevalonate pathway and Rac1 inhibition. These critical steps are responsible for reducing NADPH-oxidase activity and improving tetrahydrobiopterin bioavailability and nitric oxide synthase (NOS) coupling in human vessels. However, mevalonate pathway inhibition has been also held responsible for some of the side effects observed after statin treatment. In this review we summarise the existing knowledge on the effects of statins on vascular biology by discussing key findings from basic science as well as recent evidence from translational studies in humans. Finally, we discuss emerging aspects of statin pleiotropy, such as their effects on adipose tissue biology and adipokine synthesis that may light additional mechanistic links between statin treatment and improvement of clinical outcome in primary and secondary prevention.

Keywords
Statins, NADPH oxidase, eNOS coupling, vascular redox, atherosclerosis

Introduction
Healthy human physiology is reliant on a complex balance of pro- and anti-oxidant mechanisms. The generation of reactive oxygen species (ROS) such as superoxide anions (O$_2^-$) in the vasculature leads to reduced nitric oxide (NO) bioavailability, endothelial dysfunction and atherogenesis (1, 2).

Reduction of low-density lipoprotein (LDL) cholesterol levels with statins (3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors) has been associated with a reduction of major cardiovascular events in both primary and secondary prevention trials (3, 4). Besides their main effect of lowering atherogenic LDL-cholesterol levels, statins have a number of pleiotropic effects which may contribute to their vascular benefits independent of lipid lowering (5–7). Studies performed in our group on humans vessels have highlighted the beneficial pleiotropic effects of short-term statin treatment on vascular redox signalling via inhibition of NADPH-oxidase activity and improvement of endothelial NOS (eNOS) coupling (8, 9).

Statins in primary and secondary prevention
Large randomised clinical trials have demonstrated the beneficial effects of lipid-lowering treatment with statins in primary (10, 11) and secondary prevention (12, 13) of cardiovascular disease. In the landmark WOSCOPS (West of Scotland Coronary Prevention Study Group) trial pravastatin reduced coronary events by 31% (95% confidence interval [CI], 17–43%) and coronary mortality by 32% (95%CI, 3–53%) in patients with hypercholesterolaemia (10). Moreover the large AFCAPS/TexCAPS trial (Air Force/Texas Coronary Atherosclerosis Prevention Study) demonstrated that statins could lower cardiovascular disease risk even in subjects with average LDL cholesterol levels; lovastatin (20–40 mg/day) treatment reduced incidence of first acute major coronary events (relative risk [RR]=0.63; 95%CI 0.50–0.79). Large randomised clinical trials that followed demonstrated a significant clinical benefit with statins on vascular outcomes also in the secondary setting: statins effectively lower cardiovascular disease risk both in stable coronary heart disease (14) and in patients with acute coronary syndromes (15).
Intervention with Pravastatin in Ischaemic Disease) trial suggested that cardiovascular risk reduction was significant even in patients with LDL cholesterol below 100 mg/dl (14). This hypothesis was further tested in the JUPITER (Justification for the Use of Statins in Prevention—an Intervention Trial Evaluating Rosuvastatin) trial (4); in 17,802 apparently healthy men and women with low LDL cholesterol levels (<130 mg/dl) and increased C-reactive protein (CRP) levels (>2.0 mg/l) rosuvastatin (20 mg/day) reduced cardiovascular risk (RR= 0.56, 95%CI, 0.46–0.69) for the combined primary end point (4). JUPITER provided thus the first strong clinical evidence for the non-lipid lowering (or “pleiotropic”) effects of statins: statins improve clinical outcome in healthy, normolipidaemic subjects with elevated CRP levels via suppression of systemic inflammation. However, although the pleiotropic effects of statins on clinical outcome are widely accepted, the underlying mechanism responsible for these effects is complex and largely unclear in human cardiovascular disease.

Inhibition of mevalonate pathway: Further to lipid lowering

Statins inhibit mevalonate formation, a critical step in the metabolic pathway of cholesterol biosynthesis, via inhibition of substrate binding to the active site of the HMG-CoA reductase. This appears to have both beneficial and deleterious effects (Fig. 1).

By inhibiting the mevalonate pathway, statins prevent the synthesis of its downstream isoprenoid intermediates, such as geranylgeranylpyrophosphate (GGPP) and farnesylpyrophosphate (FPP) (2). These moieties induce protein prenylation, i.e. the addition of a prenyl group to C-terminal cysteine residue(s) of proteins. Candidate proteins for isoprenylation by GGPP/FPP are the small GTP-binding proteins Ras, Rac and Rho, which regulate diverse cellular functions such as cell shape, motility, secretion and proliferation. Statins exert a number of LDL-independent effects in human atherosclerosis (16). By inhibiting the mevalonate pathway in the vascular wall, statins suppress the formation of GGPP/FPP and prevent the activation of Rac directly in vascular endothelial and smooth muscle cells (9, 17, 18).

Conversely, inhibition of the mevalonate pathway may also be an important mechanism that leads to some of the major side effects of statins. Ubiquinone or coenzyme Q10 is an isoprenoid derivative found mainly in the mitochondrial electron transport chain. By inhibiting the mevalonate pathway, statins deplete cellular levels of ubiquinone, the synthesis of which is dependent on mevalonate (19). Other side effects of statins, such as abnormal protein glycosylation due to dolichol deficiency or negative effects on selenoproteins and tau proteins are thought also to stem from inhibition of the mevalonate pathway (19). Depletion of GGPP by statins and inhibition of GTPase protein prenylation, such as Rac1 and Rho, has been held responsible for their myotoxicity and hepatotoxicity, by inducing mitochondrial damage (20, 21).

Effects on antioxidant defence mechanisms in the vasculature

Clinical studies have demonstrated that statin treatment has beneficial effects on plasma levels of key antioxidant enzymes, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) (22). Circulating levels of antioxidant enzymes are poor surrogate markers of cellular redox activity. However, evidence suggests that statins have significant anti-oxidant effects in a variety of cell types in the vasculature. For instance, atorvastatin up-regulates catalase expression in human endothelial cells without affecting SOD isoforms and GPx expression (23). In vascular smooth muscle cells (VSMCs) simvastatin induced heme oxygenase expression, an important antioxidant defence system, both in vitro and in vivo (24). Furthermore in animal studies, simvastatin increased both SOD and GPx expression in aortic rings from spontaneously hypertensive rats (25). Similarly, in rabbits pitavastatin administration significantly increased aortic tissue Cu/ZnSOD activity and reduced vascular O2·− production, having beneficial effects on aortic stiffness (26). These findings suggest that, by improving anti-oxidant cellular defenses, statins enhance ROS elimination at cellular level and favourably modulate vascular redox.

Effects on vascular NADPH-oxidase: Evidence from basic science

Although a direct scavenging effect of statins on free radicals has been suggested (27), their effects on vascular NADPH-oxidase activity are thought to be more important. NADPH oxidases are a group of several homologues (Nox 1–5 and Duox 1–2). Nox1, Nox2, and Nox5 are the isoforms which have been detected in endothelial cells and VSMCs (28). Nox2 has also been detected in vascular wall cells, but its function differs from that of the other vascular Nox isoforms. While the other Nox isoforms are a significant vascular source of O2·−, Nox4 produces H2O2, and its expression may be differentially regulated during atherosclerosis development (28). NADPH-oxidase is one of the main O2·− sources in human coronary arteries (29). NADPH–oxidase–derived O2·− generation is dependent on the activation of the membrane subunits of the enzyme by translocation of the p47phox and p67phox cytosolic subunits to cell membrane. The small Rac1 protein is also essential to enzyme activation. The activity of NADPH-oxidases is regulated by a variety of stimuli (28). Binding of angiotensin II to its membrane angiotensin II type 1 receptor results in downstream activation of protein kinase C, which phosphorylates p47phox, thereby increasing NADPH–oxidase activity. A variety of other pro-inflammatory stimuli, such as pro-inflammatory cytokines, growth factors, oxidised LDL, thrombin, endothelin-1 and insulin can also increase NADPH-oxidase derived ROS (28). The recently developed notion of compartmentalisation of redox signalling and cross-talk between subcellular components could mean that ROS generated by other sources such as mitochondria could also affect the enzymatic activity of membrane-bound Nox.
isoforms (30). Guzik et al. (29) have elaborately demonstrated that NADPH-oxidase activity and subunits’ expression are significantly upregulated in the coronary arteries of patients with established atherosclerosis, suggesting an important role of NADPH-oxidase in the pathophysiology of coronary atherosclerosis.

The effects of statins on vascular Nox isoforms activity have been well documented. Importantly, the ability of statins to suppress NADPH-oxidase activity appears to be a class effect (23, 31, 32). Studies in rat aortic VSMCs in vitro and in an in vivo model of spontaneously hypertensive rats have shown that atorvastatin down-regulated Nox1 mRNA expression and inhibited Rac1 membrane translocation, suppressing O2- generation in a mevalonate-inhibitable way (23). Statins also inhibit the NADPH-oxidase activity of THP-1 monocytes, which may be pivotal given the importance of this cell type in the atherosclerotic process and vascular wall inflammation (32). In mouse models of angiotensin infusion and ApoE deficiency, chronic atorvastatin treatment reduces expression of all Nox1, Nox2 and Nox4 homologues in vascular tissue (5). These effects of statins are mainly dependent on inhibition of GGPP formation downstream of mevalonate; mevalonate or GGPP addition completely reverses these effects on NADPH-oxidase subunits expression and enzyme activity, while FPP causes only a partial reversal. GGPP is responsible for the membrane translocation of the small GTP-binding Rac1 and activation of the NADPH-oxidase membrane bound complex. This has been elegantly demonstrated in a mouse model where atorvastatin significantly reduced NADPH-oxidase activity and improved ex vivo vasorelaxation of aortic rings (33). These effects were blunted in adenovirus-transfected mice which expressed a constitutively active Rac1 isoform, suggesting that inhibition of Rac1 activation is the pivotal step in mediating the effects of statins on NADPH-oxidase (33).

Effects on NO bioavailability: Evidence from basic science

Vascular NO bioavailability is a major determinant of vascular homeostasis and global vascular function. NO is a strong vasodilator, activating guanylyl cyclase in VSMC, increasing guanosine triphosphate (GTP) and inducing VSMC relaxation via changes in calcium intracellular concentrations. However NO also exerts pleiotropic effects on the vasculature that cumulatively have an

\[ \text{Figure 1: Endpoints of the mevalonate pathway. HMG-CoA reductase inhibition by statins blocks the mevalonate pathway which is critical for cholesterol and other steroids biosynthesis. Prenoid intermediates in the mevalonate pathway, such as geranylgeranylpyrophosphate (GGPP) and farnesylpyrophosphate (FPP), induce posttranslational modification of small proteins, regulating various aspects of cellular homeostasis. Inhibition of mevalonate pathway and GGPP formation by statins is mainly responsible for their beneficial pleiotropic, non-lipid lowering effects in the vasculature. However, side effects of statin use also stem from blockade of the mevalonate pathway, which concomitantly inhibits biosynthesis of ubiquinone (coenzyme Q10), dolichols and selenoproteins. DMAPP = dimethylallyl pyrophosphate; GPP = geranylpyrophosphate; IPP = isopentenyl-5-pyrophosphate,} \]
anti-thrombotic, anti-inflammatory and anti-atherogenic potential (34).

NOS isoforms are dimers which use L-arginine and molecular oxygen as substrate, producing L-citrulline and NO. The co-factor tetrahydrobiopterin (BH₄) is critical for coupled electron transfer and the generation of NO (35). However, BH₄ itself is prone to oxidation. Thus, in vascular disease states associated with high oxidative stress, vascular BH₄ is depleted, NOS is rendered uncoupled and is converted into a source of superoxide anions instead of NO (36). Statins beneficially affect vascular NO bioavailability by exerting favourable effects on both eNOS and BH₄ bioavailability.

Direct effects on NOS at transcriptional, translational, and posttranslational level

Statins have beneficial effects on endothelial NOS (eNOS) production. In cell cultures statins can up-regulate eNOS gene expression due to an inhibition of Rho GTPase protein signalling. This effect is reversed by the addition of GGPP and L-mevalonate (but not by FPP or LDL) (7). Rho signalling inhibition has been implicated in eNOS mRNA stabilisation by statins (6). Treatment of endothelial cells with either simvastatin or rosuvastatin resulted in a time- and dose-dependent increase in the eNOS transcripts with long poly(A) tails; this effect conferred two- or three-fold increased stability to eNOS mRNA and was associated with Rho inhibition (6). Phosphorylation of eNOS protein at Ser/Thr residues is a well-known mechanism affecting eNOS enzymatic activity. Five Ser/Thr phosphorylation sites in human eNOS have been identified up to present: Ser114, Thr495, Ser615, Ser633 and Ser1177. In endothelial cells simvastatin induces eNOS Ser633 phosphorylation in an AMP-activated protein kinase (AMPK)-mediated way (37). In animal models, statins induce AMPK signalling and increase eNOS protein phosphorylation at Ser1177, in an L-mevalonate inhabitable way, resulting in improved acetylcholine-induced vasorelaxations (38). Therefore, statin-mediated phosphorylation of eNOS protein at both Ser1177 and Ser633 might be mechanisms by which statins confer enhanced eNOS activity and increase NO bioavailability. Other effects of statins on eNOS at the posttranslational level include beneficial effects on eNOS – caveolin interactions as well as interactions with heat shock protein 90 (Hsp90) that alter eNOS cytosolic abundance and enzymatic activity (39).

Effects on NOS coupling, the role of BH₄

However, increased eNOS activity (through changes in its phosphorylation status) can also result in increased O₂⁻ generation instead of NO in the absence of sufficient BH₄ to maintain eNOS enzymatic coupling. Thus statins provide a unique, multi-level therapeutic strategy that increases eNOS activity with simultaneous increase of BH₄, vascular bioavailability.

Statins up-regulate GTP cyclohydrolase I (GTPHC) gene expression, the main enzyme determining de novo BH₄ biosynthesis. Increased GTPCH expression is a key regulator of BH₄ bioavailability and eNOS coupling in human atherosclerosis, making it an attractive therapeutic target in vascular disease (40). In this way, statins directly increase BH₄ bioavailability in vascular endothelium and enhance NOS coupling (41). Statins are also able to indirectly increase BH₄ levels by reducing ROS generation from other sources, such as NADPH-oxidase-derived O₂⁻, thereby allowing eNOS to remain coupled.

Translating findings from cell/animal models to humans

Substantial work over the past years has elucidated aspects of vascular redox biology in human disease. Translational studies have further clarified the main mechanisms by which statins confer beneficial effects on vascular redox signalling in human vessels. Rueckschloss et al. (42) have demonstrated that statin treatment in patients undergoing coronary bypass surgery (CABG) is associated with lower gp91phox mRNA expression in the internal mammary arteries. Rac1 inhibition seems to be the main mechanism for statin-mediated effects on NADPH-oxidase activity in human vessels. We have demonstrated that short-term atorvastatin treatment rapidly improves saphenous vein grafts redox state by reducing NADPH-oxidase-related O₂⁻ production from patients undergoing CABG (9). Even though atorvastatin pre-treatment did not significantly change vascular protein levels of Nox1, Nox2 and Nox4 isoforms, it had a significant effect on NADPH-oxidase activity. Our findings from ex vivo incubations of saphenous vein rings with atorvastatin suggested that this effect was due to a striking reduction in Rac1 activation and membrane-bound Rac1 and p67phox subunit (9).

The beneficial effects of statins on vascular NO bioavailability have been confirmed in many clinical studies. In ex vivo models, chronic statin administration is associated with improved acetylcholine-induced vasorelaxation of saphenous vein rings harvested from patients undergoing CABG (8). Further to their beneficial effects on NO bioavailability through the Rho pathway, we recently highlighted the importance of Rac1 inhibition by statins on eNOS coupling in human vessels (8). Short-term administration of atorvastatin in patients undergoing CABG is associated with reduced O₂⁻ generation and improved eNOS coupling in the internal mammary artery of these patients (8). These effects are mevalonate-inhibitable and dependent on Rac1 inhibition by atorvastatin, which results in up-regulation of vascular GTPCH expression and improvement of vascular BH₄ bioavailability (8).

In clinical studies statins consistently improve endothelial function in vivo in subjects with cardiovascular risk factors (43, 44), established coronary artery disease (45) or heart failure (46). Notably, even short-term statin administration for three days induces a significant improvement in endothelium-dependent vasodilatation of brachial artery (44). In studies using magnetic resonance imaging, initiation of statin treatment is associated with improvement of endothelial function and aortic distensibility as well as re-

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gession of plaque index in aorta and carotid arteries at three months (47).

While the lipid-lowering effects of statins are considered to be a class effect, differences exist in the pleiotropic effects of statins. Lipophilic statins, such as atorvastatin and simvastatin, are thought to have more potent vascular effects than hydrophilic statins (e.g. pravastatin) which are not easily diffused through cell membranes. While atorvastatin and pravastatin have similar effects on endothelial function in vivo, atorvastatin is associated with a greater reduction in lipid markers of oxidation (48). This notion is not though consistently confirmed in clinical studies; for example it has been demonstrated that the hydrophilic rosuvastatin is a more potent inhibitor of ROCK kinase and more efficient than atorvastatin in improving endothelial function in patients with atherosclerosis (49). Finally the distinct metabolic effects of statins could also contribute to their differential vascular effects as discussed next (50).

From vascular redox regulation to suppression of vascular inflammation

Favourable modulation of vascular redox state both by improving antioxidant defences and NO bioavailability and by reducing NADPH oxidase activity has beneficial effects on vascular biology and global vascular function. Statins blunt the activation of redox sensitive pathways such of nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1), which lead to proinflammatory gene expression (1). The expression of proinflammatory cytokines and chemokines by activated endothelial cells and VSMCs leads to perpetuation of vascular wall inflammation. This feed forward proinflammatory loop is blunted by inhibition of toll-like receptor 4 signalling in endothelial cells (51). An additional pathway via which statins suppress vascular inflammation is by inhibiting oxidised LDL (ox-LDL) signalling in vascular wall. Ox-LDL is a potent atherogenic molecule that elicits a pro-inflammatory cascade in en-
dothelial cells by binding to LOX-1, the lectin-like receptor for oxLDL. Statins prevent oxidative modification of LDL both by suppressing vascular oxidative stress and directly by their free radical-scavenging properties (52). In addition statins inhibit vascular signalling of ox-LDL by decreasing expression of LOX-1 on endothelial cells surface (53). Lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme produced by inflammatory cells that travels together with LDL particles, is closely linked with atherogenesis development and homing of inflammatory cells in vascular lesions (54). Reduction of soluble Lp-PLA2 mass and activity is considered an additional important anti-inflammatory effect of statins (54). Furthermore statins blunt adhesion molecule expression (55), which promotes infiltration of circulating monocytes and inflammatory cells in the sub-endothelial space. Statins also enhance endothelial cell barrier protection, an effect dependent both on RhoA and Rac1 inhibition (56).

VSMCs proliferation is one of the main mechanisms of saphenous vein grafts occlusion post CABG as well as of post-angioplasty restenosis. Direct inhibitory effects of statins on VSMC proliferation are considered an important mechanism of their anti-atherogenic lipid-lowering independent potential. The small GTP-binding Ras and Rho protein are involved in cell cycle regulation (57); in cell studies in vitro inhibition of Rho pathway signalling by statins blunts human saphenous VSMCs proliferation (58). Apoptosis induction (59), accelerated DNA repair (60) and reduced vascular calcification (61) are additional beneficial effects of statins on VSMCs. Finally matrix metalloproteinases expression, responsible for extracellular matrix degradation, is also blocked by statins (62).

In summary statin-mediated inhibition of redox sensitive transcriptional factors at cellular levels blocks the vicious cycle of vascular inflammation and oxidative stress and the resulting proatherogenic vascular phenotype (Fig. 2).

**Indirect effects of statins on the vascular wall Immunomodulatory effects**

Further to their effects on pro-inflammatory pathways in endothelial cells and VSMC, statins reduce vascular wall inflammation by their direct effects on inflammatory cells. Major histocompatibility (MHC) class II expression by antigen-presenting cells is reduced by statins. Furthermore, statins reduce interferon-gamma-mediated MHC class II expression in stimulated macrophages and endothelial cells (63). Given the role of MHC class II in T-cell activation and immunity regulation, this effect of statins is considered as a major immunosuppressive mechanism. Another important immunosuppressive effect of statins is the blocking of β2 integrin, leukocyte function antigen-1 (LFA-1) on leukocytes surface, which is important for leukocytes’ adhesion and co-stimulation. In vitro studies have demonstrated that statins inhibit proinflammatory cytokine expression from T-cells (64) and peripheral blood mononuclear cells (65). Statins also reduce lipopolysaccharide-stimulated B-lymphocyte proliferation. The expression of chemokines in the vascular wall, such as RANTES, monocyte chemo-attractant protein-1 (66) and macrophage inflammatory protein-1α by stimulated THP-1 monocytes (67), is also reduced by statins. Cumulatively, these immunomodulatory effects of statins lead to reduced vascular wall inflammation in experimental animal models (66, 68), and have stimulated interest in statin use in autoimmune disease states (3).

**Effects on platelet – endothelium interactions**

Platelet activation also contributes to endothelial dysfunction and atherothrombosis (69). Activated platelets exhibit lower NO formation, increased ROS generation and enhanced release of proinflammatory mediators (69). Statins reduce platelet activation and aggregation by exerting favourable effects on platelet redox state (70). Treatment of hypercholesterolaemic patients with fluvasatin reduces ADP-mediated platelet aggregation, enhances glutathione expression by platelets and platelet-derived NO synthesis (71). These effects seem to be dependent on GGPP inhibition (71). Furthermore CD40/CD40 ligand signalling can be efficiently inhibited by statins, CD40/CD40 ligand is a pivotal mediator of the interactions between platelets and vascular endothelium (69); CD40/CD40L signalling leads to activation of pro-inflammatory pathways in endothelial cells, inducing adhesion molecule expression and chemotaxis of inflammatory cells (72). Monocyte infiltration inside the vascular wall feed-forwards vascular wall inflammation and ROS generation by endothelial cells and VSMC (72). In endothelial cells statins decrease in vitro CD40L surface expression (73) and prevent thrombin-mediated down-regulation of CD39/ADPase in a Rho dependent way (74), thus reducing platelet-endothelial cell interactions. Furthermore statins attenuate platelet-derived growth factor induced migration of VSMC (75), a critical step in atherogenesis.

**Effects on the crosstalk between adipose tissue and the vascular wall**

The modulation of adipose tissue biosynthetic activity might be an additional mechanism via which statins alter vascular redox state. Adipose tissue may affect vascular function and atherosclerosis development via the release of bioactive molecules (adipokines) in a paracrine or endocrine manner (76). Even though statins do not affect insulin resistance in adipose tissue, it has been demonstrated that lipophilic statins can indeed change the expression of adipokines. Pravastatin does not alter gene expression of pro-inflammatory cytokines (such as interleukin-6 and tumour necrosis factor-α) but it significantly up-regulates adiponectin (an important anti-inflammatory adipokine) expression from the mediastinal fat depot of patients with coronary heart disease (77). This might be particularly important given the beneficial effects of adiponectin on eNOS expression and NO bioavailability in the vascular endothelium (76). However no data is available on the effects of statins on epicardial adipose tissue biosynthetic activity, which may be more relevant to coronary heart disease. Notably, the effects of
Statins on adipose tissue might be dependent on the type of statin used, as well as the anatomical site of adipose tissue. Experimental and clinical studies have demonstrated that statins have distinct metabolic effects (78); simvastatin-induced changes in adipose tissue morphology properties have adverse effects on adiponectin secretion from adipocytes and lead to lower circulating levels of high-molecular-weight adiponectin, the isoform mainly responsible for the beneficial vascular effects of adiponectin (79). On the contrary, pravastatin has been consistently associated with a beneficial effect on adiponectin mRNA expression (78). Recent findings on the effects of statins on perivascular adipose tissue have highlighted an additional beneficial effect on vascular function by modulation of perivascular tissue biology; atorvastatin (but not pravastatin) increases the vasodilatory effect of periaortic adipose tissue in rats by augmenting adipose tissue-derived H2S (80). This is mediated by depletion of coenzyme-Q bioavailability by statins, which is responsible for H2S cabalism through mitochondrial oxidation (80). The effects of statins on adipokine biosynthesis and their role in the crosstalk between adipose tissue and vascular wall warrant further investigation.

Conclusions

Statins are powerful lipid-lowering drugs that improve clinical outcome and secondary prevention of cardiovascular disease. The putative pleiotropic effects of statins on vascular wall have been consistently demonstrated in basic science models. In cell and animal models statins suppress the activation of pro-inflammatory pathways, lower vascular ROS generation and ameliorate NO bioavailability. Translational research has further confirmed that suppression of NADPH-oxidase activity and improvement of NOS coupling are major mechanisms responsible for improvement of vascular function in human atherosclerosis. Inhibition of GGPP formation and subsequent Rac1 activation is a key step for mediating the pleiotropic effects of statins on human vascular tissue and a promising therapeutic target. The immunomodulatory properties of statins and effects on platelets are also responsible for suppression of vascular wall inflammation. Other emerging aspects of statin pleiotropy, such as effects on perivascular adipose tissue, might be equally important for their beneficial effects on vascular function. Better understanding of the pleiotropic mechanisms by which statins affect vascular function leading to improvement of clinical outcome in primary and secondary prevention, may allow the identification of novel therapeutic targets in atherosclerosis. This will fulfill our expectations from translational science: to translate basic science to clinical practice, and allow the development of novel areas of basic science through observations derived from clinical practice.

Conflicts of interest

None declared.

References


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