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Statins and myocardial hypertrophy

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Abstract

Cardiac hypertrophy is a physiological adaptive response by the heart to pressure overload. However, after prolonged periods, this initial adaptive response becomes maladaptive, leading to increased mortality and morbidity from heart failure. Recently, 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been shown to inhibit cardiac hypertrophy by cholesterol-independent mechanisms. Statins block the isoprenylation and activation of members of the Rho guanosine triphosphatase (GTPase) family, such as RhoA and Rac1. Since Rac1 is a requisite component of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is a major source of reactive oxygen species (ROS) in cardiovascular cells, the ability of statins to inhibit Rac1-mediated oxidative stress makes an important contribution to their inhibitory effects on cardiac hypertrophy.

Keywords

cardiac hypertrophy; 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors; statins; antioxidants; small GTP-binding proteins

Introduction

Several clinical trials with 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have shown that they reduce the incidence of myocardial infarction and ischemic disease [1–3]. Although the beneficial effects of statins have been attributed to their lipid-lowering effects, subgroup analysis of the WOSCOP and CARE trials suggests that statin-treated individuals have significantly lower risks for coronary heart disease compared to age-matched placebo-treated individuals, despite comparable serum cholesterol levels [1–3]. Indeed, experimental evidence indicates that some of the cholesterol-independent or 'pleiotropic' effects of statins involve the improvement or restoration of endothelial function, an increase in the stability of atherosclerotic plaques, and a decrease in vascular inflammation [4–6].

Cardiac hypertrophy and small G proteins

Cardiac hypertrophy is an adaptive response of the heart to pressure overload. The molecular response to pressure overload is complex and it may include modulation of various intracellular signal pathways, such as activation of many protein kinases (mitogen activated protein kinase [MAPK] and phosphatidylinositol 3 [PI3] kinase), expression of cardiac fetal genes (atrial

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Conflicts of interest: none

natriuretic factor [ANF] and myosin light chain), and increase of protein synthesis. Furthermore, pressure overload leads to the release of secretion and production of vasoactive peptides, such as angiotensin II and endothelin-1, which play pivotal roles in the induction of these hypertrophic responses [7,8]. Since cardiac myocytes convert the pressure overload into intracellular biochemical signals, the blockade of critical signaling pathways leading to cardiac hypertrophy may have therapeutic benefits. One such pathway, which involves increase in intracellular myocardial oxidative stress is mediated by small GTP-binding proteins.

Ras, Rho and Rac are members of a family of small GTP-binding proteins, which exert diverse cellular functions. They participate in cell locomotion, cytokinesis, and cytoskeletal remodeling in non-muscle cells [9,10]. In the heart, Ras, Rho and Rac are involved in the hypertrophic response [11,12]. Ras-mediated cardiac hypertrophy has been demonstrated both *in vitro* [13] and *in vivo* [14]. Transgenic mice that over-express RhoA in heart develop loss of systolic function and dilated cardiomyopathy. However, the development of cardiomyopathy is due to abnormal conduction abnormalities rather than a direct modification of myocardial architecture [15]. This effect of RhoA was unanticipated, because previously, several *in vitro* studies implicated RhoA in the development of hypertrophy [16]. Other studies using cultured cardio-myocytes revealed that the activation of Rac is required in phenylephrine-induced cardio-myocyte hypertrophy. In those studies, transfection of myocytes with a dominant-negative mutant of Rac1 completely inhibited the hypertrophic response to phenylephrine [11]. In addition, transgenic mice that specifically expressed activated Rac1 in the myocardium, showed severe cardiac hypertrophy and dilatation [17].

In the cholesterol biosynthetic pathway, conversion of HMG-CoA to mevalonate by HMG-CoA reductase is a rate-limiting step. Inhibition of this enzyme by statins not only leads to the reduction of cholesterol biosynthesis in the liver, but also to the reduction of the synthesis of several isoprenoid intermediates (Figure 1). These intermediates, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), serve as important lipid attachments for post-translational modification of signaling proteins, including the gamma subunit of heterotrimeric G proteins, heme-a, nuclear lamins, as well as Ras and Ras-like proteins, such as Rho and Rac [18]. Thus, protein isoprenylation allows the covalent attachment, sub-cellular localization, and intracellular trafficking of membrane-associated proteins.

Members of Ras and Rho guanosine triphosphatase (GTPase) family are major substrates for post-translational modification by isoprenylation [18,19]. Ras translocation from the cytoplasm to the plasma membrane is dependent on farnesylation, whereas Rho translocation is dependent on geranylgeranylation [20,21]. These biochemical analyses showed that statins inhibit the development of cardiac hypertrophy through inhibition of Ras and Rho isoprenylation, leading to the accumulation of inactive Ras and Rho in the cytoplasm [22,23]. We have recently shown that Rac1 is a key mediator in the hypertrophic response. Over-expression of a dominant-negative mutant of Rac1 (N17Rac1), and to a less extent, RhoA (N19RhoA), inhibited angiotensin II-induced ANF promoter activity. Co-treatment with statins further decreased ANF promoter activity in cells transfected with N19RhoA and N17Cdc42, but not those transfected with N17Rac1. Similarly, co-treatment with GGPP reversed the inhibitory effects of statins, while GGPP could not reverse the inhibitory effect of N17Rac1 on ANF promoter activity [22].

Reduced nicotinamide adenine dinucleotide phosphate oxidase in cardiac myocyte

Growing evidence suggests that reactive oxygen species (ROS) may be involved in the process of cardiac hypertrophy [24,25]. Recent works strongly suggest that reduced nicotinamide

adenine dinucleotide phosphate (NADPH) oxidase is a major source of superoxide in cardiovascular cells [26]. In the resting inactive cell, three of these five components, $p40^{PHOX}$(PHOX for Phagocyte Oxidase), $p47^{PHOX}$ and $p67^{PHOX}$, exist in the cytosol, forming a complex. The other two components, $p22^{PHOX}$, $gp91^{PHOX}$, are bound to the membranes. Various stimuli lead to the phosphorylation of the cytosolic components and the entire cytosolic complex then migrates to the membrane (Figure 2). Importantly, not only are the core subunits required for activation, but also two low-molecular-weight guanine nucleotide-binding proteins, Rac and Rap. During activation, Rac binds guanosine triphosphate (GTP) and migrates to the membrane with the core cytosolic complex. Therefore, it has been suggested that Rac may be involved in the activation of cardiovascular NADPH oxidase.

One of the most important attributes of cardiovascular oxidase is its responsiveness to local metabolic changes, hemodynamic forces, and hormones, such as the potent vasoconstrictor angiotensin II. Angiotensin II increases the activity of vascular oxidase through NADPH oxidase activation [26,27]. Thrombin, platelet-derived growth factor (PDGF) and tumor necrosis factor-á (TNF-á) also stimulate NADPH oxidase-dependent superoxide production in vascular smooth muscle cells (SMCs) [28–30]. Recent analysis of the $gp91^{PHOX}$ deficient mice demonstrated that angiotensin II treatment increased cardiac hypertrophy and collagen content in wild-type but not $gp91^{PHOX}$ deficient mice [31]. This evidence further supports the hypothesis that oxidative stress, in particular NADPH oxidase, plays a crucial role in cardiac hypertrophy. For these reasons, it is likely that statins would inhibit cardiac hypertrophy through an antioxidant mechanism involving inhibition of Rac1 geranylgeranylation. Indeed, statins inhibit angiotensin II-induced oxidative stress and cardiac hypertrophy in rodents [22]. Perhaps, this is the mechanism by which statins inhibit cardiac hypertrophy in humans with hypercholesterolemia [32].

In summary, strong experimental evidence indicate that statins can prevent cardiac hypertrophy. This effect is mediated by Rac 1 and includes a reduction in oxidative stress. These results suggest a novel pharmacological approach to treating cardiac hypertrophy.

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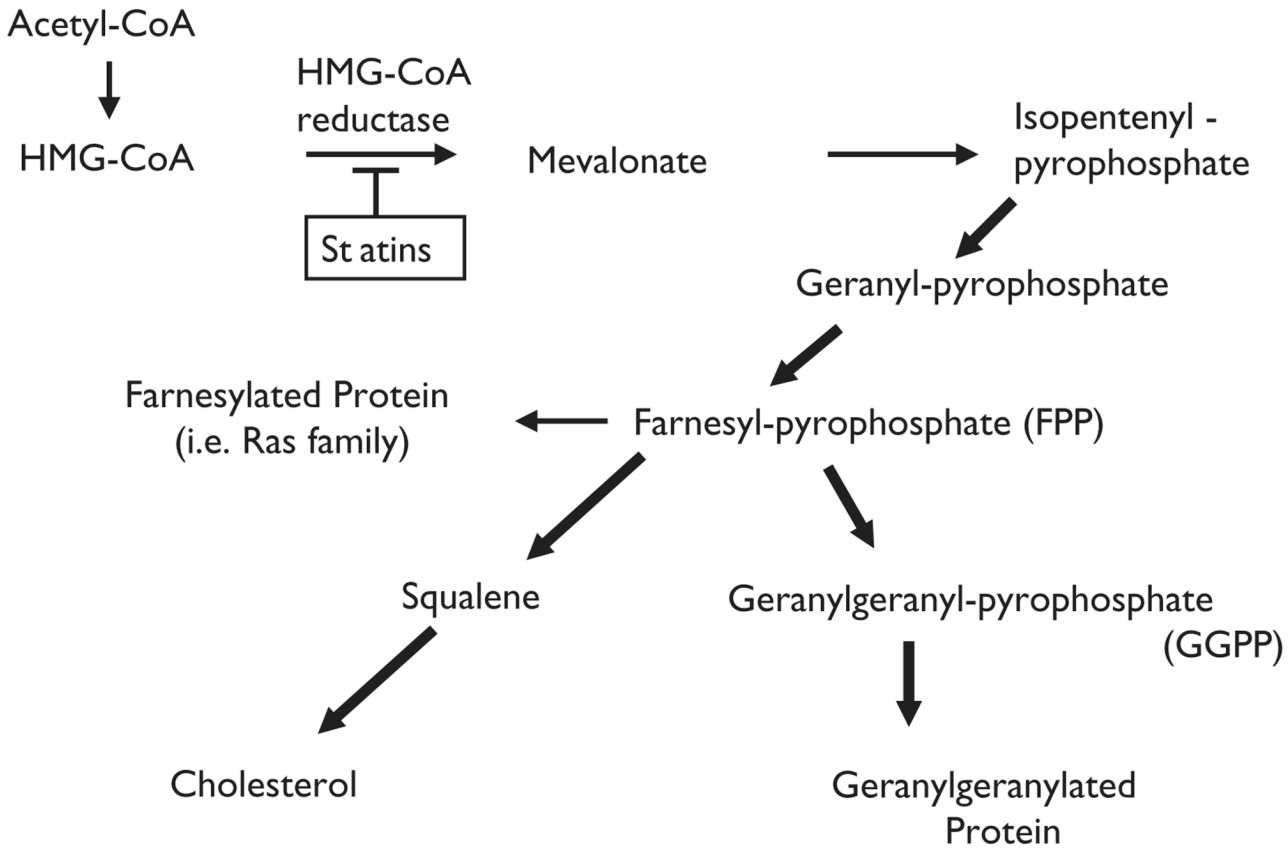

Fig. 1.
Cholesterol biosynthetic pathway. HMG-CoA indicates 3-hydroxyl-3-methylglutaryl coenzyme (A) HMG-CoA reductase is a rate-limiting enzyme and this blockade (statins) leads to the reduction of other isoprenoid intermediates as well as intracellular cholesterol.

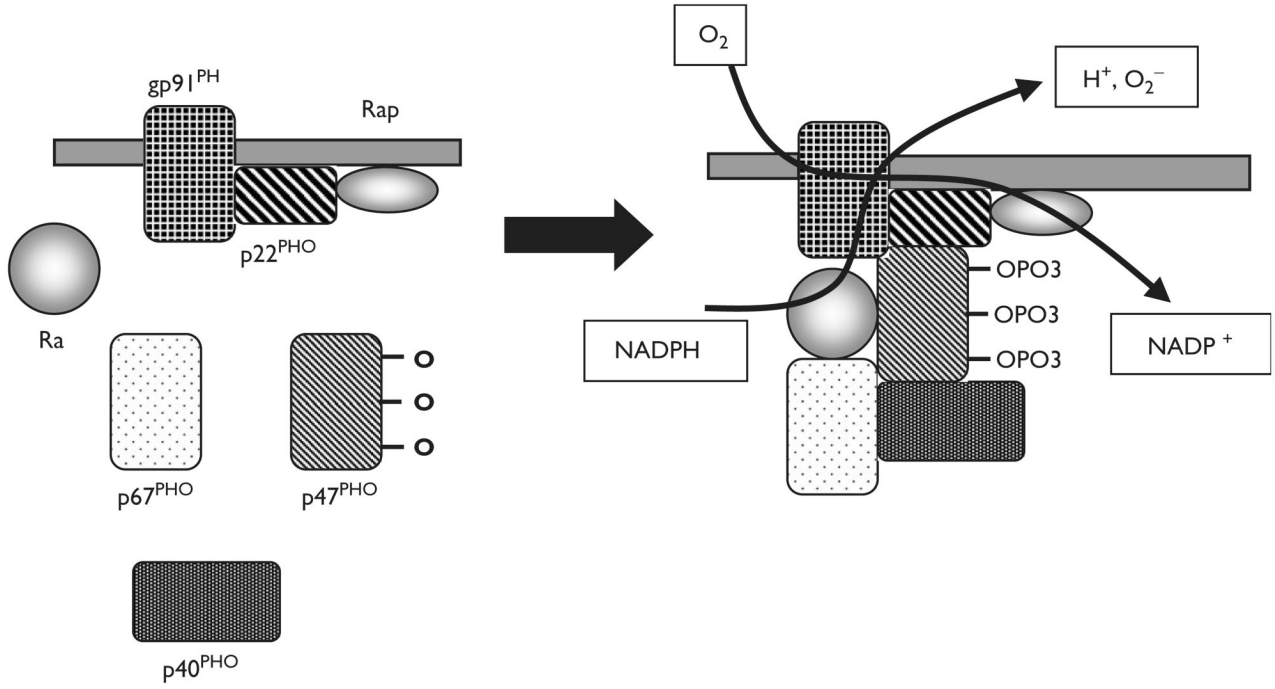

Fig. 2.

NADPH oxidase. The core enzyme comprises five components: $p40^{PHOX}$ (PHOX for Phagocyte Oxidase), $p47^{PHOX}$, $p67^{PHOX}$, $p22^{PHOX}$ and $gp91^{PHOX}$. In the resting cell (left panel), three of these five components, $p40^{PHOX}$, $p47^{PHOX}$ and $p67^{PHOX}$, exist in the cytosol as a complex. The other two components, $p22^{PHOX}$, $gp91^{PHOX}$, are located in the membranes. When it was stimulated, the cytosolic component becomes heavily phosphorylated and the entire cytosolic complex migrates to the membrane. Activation requires the participation, not only of the core subunits, but also of two low-molecular-weight guanine nucleotide-binding proteins, Rac and Rap. During activation, Rac binds guanosine triphosphate (GTP) and migrates to the membrane along with the core cytosolic complex.