Inhibition of RhoA or Rac1? Mechanism of Cholesterol-Independent Beneficial Effects of Statins

Yoshiyuki Rikitake, MD***; Ken-ichi Hirata, MD*

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have beneficial effects on cardiovascular and cerebrovascular diseases, including acute coronary syndrome and stroke. Their actions have been intensively studied and show that statins are capable of inhibiting the proliferation of vascular smooth muscle, restoring endothelial dysfunction, reducing platelet aggregation, and increasing the stability of atherosclerotic plaque. Although statins primarily act to block HMG-CoA reductase, the rate-limiting enzyme in the de novo synthesis of cholesterol in the liver, which results in a decrease in serum cholesterol levels, many (if not all) of these beneficial effects are postulated to arise from the inhibition of the actions of small G proteins. In addition to inhibiting cholesterol synthesis, statins also block the synthesis of isoprenoid intermediate metabolites in the biosynthetic pathway, such as farnesylpyrophosphate (FPP), geranylgeranylporphosphate (GGPP) (Fig 1). FPP and GGPP are important lipid attachments for the post-translational modification of a variety of cellular proteins, including the Ras and Rho family small G proteins. Isoprenylation of small G proteins is critical for their regulation of intracellular trafficking and the interactions with their regulators and effectors. For instance, modification with FPP is necessary for proper localization of Ras family small G proteins, whereas GGPP is required for that of Rho family small G proteins. Statins prevent isoprenylation of Rho family small G proteins, which inhibits these signaling molecules. However, because previous studies have been either performed in vitro or in animals, whether the inhibition of small G proteins actually contributes to the pleiotropic actions of statins in cardiovascular disease in humans remains largely unclear and, if so, which small G protein(s) would be the critical target of statins.

In this issue of the Journal, Rashid et al investigate the inhibition of which small G protein(s) that plays a role in the beneficial effects of statins. They clearly demonstrate that clinical doses of statins significantly inhibit Rac1, but not RhoA or Ras in cultured endothelial cells and in rats. Interestingly, they also demonstrate that clinical doses of statins significantly inhibit Rac1, but not RhoA/Rho-associated kinase (ROCK) activity in circulating leukocytes of healthy human volunteers. Rho family small G proteins, which consist of Rho, Rac, and Cdc42 subfamily G proteins, are key regulators of actin cytoskeleton dynamics and are implicated in a variety of cellular processes, such as morphogenesis, cell polarity, cell migration, cell division, cell adhesion, vesicle trafficking, cytokinesis, cell cycle progression, and gene expression. It is well known that the actions of Rho family small G proteins are implicated in diverse aspects of cardiovascular diseases. For example, Rho regulates vascular tone by smooth muscle contraction. The activation of Rho promotes smooth muscle contraction whereas the activation of endothelial Rho decreases nitric oxide (NO) production by reducing the expression of endothelial NO synthase (eNOS) and inhibiting eNOS activity. Statins upregulate eNOS expression by inhibiting Rho in a cholesterol-independent manner, and subsequently increase the bioavailability of NO. The ability of statins to increase the expression and activity of eNOS is an important mechanism by which the drugs improve endothelial function in patients with atherosclerosis. On the other hand, Rac is a component of the NADPH oxidase complex that drives superoxide generation and plays a pivotal role in cardiovascular disorders; in particular, atherosclerosis and cardiac hypertrophy, both of which are associated with oxidative stress. The inhibition of Rac by statins leads to the reduction of oxidative stress and subsequently prevents cardiac hypertrophy. In contrast to the extensive characteri-

**Fig 1.** Actions of statins and Rho-associated kinase (ROCK) inhibitors on the cholesterol biosynthesis pathway. Co-A, coenzyme-A; HMG, 3-hydroxy-3-methylglutaryl; PP, pyrophosphate.
zation of the roles of RhoA and Rac1 in cardiovascular diseases, the role of Cdc-42 remains relatively understudied. Further studies are needed to examine the possibility that small G proteins other than Rho family small G proteins, including Rap, Ran and Rab, might be involved in the pleiotropic effects of statins.

ROCK is one of the best-characterized downstream mediators of the action of Rho. Evidence obtained from recent studies suggests that the Rho/ROCK signaling pathway is overactivated and plays an important role in numerous cardiovascular diseases, such as hypertension, pulmonary hypertension, coronary artery diseases, atherosclerosis, and cardiac hypertrophy. Indeed, the inhibition of the Rho/ROCK signaling pathway by statins and ROCK inhibitors effectively improves these pathological conditions. Interestingly, in this issue of the Journal, Rashid et al show the beneficial effects of a ROCK inhibitor in addition to statins. They propose a potential advantage of combination therapy with a statin and a ROCK inhibitor compared with monotherapy with statins at clinical doses and a ROCK inhibitor, which are capable of inhibiting predominantly Rac1 and solely ROCK, respectively. However, because ROCK inhibitors are not yet clinically available for the treatment of cardiovascular diseases, there is currently not abundant evidence that ROCK inhibitors are beneficial for the treatment of cardiovascular diseases and it is unknown whether co-treatment with statins and ROCK inhibitors would give more benefits than monotherapy. Further studies are required to explore whether combination therapy with statins and ROCK inhibitors would be a more powerful strategy for treating cardiovascular disease.

References