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EDITORIAL

Mevalonate Pathway Is a Novel Target for Hypertension

Takuya Kishi, MD, PhD

The mevalonate pathway is an important metabolic pathway that plays a key role in multiple cellular processes by synthesizing sterol isoprenoids, like cholesterol, and non-sterol isoprenoids, including farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP).[1] These non-sterol isoprenoid intermediates of the mevalonate biosynthetic pathway play important roles in the post-translational modification of small GTP-binding proteins (GTPases), such as Ras and Rho. 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.[2,3] Isoprenylation of small G proteins is critical for their regulation of intracellular trafficking and the interactions with their regulators and effectors.[2,3] 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.[2,3] It has been demonstrated that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) prevent isoprenylation of Rho family small G proteins, which inhibits these signaling molecules.[4–7]

Article p1409

In this issue of the Journal, Han et al examined the expression of key enzymes in the mevalonate pathway in liver, heart and aorta during the process of hypertension in spontaneously hypertensive rats (SHR), including 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR), phospho-HMGR, farnesyl diphosphate synthase, squalene synthase, farnesyltransferase (FNT) α, FNT β and geranylgeranyltransferase type I (GGTase-I).[8] The study results suggest that alteration of key enzyme expressions in the mevalonate pathway in the heart and aorta are implicated in the process of cardiovascular remodeling in SHR, probably through activating small GTPases.[8] Because cardiovascular remodeling in hypertension causes and indicates various organ damage, these results also suggest that the mevalonate pathway should be inhibited in hypertension.

Statins have beneficial effects on cardiovascular and cerebrovascular diseases, including acute coronary syndrome and stroke. Many previous studies have suggest that pleiotropic effects of statins are thought to be mediated through inhibition of small GTP-binding proteins, such as Rho, Rac and Ras, whose correct membrane localization and GTPase activity are dependent on isoprenylation.[4–7] Statins could also inhibit the synthesis of important isoprenoid intermediates, such as FPP and GGPP, which lie downstream from l-mevalonic acid.[1] These intermediates serve as important lipid attachments for the post-translational modification of intracellular proteins such as nuclear lamins, Ras, Rho, Rac and Rap.[7] Among them, Rho-kinase is one of the downstream effectors of the small G-protein, Rho. Previous reports show that both the Rho/Rho-kinase and Rac pathway may be involved in the pathogenesis of cardiovascular diseases.[7] The Rho/Rho-kinase pathway has an important role in mediating various cellular functions, including contraction, actin cytoskeleton organization, cell adhesion and motility, proliferation, cytokinesis and gene expression, all of which are involved in the pathogenesis of cardiovascular diseases.[9] Furthermore, it was also been demonstrated that the pleiotropic effects of statins are mediated predominantly though inhibition of the Rac1 signaling pathway, but not the RhoA/Rho-kinase or Ras signaling pathway, at the clinical and maximum doses used in Asian countries.[10] In their study, Rashid et al found that the clinical concentration/dose of statins only inhibited Rac1 in vitro and in vivo, suggesting that combination therapy with statins and Rho-kinase inhibitors would be effective for cardiovascular diseases.[10] My group also demonstrated that intra-arterial infusion of a Rho-kinase inhibitor, fasudil, causes a preferential increase in forearm blood flow in patients with heart failure, compared with control subjects.[11] Taking together the benefits of statins on the mevaonate pathway and the results of Han et al, statins should be administered to the patients with hypertension.

Interestingly, Rho, Rac, and Ras are expressed not only in the aorta and heart but also in the brain, and are key mediators of the regulation of activity of the sympathetic nervous system. Hirooka et al have demonstrated that Rho/Rho-kinase in the brainstem increases the activity of the sympathetic nervous system,[12] and my group also previously reported that intracerebroventricular infusion of atorvastatin reduces both oxidative stress and the activity of the sympathetic nervous system through inhibition of the membrane translocation of Rac1 in the brain of hypertensive rats.[13] Furthermore, we demonstrated that Ras is activated in the brainstem of hypertensive rats, and that inhibition of Ras in the brain decreased the activity of the sympathetic nervous system.[14] Based on these results, inhibition of the mevalonate pathway in the brain might cause sympatho-inhibition. Therefore, we con-

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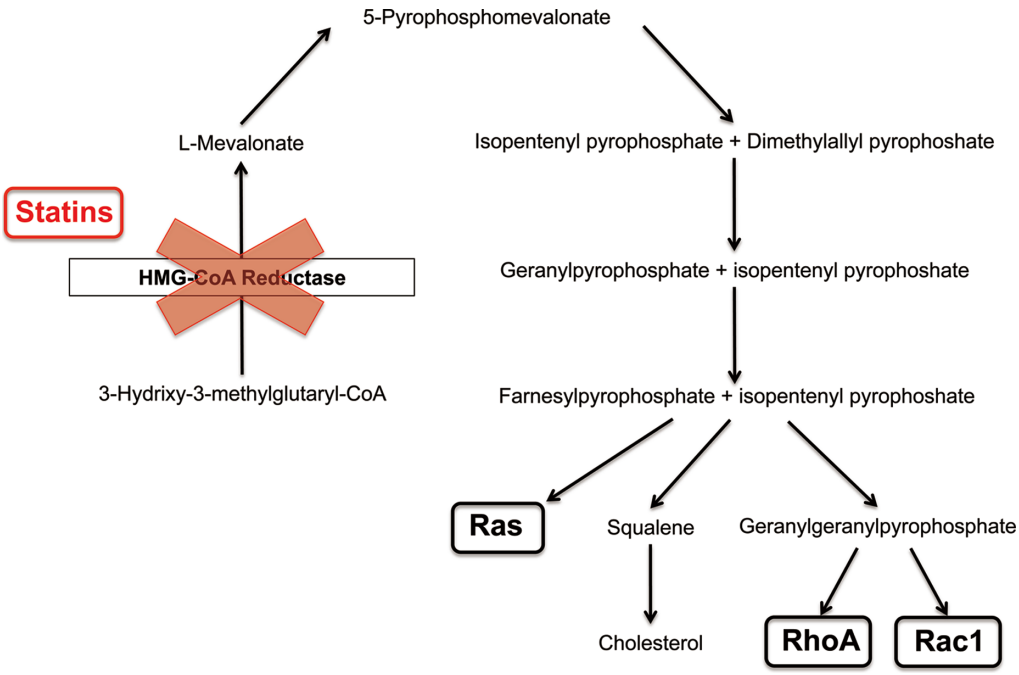

Figure. Biological actions of isoprenoids. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and decrease the isoprenylation of intracellular signaling molecules, such as RhoA, Rac1 and Ras.

sider that statins might be a sympatho-inhibitory agent via blockade of the mevalonate pathway in the brain.[15]

In conclusion, the report by Han et al has many important clinical implications. Interestingly, they demonstrate that the key enzymes in the mevalonate pathway change in the various organs of hypertensive rats. As summarized in the **Figure**, statins inhibit Rho, Rac1, and Ras via blockade of the mevalonate pathway. Further studies are needed to determine the mechanisms by which the mevalonate pathway is activated; however, the pathway has the potential to be a novel target of the treatment of hypertension, and statins should be considered as an inhibitor of the mevalonate pathway.

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