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An overview of pleiotropic effect of statins in cardiovascular disease

Abstract

HMG CoA-reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) inhibitors, also called statins, are at present exerting an effect on the therapeutic treatment decision for hypercholesterolemia. Hypercholesterolemia is a known risk factor for cardiovascular malady, and statin treatment has prompted a significant decline in grimness and mortality from undesirable cardiovascular events, stroke, and fringe blood vessel malady. Notwithstanding accomplishing a remedial diminishing in serum cholesterol levels, statin treatment appears to advance different impacts that are autonomous of changes in serum cholesterol. These "pleiotropic" impacts incorporate constriction of vascular aggravation, enhanced endothelial cell work, adjustment of atherosclerotic plaque, diminished vascular smooth muscle cell relocation and expansion, and restraint of platelet total. This review an attempt to compile published reports on the pleiotropic impacts of statins at the cellular level.

Keywords: statins, pleiotropic effects

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Shivani Sharma,[1] Rajdeep Kaur,[2] Kumud Upadhyaya,[1] Rajiv Gupta[2]
[1]Department of Pharmaceutical Sciences, Kumaun University Bhimtal Campus, India
[2]School of Pharmacy, BBD University, India

Correspondence: Rajiv Gupta, School of Pharmacy, BBD University, Lucknow 226028 (U.P.), India, Tel +91-9839278227, Email rajev961@rediffmail.com

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Introduction

Statins also known as 3-hydroxy-3-methylglutaryl co-protein A (HMG-CoA) reductase inhibitors. These are the medications regularly utilized to lower down the cholesterol and appeared to decrease the frequency of essential and optional coronary illness in clinical trials.[1–3] They were found in 1970s. Statins are competitive inhibitors of hydroxylmethyl glutaryl coenzyme-A reductase (HMGCR), which is the rate limiting enzyme in cholesterol biosynthesis.[4,5] The positive results of statin treatment in experimental animals were confirmed and reached out to patients in extensive scale clinical investigations that built up a strong influence of statin in the treatment associated with fundamentally lessened,rates of mortality in patients with atherosclerosis.[4,6,7] Nevertheless evoking helpful impacts in the cardiovascular framework that incorporates enhanced endothelial function furthermore, neo-angiogenesis, HMG COA inhibitors apply pleiotropic activities in different tissues including the focal apprehensive framework. For example, statins seem to apply mitigating activities in illnesses, for example, rheumatoid joint inflammation, Alzheimer and Parkinson's ailment, and various sclerosis.[8]

Statins pleiotropy: associated with lowering of cholesterol

Statins are believed to have "pleiotropic effects", which is a term referred as the useful impacts of statins which are not dependent on levels of cholesterol (Figure 1).[8,9] According to these pleiotropic impacts, positive results utilizing statin treatment have been acknowledged in cardiovascular disease (CVD) and in addition other ailment states including disease, sepsis, dementia, immune system ailment, macular degeneration, osteoporosis, and incendiary gut infection.[8–15] The water solvency of statins may decide some of their pleiotropic impacts and is straightforwardly inferable from their chemical structure.[16] As 60-70% of serum cholesterol is synthesised from liver and HMG-CoA reductase is the vital, rate-constraining compound in the cholesterol biosynthetic pathway, hindrance of this enzyme by statins brings about an dramatic lessening in low density lipoprotein (LDL)-cholesterol (Figure 2). Likewise, lessening of LDL-cholesterol prompts upregulation of the LDL receptor and expanded LDL leeway. The downfall in serum cholesterol levels is in this manner thought to be the essential component fundamental the helpful advantages of statin treatment in cardiovascular sickness.[17,18]

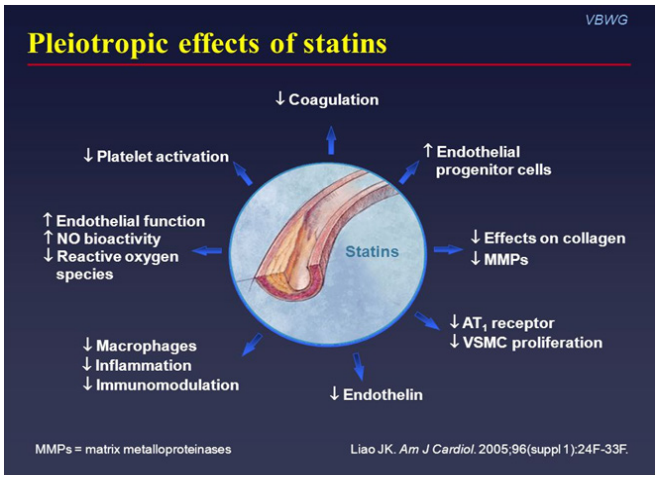

Figure 1 Pleiotropic effects of statins.

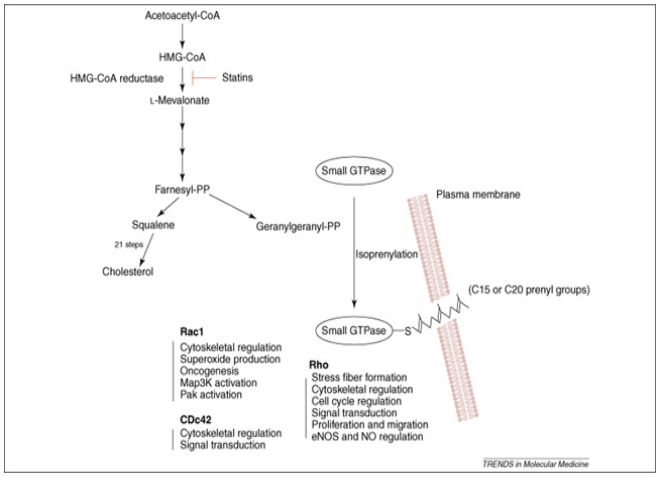

Figure 2 Isoprenoids and statins: cholesterol biosynthesis pathway and the impacts of HMG-CoA-reductase hindrance by statins.

Statins exerts their pleiotropic effects by hindering the conversion of HMG-CoA to L-mevalonic corrosive, statins keep the union of imperative isoprenoids, for example, farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), which are antecedents of cholesterol biosynthesis (Figure 1).[19] These intermediates fill in as imperative lipid connections for the post-translational change of proteins, for example, nuclear lamins, Ras, Rho, Rac and Rap.[20] Protein isoprenylation empowers appropriate subcellular confinement and trafficking of intracellular proteins. Given that isoprenylated proteins might control various cell capacities, it is not amazing that statins may have extra impacts past lipid lowering. In fact, late examinations propose that statins may be included in immunomodulation, neuroprotection and cell senescence.[21–26] Rho is the real focus of GGPP; in this way, restraint of Rho and its downstream target, Rho kinase is a probable system intervening a portion of the pleiotropic impacts of statins on the vascular membrane.[27,28,31] Rho kinase increase the affectability of vascular smooth muscle to calcium in hypertension, and coronary spasm. Conversely, activation of Rac prompts the development of lamellipodia, membrane unsettles, and oxidative anxiety, while initiation of Cdc42 initiates actin-rich surface projections called filopodia.[29–31]

Statins associated with lowering of cholesterol

A study known as "Framingham Heart study" has shown that hoisted cholesterol is a vital risk factor for cardiovascular illnesses and lower cholesterol levels are related with lower cardiovascular dangers.[24] Late proof likewise demonstrates that more escalated bringing down of LDL- cholesterol by statins is related with more prominent clinical advantages.[25] The systems credited to lipid bringing down with statin treatment incorporate atheromatous plaque adjustment, change of the atherosclerosis movement and enhanced endothelial capacities.[26] Consequently, statins diminish cardiovascular occasions in hypercholesterolemic as well as normocholesterolemic patients with coronary illness (CHD) or cardiovascular risks.[17]

Atherosclerotic plaque and endothelial injury

Atherosclerosis is responsible for the continual process of endothelial injury and dysfunction with subsequent remodeling and repair.[32] After endothelial damage happens, platelets are among the first to react by clinging to the damage site and selecting macrophages to the range of damage.[33,34] Macrophages phagocytize lipid-loaded platelets and move into the intima where they take in more lipids. These macrophages are commonly alluded to as ''froth cells,'' as the substantial measure of lipid they ingest gives them a frothy appearance when seen minutely.[35] Furthermore, VSMCs move from the media to the intima close to the territory of endothelial damage with a large portion of them taking in a lot of lipid to likewise move toward becoming froth cells. Serum lipoproteins amass in the intima at these territories of damage and alongside these three cell sorts, turn out to be a piece of what is named the ''greasy streak''-the most punctual sore in the arrangement of atherosclerotic plaque.[33]

Fatty streak is the first visible lesion in the process of atherosclerosis. It appears as an irregular yellow-white discoloration on the luminal surface of an artery. They can be visualized without magnification. The fatty streak experiences additionally renovating to frame a sinewy top made for the most part out of VSMCs and the extracellular lattice they emit. Hidden this top is a center of necrotic cell flotsam and jetsam and froth cells pressed with lipid.[35] Interruption of the sinewy top starts a provocative reaction that can prompt thrombus arrangement, with possible joining into the complex atherosclerotic plaque itself.[33] The final product of this procedure is narrowing or finish blockage of the vascular lumen with a resultant trade off in blood stream. *A systematic assessment of fatty streak formation carried out in fetal aortas from normocholesterolemic mothers, hypercholesterolemic mothers and mothers who were hypercholesterolemic only during pregnancy suggests that intimal LDL accumulation and oxidation contributes to monocyte recruitment in vivo.*[33]

Neointimal hyperplasia associated blood vessel wall injury

Neointimal hyperplasia is a noteworthy reason for reconstructive disappointment in patients after angioplasty, stenting, and sidesteps procedures.[36] Both open and endovascular strategies create blood vessel harm that triggers a physiologic reaction.[36] Platelets quickly cause thrombus development at the surface of vessel divider damage.[36,37] An incendiary course follows, with monocytes, neutrophils, and lymphocytes moving to the region of intimal damage.[35] Average VSMCs move to this region of intimal damage too, and throughout the following a while they multiply and deliver a lot of extracellular framework.[38–40] The entirety of these cell and sub-atomic reactions prompts neointimal hyperplasia and restenosis of the instrumented vein.[40]

Targets of statins

There are some main targets of statins like Isoprenylated Proteins, Rho/Rho Kinase, Rac and Peroxisome Proliferator–Activated Receptor

Statins: isoprenylated proteins

By restraining mevalonic acid biosynthesis, HMG COAR Inhibitors keep the blend of isoprenoid intermediates farnesylpyrophosphate and geranylgeranylpyrophosphate.[41] FPP and GGPP fill in as lipid connections for the post-translational modification of heterotrimeric G proteins, including Ras and Rho.[42] Ras and Rho control cell expansion, separation, apoptosis, and the cytoskeleton.[43] In endothelial cells (ECs), Ras translocation is subject to farnesylation, while Rho translocation is reliant on geranylgeranylation.[44,45] Although the restraint of isoprenoid moderate amalgamation is vital to the conceivable pleiotropic impacts of statins, it is un-clear whether the essential LDL-C–lowering advantage of statins is a direct result of diminished cholesterol generation and lessened mevalonic corrosive creation or upregulation of the LDL receptor.[46] There is a relative scarcity of human examinations on the levels of FPP and GGPP with perpetual statin treatment.

Statins: Rho/Rho kinase

The organic impacts of Rho are interceded by its downstream effectors, including ROCK, protein kinase N-related kinases, citron kinase, rhotekin, mDia and the myosin restricting subunit of myosin light-chain (MLC) phosphatase.[47] Rho kinases (ROCKs) are protein serine/threonine kinases of 160 kDa that add to the downstream impacts of Rho GTPases. ROCK movements to a dynamic open adaptation when RhoA ties to ROCK.[48] ROCKs control actin cytoskeletal changes through impacts on myosin light chain phosphorylation. This influences central attachment complex arrangement, smooth muscle withdrawal, cell relocation, and quality expression.[49] ROCK activity is frequently hoisted in disorders of the cardiovascular framework.[50] Accordingly, statins could influence vascular smooth-muscle compression in any event somewhat through impacts on Rho/ROCK.[51,52] Through hindrance of isoprenylation of Rho, translocation of Rho to the cell layer is hindered and the downstream initiation of ROCK is diminished.[53] Without a doubt,

ROCK inhibitors anticipate cerebral vasospasm after subarachnoid discharge,[54] hinder the advancement of atherosclerosis[55] and anticipate blood vessel renovating after vascular damage.[56]

The Rho/ROCK pathway could likewise control cell works other than the actin cytoskeleton. For instance, ROCK can phosphorylate insulin receptor substrate-1 (IRS-1) and adjust the insulin/PI3K/Akt pathway. The Rho/ROCK pathway is included in oxidative push, aortic firmness and changes in circulatory strain. Besides, ROCK controls cell survival through phosphorylation of the protein kinase B/Akt and FOXO.[57–59] ROCK can likewise control adipogenesis and myogenesis. In p190-B Rho GAP-insufficient mice, the Rho/ROCK pathway is actuated constantly and there is a deformity in adipogenesis with a preference towards myogenesis. Different procedures or conditions including the RhoA/ROCK pathway incorporate angiogenesis, hypertension, cardiovascular hypertrophy, perivasclar fibrosis and aspiratory hypertension. Fasudil, a particular ROCK inhibitor, enhances endothelial capacity in patients with coronary conduit ailment.[60–64] These discoveries propose that ROCK restraint may add to a portion of the pleiotropic impacts of statin treatment.

Statins: RAC

Two vital effector-reaction pathways lie downstream of Rac: cytoskeletal redesigning furthermore, responsive oxygen species (ROS) era. Rac1 impacts different cytoskeletal rebuilding proteins, for example, Wiskott-Aldrich disorder protein, calmodulin-restricting GTPaseactivating proteins and p21-actuated kinase. Rac1 likewise ties to p67phox and prompts enactment of the NADPH oxidase framework and consequent era of ROS. In fact, Rac movement is firmly identified with ROS creation and ROS produced by NADPH oxidase in light of development factors and fiery cytokines is interceded by Rac.[65] Imperatively, statins hinder Rac1-intervened NADPH oxidase movement and in this manner lessen angiotensin II-actuated ROS generation and hypertrophy in smooth muscle and heart.[66,67] The initiation of Rac1 in the vascular divider has been related with atherosclerosis, neointimal multiplication, cardiovascular hypertrophy and endothelial brokenness.[68] Rac1 has numerous parts in various cell forms and cardiovascular physiology.[69] Consequently, Rac1 hindrance may likewise add to a portion of the pleiotropic impacts of statins.

Statins: peroxisome proliferator-activated receptor

Statins have been appeared to enact peroxisome proliferatorenacted receptors (PPARs).[70] Statins intensely diminish lipopolysaccharide-related aggravation in wild-sort mice yet not in PPARα-invalid mice, autonomous of cholesterol-bringing down mechanisms.[71] Statins increment PPAR-γ action and repress lipopolysaccharide instigated tumor putrefaction factor-α and monocyte chemotactic protein-1 activity.[72,73] The organization of simvastatin in mix with PPAR-γ agonists inspires added substance gainful vascular effects.[74] Atorvastatin diminishes progressed glycation finished results in rats and lessens fibroblast multiplication and heart fibrosis, which was switched with the PPAR-γ adversary GW9662.[72] Statins diminished ROS creation by expanding the mRNA articulation of the PPAR-γ coactivator, which is an essential controller of mitochondrial biogenesis. However, statins, particularly the high-power statins, increment the danger of diabetes mellitus. Thus, the capacity of the PPAR-γ agonists, thiazolidinediones, to bring down blood sugar is rather than the impacts of statins on PPAR-γ and exhibits the unpredictable idea of statin communications with different pathways, including glucose digestion.

Statins: vascular smooth muscle

The expansion of vascular SMCs is critical in vascular injury pathogenesis.[74] Transplant arteriosclerosis is an insusceptible reaction coordinated against giver ECs and vascular SMCs free of hypercholesteremia that is as yet constricted by statins.[75] Inhibition of isoprenoid blend by statins diminished platelet-determined development factor–induced DNA blend in vascular SMCs by expanding the cyclindependent kinase, p27Kip1, which was potentially intervened by Rho GTPase.[76] Simvastatin diminishes intimal thickening and lessens cell expansion, leukocyte aggregation, and platelet-determined development consider receptor phosophorylation LDL receptor–deficient mice.[77] *In vitro*, atorvastatin decreases the impacts of the proinflammatory cytokine IL-18, which hinders SMC movement, atomic factor-κB initiation, and framework metalloproteinase-9 expression. In ox-like aspiratory supply route SMCs, atorvastatin represses the relocation of pneumonic supply route SMC, which was turned around by GGPP and mevalonate, again ensnaring the potential for the Rho/ROCK pathway in SMC proliferation.[78,79]

Statins and platelet function

In (ACS) Acute Coronary Syndromes, a major factor, which plays a critical role, is platelets, which are allied in the formation of mural thrombus at the site of vascular injury and plaque rupture. This concept is directly linked with the enhanced cholesterol: phospholipid ratio in platelets.[31] HMG COA reductase inhibitors or Statins affect the functions of platelets, but there is no well understandable mechanism for this concept. According to well considered effects of endothelial NO, inhibits the platelet aggregation. Statins upregulates the endothelial nitric oxide, which considerably decreases the reactivity of platelets. Further mechanism shows the reduced production thromboxane A2 and modifies the platelet membrane cholesterol.[31,80]

Conclusion

The pleiotropic effects of statins in CVD are aid to a variety of methodology at both the sub-nuclear and cell levels. Some of these supportive effects of statins join change in endothelial cell work, limitation of platelet start/accumulation, block of VSMC migration and extension, lessened vascular aggravation, and extended soundness of atherosclerotic plaques. With these pleiotropic impacts in mind, the signs for statin use may continue growing, as the frameworks for these effects are totally outlined.

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Conflict of interest

Authors declare that there is no conflict of interest(s).

References

1. Castilla GL, Del Carmen Fernandez MM, Lopez Chozas JM, et al. Statins in stroke prevention: what an internist should know. *Eur J Intern Med*. 2008;19(1):8–14.
2. Nassief A, Marsh JD. Statin therapy for stroke prevention. *Stroke*. 2008;39(3):1042–1048.
3. van der Most PJ, Dolga AM, Nijholt IM, et al. Statins: mechanisms of neuroprotection. *Prog Neurobiol*. 2009;88(1):64–75.
4. Raghow R. Statins redux: A re-assessment of how statins lower plasma cholesterol. *World J Diabetes*. 2017;8(6):230–234.
5. Endo A. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res*. 1992;33(11):1569–1582.

6. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670–1681.

7. Stulc T, Ceška R, Gotto AM. Statin Intolerance: the Clinician's Perspective. *Curr Atheroscler Rep*. 2015;17(12):69.

8. Sadowitz B, Maier KG, Gahtan V. Basic science review: Statin therapy-Part I: The pleiotropic effects of statins in cardiovascular disease. *Vasc Endovascular Surg*. 2010;44(4):241–251.

9. Liao JK. Clinical implications for statin pleiotropy. *Curr Opin Lipidol*. 2005;16(6):624–629.

10. Almuti K, Rimawi R, Spevack D, et al. Effects of statins beyond lipid lowering: potential for clinical benefits. *Int J Cardiol*. 2006;109(1):7–15.

11. Kuoppala J, Anne L, Pukkala E. Statins and cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2008;44(15):2122–2132.

12. Wong TY, Sophie LR. Statins and age-related macular degeneration: time for a randomized controlled trial?. *Am J Ophthalmol*. 2007;144(1):117–119.

13. Falagas ME, Makris GC, Matthaiou DK, et al. Statins for infection and sepsis: a systematic review of the clinical evidence. *J Antimicrob Chemotherapy*. 2008;61(4):774–785.

14. Biskobing DM, Angela MN, Robert D. Novel therapeutic options for osteoporosis. *Curr Opin Rheumatol*. 2002;14(4):447–452.

15. Liao JK, Ulrich L. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol.* 2005;45:89–118.

16. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol.* 2005;19(1):117–125.

17. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med.* 2008;14(1):37–44.

18. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383–1389.

19. Goldstein JL, Michael SB. Regulation of the mevalonate pathway. *Nature*. 1990;343(6257):425–430.

20. Van Aelst L, D'Souza-Schorey C. Rho GTPases and signaling networks. *Genes Dev*. 1997;11(18):2295–2322.

21. Greenwood J, Steinman L, Zamvil SS. Statin therapy in autoimmunity: From protein prenylation to immunomodulation. *Nat Rev Immunol.* 2006;6(5):358–370.

22. Mangialasche F, Solomon A, Winblad B, et al. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol*. 2010;9(7):702–716.

23. Brouilette SW, Moore JS, McMahon AD, et al. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet*. 2007;369(9556):107–114.

24. Sytkowski PA, William BK, Ralph BD. Changes in risk factors and the decline in mortality from cardiovascular disease: the Framingham Heart Study. *N Engl J Med.* 1990;322(23):1635–1641.

25. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495–1504.

26. Archbold RA, Timmis AD. Cholesterol lowering and coronary artery disease: mechanisms of risk reduction. *Heart*. 1998;80(6): 543–547.

27. Takemoto M, Sun J, Hiroki J, et al. Rho-kinase mediates hypoxia-induced downregulation of endothelial nitric oxide synthase. *Circulation*. 2002;106(1):57–62.

28. Laufs U, Endres M, Stagliano N, et al. Neuroprotection mediated by changes in the endothelial actin cytoskeleton. *J Clin Invest*. 2000;106(1):15–24.

29. Uehata M, Ishizaki T, Satoh H, et al. Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension. *Nature*. 1997;389(6654):990–994.

30. Katsumata N, Shimokawa H, Seto M, et al. Enhanced myosin light chain phosphorylations as a central mechanism for coronary artery spasm in a swine model with interleukin-1β. *Circulation*. 1997;96(12):4357–4363.

31. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. *Am J Cardiol*. 2005;96(5A):24F–33F.

32. Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med*. 1999;340(2):115–126.

33. Ruggeri ZM. Platelets in atherothrombosis. *Nat Med.* 2002;8(11):1227–1234.

34. Siegel-Axel D, Daub K, Seizer P, et al. Platelet lipoprotein interplay: trigger of foam cell formation and driver of atherosclerosis. *Cardiovascular research*. 2008;78(1):8–17.

35. Jonasson L, Holm J, Skalli O, et al. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arteriosclerosis*. 1986;6(2):131–138.

36. Kokubo T, Hisashi U, Eric TC. Integrin alpha(v)beta(3) as a target in the prevention of neointimal hyperplasia. *J Vasc Surg*. 2007;45(Suppl A):A33–A38.

37. Kirchengast M, Klaus M. Endothelin and restenosis. *Cardiovasc Res.*1998;39(3):550–555.

38. Wu CH, Lin CS, Hung JS, et al. Inhibition of neointimal formation in porcine coronary artery by a Ras mutant. *J Surg Res*. 2001;99(1):100–106.

39. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation*. 1988;77(2):361–371.

40. Schwartz RS, David RH, Eric JT. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. *J Am Coll Cardiol*. 1992;20(5):1284–1293.

41. Goldstein JL, Michael SB. Regulation of the mevalonate pathway. *Nature*. 1990;343(6257):425–430.

42. Van Aelst L, D'Souza-Schorey C. Rho GTPases and signaling networks. Genes Dev. 1997;11(18):2295–2322.

43. Cho KJ, Hill MM, Chigurupati S, et al. Therapeutic levels of the hydroxmethylglutaryl-coenzyme A reductase inhibitor lovastatin activate ras signaling via phospholipase D2. *Mol Cell Biol.* 2011;31(6):1110–1120.

44. Laufs U, La Fata V, Plutzky J, et al. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation*. 1998;97(12):1129–1135.

45. Laufs U, James KL. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. *J Biol Chem.* 1998;273(37):24266–24271.

46. Awan Z, Seidah NG, MacFadyen JG, et al. Rosuvastatin, proprotein convertase subtilisin/kexin type 9 concentrations, and LDL cholesterol response: the JUPITER trial. *Clin Chem.* 2012;58(1):183–189.

47. Bishop AL, Hall A. Rho GTPases and their effector proteins. *Biochemical J*. 2000;348(Pt 2):241–255.

48. Shimizu T, James KL. Rho kinases and cardiac remodeling. *Circ J.* 2016;80(7):1491–1498.

49. Noma K, Naotsugu O, James KL. Physiological role of ROCKs in the

cardiovascular system. *Am J Physiol Cell Physiol.* 2006;290(3):C661–C668.

50. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495–1504.

51. Uehata M, Ishizaki T, Satoh H, et al. Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension. *Nature*. 1997;389(6654):990–994.

52. Burridge K, Krister W. Rho and Rac take center stage. *Cell*. 2004;116(2):167–179.

53. Liao JK, Ulrich L. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol.* 2005;45:89–118.

54. Shibuya M, Suzuki Y, Sugita K, et al. Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial. *J Neurosurg*. 1992;76(4):571–577.

55. Mallat Z, Gojova A, Sauzeau V, et al. Rho-associated protein kinase contributes to early atherosclerotic lesion formation in mice. *Circ Res.* 2003;93(9):884–888.

56. Sawada N, Itoh H, Ueyama K, et al. Inhibition of rho-associated kinase results in suppression of neointimal formation of balloon-injured arteries. *Circulation*. 2000;101(17):2030–2033.

57. Farah S, Agazie Y, Ohan N, et al. A rho-associated protein kinase, ROKα, binds insulin receptor substrate-1 and modulates insulin signaling. *Journal of Biological Chemistry*. 1998;273(8):4740–4746.

58. Noma K, Goto C, Nishioka K, et al. Roles of rho-associated kinase and oxidative stress in the pathogenesis of aortic stiffness. J *Am Coll Cardiol*. 2007;49(6):698–705.

59. Nishiyama T, Isao K, Akira K. Inactivation of Rho/ROCK signaling is crucial for the nuclear accumulation of FKHR and myoblast fusion. *J Biol Chem*. 2004;279(45):47311–47319.

60. Sordella R, Jiang W, Chen GC, et al. Modulation of Rho GTPase signaling regulates a switch between adipogenesis and myogenesis. *Cell*. 2003;113(2):147–158.

61. Hyvelin JM, Howell K, Nichol A, et al. Inhibition of Rho-kinase attenuates hypoxia-induced angiogenesis in the pulmonary circulation. *Circ Res*. 2005;97(2):185–191.

62. Higashi M, Shimokawa H, Hattori T, et al. Long-term inhibition of Rho-kinase suppresses angiotensin II–induced cardiovascular hypertrophy in rats in vivo. *Circ Res.* 2003;93(8):767–775.

63. Rikitake Y, Oyama N, Wang CY, et al. Decreased perivascular fibrosis but not cardiac hypertrophy in ROCK1+/− haploinsufficient mice. *Circulation.* 2005;112(19):2959–2965.

64. Nohria A, Grunert ME, Rikitake Y, et al. Rho kinase inhibition improves endothelial function in human subjects with coronary artery disease. *Circ Res.* 2006;99(12):1426–1432.

65. Sundaresan M, Yu ZX, Ferrans VJ, et al. Regulation of reactive-oxygen-species generation in fibroblasts by Rac 1. *Biochem J.* 1996;318(Pt 2):379–382.

66. Takemoto M, Node K, Nakagami H, et al. Statins as antioxidant therapy for preventing cardiac myocyte hypertrophy. *J Clin Invest.* 2001;108(10):1429–1437.

67. Wassmann S, Laufs U, Bäumer AT, et al. Inhibition of geranylgeranylation reduces angiotensin II-mediated free radical production in vascular smooth muscle cells: involvement of angiotensin AT1 receptor expression and Rac1 GTPase. *Mol Pharmacol*. 2001;59(3):646–654.

68. Gregg D, Frederick MR, Pascal JG. Rac regulates cardiovascular superoxide through diverse molecular interactions: more than a binary GTP switch. *Am J Physiol Cell Physiol*. 2003;285(4):C723–C734.

69. Hordijk PL. Regulation of NADPH oxidases: the role of Rac proteins. *Circ Res.* 2006;98(4):453–462.

70. Yano M, Matsumura T, Senokuchi T, et al. Statins Activate Peroxisome Proliferator-Activated Receptor γ Through Extracellular Signal-Regulated Kinase 1/2 and p38 Mitogen-Activated Protein Kinase–Dependent Cyclooxygenase-2 Expression in Macrophages. *Circ Res*. 2007;100(10):1442–1451.

71. Paumelle R, Blanquart C, Briand O, et al. Acute antiinflammatory properties of statins involve peroxisome proliferator–activated receptor-α via inhibition of the protein kinase C signaling pathway. *Circ Res.* 2006;98(3):361–369.

72. Pucci A, Formato L, Muscio M, et al. PPAR γ in coronary atherosclerosis: *in vivo* expression pattern and correlations with hyperlipidemic status and statin treatment. *Atherosclerosis*. 2011;218(2):479–485.

73. Corti R, Osende JI, Fallon JT, et al. The selective peroxisomal proliferator-activated receptor-gamma agonist has an additive effect on plaque regression in combination with simvastatin in experimental atherosclerosis. J *Am Coll Cardiol*. 2004;43(3):464–473.

74. Braun-Dullaeus RC, Michael JM, Victor JD. Cell cycle progression. *Circulation*. 1998;98(1):82–89.

75. Kobashigawa JA, Steven K, Hillel L, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med.* 1995;333(10):621–627.

76. Laufs U, Marra D, Node K, et al. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of p27 Kip1. *J Biol Chem*. 1999;274(31):21926–21931.

77. Chen Z, Tatsuya F, Zago AC, et al. Simvastatin reduces neointimal thickening in low-density lipoprotein receptor–deficient mice after experimental angioplasty without changing plasma lipids. *Circulation*. 2002;106(1):20–23.

78. Chandrasekar B, Mummidi S, Mahimainathan L, et al. Interleukin-18-induced human coronary artery smooth muscle cell migration is dependent on NF-κB-and AP-1-mediated matrix metalloproteinase-9 expression and is inhibited by atorvastatin. J *Biol Chem*. 2006;281(22):15099–15109.

79. Li M, Liu Y, Dutt P, et al. Inhibition of serotonin-induced mitogenesis, migration, and ERK MAPK nuclear translocation in vascular smooth muscle cells by atorvastatin. *Am J Physiol Lung Cell Mol Physiol*. 2007;293(2):L463–L471.

80. Radomski MW, Rees DD, Dutra A, et al. S-nitroso-glutathione inhibits platelet activation *in vitro* and *in vivo*. *Br J Pharmacol*. 1992;107(3):745–749.

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