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Lovastatin as a Treatment of Cardiovascular and Neurological Disorders

Mussina K, Akhmetova A and Tokay T*

Department of Biology, Nazarbayev University, Kazakhstan

***Corresponding author:** Tursonjan Tokay, Biology Department, School of Science and Technology, Nazarbayev University, Nur-Sultan, Kazakhstan, Email: tursonjan.tokay@nu.edu.kz

Review Article

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Abstract

There is evidence that statins which are mainly used in treatments of dyslipidemia can be used for attenuating symptoms of cardiovascular and neurodegenerative diseases. Lovastatin and other statins are known to function through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which is involved in the majority processes such as cell differentiation, proliferation and migration. Recently it was revealed that lovastatin is effective in the reducing total and low-density-lipoprotein cholesterol, lowering the risks of post-surgical complications and mitigation of anticancer drugs' side effects. Moreover, there are other combinations with other drugs to treat cardiovascular diseases. In addition, anti-inflammatory and immunomodulatory effects of lovastatin diminish neurological disorders such as multiple sclerosis (MS). Especially, combination treatment of lovastatin and rolipram in suboptimal doses is considered to be the most promising approach for protecting neuronal axons from demyelination and promoting neuro repair in MS. Although lovastatin demonstrates promising option for treatment of cardiovascular and neurological diseases, more clinical trials and studies in vivo and in vitro are required.

Keywords: Lovastatin; Cardiovascular Diseases; Multiple Sclerosis; Combination Treatment of Lovastatin

Introduction

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins can be used in treatments of different diseases. The main purpose of using statins is considered to be lowering the elevated different types of cholesterol levels. Starting from the ninetieth several studies discovered lovastatin as a promising tool for the treatment of various disorders such as dyslipidemia, neurodegenerative and cardiovascular diseases [1-6].

The ability of lovastatin to promote the treatments is justified on its pleiotropic effects. Inhibition of HMG-CoA reductase takes significant role in mevalonic acid pathway. Mevalonate acts as a precursor for both steroidal and non-steroidal isoprenoid intermediates. Cholesterol being the steroid has been already verified to be modulated by lovastatin in previous studies. On the other hand, non-steroidal isoprenoids affect proteins such as heterotrimeric G-proteins, HM-A, small GTP-bound protein Ras, and Ras-like proteins contributing to the intracellular signalling pathways of cell proliferation, myelination, cytoskeleton arrangement and endocytotic-exocytotic transport [7]. Therefore, since lovastatin has an impact on the mevalonate pathway it can indirectly change cell survival. The focus of this review paper is

investigation of novel applications and effects of lovastatin in cardiovascular and neurological diseases. The administration of lovastatin alone and in combination with other drugs will be also presented with explanation of lovastatin activity mechanisms.

Effects of Lovastatin on Cardiovascular Diseases

The statin is widely used in the treatment of different cardiovascular diseases (CVDs) mostly by lowering increased total cholesterol (TC), low-density-lipoprotein (LDL) cholesterol and triglycerides (TG) levels in blood. According to several meta-analyzes, statins are able to reduce the risks of major vascular events with approximately the same effectivity in both of the lowest risk categories and the higher risk categories [8-11]. The occurrence of major coronary events during 5 year period, coronary revascularisations, and ischaemic strokes was observed to be diminished after statin treatment affecting mainly LDL cholesterol levels [8-11]. Additionally, statins are administered for other purposes except the diminishing the cholesterol levels. In this section we attempted to analyze most novel mechanisms and purposes of lovastatin administration in treatments of common CVDs.

Mechanisms of Actions of Lovastatin in the Treatment of Cardiovascular Diseases

Targeting High Levels of Low-density-lipoprotein Cholesterol

There are several mechanisms proposed how lovastatin can contribute to treatment of heart-related diseases. One of such mechanisms has been suggested by recent study investigated how exposure to three statins (i.e. lovastatin, atorvastatin and pravastatin) affected the complex formation between proprotein convertase subtilisin-kexin 9 (PCSK9) and the low density lipoprotein receptor (LDLR), which is known to be important in degradation of LDLR in lysosomes. The expression of PCSK9 indirectly downregulates the LDL cholesterol levels in the blood through the receptor-mediated endocytosis mechanism [12-14]. As soon as LDL cholesterol molecule is bound to LDLR expressed on the surface of cells, the PCSK9 associates to this complex and assists with intake of the cholesterol molecule by endosomal pathway [15]. Endosomes further fuse with lysosomes where degradation of both proteins occurs. It was established that lovastatin and atorvastatin induced expression of PCSK9 and consequently resulted in lowering the LDL cholesterol concentrations, whereas pravastatin effect was opposite [15]. So, high LDL cholesterol levels in CVDs can be counteracted by lovastatin treatment.

Prevention of Post-surgical Complications

There is evidence of effective usage of statins after cardiovascular interventions in order to reduce postsurgical complications related to CVDs [16-18]. Although lovastatin is known to augment CVD treatments by mitigation of LDL cholesterol levels, the activity of lovastatin could be also explained by cholesterol-independent cardioprotective mechanism. Graft failure after the bypass surgery or angioplasty are one of those cases that frequently result in intimal hyperplasia and atherosclerosis which arise from vascular smooth muscle cells' (SMCs) dedifferentiation [19-21]. Since vascular SMCs preserve plasticity even after acquiring differentiated state expressing specific repertory of contractile proteins, ion channels and signaling molecules, dedifferentiation of SMCs' phenotype occurs as a response to vascular injuries after bypass surgery [22,23]. It was demonstrated that the complications after surgical intervention such as intimal hyperplasia and atherosclerosis are treatable with lovastatin use [24].

Wagner and colleagues [2010] established that lovastatin inhibits farnesylation of Ras homologue enriched in brain (Rheb) by blocking the activity of farnesyltransferase. Farnesylation is one type of prenylation where the farnesyl group (15-carbon isoprenoid) is covalently attached to cysteine residues near or at C-terminus of protein [25]. That in turn inhibits the activity of the mammalian target of rapamycin complex 1 (mTORC1) which is essential in vascular SMC transcription initiation under the additional action of growth factors, particular amino acids and energy stages [26-28]. By inhibiting the mTORC1 the modulation of vascular SMCs in intimal hyperplasia is held by differentiating SMCs to normal state of contraction. Thus, mTORC1 signaling pathway is suggested to be one of the mechanisms of lovastatin effects, allowing novel ways in cardiovascular treatments to emerge.

Attenuation of Anthracycline Cardiotoxicity Side-Effects

Another efficacious application of lovastatin has been shown in the alleviation of side-effects of anticancer treatments such as anthracyclines. The doxorubicin, an anthracycline derivative, is widely used in antineoplastic therapy [29]. However, doxorubicin besides its positive effects in anticancer treatment, also, leads to congestive heart diseases due to cardiomyopathy and liver damage

[30-36]. The acute (within 1-3 days), subacute (within weeks) and delayed cardiotoxicity is observed during dose-dependent doxorubicin application [34-37]. Congestive heart diseases results due to increased prolonged cardiotoxicity which was acquired through upregulation of interleukin 6 (IL-6), connective tissue growth factor (CTGF), brain natriuretic peptide (BNP) and heat shock protein A1B (Hspa1b) RNA in doxorubicin treatment (29). In addition, because of inhibition of topoisomerase II activity by doxorubicin, there was production of reactive oxygen species (ROS) and nitric oxide synthases (NOS) that contribute to doxorubicin cardiotoxicity [31,38-40]. Weinstein, et al. [41], Cole, et al. [42] and Chaiswing, et al. [43] proposed alternative solution being co-treatment for doxorubicin with antioxidant called dexrazoxane. However, the dexrazoxane demonstrated opposite effects to expected ones exaggerating the side-effect cardiotoxicity of doxorubicin. On the other hand, LDL cholesterol lowering lovastatin treatment illustrated the results of significant mitigation of cardiotoxicity when used as co-treatment with doxorubicin [34,44,45]. Lovastatin is believed to operate on reducing IL-6, CTGF, BNP and Hspa1b RNA expression by repressing Rac1 signaling pathway [33,34,46,47]. Doxorubicin upregulates expression of Rac1 which was observed to adduce to cardiomyocytes' apoptotic death and result in myocardial dysfunction by its NADPH oxidase activity and consequent ROS generation [48]. Therefore, inhibition of Rac1 by lovastatin is one of the promising approaches to ease the cardiotoxic side-effects of doxorubicin.

Concomitant Adverse Effects of Lovastatin

Upon the treatment of CVDs based on targeting reduction of total cholesterol (TL) and LDL cholesterol by statin application, there might be concerns about its own side-effects. Diabetes mellitus type 2, renal injury and myopathy rarely presented in form of rhabdomyolysis are the most recognized adverse effects of statin treatment [49-51]. Although, there are various side effects of statin treatment, it is believed that its significant effects on CVDs therapy outweigh presented side-effects. Moreover, it was established that statins do not elevate risks of cognitive disease and progression of cancer [50].

Combinatorial Treatments of Lovastatin with other Drugs in CVDs Treatment

Lovastatin is seen to be also used in combinations with other drugs to improve CVDs treatments. Lovastatin with cholestyramine and lovastatin with colestipol are ones of effective combinations used in order to reduce lesions after coronary bypass surgery [52-55]. In addition, Alsheikh-Ali and Karas et al. [16] observed that the combination of lovastatin and niacin brought the same liver damage and rhabdomyolysis progression as in the lovastatin and niacin treatments used separately and demonstrated that these adverse effects are more manifested in simvastatin treatment. Nevertheless, there are combinations that can result in ameliorated CVDs treatment methods, physicians are still concerned with adverse outcomes that these combinations can cause; thus, more studies are required to clarify the efficacy of complementary administration of lovastatin with other drugs.

From all mentioned above it can be concluded that the lovastatin treatment gives perspective opportunities for treating various CVDs by the help of its pleiotropic activities. It was noted that there were eight most cited studies [1-6,56,57] all of them indicating that lovastatin is one of the effective statins that positively influence the treatment of coronary atherosclerosis and cardiovascular events. However, the validity of those studies' results can be put under questioning, since all of them were performed between 1991 and 1999 and concomitant therapies such as blood pressure lowering, diuretics, anticoagulants were used in different way compared to care standard to date back [10]. Therefore, there is a necessity of new clinical trials with higher sample sizes to investigate the effect of lovastatin use in CVDs therapy methods.

Effect of Lovastatin to Neurodegenerative Diseases

Multiple Sclerosis

Early studies have revealed that lovastatin in addition to lipid-lowering effects, have anti-inflammatory and immunomodulatory characteristics [58]. These characteristics of statins are suggested to have valuable effects for immune mediated neurological abnormalities. In this section we will focus on the mechanisms and effects of two drug combination treatments with lovastatin on the multiple sclerosis neurological disease. Multiple sclerosis (MS) is a demyelinating disease of central nervous system (CNS) that leads to motor, sensory and cognitive impairment. There are variety of studies that indicated both genetic and environmental factors to have impacts on the process of demyelination of CNS. Moreover, the viral infections are considered to be the main cause for the disease, while it was noted that several patients had genetically promoted MS [59].

Demyelination of axons results in the deficiency and complete absence of nerve impulse transmission due to the infiltration of leukocytes from vasculature to the neural tissue [59,60]. The migration of transendothelial lymphocyte in the CNS is contingent on activation of lymphocytes and capability of leukocytes to induce signaling responses in endothelial cells. These CNS endothelia are connected by tight junctions who form blood-brain barrier (BBB) [60]. The BBB plays a crucial role in the restriction transmigration of cells from peripheral blood to the CNS; hence, provides an immune system and homeostasis to the CNS. During the immune mediated multiple sclerosis the transmigration of antigen, the infiltration of inflammatory cells through the BBB and the neuronal damage are known to take place.

Experimental Autoimmune Encephalomyelitis (EAE)

In order to obtain a disease mechanism, several models have been established. Much comprehensive research on MS disease has been accomplished predominantly in animal model which is called experimental autoimmune encephalomyelitis (EAE). Since it is one of the best studied models for human immune mediated disease, EAE animal models used as a potential treatment of MS. Disease in the EAE are induced by T cells. It starts from brain inflammation by crossing the leukocytes through endothelial cells, consequently migrating through blood-brain barrier (BBB) to the CNS. Within CNS, antigen-presenting cells (APCs) introduce MHC class II associated peptides which causes myelin-specific T-cell reactivation. It initiates signaling cascade of secretion of chemokines that induces macrophages to the sites of T-cell activation. As a result, chemokines and cytokines are released that produce inflammation. This neuroinflammatory response leads to infiltration of leukocytes and demyelination of axons in CNS which is analogous to the pathology identified in MS. Due to this correlation, EAE is accepted as a model of MS [60].

Nowadays several therapeutics are useable, however, even though they are very effective treatment of MS, they have serious side effects. Therefore, in order to overcome these complications lovastatins are introduced which are considered to be the most promising approach. Statins have multiple effects such as anti-inflammatory effects, antioxidant effects, immunomodulatory effects, plague stability, thrombus formation. These numerous lipid-independent effects are known as “pleiotropic effects” of lovastatin. Lovastatins develop the immune function in EAE, as a result, immune response from Th1 to the protective Th2 is induced in EAE [59,7].

Anti-Inflammatory Effects of Lovastatin

The anti-inflammatory effect of lovastatin specifically targets mitigation of leukocyte migration across BBB. There are two studies demonstrating that lovastatins reduce migration of intercellular adhesion molecule-1 (ICAM-1; CD54) on CNS endothelium which does not allow interacting with T cell integrin αLβ2 (lymphocyte function-associated antigen) (LFA-1) [60,61]. Recent studies identified that ICAM-1 does not only act as adhesion molecule, but also promotes lymphocyte transendothelial migration. The efficient ICAM-1 signal transmission depends on functional Rho GTPase. Statins reduce Rho prenylation, hence antagonize leukocyte migration across endothelial cells [60,61].

Immunomodulatory effect of Lovastatin

Combination Treatment of Lovastatin and Rolipram

The immunomodulatory effects of lovastatin treatment are observed in co-administration therapies of lovastatin with other drugs. Several studies support that the combination of lovastatin with rolipram (RLP) can prevent the progression of MS by different mechanisms. The RLP is a phosphodiesterase-4 inhibitor which prevents the degradation of cyclic AMP (cAMP) and induces immunomodulation of myelin-reactive Th1 to Th2. Therefore, combination therapy promotes neurorepair of demyelinated axons in MS model [62-64]. Moreover, reduced doses of drugs in combination are more efficient in lowering CNS demyelination and promoting neurorepair. However, the explanation of such observations have not yet established. Early studies demonstrated that optimal dose of lovastatin and RLP was ≥2mg/kg for repression of inflammation in EAE [64]. However, recent researches determined that suboptimal doses (≥1mg/kg) of lovastatin and RLP are more efficient in reducing disease conditions [62]. Treatment with these drugs is conducted after demyelination symptoms appeared. As a result, leukocyte infiltration and some pathological changes were dramatically declined by drug combination therapy. Since CNS demyelination is associated with an increase of cellular infiltration, drug combination treatment reduces the loss of neuronal axons and degeneration of oligodendrocytes in EAE animal models.

The mechanism of drug combination therapy of lovastatin and RLP is as follows. As it was mentioned before RLP prevents the degradation of cAMP which is very crucial step in therapy [65]. Activation starts from

specific pathways including nuclear-cytoplasmic CREB-protein (cAMP responsive element binding protein) which initiates gene transcription with cAMP in the promoter region. cAMP induces the phosphorylation and activates CREB protein. Consequently, it promotes the activation of protein kinase cascade in neurons, PKA [66]. As a result, elevated level of cAMP regulates by decreasing the demyelination of axons in CNS. This can be achieved by combination of lovastatin and RLP therapy. In addition, it was verified that PKA activity was relatively lower when lovastatin or RPL was applied separately rather than in combination [67].

Another effect of combination therapy of lovastatin and RLP is neurorepair in CNS. Induction of platelet derived growth factor-α receptor (PDGF-αR) and marker of myelin-forming oligodendrocyte (MBP) initiates myelin repair in the drug combination treatment. Moreover, oligodendrocytes transcription factors also increased due to the combination therapy which led to myelin repair. Transcripts for neurotrophins such as ciliary neurotrophic factor (CNTF) and NT-3 which are essential in myelin repair also were increased by drug combination therapy [68,69]. To sum up, combinatorial therapy of lovastatin and RLP seems to protect neuronal axons from demyelination and induce a spontaneous myelin repair by increasing the development of oligodendrocytes.

Since the combination therapy of lovastatin and RLP has synergistic effects, acts with different mechanisms, has no additional toxicities and severe side effects, it is more promising tool for preventing MS development. In addition, lovastatin and RLP both are able to cross the BBB and induce neurorepair of CNS. On the basis of these findings, the combination of lovastatin and RLP is likely to be an excellent approach for MS prevention, by using suboptimal doses of drugs.

Combination Treatment of Lovastatin and AICAR

Another promising approach is a combination therapy of lovastatin and 5- aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), an immunomodulating agent that activates AMP-activated protein kinase. It affects with the same mechanism as the combination of lovastatin and RLP but with difference in their doses, RLP (≥1 mg/kg) whereas AICAR (≥50 mg/kg) [62]. Suboptimal doses of drugs in combination of lovastatin and AICAR decline leukocyte infiltration and proinflammatory immune response but it induces the anti-inflammatory immune response. Treatment with AICAR promotes the immune response from myelin-reactive T-cells to Th2 differentiation and develops immunomodulatory effect in APC by activating secretion of anti-inflammatory cytokines. As a result, it increases the survival of neurons and develops neuroprotective ability against CNS demyelination. Since the combination of lovastatin and AICAR results in progress of protective Th2 immune response, it is concluded that this combination could be one of the approaches for the treatment of CNS inflammation and neurodegeneration in MS. By summarizing all arguments which were mentioned above, it can be concluded that lovastatin in combination with RLP and AICAR are known to be promising and efficient approaches for the treatment of MS introducing minimal adverse and toxic effects. Moreover, other studies suggest that lovastatin can be used as a therapy for other neurological disorders such as Alzheimer's disease, Early Stage Parkinson's Disease and other peripheral nerve injuries that works with the same mechanism which was discussed above [69-74]. Therefore, for the future perspectives it is necessary to conduct clinical trials to investigate the effects of these combination therapies in other neurodegenerative abnormalities.

Conclusion

After analyzing the most recent research papers, it was concluded that lovastatin is one of the most perspective treatments of both CVDs and MS. Additionally, more studies in vitro and in vivo are required to fully evaluate the effectiveness of lovastatin in different diseases.

References

1. Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Hemphill CL, et al. (1993) Coronary Angiographic Changes with Lovastatin Therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med 119(110): 969-976.

2. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, et al. (1998) Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279(20): 1615-1622.

3. Furberg CD, Adams HP, Applegate WB, Byington RP, Espeland MA, et al. (1994) Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events. Asymptomatic Carotid Artery Progression

Study (ACAPS) Research Group. Circulation 90(4): 1679-1687.

4. Sahni R, Maniet AR, Voci G, Banka VS (1991) Prevention of Restenosis by Lovastatin After Successful Coronary Angioplasty. Am Heart J 121(6): 1600-1608.

5. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, et al. (1994) Effects of Monotherapy with an HMG-CoA Reductase Inhibitor on the Progression of Coronary Atherosclerosis as Assessed by Serial Quantitative Arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 89(3): 959-968.

6. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, et al. (2002) The HMG- CoA Reductase Inhibitor, Atorvastatin, Promotes a Th2 Bias and Reverses Paralysis in Central Nervous System Autoimmune Disease. Nature 420(6911): 78-84.

7. Vasnawala H, Kavalipati N, Shah J, Ramakrishan A (2015) Pleiotropic Effects of Statins. Indian J Endocrinol Metab 19(5): 554-562.

8. Cholesterol Treatment Trialists' (CTT) Collaborators (2012) The Effects Of Lowering LDL Cholesterol With Statin Therapy In People At Low Risk Of Vascular Disease: Meta-Analysis Of Individual Data From 27 Randomised Trials. The Lancet 380(9841): 581-590.

9. Cholesterol Treatment Trialists' Collaborators (CTT) (2015) "Efficacy and Safety Of LDL-Lowering Therapy Among Men And Women: Meta-Analysis of Individual Data From 174 000 Participants In 27 Randomised Trials. The Lancet 385(9976): 1397-1405.

10. Mills EJ, WU P, Chong G, Ghement I, Singh S, et al. (2010) Efficacy And Safety Of Statin Treatment For Cardiovascular Disease: A Network Meta-Analysis Of 170 255 Patients From 76 Randomized Trials. QJM 104(2): 109-124.

11. Mario P, Costanzo P, Perrone-Filardi P, Chiariello M (2010) Impact Of Gender In Primary Prevention Of Coronary Heart Disease With Statin Therapy: A Meta-Analysis. Int J Cardiol 138(1): 25-31.

12. McNutt MC, Kwon HJ, Chen C, Chen JR, Horton JD, et al. (2009) Antagonism of Secreted PCSK9 Increases Low Density Lipoprotein Receptor Expression in HepG2 Cells. J Biol Chem 284(16): 10561-10570.

13. Qian YW, Schmidt RJ, Zhang Y, Chu S, Lin A, et al. (2007) Secreted PCSK9 Downregulates Low Density Lipoprotein Receptor Through Receptor-Mediated Endocytosis. J Lipid Res 48(7): 1488-1498.

14. Tveten K, Holla OL, Cameron J, et al., Interaction Between the Ligand-Binding Domain of the LDL Receptor and the C-Terminal Domain of PCSK9 is required for PCSK9 to Remain Bound to the LDL Receptor During Endosomal Acidification. Hum Mol Genet 21(16): 1402-1409.

15. Quantil MM, Wooten CJ, Lopez D (2017)"Atorvastatin And Lovastatin, But Not Pravastatin, Increased Cellular Complex Formation Between PCSK9 And The LDL Receptor In Human Hepatocyte-Like C3A Cells". Biochemical and Biophysical Research Communications 492(1): 103-108.

16. Alsheikh-Ali, Alawi A, Karas RH (2007) Safety of Lovastatin/Extended Release Niacin Compared With Lovastatin Alone, Atorvastatin Alone, Pravastatin Alone, and Simvastatin Alone (From The United States Food And Drug Administration Adverse Event Reporting System). The American Journal of Cardiology 99(3): 379-381.

17. Christenson J (2001) Preoperative Lipid Control with Simvastatin Reduces the Risk of Graft Failure Already 1 year After Myocardial Revascularization. Cardiovasc Surg 9(1): 33-43.

18. Henke PK, Blackburn S, Proctor MC, Stevens J, Mukherjee D, et al. (2004) Patients Undergoing Infrainguinal Bypass to Treat Atherosclerotic Vascular Disease is Under Prescribed Cardioprotective Medications: Effect on Graft Patency, Limb Salvage and Mortality. J Vasc Surg 39(2): 357-365.

19. Corpataux JM, Naik J, Porter KE, London NJ (2005) A Comparison of Six Statins on the Development of Intimal Hyperplasia in a Human Vein Culture Model. Eur J Vasc Endovasc Surg 29(2): 177-181.

20. Corpataux JM, Naik J, Porter KE, London NJ (2005) The Effect of Six Different Statins on the Proliferation, Migration, and Invasion of Human Smooth Muscle Cells. J Surg Res 129(1): 52-56.

21. Miyauchi K, Kasai T, Yokayama T, Aihara K, Kurata T, et al. (2008) Effectiveness of Statin-Eluting Stent on Early Inflammatory Response and Neointimal

Thickness in a Porcine Coronary Model. Circ J 72(5): 832-838.

22. Owens GK (1995) Regulation of Differentiation of Vascular Smooth Muscle Cells. Physiol Rev 75(3): 487-517.

23. Somlyo AP, Somlyo AV (2003) Calcium Sensitivity of Smooth Muscle And Nonmuscle Myosin II: Modulated By G Proteins, Kinases and Myosin Phosphatase. Physiological Reviews 83(4): 1325-1358.

24. Wagner RJ, Martin KA, Powell RJ, Rzucidlo PM (2010) Lovastatin Induces VSMC Differentiation Through Inhibition Of Rheb And Mtor. AJP: Cell Physiology 299(1): C119-C127.

25. Zhang F, Casey P (1996) Protein Prenylation: Molecular Mechanisms and Functional Consequences. Annu Rev Biochem 65: 241-269.

26. Gingras AC, Raught B, Sonenberg N (2001) Regulation of Translation Initiation by FRAP/mTOR. Genes Dev 15(7): 807-826.

27. Martin KA, Blenis J (2002) Coordinate Regulation of Translation by the PI 3-kinase and mTOR Pathways. Adv Cancer Res 86: 1-39.

28. Sarbassov DD, Ali SM, Sabatini DM (2005) Growing Roles for the mTOR Pathway. Curr Opin Cell Biol 17(6): 596-603.

29. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L (2004) Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity. Pharmacol Rev 56(2): 185-229.

30. van Dalen EC, van der Pal HJ, Kok WE, Caron HN, Kremer LC (2006) Clinical Heart Failure in a Cohort of Children Treated With Anthracyclines: a Long-Term Followup Study. Eur J Cancer 42(18): 3191-3198.

31. Ferreira AL, Matsubara LS, Matsubara BB (2008) Anthracycline-Induced Cardiotoxicity. Cardiovasc Hematol Agents Med Chem 6: 278-281.

32. Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA (2001) Anthracycline induced Clinical Heart Failure in a Cohort of 607 Children: Long-Term Follow-up Study. J Clin Oncol 19(1): 191-196.

33. Huelsenbeck J, Henninger C, Schad A, Lackner KJ, Kaina B, et al. (2011) Inhibition Of Rac1 Signaling By Lovastatin Protects Against Anthracycline-Induced Cardiotoxicity. Cell Death and Disease 2(8): e190.

34. Huelsenbeck SC, Schorr A, Roos WP, Huelsenbeck J, Henninger C, et al. (2012) Rac1 Protein Signaling is Required for DNA Damage Response Stimulated by Topoisomerase ii Poisons. J Biol Chem 287(46): 38590-93859.

35. Riad A, Bien S, Westermann D, Becher PM, Loya K, et al. (2009) Pretreatment with Statin Attenuates the Cardiotoxicity of Doxorubicin in Mice. Cancer Res 69(2): 695-699.

36. Yoshida M, Shiojima I, Ikeda H, Komuro I (2009) Chronic Doxorubicin Cardiotoxicity is Mediated by Oxidative DNA Damage-atm-p53-Apoptosis Pathway and Attenuated by Pitavastatin through the Inhibition of Rac1 Activity. J Mol Cell Cardiol 47(5): 698-705.

37. Feleszko W, Mlynarczuk I, Balkowiec-Iskra EZ, Czajka A, Switaj T, et al. (2000) Lovastatin Potentiates Antitumor Activity and Attenuates Cardiotoxicity of Doxorubicin in Three Tumor Models in Mice. Clin Cancer Res 6(5): 2044-2052.

38. Fogli S, Nieri P, Breschi MC (2004) The Role of Nitric Oxide in Anthracycline Toxicity and Prospects for Pharmacologic Prevention of Cardiac Damage. FASEB J 18(6): 664-675.

39. Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, et al. (2007) Topoisomerase IIbeta Mediated DNA Double-Strand Breaks: Implications in Doxorubicin Cardiotoxicity and Prevention by Dexrazoxane. Cancer Res 67(18): 8839-8846.

40. Weinstein DM, Mihm MJ, Bauer JA (2000) Cardiac Peroxynitrite Formation and Left Ventricular Dysfunction Following Doxorubicin Treatment in Mice. J Pharmacol Exp Ther 294(1): 396-401.

41. Cole MP, Chaiswing L, Oberley TD, Edelmann SE, Piascik MT, et al. (2006) The Protective Roles of Nitric Oxide and Superoxide Dismutase in Adriamyc Ininduced Cardiotoxicity. Cardiovasc Res 69(1):186-197.

42. Chaiswing L, Cole MP, Ittarat W, Szweda LI, St Clair DK, et al. (2005) Manganese Superoxide Dismutase and Inducible Nitric Oxide Synthase Modify Early Oxidative Events in Acute Adriamycin-Induced Mitochondrial Toxicity. Mol Cancer Ther 4(7): 1056-1064.

43. Damrot J, Nuebel T, Epe B, Roos WP, Kaina B, et al. (2006) Lovastatin Protects Human Endothelial Cells From the Genotoxic and Cytotoxic Effects of the Anticancer Drugs Doxorubicin and Etoposide. Br J Pharmacol 149(8): 988-997.

44. Henninger C, Huelsenbeck J, Huelsenbeck S, Grosch S, Schad A, et al. (2012) The Lipid Lowering Drug Lovastatin Protects against Doxorubicin-Induced Hepatotoxicity. Toxicol Appl Pharmacol 261(1): 66-73.

45. Nuebel T, Damrot J, Roos WP, Kaina B, Fritz G (2006) Lovastatin 11Protects Human Endothelial Cells from Killing by Ionizing Radiation Without Impairing Induction and Repair of DNA Double-Strand Breaks. Clin Cancer Res 12(3): 933-939.

46. Christian H, Huelsenbeck S, Wenzel P, Brand M, Huelsenbeck J, et al. (2015) Chronic Heart Damage Following Doxorubicin Treatment Is Alleviated By Lovastatin. Pharmacolo Res 91: 47-56.

47. Rashid M, Tawara S, Fukumoto Y, Seto M, Yano K, et al. (2009) Importance of Rac1 Signaling Pathway Inhibition in the Pleiotropic Effects of HMG-CoA Reductase Inhibitors. Circ J 73(2): 361-370.

48. Jian M, Wang Y, Zheng D, Wei M, Xu H, et al. (2012) Rac1 Signalling Mediates Doxorubicin-Induced Cardiotoxicity Through Both Reactive Oxygen Species-Dependent and-Independent Pathways. Cardiovascular Research 97(1): 77-87.

49. Cindy LC, Jones PH, Suki WN, Lederer ED, Quinones MA, et al. (1988) Rhabdomyolysis And Renal Injury With Lovastatin Use. JAMA 260(2): 239-241.

50. Wouter JJ, Cannon CP, de Craen AJM, Westendorp RGJ, Trompet S (2012) The Controversies Of Statin Therapy. Journal of the American College of Cardiology 60(10): 875-881.

51. Reith C, Blackwell L, Emberson J, Mihaylova B, Armitage J, et al. (2016) Protocol For Analyses Of Adverse Event Data From Randomized Controlled Trials Of Statin Therapy. Am Heart J 176: 63-69.

52. Brown BG, Bardsley J, Poulin, Hillger LA, Dowdy AD, et al. (1997) Moderate dose, Three Drug Therapy with Niacin, Lovastatin, and Colestipol to Reduce Low-Density Lipoprotein Cholesterol <100 mg/dl in Patients with Hyperlipidemia and Coronary Artery Disease. Am J Cardiol 80(2): 111-115.

53. Domanski M, Tian X, Fleg J, Coady S, Gosen C, et al. (2008) Pleiotropic Effect of Lovastatin, With and Without Cholestyramine, in The Post Coronary Artery Bypass Graft (Post CABG) trial. Am J Cardiol 102(8): 1023-1027.

54. The Post Coronary Artery Bypass Graft Trial Investigators (1997) The Effect of Aggressive Lowering of Low-Density Lipoprotein Cholesterol Levels and Low-Dose Anticoagulation on Obstructive Changes in Saphenous-Vein Coronary-Artery Bypass Grafts. N Engl J Med 336(3): 153-162.

55. Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, et al. (1991) Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 151(1): 43-49.

56. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, et al. (1990) Regression of Coronary Artery Disease as a Result of Intensive Lipid-Lowering Therapy in Men with High Levels of Apolipoprotein B. N Eng J Med 323(19): 1289-1298.

57. Kleemann A, Eckert S, von Eckardstein A, Lepper W, Schernikau U, et al. (1999) Effects of Lovastatin on Progression of Non-Dilated and Dilated Coronary Segments and on Restenosis in Patients after PTCA. The Cholesterol Lowering Atherosclerosis PTCA trial (CLAPT). Eur Heart J 20(19): 1393-406.

58. Sena A, Pedrosa R, Morais M (2003) Therapeutic Potential of Lovastatin in Multiple Sclerosis. J Neurol 250(6): 754-755.

59. Bakshi C (2017) Multiple Sclerosis: an Insight into Experimental Autoimmune Encephalomyelitis (EAE). World Journal of Pharmacy and Pharmaceutical Sciences, pp: 459-476.

60. Greenwood J Walters CE, Pryce G, Kanuga N, Beraud E, et al. (2003) Lovastatin Inhibits Brain Endothelial Cell Rho-Mediated Lymphocyte Migration and Attenuates Experimental Autoimmune Encephalomyelitis. FASEB J 17(8): 905-907.

61. Ifergan I, Wosik K, Cayrol R, Kébir H, Auger C, et al. (2006) Statins Reduce Human Blood-Brain Barrier Permeability and Restrict Leukocyte Migration: Relevance to Multiple Sclerosis. Annals of Neurology 60(1): 45-55.

62. Paintlia A, Paintlia M, Singh I, Skoff R, Singh A (2009) Combination Therapy of Lovastatin and Rolipram Provides Neuroprotection and Promotes Neurorepair in Inflammatory Demyelination Model of Multiple Sclerosis. Glia 57(2): 182-193.

63. Paintlia A, Paintlia M, Singh I, Singh A (2006) Immunomodulatory Effect of Combination Therapy with Lovastatin and 5-Aminoimidazole-4-Carboxamide-1-β-d-Ribofuranoside Alleviates Neurodegeneration in Experimental Autoimmune Encephalomyelitis. Am J Pathol 169(3): 1012-1025.

64. Paintlia AS, Paintlia MK, Singh AK, Stanislaus R, Gilg AG, et al. (2004) Regulation of Gene Expression Associated with Acute Experimental Autoimmune Encephalomyelitis by Lovastatin. J Ne uro-sci Res 77(1): 63-81.

65. Song HJ, Ming GL, Poo MM (1997) cAMP-Induced Switching in Turning Direction of Nerve Growth Cones. Nature 388(6639): 275-279.

66. Karnaukh EV, Kalyuzhka VY, Markevych MA (2015) The New Nootropic Mechanism of Action of the Modern Antidepressant Rolipram on Cognitive Functions. European Journal of Natural History 1: 31.

67. Stankoff B, Aigrot MS, Noel F, Wattilliaux A, Zalc B, et al. (2002) Ciliary Neurotrophic Factor (CNTF) Enhances Myelin Formation: a Novel Role for CNTF and CNTF-Related Molecules. J Neurosci 22(21): 9221-9227.

68. Kirstein M, Farinas I (2002) Sensing Life: Regulation of Sensory Neuron Survival by Neurotrophins. Cell Mol Life Sci 59(1): 1787-1802.

69. Sarkey J, Richards M, Stubbs E (2006) Lovastatin Attenuates Nerve Injury in an Animal Model of Guillain-Barré Syndrome. Journal of Neurochemistry 100(5): 1265-1277.

70. Ghayour M, Abdolmaleki A, Rassouli M (2017) Neuroprotective Effect of Lovastatin on Motor Deficit Induced by Sciatic Nerve Crush in the Rat. European Journal of Pharmacology 812: 121-127.

71. Yongbin L, Cheng Z, Zhao Y, Chang X, Chan C, et al. (2016) Efficacy And Safety Of Long-Term Treatment With Statins For Coronary Heart Disease: A Bayesian Network Meta-Analysis. Atherosclerosis 254: 215-227.

72. Abbruzzese TA, Havens J, Belkin M, Donaldson MC, Whittemore AD, et al. (2004) Statin Therapy is Associated with Improved Patency of Autogenous Infrainguinal Bypass Grafts. J Vasc Surg 39(6): 1178-1185.

73. Alexander, Matthew R, Owens GK (2012) Epigenetic Control of Smooth Muscle Cell Differentiation And Phenotypic Switching In Vascular Development And Disease. Ann Rev Physiol 74(1): 13-40.

74. Zeljko R (2010) Combined Therapy in the Treatment of Dyslipidemia. Fundamental & Clinical Pharmacology 24(1): 19-28.