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Review Article

Simvastatin and Its Role in Anti-Inflammation and Cancer Therapy: A Review

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ABSTRACT

3-Hydroxy-3-methylglutaryl-coenzyme, a reductase inhibitors (statins) are widely used drugs to reduce lipid levels by inhibiting cholesterol biosynthesis. Simvastatin, a lipophilic statin is one of the most frequently prescribed statin drugs throughout the world due to profound reductions in LDL-C with excellent tolerability, with very little risk of important adverse effects, to a lower extent. It also reduce triglycerides and increase high-density lipoprotein cholesterol levels. Beside this, studies on simvastatin have shown to exhibit numerous pleiotropic effects, has beneficial effect on endothelial function, smooth muscle cell function, haemostasis, vascular wall function, LDL oxidation, kidney diseases, inflammation and anticarcinogenic effects on many types of cancer including prostate, breast hepatic and colon carcinoma. In this review, we present an overview of simvastatin and its relevance in anti-inflammation and cancer management.

Keywords: *Statins, Simvastatin, CVD, Inflammation, Cancer*

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INTRODUCTION

In the late 1980s, hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) (commonly known as statins) became the drug of choice for treating dyslipidaemia.[1,2] It revolutionized the clinical management of high cholesterol. Currently, there are six statin drugs available on the market – pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin and Fluvastatin.[3] Statins are specific inhibitors of the mevalonic acid signalling pathway involved in the synthesis of cholesterol and non-sterol isoprenoids de novo.[4] It has been found that statins have an affinity for the enzyme a thousand time higher than that of the natural substrate, resulting in a lower formation of mevalonate, which leads to a decrease in the concentration of intracellular cholesterol.[5] Beyond cholesterol-lowering properties of these drugs, statins are indicated in the treatment of hypercholesterolemia for the prevention of cardiovascular risk.[6] However, statins may also exhibit numerous pleiotropic cholesterol-independent pharmacological effects (e.g., pro-angiogenic, anti-inflammatory, immune-regulatory, and antioxidative effects), which render them to become a good candidate for additional therapeutic purposes in addition to lowering cholesterol.[7] In this review, we are going to assess the most highlighted studies regarding a very prominent member of the statin family which is simvastatin with regard to pharmacology and its role in disease management .

Simvastatin, the most widely used is a lipid-lowering agent, a competitive inhibitor of hepatic hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase, This enzyme plays a

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key role in Cholesterol synthesis, which catalyses the conversion of HMG-CoA to mevalonate.[1] Simvastatin was the first hypolipidemic drug to show a reduction in cardiac mortality.[8] It was approved for marketing by the FDA in 1991 and is still widely prescribed to control hypercholesterolemia.

Biochemistry and Pharmacology

Simvastatin is basically an inactive 6-membered lactone ring which is hydrolysed in vivo from lovastatin and it is itself a fermentation product of the fungus Aspergillus terreus. Prior to simvastatin, Lovastatin was widely used as common lipid lowering agent, given to its ability to lower low-density lipoprotein cholesterol (LDL-C) and its good tolerability.[10,11] Simvastatin was first introduced in Sweden, in April 1988, by Merck & Co., that differs from lovastatin by additional methyl group on the ester side chain that enhances inhibition of 3-hydroxy-3-methyl- glutaryl-coenzyme A (HMG-CoA) reductase by ~2-folds.[11,12] Simvastatin has the molecular formula of $C_{25}H_{38}O_5$ and a molecular weight of 418.57 Da. It is a, crystalline, non-hygroscopic powder that is white in colour and insoluble in water.[11]

Simvastatin is marketed worldwide with other common names like Zocor, MK-733 and Sivastin etc. It is administered orally in solid form and recommended dose is 5 mg to 40 mg generally in case of Mixed hyperlipidaemia; and Coronary atherosclerosis.[10] It does not only affects cholesterol and lipoprotein levels in the plasma but also modulates immune responses by suppressing MHC II (Major Histocompatibility Complex II) on interferon gamma-stimulated, antigen-presenting cells such as human vascular endothelial cells.[10]

It functions as a prodrug and acts as the anthrax lethal factor endopeptidase inhibitor, and hydroxymethylglutaryl-CoA reductase inhibitor, a ferroptosis inducer and a geroprotector. Simvastatin is a delta-lactone, a fatty acid ester, a statin (semi-synthetic).[10] It has a half-life of 4.85 hours.[20] It's a small molecule of average weight 418.5662 and monoisotopic: 418.271924326. The route of elimination in a healthy individual after an oral dose of Simvastatin is 13% by urine and 60% via faeces.[18,19]

Simvastatin is prescribed to lower total cholesterol, low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), non-high density lipoprotein-cholesterol (non-HDL-C), and trigleride (TG) plasma concentrations while increasing HDL-C concentrations. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease and to predict the coronary artery disease the total cholesterol to HDL-C ratio are assessed and higher ratios indicates the higher risk of disease.[10]

Simvastatin is an antilipemic agent and commonly indicated in the treatment of primary hyperlipidaemia (Fredrickson type IIa, heterozygous familial and nonfamilial), mixed dyslipidaemia (Fredrickson type IIb), hypertriglyceridemia (Fredrickson type IV hyperlipidaemia), primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia), homozygous familial hypercholesterolemia (HoFH) as parallel treatment along with other lipid-lowering treatments, as well as adolescent patients with Heterozygous Familial Hypercholesterolemia (HeFH) (18,19). Simvastatin is also used to reduce the risk of cardiovascular morbidity and mortality including myocardial infarction, stroke, and the need for revascularization procedures. It is basically indicated in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease.[18,19] Simvastatin indicated conditions include diabetes mellitus, clinical atherosclerosis (including myocardial infarction, acute coronary syndromes, stable angina, documented coronary artery disease, stroke, trans ischemic attack (TIA), documented carotid disease, peripheral artery disease, and claudication), abdominal aortic aneurysm, chronic kidney disease, and severely elevated LDL-C levels.[15,20]

For the development of CVD the increased levels of cholesterol, particularly high low-density lipoprotein (LDL) levels are responsible.[15] Application of statins, in particular Simvastatin to target and reduce LDL levels has been shown in a lot of significant studies to effectively reduce the risk of development of CVD and all-cause mortality.[21-25] Beside these the use of Simvastatin and other statins are usually known as highly cost-effective treatment option for CVD due to their evidence of reducing all-cause mortality including fatal and non-fatal CVD and also the need for surgical revascularization or angioplasty following a heart attack.[15,20] In the field research studies has shown that even for low-risk individuals (with <10% risk of a major vascular event occurring within 5 years) statins cause a 20%-22% relative reduction in major cardiovascular events (heart attack, stroke, coronary revascularization, and coronary death) for every 1 mmol/L reduction in LDL without any significant side effects or risks.[26,27]

Mechanism of action

Since the prescribed doses of Simvastatin is relatively low, it doesn't completely blocks enzyme HMG-CoA by its activity, thus allowing a little amount of mevalonate to remain available as it is biologically necessary. Given that in the biosynthetic pathway for cholesterol, mevalonate is an early step, simvastatin therapy doesn't cause any accumulation of potentially toxic sterols. Instead, enzyme HMG-CoA is metabolized readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.[19] Also the plasma concentrations of simvastatin and its metabolites are too low to cause significant protein binding displacement reactions.

Remarkable research studies of simvastatin on animals have demonstrated that simvastatin independent of its lipid-lowering properties exerts vasculoprotective effects, also known as the pleiotropic effects of statins.[28,29] which include the improvement in endothelial functions, enhanced stability of atherosclerotic plaques, reduced oxidative stress and inflammation, and inhibition of the thrombogenic response. Studies have suggested that it also allosterically binds to the β2 integrin function-associated antigen-1 (LFA-1), playing an important role in leukocyte trafficking and in T cell activation[30] Beside these, it interacts with many other enzymes as inhibitor like Histone deacetylase 2 and 3-hydroxy-3-methylglutaryl-coenzyme A reductase which is a transmembrane glycoprotein, a crucial enzyme in the biosynthesis of cholesterol and nonsterol isoprenoids which are essential for normal functioning of the cell.[31-33]

Simvastatin acts as inhibitory allosteric modulator to the enzyme Integrin alpha-L in humans which regulates immune process like leukocyte-endothelial cell interaction, cytotoxic T-cell mediated killing, and antibody dependent

killing by granulocytes and monocytes.[34,35] Even though Simvastatin is in clinical use for moreover 40 years, still considerable efforts are needed to develop new solid dosage forms of simvastatin with better stability and higher bioavailability after oral administration. A lot of the strategies which are proposed require thermal treatment (e.g., solid dispersions in a hydrophilic polymeric matrix).[16, 17]

Absorption

According to studies conducted by Micro Labs FDA and and Health Canada Monograph, after an oral dose of Simvastatin, the peak plasma concentrations of both active and total inhibitors were attained in the span of 1.3 to 2.4 hours. Even though the dose recommended ranges from 10 to 40 mg per day, no significant deviation from linearity of AUC was manifested with an substantial increase in dose to 120 mg. when administered to the fasting individual, there was no difference in the plasma profile of inhibitors when simvastatin was given immediately before a test meal.[19,20] A pharmacokinetic study was conducted on 17 healthy Chinese volunteers with a single oral dose of 40 mg, revealed the major PK parameters as follows: Tmax 1.44 hours, Cmax 9.83 ug/L, t1/2 4.85 hours, and AUC 40.32ug·h/L.[36] The liver being primary action site and the main target organ where inhibition of HMG-CoA reductase occur, here an extensive first-pass extraction of Simvastatin occurs.[36]

The tissue selectivity and consequent low systemic exposure of the drug administered as the enzymatically active form like the open hydroxyacid is much less than in case of orally administered simvastatin.[19] In-vivo research studies on animal suggested that simvastatin when prescribed orally is found in higher concentrations in the liver relative to other tissues. The bioavailability of Simvastatin in the systemic system is quite less also because it undergoes extensive first-pass metabolism. A study of nine healthy individuals who were orally administered single dose of simvastatin, shown that less than 5% of the drug reached the general circulation in the form of active inhibitors.[19] Research studies done on rats indicated that simvastain can also cross blood brain barrier.[18]

Biomolecular Interactions And Pathways :

Simvastatin is administered as a solid lactone form. It dissolve at physiological pH and yields corresponding biologically active hydroxy acid upon hydrolysis.[9] Simvastatin and the β-hydroxyacid metabolite of Simvastain can efficiently bound upto 95% with the human plasma proteins.[18,19] Also the plasma concentrations of simvastatin and its metabolites are too low to cause significant protein binding displacement reactions. The metabolites of simvastatin which are active majorly are the β-hydroxyacid metabolite and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.[18,19]

Simvastatin metabolism is a complex process as it's an lactone in inactive form and has various inter conversion pathways to form an active acid by enzymes like, esterases, paraoxonases, and by non-enzymatic hydrolysis.[13] Oxidative metabolism of Simvastain is majorly mediated by CYP3A4 and CYP3A5 in the liver, and CYP2C8 and CYP2C9 helps in the rest of the metabolism.[43] Conversion of simvastatin acid back to simvastatin take place through the acyl glucuronide intermediate, and by the CoASH-dependent pathway.[14] Also the oxidative metabolism of Simvastain takes place by cytochrome P1450 (CYP) 3A4, and CYP 3A4 and β-oxidation enzyme systems oxidise Simvastatin acid.

The most pre-eminent metabolic pathway for simvastatin, lovastatin and atorvastatin is CYP 3A4/5 and simvastatin acts as a substrate for CYP 3A4.[37,38] Thus it can be given with other substrates of CYP 3A4 as this won't have an effect on their plasma levels. Also the evidence of simvastatin inhibiting other cytochrome isoforms wasn't found.[37] Simvastatin pharmacokinetics was shown to be impacted by the genetic differences in the OATP1B1 (Organic-Anion-Transporting Polypeptide 1B1) hepatic transporter encoded by the SCLCO1B1 gene (Solute Carrier Organic Anion Transporter family member 1B1). Research studies on the c.521T>C single nucleotide polymorphism (SNP) proved that simvastatin plasma concentrations were increased on average 3.2-fold for individuals homozygous for 521CC compared to homozygous 521TT individuals (39,40). The 521CC genotype is also leads to a significant increase in the risk of developing myopathy, similarly secondary to escalated systemic exposure.[41] Other statin drugs impacted by this polymorphism also affects other statins like rosuvastatin, pitavastatin, atorvastatin, lovastatin, and pravastatin.[42] A patient having the above genotype c.521CC OATP1B1, daily dose of maximum 20mg of simvastatin should be administered to avoid its adverse effects like muscle pain and risk of rhabdomyolysis.[19] Other Statins like rosuvastatin was shown that with contemporaneous use of statins and inhibitors of Breast Cancer Resistance Protein (BCRP) like elbasvir and grazoprevir after a little dose adjustment can enhance the concentration of these statins in the plasma. Futher fluvastatin and atorvastatin are also impacted by this polymorphism.[39]

Oxidative metabolism of Simvastain is majorly mediated by CYP3A4 and CYP3A5 in the liver, and CYP2C8 and CYP2C9 helps in the rest of the metabolism.[43] The metabolites of simvastatin which are active majorly are the β-hydroxyacid metabolite and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.[18,19] A significant increases in the plasma concentrations of the parent lactone and its hydrolysed form can be produced by the CYP 3A4 inhibitors, but basically more than 75% of the HMG-CoA reductase inhibitory activity in plasma is accounted by the combined action of the three downstream oxidised active metabolites of simvastatin.[44] But also these combined interactions lead to the side effects like the disease Myopathy.[45] As all HMG-CoA-reductase inhibitors can cause myopathy, plasma HMG-CoA reductase inhibitory activity is likely to correlate with the risk of myopathy better than the plasma concentration of the inactive parent lactone or any one particular metabolite, such as simvastatin acid.[45]

Simvastatin in anti-inflammation

Statins have anti-inflammatory properties[46] and can inhibit the activity of proinflammatory cytokines.[47] The anti-inflammatory properties of statins not only reduce cholesterol synthesis but also activate 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which in turn leads to reduction in isoprenyl and geranylgeranylated proteins, especially prenylation of Ras.[48] HMG-CoA

reductase inhibitors, such as simvastatin, reduce circulating cholesterol levels and prevent myocardial infarction. Sparrow et al (2001) used the apoE knockout mouse model to address the potential anti-inflammatory effects of simvastatin on atherosclerosis. Simvastatin significantly reduced the accumulation of cholesterol in the aorta in this model, indicating an important and direct anti-atheroma effect of Simvastatin.[49] In vitro studies have shown cellular effects of statins that may benefit atherosclerosis. These include the inhibition of leukocyte adhesion[50,51] and reduced cytokines productions.[52] Atherosclerosis is an inflammatory disease, and the in vitro observation may be considered as an anti-inflammatory.[49]

Statins cause decreased macrophage expression of soluble intercellular adhesion molecule-1 and lipopolysaccharide-induced secretion of IL-6 and TNF-α by monocytes and macrophages.[53-55] Recent data show that treatment with simvastatin for 8 weeks reduced the expression of TNF-α and IL-10 monocytes by 49% and 35%, respectively.[56] Increasing the level of soluble intercellular adhesive molecules-1 and IL-6 in blood plasma has been reported to reduce the risk of heart attack.[57,58] Other studies shown that statins help in reduction of platelet aggregation ex vivo and in vitro. Simvastatin have been shown to reduce thrombus formation and inhibits thrombin formation.[59]

Barale et al.[48] provide an early evidence that short-term treatment with simvastatin simultaneously affects a wide range of markers of inflammation and atherosclerosis, suggesting that there are several ways to better explain the rationale for simvastatin therapy in patients at high risk of cardiovascular disease. Indeed, in addition to the hypocholesterolaemic effect, treatment with it decreases proatherogenic and anti-inflammatory markers and increases antiatherosclerotic and anti-inflammatory markers. Furthermore it is also a physiological agent that reduces platelet aggregation. Because atherosclerosis is an inflammatory vascular disease characterized by the accumulation of lipids and the infiltration of inflammatory cells, dyslipidemia and systemic inflammation in diabetes generally increase the risk of cardiovascular disease (CVD).[60] A recent population study found that statin treatment lowers C-reactive protein levels and CVD events in individuals with elevated serum C-reactive protein but low-density lipoprotein cholesterol levels within the normal range. It became clear that there was less inflammation, which can help to reduce CVD events.[61] Hu et al. found that Simvastatin treatment for three months significantly reduced serum anti-inflammatory adipokines, including SAA, TNFα, IL-6, and CRP, and increased adiponectin levels in patients with type 2 diabetes with AS. These findings support a beneficial anti-inflammatory effect of statins and suggest that adipokines may be effectors and/or adipose tissue may be a target of the anti-inflammatory effect of statins and that an improved adipokine profile (decreased proinflammatory adipokines and increased anti-inflammatory adipokines) may contribute in part to the reduction of cardiovascular events with statin treatment.[62]

The anti-inflammatory properties of statins have been shown to reduce cardiovascular disease and help with other diseases that do not affect lipid levels.[63,64] Simvastatin has similar properties.[65] Mohrschladt et al [66] reported no significant decrease in C-reactive protein was observed after simvastatin administration in patients with familial hypercholesterolemia. Statins inhibit Ras to reduce the activity of the nuclear transcription factor kappa B (NF-kB) involved in the inflammatory pathway.[67] High dose of simvastatin decrease the binding activity of the proinflammatory transcription factor NF-kB and the concentrations of inflammatory molecules 48 [42] Dichtl et al [68] investigated the effects of simvastatin on transcription factors such as activator protein-1 and NF-KB, which are molecules responsible for regulating inflammation and dependent on activator-1 and NF-KB proteins. cells, which have an inhibitory effect on transcription. Similar results were reported by Ortego et al.,[69] oxidative stress (O2) was used to induce increased activation of NF-KB in cultured smooth muscle cells.

Subsequent treatment with simvastatin reduced oxidative stress-induced NF-κB activation by approximately 50%.[70] In addition to NF-KB signaling, simvastatin modulates GBPs 1-5 and JAK-STAT signaling pathways.[71] Simvastatin has also been shown to block tumor necrosis factor (TNF) -NF-κB-induced transcriptional activity and IkB phosphorylation / degradation. Interestingly, statins have also been shown to increase the expression of Kruppel-like factor-2 (KLF-2) in ECs.[72] Tuomisto et al [71] showed that KLF-2, as well as its family members KLF-3 and KLF-4, induced by simvastatin in macrophages. KLF-2 is a transcription factor identified as an "atheroprotective phenotype" of the endothelium. Its overexpression suppresses the expression of anti-inflammatory and prothrombotic genes, such as vascular cell adhesion molecule-1 (VCAM-1) and plasminogen activating inhibitor (PAI-1) and its overexpression enhance the expression of endothelial nitric oxide synthetase (eNOS) and thrombomodulin.[73-75]

Simvastatin has strong anti-inflammatory effects on macrophages, including attenuated expression of several cytokines, members of the TNF family, and some anti-inflammatory signaling molecules.[71] One of the most recent events in the pathogenesis of vascular disease is endothelial damage. As an essential interface between blood and tissue, the endothelium develops substances such as endothelial nitric oxide synthase (eNOS) and thrombomodulin that maintain blood flow by ensuring adhesion to the vessel wall and antithrombotic properties.[76] Studies have shown that statins can significantly increase the expression of endothelial nitric oxide synthesis (eNOS) in vitro when compressed with cholesterol.[77] Simvastatin increases eNOS expression by almost four times and completely prevents the reduction of oxidized LDL. A significant increase in endothelial-dependent vasodilatation was observed in patients with moderate hypercholesterolemia after 4 weeks of simvastatin treatment.[59] Previous studies suggests that simvastatin has anti-inflammatory activity that is significant to the prevention of disease. Although the mechanism is not yet established, further research may lead to new understanding of the this drug in the treatment of cardiovascular disease and other immune/ inflammatory disorders.

Simvastatin in Cancer

Beside the application of Simvastanins in the treatment of lipid disorders, research studies have been done for their anticarcinogenic effects in several models, which includes the cancers of lung, prostate, liver, breast, colon, rectum, skin (melanoma), renal cell, bladder, and multiple myeloma.[78-80]

Simvastatin has some characteristic effects on target cells that provide the evidence required for its potential application in the cancer treatment. Statins inhibit the synthesis of mevalonic acid and mevalonate is required for the isoprenoid compounds synthesis, which are precursors of cholesterol, lichol, and ubiquinone and also has functions as substrates for post-translational modifications of different proteins (29). Statin also inhibits the proliferation of smooth muscle cells in the vasculature, which lead to primary and secondary prevention of cardiovascular disorders.[81] In addition they induce apoptosis in smooth muscle cells and many types of cancer cell.[81,82] These aforementioned properties of statins provide great promise for their future application in inhibition of cancer cell proliferation and survival. Research done by Laufs et al in 1998, Rikitake et al. in 2001 and Guijarro et al. in 1998 proved that the statin dose required for the inhibition of Akt activity and cell proliferation and induction of apoptosis in malignant smooth muscle cells in atherosclerotic lesions and cancer cells is the same dose at which statins promote Akt activation and survival in endothelial cells.[77,83,84] This property of statins is very much noteworthy as through this side effects of statins when used for cancer treatment could be avoided.[85]

Reseachers have reported that the positive regulation of growth factor receptors in some tumor cells, are linked with cholesterol-dependent signalling events.[86] This indicates the potentials of the simvastatin for the prevention and treatment of some cancers like in breast cancer.[87] As the tumor cells regulates the enzyme expression of the mevalonate biosynthesis pathway by increasing it, of which simvastatin is known to be an inhibitor by a mechanism which is yet to be studied.[88,89] Since simvastatin is capable of inhibiting the HMG- CoA reductase enzyme which results into mevalonate depletion and the downstream products. Most of these products play a significant role as the mediators of the signalling pathway, integrity, and cell cycle regulation.[90] Another research findings suggest that apoptosis has a linear and dose-dependent response to simvastatin medication. The geranylgeranyl phosphates, a downstream product of the mevalonate pathway inhibits the apoptosis. Statins induce the depletion of geranylated proteins, cell apoptosis starts since mitochondrial transmembrane potential is decreased and activation of caspase-9 and caspase-3 is increased.[91]

Research by Fujiwara and colleagues exhibited that the induction of apoptosis by statins in hematopoietic tumor cells can occur via the mitochondrial apoptotic signalling pathways. They are activated by the suppression of mevalonic acid or geranyl pyrophosphate biosynthesis due to cell cycle arrest in the G1 phase by suppressing the prenylation of the rapamycin (Ras) pathway.[92] It is also proposed that since simvastatins suppress the growth of cancer cells by inducing G1- phase arrest arrest by reducing CDK4/6 and cyclin D1 which also leads to reduced cell migration.[93,94] In endothelial cells simvastatins may reduce the expression of matrix metalloproteinase-9 (MMP-9), which leads to the reduced capacity invasive cells resulting into inhibition of tumor angiogenesis.[91,93] Other research studies indicate that with the application of simvastatin the expression of c-Myc, Ras and Rho protein can be decreased and/or senescence in cancer cell lines can be induced leading to cancer cell growth suppression. Simvastatin can also inhibit the angiogenesis by increasing the inhibitory effect of TNF alpha on tumor growth and vascularization which rely on the activation of some proteins that interfere with important cell signalling pathways.[95,96] The anticarcinogenic effects of simvastatin requires different subcellular structures and overlapping molecular pathways.[97]

Kochuparambil et al. reported that simvastatin can be developed as a potential drug for the treatment of prostate cancer. Simvastatin directly regulates the functions of cell migration, invasion, proliferation, cell survival, apoptosis, and colony formation in prostate cancer cells. They found that simvastatin has the clear ability of inhibiting the pro tumorigenic functions of prostate cancer cells, inducing apoptosis, and inhibiting the tumor growth in vivo.[85] In case of prostate cancer cells, the cholesterol-lowering effect of statins is very important factor in the regulation of cellular functions. The hormone Androgens are believed to be mediator of the cholesterol metabolism in LNCaP cells involving Acyl-CoA cholesterol acyltransferase facilitating tumor progression.[98] Research studies done previously have shown that prostate cancer cells lack a sterol-mediated feedback regulation of the sterol regulatory element-binding protein-2 (SREBP-2), which is a transcription factor responsible for cholesterol homeostasis regulation,[99] in LNCaP and PC3 cells. Cholesterol accumulation has also been observed when samples are taken from patients with prostate cancer.[100] Cholesterol-rich lipid rafts are associated with tumor progression and metastasis.[101] Cholesterol-lowering agents induce apoptosis through reduced production of cholesterol-rich lipid rafts in normal prostate epithelium, human epidermoid cancer (A431), and breast carcinoma (MCF-7 and MDA-MB-231) cell lines.[102] Beside these Mevalonate pathway products also include dolichol, ubiquinol, and isoprenoids such as farnesol and geranylgeraniol. They act as lipid-anchoring units for various signalling molecules such as small GTPases, Ras, and Rho. They are known to mediate carcinogenic transformation and may be involved in non-cholesterol-mediated regulation of prostate cancer by statins.[85,103]

Research study performed on another cancer type shows that simvastatin induces apoptosis and inhibits Akt phosphorylation and Bcl-xL expression in breast cancer cells through inhibiting nuclear factor B, derepression of phosphatase and tensin homolog, and subsequent inhibition of PI3 kinase.[104] Statins have also generally been shown to inhibit Akt-mammalian target of rapamycin signaling in p53-deficient hepatocellular cancer.[105] Previous studies conducted on PC3 and LNCaP cell lines shows that simvastatin, fluvastatin, and lovastatin have profound effects on inducing a cell cycle arrest at the G1 phase through inhibition of cyclin E/cdk2 kinase, likely by the inhibition of Akt.[106,107] In addition at very low doses, close to therapeutic concentrations, simvastatin increase the inhibitory effects of acetylsalicylic acid and rosiglitazone on proliferation of normal prostatic epithelial cells and LNCaP and VCaP (vertebral cancer of the prostate) prostate cancer cells.[108] Kochuparambil et al. signified that simvastatin inhibits Akt activity in LNCaP and PC3 cells in a dose and time dependent manner. The use of simvastatin for treatment of prostate cancer cells inhibits Akt activity, prostate cancer cell functions in vitro, and tumor growth in vivo significantly and is associated with a significant reduction in PSA expression.[85] Thus administration of

simvastatin for longer time would provide beneficial effects in managing many type of cancers.

CONCLUSION

Simvastatin, commonly administered to reduce the lipid levels, is being rediscovered for exhibiting pleiotropic effects such as anti-inflammatory actions (asthma, rheumatic arthritis, stroke, and C-reactive protein levels), controlling various dementia, kidney disease and antineoplastic effects in many types of cancer. The antioncogenic properties of statins simvastatin is involved in modulating cancer cell proliferation migration, and survival of cancer cells. Although research have proven its anti-inflammatory and antitumor efficacy, the biological mechanisms for these actions are not fully elucidated and further research efforts are needed to consider the possible effective doses, and the combination of simvastatin with other generally used drug for respective disorders and to confirm its feasibility as an alternative therapeutic strategy to cancer, inflammation and other disorder treatments of other disorders.

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