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The Role of Statins in Cancer Therapy: A critical review

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Abstract

The paper demonstrates the protective association of the use of statins with different types of cancer. Statins or 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors are among the most commonly prescribed drugs worldwide. It is associated with the lower incidence of long-term adverse cardiovascular events. It is demonstrated by the growing clinical evidences that it may also be useful in the prevention and treatment of cancer independent of their effects on cholesterol levels. Different Research has shown that statin is a potent anti inflammatory agent with strong therapeutic potential against a variety of cancers. Statins have been shown to suppress tumour growth, angiogenesis and metastasis of tumors. Mevalonate pathway is inhibited by the statins which play an important role in therapy of cancer. This pathway involve in multiple cellular processes by the formation of sterol isoprenoids and non-sterol isoprenoids. These molecules are crucial for cell differentiation and cell growth. The effectiveness of statins in cancer treatment increases when statins combined with other chemotherapeutics. Statins show proapoptotic properties in different types of tumor cells. On clinical trials, statins reduce the risk of advanced prostate cancer. The current review focuses on the brief description of the biochemistry of the mevalonate pathway, molecular anti cancer mechanisms by which statin mediates its effects against various cancers and their role in the therapy of cancer.

Keywords:Statins (HMG-CoA reductase inhibitor); Cancer; Apoptosis; Tumor; Prevention

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors also known as statins are most important class of cholesterol lowering agents. Statins are the second most prescribed therapeutic drug class in the United States after painkiller acetaminophen. (Gonyeau & Yuen, 2010). In clinical trials, statins prevent from cardiovascular diseases including atrial fibrillation, myocardial infarction, renal dysfunction and stroke in ambulatory patient populations. HMG-CoA reductase catalyses the reaction in which mevalonate is formed by HMG-CoA. (Glynn et al., 2008; Young, 2003). Statins inhibit the synthesis of mevalonate pathway byproducts such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) that are important products for intracellular G-proteins and its subunits, such as Rac, Rho, and Ras and help in its post-translational modification. (Weis et al., 2002). These are necessary for many cellular functions including cell differentiation, cell signalling and proliferation, endocytotic/exocytotic transport and cytoskeleton dynamics.

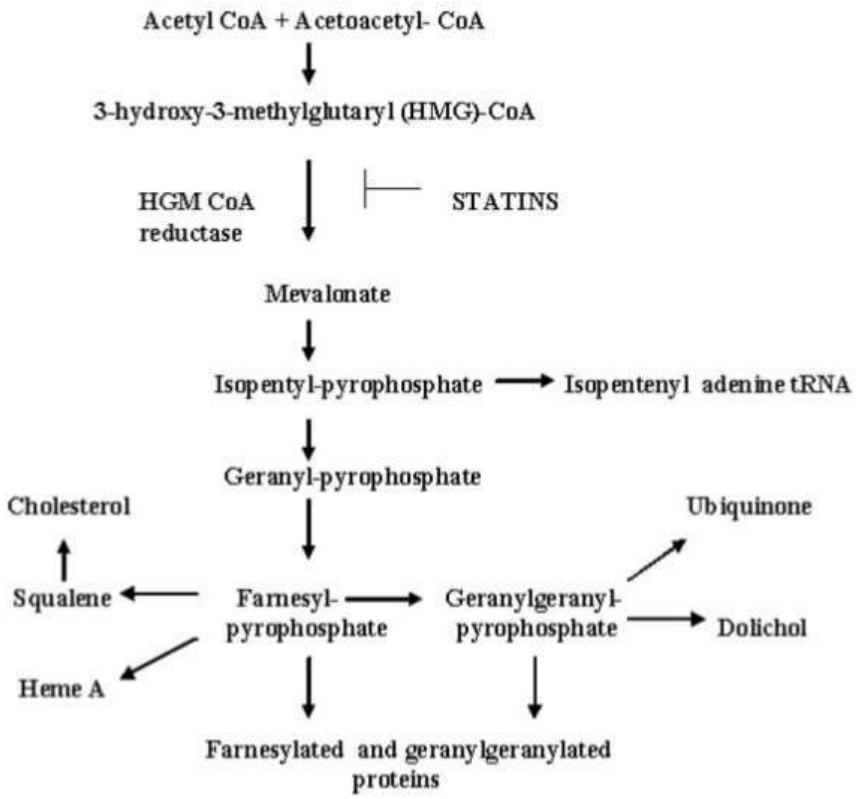

Fig.1. Scheme of mevalonate metabolism and its products affected by HMG-CoA reductase. Adapted from (Osmak, 2012)

Sterol isoprenoids, e.g. cholesterol, and non-sterol isoprenoids e.g. heme-A, dolichol, ubiquinone and isopentenyl tRNA are the end products of this pathway. By inhibiting mevalonate pathway, its downstream products are also affected. Other cellular functions may also influenced by blockage of this pathway. (Osmak, 2012).

Statins leads to the increased concentration of hepatic LDL receptors on the cell membrane. Increase in LDL receptors decrease atherogenic LDLs level. (Medizin et al., 2006). 20% to 55% reduction in blood LDL cholesterol levels (Lewis, 2002), 7% to 30% reduction in triglycerides level and 0% to ~10% elevation in HDL levels by statins users were observed. (Jones et al., 1998, Medizin et al., 2006).

The statin family consists of several drugs including pravastatin, mevastatin, simvastatin, fluvastatin, lovastatin, rosuvastatin, atorvastatin, and cerivastatin (cerivastatin was withdrawn from the market in 2001). Of these drugs, lovastatin, cerivastatin, mevastatin, simvastatin, atorvastatin and fluvastatin are lipophilic. In contrast, rosuvastatin and pravastatin are hydrophilic. (Zhang et al., 2012)

Pleiotropic effects of Statin

Recent experimental and clinical data shows that statins have therapeutic effects on different diseases including rheumatoid arthritis, autoimmune diseases, multiple sclerosis, dementia, and different types of cancer. (Buhaescu & Izzedine, 2007). Independent of cholesterol lowering action, Statins also have Pleiotropic effects as role in anti-inflammatory actions as well as their effects on plasma lipids. It also performs immunomodulatory actions by controlling immune responses and having effects on the cell proliferation, cell differentiation and secretory activity of the immune cells, mainly T cell, macrophages and monocyte. (Tandon et al., 2005). Statins also have reduced risk of dementia in neuroprotective effects, progression of chronic kidney disease, anticancer effects and positive effects on bone metabolism. These Pleiotropic effects of statin therapy beneficial for therapeutic application in cardiovascular disorders as well as in different diseases. (LaRosa, 2001, Pedersen,

2010). Statins present its anti-cancer effects by suppression of proliferation and induction of apoptosis, (Osmak, 2012), inhibition of Angiogenesis, inhibition of Tumor Cell Growth and repression of Tumor Metastases. (Hindler et al., 2006).

One of the main reasons of cancer mortality is Metastasis that has a multistep procedure including invasion, adhesion and migration. One of the common treatments is to induce apoptosis. For example overexpression of tissue inhibitors of metalloproteinase (TIMP)-3 inhibited the tumor cell invasion by inducing its apoptotic cell death. (Zhang et al., 2001).

CARCINOGENIC AND ANTI CARCINOGENIC EFFECTS OF STATINS

Carcinogenesis due to statins in most studies was due to the increased doses than those normally used for the treatment of hypercholesterolemia in humans. The recent studies suggest that high dosage levels of statins produce adverse effects. Lower doses of Lovastatin had no carcinogenic effects on rats, monkeys or dogs. (MacDonald et al., 1988). Lovastatin used for the treatment of hypercholesterolemia, if it used much above the levels than the concentrations of lovastatin create disturbances in mitoses in the cell lines. It was expected that liver cancer was found in mice or rat with lovastatin, simvastatin and pravastatin. Increased amount of Lovastatins (500 mg/kg per day) were cause an increased numbers of hepatocellular and pulmonary cancers. (Robison et al., 1994).

In mice, simvastatin and pravastatin decreased 1, 2-dimethylhydrazine (DMH)-induced colon cancer. It is also suggested that in many laboratory animal model, statins may prevent colon tumorigenesis. (Narisawa et al.,1996). Recent study suggested antitumor activity of statins and a crucial role for prevention of human cancers. (Hoque et al., 2008). Statins affect the lipid raft in plasma membrane that involve in signal transduction like cell growth, migration and survival. Statins prevent overall, prostate and colorectal cancer. Randomized controlled trials for treating cardiovascular disease showed that statins had reduced melanoma and colorectal cancer. These findings have led to great attention towards statins used in cancer prevention. (Demierre et al., 2005).

In this review, we explore the evidence from epidemiological studies examining the association of statins consumption with human cancers.

Mechanism of action

Numerous studies have demonstrated the ability of statins to suppress the growth of a variety of tumor cells. The postulated mechanisms for these anticancer effects are multiple.

Antiproliferative effects include inhibition of Mevalonate pathway, intermediates of this pathway play important role in the post translational modification of intracellular G-proteins, such as Rho, Rac, and Ras that involve in regulation of platelets, endothelial and leukocyte function. (Cipollone et al., 2003; Ridker & Cannon, 2005). Induction of apoptosis, the apoptotic pathways undergo the activation of cysteine-dependent, aspartate specific proteases (caspases) that are endoproteases and are essential to the final execution of cell death. (Kluck et al., 1997). Suppression of proteins that regulate apoptosis. Suppression of LDL and C reactive proteins level, serum amyloid A, interleukin-6, various inflammatory cytokines, including tumor necrosis factor alpha (TNF-α). Suppression of angiogenesis, a crucial step in the growth and metastasis of many cancers. Statins have anti inflammatory and antioxidant action that are important for prognosis and treatment. It also takes part in inhibition of nuclear factor κ B and matrix metalloproteinases. By inhibiting these, its effect is to modulate vascular remodeling. (Ridker et al., 2005).

Anti-cancer effects of Statins

In vitro experimental data describe that statins exhibit antitumor effects against various colorectal cancer, leukemia cells, melanoma and solid tumor cells of different origins. The statins exerts various effects that suppress proliferation and induce apoptosis. These studies show that statin associated reduction in overall prostate and colorectal cancer thus lead towards the prevention of cancer. (Demierre et al., 2005). Fluvastatin, simvastatin and lovastatin are cytotoxic against breast

adenocarcinoma cells. (Campbell et al., 2006). Similarly, simvastatin and lovastatin are cytotoxic against ovarian cancer cells and atorvastatin, simvastatin, lovastatin and cerivastatin are cytotoxic against myeloma tumor cells. (Cafforio et al., 2005).

The blockage of the mevalonate pathway has an important regulatory role in the production of isoprenoid units, which are critical for the activation of Rho, Ras and Rab proteins. (Brunsveld et al., 2006). Furthermore it also play role in regulation of proliferation and apoptosis of tumor cells by affecting MAPK and Cdk2, that reduce the expression of p21 and p27 cyclin kinase inhibitors. (Denoyelle et al., 2001)

Inhibition of tumor cell growth

Cholesterol is an essential structural component of cell membranes. Hence, Mevalonate pathway associated with cell growth processes. (Goldstein & Brown, 1990). For the synthesis of DNA, Dolichol plays a significant role and is involved in some tumor cell proteins. Intracellular G-proteins Ras and Rho are isoprenylated by isoprenoids GPP and FPP. Several membrane receptors that involved in the transcription of genes are in association with apoptosis, differentiation, cell proliferation and its signal transduction is regulated by this isoprenylation. (Wejde et al., 1998). Ras and Rho gene mutations are found in a variety of thyroid (50%), lung (30%), pancreas (90%), colon (50%), and myeloid leukemia (30%) tumor types. (Bos, 1989) e.g., lovastatin stabilize p21 and p27 that are the cell cycle kinase inhibitors and at the G1 phase of the cell cycle, it arrest breast cancer cell lines. Cerivastatin demonstrated to inhibit Rho and Ras mediated cell proliferation. This investigate that statins inhibit the growth of various types of tumor cell that include gastric and prostate as well as melanoma, colon adenocarcinoma and acute myeloid leukemia cells. (Rao et al., 1998; Denoyelle et al., 2001).

Repression of tumor metastases

Statins inhibit cell migration, invasion of the basement membrane and attachment to the extracellular matrix so impairs the metastatic potential of tumor cells. Statins reduce E-selectin, endothelial leukocyte adhesion molecule (Nubel et al., 2004) and matrix metalloproteinase (MMP)-9 expression (Wang et al., 2000). It also inhibits epithelial growth factor that induce tumor cell invasion. Atorvastatin decrease melanoma cell metastasis. However, not all studies have confirmed that statins reduce tumor metastases. For example, lovastatin failed to inhibit glioblastoma cell migration, invasion and colon carcinoma. (Hindler et al., 2006)

Cellular processes of apoptosis

The apoptotic pathways undergo the activation of cysteine-dependent, aspartate specific proteases (caspases) that are endoproteases and are essential to the final execution of cell death. (Kluck et al., 1997). The mitochondrion plays an important role in the regulation of apoptosis. Cytochrome c is released that form an “apoptosome” with ATP, Apaf-1, and procaspase-9. Procaspase-9 converted into caspase-9 after the formation of apoptosome. This caspase-9 cleaves and activates procaspase-3 that results in apoptosis. This process is well regulated. (Adams & Cory, 1998; Antonsson et al., 1997).

Statins induced apoptosis

Apoptosis induced by Statins having an increased in proapoptotic protein expression for example Bim, Bax and decreased in anti-apoptotic protein expression for example Bcl-2. It has been shown that in many cell types e.g., skeletal muscle cells the reduction in isoprenoids lead towards the induction of apoptosis. (Amie & Kimberly, 2006). Isoprenoid depletion leads to the lack of geranylgeranylation or farnesylation of proteins that result in an increase in cytosolic calcium levels. Sacher et al. shows that increased calcium levels by the statins activate calpain and translocates Bax to the mitochondria that lead to the release of cytochrome c through the mitochondrial transition pore (MTP) results in activation of caspase-9 that in turn cleaves and activates caspase-3 and leads to the apoptosis. (Sacher et al., 2005)

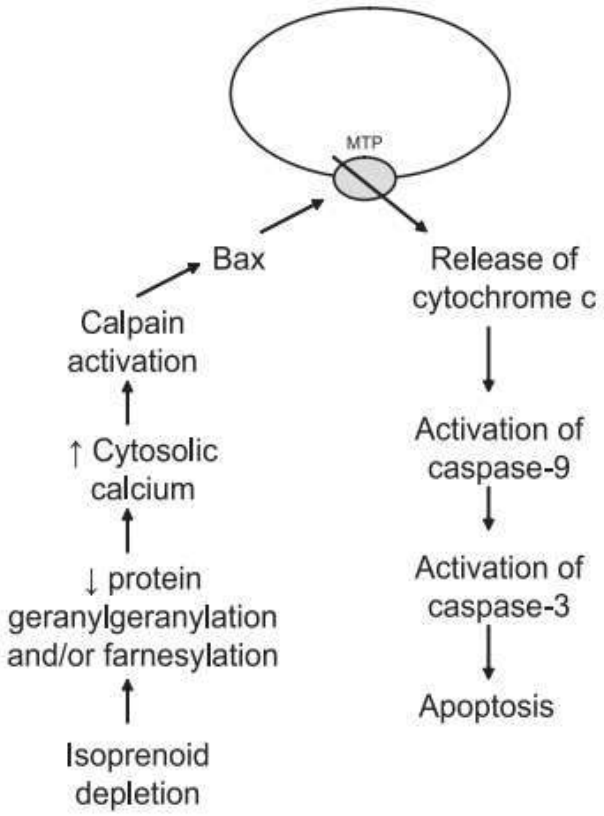

Fig.2. Hypothesized scheme of statin-induced apoptosis in skeletal muscle cells adapted from (Amie & Kimberly, 2006)

Lovastatin induces apoptosis in human glioblastoma cell lines and enhances Bim protein levels. (Agarwal et al., 1999) (Dimitroulakos et al., 2000). Cerivastatin activates caspase-3, caspase-8, and caspase-9 and induced apoptosis in human myeloma tumor cells. Similarly, lovastatin activates caspase-3 and induces apoptosis in prostatic epithelium and also activate caspase-7 that induces apoptosis in leukemia cells. (Cafforio et al., 2005). Statins induce apoptosis in a variety of cell types like smooth muscle cells and many types of cancer cells. Apoptosis induced in transformed cells slow or prevent the progression of cancer. (Amie & Kimberly, 2006).

Epidemiological studies

Statins have carcinogenic properties as shown by early studies in animal models. Lipid lowering drugs have created carcinogenic effects on rodent in new findings. All statins that are available in 1994, promote or initiate cancer in rodents at concentrations equivalent to those commonly prescribed in humans. (Newman & Hulley, 1996).

Particularly, we describe the clinical trials and observational studies that measured all cancer or site specific cancers of the breast, lung, colorectal, reproductive organs and prostate associated with statin use. A recent meta-analysis of 15 case-control studies, 10 cohort studies, and 17 RCTs found no evidence of differences in breast, lung, or prostate cancer risk by statin use. A protective effect was illustrated for liver cancer, stomach cancer, and lymphoma and an increased risk for both melanoma and non-melanoma skin cancers. The different properties of hydrophilic statins versus hydrophobic statins support opposing effects on cancer risk and may explain the increased risk of cancer found among pravastatin users in two of the large RCTs. (Kuoppala et al., 2008)

Statins and colorectal cancer

Two large observational studies presented that there is 35–43% reduction in colorectal cancer risk among statin users compared to non-users (Poynter et al., 2005, Farwell et al., 2008) and one meta-analyses of observational studies showed a modest reduction (14%) in colorectal cancer risk with statin use. (Browning & Martin, 2007)

It is concluded that there is a decreased risk of disease while treating it with long-term use of statins particularly when it is used in combination with non-steroidal anti-inflammatory drugs (NSAIDs). When we evaluate colon and rectum cancer separately, it is observed that similar 45% reduction in colon cancer risk and 62% even stronger reduction in rectum cancer risk with statin use compared to non-use. (Poynter et al., 2005). Coogan et al. evaluated in case control study that there is 30% reduction in rectum cancer risk but there is not any effect on colon cancer risk with statin use. (Coogan et al., 2007).

Different types of statins also determine the cancer risk. In studies pravastatin decrease 56% and simvastatin reduce 17–51% in colorectal cancer risk. (Poynter et al., 2005). Another study was conducted among diabetic patients in which statins reduce risk of colorectal carcinoma as compared to non-users and no association with non statin cholesterol lowering medications. (Hachem et al., 2009)

Statins and breast cancer

Two small case control studies and Six recently published large cohort studies suggested that there is no relation between statin use and incident breast cancer risk. (Boudreau et al., 2010). Cauley and colleagues reported that there is 72% reduced risk of breast cancer when hydrophobic statins are used. (Cauley et al., 2003). Setoguchi and colleagues observed and compared statins with another preventive drug for example glaucoma medications to achieve a reference group with similar characteristics as statin users. (Setoguchi et al., 2007). Setoguchi et al. observed that there is a protective effect of statins against breast cancer but it also contain certain limitations as relatively short statin exposure. In observational studies and RCTs, Bonovas and colleagues establish similar results in their meta analysis. Some other meta analysis studies site-specific cancers are evaluated. Three gives no association between breast cancer risk and statin use, (Baigent et al., 2005, Browning & Martin, 2007, Dale et al., 2006) and one an increased risk with pravastatin only. (Kuoppala et al., 2008)

Statins and lung cancer

Khurana et al. conducted a large case control study of a veteran population having 2000 lung cancer cases among statin users and found a 45% reduction in lung cancer risk among statin users when compared to non-users. (Khurana et al., 2007) When statin used for at least 6 months, it increased the relationship with a protective effect on lung cancer to 55%. Two cohort studies establish no relationship between risk of lung cancer and statin use. (Setoguchi et al., 2007, Friis et al., 2005).

A retrospective cohort study of another veteran population by Farwell and colleagues reported a 30% reduction in risk of lung cancer among statin users. There is reduction in incidence of lung cancer among statin users as compared to non users by a recently published study of statins and numerous site specific cancers. (Farwell et al., 2008)

Statins and prostate cancer

Large case-control study within 10 Veterans affairs Medical Centres (Singal et al., 2005) and a small clinic-based case-control study within Oregon Veterans Affairs (VA) Medical Centre (Shannon et al., 2005) give information about the reduced risk (54%–65%) of prostate cancer among statin users compared to non-users. With in health plan, large cohort study report a decreased risk of prostate cancer among long-term users of statins (28%) compared to non-users. There is strongest association among regular users of NSAIDs. (Flick et al.,2007). A different large cohort study taken variety of statin use but there is also no association was found between use of hydrophobic statins and prostate cancer risk.

There present an increase risk in one epidemiologic study but in some other observational studies the risk of prostate cancer and statin do not provide us the relationship between statin use and overall prostate cancer risk. On the other hand, statins provide association with a reduced risk in advanced and metastatic prostate cancer and aggressive disease. (Boudreau et al., 2010). After completion of the trial, the long-term follow-up, ten years of the West of Scotland Coronary Prevention Study newly describe an increased risk of prostate cancer among the pravastatin group compared with placebo but there is no association between statin use and overall prostate cancer risk (Ford et al., 2007).

Table.1. Statin therapy and the risk for cancer: summary of human clinical trials adapted from (Hindler et al., 2006)

Study	Statin	Cancer risk
Sacks et al.	Pravastatin	5.2% ↑ incidence of breast cancer
Coogan et al.	All statins	1.5-fold ↑ incidence of breast cancer; 1.2-fold ↑ incidence of prostate cancer
Shepherd et al.	Pravastatin	0.4% ↑ incidence of overall cancer
ALLHAT-LLT trial	Pravastatin	No higher cancer risk
LIPID trial	Pravastatin	No higher cancer risk
Pedersen et al.	Simvastatin	No higher cancer risk
Strandberg et al.	Simvastatin	No higher cancer risk
Heart Protection Study	Simvastatin	No higher cancer risk
AFCAPS/TexCAPS	Lovastatin	50% ↓ incidence of melanoma
Poynter et al.	All statins	47% ↓ incidence of colorectal cancer
Cauley et al.	All statins	72% ↓ incidence of breast cancer
Blais et al.	All statins	70% ↓ incidence of uterine cancer
Shannon et al.	All statins	56% ↓ incidence of prostate cancer

Abbreviations:

AFCAPS/TexCAPS... Air Force/Texas Coronary Atherosclerosis Prevention Study;

ALLHAT-LLT.....Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

LIPID.....Long-term Intervention with Pravastatin Ischemic Disease.

Statins and cancer prevention:

Prevention of cardiovascular disease by Randomized controlled trials showed that Statins have beneficial effects in preventing colorectal cancer and melanoma. This study leads to the effect of statins in cancer prevention. Targeted agents for cancer prevention includes to understand the angiogenesis and inflammation (the complex cellular effects), know about the molecular mechanisms of statins involve in geranylgeranylation of Rho proteins and HMG CoA-independent processes include lymphocyte-function-associated antigen 1. (Demierre et al., 2005). In mevalonate pathway, statins can also stop formation of isoprenoids. Farnesyl and geranyl geranyl groups attach to different proteins e.g., Ras/Rho superfamily. This attachments help to anchor to cell membranes and perform normal function. Statins inhibit hydrophobic modification of signalling proteins in turn effects on the growth in vitro. These in vitro effects may help in the prevention of human cancers.

The promising in vitro anticancer effects of statins have stimulated investigations into their possible application as a single anti-cancer agent in clinical practice. In cancer therapy, the first favorable effect of statins was described in 1996. The patient with anaplastic astrocytoma, induction of minor effect by lovastatin that positive results last for 8 months. (Thibault et al.,1996). The median survival rate was doubled in hepatocellular carcinoma patients by the use of pravastatin as compare with the control group. (Kawata et al., 2001).

For patients with non metastatic rectal cancer the useful effects were observed, the response is doubled in the statin group with that of the control group. (Katz et al., 2005). With advanced gastric cancer, there is no response induction in patients with lovastatins while stable disease is achieved by one patient for 16 weeks. (Kim et al., 2001). Similarly, with hepatocellular cancer, the overall survival rate of patients did not influenced by Pravastatin. Lovastatin did not improve the tumor response of patients with recurrent or metastatic squamous cell carcinoma of the head and neck. (Knox et al., 2005).

The chemotherapeutic agents such as doxorubicin, cisplatin and 5-fluorouracil (5-F U) have interaction with statins. e.g., pretreatment with lovastatin increased cisplatin and 5-FU– induced apoptosis in colon carcinoma cell lines. (Agarwal et al., 1999). Paclitaxel induced apoptosis is also increased by lovastatin in human leukemia cell lines. Lovastatin with other chemotherapeutics, improved antitumor activity of doxorubicin in colon carcinoma, murine melanoma, and lung carcinoma. (Feleszko et al., 2000; Iliskovic & Singal, 1997).

For advanced hepatocellular carcinoma, Pravastatin is used as an anticancer agent but it is not linked with better overall survival rate. In observational study, the patients of pediatric cancer were given the fluvastatin 8 mg/kg per day for 14 days every 4 weeks. It seems that 10 patients out of 12 died within 1–18 months because of their advanced disease stage and no significant changes were observed in laboratory assays during treatment. (Lopez-Aguilaret et al.,1999). There is no remarkable changes were observed when simvastatin treated 10 patients of chronic lymphocytic leukemia. The dose of simvastatin was 40 mg daily for 2 weeks. However, 40% of patients developed progressive disease during the subsequent year following statin withdrawal. (Hindler et al., 2006)

These results suggest that in vitro observed antitumor effects of statins cannot necessarily be extrapolated to clinical situations. It is important to note that the dose required for inhibition of cell proliferation that is in vitro were up to 100 times higher than the concentration used against hypercholesterolemia. Therefore, higher doses must be administered to achieve statin concentrations in the plasma comparable to those that demonstrated in vitro anticancer effects. Yet such high doses of statin were administered with no conclusive results in rare clinical studies: hepatocellular carcinoma patients did not effected by 40–80 mg/day of pravastatin and a response was not induced in patients with gastric tumors by 35 mg/kg/day of lovastatin. (Lersch et al., 2004)

In contrast, 2–45 mg/kg/day and 20–30 mg/kg/day of lovastatin had only remarkable effects on various cancers (Thibault et al., 1996) and brain tumors (Larner et al., 1998) respectively. Finally, the patients with hepatocellular carcinoma, 40 mg/day of pravastatin noticeably improved the survival of patients. The results of the above mentioned clinical studies recommends that statins seem unlikely to ever be regarded as antitumor agents given as a mono therapy for cancer treatment. (Osmak, 2012).

Combination of Statins with other drugs

The interactions between statins and anti-cancer drugs have very importance because it may particularly effect the cancer treatments. That's why the combination of statins and anticancer drugs is the main area of research that warrants future study. Statins combined with other lipid-lowering drugs and achieved target lipoprotein levels. Combination of niacin and low-dose simvastatin decrease low-density lipoprotein (LDL), and very low-density lipoprotein cholesterol (VLDL) and increase level of high density lipoprotein (HDL) cholesterol. There is 24%, 29%, 45%, and 31% reduction in total, LDL,

VLDL cholesterol and triglycerides respectively, while 31% increased in high-density lipoprotein cholesterol. (Stein et al., 1996). Statin with a bile acid binding resin is important in reducing LDL level, because there are different mechanisms for these drugs to stimulate LDL receptor and clearance of LDL. (Brown & Goldstein, 1986)

Triple therapy with niacin, resin and statin is used for satisfactory control of LDL level. Bile acid and Niacin sequestrants have significant effects on atherosclerotic lesions. In addition, the use of bile acid and niacin sequestrants results from small combination therapy trials and large immunotherapy trials. The combination of statins with niacin and bile acid sequestrants effects on atherosclerotic lesions and lipoproteins as well as depends on efficacy and safety. (Guyton, 2010) Results of statins with ezetimibe are uncertain. The ezetimibe effect on carotid atherosclerosis is unknown. Rather this, it can be used in combination to statin therapy as a secondary option for LDL-lowering. (Guyton, 2010). The use of statins or aspirin was associated with a lower incidence of adenomatous polyps. In vitro cell line studies suggest that statins and cyclooxygenase inhibitors have synergistic effects when used in combination. (Yang et al., 2010)

Discussion

Statins drug commonly used for the prevention of cardiovascular disease that result from hypercholesterolemia. Though, it is suggested by increasing evidence that independent of cholesterol reduction, it exert pleiotropic effects. Experimental evidences show that these pleiotropic effects of statin useful in various diseases e.g. cancer. Statins have anti-inflammatory, antiatherosclerotic, and antithrombotic properties. If data is obtained from both in vitro and in vivo studies, it is identified that statins also have antiproliferative, antiangiogenic, and anti-metastatic properties. By these properties of statins, it may thus represent a novel therapeutic approach for cancer prevention and treatment. (Hindler et al., 2006)

There is increasing evidence suggests that statins have a chemopreventive potential against cancer. In this study we observed that statins are the inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which is the rate-limiting enzyme in the mevalonate and cholesterol-synthesis pathway and thus inhibit cholesterol synthesis. The downstream products of this pathway also used in cell proliferation as they are needed in many cellular functions for the maintenance of protein synthesis, membrane integrity, protein signaling and progression of cell cycle. (Chan et al., 2003, Wong et al., 2002).

Further studies indicated that statins induce apoptosis (programmed cell death) and reduce cell invasiveness. This characteristic has been studied in cell lines derived from mammary carcinoma, lung, colorectal, pancreatic and prostate carcinoma. (Boudreau et al., 2010). When there is disruption in the processes in malignant cells, the gowth and metastatis of cancer is inhibited. Specially, tumor suppressor protein, p53 is common in cancer when p53 is mutated, upregulation of mevalonate pathway takes pace. (Petitjean et al., 2007) Therefore, statins reverts the malignancy phenotype of p53-mutated cancer cells by inhibition of this pathway. (Freed-Pastor et al., 2012). Statins reduces angiogenesis, reduction in the invasiveness of in situ cancers and lower production of matrix-metalloproteinase. It also associated to decrease the important cellular function in the progression of cell cycle in cancer cells with resulting antiproliferative effects and increased radiosensitization. (Chan et al., 2003; Gauthaman et al., 2009).

The prevention of human cancer by statins is remain controversial despite many non-randomized clinical trials and observational studies. A large number of trials demonstrate cancer as a secondary endpoint that limit the estimation of statins in the prevention of cancer. For this purpose randomized trials are now in progress that should help in the evaluation of true effects of statins in cancer risk. (Osmak, 2012).

The role of statins in cancer patients including the tumor types most susceptible to statin therapy have yet to be determined. Current clinical and preclinical data demonstrated that brain cancer, leukemia (Koyuturk et al., 2004) hepatocellular cancer

melanoma, (Shellman et al., 2005) and squamous cell cancer of the head and neck are potentially treated by statins. Now it is unknown that which statins are most effective for cancer prevention and treatment. Both lipophilic (e.g., simvastatin and atorvastatin) and hydrophilic (e.g., pravastatin and rusovastatin) statins exhibit antitumor effects. Of these, the less valuable intracellular agents are thought to be the hydrophilic statins. However, hydrophilic statins are linked with lower risks for hepatocellular and colorectal cancer. (Hindler et al., 2006)

Preclinical and clinical data suggest that statins alone are not effective anticancer agents but when they combined with other cytotoxic agents, it may enhance chemo therapeutic effects. Furthermore, many side effects occure in patients with cancer by statins as they often receive concomitant medications, such as erythromycin and cyclosporine, that through the hepatic cytochrome P-450 system, interfere with statin metabolism. (Asberg, 2003)

Case-control studies even found minor decreases in breast cancer risk in postmenopausal women and a 20% relative risk reduction for various cancers in a mixed population. The use of statins for 05 years was associated with a 47% relative risk reduction for colorectal cancer in a population from northern Israel. Taken together, the epidemiological data in the absence of prospective endpoint studies suggest that statin use is safe or may even have a protective effect on cancer incidence.

Conclusion

The overall evidence provides a protective role of statin intake in certain types of cancer. Cancer, one of the leading cause of death can be delayed, suppressed or reversed by statins. For potential clinical trials, the protocols must be standardized with regard to the type of statin, dose, administration regimen, and duration of follow up. However, every time this treatment is not beneficial for all cancer types. Recent studies show that the administration of statins together with chemotherapeutics could be a new and improved strategy for the treatment of certain types of cancer. (Osmak, 2012). In conclusion, statins may be beneficial for the prevention and treatment of cancer.

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