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Review Article

Evaluation of toxic effects of statins and their possible role in treatment of cancer

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ABSTRACT

Hydroxymethyl glutaryl CoA (HMG-CoA) reductase inhibitors (statins) are drugs that show hypolipidemic effect via inhibition of hydroxymethyl glutaryl CoA reductase (HMG CoA R), a rate-limiting step in the synthesis of cholesterol. The effects of statins, independent of lipid-lowering ones , are termed pleiotropic effects and these have gained importance in recent years. Potential anticancer effect, one of the pleotropic effects of statins, is remarkable. In this review we aim to summarize the possible use of statins in the treatment of cancer. Pleiotropic effects include antioxidant and antiinflammatory activities due to inhibition of new vessel formation in cancer cells, reduction of resistance to chemotherapeutic agents and inhibition of the production of reactive oxygen species (ROS) with the induction of apoptosis. The potential anticancer activity of statins against different tumor models is emphasized *in vitro* and *in vivo* conditions. For this reason, current efforts are directed to providing therapeutic benefits from statins in the treatment of cancer. This study shows that statins can be effective in preclinical models in advanced or recurrent metastatic diseases when administered alone or in combination with molecularly targeted agents. Future studies may shed further light on this topic.

Keywords: Cancer, statin, toxicity

INTRODUCTION

Statins are the first choice of drugs in the treatment of cardiovascular diseases and have been used in clinical practice for a long time (Bedi, Dhawan, Sharma, & Kumar, 2016; Sodero & Barrantes, 2020). Statins have been prescribed effectively and extensively for the therapy of hypercholesterolemia. Examples of the effects of statins are atheroma plaque stabilization, improvement in endothelial dysfunction, decrease in platelet aggregation and anti-inflammatory effects regardless of their antilipidemic effects. Statins are therefore used for primary and secondary prevention of cardiovascular diseases (Sabuncu et al., 2016). Several statins have more recently begun to be used, including atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin (Shuhaili, Samsudin, Stanslas, Hasan, & Thambiah, 2017). As with many drugs, statins have side effects. The most important of these appear to be the variability of liver enzymes and muscle-related complaints which may occur from myalgia to severe fatal rhabdomyolysis. When these side effects are investigated, the underlying molecular mechanism which is seen is that of mitochondrial damage due to the depletion of ubiquinone. Although genetic factors play a part in the development of side effects of these well-tolerated drugs, they are largely dose-dependent. Therefore, clinicians need to be more careful in this regard (Margaritis, Channon, & Antoniades, 2014; Shuhaili et al., 2017). Statins are drugs that show hypolipidemic effects by inhibition of the hydroxymethyl glutaryl CoA reductase (HMG CoA R) enzyme, which is the rate-limiting step in mevalonate pathway (Crescencio et al., 2009; Margaritis et al., 2014). The mevalonate pathway is closely related to the formation and pro-

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gression of cancer, as it is responsible for cholesterol synthesis and protein prenylation (Gruenbacher & Thurnher, 2015). The end products of this pathway, such as cholesterol, dolichol, and ubiquinone, are vital. Also, cell functions are significantly affected by inhibition of mevalonate synthesis (Osmak, 2012). Statins inhibit the mevalonate synthesis step which is shown in (Figure 1) (Osmak, 2012; Margaritis et al., 2014). The end products of this pathway cannot be formed, thereby stopping the production of sterols, which are essential cholesterol for membrane integrity, as well as blocking isoprenylation of basic oncoproteins regulating proliferation, migration, invasion, cell cycle, cell proliferation and cell fate (Osmak, 2012; Pisanti, Ciaglia, & D'Alessandro, 2014).

In this way, statins have become a promising drug group in cancer treatment since they reduce both cholesterol and isoprenoid levels in the blood. Numerous data have shown that the probable anticancer mechanisms of statins depend on many factors. The toxicity of statins is thought to be due to cell cycle arrest, inhibition of cell proliferation/angiogenesis and metastasis, promotion of apoptosis, or changes in molecular pathways. These changes may vary depending on the kind of cancer cell, the duration that these cells are exposed, and the type and dose of statin used (Gauthaman, Fong, & Bongso, 2009; Matusewicz, Meissner, Toporkiewicz, & Sikorski, 2015). Although significant anticancer effects have been observed in all statins, the available data propose that there are some differences in the antitumor effects of each statin derivative. Besides, statins have shown differences in pharmacokinetics, potency, and therapeutic efficacy.

Physical & chemical properties and toxicokinetics

Aspects that increase statin concentrations (e.g drug-drug interactions) may raise the risk of adverse effects. These interactions rely on the pharmacokinetic properties of statins: simvastatin, lovastatin, and atorvastatin are metabolized via cytochrome P450 (CYP) 3A, but others are metabolized independently of this pathway (Ho & Walker, 2012). Statins are excreted in feces, urine, bile or through renal clearances in the form of metabolites or unchanged (Çetin & Özgüneş, 2017). From a pharmacological perspective, statins are hypolipidemic drugs with inhibition of hydroxymethyl glutaryl CoA reductase (HMG CoA R), a rate-limiting step in cholesterol synthesis (Stancu & Sima, 2001).

These drugs are divided into two classes: hydrophilic and lipophilic. The lipophilicity of statins enables them to access different tissues. More lipophilic statins get higher levels of exposure in non-hepatic tissues, whereas hydrophilic statins are more hepatoselective. Thus, different effects of statins in hepatic and nonhepatic tissues can be predicted (Kato et al., 2010).

The pharmacokinetics of statins alter depending on their hydrophilic or lipophilic properties and appropriate membrane carriers. Hydrophilic statins have been shown to initially accumulate in the liver where they are taken up by the organic anion-bearing polypeptide OATP1B1, which is one of the membrane carriers. OATP1B1 is also the most important carrier of lipophilic character pitavastatin uptake. Hydrophilic pravastatin and rosuvastatin undergo little metabolism through cytochromes and are commonly excreted unchanged (Matusewicz et al., 2015). The pharmacologic properties of statins are shown below in (Table 1) (Wong, Dimitroulakos, & Minden, 2002).

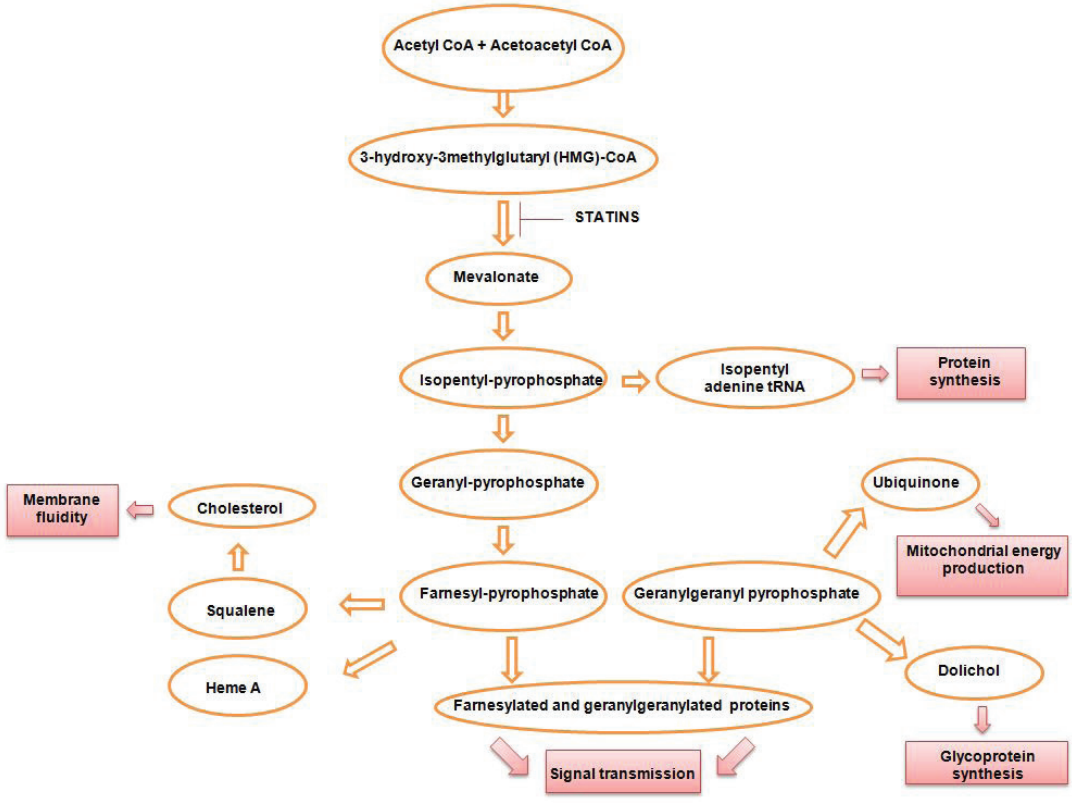

Figure 1. Statins inhibit the mevalonate synthesis step.

Table 1. Pharmacologic properties of statins.

Statins	Features				
	Lipophilicity	Structure	Source	Metabolism via cytochrome system	Daily Dose for Cholesterol Treatment (mg/day)
Lovastatin	+	Lactone	Fungal	CYP3A4	20-80
Simvastatin	+	Lactone	Fungal	CYP3A4	10-80
Pravastatin	-	Acid	Fungal	Minimum	10-40
Fluvastatin	+	Acid	Synthetic	CYP2C9, CYP2D6	20-80
Atorvastatin	+	Acid	Synthetic	CYP3A4	10-80
Rosuvastatin	-	Acid	Synthetic	CYP2C9, CYP2C19	5-80
Pitavastatin	+	Acid	Synthetic	CYP2C9, CYP2C18	4

It is known that there is no significant difference between the activities of fungal or synthetic statins. It should also be noted that lipophilic statins are substantially more effective than hydrophilic ones (Matusewicz et al., 2015).

Effects on cell cycle

Cell homeostasis depends on the balance between cell proliferation and death. (Vermeulen, Berneman, & Van Bockstaele, 2003). The complex process involving cell growth and proliferation, organism development, DNA damage and repair, tissue hyperplasia in response to damage, and diseases is called cell cycle. It is also defined as the interval between two successive mitotic divisions to reveal two cells. (Schafer, 1998; Vermeulen, Van Bockstaele, Berneman, 2003). The cell cycle is conventionally divided into two stages; interphase and mitosis. Interphase includes G0, G1, Synthesis phase (S) and G2 phases. (Gap=G) (Vermeulen, Berneman, & Van Bockstaele, 2003; Foster, 2008). The G1 phase is the stage in which preparations are made for the division of the cell by metabolic changes. At this stage growth in size of the cell occurs. DNA synthesis occurs in the S phase, and in the G2 phase, it is the period when rapid cell growth occurs and becomes ready for mitosis. Mitosis and cytokinesis occur in the mitotic (M) phase. This cycle is provided by critical checkpoints such as the G-S, G-M and the metaphase anaphase checkpoints. The cell cycle progression is regulated by several families of proteins known as cyclins (Fan, Sanyal, & Bruzzone, 2018). *In vitro* studies have shown that statins arrest cells by affecting these proteins that regulate the cell cycle. (Matusewicz et al., 2015). Cell cycle arrest is caused in G1/S and G2/M by the effect of statins on the expression of these proteins (Ahmadi et al., 2020).

There are numerous studies about this subject on the statin family. One such study evaluated the potential anticancer effect of fluvastatin in three hepatocellular cancer cell lines. (Zhang, Wu, Zhou, Xie, & Zheng, 2010). Fluvastatin was observed to induce apoptosis in a dose-dependent manner and to inhibit cell proliferation by stopping the cell cycle in the G2/M phase. As a result of the study, it was shown that fluvastatin significantly reduced the invasion potency of these cells. In another study on fluvastatin, cell cycle progression in the cervical cancer cell line was performed by flow cytometry (Campos-Lara & Mendoza-Espinoza, 2011). A moderate G1 phase arrest was observed with 48 hours of exposure to these cells with a significant decrease in the S phase percentage compared to the control. Furthermore, a significant increase in the percentage of apoptotic cells was observed. In another study on cell cycle analysis of embryonal carcinoma, ovarian cancer and colorectal cancer cells which had been exposed to simvastatin, lovastatin or mevastatin for 48 hours showed a decrease in the number of cells, such as the decrease in S phase compared to control groups (Gauthaman, Richards, Wong, & Bongso, 2007). The presence of small peaks in the sub G1 phase indicating apoptosis was significant in these three cell lines exposed with simvastatin and lovastatin. In another study, researchers emphasized that the antiproliferative effect caused by statins may be related to the increase in the percentage of cells in the G1 and G2/M phases in the cell cycle (Sánchez et al., 2008). Fluvastatin, simvastatin, and atorvastatin inhibited breast cancer cell proliferation. It has been reported that antiproliferation is related to a decrease in DNA synthesis and a cell cycle arrest in the G1 and G2/M phases, and that fluvastatin leads to a decrease in mitochondrial membrane potential. Another test was conducted to discover whether pitavastatin has an anticancer effect on the glioblastoma cell line (Jiang et al., 2014). The effects of statins on cell cycle in tumor cells were analyzed and shown to inhibit G1 / S growth in glioblastoma and breast cancer cell lines. Pitavastatin was shown to trigger the cell cycle 12 hours after treatment, and tumor cells in the S phase were significantly reduced, while the cell population in the G0 / G1 phase increased. It was also reported in this study that a high dose of pitavastatin was not able to inhibit tumor growth significantly in the glioblastoma cell line when oral gavage was administered to mice. As shown in the said study, it is important to optimize the dosage and modification of the formulation in the use of statins for anticancer therapy.

Anticancer effect

Cancer is a disease caused by uncontrolled division and proliferation of cells under the influence of genetic and environmental conditions. There are more than 100 types of known cancer. Cancer is a personal dependent disease, although standard approaches have been developed for certain types of cancer. Today, in addition to existing treatments, new meth-

ods continue to be developed with the advance of technology (Baykara, 2016). Statins are well tolerated despite their side effects. With the support of epidemiological studies and clinical data in the last 20 years, it has been emphasized that statins may play an important role in the prevention and treatment of cancer. The anticancer effect that statins can produce has not yet been fully understood. The possible anticancer effect of statins depends largely on the type of tumor and type of statin (De Wolf, De Wolf & Richardson, 2018). Studies evaluating the cytotoxic effects of many drugs in the statin family in the liver, skin, colon, pancreas and ovarian cancer cells are included in the literature, and in these studies it was found that the combination of statins with chemotherapeutic drugs in multiple drug resistance tumor cells was effective in overcoming drug resistance (You et al., 2016; Villarino et al., 2017; Yasui et al., 2007; Zhang, Zheng, Yang, Yang, & Yuan, 2017; De Wolf et al., 2018). The use of statins as anticancer drugs or as adjuvant combined with conventional chemotherapeutic drugs has been proven (Pisanti et al., 2014). Some studies have shown that coadministration of statins and antineoplastics causes synergistic sytotoxicity (De Wolf, et al., 2018; Al-Qatati, & Aliwaini, 2017). A group of scientists demonstrated that when fluvastatin, a lipophilic statin, and cisplatin were administered together synergistic cytotoxicity occured. Combined treatment of fluvastatin and cisplatin compared to a drug administration alone led to significantly more inhibition of cell proliferation (Taylor-Harding, Orsulic, Karlan, & Li, 2010).

It seems to be useful to understand the link between statins and the inhibition of cell proliferation to suggest new approaches in cancer treatment. The data obtained in the light of the studies supported the finding that high concentration and accumulation of statins in plasma and tumors will provide significant benefit to their anticancer effect (Jiang et al., 2014). Data are demonstrating that statins arrest the cell cycle in healthy cells and cancer cells at certain stages and stimulate cell death. Cell death is closely related to oxidative stress and the formation of reactive oxygen species (ROS) because these formations seriously damage vital macromolecules such as lipids, proteins, and nucleic acids. It is known that the resulting ROS and oxidative stress can damage cellular DNA, oxidize specified macromolecules, and inactivate certain enzymes and their cofactors. Oxidation leads to loss of biological properties and ultimately cell death (Sánchez et al., 2008; Tong, Chuang, Wu, & Zuo, 2015). It has been stated that statins can also contribute to cell damage by causing increased ROS production within the cell. It is considered that statins cause mitochondrial dysfunction and this results in an increase in ROS production (Li, et al., 2019).

In a study investigating the effects of statins on human breast adenocarcinoma cell line (MCF-7), cell death, production of ROS and mitochondrial membrane potential were observed. Statins have been shown to provoke both apoptosis and necrotic cell death. To determine whether statin-induced cell death is based on oxidative stress, researchers studied breast cancer cells with statins and N-acetyl cysteine, a potent antioxidant. At the end of the said study, N-acetyl cysteine was shown to stop statin-induced cell death. Researchers also noted that cell death caused by statins in MCF-7 cells was due to oxidative stress. It was emphasized that the administration of statins alone or in combination with antineoplastic agents such as doxorubicin or cisplatin may be an effective alternative in the therapy of breast cancer (Sánchez et al., 2008). There are currently more than 30 ongoing clinical trials, but there is insufficient information on the use of statins in cancer treatment (Gu, Saha, Thomas, & Kaur, 2019). Most clinical studies on statins have shown that no significant results have been achieved for the treatment of many types of cancer. Although statins with antiproliferative effects have been made with interest in *in vitro* and *in vivo* studies on breast cancer, one study reported that statins did not yield the expected results and these results were not clear (May & Glode, 2016).

Another essential mechanism that causes cell death is thought to occur through the mevalonate pathway. In this way, statins inhibit cholesterol synthesis and many molecules, for example, coenzyme Q10 (CoQ10). CoQ10 is one of the electron transport chain components known as ubiquinones. CoQ10 plays a role in the production of adenosine triphosphate (ATP) energy. Therefore, the decrease in the concentration of CoQ10 is an important issue observed especially in the regulation of mitochondrial dysfunction. Studies have shown that statins may lead to a reduction in ATP production due to the effect on CoQ10, and this effect can cause cytotoxicity (Berber, Celik, & Aksoy, 2014).

In a study of colon cancer stem cells and *in vivo* mouse tumor xenografts, a group of researchers concluded that pitavastatin inhibits these stem cells and induces cell apoptosis. In that study, it was determined that pitavastatin inhibits the growth of mouse tumor xenografts and pitavastatin has a potential role in inhibiting the proliferation of stem cells in colon carcinoma (Zhang et al., 2017).

In another study suggesting that statins have a positive effect on liver cancer, a group of scientists reported that statin use causes a 40% reduction in liver cancer risk, regardless of their exposure time, according to a meta-analysis. It was also reported that this use was inversely proportional to the risk of liver cancer (Pradelli et al., 2013). In another study, the effect of fluvastatin in the statin family on pediatric tumor treatment was explored. The patients who were due to undergo metronomic chemotherapy with thalidomide were treated with fluvastatin, carboplatin and vincristine. In that study, it was observed that the survival of pediatric patients was significantly increased in the treatment with fluvastatin and thalidomide-related carboplatin, and vincristine. It was emphasized that there was a significant decrease in tumor volume in patients with increased quality of life (López-Aguilar et al., 2008).

Numerous human clinical trials have demonstrated the anticancer effects of statins. The overall evaluation of these studies showed that the combination of statins with other agents yielded more promising results than the trials performed alone. It is clear that further studies are needed to investigate and confirm potential synergies in these combined therapies (Chae et al., 2015).

Antioxidant / oxidant effect

It is known that statins used for hypolipidemic purposes are also used in the antioxidant aspect of cardiovascular diseases by reducing oxidative stress. Many studies conducted with *in vitro* and *in vivo* models support the use of statins as protective agents in cardiac disorders by reducing ROS production. However, the effect of statins on oxidative stress varies in different tissues and organs (Liu et al., 2019). Oxidative stress is increasingly recognized as a significant cause of cancer (Schupp, Schmid, Heidland, & Stopper, 2008). In many studies, one of the mechanisms underlying statin-induced toxicity is thought to be due to oxidative stress. Lack of antioxidant defense or the overproduction of free radicals is known to cause oxidative stress (Liu et al., 2019). One of the studies that analyzed the relationship between statins and oxidative stress, showed that statins increased ROS production in freshly isolated rat hepatocytes. In the said study, researchers investigated the effect of three different statins on the cell using different concentrations. They reported an increase in lipid peroxidation in addition to ROS formation after statin administration. They observed that there was also an increase in cellular mitochondrial membrane potential. Additionally, it was shown that L-carnitine administration could be evaluated as a preventive agent by causing a decrease in these statin-induced toxicity markers (Abdoli, Azarmi, & Eghbal, 2015). Similar studies have been recorded in *in vitro* studies confirming that increased oxidative stress is caused by statins as observed in this study. A group of researchers set out to clarify the role of oxidative stress in simvastatin cytotoxicity in murine colon carcinoma and melanoma cells and they demonstrated that simvastatin induced cell death by increasing intracellular oxidative damage and promoting apoptosis (Qi et al., 2010).

Genotoxic effect

One of the most important targets of oxidative attacks is known to be DNA. It is known that if repair mechanisms cannot eliminate oxidative DNA damage, sequencing may occur in cells, including age-related functions and subsequent development of malignancy. Therefore, the effects of statins on DNA are important (Schupp et al., 2008). There are several studies about the genotoxic/antigenotoxic effects of statins. Potential genotoxic effects of statins were evaluated in *in vivo* and *in vitro* mutagenicity experiments. As an example of these studies a group of researchers observed the genotoxic potential of lovastatin examined by comet assay and repaired DNA fractures caused by doxorubicin (Damrot et al., 2006). In this study, they showed that the resistance to topoisomerase II inhibitors causes a reduction in DNA damage with lovastatin. This could be clinically useful to relieve the side effects of anticancer drugs. The possible genotoxic effect of atorvastatin, a lipophilic statin such as lovastatin on human lymphocytes was investigated by comet, chromosome aberration, and sister chromatite exchange assays (Gajski & Garaj-Vrhovac, 2007). According to the results, it was noted that human lymphocytes exposed to atorvastatin showed more genotoxic damage compared to the control for all three methods used, and statistically significant results were obtained. In the comet assay, DNA damage in human lymphocytes exposed to atorvastatin was shown to be higher than in the control cells at 24, 48 and 72 hours of exposure time for tail length, whereas the damage at 72 hours exposure time was higher for the tail moment compared to the control cells. Another group investigated the possible genotoxic effects of atorvastatin in human lymphocytes in *in vitro* conditions at 6, 24 and 48 hours exposure times (Gajski, Garaj-Vrhovac & Oreščanin, 2008). In the study, it was determined that the DNA damage caused by atorvastatin is due to oxidative stress measured by formamidopyrimidine DNA glycosylase (fpg)-modified comet assay. In addition, the researchers observed basal DNA damage in the results of the standard comet assay. Due to this determination, they emphasized that the genotoxic effect was not only due to oxidative stress, but also to other mechanisms of genotoxicity which may be involved. In another study on human lymphocytes, the genotoxic potential of rosuvastatin was evaluated by the micronucleus test, chromosome aberration, and comet assay (Gajski et al., 2008). The frequency of chromosomal aberration was shown to increase at 24 and 48 hours of exposure time and showed a significant increase in stimulation of micronucleus formation compared to the negative control. In the comet assay, tail length, tail moment and tail intensity were evaluated, and it was reported that the tail intensity increased significantly at all concentrations except one (0.0625 µg/mL). The researchers showed that rosuvastatin has cytotoxic and genotoxic potential in human lymphocyte cells. It was also recommended that patients treated with this drug should be monitored.

CONCLUSION

Some studies highlight the anticancer aspect of statins in various cancer types. According to the above studies statins have been suggested as a genotoxic agent by using standard and fpg-modified alkaline comet assay, micronucleus test, chromosome aberration, and sister chromatite exchange assays. The difference between comet parameters in the presence and absence of the fpg enzyme suggested that the DNA damage caused by statins is mediated by oxidative stress. It was emphasized that detailed studies should be carried out in mammalian systems.

The results from the studies emphasize that statins can be used alone, and there are also possible combination therapies with standard chemotherapeutics. Accordingly, in order to get benefit from cancer treatment from statins, the type of statin, dose, duration of exposure, and the type of cancer to be treated are very important. Further studies to clarify the status of statins in cancer treatment are crucial.

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