Statins in Research Studies: Selection of Statin, Concentrations, Animal Model, and Cell Line

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Abstract: Statins are prescribed for treating hypercholesterolemia. In addition to their cholesterol-lowering effects statins produce a wide variety of effects known as the pleiotropic effects across various cells including cancerous and non-cancerous cells. These effects have been extensively studied in different animal models, particularly rodents (rats and mice) and rabbits.

The diverse effects of statins have aroused considerable controversy. Many of these discrepancies stem from the research study design, such as the type of statins, their concentrations/doses, and animal models or cell lines in use. Notably, different concentrations of statin have been shown to yield paradoxical outcomes. For instance, at higher concentrations, statins provoke apoptosis and senescence in endothelial cells, whereas lower concentrations protect these cells from apoptosis and senescence.

These adverse findings may arise from the differences in the pharmaceutical properties of statins, the applied concentrations/doses, the type of animal models, or the specific cell lines used in research studies. Therefore, it is crucial to exactly consider these variables in the statins' studies. In this article, we aim to provide an overview of the criteria for selecting appropriate statins, proper concentrations/doses, and the type of animal models or cell types to achieve the most accurate results in the statins' studies.

Keywords: Animal model, research design, pleiotropic effects, statins

1. INTRODUCTION

Statins are the main prescribed medications for controlling hypercholesterolemia. Based on their polarity, statins are classified into two groups: lipophilic statins and hydrophilic statins. Lipophilic statins (atorvastatin, lovastatin, simvastatin, pitavastatin, and fluvastatin) readily cross cell membranes. In contrast, hydrophilic statins (pravastatin and rosuvastatin) rely on carrier proteins to pass through the cell membrane. Hydrophilic statins are mostly taken up by hepatocytes via human organic-anion-transporting polypeptides (OATPs) and they have limited access to the extrahepatic tissues [1-8]. Due to their insignificant accessibility to the extrahepatic tissues, hydrophilic statins cause less adverse effects on the skeletal muscles, while lipophilic statins lead to more severe side effects [9-14].

Simvastatin and lovastatin are prescribed as prodrugs in their lactone forms that are activated to their respective active acid metabolites, simvastatin hydroxy acid, and lovastatin beta hydroxy acid in the liver [15-17]. As a result, the bioavailability of these statins does not merely depend on their lipophilicity, their activation in the liver affects their systemic bioavailability and their actual bioavailability is lower than the expected amount [18, 19]. Once metabolically activated, lovastatin and simvastatin become more hydrophilic reducing their bioavailability in the extrahepatic tissues. Germershausen *et al*. reported that pravastatin concentrations in peripheral tissues were 3-6 times higher than lovastatin's and simvastatin's concentrations. Furthermore, the concentrations of lovastatin and simvastatin in the liver were approximately twice those of pravastatin [20]. These observations indicate that these lipophilic prodrugs exhibit more selectivity for the liver compared to hydrophilic pravastatin. Table **1** shows physicochemical properties of statins.

2. SELECTION OF THE PROPER STATIN TO INDUCE SPECIFIC EFFECTS

Statins provoke a wide range of effects including 1) direct inhibition of cholesterol biosynthesis, 2) direct inhibition of the cholesterol biogenesis pathway

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Table 1: Physicochemical Properties of the Most Applicable Statins

Drug	Solubility	Bioavailability%	Prodrug	T1/2 (h)	Transporter	References
Atorvastatin	lipophilic	12	no	14	OATP1B1	[20-25]
Rosuvastatin	hydrophilic	20	no	19	OATP1B1	[17, 26-28]
Pitavastatin	lipophilic	60	no	12	OATP1B1	[29-32]
Simvastatin	lipophilic	5%	yes	5	OATP1B1	[33-36]
Fluvastatin	lipophilic	<5	no	0.5-2.6	OATP1B1	[37-40]
Pravastatin	hydrophilic	18	no	1-2	OATP1B1	[17, 41-44]
Lovastatin	lipophilic	5	yes	1-1.7	OATP1B1	[17, 45]

mediators including isoprenoids and coenzyme Q [46], and 3) indirect stimulation of cholesterol synthesis and its intermediates in the extrahepatic tissues. The recent effect occurs exclusively when hydrophilic statins are used [9, 14, 16]. The direct inhibition of cholesterol and its metabolites occurs when statins such as lipophilic statins readily diffuse into the cells. Conversely, for induction of the indirect effects of statins on the extrahepatic tissues, hydrophilic statins are the appropriate alternative, since they are exclusively taken up by liver cells, the main site of cholesterol production in the body. The inhibition of cholesterol biosynthesis in the liver decreases the whole-body cholesterol levels, removing the negative autoinhibitory effect of cholesterol on its own biogenesis [47, 49, 50]. Therefore, hydrophilic statins may exert paradoxical effects in the extrahepatic tissues compared to lipophilic statins.

There are several studies indicating statins cause contradictory effects in different cells. Most of these studies showed that statins stimulate apoptotic effects in cancer cells while some others revealed statins do not produce such effects (see Table **2**). Lipophilic statins by direct inhibition of the cholesterol biogenesis, reduce isoprenoids which are crucial for cell signaling and cell survival. Lipophilic statins by lowering isoprenoids block several signaling cascades and consequently initiate the apoptosis process and cell senescence. However hydrophilic statins through indirect activation of the cholesterol biogenesis pathway may lead to anti-apoptotic effects [48-50]

In cell lines, the transport of hydrophilic statins into the cells are facilitated by OATP1B1 which is exclusively expressed in hepatocytes. Hence, for hepatocyte cell lines both hydrophilic and lipophilic statins can be used. Nonetheless, for other cell types, given the inability of hydrophilic statins to enter the cells, lipophilic statins are the most appropriate choice (see Figure **1**).

3. ANIMAL MODELS IN STATINS RESEARCH

A pile of studies of statins have been conducted in various animal models of different species including rabbits, mice, rats, hamsters, pigs, guinea pigs, and primates [51]. Exploring keywords of “statin” with different animal species on scholarly platforms like “Google Scholar” and “PubMed” shows among the animal models mice, rats, and rabbits are the most used species in statins studies.

Statins have been shown to reduce cholesterol levels more in rabbits compared to other animal models. Rabbits are a popular choice in cholesterol research due to their metabolic similarity to humans. Rabbits and humans primarily synthesize cholesterol endogenously in the liver. In contrast, most of the cholesterol in rodents comes from their diet [52].

The higher activity of cholesteryl ester transfer protein (CETP) in rabbits makes them more vulnerable to atherosclerosis. High levels of CETP lead to increased production of LDL cholesterol (LDL-C), thereby increasing the risk of dyslipidemia and atherosclerosis in these animal models. In contrast, rodents do not express CETP, resulting in lower LDL-C levels and the lower risk of atherosclerosis. Therefore, these rodent models are not suitable for atherosclerosis research [53, 54].

There is evidence supporting the use of rabbits rather than rodents in statin research. In the 1970s, Akira Endo discovered that either movastatin or compectin did not have the cholesterol lowering effect in rats. However, they showed a significant decrease in cholesterol level in rabbits [55]. Subsequent research demonstrated the cholesterol-lowering effect of various

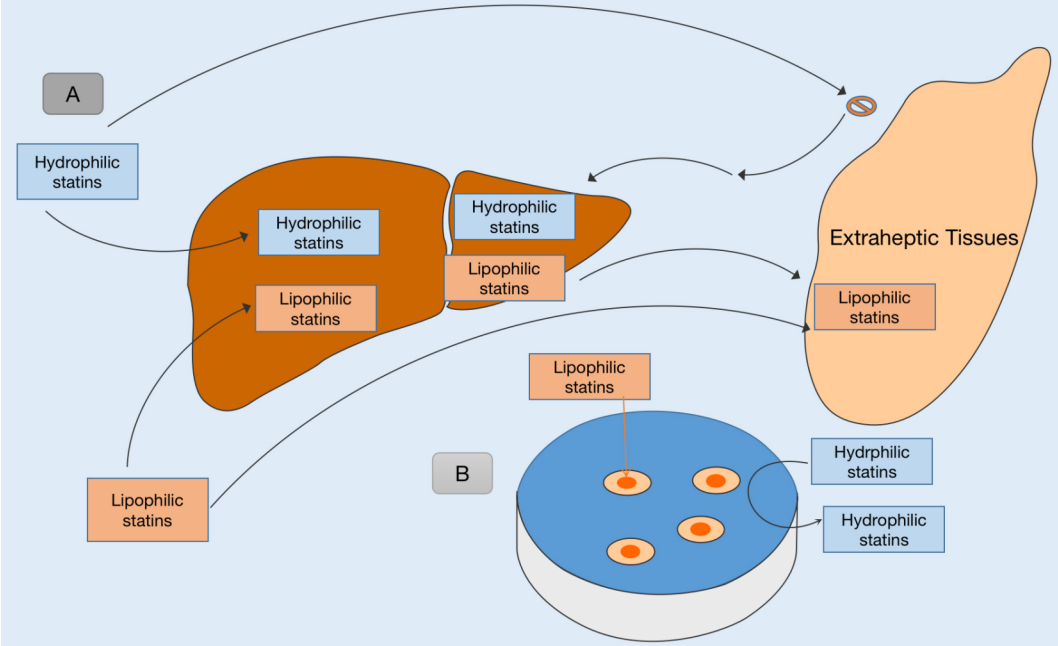

Figure 1: Bioavailability of statins in the hepatic and peripheral tissues and cells. **A**). In the liver, both hydrophilic and lipophilic statins can readily enter the cells and inhibit cholesterol biosynthesis. Lipophilic statins also diffuse into the extrahepatic tissues and inhibit cholesterol and intermediates of this pathway such as isoprenoids in these tissues. However, hydrophilic statins cannot access the extrahepatic tissues. Instead, they inhibit cholesterol production in the liver, which synthesizes approximately 70% of the body's cholesterol, and thus indirectly reduces cholesterol in the extrahepatic tissues. The concurrent absence of hydrophilic statins and the low levels of cholesterol in the extrahepatic tissues removes the inhibitory feedback of cholesterol on itself biogenesis leading to the activation of the cholesterol synthesis pathway.

B) In the context of cell culture studies, if non-hepatocyte cells are used, lipophilic statins are the preferred drugs to be used. Hydrophilic statins cannot enter the non-hepatocyte cells because these cells do not express the transporters for the statin uptake.

statins, including lovastatin, simvastatin, fluvastatin, cerivastatin, pitavastatin, and atorvastatin, as well as compectin and pravastatin, in the WHHL rabbit family. Furthermore, pravastatin has been shown to increase LDL receptor activity in WHHL rabbits (homozygotes) up to 11.2-fold. The results with the similar efficacy were shown for fluvastatin [56]. In addition to their lipid-lowering activity, statins dose-dependently induce cell death (apoptosis) and proliferation in SMC derived from rabbit arteries [57].

Rodent models have gained considerable popularity in statin research due to their cost-effective maintenance, simple maintenance, and ability to manipulate and control transgenic strains [52]; however, it is important to note that a drawback of using rodent models is their lack of the CETP enzyme and their phylogenetically different cholesterol metabolism compared to humans [58, 59]. More importantly, some studies even showed that statins (lovastatin, atorvastatin, and rosuvastatin) stimulate cholesterol biogenesis in mice; a strong induction was observed in the liver, whereas only a modest increase was shown in the proximal, middle, and distal parts of the small intestine [60].

4. INDUCTION OF THE PLEIOTROPIC EFFECTS OF STATINS (ANGIOGENESIS AND APOPTOSIS)

In different studies, statins have shown different and sometimes contradictory effects on angiogenesis and apoptosis. Addressing these inconsistencies is critical to optimizing outcomes in statin research. Angiogenesis is the process initiated by pre-existing blood vessels to sprout new capillaries. This process includes several steps including proliferation, migration and differentiation of endothelial cells, continuous remodeling of extracellular matrix and functional maturation of newly formed vessels [61].

In research studies, statins are often prescribed at much higher doses or concentrations, even more than 1000 times higher than those used in clinical settings. The pleiotropic effects of statins are usually observed at concentrations between 1 and 50 μM. However, at therapeutic doses for human, the average concentration of statins in the bloodstream is usually in the range of 1 to 15 nM. In addition, statins are highly protein bound in the blood and 95-99% of them are bound to proteins. As a result, only a very small fraction, approximately 0.01 to 0.5 nM, remains unbound and pharmacologically active [62].

Furthermore, the therapeutic dose of statins in humans usually ranges from 0.1 to 1 mg/kg body weight. In contrast, many rodent studies have examined doses of 1 to 100 mg/kg body weight, and in some cases up to 500 mg/kg. It indicates that the concentrations of statins used to induce the pleiotropic effects in animal studies are much higher, sometimes up to 1000 times, than those used in clinical practice [62].

The angiogenic effects of statins have been extensively studied and it has been revealed that statins act as a double-edged sword in angiogenesis [63-66]. At nanomolar concentrations, statins have been shown to promote angiogenesis, whereas at micromolar concentrations, they have the opposite effect [67]. These dual roles of statins have been attributed to the inhibition of the proliferation and migration of endothelial cells as well as induction of apoptosis in these cells (Figure **2**).

Clinically relevant doses of atorvastatin, typically ranging from 0.01 to 0.1 μM, have been shown to induce angiogenesis. However, at concentrations higher than 0.1 μM, atorvastatin showed the opposite effect and inhibited angiogenesis and migration of endothelial cells by inducing apoptosis. These dual activities of atorvastatin highlight the importance of the concentration of statins in modulating their effects on angiogenesis [68]. Similarly, pitavastatin exerted different effects on human microvascular endothelial cells (HMVECs) depending on its concentration. At low concentrations (0.01 mM), pitavastatin induced the migration, proliferation and viability of HMVECs. However, at higher concentrations (1 mM), it suppresses cellular processes, demonstrating the concentration-dependent nature of its effects on endothelial cells [69, 70]. At nanomolar concentrations, statins such as atorvastatin, pravastatin, and pitavastatin have been reported to suppress senescence in human umbilical vein endothelial cells (HUVECs). It may indicate that these statins have a protective effect against cellular aging at low concentrations [71].

Simvastatin was found to induce apoptosis in L6 myoblasts at a concentration of 71.6 μM. However, at a higher concentration (143 μM), it caused necrosis in these cells. This suggests that the effects of simvastatin on L6 myoblasts depend mainly on the applied concentrations. Lower concentrations cause apoptosis and higher concentrations cause necrosis [72].

The high concentrations of statins can stimulate the release of VEGF (Vascular Endothelial Growth Factor) from endothelial cells and also trigger apoptosis in the endothelial cells. This effect may arise from the inhibition of geranylgeranylation of Rho, a signaling molecule playing a dual role in angiogenesis [67, 73, 74].

5. EFFECTS OF STATINS ON THE APOPTOSIS

Most studies of the statins' effects on apoptosis have been conducted in cancer cells. Although there is not a fixed cutoff for the concentrations of statins to induce specific effects with these medications, it has been demonstrated that statins induce cytostatic effects at nanomolar concentrations [75] and cytotoxic effects at higher concentrations in cancer cells. The exact concentration required to produce these effects varies depending on the type of statin, cell line, and experimental conditions [76]. For more details about the effects of the concentrations /doses of statin on apoptosis, see Table **2**.

6. THE IMPORTANCE OF THE ANION TRANSPORTER POLYPEPTIDES (OATP) IN STATINS STUDIES

The expressions of OATPs and CYP3A4 in different animals are the important elements that should be considered in the interpretations to achieve the most accurate results. Statins have been shown to be more effective in lowering cholesterol (30%) in rabbits compared to rodents, mice (20%) and rats (10%) [92]. Although OATP1b2 in mice and rats is similar to OATP1B1 in humans with 65 and 64% amino acid identity, respectively [93-96], the recombinant monkey OATP1B1 is generally similar to those for human OATPs in terms of substrate recognition [97]. Because CYP3A4 is the major enzyme metabolizing statins, the cynomolgus monkey and the mouse seem to be proper animal models since similarity of cynomolgus monkey's CYP3A8 to the human CYP3A4 protein is 93% and CYP3A11 in mouse shares 76% amino acid homology with the human CYP3A4, but Sprague-Dawley rats are not the appropriate animal model in this regard [98-100]. As mentioned, the statin uptake is strongly mediated by OATP, particularly OATP1B1. In different cells such as liver and endothelial cells, genetic polymorphism in OATP1B1 affects the cellular uptake of statins. In addition, many chemicals change the expression of these transporters. The expression of OATPs in gastric, pancreatic and colon cancer cells is responsible for the uptake of chemicals [101]. The

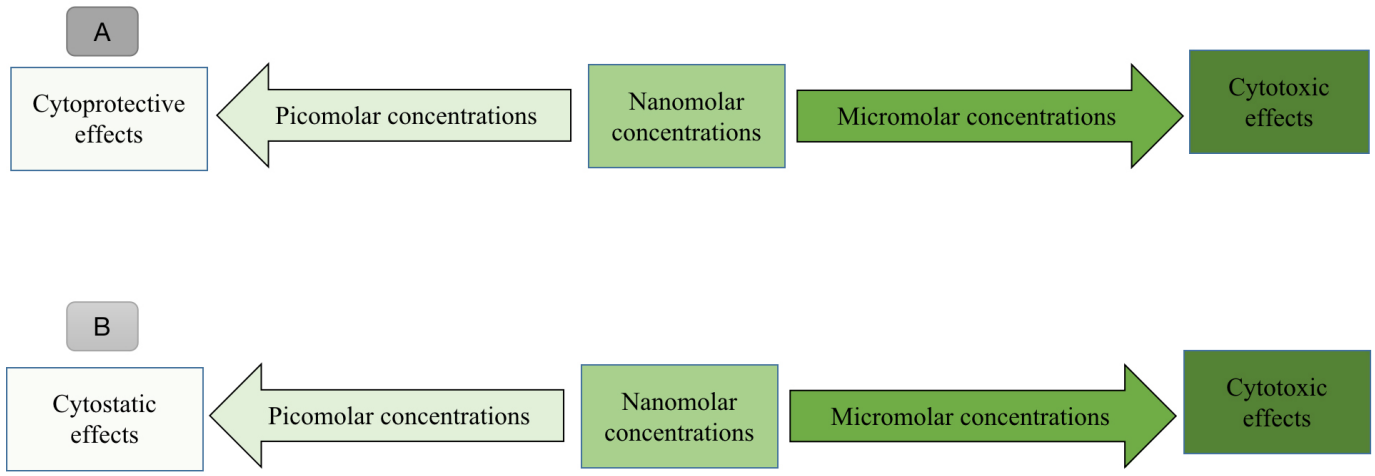

Figure 2: Selection of doses/concentrations in research studies of statin. **A**) In normal cells, particularly endothelial-derived cells, statins at lower concentrations, typically in the nanomolar ranges and lower, protect these cells from senescence and apoptosis. In contrast, higher concentrations, typically in the micromolar ranges and above, tend to induce senescence and apoptosis in this cells. **B**) in cancer cells, both low and high concentrations of statins have been reported to have destructive effects. Higher concentrations, often in the micromolar ranges and above, induce cytotoxic effects and apoptosis in these cells. Lower concentrations have been shown to primarily induce cytostatic effects rather than cytotoxic effects. The proper dose/concentration in research studies is crucial to stimulate specific effect of statins on different cell types, whether normal or cancerous.

Table 2: The Effects of Statins' Concentrations on Apoptosis

Statin	Concentration/Solvent	Cell line and effects of statins
Fluvastatin	10 μM	MCF10A (induction of apoptosis) [77]
Simvastatin Atorvastatin	Atorvastatin 0.3-49.1 μM, Simvastatin 0.2-40.8 μM	Triple-negative breast cancer (TNBC) (induction of apoptosis) [78]
Simvastatin	12 and 8 μM/DMSO and ddw	12 and 8 μM in PC3 and LNCaP cell lines respectively (induction of apoptosis) [79]
Simvastatin	0.481 μM	Adrenal carcinoma SW13 vimentin-positive (SW13-vim+) (induction of apoptosis) [80]
Simvastatin	60 μM	T47D breast cancer cell (induction of apoptosis) [81]
Atorvastatin	1.16 μM to 4.3 μM/DMSO	MDA-MB-231 cells (induction of apoptosis) [82]
Simvastatin, Fluvastatin	DMSO	PC9 and PC9 GR4 (simvastatin:4 μM, fluvastatin: 2 μM) H460, H358, and PC9 BrM3 (simvastatin:12 μM, fluvastatin: 4 μM) (induction of apoptosis) [83]
Fluvastatin	5.3 μM/DMSO	Human A549 lung adenocarcinoma cells (induction of apoptosis) [84]
Lovastatin		Anaplastic thyroid cancer cells (induction of apoptosis) [85]
Lipophilic statins		Osteosarcoma cells (induction of apoptosis) [86]
Lovastatin	0.3 μM	Human prostate cancer cells (induction of apoptosis) [87]
Pitavastatin	10 μM	Breast cancer and melanoma tumors (induction of apoptosis) [88]
Simvastatin	μM/DMSO	Primary prostatic cells, normal epithelial cell lines RWPE-1 and PWR-1E (induction of apoptosis) [89]
Simvastatin	10 μM/DMSO	Primary prostatic, normal epithelial cell lines RWPE-1 and PWR-1E cancer cells (induction of apoptosis) [89]
Lovastatin	0.3 μM	Prostate cancer cells: PC-3, DU-145, LNCaP (induction of apoptosis) [87]
Simvastatin	20 μM	MCF7 breast cancer cells, NCI-N87 human gastric cancer cells, HepG2 human hepatocellular carcinoma, Non-small cell lung carcinoma (NCH lung) cells. (Induction of apoptosis) [90]

(Table 2). Continued.

Statin	Concentration/Solvent	Cell line and effects of statins on them
Lipophilic statins	1 μM cerivastatin, 10 μM atorvastatin, and simvastatin	Osteosarcoma cell line decreased phospho-p42/p44-MAPK and Bcl-2 levels (induction of apoptosis) [86]
Simvastatin	10 μM	Glioma cells (decrease in the proliferative capacity of glioma cells) [91]
Lovastatin	0.3 μM	Human Prostate cancer cells (induce senescence and G1 cell cycle arrest) [87]
Pitavastatin	10 μM/DMSO	Breast cancer and melanoma tumors (enhance the effects of radiation on cellular senescence) [88]
Simvastatin	10 μM	Prostate epithelial cells (Induction of apoptosis) [89]
Simvastatin	0.1 μM	Prostate epithelial cells, and normal cells (cytostatic effect and partial apoptosis) [89]
Simvastatin	10 μM/DMSO	Prostate epithelial cells (induction of apoptosis) [89]
Lovastatin	0.3 μM	Prostate cancer cells (PC-3) (Induction of senescence and G1 cell cycle arrest) [89]
Simvastatin	20 μM/DMSO	MCF7 breast cancer cells, NCI-N87 human gastric cancer cells, HepG2 human hepatocellular carcinoma, Non-small cell lung carcinoma (NCH lung) cells. Induction of apoptosis [90]

expression of OATP1 in brain endothelial cells facilitates the absorption and transport of certain chemicals such as statins and contrast agents [102].

7. CONCLUSION

Based on the findings presented in Table **1**, it is recommended that statins should be administered once every 24 hours in the evening because cholesterol biosynthesis reaches its maximum level at this time.

The selection of the appropriate statin, concentration, and animal model and cell line has a paramount importance in statin studies. If a study aims to evaluate the impact of statins on the liver, hydrophilic statins are the preferred choice. In contrast, if the research focuses on the extrahepatic tissues, lipophilic statins appear to be appropriate statins, particularly statins other than lovastatin and simvastatin. These two recent statins are first absorbed and activated by the Liver which reduces their systemic bioavailability [20]. Additionally, in cell lines other than hepatocytes, lipophilic statins are more appropriate compared to hydrophilic statins.

To investigate the effects of cholesterol inhibition in the liver, synthesizing around 70% of the body's cholesterol [15], on the extrahepatic tissues hydrophilic statins seem to be more appropriate candidates. Their insignificant accessibility for the extrahepatic tissues ensures that their effects predominantly stem from reducing cholesterol levels in the liver rather than directly acting on these tissues.

Statins have been the subject of extensive cancer research and have shown the ability to induce apoptosis or angiogenesis in various cancer cells directly by inhibiting mevalonate production.

Regarding the negative feedback regulation of cholesterol on itself [103], it is essential to address the distinct effects of statins in the extrahepatic tissues. Statins that cannot diffuse into the extrahepatic tissues play a dual role in the liver and extrahepatic tissues; in the liver, all statins inhibit cholesterol biogenesis, whereas in the extrahepatic tissues, hydrophilic statins not only do not inhibit cholesterogenesis, but also stimulate this pathway. This effect appears due to the hepatoselectivity of hydrophilic statins. As a result, hydrophilic statins inhibit cholesterol synthesis in the liver. Due to their insignificant access to the extrahepatic tissues, and reduction of the total cholesterol in the body by inhibiting cholesterol biogenesis in the liver, hydrophilic statins counteract the negative inhibitory effect of cholesterol on its own synthesis in the extrahepatic tissues. It results in excessive production of cholesterol and mevalonate in the extrahepatic tissues, producing pleiotropic effects quite different from those induced by lipophilic statins.

Therefore, for assessing the effects of statins on the extrahepatic tissues it is crucial to bear in mind that lipophilic statins block cholesterol synthesis in all tissues and consequently, they can induce apoptosis in both hepatic and extrahepatic cells. Conversely, hydrophilic statins may induce different pleiotropic

effects, such as the inhibition of apoptosis or senescence in the extrahepatic tissues.

Several studies have indicated that statins do not efficiently reduce cholesterol levels in rodents [92]. There is even a study demonstrated that statins elevate the rate of cholesterol synthesis in mice [101]. Therefore, rabbits seem to be the appropriate animal model for the study of cholesterol metabolism and atherosclerosis [60].

Regarding the required concentrations to stimulate specific pleiotropic effects, it is worth noting that in cancer cells low concentrations of statins (nanomolar) are more likely to induce cell cycle arrest (cytostatic effects) rather than cytotoxic effects. However, at higher concentrations (micromolar) they tend to induce apoptosis in these cells [88]. Statins have been shown to play a constructive role in angiogenesis by protecting endothelial cells from apoptosis and senescence at lower concentrations. Nevertheless, at higher concentrations, statins stimulate apoptosis and senescence [67].

In cancer cells, concentrations below 1 μM are recommended to induce cytostatic effects, while concentrations above 1 μM are recommended to induce cytotoxic (apoptosis) effects. In epithelial cells, concentrations below 1 μM are suggested to protect against senescence, while higher concentrations may induce apoptosis and senescence in these cells.

ABBREVIATION LIST

CETP = cholesteryl ester transfer protein

ddw = double distilled water

DMSO = dimethyl-sulfoxide

HMVECs = human microvascular endothelial cells

HUVECs = human umbilical vein endothelial cells

LDL-C = low-density lipoprotein cholesterol

NSLC = non-small cell lung carcinoma

OATPs = organic-anion-transporting polypeptides

TNBC = triple-negative breast cancer

VEGF = vascular Endothelial Growth Factor

CONFLICT OF INTEREST

None.

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