Chapter

Statins: Are Lipid-lowering Drugs Useful in Sarcomas?

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Abstract

Sarcomas are rare tumors that are difficult to treat. Many of them are chemoresistant and with a high tendency to recur. Hence, finding new treatments is imperative in these tumors. Metabolic changes in tumor biology have become an essential characteristic in carcinogenesis processes, highlighting among them the role of lipids in these events, mainly cholesterol biosynthesis. Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoAR), a key enzyme in the mevalonate pathway responsible for cholesterol synthesis, have an effect beyond the reduction in plasma cholesterol levels. These are the so-called pleiotropic effects of statins, responsible for some of the antitumor action of statins. Although there are considerable epidemiological and preclinical evidences that support the use of these medicaments in the treatment of sarcomas as adjuvant reprofiled drugs, clinical trials are disparate and heterogeneous, and do not provide enough information to help determine the convenience of their use, being necessary more studies to evaluate the efficacy and safety of statins in sarcomas. The purpose of this review is to update the role played by the reprofiled statins in the treatment of sarcomas.

Keywords: sarcoma, cholesterol metabolism, mevalonate, HMGCoAR, statin, reprofiling

1. Introduction

Sarcomas are malignant uncommon heterogeneous tumors [1] derived from mesenchymal tissues [2, 3]. There are mainly bone and soft tissue sarcomas (4:1), accounting for 1% of all cancers [2]. They are responsible for 19%–21% of cancer deaths [2]. Low frequency, high diversity, and limited knowledge about the underlying biological mechanisms make it difficult to treat sarcomas [1, 2]. Chemoresistance, local recurrences (10–20%) [4], and metastatic disease (33%) are still unresolved clinical problems with no new critical improvement in sarcomas treatment [2]. In these tumors about one-third of sarcoma patients die, so it is imperative to find new therapeutic strategies for sarcomas. Since lipids, especially those derived from the cholesterol pathway, play an

important role in tumorigenesis, the purpose of this review is to update the function played by cholesterol in the treatment of sarcomas and to assess whether statins can have a place in the therapeutic treatment of sarcomas.

2. Role of lipid metabolism in tumorigenesis

Changes in cancer cell metabolism are essential in tumor behavior, but it is not known how they interrelate (**Figure 1**). The high proliferative capacity of tumor cells generates high metabolic demands [5]. Lipids are necessary for cell survival, proliferation, differentiation, motility, cell structure, and cell signaling [6, 7]. Cholesterol stands out in cancer progression because tumor cells require more cholesterol than normal cells to achieve various functions [4, 8–10]. To reach this, some tumors overexpress genes from the cholesterol biosynthetic pathway to accomplish this goal [11].

2.1 Physiology of cholesterol synthesis

Cholesterol, synthesized in the mevalonate pathway from HMGCoAR (**Figure 2**) [3], is regulated in response to different stimuli [3]. This pathway also generates [1, 2] farnesyl pyrophosphate (FPP), precursor of sterols, such as cholesterol; ubiquinone, necessary for the mitochondrial electron transport chain; dolichols, for the protein N-glycosylation; carotenoids, free radical scavengers; isoprenoids, to anchor proteins to cell membranes [2]; and geranylgeranyl pyrophosphate (GGPP), involved in a wide

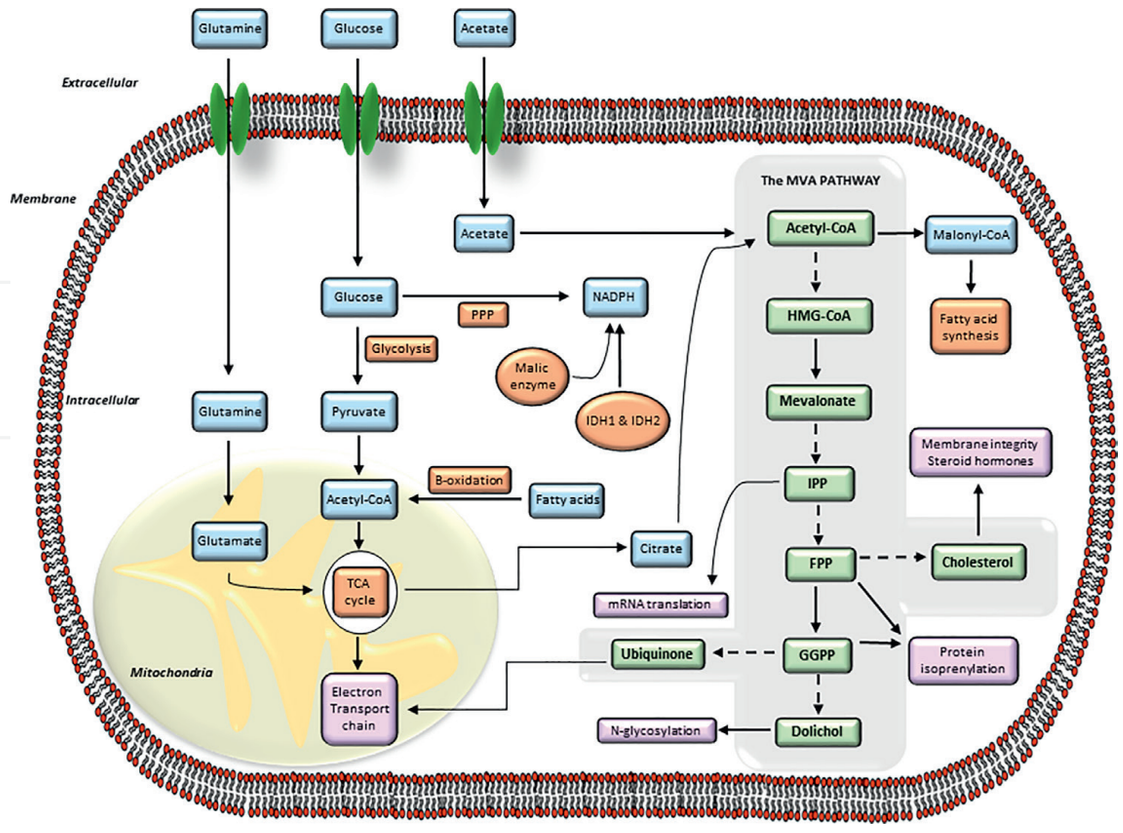

Figure 1.
The mevalonate (MVA) pathway and its connection to intracellular energy metabolism signaling. The fatty acid synthesis and β-oxidation pathway; glycolysis and the TCA cycle are noteworthy among other.

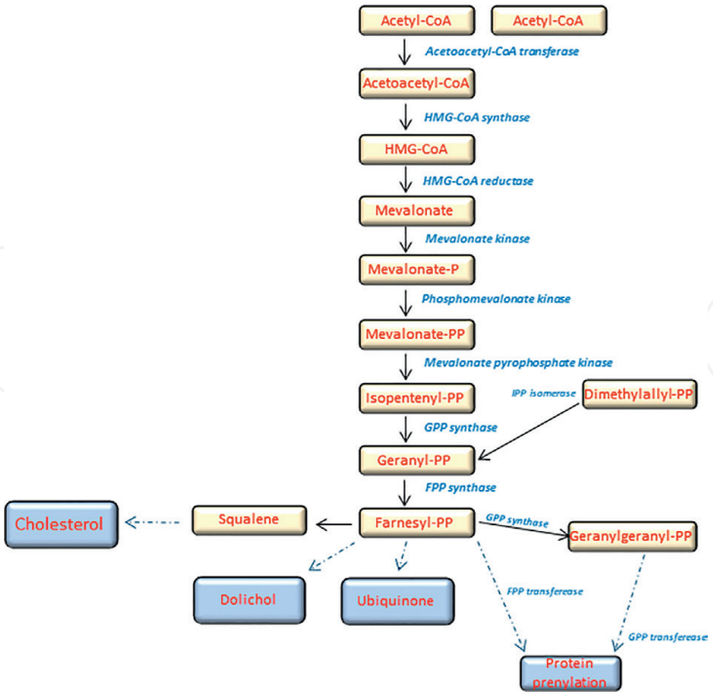

Figure 2.
Diagram of the MVA pathway. Acetyl-CoA is converted to hydroxymethylglutaryl-CoA (HMG-CoA) used by HMGC reductase (HMGCR) to synthesize MVA. MVA generates farnesyl pyrophosphate (FPP), precursor of some sterols, such as membrane cholesterol; as well as ubiquinone (Coenzyme Q) from the mitochondrial electron transport chain; dolichols, for protein N-glycosylation; carotenoids, free radicals' scavenger; and isoprenoids, for membranal protein anchoring. FPP is converted into geranylgeranyl pyrophosphate (GGPP), both essential in prenylation processes.

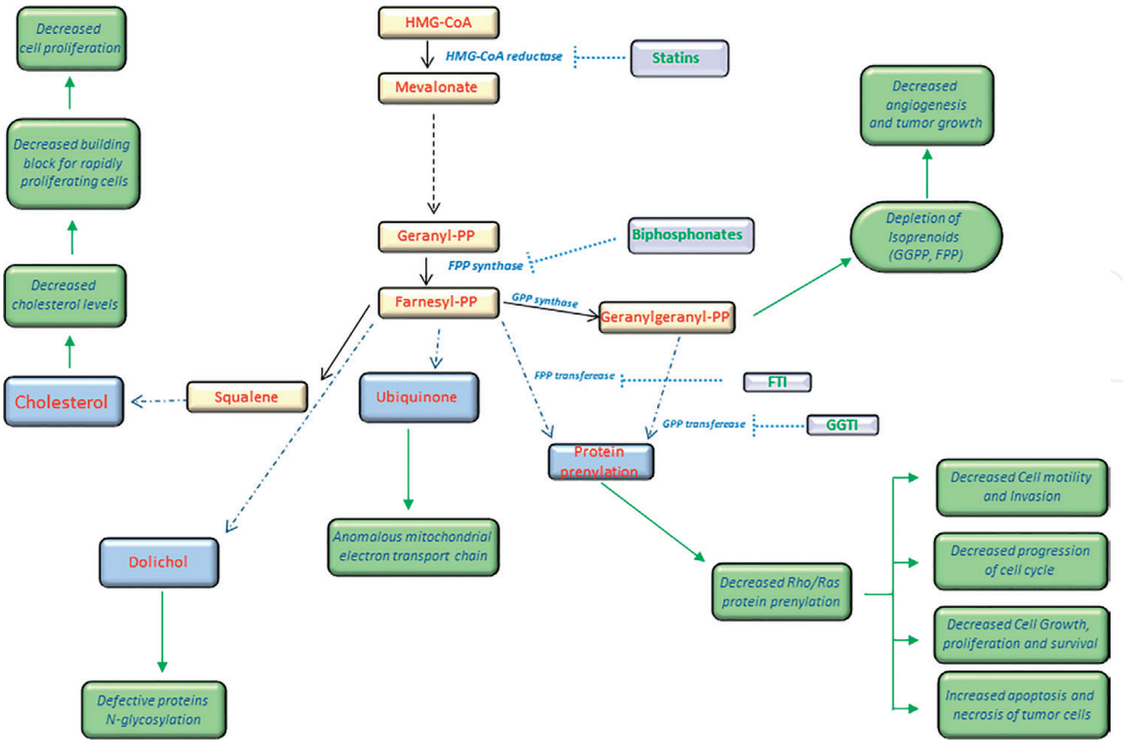

Figure 3.
Antitumoral effects of MVA pathway inhibition. MVA pathway inhibition inhibits tumor growth and progression through reduction in MVA synthesis, which decreases isoprenoid levels, preventing protein prenylation, translocation of Rho and Ras to the cell membrane, and inhibition of cholesterol synthesis.

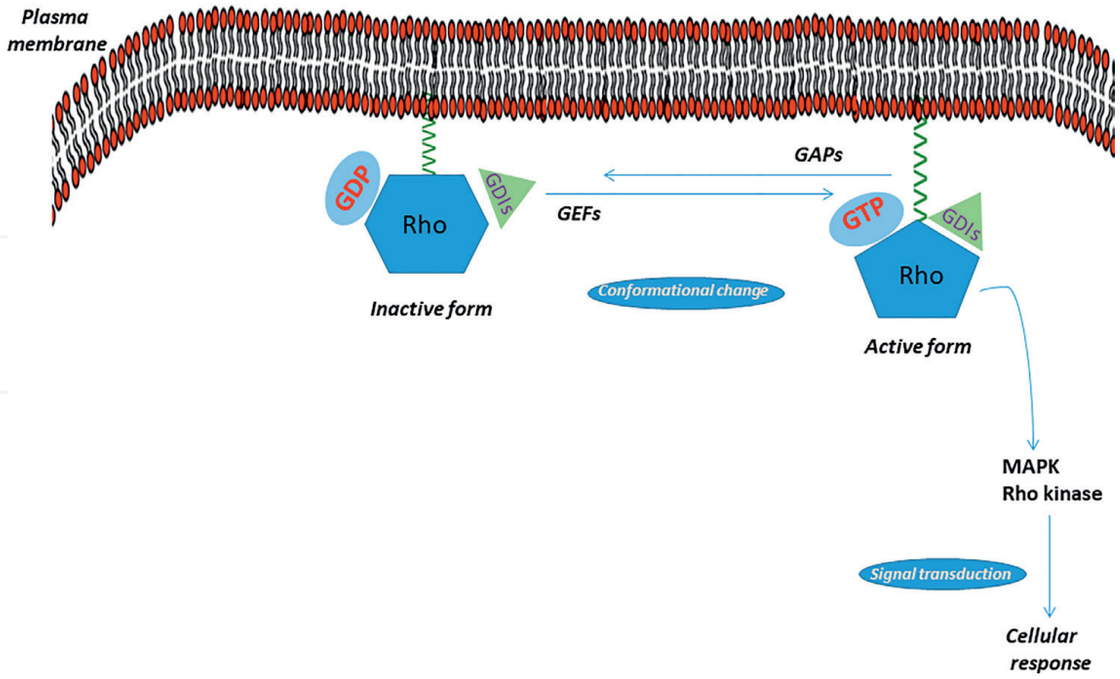

Figure 4.
*Signal transduction through Rho-GTP proteins. Rho proteins are present in an active state, bound to GTP, and an inactive state, bound to GDP. When GTP binds to Rho proteins, a change in protein structure is produced that allows information to be processed and the signal to be propagated within the cell. The Rho proteins change cyclically between their active and inactive forms, these reactions being catalyzed by the "guanine-nucleotide-exchange factors" proteins (GEFs); by the "GTPase-activating proteins" (GAPs), and by the "guanine-nucleotide" "proteins-dissociation inhibitors" (GDIs). Among the effectors downstream of Rho (***Figure 4****), the Rho-dependent kinase (ROCK) family of MAP kinase proteins stands out.*

range of cellular processes (**Figure 3**) [3]. Prenyltransferases farnesyl transferase (FTase) and geranylgeranilatransferase (GGTase I and II) activate the functions of some FPP or GGPP-dependent proteins in the cell membrane [3, 5, 12]. Thus, Ras protein regulates cell differentiation and proliferation; Rho controls the cytoskeleton and cell growth progression (**Figure 4**) [3, 13]; Rab, acts in the transport of intracellular vesicles; Rap, is essential in cell replication, platelet activation and generation of oxygen radicals; and G proteins, necessary in the signal transduction process [6]. Therefore, blocking the mevalonate pathway would lead to dysfunctional proteins due to disruption of the prenylation process (**Figure 3**) [3, 7].

2.2 HMGCoAR inhibition by statins

Statins inhibit the enzyme HMGCoAR, binding to the enzyme active site instead of HMGCoA [14]. There are differential effects of statins according to the specific tissue analyzed (liver *vs* non-hepatic) or polarity (hydrophilic *vs* lipophilic) [15]. The more lipophilic, the higher levels in non-hepatic tissues [16], while the hydrophilic are more hepato-selective [17].

2.3 Increased cholesterol needed in tumor cells

Increased cholesterol synthesis requires a rise in HMGCoAR activity; enhanced absorption of low-density lipoprotein (LDL); and/or both mechanisms [18].

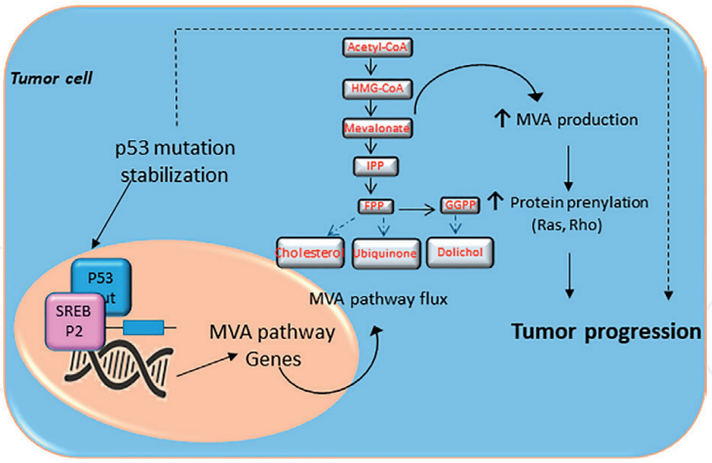

Figure 5.
The mevalonate (MVA) pathway in cancer progression. The MVA pathway is dysregulated in several cancer cells due to mutations or abnormal signaling of different proteins/pathways. Upregulation of MVA pathway drives increased protein prenylation thus promoting a malignant phenotype of cancer cells with uncontrolled cell invasive growth and survival. In cancer cells expressing a mutation of tumor protein p53, there is a positive-feedback loop where p53 interacts with sterol regulatory element-binding protein (SREBP), leading to increased activation of the MVA pathway activity and therefore higher levels of MVA. This MVA leads to the stabilization of p53 mutation as well as promotes protein prenylation, thus accelerating cancer progression.

2.3.1 Expression of HMGCoAR in tumors

Overexpression or activation of HMGCoAR [10] produces the isoprenoids necessary to maintain pro-tumor benefits (**Figure 5**) [19]. High levels of HMGCoAR, present in various types of tumors [20–22], are associated with favorable prognostic criteria [20], such as prolonged relapse-free survival [23, 24] or predicted response to treatment [24].

2.3.2 LDL receptor expression

Physiologically, plasma cholesterol transported in LDL is internalized into the cell upon contact with its receptor. If the cell needs cholesterol, it increases its synthesis and LDL receptor activity; otherwise, both activities decrease [24]. In tumor cells, higher cholesterol requirements cause an increase in LDL receptor concentration, associated with an increased plasma LDL activity and absorption [25–27].

3. Pleiotropic effects of statins beyond lowering cholesterol levels

Statins, regulators of small GTPases prenylation [26], are essential in multiple cellular processes [4, 27]. These pleiotropic effects of statins [1] are modulated either by HMGCoAR-dependent (canonical) or HMGCoAR-independent (non-canonical) ways [28]. We will focus on HMGCoAR-dependent processes, which prevent the isoprenylation of small GTPases Rho, Ras, Rac, and Cdc24 [1, 29].

3.1 Non-tumor pleiotropic effects of statins

Statins can affect several tissue functions [30]. The different pleiotropic effects are summarized in **Table 1**.

Pleiotropic effect	Main mechanism of action	Ref.
Brain		
Reduction of incidence of dementia	Reduction of embolic and ischemic stroke	[31]
Improvement psychological well-being	Cumulative reduction of levels of depression, anxiety and hostility	[32]
Vascular		
Endothelial function enhancement	Education seric cholesterol levels. Decreased vascular relaxation Restoration of NO production	[33]
Reduction of blood pressure	Reduction of blood pressure and peripheral vascular resistance	[34]
Reduction of thrombogenicity	Reduction of platelet aggregation - Reduction (TxA2) -Increase in prostacyclin synthesis	[35]
Endocrine		
Reduction of incidence of type II diabetes	Inhibition of cellular pathway insulin-dependent	[35]
Immunology		
Reduced transplanted organ rejection	Inhibition of the expression of the MTF and reduction of hypercoagulability. Decrease of TNF α, IL-6 and NBP	[36, 37]
Cardiology		
Reduction of vascular events	Ischemia reduction: -Coronary arteries, Cerebrovascular; Kidney arteries	[36, 38]
Improved VE fraction function in HF	VE fraction improvement	[32]
Bone		
Reduction of osteoporosis and the fracture risk	Stimulates ECM genes expression	[39]
	Prevention of bone resorption	[35]
	Stimulation of bone formation	[39]
	Promotes differentiation and proliferation	[39]
	Enhances bone mineral density	[39]

Table 1.
Non-tumor pleiotropic effects of statin.

3.2 Tumor pleiotropic effects of statins

3.2.1 Pleiotropic effects of statins in non-mesenchymal tumors

Inhibition of mevalonate pathway by statins (**Table 2**) (**Figure 5**) [10] prevents Rho protein isoprenylation and consequently produces apoptosis [47], decreases cell proliferation [49] and tumor cells invasiveness [42], but not in non-tumoral cells [43].

3.2.2 Pleiotropic effects of statins in mesenchymal tumors

Cholesterol is involved in the sarcomagenesis process, with an inverse relationship between increased cholesterol synthesis activity and decreased survival of patients with sarcoma [11, 55].

Pleiotropic effect	Main mechanism of action	Ref.
Cell proliferation and cell cycle arrest	Suppression of cell proliferation. Promotion of cells differentiation	[25]
	Activation (phosphorylation) of IF2α, JNK and c-Jun	[40]
	Arrest in the G0/G1 and the S phase with changes in p53, $p21^{Cip1}$, CDK1	[40]
Loss of cell viability and apoptosis	Osteosarcoma, chondrosarcoma, rhabdomyosarcoma, Ewing's sarcoma.	[22, 41–43]
	Cell detachment (anoikis) and induction of apoptosis	[27, 30]
	Increase in the bax/bcl-2 ratio (decreased expression of bcl-2)	[21, 28, 29, 41–44]
Enhancement of chemotherapeutic effect	Doxorubicin and cisplatin enhancement in osteosarcoma and rhabdomyosarcoma	[29, 45]
	Potentiating the inhibitory effect of cell migration	[45]
	Less released troponin T by cardiomyocytes in doxorubicin-treated mice	[46]
Effect on cell differentiation and ECM	Promotion of cell differentiation in Ewing's sarcoma	[44]
	Modulation of PTHrP/Ras/MAPK pathway in osteoblasts	[47]
	Increases in collagen, alkaline phosphatase, osteocalcin or BMP-2	[24]
Effect on migration and invasiveness	Reduction of cell migratory ability in sarcoma cells	[30, 48]
	Anti-angiogenic role decreasing the expression of VEGF, bFGF, HGF and TGF-β	[45, 48]
	In osteosarcoma inhibition of migration, invasiveness and metastasis	[49]
	Down-regulation in osteosarcoma of MMP-2, 9 and 14 and TIMP2 expression or activity	[50]
	MMP-3, −13, −2, −9 and TIMP-2 down-regulation in chondrosarcoma and in fibrosarcoma	[48]
	In osteosarcomas alteration of RhoA-JNK-c-Jun-MMP2 pathway	[48, 51]
	Decreased Jak2/Stat5 phosphorylation and increased expression of SOCS3 in osteosarcomas	[30]
	Growth inhibition of fibrosarcoma in animal models	[52]
	Control of tumor growth and pulmonary metastasis of rat fibrosarcoma	[22]
	In vivo potentiation of doxorubicin or cisplatin	[53]
	In a xenograft model of osteosarcoma synergy of MTX with simvastatin	[54]

Table 2.
Pleiotropic effects of statin on mesenchymal tumors.

3.2.2.1 Effects of statins on cell proliferation and cell cycle

Statins, essentially lipophilic ones [56], suppress cell proliferation [57], promote cell differentiation *in vitro* [56], mainly in tumor cells [56], and prevent the prenylation of Ras and Rho. These effects are due to the increased phosphorylation of IF2α,

JNK and c-Jun, and alteration of the p53, $p21^{Cip1}$ and CDK1 gene expression [58, 59], which arrest cells in the G0/G1 and the S phases.

3.2.2.2 Effect of statins on cell viability and apoptosis

Statin induces loss of cell viability [56, 60] and anoikis [61, 62], followed by p53 translocation, cytochrome c release [63], decreased expression of bcl-2 [64], caspase 9 and 3 activation [65], apoptosis and cell differentiation [66].

3.2.2.3 Enhancement of chemotherapeutic effect

Statins enhance the antitumor effects of chemotherapy [67]. Thus, lovastatin enhances the effect of doxorubicin on NIH-3 T3 sarcoma cells [65], and in osteosarcomas, stimulates apoptosis and invasive behavior [68]. Sublethal doses of simvastatin potentiate the cytotoxicity of doxorubicin in rhabdomyosarcomas [65], reducing *in vivo* cardiac toxicity in mice [69, 70]. It is believed that these effects are produced by the action of the p53 protein (**Figure 5**); the JNK phosphorylation [67]; the decreased MMP-2 activity [68], the decrease in drug resistance regulated by the p-glycoprotein/ABCB1 gene [71], whose expression is associated with a poor prognosis in children diagnosed with soft tissue sarcoma [62].

3.2.2.4 Effect of statins on cell differentiation and ECM composition

Simvastatin modulates cell differentiation through the IL-6-dependent PTHrP/Ras/MAPK pathway in human osteoblasts and MG-63 osteosarcoma cells, increasing the level of bone differentiation markers like alkaline phosphatase activity and/or osteocalcin [72]. BMP-2-dependent osteoblast differentiation is stimulated by lipophilic statins, while the hydrophilic statin pravastatin does not [72], also modifying osteoblast differentiation markers collagen, alkaline phosphatase, and osteocalcin [73]. Statins also promote cell differentiation of Ewing's sarcoma [66].

3.2.2.5 Effect of statins on invasive behavior

Statins, increasing the non-isoprenylated cytosolic form of Ras [64], and helped by its antiangiogenic effect and inhibition of the ECM degradation, reduce sarcoma cell invasive ability [74]. Therefore, in osteosarcoma, statin decreases the expression of the angiogenic factors secreted by the tumor VEGF, bFGF, HGF, and TGF-β [75] and inhibits the neo-vascularization. Moreover, statins inhibit invasiveness [68, 76] by MMP-3, −13, −2, −9, −14 and TIMP-2 genes down-regulation, involved in the ECM degradation, in the chondrosarcoma cell line SW1353 and in HT1080 fibrosarcoma cells [76, 77]. Among some signaling pathways [32], the RhoA-JNK-c-Jun-MMP2 pathway [76] or the Jak2/Stat5/SOCS3 pathway [74] controlled by GGPP-prenylated RhoA [78]. In animal models, statins inhibit the growth of primary tumor fibrosarcoma [50] and prevent tumor growth and pulmonary metastatic development of rat fibrosarcoma [60]. Besides, statins enhance the effect of doxorubicin or cisplatin [67]. In a xenograft model of osteosarcoma, simvastatin synergistically potentiates the action of methotrexate, enhancing tumor volume reduction, decreasing side effects, and drastically reducing lung metastases [33].

4. Mechanisms of action of statins

4.1 Effects derived from lipophilicity of statins

Lipophilicity of statins is an important factor in the effectiveness of these drugs. Lipophilic statins diffuse passively through the plasma membranes, but hydrophilic statins need transporters to cross them. Hydrophilic statins act mostly in the liver, and lipophilic statins are mainly in extra-hepatic cells [15, 79]. Lipophilicity affects antitumor actions of statins [41] inducing a cell cycle arrest in osteosarcoma [40]. Viability and apoptosis are dependent on lipophilicity, in osteosarcoma [24], chondrosarcoma [41], or rhabdomyosarcoma [43], but no clinical data related to the differential effect of lipophilic *vs* hydrophilic statin in sarcomas were found. Data from other types of tumors show this action [80], being lipophilic statins more effective.

4.2 Role of isoprenoid lipids, GTPases, and Rho in sarcomas

Members of the Rho family of small GTPases are involved in important functions involved in malignant transformation and progression, like actin reorganization, cell motility, or cell-cell and cell-ECM [55]. Rho proteins are promising targets as a novel anticancer drug in several cancers [56] including sarcoma [28]. Rho GTPases localized at membranes become activated upon stimulation of cell surface receptors. So, Rho GEFs are often oncogenic, and the expression level of Rho GTPases frequently increases with malignancy. A possible drawback of isoprenylation inhibitors is their poor selectivity for individual Rho GTPases. High levels of RhoA and/or RhoC have been observed to indicate a poor prognosis [81]. In addition, RhoA is involved in tumor progression invasion [57] and RhoC in tumor invasion. Cell growth arrest and proliferation inhibition in osteosarcoma depend on GGPP prenylation, rather than FPP and farnesylation [19]. Similarly, treatment of NIH3T3 sarcoma cells with GGTI-298 or lovastatin stops the cell cycle [82]; but FTI-277 has no such effect. So, geranylgeranylated proteins play a critical role in the cell cycle [83]. Statin-induced apoptosis is also associated with changes in RhoA protein geranylgeranylation in human chondrosarcoma [41] and osteosarcoma cell lines. Besides, in osteosarcoma cells, simvastatin induced mevalonate-dependent apoptosis [30], mediated by the MAPK-RhoA-p42/p44-bcl-2 mechanism [28]; or by activation of AMPK and p38 MAPK [84]; or is associated with the RhoA/Stat1/bcl-2 signaling pathway [24, 30]. Inhibition of geranylation by statins is also responsible for apoptosis in sarcomas [85]. Thus, in osteosarcoma and chondrosarcoma cell lines [41], geranylgeranylation inhibition induces apoptosis, which can be restored by adding GGPP, but not FPP. Similar results have been observed after treating sarcomas with GGTI-298, but not with FTI-277. This different effect of isoprenoid lipids on sarcoma cells may be due to the fact that GGPP is derived from the condensation of FPP and isopentenyl pyrophosphate (IPP). Since IPP could not be synthesized in cells treated with simvastatin, FPP could not be converted into GGPP.

4.3 Autophagic cell death

Autophagic cell death or programmed cell death (PCD) type II is a constitutively active self-degradative process of cellular constituents [86]. It is responsible for maintaining cellular homeostasis [87] under stressful conditions, such as nutrient

starvation, hypoxia, growth factor insufficiency, acidosis, or drug exposure [87]. Autophagy begins with an isolation membrane that engulfs intracellular cargo [88], degraded by lysosomal acid proteases. These lysosomal permeases and transporters export amino acids and other by-products of degradation back out to the cytoplasm, where they can be reused for building macromolecules and for metabolism [88]. Autophagy is regulated by the target of rapamycin (TOR) kinase, which is regulated by some effectors [89]. Upstream of TOR, activation of AMP-activated protein kinase AMPK in response to low ATP levels. Downstream, reduced Akt activity represses TOR kinase [89] and induces autophagy, stimulating catabolism and reducing its growth. Cholesterol depletion induced by statins produces inactivation of mTOR, which then induces autophagy [18] and also can promote cancer cell death after stimulation of ERK1/2 and Akt pathways [58]. In sarcomas, autophagy plays an important role in the pro-survival response to therapies and stress, and in the therapeutic resistance of sarcoma [87]. The cell cycle arrest and apoptosis process start with the GGPP depletion, which leads to a disrupted RhoA function, which activates AMPK and consequently inactivates mTOR [84]. Finally, statin accumulated p53 at the nucleus and induces autophagy through phosphorylation of HMGCoAR [59].

5. Evidence of the antitumor effect of statins

5.1 Epidemiological evidence of the antitumor activity of statins

Epidemiological studies have shown that statins reduce cancer mortality [74]. There is also a positive correlation between statin use and a reduction in cancer incidence [60, 74, 78]. However, other authors have not found this connection between taking statins and cancer risk [74]. Nevertheless, these epidemiological studies have been criticized for having intrinsic limitations and a retrospective approach [74]. In addition, another criticism is that the studies have been designed to evaluate the reduction of cholesterol levels and not the role it plays in oncogenesis [60], including sarcomas. Besides, clinical studies of statins and their antitumor action are few, limited, and inconclusive [61]. In addition, there is a discrepancy between data from preclinical and epidemiology regarding the lack of response to combination therapy in clinical trials. Moreover, unfortunately, clinical trials with statins and sarcomas were not found.

5.2 Combined treatment of statins with chemotherapy

Statins can be administered at high doses to cancer patients (i.e. 15 mg/kg/day for simvastatin; 25 mg/kg/day for lovastatin), but the expected effects have not been observed [62]. However, statins sensitize the tumor cells to the action of chemotherapy, improving antitumor efficacy, due to the synergism of these drugs, enhancing cytotoxicity [60], increasing the therapeutic window of statins, and reducing toxicity [63]. In sarcomas, statins increase the anti-tumor efficacy of doxorubicin or cisplatin on human osteo- and fibrosarcoma in an additive manner [53]. Besides, atorvastatin potentiates the effect on viability, migration, and cell invasion in human osteosarcoma cells [45]. In a xenograft model of human sarcoma, lovastatin enhances doxorubicin efficacy, reducing acute doxorubicin-induced heart damage [22, 46]. In the same model with osteosarcoma cells, simvastatin increased methotrexate cytotoxic effect, being necessary for lower doses of this drug and decreasing the toxicity

in the mice. Besides, increased the reduction in tumor volume caused by methotrexate and markedly decreased the rate of lung metastases [54]. In this sense, there are also some positive reports showing the efficacy of the combination of these drugs [64]. Therefore, in a patient with rhabdomyosarcoma refractory to chemotherapy, statins contributed to the improvement of the patient after receiving radiotherapy and being treated with bevacizumab [90]. However, it has also been described in other drugs that patient survival did not improve with this strategy [65].

5.3 Disadvantages and inappropriate effects of using statins

Several advantages have been associated with statin therapy, but some drawbacks have also been described. For instance, the low bioavailability of statins (5%–20%) limits their effectiveness [63, 66]. For this reason, nanocarriers have been developed [67] to overcome the lower oral bioavailability of statins [66]. Another drawback of statins may be myopathies [91], due to direct effect of statins on muscle or autoimmune responses from autoantibodies against HMGCoAR [68]. Also, statins could increase the risk of developing diabetes mellitus (in 10%–20% of patients receiving statins) [69], increase of the rate of hemorrhagic stroke when blood cholesterol levels are reduced [70], or increased liver enzymes, although hepatotoxicity is rarely observed [92].

6. Discussion

Is there enough evidence to say that statins are useful in the treatment of sarcomas? From the epidemiological studies' point of view, the results are not clear enough to advise their use since the conclusions are not homogeneous and are objectionable. Most studies are observational and retrospective [71], mainly phase I and/or phase II clinical trials, with small sample size and poor statistical support [93]. The few prospective articles published cannot assess the true extent of statins in cancer treatment. It is also difficult to draw valid conclusions from heterogeneous articles, therapeutic regimens with different types and doses of statins; not systematized frequency of administration; dispensing or not concomitantly with chemotherapy; lipophilic *vs* hydrophilic statins, etc. In addition, it is also necessary to investigate what dose and how long statin treatment is needed to prevent cancer; or what mechanism of death (apoptosis *vs* autophagy) is responsible for the observed effects [94]. In addition, it is not well known whether statins reduce the degree of tumor aggressiveness [71] or allow them to be diagnosed earlier [95]. Second, the response to statins may depend on interindividual variability that may explain the variation in pharmacological response to them [93]. HMGCoAR expression is known as a tumor biomarker. Thus, in ovarian cancer, is associated with greater survival without recurrence [96]. In colorectal cancer, the chemopreventive capacity of statins depends on polymorphisms in the HMGCoAR gene [72]. Even so, population studies have shown chemopreventive and survival benefits of statins in several types of cancer [93]. Thus, in a case-control study, cancer was diagnosed less frequently among patients who took statins (28%) [78]. Also, the use of statins in cancer patients is associated with a reduction in cancer-related mortality [74]. But in a clinical trial, designed to evaluate the effect of pravastatin combined with sorafenib on hepatocellular carcinoma, no improvement in survival was observed in these patients [73]. On the other hand, is the use of statins effective and safe in the treatment of these neoplasms? While epidemiological studies

are contradictory, preclinical studies confirm the anticancer efficacy of statins in controlling metastatic disease [20, 93] due to growth inhibition and cell death, both *in vitro* and *in vivo* [20]. These contradictory epidemiological data generate uncertainty regarding the role of cholesterol in the development of cancer [97]. Based on data from long-term studies of cardiovascular disease, neither taking statins nor lowering serum cholesterol levels increases cancer risk [76]. These discrepant data may be due to inadequate methodological designs (retrospective *vs* prospective), insufficient follow-up, and/or the different types of statins used [98]. In this sense, some mechanisms can alter cholesterol homeostasis and lead to cancer development [97]. Are statins safe or do they have any degree of toxicity? Toxicity caused by statins it is more selective in tumor than in healthy cells [99]. This fact has been observed in osteosarcoma cell lines with simvastatin [24]; or in Ewing's sarcoma cells, with lovastatin [75]. These data are critical, because these drugs are safe and well tolerated, and the achievable plasma concentration (0.1–4 μM) at a dose of 24 mg/kg/day corresponds to the dose range that can trigger apoptosis in vitro [100]. Moreover, treatment with atorvastatin, evaluated for 3 years in growing patients diagnosed with heterozygous familial hypercholesterolemia, was effective, safe, and well tolerated [9], with no impact on child growth or maturation, with only a few adverse events responsible for a 2.2% treatment withdrawal. With respect to the toxic effects of fluvastatin in terminal pediatric Ewing's sarcoma patients, fluvastatin showed that can be used safely at a dose of 8 mg/kg/day in this population [77].

In conclusion, for the above-mentioned reasons, even though many aspects remain to be resolved, we consider statins to be good potential candidates for being reprofiled in sarcomas. However, further studies in sarcoma patients, with large phase III prospective randomized controlled trials are warranted to establish the effect of statins in cancer prevention and treatment [93], and to answer the question of whether statins can be used to prevent and/or treat various types of cancer [71], including sarcomas.

Abbreviations

HMGCoAR	3-hydroxy-3-methylglutaryl coenzyme A reductase
FPP	farnesyl pyrophosphate
GGPP	geranylgeranyl pyrophosphate
FTase	farnesyl transferase
GGTase	geranylgeranyl transferase
LDL	low-density lipoprotein
Gen de ABCB1	gen del casete de unión de B1 a ATP

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