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Effects of statins on brain tumors: a review.

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Running Title: Statins and brain tumors

Abstract

Evidence from preclinical studies suggests that the competitive HMG-CoA reductase (HMGCR) inhibitors universally known as 'statins,' in addition to being powerful drugs that reduce cholesterol and improve cardiovascular risk, also have promising antitumor properties. Statins appear to enhance the treatment outcome of various cancers before and concurrent with other cancer treatment interventions. Glioblastoma multiforme (GBM), a particularly invasive cerebral tumor associated with high mortality, holds a poor median overall survival (OS) of around one year after surgical resection followed by concurrent radiation and chemotherapy. Recently, statins have increasingly appeared as potential adjuvant drugs for the treatment of GBM because of their potential to suppress cell growth, survival, migration, metastasis, inflammation, angiogenesis, and promote apoptosis during both *in vitro* and *in vivo* studies. However, the clinical outcomes of statins on the survival of patients with GBM are still controversial. This study aims to review and address some of the documented effects of statin drugs when focusing entirely on cancer treatment, especially GBM, including concurrent statin therapy with chemotherapeutic agents.

Keywords: Statin; Cholesterol; Antitumor; Glioblastoma multiforme; Apoptosis

1. Introduction

Patients of glioblastoma multiforme (GBM), one of the most invasive cerebrum tumors, have an expected lifespan of 12–18 months following diagnosis despite various treatment modalities, including maximal safe surgical resection, irradiation, and chemotherapy with temozolomide (TMZ) [1, 2]. While substantial progress has been made in understanding GBM pathogenesis, median patient overall survival (OS) has improved little throughout the last three decades [3]. Hence, owing to the poor prognosis of this malignant disease [4], the research emphasis has switched to identify and evaluate promising potential treatment adjuvants.

The mevalonate process may generate essential molecules, namely non-sterol isoprenoids, including dolichol, ubiquinol, farnesol, and geranylgeraniol, in addition to eventually allowing cholesterol to develop [5]. Such isoprenoids are the lipid anchors for several proteins that have been described initially as oncogenes, including the specific GTPases Ras, Rac1, and Rho, and that blocking this pathway may significantly impact essential cellular processes [6]. Statins are very well known and widely prescribed lipid-lowering agents, subclassified by origin as natural or fungal-derived [simvastatin, pravastatin, and lovastatin] and synthetic [atorvastatin, rosuvastatin, fluvastatin, cerivastatin, and pitavastatin]. At the molecular level, statins differ in their capability to inhibit the highly rate-limiting enzyme of the mevalonate pathway, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGCR). In turn, they block geranylgeranyl diphosphate (GGPP) and farnesyl diphosphate (FPP) synthesis, which are necessary to trigger several proteins through prenylation, including Rho, Rac1, and Ras (small G proteins) [7-9]. Alteration of the prenylation of Ras by statins regulates cell development, survival, migration, invasion, metastasis, and apoptosis through the downstream signaling pathways. Several studies have shown that statins like atorvastatin exert anticancer activity via inhibiting the mevalonate pathway [10], both *in vitro* and *in vivo* [11]. The efficacy of statins as cancer treatments in monotherapy and combination with existing chemotherapeutic agents has been evaluated in cancer patients [12]. For example, a case-control analysis documented a relatively low risk of colorectal cancer associated with the use of statins for at least five years [13]. Another case-control report has found that the risk of prostate cancer may be reduced in patients who take statins [14]. Several research studies have shown that statins activate the programmed death of the cells inside a subset of tumor-derived cell lines, suggesting a susceptibility for statin-specific apoptosis *in vivo* [15].

The mevalonate pathway and specifically HMGCR play a vital sinister role in the development of GBM. In a clinical GBM sample, the upregulation of HMGCR was observed [16]. Statins, also in GBM, could contribute to apoptosis by suppressing extracellular signal-regulated kinase (ERK) 1/2 and triggering protein kinase B (Akt), and by antiapoptotic protein Bcl-2 downregulation [17-19]. In preclinical GBM studies, statins could inhibit the invasion, migration, and differentiation of GBM cells by Ras/Rho-prenylation [20]. Although preclinical data support statin antitumor involvement in GBM, only a few clinical trials have established a connection between statins and GBM survival. In one clinical study, it has been reported that long-term statin therapy may be beneficial in GBM patients [21]. This review discusses the impact of statins and their potential molecular anticancer frameworks in preclinical studies and critically describes data on the role of statins in treating GBM.

2. Potential antitumor mechanisms of statins

Interest continues to increase regarding the potential uses and associated mechanisms of statins beyond the reduction of cholesterol, as several studies have demonstrated that some cholesterol-independent consequences of statins may have a positive effect on various diseases [22]. These benefits include increased endothelial and/or atherosclerotic plaque stability, with immunomodulatory, neuroprotective, and anti-inflammatory properties, as well as anticancer effects [23]. The cytoprotective consequences of statins can be exemplified by the fact that statins often inhibit the synthesis of several other metabolites, including isoprenoids that are used to alter several proteins (Ras, Rac1, and RhoA) after transcription [24]. These substances are essential for various cellular essential functions and can provide an explanation for the pharmacological anticancer effects of non-cholesterol-based statins (Fig. 1) [25].

In cancer, statins may have inhibitory effects on the post-translation prenylation of members of the small Rho GTPase-protein family, blocking their translocation to the plasma membrane, which results in reduced cell proliferation and the induction of apoptosis. However, according to a study by Matzno *et al.*, statin-induced apoptosis in muscle tissue was initiated by farnesylated Ras protein depletion, and not geranylated Rho protein [26]. Statins also suppress dose-dependent tumor growth, invasiveness, and metastatic lesion formation, especially in highly invasive tumor cell lines [27]. The inhibition of isoprenoids synthesis mediated by statins also contributes to apoptosis induction and prevents the development of the cell cycle in different types of cancer cells [28]. In many cancers, including melanoma, extrahepatic cholangiocarcinoma, pancreatic adenocarcinoma, non–muscle-invasive bladder cancer, hepatocellular carcinoma, thymic carcinoma, renal cell carcinoma, and in breast, colorectal, liver, lung, and prostate cancers, the effects of statins on cancer risk, recurrence and survival have been confirmed in preclinical and clinical studies [29-37]; however, some of the large-scale reviews, including systematic review and meta-analysis, have not clearly shown any beneficial impact of statins against cancer [38-40]. Recently, a major cohort study of around 200,000 individuals has reported a positive impact on the survival rates of patients with different types of cancer through long-term statin use [41]. A meta-analysis in 2017 showed that although statins as a drug class may decrease the mortality of breast cancer patients, the antitumor effect differs by statin type and is also influenced by time to follow up [42]. For instance, in patients with breast cancer, lipophilic statins, like simvastatin, atorvastatin, and fluvastatin, have shown a significant protective role. At the same time, all-cause mortality was slightly increased by hydrophilic statins, like rosuvastatin and pravastatin [43]. However, numerous studies have reported that statin users showed more prolonged medium relapse-free survival and maintained a decreased risk of recurrence in young breast cancer patients [44, 45]. Their possible anticancer mechanisms include tumor cell proliferation inhibition (by mitigating the phosphatidylinositol-3-kinase [PI3K]/Akt/mammalian target of rapamycin [mTOR] signaling pathway), cell cycle arrest promotion, apoptotic cell death induction, and cell migration/invasion/metastasis inhibition [46]. *In vivo* studies have also been performed with promising results. The tumor scale of xenografts originating from breast cancer and prostate cancer cells in mice has been shown to decrease following treatment by simvastatin [47]. In the next sections of this review, we discuss the anticancer impacts of statins, including inhibition of growth caused by cell cycle arrest and apoptosis induction, potential metastatic reduction, inhibition of angiogenesis, and the suppression of tumor differentiation.

2.1. Apoptosis initiation

A sequence of genetic modifications can be seen as a result of the transition of the normal cell into a malignant cell; therefore, induction of programmed cell death or apoptosis is one of the essential mechanisms employed in the treatment of malignancies [48]. Apoptosis happens via two pathways - intrinsic and extrinsic - and statins can significantly impact both [49]. According to one study, statins activate the mitochondrial pathway of apoptosis in various cancer cells [50]. One of the paths hypothesized for the impact of statins on cancer is to modify the expression levels of the pro- and anti-apoptotic Bcl-2 protein family (intrinsic pathway) [51]. Pharmacologically, statin-inducing apoptotic pathways are likely regulated by altered Ras or RhoA prenylation, the cytosolic release of the second mitochondria-derived activator of caspases (Smac/DIABLO), and reduction of mitochondrial membrane potential (Δψm) [50]. Several findings have shown that statins decrease the anti-apoptotic protein Bcl-2 expression levels, contributing to apoptosis induction through caspases-2/-3/-8/-9 and p53 activation, increases in Bax and Bim, as well as poly (ADP-ribose) polymerase (PARP) cleavage and DNA laddering [52-54]. Consistently, it has been found that simvastatin can activate caspases-3/-7/-9, which induces apoptosis by depleting isoprenoids as precursors for prenylation of small Rho GTPases in different human cancer cell lines [55, 56]. The data from the study by Hoque *et al.* have revealed that simvastatin and lovastatin effectively reduce the cell viability of prostate cancer cells (PC3, DU145, and LnCap) by triggering apoptosis through caspases-3/-8/-9 activation [57]. Also, Cafforio *et al.* have shown the caspase-dependent apoptotic effects of the statins on myeloma tumor cells [50]. In line with these findings, Fujiwara *et al.* have indicated that statins promote cell death by increasing the activation of caspases-3/-9, inducing Bim expression, and arresting the cell cycle at the G1 phase, and by decreasing the Δψm through inhibition of Ras/ERK and Ras/mTOR pathways, supporting the argument that statins may be promising antitumor drugs [58].

In addition to the intrinsic pathway, statins can activate the extinct death receptor (DR) pathway by upregulating Fas, the Fas-ligand (Fas-L) receptor [59]. It has been shown that statins stimulate *in vitro* the membrane Fas-L expression and lymphocyte apoptosis through the RhoA/Rho-associated protein kinase (ROCK) pathway in murine melanoma cells [60]. In line with this, simvastatin treatment results in increased mRNA and protein expression of molecules like the tumor necrosis factor (TNF) and Fas-L in mediating prostate cancer cell apoptosis [61]. In Fig. 2, we summarized the potential apoptosis-inducing mechanisms of statins in different cancer cells, and some of the critical apoptotic effects of statins on various cancer cell lines are outlined in Table 1.

2.2. Cytostatic effects of statins

As stated in the previous section, statins inhibit the production of mevalonate, a precursor of cholesterol, which is catalyzed by HMGCR [62]. Overexpression of mevalonate has been correlated with cell survival and tumor growth [51, 63]. Statins suppressing the mevalonate pathway inhibit GGPP and FPP synthesis and, consequently, several functional proteins, such as RhoA, which is essential for the post-translation of specific cell cycle regulatory proteins [64]. In particular, simvastatin targets RhoA geranylgeranylation and its translocation to the cell membrane, where it interferes with downstream effectors to regulate the cell cycle [65]. It has been proven that statins have an antiproliferative and pro-apoptotic effect in cancer cells by regulating the cell cycle [66]. Different experiments have demonstrated that statins disrupt the G1 or S phases, thus inducing *in vitro* apoptosis of several cancer cells [54, 67-69]. Mechanistically, the up-regulation of cyclin-dependent kinase (CDK, p21, and p27) inhibitors and the downregulation of cycle-dependent factors is mediated through statin-induced cell cycle arrest [70].

Simvastatin has been found to provoke the death of breast cancer cells and disabling the signaling pathways of PI3K/Akt and mitogen-activated protein kinase (MAPK)/ERK [56, 71]. Conversely, the outcomes from Wang *et al.* in bladder cancer cells have indicated that, by reducing the abundance of the protein involved in the phase regulation of the G0- and G1-phase, simvastatin had no significant impact on apoptosis and cleaved caspase-3/-9, but did inhibit proliferation and triggered cell cycle arrest in the G0/G1-phase (CDK4, CDK6, and cyclin D1) through PPAR-γ activation [72]. This shows that simvastatin modulates cell cycle-regulating genes (TP53, CDKN1A, and CDK1). It inhibits the proliferation of the cell cycle, as demonstrated by higher cell percentages in the G0/G1-phases and lower cell percentages in the S-phase [73]. Ma *et al.* further showed that simvastatin reduces the expression of cyclin D1 and CDK4 and increases p27 expression in nasopharyngeal carcinoma cells during the G1-phase [74].

The effectiveness of novel simvastatin derivatives has been shown to cause the arrest of the S-phase and apoptosis in prostate cancer [75]. Recently, it has been demonstrated that rosuvastatin polymeric nanocapsules are superior in their anticancer activity on human liver (HepG2) cancer cells through enhanced apoptosis and cell cycle arrest at the G2/M-phase, which has further highlighted their potential in the treatment of hepatic cancer [76]. The cytostatic effects of statins on the cell cycle progression in various cancer cells are summarized in Table 2.

2.3. Chemotherapeutic activity potentiation

Preclinical studies have shown that adjuvant statin utilization can potentially improve biological activity and minimize the resistance of standard anticancer treatment [55]. In this regard, statins, as well as aspirin and metformin, are associated with increased downstaging of rectal tumors and, thus, may have a role as adjuncts to neoadjuvant treatment, highlighting a potentiating effect of statins against rectal cancer [77]. Margaret *et al.* have shown that statin (atorvastatin and simvastatin) and metformin use is associated with improved OS in pancreatic ductal adenocarcinoma patients. In this study, statin, as well as metformin use, was associated with better OS in affected patients [78], suggesting that the combination of these drugs could be beneficial in the clinical setting as an adjuvant to traditional chemotherapeutic agents.

Tosedostat, an aminopeptidase inhibitor drug, has shown positive efficacy in acute myeloid leukemia (AML). Cloos *et al.* showed that some statins (fluvastatin, pravastatin, lovastatin, and simvastatin) potentiate the antitumor activity of CHR2863, a close structural analog of tosedostat, in U937 AML cells. Increased apoptosis induction and cell cycle arrest were also corroborated in the synergy of CHR2863 with statins, which increases sub-G1 fraction [79]. A retrospective review of persistent and refractory AML cases, treated with combination therapy, including tosedostat, showed a therapeutic advantage for patients with statin users. AML patients taking both statins and tosedostat had a 50% probability of six months survival compared to three months probability of survival for patients not taking statins [80].

Palko-Łabuz *et al.* have shown that mixed utilization statins (simvastatin and mevastatin, 0-120 µM) and hydroxy-flavones (50 µM) contributed to an improved inhibition of cell growth and more robust apoptosis than statin use alone. In drug-resistant cells, the combination of statins with flavones produced a more significant decrease in doxorubicin resistance than the effect observed with statins alone [81].

Statins increase low-density lipoprotein receptor (LDLR) expression, producing a prominent source for LDLR degradation and additionally upregulate proprotein convertase subtilisin/kexin type 9 (PCSK9) [82]. This provides a negative feedback response that reduces the impact of statins on lipid reduction; the design of PCSK9 inhibitors can, therefore, enhance the lipid-reducing functions of statins [83]. To date, multiple clinical studies were conducted to determine the potential relation between PCSK9 inhibitors and cancer risk [84]. Silibinin A (the principal active constituent of silymarin) therapy has been shown to suppress PCSK9 expression in HepG2 cells by reducing the activity of the PCSK9 promoter. Silibinin A specifically antagonizes the statin-induced phosphorylation pathway of p38 MAPK, indicating that silibinin A may be identified as a novel inhibitor of PCSK9 that can improve the efficacy of statin therapy [85]. Furthermore, fluphenazine and its two derivatives, along with simvastatin, enhance the cytotoxicity of doxorubicin (0–35 µM) in comparison to treatment with phenothiazine derivatives in the treatment of doxorubicin-resistant colon cancer cells. Also, Środa-Pomianekthe *et al.* have demonstrated that the treatment of colon cancer cells with simvastatin improves the anti-multidrug resistance (MDR), anti-inflammatory, and pro-apoptotic effects of phenothiazines [86]. Some of the combinational strategies-based statins against various cancer models are shown in Table 3.

2.4. Antimetastatic effects of statins

Cancer metastasis is the primary cause of cancer mortality rates, responsible for approximately 90% of cancer-related deaths [87]. Since statins can inhibit the outgrowth of metastatic tumors, they can be viewed as long term adjuvant medications to postpone clinical crises and reduce mortality in affected patients [88]. Transformed malignant cells depend primarily on the mevalonate pathway for lipid moiety, which is essential for cell growth, cell adhesion, cell cycle development, and cell signaling [89]. A wide variety of tumors have demonstrated the enhanced activity of the mevalonate pathway; therefore, inhibition of the mevalonate pathway with inhibitors of HMGCR will cause a decrease in mevalonate and its products to have a significant inhibitory impact on cancer cell metastasis [90]. Given the function of Rho, its synthesis inhibition will mitigate cell proliferation and thereby repress the initiation of the tumor [91]. Since tumors include a group of cancer stem cells that can trigger metastatic dissemination, Rho activity might, in turn, be linked to cancer stem cell activity [92]. For instance, atorvastatin (0-250 μM) exhibits anti-tumorigenic and antimetastatic effects in ovarian cancer cells *in vitro* [93], and simvastatin and atorvastatin both cause a concentration-dependent decline in colony-forming ability and cell migration of human cholangiocarcinoma cells [94]. Also, simvastatin significantly induces DNA damage and reduces cell adhesion and invasion through the Akt/MAPK signaling cascade in ovarian cancer cells [95]. The Cysteine-rich inducer 61 (Cyr61) matricellular protein is correlated with the invasion of tumors and induction of tumorigenesis in many *in vivo* malignancies. This facilitates the dissemination of tumors, chemotaxis, angiogenesis, and cellular adhesion. s ht n

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An effective mechanism of cancer metastasis is the epithelial-to-mesenchymal transformation (EMT), which is a dynamic multi-gene programming cycle [97]. Lipophilic statins have been found to antagonistically change the EMT pathways of signaling stem-like cells in breast cancer by inhibiting the mevalonate pathway [98]. Atorvastatin partially inhibits the EMT process induced by transforming growth factor (TGF)-β1 by attenuating the upregulation of SphK1 and inhibiting cell migration and actin filament remodeling in non-small cell lung cancer cells [99]. Also, carcinostatic impacts of atorvastatin in breast cancer are related to inhibiting invasion and downregulating the phosphatase and tensin homolog (PTEN)/Akt pathway via the promotion of RhoB, both *in vitro* and *in vivo* [100].

In tumorigenesis, the restructuring of the actin cytoskeleton has been one of the key pathways associated with cell migration regulation [101]. Many factors, including small GTPases like RhoA, facilitate actin reorganization and cellular migration [102]. Throughout these scenarios, simvastatin inhibits stemness-related gene expression and metastatic invasions through the degradation of the cytoskeleton in human cancer cells [103]. Atorvastatin has been shown to enhance oxidative stress and inhibit the cell proliferation of oral squamous carcinoma *in vitro* [104]. The majority of reports regarding simvastatin therapy have shown that survivin is reduced significantly and is implicated in tumorigenesis [105]. Invasion assays have revealed that simvastatin (0–50 μM) treatment inhibits the invasiveness of salivary adenoid cystic carcinoma (SACC‑ 83) cells dose‑ dependently, and downregulates survivin expression [106]. In the next section, we discuss the anticancer activity of statins, with a focus on their possible advantages in the treatment of GBM.

3. GBM and statins

GBM shows fast development, high invasiveness, and apoptosis resistance [107]. As a drug repositioning strategy, alternative treatment approaches should aim to inhibit proliferation and induce cell apoptosis [108, 109]. The inhibition of HMGCR leads to suppression of tumor growth and induction of apoptosis in multiple tumoral cell lines; however, the precise molecular pathways of statins, as potential HMGCR inhibitors, are not well known in GBM [110]. In the following subsections, we have summarized the potential mechanisms and antitumor effects of statins in GBM from both preclinical and clinical studies.

3.1. Insights from preclinical studies

As discussed earlier, the mevalonate pathway is responsible for cholesterol biosynthesis and the formation of the intermediate metabolites GGPP and FPP used in the prenylation of proteins [27]. Notably, mevalonate and GGPP pretreatment cause significant inhibition of statin-induced apoptosis [18], and simvastatin induces cell death via the intrinsic apoptotic pathway in a wide range of human tumor cell lines, including astrocytoma, neuroblastoma, and GBM [111]. For instance, atorvastatin improves the efficacy of TMZ in GBM by suppressing Ras-signaling in a prenylation-dependent way [112, 113]. Herein, cholesterol-lowering statins tend to enhance the clinical results of several malignancies by suppressing the mevalonate pathway that promotes apoptosis inhibition and cellular proliferation [114].

Laboratory evidence indicates that statins are emerging as possible future antitumor agents with pro-apoptotic, anti-proliferative, anti-invasive, radiosensitive, and radioprotective activities in

GBM [115-117]. However, these preclinical studies have included high concentrations of statins in comparison with the clinical plasma concentration utilized as a lipid-lowering agent [118, 119]. For instance, Weiss *et al.* have shown that statins have proangiogenic impacts at low therapeutic doses (nanomolar) but antiangiogenic effects at high doses (micromolar) that are reversed by GGPP [118]. One of the fundamental problems in clinical GBM therapy is the development of TMZ resistance in GBM after continuous treatment with TMZ [108]. Recently, statin therapy has demonstrated an improved anti-GBM effect of TMZ *in vitro*; however, the study used a high-dose of statins compared to clinically therapeutic concentrations [120]; therefore, the antitumor activities of statins against GBM are different from the anti-lipid effects and may rely on its concentration for efficacy [113, 121].

Recently, it has been found that the mevalonate pathway (as a metabolic regulator of autophagy) and basal autophagic flux are inherently connected to cell growth [122]. Autophagy is a catabolic process that recycles degraded proteins and organelles in metabolic stress, such as nutrient deprivation and chemotherapy treatments [123]. In GBM, it has been shown that autophagy inhibition, either at onset or in the late autolysosome fusion process, may improve apoptosis induced by TMZ, indicating that autophagy suppression would strengthen the efficacy of chemotherapy based on TMZ [124]. One problem is the fact that autophagy triggers cell apoptosis and mortality in some other circumstances so that the specific role of autophagy modulators in apoptosis-sensitive tumors needs to be studied [125].

Numerous *in vitro* findings have shown that pitavastatin, cerivastatin, and fluvastatin were the most potent autophagy-inducing agents in human cancer cells, including stem cell-like primary GBM cell lines. In line with this, the knockdown of GGPP synthetase-1 also induces robust cell autophagy and cell death *in vitro* and reduces GBM tumor growth *in vivo*. Simulated models have shown that statins cause autophagy in U251 cells and have been related to an increase in Beclin1, ATGB13, and autophagosomes [126], indicating that statins may trigger cell death by autophagy.

Pharmacologically, lovastatin potentially triggers autophagy induction by Akt/mTOR signaling cascade inhibition. Also, by suppressing lysosomal associated membrane protein-2 and dynein, lovastatin may affect the autophagosome-lysosome fusion machinery. These outcomes indicate that the efficacy of TMZ chemotherapy in GBM cells could be significantly improved by lovastatin. The mechanism can be related to impaired autophagic flux, enhancing apoptosis of the malignant cells; therefore, combining TMZ and lovastatin could be a promising GBM therapy intervention through autophagy mechanism [127]. The combinational strategy between statins and TMZ has shown promise for the treatment of GBM. Simvastatin, a blood-brain barrier permeable statin, also inhibits the autophagy flux induced by TMZ by blocking autophagolysosomal formation [125, 128]. Inconsistent with the previous studies, Oliveira *et al.* have shown that atorvastatin and TMZ treatment increase acidic vesicular organelle (AVO) presence in A172 GBM cells, an indicative of autophagy [129]. Simvastatin (0–50 μM) also was shown to cause the appearance of autophagolysosomal-like intracytoplasmic acidic vesicles in U251 and C6 GBM cells. Mechanistically, the upregulation of the autophagosome-associated LC3-II, pro-autophagic beclin-1, and the downregulation of the selective autophagic target p62 confirm the simvastatin-induced autophagy *in vitro*. Interestingly, simvastatin induces the activation of AMP-activated protein kinase (AMPK) and inhibits the mTOR, a central negative regulator for autophagy and Akt activation. With these notable findings, Misirkic *et al.* have suggested that inhibition of AMPK-dependent autophagic response might sensitize GBM cells to statin-induced apoptotic cell death [130].

Statins have also been shown to suppress tumor growth and boost apoptosis in GBM [131]. In this regard, it has been reported that lovastatin could sensitize GBM cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis [132]. In GBM cell lines, as well as tumor-bearing mice, lovastatin significantly increases the expression of DR5, inducing the extrinsic apoptosis pathway [133]. Much further along, lovastatin treatment could mitigate the ERK/MAPK and nuclear factor-kappa B (NF-κB) pathways. Still, it does activate the Janus kinase (JNK) path, indicating that lovastatin sensitizes TRAIL-induced apoptosis by the DR5 up-regulation through inhibiting NF-κB, but also directly triggers the apoptosis via MAPK pathway dysregulation [134]. Based on previous studies, lovastatin has been reported to induce GBM cell death dose-dependently and to improve short- and long-term cytotoxicity of TMZ. Also, concurrent lovastatin with TMZ behaves synergistically in cell apoptosis, indicating the potential role of lovastatin as a synthetic booster in GBM treatment [127]. Regarding the intrinsic pathway of apoptosis, atorvastatin (10 μM) induces apoptosis of GBM spheroids through caspase-8/-3 activation, downregulating Bcl-2, TRAF3IP2, and interleukin (IL)-17RA expression [135-137].

Human tumors are commonly described by a significant reduction of histone acetylation that is regarded as a global epigenetic indicator for malignancy. Histone deacetylase (HDAC) upregulation is observed in a wide variety of human cancer cells, like colon, stomach, renal, breast, and brain [138, 139]. Recent studies have revealed that statins inhibit HDAC activity and, consequently, increase p21 expression in various cancer cells, including GBM. Interestingly, it has been shown that fluvastatin in combination with valproate sodium, a well-known HDAC inhibitor, effectively induces H2A histone family member X (γ-H2AX) and apoptosis in GBM8401 cells followed by enhanced histone H3 and H4 acetylation. This combination also leads to p21 upregulation, which plays a significant part in the cell cycle and apoptosis [140].

Molecularly, in GBM, there are several main possible targets for modified anti-angiogenesis, anti-invasiveness, and apoptosis-inducing effects, including PI3K/Akt, MMPs activity, and the TGF-β signaling pathway [141, 142]. The PI3K/Akt signaling pathway is involved in the regulation of multiple cellular physiological processes by activating downstream corresponding effector molecules, which serve an essential role in the cell cycle, tumor growth, apoptosis, invasion, migration, angiogenesis, cell proliferation, and chemoresistance [143]. A common phenomenon is over-activation of the pathway that is present in human malignancies and has been implicated in cancer progression; therefore, one of the most critical approaches to the treatment of GBM is rational drug design using molecular targets in the PI3K/Akt signaling pathway [144].

Some studies have found that inhibition of the HMGCR pathway mediates the role of statins to cause apoptosis via downregulation of the PI3K/Akt pathway, the activation of JNK1/2, an increase in the expression of Bax and Bim, and caspases activation on GBM [145, 146]. In line with this, the cytotoxicity of statins (mevastatin, fluvastatin, or simvastatin, 1-20 μM) toward the C6 GBM cells have been evaluated by Yanae *et al.* Statins have been shown to suppress cell proliferation and induce apoptosis in these cells through caspase-3 activation and ERK1/2/Akt inhibition [18]. Furthermore, modulation of lipid rafts, Fas translocation, downregulation of PI3K/Akt, and caspase-3 activation is involved in the antitumor effect of simvastatin in U251 and U87 MG GBM cells, as evaluated by Wu *et al.* [147].

The invasion of cancer is a fundamental determinant of cancer malignancy assessment [148]. Numerous studies have indicated that microglia activated by GBM cells can promote cell proliferation, migration, and invasion through MMPs expression. Besides, the forced expression of HMGCR promotes the growth and migration of GBM cells while the inhibition of HMGCR expression inhibits the growth, migration, and metastasis of GBM cells [149]. Gliemroth *et al.*

have shown that simvastatin (0.2–30 μM) inhibits tumor cell growth and migration, but the invasiveness of the remaining U87 MG cells seems to be unaffected [150]. Some studies have shown that atorvastatin can decrease MMP-2/-14/-9 expression levels and significantly reduce the invasion of cancer cells via the RhoA-JNK-c-Jun-MMP-2 signaling pathway by suppressing MMP-2 activity [151, 152]. Statins have been shown to decrease MMP-2 expression significantly, which can mitigate GBM cell invasion. For instance, simvastatin and atorvastatin have been shown to inhibit proliferation and migration of U251, U87 MG, and U87 MG spheroid cells [135, 147]. The antiproliferative and anti-invasiveness effects of fluvastatin appear to be linked with p-JNK1/2 upregulation, p-ERK1/2 expression reduction, and a decrease in the MMP-9 activity in C6 rat malignant GBM cells [153]. Sundararaj *et al.* have shown that simvastatin can repress lipopolysaccharide-induced expression of MMP-1 in U937 cells by targeting ERK activation through protein isoprenylation [154]. GBM also manipulates membrane type (MT)-1-MMP expression in tumor-related microglial cells, promoting the expansion and invasion of GBM via the toll-like receptor (TLR) signaling pathway. In a study by Yongjun *et al.*, it has been found that atorvastatin suppresses GBM invasion and migration by reducing microglial MT1-MMP expression, which leads to suppression of MMP-2 activity [155].

RhoA activation results in integrin clustering, facilitating focal adhesion (FA) kinase activation (FAK) by tyrosine phosphorylation 397 [156]. FAK signaling cascades govern the invasion and metastasis of cancer cells by regulating MMP expression and the assembly of the focal complex at the leading edge and the disassembly of the FA at the trailing edge of the cell [157, 158]. In a study done on GBM cells, cerivastatin was used to inactivate FAK by disrupting the cytoskeleton, leading to the inhibition of migration [159], suggesting that cerivastatin may be beneficial for combination therapy with conventional anticancer drugs by inhibiting the invasion of GBM.

In the inflammatory pathway of TGF-β, cerivastatin drives the expression of p21 and other tumor suppressors. It acts to curb the cell cycle and stimulates EMT, fostering invasion, metastasis, and possibly treatment resistance [160]. Recently, a probable link has been noted between the statins and TGF-β in various cancer cells. Blockade of the Ras/MEK/ERK and Ras/PI3K/Akt pathways by statins through mevalonate reduces the expression of TGF-β as an angiogenic factor [161]. Xiao *et al.* have found that simvastatin (0–50 μM) affects human GBM cells (U87 MG, U251 MG, and T98G cells) through TGF-β inhibition, inducing angiogenesis inhibition. Other experiments in this study have shown that simvastatin reduces GBM migration and invasion, and induces apoptosis and autophagy, both *in vitro* and *in vivo* [162]. These studies have confirmed that statins are of critical significance for GBM patients undergoing angiogenesis target therapy. For instance, atorvastatin has a potent anti-angiogenic effect against GBM spheroids via downregulating the expression of vascular endothelial growth factor (VEGF) and CD31, as demonstrated in a three-dimensional *in vitro* model [136]. Also, it has been shown that low-dose simvastatin increases necrosis and apoptosis compared to both control and high-dose simvastatin groups, *in vivo*. High-dose simvastatin increases vessel caliber by reducing pericytic cells along the tumor vessel wall compared to both control and low-dose simvastatin groups, demonstrating a dual role for simvastatin in GBM [163]. In the framework of stimulation of the Ras–Raf–MEK–ERK pathway, prenylation by FPP and GGPP is required for the oncogenic activity of Ras and Rho proteins [164]. Another point from the studies on HMGCR inhibitors is that statins reduce the levels of FPP and GGPP and decrease ERK signaling, which mitigate cancer cell migration and proliferation [165]. It has been stated that lovastatin affects H-Ras and Rac1 post-translation modifications and influences the mevalonate and Ras–Raf–MEK–ERK regulation in U343 and U87 MG GBM cells

[164]. Even so, it is necessary for these results to be verified by sufficiently scaled randomized controlled studies and meta-analysis of available data.

4. Observations from clinical studies

An increasing body of preclinical data indicates that statins may have powerful antitumor effects, but their interaction with standard therapy and clinical results in cancer patients is less clear [166]. Recently, in a study involving 303 patients with advanced pancreas adenocarcinoma, Iarrobino *et al.* have demonstrated the impact of statin use on outcomes, and it was found that statin (simvastatin and atorvastatin) usage is correlated with increased OS in affected patients. Statin usage has also been reported to have been associated with significantly reduced all-cause mortality, mainly by lowering the risk of distant metastases before or during diagnosis [167]. Furthermore, in patients undergoing radiation therapy, surgery, and chemotherapy, statin treatment is correlated with a 2-year increase in the OS of patients, suggesting that statins may work to improve outcomes for advanced-stage pancreatic cancer interventions [168]. In another study, Lin *et al.* have shown the efficacy of statin use in a large cohort of patients with stage IV non-small-cell lung cancer. In the statin group, median survival was seven months compared to four months in non-statin patients. Also, statin use was associated with improvement in OS and lung cancer-specific survival [169]. Conversely, Omori *et al.* have found that OS was not improved; however, they did show that statins improve OS in patients previously treated with nivolumab for advanced non- small cell lung cancer [170].

Although some findings have shown that statin use has a possible chemical-preventative impact on the treatment of cancer, the effects of statins on the prognosis of GBM have yet to be examined. Gaist *et al.* and Chen *et al.* have shown that long-term prediagnostic statin use may improve the survival of GBM patients and reduce the risk of brain cancer [21, 171]. Also, for patients with GBM who were taking a statin for >1 year, a significant enhancement in OS was observed. Although based on limited statistical precision, the probable chemoprevention impact was restricted to lipophilic statin consumers. This may be explained by the biochemical properties of lipophilic statins, with their higher capacity than hydrophilic statins, to cross the blood-brain barrier [172]. Conversely, the use of perioperative statins is not associated with improvement in progression-free survival (PFS), and mortality was similar between both groups of GBM patients [114]. In line with this finding, a secondary analysis of two large GBM trials was unable to detect evidence for an association of the use of statins with outcomes in patients with newly diagnosed GBM [173]. A study by Seliger *et al.* has shown that the use of statins was unrelated to OS or PFS of GBM patients [174], and the use of statins was not associated with the risk of GBM [175]. Furthermore, Cote *et al.* have found a borderline increased risk of GBM with statin use [176]. A phase II study of atorvastatin in combination with radiotherapy and TMZ in patients with GBM is ongoing (NCT02029573) [177].

Lovastatin with and without radiation therapy has been well-tolerated in phase I/II trial of 18 patients with malignant GBM, and a marginal effect on tumor development has been reported thus far [178]. A case-control study has shown the risk of GBM among statin users, stating that simvastatin therapy for more than six months was inversely associated with glioma risk [179]. In Table 4, we summarized recent combinational therapies-based statins affecting GBM in both preclinical and clinical studies.

Concluding remarks

Statins have non-lipid-related effects, widely recognized as pleiotropic drugs, exert anti-inflammatory, immunomodulatory, and antioxidant activities [180-184]. During the past few years, a plethora of evidence has shown that statins activate apoptosis and inhibit cell growth of various types of malignant cells *in vitro* and *in vivo*. Statins display such effects in humans, which increase the prospects for their potential future effectiveness in preventing and/or treating some malignancies. These outcomes are gaining interest in the treatment of cancer; therefore, preclinical findings from antitumor activities of statins require special consideration as a possible therapeutic strategy.

Standard anticancer treatment for GBM, one of the deadliest and most invasive brain cancers, remains unreliable. The impact of statins on GBM, a group of mainly unknown etiological brain tumors, is a field of inquiry that needs special attention [185]. In this review, we highlighted a variety of new hypotheses regarding the potential re-targeting of statins for GBM patients. In this regard, we showed that targeting the mevalonate pathway, and consequently GTPases (Rho, Rac1, Ras), could be a potential target for treating GBM through autophagy, apoptosis, and metastasis modulation. Statins could help to improve this situation by regulating several signaling pathways, including: (1) potentiating the anti-GBM activity of chemotherapeutic drugs, (2) activating the intrinsic and extrinsic apoptosis pathways, (3) autophagy modulation, (4) EMT outgrowth and metastatic behavior regulation, (5) the destruction of angiogenic blood vessels, and (6) TGF-β modification (see Fig. 3). In light of the generally positive results from statin use in GBM in preclinical and small-scale clinical studies, larger-scale prospective clinical findings are much needed. The lack of financial benefit from performing major randomized controlled trials (RCTs) may be a significant reason for the current lack of studies with this focus. It is our intent that this review will act as a catalyst for others to concentrate on this emerging and essential issue.

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Conflicts of Interest

The authors declare no conflict of interest.

Table 1. Apoptosis-inducing impacts of statins in various cancer cells.

Statin (s)	Type of study	Dose of administration	Primary mechanism (s)	Reference
Simvastatin	*In vitro* (HT-29 cells)	2.5–20 µM	1- Apoptosis-inducing effects via caspase-3 activation 2- Inhibiting IGF- 1- induced ERK and Akt expression via the downregulation of IGF- 1R expression and pro-apoptotic ERK activation	[186]
Simvastatin-loaded emulsomes	*In vitro* (MCF-7 cells)	0.1, 1, 10, 100, 1000 µM	1- An increase in early and late apoptosis 2- An increase in caspase-3 and Bax	[187]
Atorvastatin, fluvastatin and simvastatin	*In vitro* (A20 and EL4 cells)	0–5 µM	1- DNA fragmentation 2- Activation of pro-apoptotic members, like PARP, caspase-3, and Bax 3- Suppressing the activation of Bcl-2 4- Promoting intracellular ROS generation 5- Regulating Akt, ERK and p38 MAPK signals via inhibition of the mevalonate pathway	[188]
Atorvastatin, pravastatin, lovastatin, and simvastatin	*In vitro* (rat vascular smooth muscle cells)	0–100 µM	Inducing apoptosis	[189]
Simvastatin	*In vitro* (human leiomyoma cells)	0–10 µM	1- An increased expression of Bim	[190]
			2- Increased Bim_{EL} activity and mitochondrial leakage of apoptosis-initiating proteins, such as cytochrome c 3- Decreased ERK activation 4- Calcium-dependent apoptosis	
Simvastatin and fluvastatin	*In vitro* (PC3 cells)	0–20 µM	1- A decrease in cell proliferation 2- Inducing cell apoptosis via downregulation of AKT/FOXO1 phosphorylation	[191]
Simvastatin	*In vitro* (HCT116 cells) *In vivo* (tumor xenograft model)	0–50 µM	1- Suppressing survivin expression through activating p38 MAPK and p53 2- Inducing cell apoptosis through activating p38 MAPK 3- Suppressing survivin expression and tumor growth in the xenograft tumor model	[192]
Lovastatin and atorvastatin	*In vitro* (Hey 1B and Ovcar-3 cells)	0–20 µM	1- Activation of JNK 2- Enhancement of Bim expression 3- Suppressed anchorage-independent growth	[193]
Simvastatin	*In vitro* (Daoy, D283, and D341 cell lines)	0.5–20 µM	1- Inducing caspase-dependent apoptosis via the mevalonate pathway	[194]
Atorvastatin, rosuvastatin, pravastatin, and simvastatin	*In vitro* (MCF-7, MDA-MB-231, SF-295, DU-145, and DU-145 cells)	0–60 µM	1- Suppressing micrometastasis outgrowth 2- Inhibition of PI3K signaling through Akt 3- A decrease in EGF-mediated phosphorylation of Akt	[11]
Fluvastatin and pravastatin	*In vitro* (Huh-7 and HepG2)	Fluvastatin: 0–50 µM Pravastatin: 0–500 µM	1- Inducing apoptosis 2- A breakdown of the MMP 3- Caspase activation and nuclear degradation	[70]
Simvastatin	*In vitro* (MCF-7, T47D, MDA-MB-231, and BT-549) *Clinical study*	0–50 µM	1- Inhibiting MAPK/ERK pathway by dephosphorylating sequential cascades, like ERK1/2 and MEK1/2 2- Deactivating PI3K/Akt/mTOR	[71]

Fluvastatin	*In vitro (PCa cells) Clinical study (NCT01992042)*	In vitro: 0.0–1.1 µM Clinical trial: 80 mg for 4–12 weeks	1- Inducing cell death, dose- and time- dependently 2- An increase in caspase-3 activity	[195]
Simvastatin, pravastatin, mevastatin and lovastatin	*In vitro* (Human embryonic stem cells (hESC) (HES3), karyotypically abnormal hESC (BG0IV), embryonal carcinoma (NTERA-2), ovarian (TOV-112D) and colorectal cancer (HT-29) cells)	0–20 µM	1- Inhibiting cell proliferation via an increase in the activity of apoptotic genes 2- Inhibition of stemness-related genes on chromosomes 12 and 17	[196]
Atorvastatin	*In vitro* (MCF-7 cells)	0–80 µM	Induction of both apoptosis and autophagy	[197]
Simvastatin	*In vitro* (UMR-106)	0–10 µM	Inducing apoptosis	[198]
Simvastatin and atorvastatin	*In vitro* (LU1205, WM9, WM35, WM164, WM793, WM852 [58], FEMX, LOX, HHMSX A375 and HTB-11 cells)	20–40 µM	1- Increased TRAIL-induced apoptosis 2- Suppression of the NF-κB and STAT3-transcriptional targets (including COX-2) 3- Downregulation of cFLIP-L protein level	[199]
Simvastatin, lovastatin, and pravastatin	*In vitro* (OE33 and BIC-1 EAC cells)	0–100 µM	1- Inhibition of Ras farnesylation 2- Inhibition of the ERK and Akt signaling pathways	[200]
Simvastatin	*In vitro* (SNU-245)	0–500 µM	1- G1 phase cell cycle arrest 2- Inducing apoptosis via caspase-3 activation, 3- Downregulation of Bcl-2 expression and enhancement of Bax expression 4- Suppressing IGF-1R expression and IGF-1-induced ERK/Akt activation	[201]
Simvastatin	*In vitro* (MCF-7 and MDA-MB 231 cells)	0–200 µM	Inducing apoptosis via involvement of JNK independent of their ER or p53 expression status	[56]
Simvastatin	Clinical study	0–120 µM	Apoptosis initiating by the mitochondrial caspase-9, which indirectly leads to activation of caspase-3/-8	[202]
Simvastatin	*In vitro* (AXT, Saos2, and U2OS cells) *In vivo*	0–5 µM	1- Inducing apoptosis via activation of AMPK and p38 MAPK 2- Inhibiting migration	[203]
Simvastatin	*In vitro* (MNNG/HOS osteosarcoma cells)	0–64 µM	Apoptosis induction through inactivation of PI3K/Akt signaling pathway	[204]
Atorvastatin	*In vitro* (HCC cells)	0–40 µM	1- Inducing cell growth inhibition and G0/G1 phase cell cycle arrest, leading to senescence 2- A decrease in tumor growth in mouse xenograft models 3- A reduction in the IL-6, p-STAT3, and hTERT levels 4- An increase in β-gal expression in tumor sections	[205]
Lovastatin	*In vitro* (Fadu hypopharyngeal carcinoma cells)	0–50 µM	cell death via AMPK-p63-survivin signaling cascade	[206]
Lovastatin	*In vitro* (MCF-7 cancer cells)	0–50 µM	1- The p53 activation 2- Cell death via LKB1-AMPK-p38MAPK-p53-survivin signaling cascade	[207]

Atorvastatin	*In vitro* (K562 and HL60 cells)	0–80 µM	1- Inducing apoptosis via an increase of ROS and Bax/Bcl-2 ratio, loss of MMP 2- Activation of Bax/Caspase-9/Caspase-3/PARP pathway	[10]
Simvastatin	*In vitro* (MDA-MB-231 cells)	0–5 µM	Cell death through oxidative stress upregulating miR-140-5p	[208]
Pitavastatin	*In vitro* (SCC15 and SCC4 cells)	0–0.5 µM	1- Suppressing cell proliferation 2- Inducing intrinsic apoptosis in a FOXO3a-dependent manner 3- Inducing the nuclear translocation of FOXO3a via dual regulation of two upstream kinases, AMPK and Akt, resulting in the up-regulation of PUMA	[209]
Simvastatin	*In vitro* (ER-positive (MCF-7, T47D) and ER-negative (MDA-MB-231, BT-549) breast cancer cells)	0–50 µM	1- Inducing apoptosis and inhibiting proliferation 2- Suppressing PI3K/Akt/mTOR pathway via PTEN upregulation and dephosphorylating downstream cascades including Akt, mTOR, p70S6K, S6RP, and 4E-BP1 3- Inhibiting MAPK/ERK pathway by dephosphorylating sequential cascades such as c-Raf, MEK1/2, and ERK1/2	[71]
Encapsulation of Lovastatin in Zein Nanoparticles	*In vitro* (HepG2 cells)	0–30 µM	1- Induction of apoptosis via caspase-3 activation 2- Inducing a significant cell accumulation in the G2/M and pre-G phases	[210]
Simvastatin	*In vitro* (LipPD1 cells)	0–10 µM	1- Inducing PTEN transcriptional upregulation by increasing PPAR-γ expression 2- Reducing cell viability and inducing apoptosis 3- An increase in the mRNA expression of cellular PTEN 4- Inhibition of the phosphorylation of Akt and downstream targets of mTOR and 4E- BP- 1	[211]
Atorvastatin	*In vitro* (HepG2 hepatocellular carcinoma cells)	0–30 µM	1- Increasing activities of caspases-9, -3 and -7 2- An increase in protein expression of pGSK3, p53, and Mdm2 3- A decrease in protein expression of PI3K, p-AKT, and AKT 4- Modulating expression of miR-145	[212]
Simvastatin-alpha lipoic acid nanoparticles	*In vitro* (breast carcinoma cell lines MCF-7)	0–50 µM	1- DNA fragmentation 2- Inducing cell death	[213]

Table 2. The effects of statins on the cell cycle of multiple cancerous cells.

Statin (s)	Cell line	Dose of administration	Main finding (s)	Reference
Pravastatin and fluvastatin	Hepatocellular carcinoma cells	Fluvastatin: 0–50 µM Pravastatin: 0–500 µM	G1/S cell cycle arrest	[70]
Simvastatin	Hepatocellular carcinoma cells	0–20 µM	G0/G1 arrest by inducing p21 and p27 accumulation through inhibition of STAT3/SKP2 axis and activation of AMPK	[214]
Fluvastatin and simvastatin	Human acute promyelocytic leukemia cells	0–100 µM	1- Cell cycle arrest at G1 phase via p27 upregulation 2- Inhibition of Ras/ERK and Ras/mTOR pathways	[58]
Fluvastatin and pitavastatin	Vascular smooth muscle cells	0–10 µM	Suppressing the protein expressions of cyclin D1 and CDK4, but inducing p27	[215]
Fluvastatin and Simvastatin	Jurkat and CCRF-CEM cells	0–200 µM	1- Arresting in G1 phase through inhibition of the Akt pathway 2- Upregulation in p21 and p27 protein expression 3- Downregulating in cyclin D1	[216]
Simvastatin	HC15 cells	0–25 µM	Inducing the arrest of the cell cycle in the G1/S phase through downregulation of cyclin A	[217]
Simvastatin	MCF-7 cells	0–1000 µM	Inducing cell cycle arrest and apoptosis	[218]
Pravastatin	Multiple myeloma cells	0–0.9 µM	Arrest in the G0/G1 phase of the cell cycle	[219]
Atorvastatin calcium	Vascular smooth muscle cells	0–10 µM	G0/G1 cell cycle arrest and suppression of the PDGFRβ-Akt signaling cascade	[220]
Simvastatin	MNNG/HOS osteosarcoma cells	0–64 µM	G0/G1 phase arrest via down-regulation of cyclin D1, CDK2, CDK4 as well as up-regulation of p21 and p27	[204]
Simvastatin	THP1 cells	0–100 µM	Cell cycle arrest	[221]
Lovastatin	Sphere-forming cells derived from the 5-8F and 6-10B NPC cells	0–10 µM	Cell cycle arrest at the G2/M phase	[222]
Lovastatin	Fadu hypopharyngeal carcinoma cells	0–50 µM	Sub-G1 peak apoptosis	[206]
Simvastatin	T47D breast cells	0–50 µM	Decrease in the cyclin D1 expression, inducing apoptosis	[223]
Pitavastatin	Huh-7 and SMMC7721 cancer cells	0–20 µM	Inhibiting growth and colony formation Inducing arrest at the G1 phase Promoting caspase-9/-3 cleavage	[224]

Table 3. Combinational strategies with statins in various cancer models.

Combination regimens	Type of study	Main effect (s)	Reference
Pravastatin + sorafenib	*Phase III, multicenter study*	Did not improve OS in the affected population	[225]
Pitavastatin and fluvastatin + erlotinib	*In vitro*	1- Synergistically enhanced cytotoxicity compared to pitavastatin monotherapy 2- Induction of alternative regulated cell death pathways	[226]
Statins + metformin	*Clinical study*	No beneficial effect was observed for dual users	[31]
Low-dose mixed micellar simvastatin + alendronate sodium	*In vitro*	1- Inhibiting the cell growth	[227]
		2- Inhibiting the cell multiplication in the S phase and resulted in high % of late apoptotic and necrotic cells	
Simvastatin/fluvastatin + everolimus	*In vitro* *In vivo* *Clinical study*	1- An improve in PFS of patients treated with everolimus 2- Showing the combined effect *in vitro* and *in vivo* assays 3- Impeding the prenylation of KRAS or Rac1 to sensitize cells to mTOR inhibition with RB protein activation 4- Enhancing the efficacy of an mTOR inhibitor in vivo	[228]
Mevastatin + LBH589	*In vitro* *In vivo*	1- Cell cycle arrest in the G2/M phase and induced corresponding expression changes of proteins regulating the cell cycle 2- An increase in apoptosis both *in vitro* and *in vivo*, and reduced tumor volumes in xenografted mice	[229]
Simvastatin + celecoxib	*In vitro*	A significant reduction in tumor cell viability, proliferation, and secretion of IL-6 and IL-8	[230]
Pitavastatin + dacarbazine	*In vitro*	1- G1 cell cycle arrest 2- Activating apoptosis via an increase in the levels of active caspase-3 and cleaved PARP and release of cytochrome c 3- Autophagy induction	[231]
Simvastatin + doxorubicin	*In vitro*	1- A decrease in the colony- forming ability of cells 2- An increase in ROS levels 3- A drop in expression of the cell cycle regulatory protein, including CDK2, CDK4, and CDK6 4- Inducing expression of the cyclin- dependent kinase inhibitor p21, increased cytochrome c and caspase-3 expression and reduced cyclin D1 expression	[232]
Fluvastatin + ALA and EA in an NLC[1] formula	*In vitro*	A significant increase in pre-G1 phase, inducing cell death	[233]
Simvastatin + herceptin-conjugated liposomes co-loaded with doxorubicin	*In vitro* *In vivo*	1- A potent proliferation inhibition of cancer cells 2- A synergistic anti-angiogenesis effects	[234]
Pitavastatin + doxorubicin	*In vitro*	1- Increasing levels of p53 and the cell cycle regulator p21 2- Inducing apoptosis via activation of caspase-9, caspase-7 and the reduction of Bcl-2 level	[235]
Lovastatin + cisplatin	*In vitro and in vivo*	1- Sensitizing the cells to cisplatin-induced apoptosis and suppressed the activation of CHK1, CHK2, and H2AX during DNA damage response 2- Promoting the therapeutic efficacy of cisplatin, and significantly prolonged the survival times of tumor-bearing mice	[236]
Atorvastatin + nobiletin	*In vitro* *In vivo*	1- Synergistically inducing extensive cell cycle arrest and apoptosis 2- A decrease in colonic tumor incidence and multiplicity	[237]
Atorvastatin + cyanidin-3-glucoside	*In vitro*	1- Exhibiting a synergistic effect in inhibiting proliferation and migration by enhancing cell cycle arrest 2- A decrease in MAPK activity by attenuating the expression of p-p38, p-ERK1/2, and p-JNK 3- Modulating the PI3K/Akt pathway and upregulating p21Cip1	[238]

Troglitazone + lovastatin	*In vitro and in vivo*	1- Tumor regression in a mouse xenograft model 2- Cell cycle arrest at the G0/G1 phase, as evidenced by the induction of cyclin-dependent kinase inhibitors, p21cip and p27kip, and the reduction of hyperphosphorylated retinoblastoma protein (pp-Rb)-E2F1 signaling	[239]
Simvastatin + metformin	*In vitro*	1- Apoptosis induction 2- The mTOR pathway inhibition	[240]
Simvastatin + irinotecan	*In vitro*	1- A significant inhibition of cell growth 2- A remarkable increase in the percentage of apoptotic cells and those accumulated at the G0/G1 phase 3- Caspase-independent apoptosis	[241]
		4- Upregulation of GRP-78 level and downregulation of Mcl-1 levels in a time-dependent manner	
Simvastatin + bergamottin	*In vitro*	1- Apoptosis induction by TNF 2- Down-regulation of various gene products that mediate cell proliferation (cyclin D1), cell survival (cIAP-1, Bcl-2, Bcl-xL, and Survivin), invasion (MMP-9) and angiogenesis (VEGF), regulated by NF-κB 3- Producing TNF-induced cell-cycle arrest in S-phase 4- inhibiting TNF-induced NF-κB activation, IκBα degradation and p65 translocation to the nucleus	[242]
Simvastatin + paclitaxel lipid nano emulsions	*In vivo*	1- Tumor-growth inhibition 2- An increase in the expression of p21 3- A decrease in the expression of cyclin D1	[243]
Simvastatin+ pentoxifylline	*In vitro*	1- An increase in ERK1/2 and Akt activation 2- Suppression of the NF-κB pathway 3- Arrest at the G0/G1 phase 4- Attenuating colony-forming ability 5- Induction of autophagy	[244]
Simvastatin + tamoxifen	*In vitro* *In vivo*	1- Inhibiting the increase in oxidative stress markers, LDH, and NF-κB 2- A decrease in the total apoptotic ratio, caspase-3 activity, and glucose uptake, without a significant change in Bax/Bcl-2 ratio 3- Exerting antagonistic effects	[245]
Simvastatin + IR	*In vitro*	1- A decrease in G2/M arrest and DNA damage 2- MDM2 suppression 3- Accumulation of the FOXO3a, E-cadherin, and p21 tumor suppressor proteins, which are downstream factors of MDM2	[246]
Atorvastatin + IR	*In vitro*	Enhancing radiosensitivity HIF-1α inhibition	[247]
Atorvastatin + metformin	*In vitro*	1- Cell growth inhibition and apoptosis induction 2- Inhibiting cell migration and the formation of tumor spheres 3- Potent inhibitory effect on NF-κB activity and caused substantial decreases in the expression of its downstream antiapoptotic gene Survivin 4- Reduction in the levels of phospho-Akt and phosphor-ERK1/2	[248]
Atorvastatin + caffeine	*In vitro*	1- Cell growth inhibition and apoptosis induction 2- Inhibiting invasion, migration, and the formation of tumor spheres 3- Downregulating phospho-ERK1/2, phospho-Akt, Bcl-2 and Survivin protein levels	[249]
Simvastatin + receptor-interacting protein 140	*In vitro*	Inhibition of cell proliferation and survival, through the Wnt/β- catenin signaling pathway	[250]
Simvastatin + oxicam derivates	*In vitro*	1- Inducing apoptosis through a caspase-3-dependent pathway upregulated Bax expression, and down-regulated Bcl-2 expression reduced expression and activity of COX2	[251]
Simvastatin + tamoxifen	*In vitro and in vivo*	1- An increase in the apoptotic and necrotic cell death 2- A decrease in VEGF and MMP-2/-9	[252]

Fluvastatin + vorinostat	*In vitro and in vivo*	1- A robust apoptosis induction and inhibiting cancer growth 2- Enhancing vorinostat- induced histone acetylation 3- Inducing ER stress 4- Inhibiting the mTOR pathway and AMPK activation	[253]
Pitavastatin + gemcitabine	*In vitro and in vivo*	1- Synergistically suppression of the cell proliferation through sub-G1 and S-phase cell cycle arrest 2- Apoptosis induction 3- Autophagy induction 4- Inhibition of tumor growth	[254]

[1] Nanostructured lipid carrier

Table 4. Combinational therapies-based statins in GBM.

Combinational therapy	Type of study	Dose of administration	Main mechanism (s)	Reference (s)
Atorvastatin + TMZ	*In vitro*[1] *In vivo*[2]	5, 10, and 20 μM	1- A dose-dependent cell proliferation inhibition 2- Inhibition of protein prenylation 3- Suppressing the Ras activation, leading to decreased activation of Ras and its downstream signaling pathways, including ERK, rS6, and eIF4E	[113]
Atorvastatin + TMZ	*Clinical trial*[3]	Maintenance dose: 80 mg PO daily until disease progression or unacceptable toxicity Loading dose: 40 mg PO daily for the first 21 days)	-	-
Atorvastatin + Biochanin A	*In vitro*[1]	-	1- Reduced invasion 2- A decrease in glycolytic activity 3- An increase in mitochondrial respiration	[255]
Lovastatin + TMZ	*In vitro*[1]	0–20 μM	1- Enhancing the cytotoxicity of TMZ 2- An increase the TMZ-induced cellular apoptosis 3- Impair the autophagic flux via the inhibition of the Akt/mTOR signaling pathway 4- Suppression of autophagosome-lysosome fusion machinery	[127]
Fluvastatin + celecoxib	*Clinical trial*[4]	Escalation dose: Level 1: 2mg/kg/day. Level 2: 4mg/kg/day. Level 3: 6mg/kg/day. Level 4: 8mg/kg/day.	-	-
Simvastatin + fenretinide[5]	*In vitro*[1] *In vivo*[2]	0–20 μM	1- Repolarizing the tumor-associated macrophages from the M2 phenotype to M1 via regulating the STAT6 pathway 2- Inducing the ROS-mediated mitochondrial apoptosis by inhibiting the Ras/Raf/p-ERK pathway	[256]
Lovastatin + gefitinib	*In vitro*[1]	Lovastatin: 0–25 μM Gefitinib: 0–25 μM	1- Enhancing the sensitivity of GBM cells to the EGFR kinase inhibitor gefitinib 2- Inducing potent synergistic cytotoxicity, irrespective of EGFRvIII and PTEN status	[257]
Lovastatin + IR	*In vitro*[1]	Lovastatin: 5–50 μM IRR: 4 Gy	1- A decrease in clonogenicity and cell number 2- Inducing cell cycle arrest	[258]
Atorvastatin or lovastatin + pioglitazone	*In vitro*[1] *In vivo*[2]	*In vitro*: Lovastatin: 5 μM Atorvastatin 1.5 μM pioglitazone: 5 and 40 μM *In vivo*: Atorvastatin: 40 mg/kg Lovastatin: 50 mg/kg Pioglitazone: 5 mg/kg	1- A marked increase in caspase 3 activity 2- Significant reduction in tumor volume by approximately 40%	[16, 259]
Pitavastatin + irinotecan	*In vitro* *In vivo*	*In vitro:* Pitavastatin: 0–10 μM Irinotecan: 0–10 μM *In vivo:* low dose of pitavastatin: 0.5 mg/kg Irinotecan: 0.5–5 mg/kg	1- Inducing cell death 2- Inducing autophagy 3- Suppression of MDR-1 4- Enhancing antitumor efficacy 5- Lowering the IC_{50} values for irinotecan by 40- to 70-fold 6- Arresting in the G0/G1 phase	[131]

[1]A172, T98G, DBTRG, MO59 J, U118, LN 405, LN443, Stem cell-like GBM, rat RG II, U87 MG, and U251 GBM

cells

[2]Subcutaneous injection of GBM cells (xenograft mouse model)

[3]A phase II of a clinical trial (NCT02029573)

[4]A phase I of a clinical trial (NCT02115074)

[5]The drugs were co-encapsulated into a TPGS-TAT-embedded lactoferrin nanoparticle system

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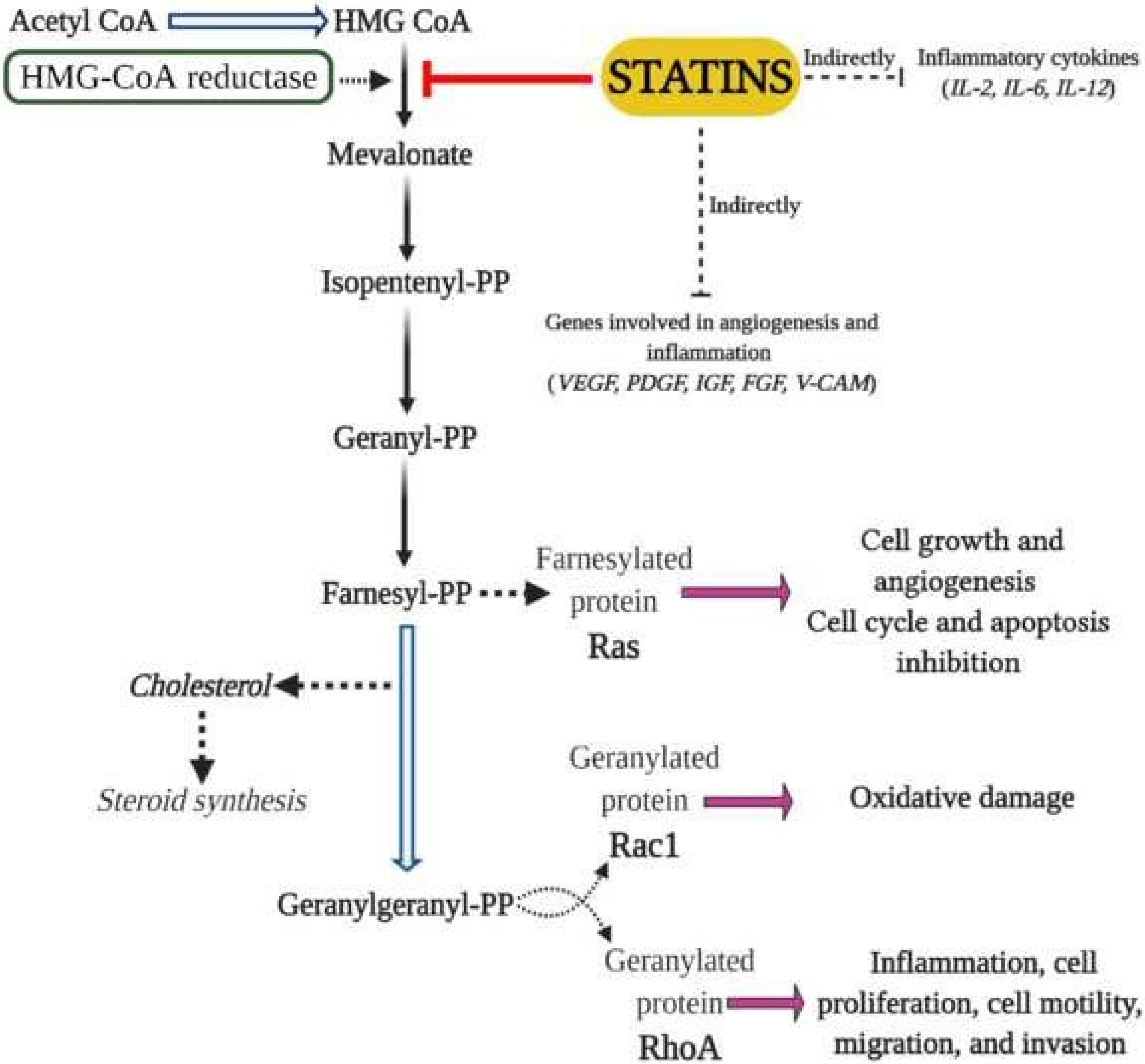
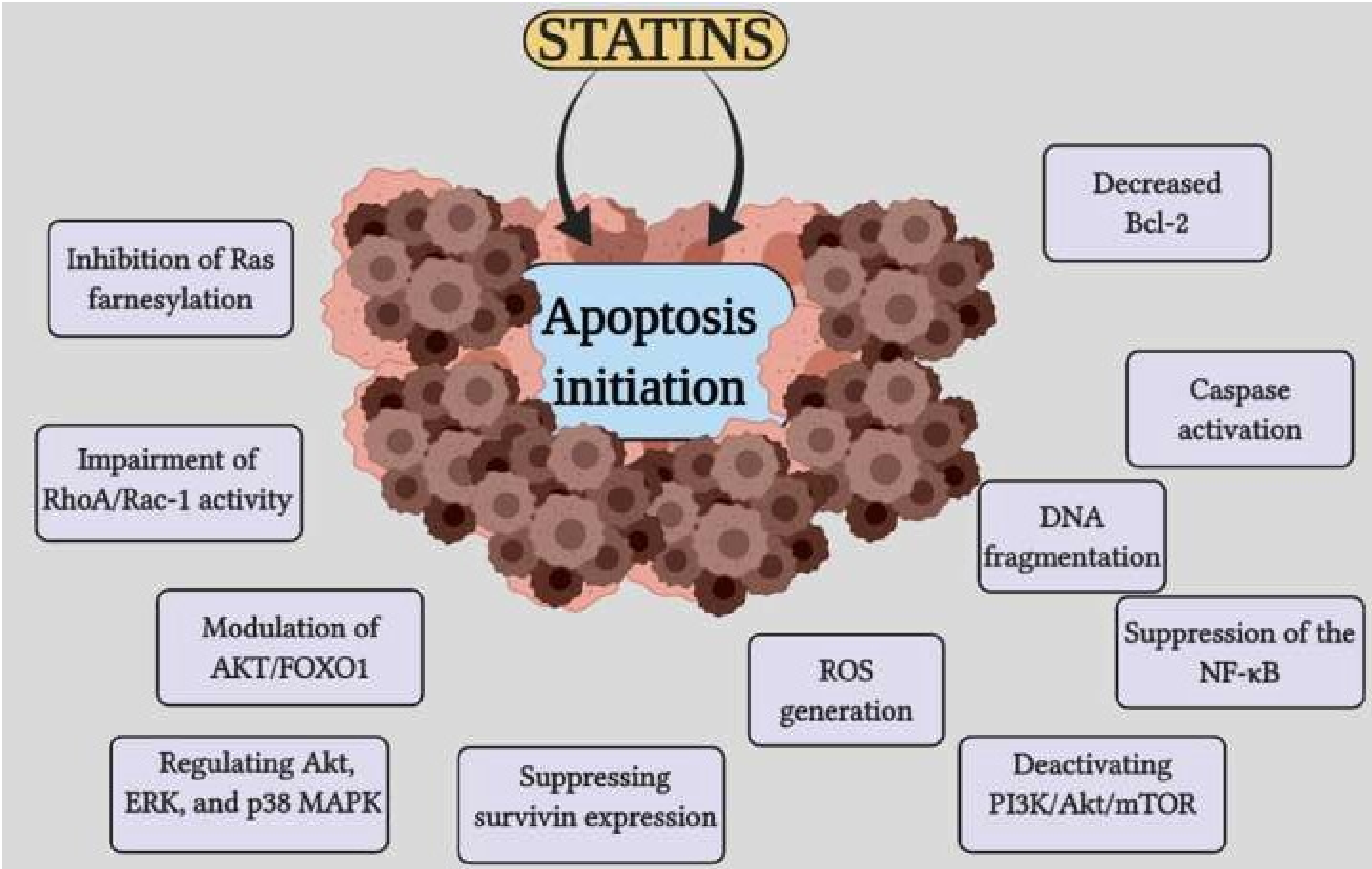
Figure legends

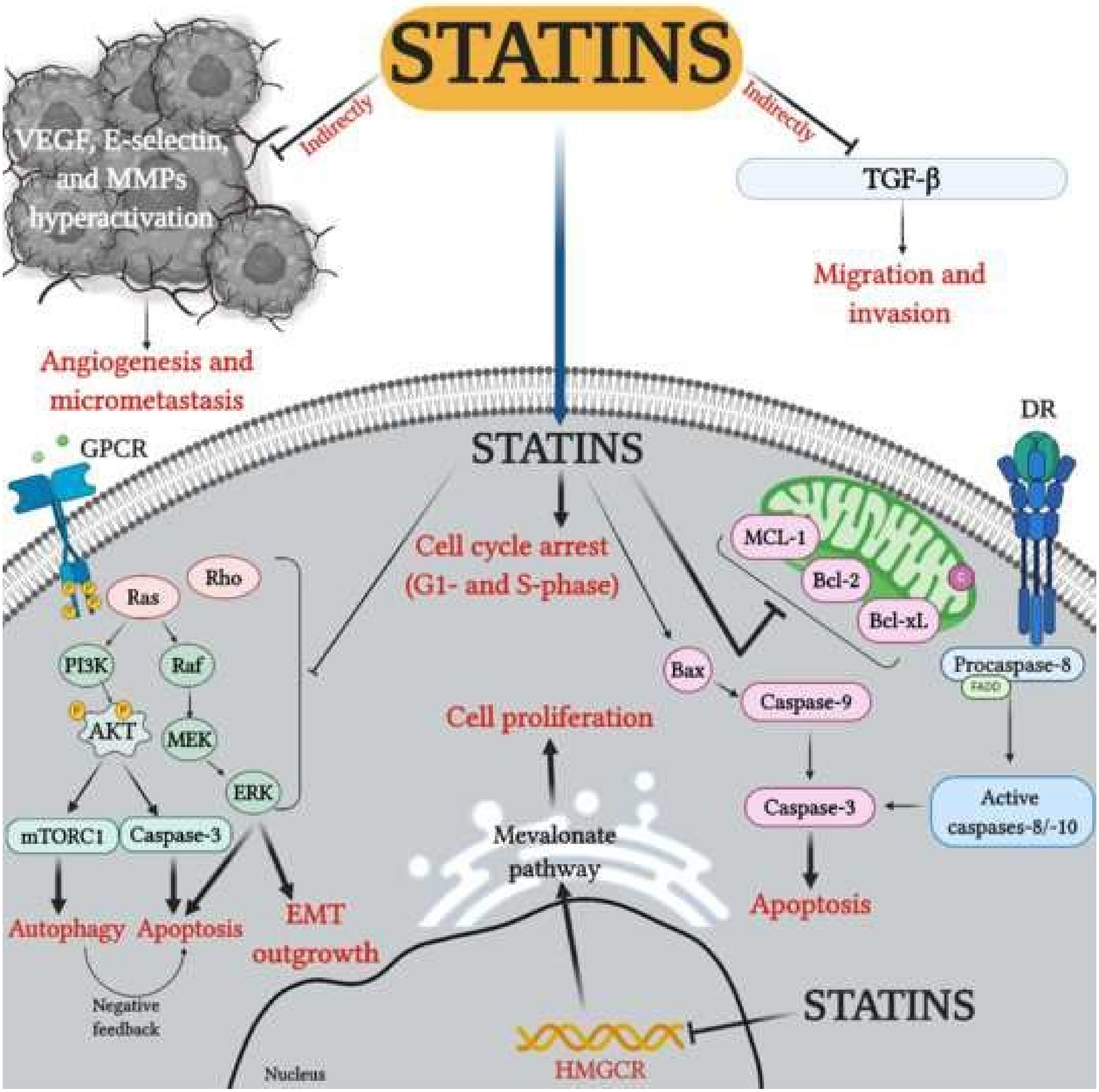
Figure 1. The mechanism of action of statins in cancer. Downstream products of the mevalonate pathway are essential for the prenylation of cellular proteins Ras, Rho, and Rac1, as small GTPases, which are critical for regulating cell growth and the cell cycle, angiogenesis, apoptosis, oxidative damage, invasion, and survival.

Figure 2. Potential apoptosis-inducing effects of statins in cancer.

Figure 3. The schematic representation of molecular mechanisms of statins in GBM.


Acetyl CoA
HMG CoA
HMG-CoA reductase
STATINS
Indirectly
Inflammatory cytokines
(IL-2, IL-6, IL-12)
Mevalonate
Indirectly
Isopentenyl-PP
Genes involved in angiogenesis and inflammation
(VEGF, PDGF, IGF, FGF, V-CAM)
Geranyl-PP
Farnesyl-PP
Farnesylated protein
Ras
Cell growth and angiogenesis
Cell cycle and apoptosis inhibition
Cholesterol
Steroid synthesis
Geranylated protein
Rac1
Oxidative damage
Geranylgeranyl-PP
Geranylated protein
RhoA
Inflammation, cell proliferation, cell motility, migration, and invasion


STATINS
Apoptosis initiation
Inhibition of Ras farnesylation
Impairment of RhoA/Rac-1 activity
Modulation of AKT/FOXO1
Regulating Akt, ERK, and p38 MAPK
Suppressing survivin expression
ROS generation
Deactivating PI3K/Akt/mTOR
Decreased Bcl-2
Caspase activation
DNA fragmentation
Suppression of the NF-κB



STATINS
Indirectly
Indirectly
VEGF, E-selectin, and MMPs hyperactivation
TGF-β
Migration and invasion
Angiogenesis and micrometastasis
DR
GPCR
STATINS
Cell cycle arrest (G1- and S-phase)
MCL-1
Bcl-2
Bcl-xL
Rho
Ras
PI3K
Raf
AKT
MEK
ERK
Bax
Caspase-9
Procaspase-8
FADD
Cell proliferation
Caspase-3
Active caspases-8/-10
mTORC1
Caspase-3
Mevalonate pathway
Autophagy
Apoptosis
EMT outgrowth
Apoptosis
Negative feedback
STATINS
Nucleus
HMGCR