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Review Article

Application of statins in management of glioma: Recent advances

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Abstract

Gliomas are common primary intra-cerebral tumors in adults, and seriously threaten the health and life of affected patients, especially highly-malignant gliomas, such as glioblastoma multiforme. The clinical prognosis of glioma patients is poor, even for those who have received comprehensive treatment including surgery and concurrent chemo- and/or radio-therapy. As a structural analog of β-hydroxy-β-methylglutaryl coenzyme A (HMG CoA) reductase, statins are a restrictive enzyme in the metabolism of cholesterol. Recent laboratory studies and clinical trials have demonstrated that statins can exert anti-tumor effect, improve clinical prognosis and significantly prolong the survival time of glioma patients. This article is aimed to highlight the mechanisms of the anti-glioma effect of statins and review recent advances in the management of the disease.

Keywords: *Glioma, Glioblastoma multiforme, Intra-cerebral tumors, Statins, Prognosis, Survival time, β-Hydroxy-β-methylglutaryl coenzyme A (HMG CoA) reductase*

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INTRODUCTION

As a type of intra-cerebral neoplasm, gliomas are derived from the glial cells of the brain or the spine. According to the World Health Organization (WHO), gliomas can be classified into four malignancy grades I-IV [1-3]. Malignant gliomas are classified as a type of grade IV tumor, which are the most aggressive and highly-invasive tumors of the central nervous system with an annual incidence rate of approximately 0.03 - 0.05 % worldwide [4,5]. As the most common type of malignant glioma, glioblastoma multiforme (GBM) is another category of glioma, accounting for 30 % of primary brain tumors [6]. Despite recent advancements in the treatment of GBM, the clinical prognosis of GBM patients remains poor. Following the standard-of-care treatment, such as surgical resection and chemo- or radio-therapy, GBM patients obtain a median survival of 15 months. The 5-year survival rate merely achieves 3.3 % [7,8].

Statins are common prescription drugs to lower the serum level of lipid, treat dyslipidemias and prevent cardiovascular diseases [9]. In addition, statins have been proven to exert multiple biological functions including anti-inflammation

[10], anti-oxidant [11,12], angiogenic and vascular protection [13,14], and anti-cancer effects [15-19]. Previous studies have indicated the potential chemo-preventive role of statins upon the risk of malignant tumors and statins can reduce the mortality rate of cancer patients and the incidence rate of gliomas [15-22]. Previous laboratory studies have demonstrated that statins can exert anti-tumor effect through inhibiting the growth, cellular proliferation and migration by inducing cellular apoptosis [15,18,23-26]. In this article, we summarized the most recent studies related to the role of statins in gliomas, aiming to unravel the potential mechanism underlying the anti-glioma effect of statins.

EFFECT OF STATINS ON GLIOMA CELL PROLIFERATION

As a type of primary intra-cerebral tumor, the clinical prognosis of patients diagnosed with gliomas is still poor mainly due to the alarmingly high proliferation rate of glioma cells. How to suppress and prevent the rapid proliferation of glioma cells has captivated widespread attentions from the oncologists. Previous studies have demonstrated that statins are able to suppress the invasion and growth of HMG-CoA-R and glioma cells and function to induce the cellular apoptosis [28,29]. Recent studies have indicated that the incidence of glioma is considerably decreased in those who are administered with long-term statins. Moreover, statins can promote the apoptosis of glioma cells and suppress the proliferation of tumor cells [18,25-27].

Fas translocation and PI3K/Akt/mTOR, caspase-3

PI3K/Akt signaling pathway is involved in the proliferation, migration and invasion of glioma cells [30]. Wu *et al* [25] have proposed that simvastatin can suppress the cellular proliferation and migration, and induce the apoptosis of U87 and U251 cells in a dose- and time-dependent pattern. Simvastatin is capable of lowering the cholesterol level on the glioma cell membrane, disrupting the structure of lipid rafts and down-regulating the PI3K/Akt pathway. Additionally, the signaling mechanism of Fas translocation and PI3K/Akt/caspase-3 pathway is involved with the anti-tumor effects of simvastatin. Maja Misirkica *et al* [31] have also demonstrated that simvastatin can mediate the induction of Beclin-1 and autophagy of glioma cells are correlated with the down-regulation of basal mTOR activity.

Simvastatin has been proven to trigger the AMPK/Akt/mTOR autophagy, prevent glioma cells from apoptotic death. In addition, statins have been validated to induce cell autophagy and regulate cell necrosis [32-35]. Therefore, Akt-related molecular signaling pathways are of vital significance in the proliferation of glioma cells. HMG CoA reductase specifically suppresses the expression of Akt by inhibiting AMPK or PI3K activity, thereby suppressing the cell autophagy pathway and promoting the necrosis of glioma cells, as illustrated in Figure 1.

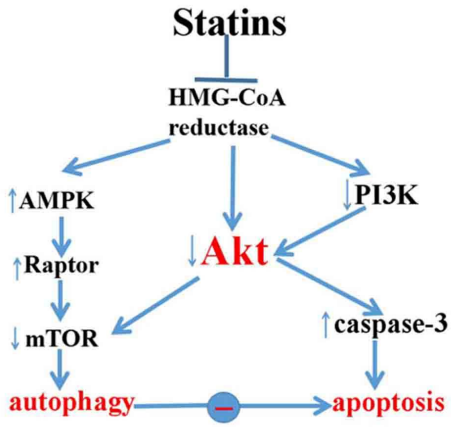

Figure 1: Molecular signaling pathways of autophagy and apoptosis by Akt

JNK/ATF-2 signaling pathway

JNK/ATF-2 molecular signaling pathway is intimately correlated with cell proliferation. The trans-activation capacity of N-terminal domains of c-jun and ATF-2 is strengthened via the phosphorylation of JNK and p38 kinase [36]. ATF-2 is involved in JNK- and p38 kinase-dependent ATF-2 N-terminal phosphorylation to cell stress, which has been validated in multiple cellular stress responses [37]. Meral Koyuturk *et al* [38] have also demonstrated that simvastatin can reduce cell proliferation and induce apoptotic death in C6 glioma cells in a time- and concentration-dependent pattern. The mechanism is the simvastatin-induced activation of JNK in glioma cells via the induction of c-jun and the activation of ATF-2. Subsequently, the death of glioma cells is aggravated. Ohba *et al* [39] have found that similar molecular mechanisms of c-Jun-associated responses are vital events in the cyto-protection of temozolomide (TMZ)-treated glioma cells mediated by JNK.

TRAIL signaling pathway

The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the TNF super-family, and able to bind to death receptors including DR5 and DR4, thereby inducing cell apoptosis in multiple cancer cells but inducing no

harm to normal cells [40-42]. David *et al* [42] have demonstrated that lovastatin can sensitize the TRAIL-induced cell death, and two of the tested glioblastoma cell lines are resistant to TRAIL-induced apoptosis. Therefore, lovastatin can sensitize glioblastoma cells via the effect upon the TRAIL receptor signaling pathway, and equally triggers an unknown mechanism.

Lovastatin is a cytostatic agent that supports TRAIL-induced cell apoptosis in glioblastoma cells. TRAIL-induced cell death mechanism has been evaluated in the colon and pulmonary tumors [43]. Combined regime of TRAIL, non-chemotherapeutic agents and statins might provide a potentially novel option for the clinical treatment of gliomas.

Raf/MEK/ERK signaling pathway

Changes in the Ras/Rho-mediated signaling transduction, including the Ras-Raf-MEK-ERK signaling pathway, play a central role in the molecular pathogenesis of GBM [5,18]. Sarah *et al* [18] have reported that lovastatin and perillyl alcohol disrupt the regulatory effect of Ras-Raf-MEK-ERK and MVA- and the signaling pathways in U343 and U87 cells, which equally affect the modification of H-Ras and Rac1 post-translation, and data on these compounds strengthen the effect of isoprenoids FPP and GGPP upon modification of small GTPases post-translation and accelerating the proliferation of glioma cells. Statins plays an essential role in alternative types of cancer.

Wu *et al* [44] have found that statins are able to trigger cell apoptosis by regulating the Raf/MEK/ERK signaling pathway. Down-regulating the Raf/MEK/ERK signaling pathway can potentiate cell apoptosis induced by statins when exposed to D98059, a MEK1 inhibitor and can sensitize AML cells to a low concentration of lovastatin. Du *et al* [45] have demonstrated that cell apoptosis induced by dihydroartemisinin is accompanied with the PI3K/AKT and Raf/MEK/ERK signaling pathway inactivation, besides down-regulating the expression of Mcl-1 and Bcl-2, anti-apoptotic proteins. Roberts *et al* [46] have demonstrated that dys-regulation of the Raf/MEK/ERK signaling pathway is correlated with the incidence of multiple types of human tumors and suppressing the Raf/MEK/ERK signaling pathway serves as a novel option for cancer management.

Alternative signaling pathways

Previous studies have proposed multiple mechanisms and molecular signaling pathways are associated with the effect of statins upon inducing the apoptosis of glioma cells. However, which signaling pathway plays the most pivotal role in these events have been largely unknown. Accumulated recent evidence has demonstrated that the cell autophagy-related signaling pathways, such as the PI3K/Akt/mTOR and MAPK signaling pathways, exert the primary effect upon the death and apoptosis of glioma cells [32-35,47].

EFFECT OF STATINS ON GLIOMA CELL INVASION

Cancer invasion is a very important indicator in terms of evaluating the cancer malignancy. Recent studies have shown that microglia can promote the growth of glioma cells [48]. Glioma cells can activate the microglia to express matrix metalloprotease (MMPs), which can promote the glioma cell invasion. Some studies have also demonstrated that atorvastatin can down-regulate the expression levels of matrix metalloprotease 2 (MMP-2), MMP-14 and MMP-9, whereas it suppresses the invasion of osteosarcoma by suppressing MMP-2 activity via RhoA-JNK-c-Jun-MMP2 signaling pathway [49-52].

Yi *et al* [53] have demonstrated that atorvastatin can mitigate the pro-tumorigenic effect of microglia upon the glioma invasion and migration by down-regulating MT1-MMP expression in microglia. A potential mechanism of down-regulating MT1-MMP in microglia is associated with the p38 MAPK signaling pathway. Fromigue *et al* [52] also reported that inhibiting HMG-CoA reductase via statins and decreasing RhoA-GTPase prenylation reduces MMP2 activity in the JNK-cJun signaling pathway of osteosarcoma cells. Markovic *et al* [48] have found that glioma manipulates tumor-associated microglial cells through TLR signaling pathway for MT1-MMP expression, thereby promoting the expansion of glioma. The pro-tumorigenic effect of microglial cells serves as a target for the management of new brain tumors.

Statins significantly down-regulate MMP-2 expression, which can reduce the invasion of glioma cells. It also acts as a promising tool to reduce the invasion of microglia-promoted tumors. Regarding other mechanisms, Cordle *et al* [54] have shown that statins can inhibit the actions of Rho GTPases of microglia. Sundararaj *et al* [55] have demonstrated that inhibiting LPS-indiced ERK activation by simvastatin is counteracted by GGPP and simvastatin can suppress MMP-1 expression induced-LPS in U937 cells via targeting ERK activation mediated

by protein isoprenylation. These findings indicate that statins can suppress the invasion of glioma cells and enhance the clinical prognosis of glioma patients.

EFFECT OF STATINS ON GLIOMA CELL MIGRATION

Although distant migration of glioma is rare, it also indicates the end-stage of the disease and a poor outcome. Glioma cell migration interferes with a good prognosis. Statins may play an important role in preventing glioma migration [15,18,20,26,31]. However, the specific molecular mechanism remains elusive. Nawaz *et al* [56] have indicated Cbx7 potentiation within glioma cells leads to YAP/TAZ loss, which drives the transcriptome, as evidenced by the negative enrichment of the YAP/TAZ targets. Cbx7 can regulate SAPK/JNK activity via modulating CTGF, and this Hippo signaling pathway is evaluated by detecting YAP/TAZ-dependent transcriptional activity, which is less effective in the of migration of glioblastoma.

Yi *et al* [53] have demonstrated atorvastatin reduces the pro-tumorigenic effect of microglia upon the migration of glioma by down-regulating the expression level of MT1-MMP. Therefore, down-regulating MT1-MMP is regulated by p38 MAPK signaling pathway in microglia. Obara *et al* [57] have demonstrated that cerivastatin is capable of mediating FAK tyrosine phosphorylation and influencing different cell effects by interacting with several cell signaling pathways associated with cell migration. These studies support further research on statins, as a candidate, and targeting the signal transduction pathways related to glioblastoma biology probably serves as a potential treatment for glioma. Large sample size clinical trials of statins or drugs with similar structures are urgently required to enhance the quality of life of glioma patients.

EFFECT OF STATINS ON GLIOMA ANGIOGENESIS

Angiogenesis plays a vital role in the progression and metastasis of tumors because cancer cells can retain persistent proliferation via acquiring oxygen and nutrients from the blood vessels [58,59]. Consequently, anti-angiogenesis is a therapeutic strategy to target malignant tumors. Inhibition of the activity of vascular endothelial growth factor (VEGF) is an effective approach to inhibit the proliferation of GBM cells.

The significance of VEGF/VEGFR-2 signaling pathway has been proven in the endothelial cell function of malignant tumors. VEGF and VEGF receptor (VEGFR) play a vital role in the lymphangiogenesis angiogenesis [60]. Recent research has demonstrated that angiogenesis is a complicated event, which regulated by multiple stimulating and inhibiting factors. Although multiple molecules associated with angiogenesis, VEGF/VEGFR signaling pathway is a major regulator of angiogenesis, and it is significantly expressed in glioblastoma and other types of cancer [61,62].

Additionally, there are many possible molecular targets for modified anti-angiogenesis intervention, such as the TGFβ signaling pathway [63,64], VEGFR-2/Flk-1 [65,66] and the RTK/PI3K/Akt/mTOR signaling pathways [67,68], as illustrated in Figure 2 [69]. Dong Huang *et al* [70] have demonstrated that statins can promote the angiogenesis in diabetic rat models with MI, probably mediated by up-regulating the VEGF-dependent Akt/eNOS pathway. Chang *et al* [71] have found that rosuvastatin can alleviate experimental HPS via blocking pulmonary inflammatory angiogenesis via TNF-α/NF-κB and down-regulation of VEGF/Rho-associated A kinase signaling pathway. Wu *et al* [72] have also demonstrated that simvastatin can promote TBI-induced angiogenesis at the margins of the lesions and hippocampus as well as accelerate function recovery whereas accelerate *in vitro* angiogenesis, which are probably associated with activation of the VEGFR-2/Akt/endothelial nitric oxide synthase signaling pathway induced by simvastatin. Both studies have demonstrated that statins play a crucial role in angiogenesis-target therapy in glioma patients. Nevertheless, a large clinical randomized controlled trial (RCT) and evidence-based medicine are still urgently needed to confirm these findings.

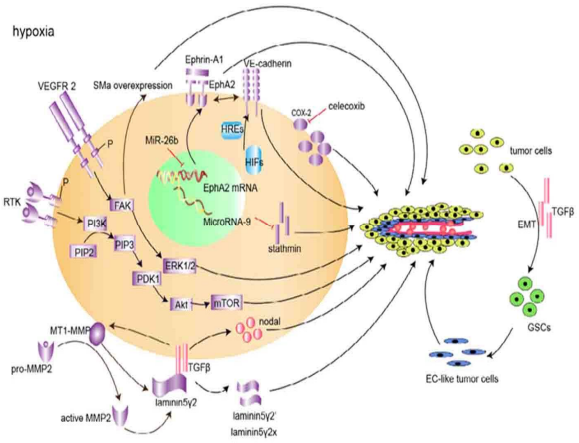

Figure 2: Schematic graph of signaling pathways involved with glioma vasculogenic mimicry (VM). VM process proceeds under hypoxic condition. Signaling molecules modulated by small inhibitory RNAs, small

molecular inhibitors or blocking antibodies are illustrated to represent the direct or indirect effect upon VM. They are classified into embryonic/stem cell (red), microenvironment (purple) and hypoxia signaling pathways (blue). No boundary lines exist among three parts and the overlap among major VM signaling pathways indicates the coordination of these pathways

CLINICAL TRIAL PROGRESS

Many studies have confirmed that statins safe are and effective for treating glioma and other types of cancers. However, the results of clinical studies have been inconsistent and contrasting. Besides, the clinical efficacy of statins in patients with glioma has been controversial (Table 1). Unfortunately, relevant data obtained from RCT are still lacking. A nationwide case-control study including 2656 patients and 18 480 healthy controls in Denmark proposed that the incidence of glioma is decreased among those with long-term use of statin their counterparts never use of statins, which is negatively associated with the intensity of statin administration [17].

Another similar clinical trial including 339 GBM patients has demonstrated that statin use before diagnosis can decrease the HR of death. HR decreases over prolonged intensity and duration of pre-diagnostic statin use [19]. Therefore, long-term pre-diagnostic statin use may improve the survival of GBM patients. In contrast, Seliger *et al* [73] opposed of the notion that negative association exists between use of statins and risk of glioma in a case-control investigation from the UK-based Clinical Practice Research Datalink to analyze of the administration of statins among 2469 glioma patients and 24,690 healthy controls. Ferris *et al* [22] have found that both statins and non-steroidal anti-inflammatory drugs possess significantly inverse trends between the duration of drug use and glioma risks, and drug intake for longer than 120 months demonstrates the most significant associations for both medication types. Another preoperative statin use study included 78 patients taking statins preoperatively, while 206 patients did not. The results had similar progression-free survival before and after propensity score matching. Also, the mortality is similar between the two groups [74]. These studies were not RCTs.

Therefore, the evidence rank is relatively low. A large sample size, randomized and placebo-controlled trial is urgently needed. Of note, there are two clinical trials about statins and glioma registered on clinicaltrials.gov. Altwairgi [75] aims to evaluate the clinical efficacy and safety of atorvastatin in combination with radiotherapy and temozolomide in glioblastoma (ClinicalTrials.gov Identifier: NCT02029573), and Centre Oscar Lambret wanted to explore safety of Fluvastatin-Celebrex Association in Low-grade and High Grade Optico-chiasmatic Gliomas (FLUVABREX) (ClinicalTrials.gov Identifier:NCT02115074). Further results and more RCT studies are urgent required to explore the role of statins in glioma.

CONCLUDING REMARKS

Previous studies have suggested that statins can reduce the morbidity of glioma patients with long-term use and improve the clinical prognosis and prolong the survival time of glioma patients, which has been validated by numerous laboratory studies. In addition, clinical studies have yielded negative results. Nevertheless, these negative outcomes do not interfere with further evaluation of the safety and clinical efficacy of statins administration in glioma patients. Large-scale research and RCT studies are still urgently required to investigate the clinical benefits of statin use in glioma patients.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Table 1: Summary of relevant clinical trials of statins and glioma in the period 2012 - 2016

Clinical trial	RCT	N (s/c)	Evaluation	Conclusion
Gaist *et al* [17], 2013	No	2656/18480	Glioma morbidity	Reduce morbidity
Gaist *et al* [19], 2014	No	113/226	Survival	Prolong survival. No effect
Seliger *et al* [75], 2016	No	2469/24690	Glioma morbidity	Reduce morbidity
Ferris *et al* [23], 2012	No	517/400	Glioma morbidity	No effect
Bhavsar *et al* [76], 2016	No	78/206	Survival and mortality	

Abbreviation: RCT: Randomized controlled trial, N: included patients, s: statins used and c: control group

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