Review (unsolicited)

Cell Transplantation
Volume 31: 1–6

DOI: 10.1177/09636897221102903
journals.sagepub.com/home/cll
SAGE

Effects of Lovastatin on Brain Cancer Cells

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Abstract

Although brain tumors occur less frequently than other forms of cancer, they have one of the bleakest prognoses with low survival rates. The conventional treatment for brain tumors includes surgery, radiotherapy, and chemotherapy. However, resistance to treatment remains a problem with recurrence shortly following. The resistance to treatment may be caused by cancer stem cells (CSCs), a subset of brain tumor cells with the affinity for self-renewal and differentiation into multiple cell lineages. An emerging approach to targeting CSCs in brain tumors is through repurposing the lipid-lowering medication, lovastatin. Lovastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that impacts the mevalonate pathway. The inhibition of intermediates in the mevalonate pathway affects signaling cascades and oncogenes associated with brain tumor stem cells (BTSC). In this review, we show the possible mechanisms where lovastatin can target BTSC for different varieties of malignant brain tumors.

Keywords

brain cancer, signaling pathways, statins, stem cells

Brain Cancer Epidemiology

Out of all the solid cancers, brain tumors have the highest morbidity and mortality rates[1]. Approximately only one-third of patients with a form of brain or other central nervous system (CNS) tumor will survive at least 5 years after diagnosis[2]. Brain tumors account for less than 2% of malignancies, yet they are the leading cause of cancer-related deaths in children and fourth leading cause in adults[1]. In 2021, 83,570 people living in the United States are estimated to be diagnosed with some form of brain or CNS tumor and 18,600 individuals will succumb to the disease[2]. The incidence of brain tumors is increasing in certain cohorts possibly due to advances in primary brain tumor detection or improvement in the treatment of systematic cancers[3]. There are over 120 different types of brain tumors. These lesions can be grouped into either primary brain tumors which are defined based on the cell of origin or secondary brain tumors which originate from metastatic cells of peripheral sites[4]. The most common malignant primary brain tumor is glioma, of which over 50% comprise grade IV glioblastoma (GBM)[4]. Malignant brain tumors are more common and are approximated to outnumber primary brain tumors by a factor of four[4]. Metastasis to the brain occurs in approximately 10% to 30% of cancer patients with 70% to 80% of those individuals developing multiple lesions, most commonly in the cerebrum[5,6].

Management of Malignant Brain Tumors

The treatment of malignant primary brain tumors includes a combination of surgical resection, radiation, chemotherapy, and symptomatic control. Surgical resection is the initial approach for treating most malignant primary brain tumors[7]. Studies suggest that extent of resection is correlated with both progression-free and overall survival[8]. Radiation is often used in conjunction with surgery, but as the study by Grunert *et al.*[9] notes, there is potential for inducing cognitive decline, forming new tumors and developing more proliferative and treatment-resistant cancer strains. In the case of chemotherapy, a higher dosage is necessary in treating brain cancer compared with other cancers due to the blood–brain barrier[10]. This problem has led to the continued development

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Submitted: March 28, 2022. Revised: April 22, 2022. Accepted: May 9, 2022.

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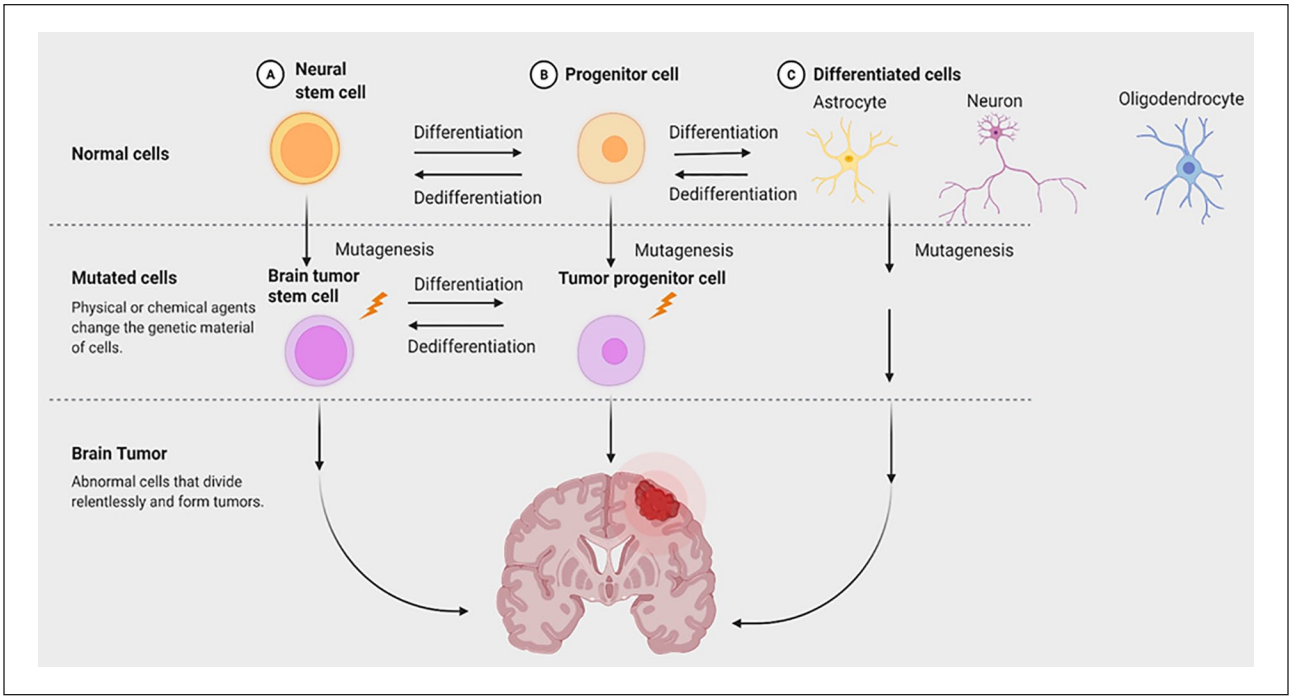

Figure 1. Diagram of neural versus cancer stem cell differentiation. The model is a simplified version of the differentiation between neural stem cells (yellow) and brain tumor stem cells (purple) in the formation of brain tumors. Neural stem cells and brain tumor stem cells share similar characteristics such as self-renewal and differentiation. Neural stem cells differentiate into unrestricted progenitor cells which give rise to either glial progenitors or neural progenitors. The glial precursors differentiate into astrocytes and oligodendrocytes while the neural precursor will form the neuron. Similarly, brain tumor stem cells have the ability to generate a wide range of differentiated progeny. Brain tumor stem cells can develop from mutations accumulated in neural stem cells and in both their restricted and unrestricted progeny that have the ability to self-renew.

of alternative strategies like the use of nanotechnology to deliver the medications[11]. However, as of yet, there is no widely accepted standard for the treatment of metastatic brain tumors, and the response will depend on the tumor type and overall prognosis[3]. Despite advances in treatment protocols, malignant brain tumors remain a clinical challenge with recurrence a few months after treatment and median survival of 8 months for brain metastasis and 14.2 months for malignant primary brain tumors[5].

Brain Tumor Stem Cells

The cancer stem cell (CSC) hypothesis can apply to multiple solid tumors, particularly in the brain. Singh *et al.*[12] in 2004 was the first study that identified a subpopulation of CD133+ human brain tumor cells *in vitro* with stem cell activity. Future studies expand on this work and show that brain tumor stem cells (BTSCs) have properties similar to neural stem cells (NSCs) such as the ability to grow as neurospheres, perpetual self-renewal, and extensive brain parenchymal migration[13,14] (see Fig. 1). Another similarity between BTSCs and NSCs is the molecular pathways involving self-renewal. In particular, the Shh and Notch pathways are implicated in the proliferative capacity of human glioma cells and initiation of medulloblastomas[1]. BTSCs possess certain traits that impact treatment outcomes and recurrence rates of malignant brain tumors. Postoperative wounds can change the tissue microenvironment initiating differentiation or de-differentiation of persistent BTSCs[15]. BTSCs also overexpress multidrug resistance proteins that protect them from cytotoxic drugs that kill differentiated brain tumor cells[12]. Human glioma cells can activate DNA repair mechanisms more efficiently than regular brain tumor cells, making the subpopulation of tumor cells more resistant to radiotherapy[16]. With the discovery of BTSCs and their role in conventional treatment failures of malignant brain tumors, additional strategies suggest treating brain cancer based on a stem cell model.

Cancer Stem Cells

Recent studies show that only a small subset of tumor cells display key characteristics similar to somatic stem cells such as long-term replicative potential, extensive self-renewal, and multilineage differentiation[14]. Inappropriate activation of certain pathways, such as Wnt/β-catenin, Sonic hedgehog (Shh), Notch, and bone morphogenetic protein, involved in the differentiation and self-renewal of stem cells are implicated in a variety of cancers[15]. This concept, which was built from prior work on acute myeloid leukemia, established evidence for the existence of CSCs[17].

Statins for Treating Brain Cancer

Statins are a class of drugs commonly used in the treatment of cardiovascular disease as a result of their inhibitory effects on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme of the mevalonate pathway and cholesterol biosynthesis[18]. Clinical data have frequently demonstrated that statins are a safe and effective therapy in treating cardiovascular disease across a wide range of demographics[19], significantly reducing low-density lipoprotein and triglyceride levels while improving high-density lipoprotein levels in patients[18]. Moreover, statin therapies are reliably found to reduce mortality and morbidity due to complications such as strokes or cardiovascular events[18,19]. Despite their overall benefit, statins are still noted for carrying a wide range of adverse effects such as muscle breakdown and dysfunction, hepatic dysfunction, increased risk of diabetes mellitus, and renal insufficiency[18]. In addition, other products potentially involved in cell survival, such as coenzyme Q10, are also targeted by statin-mediated inhibition of HMG-CoA, yielding mitochondrial defects and pro-apoptotic signaling[19]. The toxicity of atorvastatin has been examined along with temozolomide and radiotherapy for GBM treatment[20]. Patients were started on 40 mg of atorvastatin per day for the first 21 days of the study after which the dosage was increased to 80 mg per day and continued until early termination by the participants, disease progression, or serious adverse effects[20]. In total, 11% of the patients stopped the treatment during the adjuvant and concomitant therapy periods[20], suggesting that the adverse effects of statins do not follow a strict dose-dependent pattern. Future studies investigating dosage and adverse effects may help optimize statin therapy to minimize side effects[20].

Growing interest has shifted toward investigating the non-cardiovascular benefits of statin therapy as a result of the application of their pro-apoptotic effects in cancer therapy. Early comparative analysis in Danish populations showed that statin-users had a slightly reduced overall incidence of cancer compared with non-users and users of other lipid-lowering drugs, although there was no demonstrable effect on any organ-specific cancers[21]. More recently, similar nationwide study populations have shown that statin use reduced cancer-related mortality, although they again did not significantly influence cancer incidence[22]. This distinction has been reiterated in studies investigating prostate, colorectal, and breast cancer, wherein it was reported that stains could improve outcomes and protect against advanced progression of cancer without affecting cancer incidence[23–25].

Outside of clinical data, there is evidence of statin demonstrating anticancer effects through modulation of stem cells in laboratory settings. Statin treatment demonstrated reduced cell proliferation in human embryonic stem cell lines, as well as ovarian and colorectal cancer cell lines, as a result of inhibition of the mevalonate pathway[26]. Furthermore, in work done in mesenchymal stem cells (MSCs), statins were also shown to reduce differentiation potential in addition to promoting senescence and apoptosis[27]. However, certain evidence suggests that statins are not always pro-apoptotic modulators of stem cells. In the context of stem cell-based transplantation for heart disease, certain statins have been shown to promote stem cell survival, differentiation, and promotion[28], with lovastatin being among them.

Lovastatin, or Monacolin K, was first isolated and described in 1979 by Japanese biochemist Akira Endo, being noted primarily for its use as a potential therapeutic for hypercholesterolemia[29]. Further work has since demonstrated that lovastatin also possesses both anticancer effects, particularly in preventing metastasis in breast cancers[30,31] and neuroprotective effects among differentiated nerve cells by inhibiting apoptosis[32]. Lovastatin has also shown to promote differentiation and proliferation among various stem cell types, including human gingiva-derived stem cells, MSCs, and NSCs[33–35]. Differentiation into osteoblastic lineages is predominantly reported in literature following lovastatin treatment of stem cells[34,36]; however, MSC differentiation into neuroglial cells has also been observed[35]. Among MSCs and NSCs in particular, lovastatin is also shown to protect against apoptosis induced as a result of both hypoxia[37], as in the case of MSCs, and oxidative stress, as in the case of NSCs[33]. Taken all together, these characteristics would seem to suggest that lovastatin could potentially play a role in both treating brain cancer and promoting subsequent regeneration of lost brain matter.

Lovastatin for Targeting Brain Cancer Stem Cells

Lovastatin Targeting GBM Stem Cells

Glioblastomas (GBM) contain CSCs located in the tumor bulk[38]. CSCs in GBM contribute to tumor initiation, recurrence, and resistance to chemotherapy and radiotherapy. Statins show promise as a repurposed drug in the treatment of GBM[39]. As discussed above, statins inhibit the enzyme HMG-CoA reductase which prevents the synthesis of mevalonate and downstream intermediates involved in CSC self-renewal, differentiation, and proliferation. Although the characterization of the antiproliferative effects lovastatin has with GBM stem cells is not completely understood, certain studies highlight the possible mechanisms where lovastatin can target GBM CSCs.

One potential mechanism where lovastatin can inhibit glioma stem cell proliferation is through S-phase kinase-associated protein 2 (Skp2) degradation. Skp2 is a member of the F-box protein family that targets the cell cycle through degradation of CDK inhibitors $p27^{Kip1}$ and $p21^{Cip1/Waf140}$. Lovastatin downregulates Skp2 possibly from the depletion of geranylgeranyl pyrophosphate, a downstream intermediate of the mevalonate pathway[41]. In 2020, Yi *et al.*[30] demonstrated that lovastatin induced degradation of Skp2 in glioma

cells which lead to decreased glioma neurosphere formation, proliferation, and stem cell markers Sox2 and Nestin.

Another plausible mechanism where lovastatin can potentially target glioma stem cells is through modulation of doublecortin (DCX) expression. DCX is a brain-specific gene involved in neuroblast and differentiating neuron migration in the developing brain[42]. Previous studies show DCX synthesis induces terminal differentiation of BTSCs[43]. In 2011, Santra *et al.*[44] demonstrated that statin treatment had favorable effects on mice survival by inducing apoptosis of BTSCs by strengthening the activity of DCX and neurabin II. They found that statin treatment led to activation of c-jun NH2-terminal kinase 1 which in turn increased activation of the caspase-3 pathway via effects on DCX and neurabin II.

In addition to its role as a potential targeted therapy, lovastatin is generating interest in its use as an adjuvant therapy for glioma tumors. One example of lovastatin as an adjuvant in the treatment of GBM would be its use in combination with Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL). Evidence shows that lovastatin may inhibit the nuclear factor-κB pathway which sensitizes TRAIL mediated apoptosis through upregulation of death receptor 5 on the cell surface of GBM cell lines[45]. There is also evidence of the interaction between lovastatin and radiation in the treatment of GBM. In 2008, Gabryś *et al.*[46] studied the effects of lovastatin with and without radiation in the treatment of U87MG glioma cells. The investigators reported that lovastatin by itself decreased cell proliferation but did not enhance the effect of radiation therapy.

Lovastatin Targeting Medulloblastoma Stem Cells

Medulloblastomas contain a subpopulation of CSCs responsible for tumor proliferation, metastasis, recurrence, and resistance to conventional treatment[47]. Preclinical studies show lovastatin prevents proliferation and induces apoptosis in medulloblastoma cell lines[48,49]; however, the exact relation between lovastatin and medulloblastoma CSC remains unclear.

One studied target for lovastatin inhibition of medulloblastoma CSCs is Myc expression. Myc amplification is associated with group 3 medulloblastomas which has the worst prognosis of the four groups of medulloblastomas[50]. Previous studies show that c-myc and n-myc are critical for neurosphere formation and expansion of CD133+ malignant medulloblastoma tumor cells[51,52]. Lovastatin is shown to indirectly target c-myc through the modulation of miRNA[53]. In 2012, Takwi found that lovastatin induced miR-33b expression which led to the decreased expression of c-myc and function of the medulloblastoma cells[53].

Another potential pathway where lovastatin can target medulloblastoma CSCs is through modulation of Shh signaling. Shh is associated with group 2 medulloblastomas which comprises 25% of all cases[50]. One of the major drivers of the Shh pathway is protein patched homolog 1 (Ptch)[54]. Tumors in $Ptch^{+/-}$ medulloblastoma mice were found to contain self-renewing, long-term stem cells[54]. In 2018, Gordon *et al.*[55] studied the interaction between statin therapy, Shh signaling, and medulloblastoma progression. The investigators found that cholesterol dysregulation mediates Shh medulloblastomas. They believed that the loss of cholesterol homeostasis may have been caused by a mutation in Ptch1. Inhibition of cholesterol biosynthesis by statin treatment repressed medulloblastoma proliferation.

Conclusion

Malignant brain tumors house a subpopulation of CSCs which are responsible for recurrence, metastasis, and maintenance of the tumor. Conventional therapy such as surgical resection, radiotherapy, and chemotherapy only target the bulk tumor leading to proliferation of the CSCs. Lovastatin shows potential as a novel therapy for malignant brain tumors because of its ability to target BTSC. Prior studies demonstrate efficacious treatment of glioma and medulloblastoma stem cells with lovastatin. Lovastatin can potentially target glioma stem cells through the modulation of Skp2 and DCX. Potential mechanisms for lovastatin treatment for medulloblastoma stem cells include a change in Myc expression and Shh signaling. Although the initial preclinical results for lovastatin have been generally positive, further research should be conducted both *in vitro* and *in vivo* to elucidate the exact mechanisms of how lovastatin interacts with BTSCs.

Acknowledgments

Figure 1 was created with BioRender.com.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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