Review Article

Current perspectives on statins as potential anti-cancer therapeutics: clinical outcomes and underlying molecular mechanisms

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Abstract: Statins have been shown to inhibit cell proliferation *in vitro* and tumor growth in animal models. Various studies have also shown a decreased cancer-specific mortality rate in patients who were prescribed these medications. Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate pathway. Statins induce tumour-specific apoptosis through mitochondrial apoptotic signaling pathways, which are activated by the suppression of mevalonate or geranylgeranyl pyrophosphate (GGPP) biosynthesis. However, there is no consensus on the molecular targets of statins for their anti-cancer effects. Several studies have been conducted to further assess the association between statin use and mortality in different types of cancer. In this review, current perspectives on clinical significance of statins in prevention and treatment of various types of cancers and proposed mechanisms are discussed.

Keywords: Statins; cancer; clinical outcomes; cancer therapeutics; cellular and molecular cancer

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Introduction

According to the World Health Organization (WHO) cancer is a generic term for a large group of diseases that can affect any part of the body, and metastases are a major cause of death from cancer. Based on WHO statistics, cancer is the second leading cause of death globally. The economic burden of cancer is significant as its estimated total annual cost has been over US$ 1.1 trillion over the past decade. The health and socioeconomic implications of cancer underscore an urgent need for identifying and applying successful preventative and therapeutic options (1).

Chemotherapy is a common approach to cancer management, which is currently used in a curative, palliative, or adjuvant capacity. Several classes of chemotherapeutic medications have been used clinically, including DNA alkylating agents, platinating agents, and antimetabolites. Although these drugs have had varying degrees of success, they also possess significant undesired side effects resulting in their diminished utility. Further complicating matters, in cases where these drugs initially prove efficacious, tumours can develop mechanisms of drug resistance. Such mechanisms include increasing the expression of multidrug efflux pumps, altering the expression of the drug's target, and upregulating survival pathways. To resolve these issues and improve treatment outcomes, researchers are keen on developing tumour-specific agents.

Many current chemotherapeutics have been shown to kill tumour cells by inducing apoptosis (2). Apoptosis which is a genetically programmed cell death is executed by two major pathways: the extrinsic pathway and the intrinsic pathway. Apoptotic pathways require an array of functional interactions that would ensure effective regulation of programmed cell death. A tumour could acquire a host of mutations or alterations in order to evade apoptosis. Although escaping programmed cell death is a pivotal characteristic for tumourigenesis, it does not seem to be a general response to all apoptotic stimuli. Paradoxically,

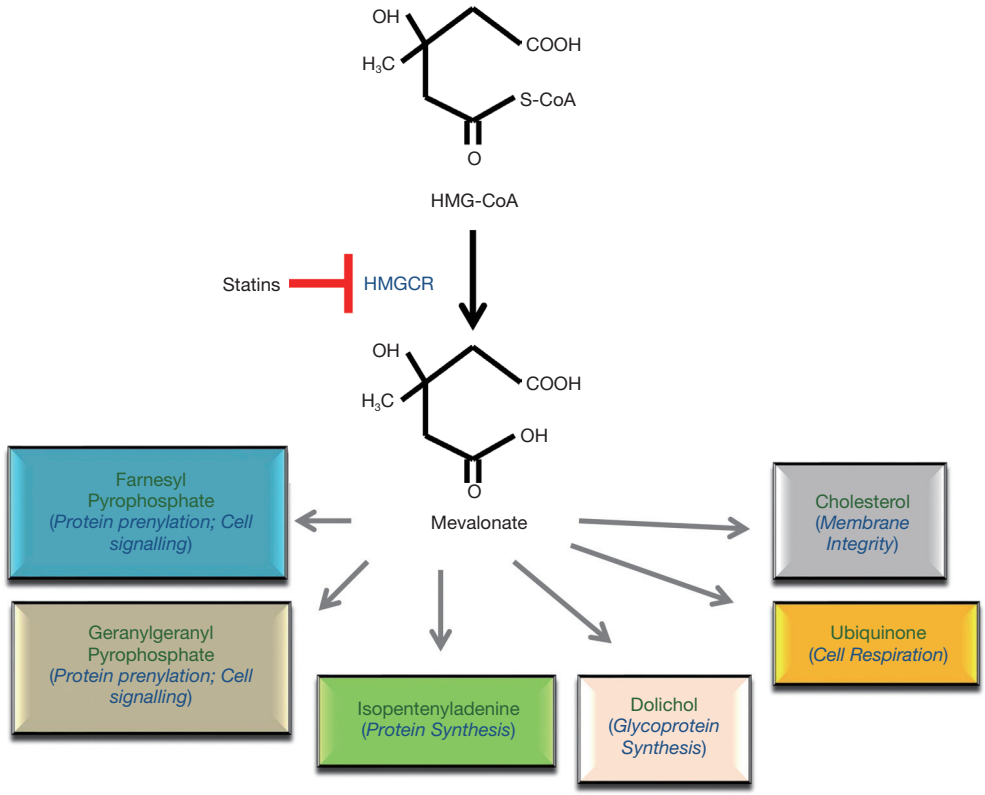

Figure 1 Mevalonate pathway and its downstream products with their main function in brackets.

much of the apoptotic machinery and pathways remain intact in tumours, making them attractive targets for therapeutic intervention (3).

Statins are among drugs that have been shown to possess apoptosis-inducing effects. They were originally developed as a treatment for hypercholesterolemia in the 1970s, and shortly after the discovery of mevastatin, its analogues including simvastatin, lovastatin, and pravastatin were developed (4). Statins target and inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the highly regulated rate-limiting enzyme in the mevalonate (MVA) pathway (*Figure 1*). Statins can be classified as natural or fungal-derived (lovastatin, simvastatin, pravastatin), and synthetic (fluvastatin, atorvastatin, rosuvastatin, pitavastatin, and cerivastatin). The two groups differ in their ability to inhibit HMGCR and in their lipophilicity. Among these agents, lovastatin, simvastatin, atorvastatin, and fluvastatin are lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic. The pharmacological activity of statins is dictated by their different chemical structures, lipophilicity/hydrophilicity, kinetic profile, rate of metabolism, and the formation of active and inactive metabolites (5). The most severe side effect of statins is myotoxicity and rhabdomyolysis, which appears to be associated with the presence of co-existing conditions, including hepatic insufficiency, cholestasis or renal diseases (6).

In cancer patients, the efficacy of statins as anticancer agents has been evaluated both in monotherapy and in combination therapy with currently used chemotherapeutics (5). Many studies have also shown that statins induce programmed cell death in a subset of cell lines derived from tumours in tissue culture, implying that the corresponding cancers could be sensitive to statin-specific apoptosis *in vivo* (7-9). The objectives of this article are two-fold: (I) to review the latest preclinical and clinical literature focused on the potential utility of statins as anticancer drugs; and (II) to discuss the molecular mechanisms driving their effects.

Observations from clinical studies

The efficacy of statins as anticancer agents has been evaluated both in monotherapy and in combination therapy with currently used chemotherapeutic drugs. To a varying degree of success, studies have shown the potential

mortality benefits of statin consumption in patients with different types of cancers, which include esophageal, breast, lung, liver, pancreatic, endometrial, and colorectal cancer (10-20).

In a randomized control trial by Kawata and colleagues, the efficacy of pravastatin in chemotherapy was tested in patients with unresectable hepatocellular carcinoma (21). Results showed that pravastatin slowly, but significantly, reduced the diameter of the main hepatic lesions 1 year after the start of the treatment. Complete remission was obtained in 73% (11/15) of new patients and in 41% (9/22) of salvage patients (22). A retrospective cohort study was conducted on data obtained from Central Cancer Registry on 15,422 patients who were diagnosed with hepatocellular carcinoma between 2002 and 2016. The study concluded that post-diagnosis statin use was associated with reduced mortality in hepatocellular carcinoma (23).

A large population-based cohort of 12,572 patients ages 65 years or older supports potential benefits of statins on improving survival among elderly patients with primary pancreatic ductal adenocarcinoma (24). Another recent meta-analysis of 26 studies performed on more than 3 million participants and 170,000 pancreatic cancer patients suggested that statins might have a preventive effect on pancreatic cancer. However, authors of this article believed that more high-quality randomized clinical trials and cohort studies should be carried out to arrive at a convincing conclusion regarding this protective effect of statins against pancreatic cancer (12).

A phase I clinical trial showed the safety and overall positive response of adding pravastatin to idarubicin and high-dose cytarabine in patients with acute myelogenous leukemia (AML) (22). Furthermore, a number of Phase II randomized control trials were specifically designed to answer questions such as effect of atorvastatin versus placebo for lowering mammography-defined breast density and other surrogate markers associated with breast cancer risk; the effects of atorvastatin on tumour proliferation in postmenopausal women undergoing treatment for breast cancer; and fluvastatin's effect on biomarkers in women undergoing surgery for ductal carcinoma *in situ* or stage I breast cancer (25-28). A Swedish nation-wide retrospective cohort study of 20,559 Swedish women diagnosed with breast cancer between July 2005 through 2008 revealed that compared to non- or irregular use, regular pre-diagnostic statin use was associated with lower risk of breast cancer related deaths. The same study also showed that even post-diagnostic statin use compared to non-use was associated with lower risk of breast cancer-related deaths (29).

A retrospective population-based study concluded that statin use has been associated with superior survival in patients suffering from ovarian cancer (16). In an ongoing study patients have been recruited for a Phase II trial to study the synergistic interaction between lovastatin and paclitaxel for women with refractory or relapsed ovarian cancer. In a recent clinical trial, it was found that in patients with prostate cancer treated with a moderate hypofractionated intensity-modulated radiotherapy schedule, use of statins lowered the incidence and grade of acute rectal toxicity (30). A Finnish nationwide cohort study revealed that patients taking statins had significantly lower risk of starting androgen deprivation therapy and decreased mortality rate related to prostate cancer. This study concluded that the risk was lower especially among men with statin use before prostate cancer diagnosis and in men who used statins at high-dose (31). Although accumulating evidence supports statins' radiosensitizing properties and their beneficial antitumor effects in prostate cancer, more clinical trials are warranted prior to the routine implementation of statins in treatment regimes.

In a propensity-matched study, it was shown that among patients who were suffering from non-small cell lung cancer, statin administration was associated with positive outcomes (32). These included cancer characteristics, staging work-up and chemotherapy use. An observational study reported by Omori indicated that non-small cell lung cancer patients who have been previously treated with nivolumab had an increased response rate and longer time-to-treatment failure if prescribed statins. However, this response was not statistically significant for overall survival (33). A meta-analysis of observational studies concluded that statin-administered patients suffering from lung cancer had significantly improved overall survival (34). Subgroup analyses performed in this study revealed that statin users were more probable to have better survival rate in stage IV lung cancer patients (HR 0.77, 95% CI: 0.74–0.79) than in mixed stage (I–IV or I–III) patients (34). Khurana *et al.* conducted a large case controlled study of a veteran population with almost 200 lung cancer cases among statin users and found a 45% reduction in lung cancer risk among statin users when compared to non-users (35). Farwell and colleagues reported a 30% reduction in lung cancer risk among statin users in a retrospective cohort study of another veteran population (36).

Insights from preclinical studies

Molecular mechanisms

Understanding the exact mechanisms underlying statin-induced apoptosis is an emerging topic in cancer research that requires further investigation. Nonetheless, it has been shown that statins induce apoptosis in sensitive cells directly via the inhibition of HMGCR activity. It is the biologically active, open-ring structure of each statin that blocks HMGCR activity to trigger apoptosis (37). Moreover, cells have been made statin-resistant after being cultured in the presence of increasing statin concentrations by amplifying the gene for HMGCR (38). In addition, when cells sensitive to statin-induced apoptosis were co-incubated with statins and mevalonate, the direct product of HMGCR activity, apoptosis was inhibited (39). In other studies, statin-sensitive cells were co-incubated with each mevalonate end product and a statin to ascertain which molecules in the pathway could prevent statin-induced apoptosis. Interestingly, most reports indicate that only geranylgeranyl pyrophosphate (GGPP) is able to inhibit statin-induced apoptosis (39). Based on these observations, it is believed that upon statin treatment, cellular GGPP levels are depleted, resulting in deficient isoprenylation of proteins upon which tumour cells are dependent upon. This, in turn, would lead to mislocalization and malfunction of such proteins, ultimately causing the tumour cell to undergo apoptosis.

The MVA pathway and HMGCR regulation

HMGCR is tightly regulated at transcriptional, translational and post-translational levels. Inhibition of HMGCR with statins deprives the cell of the end products of the MVA pathway, and results in a feedback response that leads to the upregulation of the MVA pathway (40). The protein level and activity of HMGCR is also regulated by phosphorylation and degradation. Mechanistically, the increase in the rate of HMGCR degradation when sterol concentrations are high was studied using a number of either mutant or deletion forms of HMGCR (41,42). These studies highlighted that the element responsible for the regulated degradation of HMGCR resides in the transmembrane region, and in contrast, the degradation of the cytoplasmic portion of the protein is not influenced by sterols. Furthermore, the kinase that regulates HMGCR activity is AMPK, which phosphorylates serine-872, and results in reduced enzymatic activity.

A growing number of studies suggest that the MVA pathway plays a significant role in the regulation of cellular proliferation and transformation. Overall, it has been established that statin treatment of hypercholesterolemia results in depletion of the MVA intermediates, including farnesyl pyrophosphate (FPP) and GGPP, which are required for proper function of small GTPases. Given many Ras proteins are prevalently mutated in pancreatic cancer, attempts have been made to examine the effect of three key intermediates of the MVA pathway on GFP-K-Ras protein localization and the gene expression profile in pancreatic cancer cells after exposure to individual statins by whole genome DNA microarray analysis. Based on some recent observations, it has been suggested that the anticancer effects of statins most likely were mediated through isoprenoid intermediates of the MVA pathway, as they influenced expression of genes involved in multiple intracellular pathways (8,37,43). *Figure 2* summarizes potential mechanisms of HMGCR dysregulation in cancer.

Liver kinase B1 (LKB1) and AMPK involvement

The LKB1, encoded by the tumour suppressor gene *STK11*, is a serine/threonine kinase which harbors germ-line mutations in Peutz-Jeghers syndrome (PJS), an inherited cancer predisposition, and somatic mutations in sporadic cancers (44). By phosphorylating several key cellular kinases, LKB1 regulates cellular metabolism; cell polarity; and a variety of other functions ranging from proliferation and migration to senescence, apoptosis, DNA damage response and differentiation (45). LKB1 has been shown to be the major upstream kinase and activator of 5' adenosine monophosphate-activated protein kinase (AMPK) (46,47). On the other hand, the kinase that has been shown most to regulate HMGCR activity is AMPK, which phosphorylates serine-872 (S872), and results in reduced HMGCR enzymatic activity (48,49).

A combination therapy of mevastatin and LBH589, a histone deacetylase inhibitor (HDACi) was shown to inhibit autophagic flux by preventing Vps34/Beclin 1 complex formation and downregulating prenylated Rab7, an active form of the small GTPase necessary for autophagosome-lysosome fusion. Mevastatin also was reported to increase HDACi LBH589-induced cell death in triple-negative breast cancer (TNBC) cells suggesting co-treatment with mevastatin and LBH589 activated LKB1/AMPK signaling

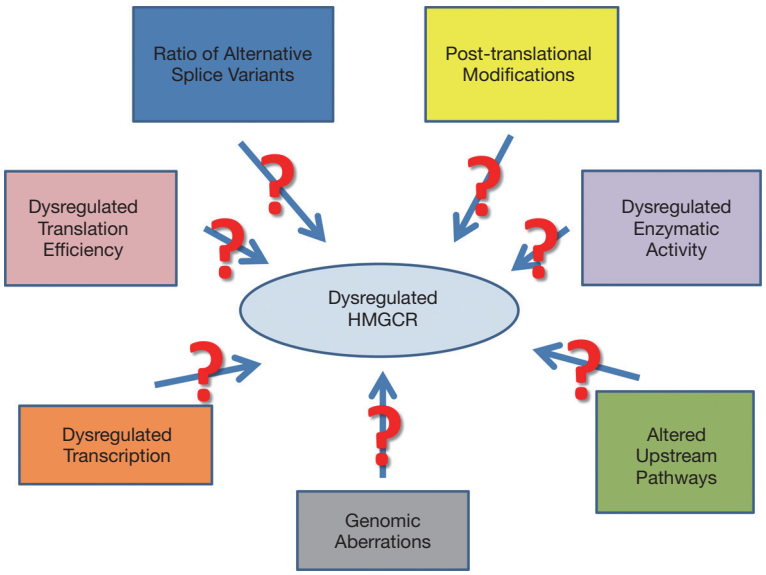

Figure 2 Potential mechanisms of HMGCR dysregulation in cancer. HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase.

and subsequently inhibited mTOR (50).

Other putative pathways

Several other putative mechanisms have been proposed to play an important role in driving the observed anticancer effects of statins. The synergistic effect of rosuvastatin with dasatinib against hepatocellular carcinoma is believed to be mediated by a decrease in the p-FAK/p-Src, p-Ras/c-Raf, p-STAT-3, and p-Akt levels which could result in an enhancement of apoptosis by an increase in caspase-3 level and a decline in survivin level (51). In a study investigating the effects of simvastatin treatment on hepatocellular carcinoma, it was found that simvastatin induces G0/G1 arrest by upregulating p21 and p27 by activating AMPK and inhibiting the STAT3-Skp2 axis, respectively (52). Simvastatin also induced caspase-dependent apoptosis in A549 lung cancer cells, where it was associated with a decrease in the expression of phosphorylated Akt and down-regulated survivin mRNA and protein (53).

As Wang and colleagues showed, atorvastatin and caffeine in combination cause down-regulation of phospho-Akt, phospho-Erk1/2, anti-apoptotic Bcl-2 and survivin protein levels in prostate cancer cells lines. This is suggestive that such a combination therapy may be effective in inhibiting the growth of prostate cancer (54). In another study on prostate cancer, using microarrays, it was shown that simvastatin treatment resulted in up-regulation of annexin A10 (ANXA10) in PC-3 cells. ANXA10 is believed to have antitumor effects (55). Statins have also been shown to affect the Rho signalling pathway in inducing tumour-specific apoptosis (56). Both lovastatin and simvastatin induced activation of caspase-8, caspase-3, and, to a lesser extent, caspase-9. Additionally, both drugs suppressed expression of Rb, phosphorylated Rb, cyclin D1, cyclin D3, CDK4, and CDK6, but induced p21 and p27 expression in prostate cancer cells. Furthermore, lovastatin and simvastatin suppressed RhoA activation and c-JUN expression, but not cyclooxygenase-2 expression (56). This data suggests that the underlying molecular mechanism of statins' action is mediated through inactivation of RhoA, which in turn induces caspase enzymatic activity and/or G(1) cell cycle.

Research done by Tsubaki *et al.* found that the sensitivity of head and neck carcinoma cells to statins is related to the expression of their Ras expression status, and statin-induced apoptosis is mediated via suppression of the Ras/ERK and Ras/mTOR pathways (57). Statin-induced apoptosis and the Ras signalling pathway have also been implicated in human hematopoietic tumour cells (58). Fujiwara and colleagues found that statins induce apoptosis by decreasing the mitochondrial transmembrane potential, increasing the activation of caspase-9 and caspase-3, enhancing Bim expression, and inducing cell-cycle arrest at G1 phase through inhibition of Ras/extracellular signal-regulated kinase and Ras/mammalian target of rapamycin

pathways (58).

In a study considering glioblastoma cell lines, it was shown that statins induced apoptosis via the suppression of ERK1/2 and Akt activation through inhibition of GGPP biosynthesis. The authors also observed an increase in caspase-3 activity. The apoptosis induced by statins was not inhibited by the addition of FPP, squalene, ubiquinone, and isopentenyladenine, but by GGPP (59). Increased caspase activity and depolarization of the mitochondrial membrane secondary to mevastatin exposure was also noted in myeloma cells. In this study, expression of Bcl-2 mRNA and protein was down-regulated, with no change in Bax or Bcl-XL protein production (60).

Another study suggested that the antiproliferative effects of simvastatin on murine melanoma cells were mediated mainly via suppression of the heterodimeric transcription factor hypoxia-inducible factor (HIF-1α) (61). Simvastatin may act as a heat shock protein 90 (Hsp90) inhibitor to prevent the formation of the K292-acetylated Hsp90/Cdc37 complex in TNBC cells (62). Recent work focusing on osteosarcoma cell lines indicated that simvastatin significantly induced apoptosis, increased the Bax/Bcl-2 ratio, and cleavage of caspase-3 (63).

Finally, as Martirosyan and colleagues showed, lovastatin drives ovarian tumor cell death by two mechanisms: first, by blocking HMG-CoA reductase activity, and second, by sensitizing multi-drug resistant cells to doxorubicin by a novel mevalonate-independent mechanism. This inhibition of drug transport, likely through inhibition of P-glycoprotein, potentiates both DNA damage and tumor cell apoptosis (64).

Conclusions

Numerous studies have shown that statins have anticancer benefits in many tumour types. In breast and colorectal cancers, there are epidemiological studies suggesting an association between statin use and lower cancer risk. Although many studies have shown promising benefits for using statins among cancer patients, there is still a need for a better understanding of the molecular determinants of statin-sensitivity in various cancer types to advance personalized medicine and to develop biomarkers of statin-sensitive tumours.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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