Dear editor and reviewers

We appreciated to your consideration of my article for potentially accepting on World Journal of Gastrointestinal Oncology. We carefully address responses to the comments from reviewers and editors as followed as below, and check all the formatting requests.

Reviewer

This review summarized recent advances in statin research in some cancers and evaluated the utility of statins as anticancer agents, suggests important considerations for the clinical use of statins to improve outcomes for cancer patients. The content of this review is significant and comprehensive, so this review is acceptable. However the language quality of this article need to be improved, such as the “and” in Line 48 need to be removed.

Response: Thanks for your suggestion, sorry about our mistakes in writing. I removed “and” in Line 48. I checked the quality of the language and corrected the mistake. I made changes abbreviation according to the abbreviation rules.

Review article

Statin as a therapeutic agent in gastroenterological cancer

Norio Uemura, Hiromitsu Hayashi, and Hideo Baba

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

Corresponding author: Hiromitsu Hayashi, MD, PhD, FACS,

E-mail: hhayasi@kumamoto-u.ac.jp

ORCID number:

Norio Uemura; https://orcid.org/0000-0003-3192-4153

Hiromistu Hayashi; https://orcid.org/0000-0002-1832-4287

Hideo Baba; https://orcid.org/0000-0002-3474-2550

Supportive foundations: None

Running title: Anticancer effect of statins

Abstract: Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate (MVA) pathway and are used

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删除[ ]: Department of Gastroenterological Surgery, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan.

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clinically as a safe and effective approach in the control of hypercholesterolemia. The ~~mevalonate~~ MVA pathway is an essential metabolic pathway that uses acetyl-CoA to produce sterols and isoprenoids that are integral to tumor growth and progression. Multiple studies have indicated that statins improve patient prognosis in various carcinomas. Basic research on the mechanisms underlying the antitumor effects of statins is underway. The development of new anti-cancer drugs is progressing but increasing medical costs from drug development has become a major obstacle. Readily available, inexpensive and well-tolerated drugs like statins have not yet been successfully repurposed for cancer treatment. Identifying the cancer patients that may benefit from statins is key to improved patient treatment. This review summarizes recent advances in statin research in cancer and suggests important considerations for the clinical use of statins to improve outcomes for cancer patients.

Key words: Statin; HMG CoA reductase inhibitor; mevalonate pathway; cancer

Core tip: Novel pharmacological therapies for cancer are in development, but the expense of new drug development has increased medical costs and placed a heavy financial burden on governments worldwide. Therefore, drug repositioning has become a major focus for new drug development because of

reliability and cost effectiveness. Statins are one of the most studied drugs with potential drug repositioning for cancer treatment, but they have not reached clinical application. This review summarizes the results of recent research and clinical studies of statins in cancer, suggests strategies for clinical trial planning, and discusses the potential clinical application of statins for cancer treatment.

Introduction: Since the clinical application of statins in the late 1980s, statins have dramatically improved the clinical management of high cholesterol and ischemic heart disease and have become widespread worldwide. Statins are specific inhibitors of the mevalonate (MVA) pathway, which is involved in the synthesis of cholesterol and other nonsterol isoprenoids de novo. The rate-limiting enzyme in mevalonate synthesis is 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) [1,2]. Statins function by inhibiting HMGCR ~~and~~ are effective in the management of hypercholesterolemia.

In addition to its role in normal physiology, the MVA pathway is known to support tumorigenesis and be deregulated in human cancers[3-5]. The MVA pathway is an essential metabolic pathway that uses acetyl-CoA to produce sterols and isoprenoids, which are integral to tumor growth and progression. Therefore, there is a great deal of interest in diverting statins as anticancer drugs. Numerous retrospective studies have reported that statin use is associated with lower risk of cancer, lower cancer grade and stage at diagnosis, and lower recurrence and cancer-specific mortality[6]. Several randomized clinical trials have evaluated the benefits of adding statins to chemotherapeutic treatment. However, most of the trials did not show an improvement in prognosis and have

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Many oncogenic signal pathways have been shown to increase the activity and expression of MVA pathway enzymes

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not led to the clinical application of statins. The development of new anti-cancer drugs is progressing but increasing medical costs from drug development ~~has~~ have become a major obstacle. Readily available, inexpensive and well-tolerated drugs like statins have not yet been successfully repurposed for cancer treatment. Planning clinical trials is difficult, and it is possible that the previous clinical trials were poorly designed [7]. In the age of precision medicine, defining the cancer patients that may benefit from statins is critical.

This review summarizes the results of recent basic research and clinical studies on statins in cancer and suggests strategies for future clinical trial planning. In addition, the potential for the clinical application of statins in cancer treatment is discussed.

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Mechanisms of action of statins

The MVA pathway is an essential metabolic pathway that uses acetyl-CoA to produce sterols and isoprenoids, which are integral to tumor growth and progression. In the first step of the ~~mevalonate~~ MVA pathway, the rate-limiting enzyme HMGCR converts HMG-CoA to mevalonate (Figure 1). Mevalonate is further metabolized to farnesyl pyrophosphate (FPP). FPP is the precursor in

cholesterol and steroid biosynthesis as well as in the biosynthesis of dolichols. Intracellular cholesterol retains the sterol regulatory element-binding protein (SREBP) in its full-length, inactive form. In response to cholesterol depletion, the SREBP protein is cleaved, and the active transcription factor involved in the MVA pathway and cholesterol transport.

Statins bind to the active site of HMGCR, compete with HMG-CoA, and reduce MVA synthesis. As a result, statins deplete intracellular cholesterol, causing a homeostatic feedback mechanism by the SREBP family of transcription factors. Activation of SREBP increases the gene expression of low density lipoprotein (LDL) receptor (LDLR). Increased membrane expression of LDLR promotes the uptake of LDL cholesterol ~~(LDL-C)~~ from the bloodstream and effectively lowers serum cholesterol levels. Statins are commonly prescribed to lower blood cholesterol, reduce the risk of cardiovascular disease, or improve the survival rate of patients with cardiovascular disease.

MVA pathway in cancer

The MVA pathway has been shown to play a multifaceted role in tumorigenesis [4] [8]. The PI3K-AKT signal pathway is a major regulator of cell survival and proliferation in response to growth factors. PI3K-AKT signaling activates the

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MVA pathway through increasing the expression of SREBP. The increase in lipid and cholesterol production mediated by the PI3K-AKT-SREBP axis promotes the proliferation of cancer cells and tumorigenesis [9, 10]. Conversely, inhibition of the MVA pathway decreases PI3K activity through decreased RAS isoprenylation [11]. Two p53 mutants with gain-of-function mutations were shown to functionally interact with nuclear SREBP2 and increase the transcription of MVA pathway genes [12]. Conversely, wild-type p53 reduces lipid synthesis under conditions of glucose starvation by inducing the expression of LPIN1[13]. The tumor suppressor protein RB has also been implicated as a regulator of the MVA pathway by interacting with SREBP and reducing SREBP binding to promoters of target genes [14, 15]. The oncoproteins Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), both mediators of the Hippo pathway, are controlled by the SREBP/~~mevalonate~~ MVA pathway [16]. The geranylgeranyl pyrophosphate produced by the mevalonate cascade is required for activation of Rho GTPases that, in turn, activate YAP/TAZ by inhibiting their phosphorylation and promoting their nuclear accumulation (Figure 2).

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The Hedgehog (HH) signaling pathway, which has important roles in tumorigenesis, is regulated by cholesterol. Cholesterol and cholesterol-derived

oxysterols activate HH signal transduction [17], whereas inhibition of the MVA pathway or downstream sterol biosynthesis decreases HH signaling and reduces cell proliferation.

Cholesterol is the precursor for steroid hormones such as estrogen and androgen. These hormones are involved in hormone-driven breast cancers and prostate cancers via the activation of estrogen receptor-α (ERα) and androgen receptor ~~(AR)~~, respectively [18, 19]. Perhaps because of these functions, research into the antitumor effects of statins is the most advanced in the fields of breast cancer, ovarian cancer, and prostate cancer.

A recent report showed that the ~~mevalonate~~ MVA pathway is involved in T lymphocyte metabolism and regulates T cell differentiation [20]. Improved understanding of mevalonate metabolism will enable more effective T cell manipulation for immunotherapeutic purposes in cancer.

Statins and esophageal cancer

Three meta-analyses have been conducted on the effects of statins on esophageal cancer. In a meta-analysis of five cohort studies comprising 24576 patients, Zhou et al. [21] reported that statin use in esophageal cancer patients

was associated with a 26% improved overall survival (95%CI, 0.75–0.94) and disease-free survival (95%CI, 0.75–0.96) [22-26]. Deng et al. [27] reported that statin use after diagnosis of esophageal cancer was significantly correlated to decreased all-cause (random effects: HR=0.81, 95%CI, 0.75–0.89, P<0.001) and cancer-specific mortality (fixed effects: HR=0.84, 95%CI, 0.78–0.89, P<0.001) in esophageal cancer patients from four cohort studies involving a total of 20435 esophageal cancer patients [25]. In the subgroup analysis, both meta-analyses showed an effect of statins on improving prognosis regardless of the histological type of squamous cell carcinoma and adenocarcinoma. Thomas et al. [28] reported that statins ~~may~~ might play a preventive role against esophageal cancer development in subjects with or without Barrett's esophagus.

Statins and gastric cancer

Two randomized controlled ~~trial~~ trials (RCT) have examined the effects of statin combination therapy on gastric cancer. A phase III study that examined simvastatin (40 mg/day) plus capecitabine-cisplatin compared with capecitabin-cisplatin alone did not show any increased ~~progression-free~~ the progression-free survival (PFS) [29]. A phase II study that examined pravastatin (40mg/day) plus standard chemotherapy revealed no improvement of

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progression-free the progression-free survival rate at 6 months compared with standard chemotherapy alone [30]. A matched case-control study reported that statin users in patients that underwent radical gastrectomy for stage II and III gastric cancer showed a good prognosis. No significant differences were found in RFS or OS between statin users and non-users. However, subgroup analysis showed that patients who used statins for more than 6 months had more favorable outcomes than non-users or those who used statins for less than 6 months [31]. A population-based cohort study including 3833 patients with gastric cancer showed that statin use after diagnosis was associated with reduced cancer-specific mortality (adjusted HR 0.83; 95%CI, 0.74–0.92) [32]. Several studies have shown that the use of statins reduces the risk of gastric cancer [33-35].

Statins and colorectal cancer (CRC)

Many epidemiologic and clinical studies have been performed on statins and colorectal cancer. However, the results have been inconsistent. One notable observational study from Israel found that 5 or more years of statin use was associated with a 45% reduction in CRC risk (95%CI, 0.40–0.74) [36]. A large cohort study of US veterans also showed a 35% reduction in CRC risk with statin

use (95%CI, 0.55–0.78) [37]. In contrast, several meta-analyses of case-control and cohort studies have shown smaller risk reductions [38, 39] or no association [40, 41]. The inconsistent results from observational studies could be a result of healthier behaviors among statin users compared with nonusers, the ~~difference~~ different durations of statin intake [39], different hydrophilicity of specific statins [42], or different effects of statins on colon or rectal cancers [43, 44].

Statins and hepatocellular carcinoma (HCC)

A nationwide population-based nested case-control study of patients with diabetes indicated a dose-dependent reduction of HCC incidence with statin treatment[45]. In this study, statin users had a dose-dependent (cumulative defined daily dose (cDDD)) reduced risk of developing HCC. (ORs 0.53, 0.36, 0.32, and 0.26 in ≤60, 60–180, 181–365, and >365 cDDD, respectively; P for trend <0.0001). The study also suggested that risk reduction was apparent in the presence of liver disease like chronic viral hepatitis, liver cirrhosis, alcoholic liver disease, and previous cancer (OR=0.27, 95%CI, 0.14–0.50), but not significant in the absence of liver disease (OR=0.64, 95%CI, 0.32–1.29). Similar reports from Taiwan showed a dose-response relationship between statin use and the risk of HCC in an HBV cohort (HRs 0.66, 0.41, and 0.34 in 28–90, 91–365, and

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>365 cDDD, respectively; P for trend <0.0001) and HBV cohort (HRs 0.66, 0.47, and 0.33 in 28–89, 90–180, and >180 cDDD, respectively; P for trend <0.0001) [46] [47]. In a cohort of 7248 HCV-infected patients in the US ERCHIVES database, statin use was associated with a 44% reduction in the development of cirrhosis and a 49% reduction in incident HCC. Atorvastatin and fluvastatin were associated with more significant antifibrotic effects than other statins [48] ~~In~~ in 18080 patients with ~~NAFLD~~ nonalcoholic fatty liver disease without cirrhosis, even higher HCC suppressive effects were suggested (HR 0.29) [49]. Several reports have indicated that statins prevent liver fibrosis, and statins may delay the development of HCC by preventing fibrosis and inflammation of the liver [50]. A phase II trial to evaluate the effect of a simvastatin intervention versus placebo on the change in serum AFP-L3% from baseline to 6 months following treatment initiation in patients with liver cirrhosis with end-stage liver disease (NCT02968810) is currently underway. Atorvastatin is being evaluated for tertiary prevention after complete HCC resection or ablation (Statin for preventing HCC recurrence after curative treatment [SHOT] trial, NCT03024684).

Statins and pancreatic cancer

A meta-analysis of 26 studies showed a significant decrease in pancreatic cancer risk with statin use (RR, 0.84; 95%CI, 0.73–0.97; P < 0.001) [51]. A meta-analysis of 26 studies showed a significant decrease in pancreatic cancer risk with statin use (RR, 0.84; 95%CI, 0.73–0.97; P < 0.001) [52]. In subgroup analyses of the study, a non-significant association was detected between long-term statin use and the risk of pancreatic cancer (RR, 0.98; 95%CI, 0.86–1.11; P=0.718). There was a non-significant association between the use of lipophilic statins and the risk of pancreatic cancer (RR, 0.98; 95% CI, 0.84–1.15; P=0.853). While several studies showed a decreased risk of pancreatic cancer among statin users [52-54], other reports showed no evidence of an association between statin use and pancreatic cancer [52, 55]. A retrospective study of 2427 pancreatic cancer patients demonstrated a 31% decrease in mortality in the group taking simvastatin and a 39% decrease in the group taking atorvastatin [56, 57]. In another study of 1761 pancreatic cancer patients, the 5-year overall survival was 16.6% for statin users and 8.9% for nonusers (P=0.012) [57]. Among 226 patients undergoing resection for pancreatic cancer, active use of moderate- to high-dose simvastatin was associated with improved overall and disease-free survival [58].

RCTs

Many retrospective studies of patients taking statins to control cholesterol have identified a reduced risk of cancer mortality. However, prospective clinical studies have mostly not been successful (Table 1) [29, 30, 59-61]. Several factors might explain these differences, including interpatient differences in the type of statins and the dose and duration of statin use. Furthermore, it is possible that not all cancer patients benefit equally from statin therapy.

There are six types of statins (simvastatin, atorvastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, pravastatin) that can be prescribed for hypercholesterolemia worldwide (Table 2). However, the statins that are most effective against cancer remains unclear. In many in vitro studies, lipophilic statins are more effective in anti-proliferation ability. ~~Because lipophilic statins could cross biological membranes without specific transporter, lipophilic statins have greater intracellular access, and said to be more effective compared with hydrophilic statins.~~ Because lipophilic statins have greater intracellular access and could cross biological membranes without requiring specific transporter, lipophilic statins have greater intracellular access and are said to be more

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effective mechanisms than hydrophilic statins. One report examined differences in the effect of statins on pancreatic cancer using in vivo studies [62]. While simvastatin exerted the highest tumor suppressive effects in vitro, rosuvastatin and fluvastatin were the most potent compounds in an animal model. ~~In a~~ A retrospective cohort study examining the effects of different ~~type~~ types of statins on advanced prostate cancer treated with androgen deprivation therapy, atorvastatin, pravastatin, rosuvastatin or pitavastatin showed a stronger effect on reduction in mortality compared with other statins [63]. ~~To plan an optimal RCT, it is necessary to determine the type of statin that is most effective against cancer~~ It is necessary to determine the type of statin most effective against cancer to plan an optimal RCT.

The RCTs used pravastatin and simvastatin at 40 mg/day, which are moderate-intensity prescriptions (Table 1), and therefore higher doses or prescription of a higher-intensity statin might have yielded greater responses in these studies. Drug combination strategies to potentiate the anti-cancer activity of statin drugs might also be considered for future RCTs.

Biomarkers to identify cancers for which statins are effective

SREBP proteins

The SREBP family of transcription factors controls the upregulation of HMGCR and other lipid metabolism genes and are activated to restore homeostasis in response to cholesterol depletion (Figure 1). A subset of cell lines and primary cells from multiple myeloma patients are unable to induce the expression of SREBP target genes following statin treatment and readily undergo apoptosis [64]. In contrast, cell lines with potent statin-induced SREBP activation were resistant to statin exposure. In prostate cancer, this sterol-regulated feedback loop may modulate statin sensitivity, and a combination therapy of statins and SREBP inhibitors has a synergistic effect in prostate cancer [65]. Although it is theoretically convincing that feedback dysregulation of the MVA pathway is involved in statin sensitivity, further research is required to verify whether SREBP can be a clinically useful biomarker.

HMGCR

~~HMGCR is directly inhibited by statins, and its expression is increased by SREBP through the feedback mechanism induced when intracellular cholesterol is depleted~~ HMGCR is directly inhibited by statins, and SREBP increases HMGCR expression through the feedback mechanism induced when

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intracellular cholesterol is depleted (Figure 1). High HMGCR protein expression is associated with poor prognosis in various cancers [65-67]. ~~Statin sensitivity~~ The efficacy of statins to cancer has been inversely associated with high expression of cholesterol biosynthesis genes, including the HMGCR gene [68] [64]. However, other reports suggested that HMGCR expression alone could not accurately predict ~~statin sensitivity~~ the effect of statins [65, 69]. Whether HMGCR expression alone can accurately predict statin susceptibility remains unclear. One possible explanation for the conflicting data is the poor specificity of many commercially available HMGCR antibodies [70]. Further comprehensive studies using validated HMGCR reagents are needed to accurately evaluate the utility of HMGCR expression ~~as a predictive biomarker of statin sensitivity~~ for predicting the effects of statins.

A population-based case-control study of incident CRC in northern Israel showed that specific polymorphisms in the HMGCR gene modify the protective association between statins and CRC risk. Compared with non-statin users, the unadjusted odds ratio of CRC among statin users with the A/A genotype of rs12654264 in HMGCR was 0.3 (95%CI, 0.18–0.51) and 0.66 among statin users with the T/T genotype (95%CI, 0.41–1.06; P-interaction = 0.0012) [71].

312 **Mesenchymal cell markers**

313 Several studies have demonstrated that tumor cells with higher expression of
314 the mesenchymal cell marker vimentin and lower expression of the epithelial cell
315 marker E-cadherin are highly sensitive to statin treatment [72-74]. Total vimentin
316 and E-cadherin expression are not suitable markers for the sensitivity of statins,
317 but abundant cytosolic vimentin and absent cell surface E-cadherin expression
318 indicate sensitivity to statins [73]. HRAS-induced epithelial-to-mesenchymal
319 transition (EMT) through activation of zinc finger E-box binding homeobox 1
320 (ZEB1) sensitized tumor cells to the antiproliferative activity of statins [74]. These
321 studies also showed that statins preferentially kill cells induced to EMT,
322 suggesting that statins may be more effective against metastatic disease and
323 prevent metastasis.

324 **p53**

325 Wild-type p53 represses the MVA pathway [12], while loss of p53 and two
326 gain-of-function p53 mutants have been shown to induce the expression of MVA
327 pathway genes [11] [75]. Tumors with loss of p53 or the two gain-of-function
328 mutations are particularly vulnerable to statin treatment [76-78].

329 **RAS mutation**

The FPP and GGPP produced by the MVA pathway serve as substrates for the post-translational prenylation of RAS. Therefore, RAS mutations have been hypothesized as potential biomarkers of statin sensitivity. ~~However, some pre-clinical studies have shown that statin susceptibility cannot be predicted by RAS mutation alone~~ However, some pre-clinical studies have shown that RAS mutation alone cannot predict statin susceptibility [74, 79]. In a subgroup analysis of retrospective studies of colorectal cancer, statins were shown to have a higher prognostic effect in cancers with KRAS mutation [80]. However, other studies reported that there was no association between statin effects on colorectal cancer and KRAS status [39, 81]. Further studies are needed to evaluate the utility of KRAS mutation status to predict ~~statin sensitivity~~ the effect of statins on cancer.

ER

In breast cancer, the effect of statins has been associated with ER status, in which ER-negative breast cancer cells are particularly sensitive to statin exposure[67]. These pre-clinical observations are further supported by clinical data demonstrating greater tumor cell apoptosis after fluvastatin treatment in women with ER-negative breast cancer [82].

Combination of statins with epidermal growth factor receptor (EGFR) inhibitors

Several clinical trials have examined the introduction of simvastatin to EGFR inhibitors therapy for KRAS-mutated CRC patients. ~~The hypothesis in these clinical trials was that statin-induced depletion of mevalonate inhibits KRAS prenylation and impedes membrane localization, making EGFR inhibitors more sensitive[83] [84]. Unfortunately, most trials have failed to show significant survival benefits[85-87].~~ The hypothesis in these clinical trials is that the statin-induced depletion of mevalonate inhibits KRAS prenylation, inhibits membrane localization, and enhances the effectiveness of EGFR inhibitors [83] [84]. Unfortunately, most trials have failed to show significant survival benefits with statins[85-87]. These results may suggest that KRAS mutation status is not a predictive biomarker for statin treatment response. Another clinical trial demonstrated that the addition of simvastatin to a cetuximab/irinotecan regimen overcame cetuximab resistance [88]. ~~However, therapeutic benefit was only observed in patients bearing tumors with KRAS mutation and a low Ras signature[88].~~ In this clinical trial, the therapeutic benefit with the statin was only

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366 observed in patients bearing tumors with KRAS mutation and a low Ras
367 signature [88]. The Ras signature score is derived from the expression of Ras
368 pathway-related genes across multiple databases and reflects other possible
369 aberrations such as BRAF and PI3KCA mutation. Therefore, factors other than
370 KRAS mutation must be considered to predict the usefulness of statins in
371 overcoming resistance to anti-EGFR therapy.
372
373 **Combination of statins with radiation therapy (RT)**
374 Statins may have synergistic effects with RT on cancer and may reduce
375 inflammation and gut and skin toxicities induced by RT. In retrospective clinical
376 studies, patients taking statins during RT or chemo-RT for rectal, bladder or
377 prostate cancer treatment had significantly higher rates of pathological complete
378 response (CR), local control and progression-free survival [89] [90] [91] [92] [93].
379 However, no study has shown an apparent benefit [94]. Furthermore, statins
380 significantly reduced RT-induced bowel toxicity and skin injury [95-97]. However, a
381 single-arm phase 2 trial of 53 prostate cancer patients taking lovastatin showed
382 no reduced incidence of grade 2 or higher rectal toxicity ~~compared with~~ than
383 historical controls [98]. An RCT of simvastatin combined with standard

chemotherapy and radiation in preoperative treatment for rectal cancer is underway.

Combination of statins with immunotherapy

Mevalonic acid metabolism is involved in controlling T cell activation[19] [20] [99] [100]. Statins inhibit the geranylgeranylation of small GTPases, resulting in arrested endosomal maturation, prolonged antigen retention, enhanced antigen presentation, and T cell activation. A study reported that statins inhibit the geranylgeranylation of small GTPases resulting in arrested endosomal maturation, prolonged antigen retention, enhanced antigen presentation, and T cell activation. They demonstrated in multiple mouse cancer models, the ~~mevalonate~~ MVA pathway inhibitors are robust for cancer vaccinations and synergize with anti-PD-1 antibodies [101]. The tumor microenvironment is enriched with cholesterol. The high cholesterol in the tumor microenvironment induces CD8+ T cell exhaustion and upregulates immune checkpoints PD-1, 2B4, TIM-3, and LAG-3[102]. Furthermore, lowering cholesterol levels in the tumor microenvironment by simvastatin restores the antitumor activity of CD8+ T cells. Many preclinical studies have demonstrated that the ~~mevalonate~~ MVA pathway

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is involved in immune regulation. Future research into the immunomodulatory properties of statins has important clinical implications for cancer immunotherapy.

Conclusions

Clinical data that evaluated the utility of statins as anticancer agents have shown responses in some but not all cancers. Optimizing the type, dose, and duration of statins, discovering biomarkers to identify responders and developing combination therapies will further enhance the utility of statins in cancer treatment.

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Figure Legends

Figure 1: The MVA pathway and the SREBP-mediated feedback response.

The MVA pathway converts acetyl-CoA into cholesterol and many nonsterol isoprenoids that play important roles in cell growth and survival. Under homeostatic conditions, intracellular cholesterol retains the ~~sterol regulatory element-binding protein (SREBP)~~ SREBP in its full-length, inactive form. In response to cholesterol depletion, such as during treatment with statins, the SREBP protein is cleaved, and the active transcription factor is released and relocalized to the nucleus. Activated SREBP induces the transcription of genes involved in the MVA pathway and cholesterol transport. HMGCS1: HMG-CoA synthase 1, HMGCR: HMG-CoA reductase; LDL-C: low-density, lipoprotein cholesterol, LDLR: low-density, lipoprotein receptor.

Figure 2: Activation of the MVA pathway drives oncogenic signaling pathways.

The geranylgeranyl pyrophosphate produced by the mevalonate cascade is required for activation of Rho GTPases that, in turn, activate YAP/TAZ by inhibiting their phosphorylation and promoting their nuclear accumulation.

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The Hedgehog (HH) signaling pathway is regulated by cholesterol. Cholesterol

435 and cholesterol-derived oxysterols activate HH signal transduction, whereas
436 inhibition of the MVA pathway or downstream sterol biosynthesis decreases HH
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438 Cholesterol is the precursor for steroid hormones such as estrogen and
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440 prostate cancers via the activation of ~~estrogen receptor-α (ERα)~~ Erα and
441 androgen receptor (AR), respectively.
442

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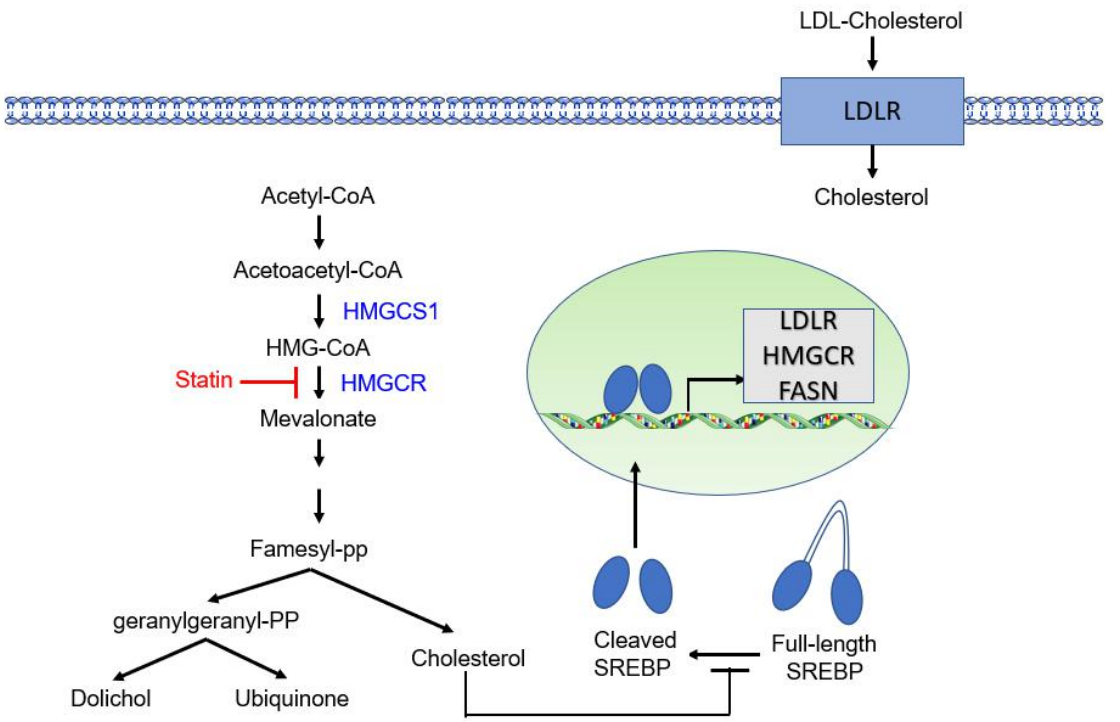
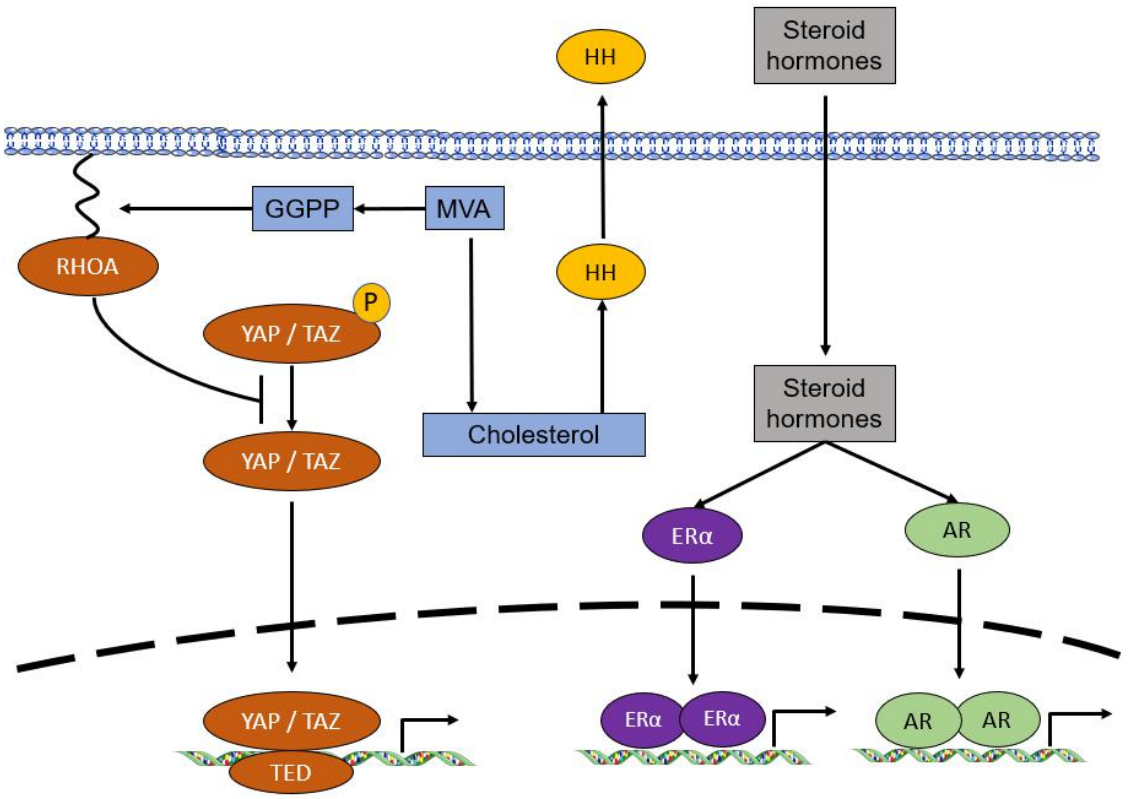
Figure 1. The MVA pathway and its SREBP-mediated feedback response.



838 Figure 2. Activation of the MVA pathway drives oncogenic signalling pathways.



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841 Table 1. RCT of statins combination therapy.

Cancer type	**Study type**	**Statin (Dose)**	**Combination therapies**	**Outcome**
Gastric cancer	Phase III	Simvastatin (40 mg/d)	Capecitabine and cisplatin	Simvastatin + capecitabine-cisplatin did not increase PFS compared to capecitabin-ecisplatin alone
	Phase II	Pravastatin (40 mg/d)	Epirubicin, cisplatin and capecitabine	Pravastatin + standard chemotherapy was well tolerated, but did not improve progression-free rate at 6 months compared to chemotherapy alone
Colorectal	Phase III,	Simvastatin (40 mg/d)	FOLFIRI/XELIRI	Simvastatin + FOLFIRI/XELIRI did not increase PFS compared to FOLFIRI/XELIRI alone
Hepatocellular	Phase III	Pravastatin (40 mg/d)	Sorafenib	Pravastatin + sorafenib did not improve OS or PFS compared to sorafenib alone
	Phase II	Pravastatin (40 mg/d)	Transcatheter arterial embolization followed by fluorouracil	Pravastatin + standard therapy prolonged OS compared to standard therapy alone
Pancreatic	Phase II	Simvastatin (40 mg/d)	Gemcitabine	Simvastatin + gemcitabine was well tolerated, but did not decrease TTP compared to gemcitabine alone

842

843 Table 2. Properties of statins.

Statin	Solubility [3]	Metabolism [3]	Human dose to lower cholesterol (mg)		
			Low	Moderate	High
Simvastatin	Lipophilic	CYP3A4	10	20-40	-
Atorvastatin	Lipophilic	CYP3A4/2C9	-	10-20	40-80
Fluvastatin	Lipophilic	CYP2C9	20-40	80	-
Pitavastatin	Lipophilic	Non-CYP450	-	1-4	-
Lovastatin	Lipophilic	CYP3A4/2C9	20	40-80	-
Rosuvastatin	Hydrophilic	Non-CYP450	-	5-10	20-40
Pravastatin	Hydrophilic	Non-CYP450	10-20	40-80	-

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