Statins as Anticancer Agents in the Era of Precision Medicine

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ABSTRACT

Statins are widely prescribed cholesterol-lowering drugs that inhibit HMG-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate metabolic pathway. Multiple lines of evidence indicate that certain cancers depend on the mevalonate pathway for growth and survival, and, therefore, are vulnerable to statin therapy. However, these immediately available, well-tolerated, and inexpensive drugs have yet to be successfully repurposed and integrated into cancer patient care. In this review, we highlight recent advances and outline important considerations for advancing statins to clinical trials in oncology.

Introduction

Since their approval by the FDA in the late 1980s, statins have revolutionized the clinical management of high cholesterol. Statins are specific inhibitors of the mevalonate pathway, which is responsible for the *de novo* synthesis of cholesterol and nonsterol isoprenoids (**Fig. 1**). Specifically, statins inhibit the conversion of HMG-CoA to mevalonate by inhibiting the rate-limiting enzyme of the mevalonate pathway, HMG-CoA reductase (HMGCR). In addition to its important roles in normal physiology, the mevalonate pathway supports tumorigenesis and is known to be deregulated in human cancers (1–4). As such, there is significant interest in repurposing statins as anticancer agents. Statins have been shown to induce potent tumor-specific apoptosis (5–7). Moreover, many retrospective studies have reported that statin use is associated with reduced cancer risk (8–11), lower cancer grade and stage at diagnosis (12, 13), and reduced recurrence and/or cancer-specific mortality (14–18). Given that statins are FDA-approved, well-tolerated, and are available as generic drugs, they offer an immediate, safe, and inexpensive opportunity to improve cancer patient care and treatment outcomes.

Despite these promising observations, statins have yet to be repurposed and integrated into cancer patient care. Emerging evidence suggests that certain molecular subtypes of cancer are more susceptible to statin therapy than others, highlighting the importance of predictive biomarkers for patient stratification. Moreover, recent clinical trials have provided important insights into how to realistically use these agents in an oncology setting. In this review, we highlight the gaps in knowledge that have precluded the repurposing of statins as anticancer agents, as well as recent advances that will help inform future clinical trial design.

Statin Mechanism of Action

Statins compete with HMG-CoA for binding to the active site of HMGCR, thereby reducing mevalonate synthesis. As a consequence, statins deplete intracellular cholesterol, which triggers a homeostatic feedback mechanism governed by the sterol regulatory element-binding protein (SREBP) family of transcription factors (**Fig. 1**). Activation of the SREBPs results in the increased expression of mevalonate pathway and sterol metabolism genes, including *HMGCR* and the low-density lipoprotein (LDL) receptor (*LDLR*). Increased membrane expression of LDLR leads to enhanced LDL cholesterol (LDL-C) uptake from the bloodstream, thus effectively lowering serum cholesterol levels. As a result, statins are commonly prescribed to reduce the risk of cardiovascular disease or improve survival in patients with cardiovascular disease.

Cholesterol has also been shown to play multifaceted roles in tumorigenesis (reviewed in refs. 1, 19). In specific contexts, statins have been shown to elicit their anticancer effects through the depletion of cholesterol. For example, one study demonstrated that simvastatin decreases the cholesterol content of lipid rafts in prostate cancer cells, which hinders AKT signaling and induces apoptosis (20). Moreover, in a subset of medulloblastoma driven by aberrant Hedgehog signaling, the depletion of cholesterol impairs signal transduction and inhibits cancer cell growth (21). However, in the majority of other reports, exogenous cholesterol is unable to rescue statin-induced apoptosis, highlighting a role for other end products of the mevalonate pathway in cancer cell survival.

In addition to cholesterol, statins also reduce the synthesis of nonsterol isoprenoids, including geranylgeranyl pyrophosphate (GGPP; **Fig. 1**). Several studies have shown that statin-induced apoptosis can be consistently and fully rescued by exogenous mevalonate or mevalonate-derived GGPP (22–25). These studies not only support that statin-induced apoptosis is an on-target effect, but also reveal that certain cancers rely on GGPP synthesis for survival. GGPP can serve as a substrate for protein prenylation, or as a precursor for the synthesis of other metabolites, such as coenzyme Q (CoQ) and dolichols (1). In recent years, it has become apparent that different cancer cell types have a dependency on distinct fates of GGPP (22–24, 26, 27). In acute myeloid leukemia and multiple myeloma cells, statin-induced apoptosis can be phenocopied by prenylation inhibitors, which suggests that these cancers rely on GGPP synthesis, at least in part, for protein prenylation (22, 23, 28). However, in other cancers where statin-induced cell death can be rescued by exogenous GGPP, statin sensitivity can be uncoupled from effects on protein prenylation (24). Indeed, recent studies have shown that

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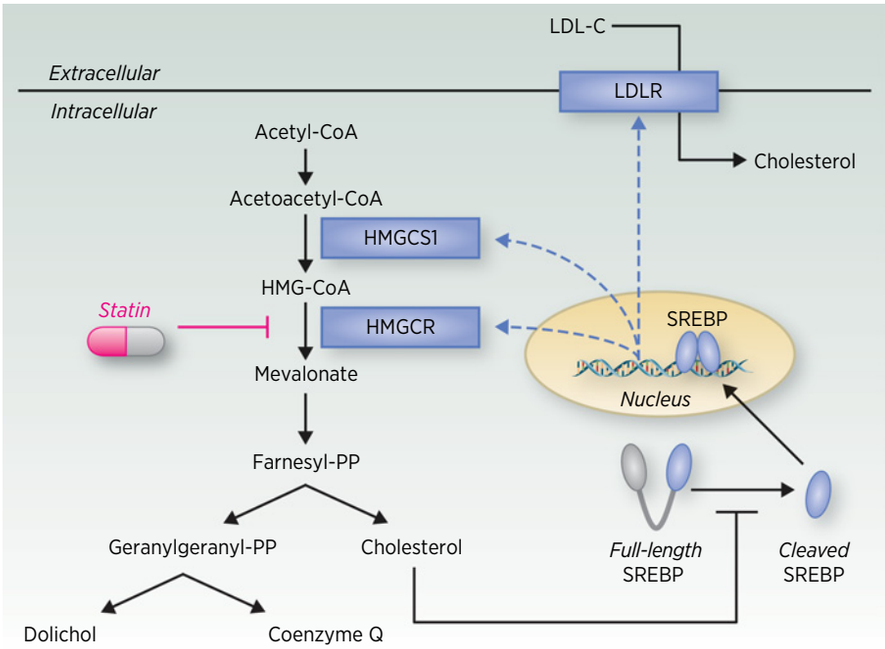

Figure 1.
Schematic of the mevalonate pathway and its SREBP-mediated feedback response. The mevalonate pathway converts acetyl-CoA to cholesterol and a number of non-sterol isoprenoids that play important roles in cell growth and survival. Under homeostatic conditions, intracellular cholesterol retains the SREBPs in their full-length, inactive form. In response to cholesterol depletion, such as when cells are treated with a statin, the SREBPs are cleaved, thus liberating the active transcription factor. Nuclear SREBP induces the transcription of genes involved in the mevalonate pathway and cholesterol transport. HMGCS1, HMG-CoA synthase 1.

certain tumors rely on the mevalonate pathway for the synthesis GGPP-derived CoQ (26, 27). In these cells, statin treatment leads to oxidative stress and apoptosis (26, 27), which can be rescued by exogenous CoQ (26).

Despite numerous studies implicating the direct, intratumoral inhibition of HMGCR as the mechanism by which statins elicit their anticancer effects, systemic contributions are also likely. It is important to note that, unlike in humans, statin treatment does not reduce serum cholesterol levels in mice (20, 29). While reducing circulating cholesterol levels may add to the benefit of statin therapy in patients with cancer, evidence from preclinical studies support a direct mechanism. Thus, in this review, we focus primarily on the direct effects of statins on cancer cells.

Identifying Statin Vulnerable Tumors

While many epidemiologic studies report positive associations between statin use and cancer patient outcomes, the extent to which statin use confers a benefit is variable between studies (14–18). Several factors might explain this heterogeneity, including interpatient differences in the type of statin, dose, and duration of statin use (discussed further in the next section). Furthermore, it is possible that not all patients with cancer benefit equally from statin therapy. Consistent with this hypothesis, highly heterogeneous responses to statin exposure across panels of cancer cell lines have been reported (23, 24, 30–32), and biomarkers of statin sensitivity have recently been described (**Fig. 2**). Hence, different tumor subtypes are not equally vulnerable to statin therapy.

If statins are to be repurposed for the precise treatment of cancer, we must first identify which tumor subtypes are vulnerable to statin-mediated HMGCR inhibition. In breast cancer, for example, statin sensitivity has been associated with estrogen receptor (ER) status, where ER-negative breast cancer cells are particularly sensitive to statin exposure (31). These preclinical observations are further supported by clinical data demonstrating greater tumor cell apoptosis after fluvastatin treatment in women with ER-negative breast cancer (33). Independent studies have demonstrated that tumor cells of various origins with higher expression of mesenchymal cell markers (e.g., vimentin) and/or lower expression of epithelial cell markers (e.g., E-cadherin) are highly sensitive to statin treatment (24, 34, 35). Furthermore, statins have been shown to preferentially kill cells induced to undergo epithelial-to-mesenchymal transition (24), suggesting that they may be effective at impairing metastatic disease. Whether ER-negative breast tumors are more sensitive to statins because they are more mesenchymal remains to be determined. Moreover, it remains poorly understood why cancer cells in a mesenchymal state are vulnerable to HMGCR inhibition. Nonetheless, these data further support the concept that statin sensitivity can be stratified by tumor subtype.

Aberrant sterol metabolism

In some cancer cells, statin sensitivity is inversely associated with the ability to activate a feedback mechanism in response to mevalonate pathway inhibition. In response to cholesterol depletion, the SREBP family of transcription factors is activated to restore homeostasis (**Fig. 1**). In certain cancer cells, this feedback mechanism is impaired, which renders them vulnerable to HMGCR inhibition. In multiple myeloma, for example, it was shown that a subset of cell lines and primary patient-derived cells fail to induce the expression of SREBP target genes following statin treatment and readily undergo apoptosis (36). In contrast, cell lines and primary cells with robust statin-induced SREBP activation were resistant to statin exposure (36). Statin sensitivity has subsequently been associated with impaired feedback regulation of the mevalonate pathway in other cancer types, including prostate cancer (32). Further research is required to better understand why some cancer cells have impaired feedback regulation of the mevalonate pathway, and to identify a clinically amenable biomarker that can stratify patients on the basis of this dampened homeostatic response.

In breast cancer, statin sensitivity has been inversely associated with high basal expression of cholesterol biosynthesis genes, including *HMGCR* (37). This is consistent with a report that acquired resistance to statin exposure *in vitro* is associated with significantly elevated

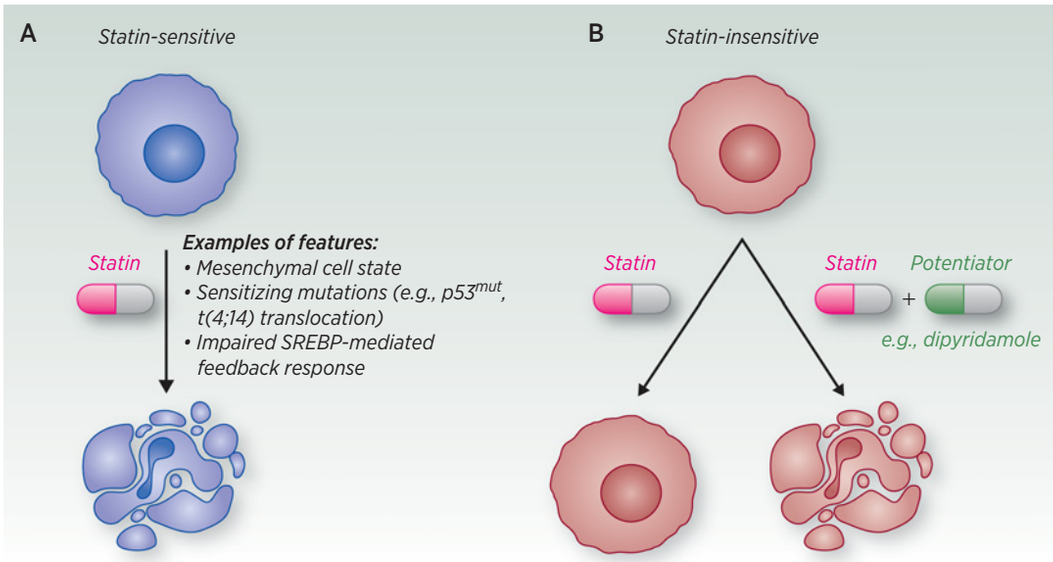

Figure 2.

Identifying statin vulnerable tumors. Cancer cells display a wide range of statin drug sensitivities, highlighting that not all tumors are vulnerable to mevalonate pathway inhibition. **A,** Statin sensitivity has been associated with various molecular features, including tumor-specific genetic lesions and deficiencies in regulating the mevalonate pathway. Treatment of these tumor cells induces cell death in a dose- and time-dependent manner. **B,** In other tumor cells, a statin alone is insufficient to induce cell death; however, cotreatment with additional targeted agents can sensitize these cells to statin treatment. For example, the drug dipyridamole prevents the compensatory activation of the SREBPs following statin treatment, thereby potentiating statin-induced cell death.

HMGCR expression (38). However, studies that have evaluated HMGCR expression as a predictive biomarker of statin sensitivity have yielded conflicting results (31, 36–39). This is likely due, in part, to the lack of specificity of many commercially available HMGCR antibodies (2, 37, 40). These observations also suggest that there is a complex relationship between HMGCR expression and statin sensitivity in cancer. On one hand, elevated HMGCR expression and deregulated mevalonate pathway activity can support tumorigenesis and render cancer cells vulnerable to statin treatment (2, 41). In these tumors, elevated HMGCR expression may indicate a tumor dependency, whereby even a slight dampening of mevalonate pathway activity is sufficient to induce tumor-specific cell death. On the other hand, as HMGCR expression continues to increase (e.g., via elevated SREBP activity), higher statin drug concentrations are required to inhibit the mevalonate pathway, thereby decreasing statin sensitivity (32, 36, 38, 42). Hence, careful consideration is required when evaluating the utility of HMGCR expression as a predictive biomarker of statin sensitivity in cancer.

Mutations and altered cell signaling

There is extensive interplay between the mevalonate pathway and signal transduction in cancer (reviewed in ref. 1), and, therefore, aberrant cell signaling in tumors may confer increased sensitivity to statin therapy. For example, mevalonate-derived farnesyl pyrophosphate (FPP) and GGPP serve as substrates for the posttranslational prenylation of oncoproteins such as RAS and RHO, which is important for their proper localization and function (43). As such, it has long been hypothesized that RAS mutations may be potential biomarkers of statin sensitivity. While activated RAS can sensitize some cells to statins (24, 44), preclinical studies have shown that statin-induced apoptosis is independent of RAS localization and function (23, 24, 44). Moreover, several clinical trials have evaluated statin therapy in patients with RAS-mutant tumors, but the majority of trials failed to demonstrate promising therapeutic responses (45–48). Hence, despite the interplay between RAS and the mevalonate pathway in cancer, RAS status is a poor predictor of statin sensitivity.

A number of recent studies have also implicated *TP53* status in modulating cancer cell sensitivity to statins. While wild-type p53 represses the mevalonate pathway (49), loss of p53 and certain gain-of-function p53 mutants have been shown to induce the expression of mevalonate pathway genes (41, 49, 50). Consistently, it has been demonstrated that these p53-null (26) or -mutant (50–52) tumors are dependent on the mevalonate pathway and particularly vulnerable to statin treatment. The latter has been attributed to the roles of the mevalonate pathway in the stability of mutant p53 protein (51–53).

Cancer type–specific biomarkers of statin sensitivity may also exist. For example, in clear-cell renal cell carcinoma, cells driven by loss of the tumor suppressor, von Hippel-Lindau (*VHL*; ∼90% of tumors), were found to be dependent on the mevalonate pathway for proper RHO and RHO kinase (ROCK) signaling, and were more sensitive to statin treatment compared with *VHL* wild-type cells (54). Moreover, in multiple myeloma, cancer cells driven by a t(4;14) chromosomal translocation are highly dependent on GGPP synthesis and more sensitive to statin-induced apoptosis compared with other multiple myeloma subtypes (55). While *TP53, VHL*, and t(4;14) status can potentially predict statin sensitivity, further validation in patients will be required before these biomarkers can be used clinically.

Considerations for Advancing Statins to Clinical Trials in Oncology

After identifying which patients with cancer might benefit from the addition of a statin to their treatment regimen, the next step is

evaluating how best to prescribe these drugs as anticancer agents. Data from epidemiologic, preclinical, and early-phase clinical studies have demonstrated that statin type, dose, and treatment duration are all important variables to consider when evaluating statins as anticancer agents. While all FDA-approved statins are effective in lowering serum cholesterol by inhibiting HMGCR activity in the liver (**Table 1**), their ability to directly inhibit HMGCR in extrahepatic tumor tissues may be statin type specific. It has been hypothesized that the lipophilic statin drugs are more likely to reach and readily enter extrahepatic cells, whereas hydrophilic statins are more hepatoselective (56). Consistent with this hypothesis, epidemiologic studies have reported that lipophilic, but not hydrophilic, statin use is associated with reduced cancer incidence (10) and recurrence (15) in patients with breast cancer.

Recent clinical studies have reported that the lipophilic statins, atorvastatin (57) and fluvastatin (58), are measurable in prostatic tissue at low nanomolar concentrations after short-term treatment with a typical cholesterol-lowering dose (80 mg/day). While these concentrations are less than those evaluated in most *in vitro* studies, these lower concentrations, when prescribed in the neoadjuvant setting (discussed further in the next section), were shown to reduce tumor cell proliferation (59) or induce apoptosis (58) in a time-dependent manner. These observations are consistent with epidemiologic (60, 61), preclinical (30, 31, 58, 62), and clinical (33, 58, 59) data, all of which indicate that the anticancer effects of statins are both dose- and time-dependent. This implies that comparable anticancer responses may be achieved using lower statin doses over longer durations versus higher statin doses over a shorter period of time. Phase I dose escalation studies have indeed demonstrated that statins are well-tolerated at doses much higher than typically prescribed for cholesterol management ($\sim$10–30 $\times$ higher), at least for defined periods of time (63–66).

Interestingly, while similar concentrations of atorvastatin and fluvastatin were measured in prostatic tissue following acute treatment, only atorvastatin was found to accumulate within the prostate relative to the serum (57, 58). This may have important implications for longer treatment schedules, as the pharmacokinetic properties of specific statins may enable higher achievable drug concentrations within certain tumor tissues over time. The choice of statin and dosing schedule will likely depend on the type of cancer being treated.

Neoadjuvant statin therapy

A promising therapeutic space for the use of statins is soon after diagnosis to delay the need for more aggressive treatment and/or improve the outcome of first-line therapy. In a series of window-of-opportunity trials in breast and prostate cancer, lipophilic statin treatment showed evidence of reduced tumor cell proliferation and increased apoptosis in a subset of patients. In these studies, short-term neoadjuvant treatment (between 1.5 and 12 weeks) with a cholesterol-lowering dose of either fluvastatin (33, 58) or atorvastatin (39, 59) was evaluated. In all four studies, pretreatment biopsy samples were compared with surgical material obtained after statin treatment. Immunohistochemistry was then performed to evaluate markers of tumor cell proliferation (Ki67) and/or apoptosis (cleaved caspase-3). Fluvastatin treatment was reported to increase tumor cell apoptosis in patients with high-grade breast cancer (33) and localized prostate cancer (58), where greater increases were observed in patients on a higher dose (33) or treated for longer durations (58). Similarly, neoadjuvant atorvastatin therapy was shown to reduce tumor cell proliferation in patients with primary invasive breast cancer (39). Subsequent microarray analysis in these same paired clinical samples revealed atorvastatin-induced effects on genes associated with apoptosis and reduced MAPK signaling (67). While neoadjuvant atorvastatin therapy was not found to reduce intratumoral Ki67 staining in patients with prostate cancer overall, a significant decrease in Ki67 was observed in patients on atorvastatin for greater than 28 days (59); however, a similar response in Ki67 was not observed following fluvastatin therapy (58).

Not only do these studies reinforce that the anticancer effects of statins are both dose- and time-dependent, but they further highlight that certain subgroups of patients may benefit more than others. For example, neoadjuvant fluvastatin treatment in breast cancer was found to decrease Ki67 and increase cleaved caspase-3 expression in patients with ER-negative, high-grade tumors (33), which is consistent with ER-negative breast cancer cells being particularly vulnerable to statin exposure (31). Future studies are needed to evaluate the potential long-term benefits that these effects may have on disease progression.

Statins in combination with standard chemotherapy

In phase I/II studies that have evaluated statins in combination with various standard-of-care therapies, promising responses have been reported in some patients, ranging from stable disease to complete responses (64, 66, 68, 69). While it is premature to draw conclusions about statin efficacy from these studies, these data provide important information that should be considered when designing future randomized controlled trials (RCTs). For example, the variable responses observed when considering mixed patient populations suggest that there are likely specific subsets of patients with cancer who might

Table 1. Properties of different statin drugs.

Statin drug (trade name)	Human dose (mg; ref. 103) Low (↓ LDL-C <30%)	Moderate (↓ LDL-C 30%–49%)	High (↓ LDL-C ≥50%)	Metabolism (104)	Solubility (104)
Atorvastatin (Lipitor)	N/A	10–20	40–80	CYP3A4	Lipophilic
Rosuvastatin (Crestor)	N/A	5–10	20–40	Non-CYP450 (limited CYP2C9/8)	Hydrophilic
Simvastatin (Zocor)	10	20–40	N/A	CYP3A4	Lipophilic
Pravastatin (Pravachol)	10–20	40–80	N/A	Non-CYP450	Hydrophilic
Lovastatin (Mevacor)	20	40–80	N/A	CYP3A4	Lipophilic
Fluvastatin (Lescol)	20–40	40 mg 2 $\times$/day or XL 80 mg	N/A	CYP2C9	Lipophilic
Pitavastatin (Livalo)	N/A	1–4	N/A	Non-CYP450 (limited CYP2C9/19)	Lipophilic

Abbreviation: XL, extended release.

Table 2. Summary of RCTs of statins combined with other therapies in oncology.

Cancer type	Statin (dose)	Type of study	Other therapies	Outcome	Reference
Lung (SCLC)	Pravastatin (40 mg/day)	Phase III, double-blind, placebo-controlled	Etoposide plus cisplatin or carboplatin	Pravastatin + standard chemotherapy did not offer additional benefit compared with chemotherapy alone	70
Lung (NSCLC)	Simvastatin (40 mg/day)	Phase II	Gefitinib	Simvastatin + gefitinib resulted in higher tumor response rates and longer PFS compared with gefitinib alone only in subgroup of patients with $EGFR^{WT}$ nonadenocarcinomas	92
	Simvastatin (40 mg/day)	Phase II	Afatinib	Simvastatin + afatinib was well-tolerated, but did not improve response rates compared with afatinib alone in patients with nonadenocarcinomas	93
Hepatocellular	Pravastatin (40 mg/day)	Phase II	Transcatheter arterial embolization followed by fluorouracil	Pravastatin + standard therapy prolonged OS compared with standard therapy alone	105
	Pravastatin (40 mg/day)	Phase III	Sorafenib	Pravastatin + sorafenib did not improve OS or PFS compared with sorafenib alone	72
Gastric	Pravastatin (40 mg/day)	Phase II	Epirubicin, cisplatin and capecitabine	Pravastatin + standard chemotherapy was well-tolerated, but did not improve progression-free rate at 6 months compared with chemotherapy alone	106
	Simvastatin (40 mg/day)	Phase III, double-blind, placebo-controlled	Capecitabine and cisplatin	Simvastatin + capecitabine–cisplatin did not increase PFS compared with capecitabine–cisplatin alone	73
Colorectal	Simvastatin (40 mg/day)	Phase III, double-blind, placebo-controlled	FOLFIRI/XELIRI	Simvastatin + FOLFIRI/XELIRI did not increase PFS compared with FOLFIRI/XELIRI alone	71
Pancreatic	Simvastatin (40 mg/day)	Phase II, double-blind, placebo-controlled	Gemcitabine	Simvastatin + gemcitabine was well-tolerated, but did not decrease TTP compared with gemcitabine alone	48
Multiple myeloma	Lovastatin (0.5–2 mg/kg)	Phase II	Thalidomide and dexamethasone	Lovastatin + thalidomide–dexamethasone prolonged OS and PFS compared with thalidomide–dexamethasone alone	68

Abbreviations: OS, overall survival; TTP, time to progression.

benefit from statin therapy, highlighting the need for predictive biomarkers to inform patient stratification.

Statin therapy has been evaluated in a number of RCTs (**Table 2**), including phase III trials in patients with small-cell lung cancer (SCLC; ref. 70), metastatic colorectal cancer (71), advanced hepatocellular carcinoma (72), or advanced gastric cancer (73). In these studies, the addition of 40 mg/day pravastatin (70, 72) or simvastatin (71, 73) to standard chemotherapy offered no additional benefit compared with chemotherapy alone. While disappointing, these studies were designed and initiated prior to evidence demonstrating that specific tumor subtypes are more vulnerable to statins than others. No phase III study to date has stratified patients on the basis of molecular markers predictive of statin sensitivity; however, *post hoc* analyses may uncover that a particular subgroup of patients benefited from statin therapy in these phase III trials. Moreover, given our increasing understanding of the differences between statin drugs and their differential ability to accumulate in extrahepatic tissues (57, 58, 74), choice of statin drug is an important factor. Both pravastatin and simvastatin at 40 mg/day 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 anticancer activity of statin drugs might also be considered for future RCTs.

Combining Statins With Molecular-targeted Therapies

Statins have been evaluated in combination with various classes of other anticancer agents, including targeted therapeutics against different oncogenic signaling pathways and epigenetic modifiers (**Table 3**). Combining a statin with other targeted therapies can enhance their anticancer activity and overcome potential drug resistance mechanisms.

As with any combination therapy approach, not only is there the potential for synergistic anticancer activity, but there is also the possibility of drug–drug interactions that lead to increased toxicity. Hence, careful consideration must be given to drug selection. In addition to differences in solubility, statins also differ from one another in how they are metabolized (**Table 1**). For example, atorvastatin is highly lipophilic, but is primarily metabolized by cytochrome P450 (CYP450) 3A4 (CYP3A4). CYP3A4 function is modulated by certain foods and several commonly prescribed medications (including many chemotherapeutics), and, therefore, lipophilic statins metabolized by other enzymes, such as fluvastatin or pitavastatin, may offer a lower potential for unwanted drug–drug interactions (75). Moreover, some statins, such as lovastatin, have been shown to interact with and modulate P-glycoprotein activity (a major drug efflux pump; refs. 30, 76). These factors must be considered when evaluating statins in combination with other targeted therapies.

Table 3. Statin combinations with small-molecule inhibitors to increase anticancer efficacy.

Agent	Molecular target(s)	Cancer type(s)	Proposed mechanism(s) of interaction	Reference
Dipyridamole	Polypharmacology with activity against SREBP	Multiple cancer types, including AML, multiple myeloma, prostate, and breast	Dipyridamole inhibits statin-induced SREBP activation and potentiates statin-induced apoptosis of tumor cells	32, 38, 42
Zoledronic acid	FPP synthase	Multiple cancer types, including lymphoma, breast, and ovarian	Combined inhibition of the mevalonate pathway	52, 107, 108
Abiraterone acetate Enzalutamide	AR	Prostate	Enhanced suppression of AR signaling; statins reduce AR expression and activity	82–84
Venetoclax	BCL2	Hematologic cancers	Statins suppress protein geranylgeranylation, resulting in PUMA upregulation and venetoclax sensitization	109
Selumetinib	MEK, Cys-Glu antiporter	Pancreatic	Enhanced oxidative stress	27
Erlotinib Gefitinib	EGFR	Multiple cancer types, including NSCLC and HNSCC	Enhanced suppression of EGFR signaling; statins inhibit ligand-induced EGFR activation and AKT signaling	87–91
Vismodegib	Smoothened	Medulloblastoma	Enhanced suppression of Hedgehog signaling	21
JQ1	BET bromodomains	Pancreatic	Combined inhibition of processes downstream of acetyl-CoA	3
Vorinostat Panobinostat	HDACs	Multiple cancer types, including renal and breast	Impaired autophagic flux, AMPK activation	94–96
Celecoxib	COX2	Multiple cancer types, including prostate and colorectal	Unknown	110–112
Metformin	Polypharmacology, indirect activation of AMPK	Multiple cancer types, including prostate and endometrial	Unknown; possibly enhanced AMPK activation	113, 114
Anti-PD-1 antibody	PD-1	Multiple cancer types, including melanoma	Enhanced T-cell activation and antitumor immunity	102

Abbreviations: AML, acute myeloid leukemia; HNSCC, head and neck squamous cell carcinoma.

SREBP inhibition

One approach to potentiate statin-induced apoptosis is via combination treatment with SREBP inhibitors. Similar to normal cells, statin treatment triggers the activation of the SREBPs in most cancer cells (**Fig. 1**). Statin-mediated activation of the SREBPs, particularly SREBP2, results in the induction of mevalonate pathway gene expression, including the upregulation of HMGCR. Knockdown of *SREBF2* (the gene that encodes SREBP2) via RNAi suppresses this feedback loop and sensitizes cancer cells to statin-induced death (32, 77). Consistent with this result, our group identified that the drug dipyridamole, an agent approved for the secondary prevention of cerebral ischemia, could synergize with statins to induce apoptosis in hematologic cancer (42) and prostate cancer (32) cells. Mechanistically, we and others have shown that dipyridamole inhibits statin-induced SREBP activation, thereby preventing the upregulation of mevalonate pathway genes in response to statin exposure (32, 38, 42). By impairing this feedback mechanism, dipyridamole significantly reduces the concentration of statin drug needed to inhibit the mevalonate pathway and induce apoptosis. Because both statins and dipyridamole are FDA-approved drugs, there is interest in advancing this drug combination to clinical trials in oncology.

Antiandrogen therapy

Epidemiologic evidence supports a positive association between statin use and response to antiandrogen therapy in patients with prostate cancer (78–81). These data are further supported by preclinical studies showing that the combination of a statin with either abiraterone acetate or enzalutamide enhances cytotoxicity in prostate cancer cell lines (82, 83). Moreover, enzalutamide-resistant prostate cancer cells upregulate HMGCR expression, and treatment with simvastatin resensitizes these cells to enzalutamide (84).

A number of mechanisms have been proposed for the interaction between statins and antiandrogen therapy. First, cholesterol is a precursor for androgen biosynthesis, and, therefore, statin-mediated cholesterol depletion may also reduce intratumoral androgen levels. Consistent with this hypothesis, statins have been shown to inhibit androgen receptor (AR) activity in prostate cancer cell lines (82–85). In these same studies, statins were also found to reduce AR expression (82–85), possibly via the inhibition of AKT/mTOR signaling (84). Moreover, statin use has been associated with reduced serum PSA levels in patients with prostate cancer (86), which is regulated by AR. Finally, certain statin drugs can compete with dehydroepiandrosterone sulfate, a testosterone precursor, for binding to a transporter at the surface of prostate cancer cells, and, therefore, block androgen uptake (78). Taken together, statins can enhance antiandrogen therapy through multiple mechanisms. Prospective clinical trials are warranted to evaluate the combination of a statin and antiandrogen therapy in patients with advanced prostate cancer and other steroid hormone–driven malignancies.

EGFR inhibitors

Given the interplay between the mevalonate pathway and oncogenic signal transduction (1), numerous studies have evaluated the combination of a statin with various agents that target cell signaling (**Table 3**). For example, statins synergize with EGFR inhibitors, including erlotinib and gefitinib, to induce cell death in a number of different cancer

cell types *in vitro* (87). Statins have been shown to inhibit ligand-induced EGFR activation and downstream AKT signaling, which can be reversed by exogenous GGPP (88, 89). Statin-mediated inhibition of AKT has further been implicated as a mechanism for overcoming resistance to EGFR inhibitors in non–small cell lung cancer (NSCLC) cells (90, 91). Combined treatment with a statin and EGFR inhibitor has been evaluated in phase II RCTs in patients with NSCLC (**Table 2**). Simvastatin (40 mg/day) in combination with gefitinib resulted in higher tumor response rates and longer progression-free survival (PFS) compared with gefitinib alone in patients with EGFR wild-type nonadenocarcinomas (92); however, similar responses were not observed when simvastatin was combined with afatinib, a second-generation EGFR inhibitor (93).

Epigenetic inhibitors

An emerging area of investigation is the combination of statins and epigenetic inhibitors, including histone deacetylase (HDAC) and bromodomain inhibitors (refs. 3, 94–96; **Table 3**). A series of dual-action compounds has also been developed, where the hydroxamate group of vorinostat, an HDAC inhibitor, was fused to lovastatin (97). The resulting HMGCR-HDAC dual inhibitors have been shown to possess potent and selective anticancer activity (98, 99). In mouse models of colorectal cancer, treatment with a dual HMGCR-HDAC inhibitor significantly reduced intestinal inflammation, decreased tumor burden, and impaired metastasis (98).

The mechanism by which statins and different epigenetic inhibitors interact remains poorly characterized. However, given that acetyl-CoA is required for both protein acetylation and mevalonate metabolism, it is possible that simultaneously inhibiting multiple acetyl-CoA–dependent processes is detrimental to tumor cells. Indeed, both histone acetylation and mevalonate pathway gene expression are upregulated in pancreatic adenocarcinoma (PDAC) tumors, and cotreatment with atorvastatin and a bromodomain inhibitor, JQ1, significantly impairs PDAC cell growth (3).

Immunotherapy

Statins have also been shown to elicit immunomodulatory effects (reviewed in ref. 100). High cholesterol in the tumor microenvironment and in tumor-infiltrating $CD8^+$ T cells is associated with elevated expression of immune checkpoint proteins and enhanced T-cell exhaustion, which allows tumor cells to escape immune surveillance (101). Importantly, reducing cholesterol levels in the tumor microenvironment or in $CD8^+$ T cells restores T-cell anti-tumor activity (101). These critical observations highlight the potential for statins to be combined with immunotherapy for the treatment of cancer. An independent study that evaluated the vaccine adjuvant activity of statins revealed that lipophilic statins, such as simvastatin, induce a strong Th1 and cytotoxic T-cell response in mice and enhance the therapeutic response to cancer vaccination (102). In particular, the inhibition of protein prenylation in antigen-presenting cells enhanced antigen presentation and T-cell activation (102). This favorable antitumor response was further potentiated by programmed cell death protein-1 (PD-1) blockade, which resulted in prolonged survival in mice inoculated with melanoma or human papillomavirus–associated tumors (102). As most preclinical studies to date have evaluated the anticancer activity of statins *in vitro* or in immunocompromised animal models, future investigation into the immunomodulatory properties of statins will undoubtably open exciting avenues of research with important clinical implications.

Outlook

If statins are to be integrated into cancer patient care, a precision medicine approach is necessary. In this review, we highlighted recent advances and outlined important considerations for advancing statins to clinical trials in oncology. We also proposed key questions that should be the focus of future research (**Table 4**). As not all tumors are vulnerable to statin-mediated mevalonate pathway inhibition, the development of predictive biomarkers of statin sensitivity is crucial for patient stratification. We have highlighted some promising preclinical biomarkers of statin sensitivity, which can be validated in future clinical trials by enriching for patients with these tumor features. In addition, *post hoc* analyses of completed, unbiased RCTs may similarly reveal novel biomarkers of statin response. However, few statin RCTs in oncology have been performed to date, and those that have been performed evaluated moderate-intensity statin regimens. Given the increasing evidence that certain statins may be better suited as anticancer agents than others, coupled with data indicating that statin-induced apoptosis is both dose- and time-dependent, careful consideration is required when deciding which statin(s) and dosing schedules to evaluate clinically. It is also unlikely that statins will be prescribed as a monotherapy, and, therefore, further investigation into drug combination strategies will remain an important area of research. As a number of preclinical potentiators of statin-induced cancer cell death have already been described, many of which are FDA-approved, immediate phase I/II studies are possible. The outcome of these studies will provide important insights into how to realistically use these immediately available, well-tolerated, and inexpensive agents as precision anticancer therapeutics.

Table 4. Future research.

(i)	With improvements in reagents to study the mevalonate pathway, including validated HMGCR antibodies, further research into the mechanisms of mevalonate pathway deregulation in cancer is needed.
(ii)	Promising predictive biomarkers have been described in cell line models, which warrant further characterization and validation in relevant patient-derived models and clinical trials. These may inform patient inclusion in future RCTs.
(iii)	Impaired feedback regulation of the mevalonate pathway has been described as a feature of statin sensitivity in different cancer cell lines; however, the extent of this deregulation in human tumors remains to be characterized. A better understanding of the mechanisms behind this impairment will allow for the development of additional predictive biomarkers of statin sensitivity.
(iv)	As some statin drugs may have a greater propensity to accumulate in certain tumor tissues than others, a direct comparison of the achievable concentrations of different statins in distinct tissues is needed.
(v)	Studies are required to evaluate and compare the efficacy of different statins as anticancer agents at various doses (typical cholesterol-lowering doses vs. dose escalation) and treatment durations. The development of dynamic biomarkers of statin response will facilitate real-time monitoring of treatment efficacy.
(vi)	A better understanding of the mechanisms by which different classes of agents potentiate the anticancer activity of statins will allow for the future development of effective drug combinations.
(vii)	A number of preclinical potentiators of statin-induced cell death have been described and need to be evaluated in RCTs.
(viii)	Statins have known immunomodulatory properties, which to date have been poorly studied in the context of cancer. Further research in this area is imperative. How these properties influence their interaction with different immunotherapies should also be explored.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense.

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References

1. Mullen PJ, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. Nat Rev Cancer 2016;16:718–31.
2. Clendening JW, Pandyra A, Boutros PC, El Ghamrasni S, Khosravi F, Trentin GA, et al. Dysregulation of the mevalonate pathway promotes transformation. Proc Natl Acad Sci U S A 2010;107:15051–6.
3. Carrer A, Trefely S, Zhao S, Campbell SL, Norgard RJ, Schultz KC, et al. Acetyl-CoA metabolism supports multistep pancreatic tumorigenesis. Cancer Discov 2019;9:416–35.
4. Duncan RE, El-Sohemy A, Archer MC. Mevalonate promotes the growth of tumors derived from human cancer cells *in vivo* and stimulates proliferation *in vitro* with enhanced cyclin-dependent kinase-2 activity. J Biol Chem 2004; 279:33079–84.
5. Newman A, Clutterbuck RD, Powles RL, Catovsky D, Millar JL. A comparison of the effect of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors simvastatin, lovastatin and pravastatin on leukaemic and normal bone marrow progenitors. Leuk Lymphoma 1997;24:533–7.
6. Dimitroulakos J, Nohynek D, Backway KL, Hedley DW, Yeger H, Freedman MH, et al. Increased sensitivity of acute myeloid leukemias to lovastatin-induced apoptosis: a potential therapeutic approach. Blood 1999;93:1308–18.
7. Wong WWL, Tan MM, Xia Z, Dimitroulakos J, Minden MD, Penn LZ. Cerivastatin triggers tumor-specific apoptosis with higher efficacy than lovastatin. Clin Cancer Res 2001;7:2067–75.
8. Graaf MR, Beiderbeck AB, Egberts ACG, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol 2004;22:2388–94.
9. Poynter JN, Gruber SB, Higgins PDR, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184–92.
10. Cauley JA, McTiernan A, Rodabough RJ, LaCroix A, Bauer DC, Margolis KL, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. J Natl Cancer Inst 2006;98:700–7.
11. Kuoppala J, Lamminpää A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. Eur J Cancer 2008;44:2122–32.
12. Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. Cancer Epidemiol Biomarkers Prev 2007;16:2213–7.
13. Kumar AS, Benz CC, Shim V, Minami CA, Moore DH, Esserman LJ. Estrogen receptor-negative breast cancer is less likely to arise among lipophilic statin users. Cancer Epidemiol Biomarkers Prev 2008;17:1028–33.
14. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792–802.
15. Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. J Natl Cancer Inst 2011;103:1461–8.
16. Park HS, Schoenfeld JD, Mailhot RB, Shive M, Hartman RI, Ogembo R, et al. Statins and prostate cancer recurrence following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. Ann Oncol 2013;24:1427–34.
17. Sanfilippo KM, Keller J, Gage BF, Luo S, Wang TF, Moskowitz G, et al. Statins are associated with reduced mortality in multiple myeloma. J Clin Oncol 2016; 34:4008–14.
18. Zhong S, Zhang X, Chen L, Ma T, Tang J, Zhao J. Statin use and mortality in cancer patients: systematic review and meta-analysis of observational studies. Cancer Treat Rev 2015;41:554–67.
19. Riscal R, Skuli N, Simon MC. Even cancer cells watch their cholesterol! Mol Cell 2019;76:220–31.
20. Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. J Clin Invest 2005;115:959–68.
21. Gordon RE, Zhang L, Peri S, Kuo YM, Du F, Egleston BL, et al. Statins synergize with hedgehog pathway inhibitors for treatment of medulloblastoma. Clin Cancer Res 2018;24:1375–88.
22. Xia Z, Tan MM, Wong WW, Dimitroulakos J, Minden MD, Penn LZ. Blocking protein geranylgeranylation is essential for lovastatin-induced apoptosis of human acute myeloid leukemia cells. Leukemia 2001;15:1398–407.
23. Wong WW-L, Clendening JW, Martirosyan A, Boutros PC, Bros C, Khosravi F, et al. Determinants of sensitivity to lovastatin-induced apoptosis in multiple myeloma. Mol Cancer Ther 2007;6:1886–97.
24. Yu R, Longo J, van Leeuwen JE, Mullen PJ, Ba-Alawi W, Haibe-Kains B, et al. Statin-induced cancer cell death can be mechanistically uncoupled from prenylation of RAS family proteins. Cancer Res 2018;78:1347–57.
25. Taylor-Harding B, Orsulic S, Karlan BY, Li AJ. Fluvastatin and cisplatin demonstrate synergistic cytotoxicity in epithelial ovarian cancer cells. Gynecol Oncol 2010;119:549–56.
26. Kaymak I, Maier CR, Schmitz W, Campbell AD, Dankworth B, Ade CP, et al. Mevalonate pathway provides ubiquinone to maintain pyrimidine synthesis and survival in p53-deficient cancer cells exposed to metabolic stress. Cancer Res 2020;80:189–203.
27. McGregor GH, Campbell AD, Fey SK, Tumanov S, Sumpton D, Blanco GR, et al. Targeting the metabolic response to statin-mediated oxidative stress produces a synergistic antitumor response. Cancer Res 2020;80:175–88.
28. van de Donk NWCJ, Kamphuis MMJ, van Kessel B, Lokhorst HM, Bloem AC. Inhibition of protein geranylgeranylation induces apoptosis in myeloma plasma cells by reducing Mcl-1 protein levels. Blood 2003;102:3354–62.
29. Sparrow CP, Burton CA, Hernandez M, Mundt S, Hassing H, Patel S, et al. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol 2001;21:115–21.
30. Martirosyan A, Clendening JW, Goard CA, Penn LZ. Lovastatin induces apoptosis of ovarian cancer cells and synergizes with doxorubicin: potential therapeutic relevance. BMC Cancer 2010;10:103.
31. Goard CA, Chan-Seng-Yue M, Mullen PJ, Quiroga AD, Wasylishen AR, Clendening JW, et al. Identifying molecular features that distinguish fluvastatin-sensitive breast tumor cells. Breast Cancer Res Treat 2014;143:301–12.
32. Longo J, Mullen PJ, Yu R, van Leeuwen JE, Masoomian M, Woon DTS, et al. An actionable sterol-regulated feedback loop modulates statin sensitivity in prostate cancer. Mol Metab 2019;25:119–30.
33. Garwood ER, Kumar AS, Baehner FL, Moore DH, Au A, Hylton N, et al. Fluvastatin reduces proliferation and increases apoptosis in women with high grade breast cancer. Breast Cancer Res Treat 2010;119:137–44.
34. Warita K, Warita T, Beckwitt CH, Schurdak ME, Vazquez A, Wells A, et al. Statin-induced mevalonate pathway inhibition attenuates the growth of mesenchymal-like cancer cells that lack functional E-cadherin mediated cell cohesion. Sci Rep 2014;4:1–8.
35. Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, et al. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. Nature 2017;547:453–7.
36. Clendening JW, Pandyra A, Li Z, Boutros PC, Martirosyan A, Lehner R, et al. Exploiting the mevalonate pathway to distinguish statin-sensitive multiple myeloma. Blood 2010;115:4787–97.

37. Kimbung S, Lettiero B, Feldt M, Bosch A, Borgquist S. High expression of cholesterol biosynthesis genes is associated with resistance to statin treatment and inferior survival in breast cancer. Oncotarget 2016;7:59640–51.
38. Göbel A, Breining D, Rauner M, Hofbauer LC, Rachner TD. Induction of 3-hydroxy-3-methylglutaryl-CoA reductase mediates statin resistance in breast cancer cells. Cell Death Dis 2019;10:91.
39. Bjarnadottir O, Romero Q, Bendahl PO, Jirström K, Rydén L, Loman N, et al. Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. Breast Cancer Res Treat 2013;138:499–508.
40. Bjarnadottir O, Feldt M, Inasu M, Bendahl PO, Elebro K, Kimbung S, et al. Statin use, HMGCR expression, and breast cancer survival – The Malmö Diet and Cancer Study. Sci Rep 2020;10:558.
41. Freed-Pastor WA, Mizuno H, Zhao X, Langerød A, Moon SH, Rodriguez-Barrueco R, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. Cell 2012;148:244–58.
42. Pandyra A, Mullen PJ, Kalkat M, Yu R, Pong JT, Li Z, et al. Immediate utility of two approved agents to target both the metabolic mevalonate pathway and its restorative feedback loop. Cancer Res 2014;74:4772–82.
43. Wang M, Casey PJ. Protein prenylation: unique fats make their mark on biology. Nat Rev Mol Cell Biol 2016;17:110–22.
44. DeClue JE, Vass WC, Papageorge AG, Lowy DR, Willumsen BM. Inhibition of cell growth by lovastatin is independent of ras function. Cancer Res 1991;51: 712–7.
45. Lee J, Hong YS, Hong JY, Han SW, Kim TW, Kang HJ, et al. Effect of simvastatin plus cetuximab/irinotecan for KRAS mutant colorectal cancer and predictive value of the RAS signature for treatment response to cetuximab. Invest New Drugs 2014;32:535–41.
46. Baas JM, Krens LL, Ten Tije AJ, Erdkamp F, Van Wezel T, Morreau H, et al. Safety and efficacy of the addition of simvastatin to cetuximab in previously treated KRAS mutant metastatic colorectal cancer patients. Invest New Drugs 2015;33:1242–7.
47. Baas JM, Krens LL, Bos MM, Portielje JEA, Batman E, Van Wezel T, et al. Safety and efficacy of the addition of simvastatin to panitumumab in previously treated KRAS mutant metastatic colorectal cancer patients. Anticancer Drugs 2015;26:872–7.
48. Hong JY, Nam EM, Lee J, Park JO, Lee SC, Song SY, et al. Randomized double-blinded, placebo-controlled phase II trial of simvastatin and gemcitabine in advanced pancreatic cancer patients. Cancer Chemother Pharmacol 2014;73: 125–30.
49. Moon SH, Huang CH, Houlihan SL, Regunath K, Freed-Pastor WA, Morris JP, et al. p53 represses the mevalonate pathway to mediate tumor suppression. Cell 2019;176:564–80.
50. Turrell FK, Kerr EM, Gao M, Thorpe H, Doherty GJ, Cridge J, et al. Lung tumors with distinct p53 mutations respond similarly to p53 targeted therapy but exhibit genotype-specific statin sensitivity. Genes Dev 2017;31:1339–53.
51. Parrales A, Ranjan A, Iyer SV, Padhye S, Weir SJ, Roy A, et al. DNAJA1 controls the fate of misfolded mutant p53 through the mevalonate pathway. Nat Cell Biol 2016;18:1233–43.
52. Tutuska K, Parrilla-Monge L, Di Cesare E, Nemajerova A, Moll UM. Statin as anti-cancer therapy in autochthonous T-lymphomas expressing stabilized gain-of-function mutant p53 proteins. Cell Death Dis 2020;11:274.
53. Ingallina E, Sorrentino G, Bertolio R, Lisek K, Zannini A, Azzolin L, et al. Mechanical cues control mutant p53 stability through a mevalonate-RhoA axis. Nat Cell Biol 2018;20:28–35.
54. Thompson JM, Alvarez A, Singha MK, Pavesic MW, Nguyen QH, Nelson LJ, et al. Targeting the mevalonate pathway suppresses VHL-deficient CC-RCC through an HIF-dependent mechanism. Mol Cancer Ther 2018;17: 1781–92.
55. Longo J, Smirnov P, Li Z, Branchard E, van Leeuwen JE, Licht JD, et al. The mevalonate pathway is an actionable vulnerability of t(4;14)-positive multiple myeloma. Leukemia 2020.
56. Duncan RE, El-Sohemy A, Archer MC. Statins and the risk of cancer. JAMA 2006;295:2720–2.
57. Knuuttila E, Riikonen J, Syvälä H, Auriola S, Murtola TJ. Access and concentrations of atorvastatin in the prostate in men with prostate cancer. Prostate 2019;79:1412–9.
58. Longo J, Hamilton RJ, Masoomian M, Khurram N, Branchard E, Mullen PJ, et al. A pilot window-of-opportunity study of preoperative fluvastatin in localized prostate cancer. Prostate Cancer Prostatic Dis 2020.
59. Murtola TJ, Syvälä H, Tolonen T, Helminen M, Riikonen J, Koskimäki J, et al. Atorvastatin versus placebo for prostate cancer before radical prostatectomy-a randomized, double-blind, placebo-controlled clinical trial. Eur Urol 2018;74: 697–701.
60. Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, et al. Statin drugs and risk of advanced prostate cancer. J Natl Cancer Inst 2006; 98:1819–25.
61. Hamilton RJ, Banez LL, Aronson WJ, Terris MK, Platz EA, Kane CJ, et al. Statin medication use and the risk of biochemical recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cancer 2010;116:3389–98.
62. Jiang P, Mukthavaram R, Chao Y, Nomura N, Bharati IS, Fogal V, et al. *In vitro* and *in vivo* anticancer effects of mevalonate pathway modulation on human cancer cells. Br J Cancer 2014;111:1562–71.
63. Thibault A, Samid D, Tompkins AC, Figg WD, Cooper MR, Hohl RJ, et al. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. Clin Cancer Res 1996;2:483–91.
64. Knox JJ, Siu LL, Chen E, Dimitroulakos J, Kamel-Reid S, Moore MJ, et al. A phase I trial of prolonged administration of lovastatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or of the cervix. Eur J Cancer 2005;41:523–30.
65. van der Spek E, Bloem AC, van de Donk NWCJ, Bogers LH, van der Griend R, Kramer MH, et al. Dose-finding study of high-dose simvastatin combined with standard chemotherapy in patients with relapsed or refractory myeloma or lymphoma. Haematologica 2006;91:542–5.
66. Kornblau SM, Banker DE, Stirewalt D, Shen D, Lemker E, Verstovsek S, et al. Blockade of adaptive defensive changes in cholesterol uptake and synthesis in AML by the addition of pravastatin to idarubicin + high-dose Ara-C: a phase 1 study. Blood 2007;109:2999–3006.
67. Bjarnadottir O, Kimbung S, Johansson I, Veerla S, Jönsson M, Bendahl PO, et al. Global transcriptional changes following statin treatment in breast cancer. Clin Cancer Res 2015;21:3402–11.
68. Hus M, Grzasko N, Szostek M, Pluta A, Helbig G, Woszczyk D, et al. Thalidomide, dexamethasone and lovastatin with autologous stem cell transplantation as a salvage immunomodulatory therapy in patients with relapsed and refractory multiple myeloma. Ann Hematol 2011;90:1161–6.
69. Goss GD, Jonker DJ, Laurie SA, Weberpals JI, Oza AM, Spaans JN, et al. A phase I study of high-dose rosuvastatin with standard dose erlotinib in patients with advanced solid malignancies. J Transl Med 2016;14:83.
70. Seckl MJ, Ottensmeier CH, Cullen M, Schmid P, Ngai Y, Muthukumar D, et al. Multicenter, phase III, randomized, double-blind, placebo-controlled trial of pravastatin added to first-line standard chemotherapy in small-cell lung cancer (LUNGSTAR). J Clin Oncol 2017;35:1506–14.
71. Lim SH, Kim TW, Hong YS, Han SW, Lee KH, Kang HJ, et al. A randomised, double-blind, placebo-controlled multi-centre phase III trial of XELIRI/FOLFIRI plus simvastatin for patients with metastatic colorectal cancer. Br J Cancer 2015;113:1421–6.
72. Jouve JL, Lecomte T, Bouché O, Barbier E, Khemissa Akouz F, Riachi G, et al. Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma. J Hepatol 2019;71:516–22.
73. Kim ST, Kang JH, Lee J, Park SH, Park JO, Park YS, et al. Simvastatin plus capecitabine-cisplatin versus placebo plus capecitabine-cisplatin in patients with previously untreated advanced gastric cancer: a double-blind randomised phase 3 study. Eur J Cancer 2014;50:2822–30.
74. Chen C, Lin J, Smolarek T, Tremaine L. P-glycoprotein has differential effects on the disposition of statin acid and lactone forms in mdr1a/b knockout and wild-type mice. Drug Metab Dispos 2007;35:1725–9.
75. Kapur NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. Vasc Health Risk Manag 2008;4:341–53.
76. Goard CA, Mather RG, Vinepal B, Clendening JW, Martirosyan A, Boutros PC, et al. Differential interactions between statins and P-glycoprotein: implications for exploiting statins as anticancer agents. Int J Cancer 2010;127:2939–48.
77. Pandyra AA, Mullen PJ, Goard CA, Ericson E, Sharma P, Kalkat M, et al. Genome-wide RNAi analysis reveals that simultaneous inhibition of specific mevalonate pathway genes potentiates tumor cell death. Oncotarget 2015;6: 26909–21.
78. Harshman LC, Wang X, Nakabayashi M, Xie W, Valenca L, Werner L, et al. Statin use at the time of initiation of androgen deprivation therapy and time to progression in patients with hormone-sensitive prostate cancer. JAMA Oncol 2015;1:495–504.
79. Di Lorenzo G, Sonpavde G, Pond G, Lucarelli G, Rossetti S, Facchini G, et al. Statin use and survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol Focus 2018;4:874–9.

80. Gordon JA, Buonerba C, Pond G, Crona D, Gillessen S, Lucarelli G, et al. Statin use and survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide after docetaxel failure: the international retrospective observational STABEN study. Oncotarget 2018;9:19861–73.
81. Anderson-Carter I, Posielski N, Liou J-I, Khemees TA, Downs TM, Abel EJ, et al. The impact of statins in combination with androgen deprivation therapy in patients with advanced prostate cancer: a large observational study. Urol Oncol 2019;37:130–7.
82. Miller DR, Ingersoll MA, Chou Y-W, Wakefield CB, Tu Y, Lin F-F, et al. Anti-androgen abiraterone acetate improves the therapeutic efficacy of statins on castration-resistant prostate cancer cells. J Oncol Res Ther 2017;3:1173–8.
83. Syvälä H, Pennanen P, Bläuer M, Tammela TLJ, Murtola TJ. Additive inhibitory effects of simvastatin and enzalutamide on androgen-sensitive LNCaP and VCaP prostate cancer cells. Biochem Biophys Res Commun 2016;481:46–50.
84. Kong Y, Cheng L, Mao F, Zhang Z, Zhang Y, Farah E, et al. Inhibition of cholesterol biosynthesis overcomes enzalutamide resistance in castration-resistant prostate cancer (CRPC). J Biol Chem 2018;293:14328–41.
85. Yang L, Egger M, Plattner R, Klocker H, Eder IE. Lovastatin causes diminished PSA secretion by inhibiting AR expression and function in LNCaP prostate cancer cells. Urology 2011;77:1508.
86. Hamilton RJ, Goldberg KC, Platz EA, Freedland SJ. The influence of statin medications on prostate-specific antigen levels. J Natl Cancer Inst 2008;100: 1511–8.
87. Dimitroulakos J, Lorimer IA, Goss G, Lynch T, Heymach J, Eisen T, et al. Strategies to enhance epidermal growth factor inhibition: targeting the mevalonate pathway. Clin Cancer Res 2006;12:4426–32.
88. Mantha AJ, Hanson JEL, Goss G, Lagarde AE, Lorimer IA, Dimitroulakos J. Targeting the mevalonate pathway inhibits the function of the epidermal growth factor receptor. Clin Cancer Res 2005;11:2398–407.
89. Zhao TT, Le Francois BG, Goss G, Ding K, Bradbury PA, Dimitroulakos J. Lovastatin inhibits EGFR dimerization and AKT activation in squamous cell carcinoma cells: potential regulation by targeting rho proteins. Oncogene 2010; 29:4682–92.
90. Hwang KE, Kwon SJ, Kim YS, Park DS, Kim BR, Yoon KH, et al. Effect of simvastatin on the resistance to EGFR tyrosine kinase inhibitors in a non-small cell lung cancer with the T790M mutation of EGFR. Exp Cell Res 2014;323:288–96.
91. Chen J, Bi H, Hou J, Zhang X, Zhang C, Yue L, et al. Atorvastatin overcomes gefitinib resistance in KRAS mutant human non-small cell lung carcinoma cells. Cell Death Dis 2013;4:e814.
92. Han JY, Lee SH, Yoo NJ, Lee SH, Moon YJ, Yun T, et al. A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer. Clin Cancer Res 2011;17: 1553–60.
93. Lee Y, Lee KH, Lee GK, Lee SH, Lim KY, Joo J, et al. Randomized phase II study of afatinib plus simvastatin versus afatinib alone in previously treated patients with advanced nonadenocarcinomatous non-small cell lung cancer. Cancer Res Treat 2017;49:1001–11.
94. Kou X, Yang Y, Jiang X, Liu H, Sun F, Wang X, et al. Vorinostat and simvastatin have synergistic effects on triple-negative breast cancer cells via abrogating Rab7 prenylation. Eur J Pharmacol 2017;813:161–71.
95. Okubo K, Isono M, Miyai K, Asano T, Sato A. Fluvastatin potentiates anticancer activity of vorinostat in renal cancer cells. Cancer Sci 2020;111:112–26.
96. Lin Z, Zhang Z, Jiang X, Kou X, Bao Y, Liu H, et al. Mevastatin blockade of autolysosome maturation stimulates LBH589-induced cell death in triple-negative breast cancer cells. Oncotarget 2017;8:17833–48.
97. Chen J-B, Chern TR, Wei TT, Chen CC, Lin JH, Fang JM. Design and synthesis of dual-action inhibitors targeting histone deacetylases and 3-hydroxy-3-methylglutaryl coenzyme a reductase for cancer treatment. J Med Chem 2013;56:3645–55.
98. Wei TT, Lin YT, Chen WS, Luo P, Lin YC, Shun CT, et al. Dual targeting of 3-hydroxy-3-methylglutaryl coenzyme a reductase and histone deacetylase as a therapy for colorectal cancer. EBioMedicine 2016;10:124–36.
99. Wei TT, Lin YT, Tseng RY, Shun CT, Lin YC, Wu MS, et al. Prevention of colitis and colitis-associated colorectal cancer by a novel polypharmacological histone deacetylase inhibitor. Clin Cancer Res 2016;22:4158–69.
100. Thurnher M, Gruenbacher G. T lymphocyte regulation by mevalonate metabolism. Sci Signal 2015;8:1–10.
101. Ma X, Bi E, Lu Y, Su P, Huang C, Liu L, et al. Cholesterol induces CD8+ T cell exhaustion in the tumor microenvironment. Cell Metab 2019;30:143–56.
102. Xia Y, Xie Y, Yu Z, Xiao H, Jiang G, Zhou X, et al. The mevalonate pathway is a druggable target for vaccine adjuvant discovery. Cell 2018;175:1059–73.
103. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139:E1082–143.
104. Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. Circ Res 2019;124:328–50.
105. Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 2001;84:886–91.
106. Konings IRHM, Van Der Gaast A, Van Der Wijk LJ, De Jongh FE, Eskens FALM, Sleijfer S. The addition of pravastatin to chemotherapy in advanced gastric carcinoma: a randomised phase II trial. Eur J Cancer 2010;46:3200–4.
107. Göbel A, Thiele S, Browne AJ, Rauner M, Zinna VM, Hofbauer LC, et al. Combined inhibition of the mevalonate pathway with statins and zoledronic acid potentiates their anti-tumor effects in human breast cancer cells. Cancer Lett 2016;375:162–71.
108. Abdullah MI, Abed MN, Richardson A. Inhibition of the mevalonate pathway augments the activity of pitavastatin against ovarian cancer cells. Sci Rep 2017;7: 8090.
109. Lee JS, Roberts A, Juarez D, Vo TTT, Bhatt S, Herzog LO, et al. Statins enhance efficacy of venetoclax in blood cancers. Sci Transl Med 2018;10:eaaq1240.
110. Zheng X, Cui XX, Avila GE, Huang MT, Liu Y, Patel J, et al. Atorvastatin and celecoxib inhibit prostate PC-3 tumors in immunodeficient mice. Clin Cancer Res 2007;13:5480–7.
111. Xiao H, Zhang Q, Lin Y, Reddy BS, Yang CS. Combination of atorvastatin and celecoxib synergistically induces cell cycle arrest and apoptosis in colon cancer cells. Int J Cancer 2008;122:2115–24.
112. Zheng X, Cui XX, Gao Z, Zhao Y, Lin Y, Shih WJ, et al. Atorvastatin and celecoxib in combination inhibits the progression of androgen-dependent LNCaP xenograft prostate tumors to androgen independence. Cancer Prev Res 2010;3:114–24.
113. Babcook MA, Shukla S, Fu P, Vazquez EJ, Puchowicz MA, Molter JP, et al. Synergistic simvastatin and metformin combination chemotherapy for osseous metastatic castration-resistant prostate cancer. Mol Cancer Ther 2014;13: 2288–302.
114. Kim JS, Turbov J, Rosales R, Thaete LG, Rodriguez GC. Combination simvastatin and metformin synergistically inhibits endometrial cancer cell growth. Gynecol Oncol 2019;154:432–40.