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MINI REVIEW

Statins are logical candidates for overcoming limitations of targeting therapies on malignancy: their potential application to gastrointestinal cancers

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Abstract
Purpose Molecular targeting approaches have been an intensive focus of treatment strategies against advanced gastric and colorectal cancers. Recent clinical trials have demonstrated promising survival prolongation of targeted human epidermal growth factor receptors; however, patients harboring mutations in the K-Ras gene (human homolog of the Kirsten rat sarcoma-2 virus oncogene) do not derive benefit from the anti-epidermal growth factor receptor antibodies. K-Ras mutations cause a stimuli-independent activation of a large cohort of downstream effectors that permit cells to acquire a sustained growth. The perpetuated growth activation manifests resistance to molecular targeting therapies.
Methods Literature review has been made to explore the possibilities that, given that K-Ras or downstream effector proteins require farnesyl or geranylgeranyl moiety for their activity (e.g., prenylation), statins are logical candidates to overcome the limitations of or to potentiate the effect of molecular targeting therapies as statins suppress the mevalonate pathway leading to depletion of an end product of mevalonate such as farnesylpyrophosphate and geranylgeranylpyrophosphate, which are used as substrates by their respective transferase enzyme for protein prenylation, and ultimately impair functions of K-Ras and downstream effector proteins.
Results In the last few years, statins have gained interest in therapeutic value for anticancer treatments extending beyond their lipid-lowering effects as single agents or in combined use with other chemotherapeutic agents. This review provides insights into possible anticancer mechanisms of statins and introduces current achievements or ongoing studies of statins in the field of cancer treatment in single or combined uses. This review also offers information to help establish optimal treatment schedules of statins that overcome current limitations of molecular targeting therapies.
Conclusions It is expected that therapeutic scope of statins will expand considerably in the future as anticancer agents in addition to their proven benefits of hyperlipidemia.

Keywords Statins · K-Ras oncogene · Gastric cancer · Colorectal cancer · Molecular targeting therapy

Abbreviations

AKT	v-akt murine thymoma viral oncogene homolog
AVAGAST	First-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer
CRC	Colorectal cancer
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
EXPAND	Erbitux in combination with xeloda and cisplatin in advanced esophagogastric cancer
GC	Gastric cancer
FOLFIRI	Leucovorin + fluorouracil + irinotecan
FOLFOX	Leucovorin + fluorouracil + oxaliplatin
FP	5-fluorouracil and cisplatin
FTase	Farnesyltransferase
FTI	Farnesyltransferase inhibitor
GDP	Guanosine 5′-diphosphate
GGTase	Geranylgeranyltransferase

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GGTI	Geranylgeranyltransferase inhibitor
GTP	Guanosine 5′-triphosphate
HER	Human epidermal growth factor receptor
HMG-CoA	3-hydroxy 3-methylglutaryl-coenzyme A
K-Ras	Human homolog of the Kirsten rat sarcoma-2 virus oncogene
MAPK	Mitogen-activated protein kinase
MSTs	Median survival times
PI3K	Phosphatidylinositol 3-kinase
PKB	Protein kinase B
RCTs	Randomized controlled trials
Rho	Ras-homologous
SPIRITS	S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer
ToGA	Trastuzumab for gastric cancer
VEGF	Vascular endothelial growth factor

Introduction

Recent randomized controlled trials (RCTs) have demonstrated promising combination chemotherapy regimens in the treatment of advanced gastric and colorectal cancers. In advanced gastric cancer (GC), cisplatin in combination with S-1, a novel fluoropyrimidine derivative, has provided median survival times (MSTs) of 12 months (SPIRITS trial) [1], which is 8 months longer when compared with that of the best supportive care [2]. In advanced colorectal cancer (CRC), infusional fluorouracil and leucovorin in combination with oxaliplatin (FOLFOX) [3] or irinotecan (FOLFIRI) [4] have exhibited significantly longer MST than irinotecan and bolus fluorouracil and leucovorin. However, especially in advanced GC, subsequent doublet [5] or triplet [6] chemotherapy regimens demonstrated —at best—a clinically relevant but only slight (2 months) mean average survival benefit when compared with a SPIRITS regimen, underscoring that the treatment advancement has been still painfully slow. Evidently, there is a clear need for more active new agents and regimens. Against these backgrounds, a new generation of therapies designed to target specific signal transduction processes that promote tumor growth and survival have been very recently introduced. These molecular targeting therapies include the use of growth factor receptor antibodies, inhibitors of subsequent cellular responses, and antiangiogenic agents, with expectations of providing the next breakthrough in the treatment of advanced GC and CRC patients. However, there remain several limitations even with these new biologics. First, the new molecular targeting therapies do not necessarily result in dramatic survival improvements. Only 10–20% of chemotherapy refractory and epidermal growth factor receptor (EGFR) expressing metastatic CRC patients benefited from EGFR-targeted therapies when used as monotherapy [7]. Second, the clinical activity of these new biologics depends on the specific resistance profiles. Therefore, elucidation of the mechanisms of resistance and identification of agents that potentiate or have synergy with these new biologics may uncover novel therapeutic approaches circumventing limitations with efficacy and resistance for these biologics.

Statins are potent inhibitors of 3-hydroxy 3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-controlling enzyme at the apex of the mevalonate pathway. Mevalonate is an initial molecule of a diverse array of end products, which are important for the intracellular growth signal transduction responsible for cell growth, proliferation, migration, and survival. A depletion of mevalonate and subsequent perturbation of growth signal processes by statins in tumor cells or endothelial cells may contribute to inhibit tumor growth, tumor angiogenesis, and metastasis. In this regard, statins, besides lowering cholesterol, are considered to have therapeutic potentials against cancer and have become a subject of increased interest as anticancer agents [8].

This review focuses on the current achievements of molecular targeting therapies against gastric and colorectal cancers along with future potential therapeutic applications of statins that yield synergism with molecular targeting therapies. This knowledge should help establish further innovative treatments with the anticipation of providing means for resolving problems concerning current limitations of molecular targeting therapies.

Molecules that contribute to cell growth are considered therapeutic targets

Four members of the human epidermal growth factor receptor (HER) family have been identified: HER1 (also known as EGFR), HER2, HER3, and HER4 [9]. Ligand binding to these receptors causes the formation of a functionally active homodimer (EGFR-EGFR) or a heterodimer (e.g., EGFR-HER2) and subsequently activates an autophosphorylation of the intracellular tyrosine kinase domain of the receptors. The tyrosine-phosphorylated growth factor receptor recruits and activates Ras protein; it eventually initiates a series of mitogenic signaling cascades via several pathways including Raf/MAPK (mitogen-activated protein kinase, also known as extracellular signal-regulated kinases; ERKs), Rac/Rho (Ras-homologous), and PI3 K/PKB (phosphatidylinositol 3-kinase/protein kinase B, also known as AKT) that are indispensable for cell growth, proliferation, migration, angiogenesis, and survival [10]. Briefly, Ras activates Raf, which subsequently

phosphorylates MAPKs, such as $p44^{MAPK}$ and $p42^{MAPK}$ (also known as ERK1 and 2). Activated MAPK is translocated to the nucleus and activates a variety of downstream target genes associated with cell proliferation. Ras also activates Rac/Rho, which leads to regulation of the cytoskeleton and morphologic changes that increase cell invasive properties [11]. PI3 K is also a direct target of Ras [12] and linked to antiapoptosis, the prevention of cellular senescence, and motility-dependent cell dissemination. Although the means by which Ras integrates proteins responsible for cell cycle machinery depends on cell types [13], Ras functions as a cornerstone molecule that transmits signals from upstream of receptor tyrosine kinases to downstream messenger proteins. Inhibiting the activation of HER and the abrogation of subsequent cell survival signals, alone or in combination with standard chemotherapies, have therefore been proposed as another plausible target for antitumor treatment. In order to realize HER inhibition, two therapeutic approaches have been developed. One is monoclonal antibodies against EGFR such as cetuximab (a chimeric monoclonal immunoglobulin G1 antibody) and panitumumab (a fully human monoclonal immunoglobulin G2 antibody), or a monoclonal antibody against HER2 (trastuzumab). The other is intracellular kinase domain inhibitors such as gefitinib and erlotinib [9].

Evidence has been accumulated that tumor angiogenesis is correlated with tumor invasion and metastasis. Among angiogenic factors stimulating tumor angiogenesis, vascular endothelial growth factor (VEGF) is one of the most potent angiogenic factors and Rho proteins are involved in the event of VEGF-mediated angiogenesis. For example, the initial step in VEGF stimulation during angiogenesis is the tyrosine phosphorylation of the VEGF receptor and Rho proteins are necessary for this process [14]. In addition, Rho proteins are direct target and essential downstream effectors of VEGF [15, 16]. Since the overexpression of VEGF has been proved to be correlated with the aggressiveness of gastric and colorectal cancers [17–21], bevacizumab, a monoclonal antibody developed to target VEGF, is anticipated to prevent tumor invasion and metastasis through the inhibition of tumor angiogenesis.

Current achievements of molecular targeting therapies against advanced GCs and CRCs

Advanced GC

Trastuzumab has been widely used for the treatment of HER2-positive breast cancer. In GC, approximately 20% of patients harbor a positive HER2 protein or amplified HER2 gene [22]. Subsequently, a global RCT (ToGA trial) has evaluated the efficacy and safety of trastuzumab in combination with 5-fluorouracil (or capecitabine) and cisplatin (FP) in HER2-positive 594 gastric cancer patients [23]. MST and response rate were, respectively, 13.8 months and 47% in trastuzumab with an FP arm, which were significantly ($P < 0.005$) better than those (11.1 months and 35%) of an FP only arm. Another RCT with cetuximab is now ongoing (EXPAND trial: NCT00678535) [24], in which GC patients have been randomly allocated to capecitabine and oxaliplatin treatment with or without cetuximab.

The AVAGAST trial is the first RCT investigating the efficacy of bevacizumab, in which GC patients were randomized to 5-fluorouracil (or capecitabine) and cisplatin with or without bevacizumab [25]. Adding bevacizumab achieved a longer progression-free survival and higher overall response rate; however, it failed to produce significant MST prolongation.

Advanced CRC

Cetuximab has been currently one of the most intensively investigated molecules in the field of molecular targeting therapy against advanced CRC patients. Initially, the efficacy of cetuximab has been demonstrated in phase III trials on the second- or third-line setting. Cetuximab in combination with irinotecan resulted in a higher response rate and longer progression-free survival than cetuximab alone (BOND trial) [26] or irinotecan alone (EPIC trial) [27]. In addition, cetuximab produced longer overall survival than did the best supportive care alone [28]. Subsequently conducted phase III trials demonstrated the efficacy of the first-line usage of cetuximab. In the CRYSTAL trial, cetuximab in combination with FOLFIRI reduced the risk of progression of metastatic CRC more than FOLFIRI alone [29]. Cetuximab in combination with FOLFOX4 produced a marginally significant improvement in response rate when compared with FOLFOX4 alone [30].

The efficacy of panitumumab has been investigated in phase III trials comparing the best supportive care in metastatic CRC patients who had progressed after standard chemotherapy [31]. Progression-free survival was significantly better by panitumumab [31].

Current problems in the use of molecular targeting therapies

In spite of the above promising treatment results, there are several limitations even with these molecular targeting therapies. First, these molecular targeting agents do not necessarily provide dramatic improvements in response rate and survival. The ToGA trial revealed that the

response rate by adding trastuzumab to chemotherapy was at best 50% even among the HER2-positive GC patients. Although the ToGA trial yielded a promising MST (13.8 months), it was improved only marginally when compared with those of another promising regimen such as cisplatin and S-1 combination (SPIRITS trial). Regrettably, the AVAGAST trial failed to realize a prolongation of MST [25]. Second, the overexpression of targeted receptors, for example, EGFR, is not necessarily correlated with the clinical response of anti-EGFR therapies [26, 32, 33], findings that contrast with the positive correlation between the overexpression of HER2 protein and effectiveness of trastuzumab against breast cancer. Third, especially in advanced CRC, the treatment outcomes of molecular targeting therapies depend on the mutation status of K-Ras (human homolog of the Kirsten rat sarcoma-2 virus oncogene) or B-Raf, a downstream protein of Ras/Raf/MAPK axis [34]. As described later, mutant K-Ras or mutant B-Raf disturbs and causes cells to escape from adequately controlled cell proliferation, which consequently confers resistance to anti-EGFR therapies. Retrospective analyses of the phase II and III clinical trials demonstrated that the benefit of cetuximab was limited only among patients with wild-type K-Ras [35, 36]. The efficacy of panitumumab is also restricted to wild-type K-Ras carriers while K-Ras mutations predict a lack of clinical benefit from panitumumab [37]. Interestingly, none of the K-Ras mutation carriers have concomitant B-Raf mutation [38], suggesting that K-Ras and B-Raf mutations are mutually exclusive in CRC [34]. Therefore, a K-Ras or B-Raf mutational status is a highly predictive selection criterion before any use of anti-EGFR monoclonal antibodies. Accordingly, due to the higher cost of molecular targeting therapies, the American Society of Clinical Oncology has issued a provisional statement that testing for K-Ras gene mutations is needed before the use of anti-EGFR monoclonal antibodies to maximize cost-effectiveness by selecting patients with the highest chance of benefiting from them and by selecting patients with the administration to be presumably ineffective [35].

Understanding the signal transduction mechanisms provides hints for solving the above problems

For several proteins (e.g., Ras/Raf and Rho) involved in the signal transduction pathways to be active, they should be localized on the inner surface of the cell membrane [10, 39–41] by undergoing posttranslational modifications. The C-terminus of Ras/Rho proteins contains a so-called CAAX box, where C is cystein, A is aliphatic acid—usually valine, leucine, and isoleucine—and X is any amino acid. Via the cystein residue in this tetrapeptide, farnesyl (C15) and geranylgeranyl (C20) moieties are, respectively, transferred by farnesyltransferase (FTase) and geranylgeranyltransferase (GGTase), a reaction called prenylation [42, 43]. In these processes, X directs enzyme FTase or GGTase specificity and determines which specific isoprenoid group is transferred onto the protein. If X is L, F, or N, the protein is geranylgeranylated, and if X is A, S, M, or C, the protein is farnesylated [44–47]; consequently, the farnesyl moiety binds to Ras and the geranylgeranyl moiety binds to Rho [47, 48]. Therefore, CAAX prenylation is a lipid modification of protein leading to an increase in protein hydrophobicity; thus, it provides lipid anchor facilitating protein translocation from cytosol to the membrane and subcellular protein docking. Similarly, Raf is targeted to the plasma membrane by the addition of the CAAX of K-Ras [40]. Under the conditions of membrane localization, Ras/Rho proteins act as a molecular switch cycling between an inactive guanosine 5′-diphosphate (GDP)-bound state to an active guanosine 5′-triphosphate (GTP)-bound state; the latter state is in the switch-on position when extracellular signals stimulate their respective HER(s) that eventually activate a large cohort of downstream effectors, thereby activating the subsequent signal cascade. Also during angiogenesis, endothelial cell survival and angiogenesis depend on Rho family membrane localization [49]. Therefore, the prenylation of proteins is a prerequisite to maintain their differential intracellular membrane localization and proper functioning.

Mutations of these proteins entail an active GTP-bound form causing a continuous ‘switch-on’ state that triggers the aberrant activation of downstream signal cascades even in the absence of extracellular growth stimuli or in the presence of EGFR inhibition, thus permitting stimuli-independent and sustained cell growth. The K-Ras mutation in cancer treatment is underscored by the findings that human cancers harbor mutations in K-Ras with various incidences among the different tumor types, being 38–47% in CRC [50, 51]. In contrast to Ras, although convincing evidence for active RhoA mutation in human tumors has been missing [52], several investigators found RhoA overexpression in GC [53, 54] and CRC [52]. Bearing in mind that proper Ras/Raf and Rho protein functions require their prenylation reaction and their eventual membrane localization, it is tempting to speculate that any kind of the pharmacological interference with the prenylation may be the Achilles heel of the Ras/Rho-dependent cell transformation. Indeed, a complete inhibition of farnesylation causes Ras to accumulate in a cytosol pool where it is unable to transmit mitogenic signals from the upstream effectors [44]. One option for interfering with the prenylation is the use of inhibitors of FTase or GGTase. Although several experimental studies [44, 55] have provided

promising results in principle, a farnesyltransferase inhibitors (FTIs) strategy has been hindered by interrelated problems. K-Ras is alternatively geranylgeranylated by GGTase when farnesylation is blocked [48, 56], which renders it refractory to FTI therapies. Accordingly, FTIs failed to improve overall survival compared with BSC in chemotherapy-refractory advanced CRC patients [57]. Since geranylgeranylation is another principal prenylation reaction relevant to cell signaling, this alternative prenylation by GGTase is thought to be a compensating mechanism of cell survival. In this context, geranylgeranyltransferase inhibitors (GGTIs) have been developed and have shown to have anti-cell growth and antiproliferative properties in vitro [58] and in vivo [59]; however, dose-limiting toxicities preclude its use in the clinical settings [60]. Furthermore, in addition to the compensating geranylgeranylation, various cell surviving pathways have been identified as a result of Ras activation [10]. Therefore, a comprehensive inhibition of protein prenylation is needed to inhibit more effectively the aberrantly activated signal cascades.

Statins are a potential breakthrough to overcome the resistance of molecular targeting therapies

Statins prevent the conversion of HMG-CoA to mevalonate, which, besides being a precursor of ring structures such as cholesterol, is a substrate of the long hydrophobic chain farnesyl and geranylgeranyl moieties [61]. Since farnesyl and geranylgeranyl moieties are membrane anchor prerequisites for the Ras/Rho function, any depletion of mevalonate metabolites such as the farnesyl and geranylgeranyl moieties and the subsequent inhibition of Ras/Rho prenylation result in a comprehensive inhibition of the Ras/Rho function at a more upstream level. Therefore, it is postulated that statins could theoretically overcome the resistance to anti-EGFR therapies seen among patients with a K-Ras mutation or overcome the resistance to anti-VEGF therapies through inhibition of the proper RhoA function. Since statins belong to the most widely prescribed drugs in patients with hypercholesterolemia and the adverse event profiles have been well established, application of statins for cancer therapy is clinically realistic with minimal further effort and time.

There is mounting in vitro evidence that statins target Ras/Rho and several downstream signal peptides and consequently inhibit cell proliferation and angiogenesis, or stimulate apoptosis [62]. Lovastatin [63, 64], atorvastatin [65], or simvastatin [66] induce cell senescence or decrease the cell invasive ability and capillary tube formation through Ras [63] or Rho proteins [64–66] delocalization from the cell membrane. In addition, EGF-induced translocation of RhoA from cytosol to membrane is inhibited by fluvastatin through preventing the geranylgeranylation of RhoA [67]. Such Ras/RhoA inactivation by statins is reversed, at least partially, by a coadministration of mevalonate, geranylgeranylpyrophosphate, or farnesylpyrophosphate, suggesting that the observed effects of statins are mediated through HMG-CoA reductase inhibition and subsequent lack of prenylation [67–73]. Furthermore, statins also inhibit the expression of several downstream proteins involved in Ras- or Rho-mediated signal cascades. MAPK (or ERK1/2) or the phosphorylation of AKT is inhibited by lovastatin [74, 75], pravastatin [73, 76, 77], fluvastatin [70, 78, 79], mevastatin [80], atorvastatin [77], and simvastatin [81–83]. Rho-mediated signaling is also attenuated by atorvastatin [65] or fluvastatin [79]. Moreover, lovastatin or simvastatin induces apoptosis through caspase-dependent mechanisms [69]. Also in CRC, lovastatin [84], simvastatin [87], and pravastatin [88] inhibit colon cancer tumorigenesis partly through the induction of apoptosis. These preclinical data support the hypothesis that statins could have antitumor effects through interfering with Ras/RhoA functional localization as well as inhibiting the downstream protein kinases interacting with them.

Clinical trials of statins as anticancer agents

Single use

Based on the above in vitro results, the single use of statins as anticancer agents has been investigated in several clinical trials. It should be noted that statin concentrations showing antiproliferative or antiangiogenic effects in in vitro conditions are 10–100 times higher than those of the clinically relevant doses as well as varying considerably depending on the cell type and statins (Table 1) [85]. Therefore, the required statin dose for the purpose of anticancer agents may be higher than those used against hypercholesterolemia in order to achieve plasma concentrations relevant to those in in vitro studies. Accordingly,

Table 1 Statin concentrations exerting antiproliferative effect in in vitro conditions and plasma statin concentrations in human

Statins	In vitro (mM)	In human* (mM)
Lovastatin	1–60 [63, 64, 67–69, 72–75, 86]	0.025–0.05 [89]
Fluvastatin	1–50 [67, 70, 78, 79]	1.09 [89]
Pravastatin	1–500 [69, 71, 73, 76–78]	0.106–0.129 [89]
Simvastatin	0.5–10 or more [66, 69, 73, 81–83, 87]	0.024–0.081 [89]
Atorvastatin	1–3 [65, 77]	0.048–0.118 [89]

* Peak plasma concentrations by 40 mg dose

Table 2 Clinical trials of single statin use as antitumor agents

Statin and dose	Phase	*n*	Tumor type	Results
Lovastatin				
2–45 mg/kg/day [90]	I	88	Various	1 minor response
35 mg/kg/day [91]	II	16	Stomach	No response
7.5 mg/kg/day [92]	I	26	HNSCC, cervical	No response
20–30 mg/kg/day [93]	I/II	18	Brain	1 partial response, 1 minor response
Pravastatin				
40 mg/day [94]	III	83	HCC	Better survival in pravastatin arm
40–80 mg/day [95]	ND	19	HCC	Survival not improved

HNSCC head and neck squamous cell cancer, *HCC* hepatocellular carcinoma, *ND* not described

the reported dosages of lovastatin were 2–45 mg/kg/day, which were higher than those in the clinical use (Table 2) [90–93]. Even the use of such high doses of lovastatin at last achieved a plasma concentration of 0.1–3.9 μM, which was comparable to those in in vitro studies [90]. Nevertheless, clinical efficacy remained unsatisfactory and only modest even with these higher doses of lovastatin. Moreover, the higher dose of lovastatin required ubiquinone supplementation to rescue high-dose statin-induced myotoxicity [91], thereby being sometimes less realistic. With regard to pravastatin, one study reported improved survival at a daily dose [94], while other investigators failed to find such effect even at a higher (40–80 mg) dose [95] (Table 2). One RCT (NCT01038154) [24] is even now investigating the efficacy of pravastatin on the survival of advanced gastroesophageal cancer at a dose of 40 mg/day. These results suggest that antitumor effects of statins as observed in vitro at high concentrations cannot necessarily be extrapolated into a clinical situation. Moreover, in these clinical studies, the limited number of patients taking statins, the advanced stage of the disease, and overly short MSTs may affect the statistical potency of these studies.

Combined use

Taking into account the biological action of statins, they could be candidates to yield synergism or additivity when used in combination with other anticancer agents including molecular targeting antibodies. The hypothesis that such combinations will reduce statin concentrations to a therapeutically realistic level has been supported by in vitro studies. Atorvastatin [77] or simvastatin [69] potentiated the effect of commonly used cytotoxic agents, such as doxorubicin, 5FU, cisplatin, and paclitaxel, and decreased the effective concentration of these drugs. Ten- to 500-fold lesser concentrations of 5FU, when combined with cerivastatin, exhibited the same cytotoxic effect of 5FU alone [96]. A lovastatin dose exhibiting inhibition of cell viability, which was clinically irrelevant when used as a single agent (1–2 μM), fell within the relevant level (0.1–0.5 μM) when combined with doxorubicin [97] or cisplatin [98], suggesting synergy between lovastatin and chemotherapeutic agents. Fluvastatin could be reduced to a 100-fold lesser concentration, which reached a therapeutically relevant dose, when combined with the gemcitabine. Importantly, this synergism was achieved in K-Ras-mutated pancreas cancer cells [70] or colon cancer cell lines [97]. The combination of simvastatin with β-interferon produced a synergistic antigrowth effect with a reduced, clinically achievable simvastatin concentration (0.001 μM): at such doses, simvastatin alone could inhibit cell growth only by 10% [99]. From these findings, synergism could occur in the context that statins potentiate anticancer drugs or vice versa.

These findings compelled the development of a combined use of statin and anti-HER antibodies to overcome resistance to molecular targeting therapies. Synergy was observed by fluvastatin in combination with cetuximab [100] or with trastuzumab [101], and the latter combination achieves a fluvastatin dose at the clinically relevant level. Lovastatin has the potential to augment the cytotoxic effect of gefitinib [102, 103] even in the constitutively active EGFR mutant [102]. These results suggest that the combined use of statin with other antitumor agents may realize a dose reduction in statins to clinically realistic levels, which enables professionals to translate in vitro results into clinical application. Based on these results, several clinical trials have been ongoing or planned to validate the antitumor effects of statins, mostly at daily doses, in combination with chemotherapies or molecular targeting therapies (Table 3) [24].

Future perspectives

As the field of molecular targeting therapies continues to evolve, the results of clinical trials of molecular targeting agents (e.g., cetuximab), especially in colorectal cancers, are exciting. Nevertheless, these anti-EGFR antibodies have little survival impact on K-Ras mutant carriers and it is also a fact that there is also significant proportion of patients with neither K-Ras nor B-Raf mutations who do not show a response to targeting EGFR therapies. Statins,

Table 3 Ongoing or planned clinical trials of statins with other antitumor agents listed in the ClinicalTrial.gov

Statin and dose	Combined agents	Cancer type	Phase	Trial number
Lovastatin				
40 mg/day	Paclitaxel	Ovary	II	NCT00585052
2–24 mg/kg/day	Docetaxel	Any, breast	I/II	NCT00584012
Pravastatin				
ND	Etoposide, cisplatin, or carboplatin	SCLC	III	NCT00433498
ND	Sorafenib	HCC	III	NCT01075555
Simvastatin				
40 mg/day	Gefitinib	NSCLC	II	NCT00452244
40 mg/day	Irinotecan, cisplatin	SCLC	II	NCT00452634
ND	FOLFIRI	CRC	II	NCT00313859
ND	Panitumumab	CRC	II	NCT01110785
ND	Gemcitabine	Pancreas	II	NCT00944463
40 mg/day	Capecitabine, cisplatin	Stomach	III	NCT01099085
Rosuvastatin starting at 1 mg/kg/day	Erlotinib	Squamous cell cancer or NSCLC	I	NCT00966472

ND not described, *FOLFIRI* leucovorin + fluorouracil + irinotecan, *SCLC* small cell lung cancer, *HCC* hepatocellular carcinoma, *NSCLC* non-small cell lung cancer, and *CRC* colorectal cancer

by the nature of their biological actions, could inhibit even the sustained growth signal stimulation occurring in K-Ras mutation; thus, statins and anti-EGFR antibodies may act synergistically. However, researches concerning statins as anticancer agents raise as many questions as are answered.

First, various mitogenic pathways connect with each other and such close interlink among those pathways may provide escape mechanisms that allow tumors to escape from one pathway that is pharmacologically blocked. Therefore, understanding the full range of the immediate downstream effectors of Ras beyond the canonical Raf/MAPK axis could help shed light on the precise mechanisms concerning the primary resistance of molecular targeting therapies and, ultimately, elucidate how statins potentiate the effect of the new therapeutics.

Second, the optimal statin administration dose(s) and schedule(s) remain to be determined. Regrettably, as described earlier, antiproliferative effects of statins observed at specific concentrations in vitro are too high to approximate clinical reality. In addition, statins may simultaneously exert variable and occasionally opposite effects on cell survival signals, depending on their concentrations and the cell types examined. A low dose of statin sometimes confers resistance to cytostatic agents, suggesting that a dose-dependent opposite effect may exist [86]. Clearly, the continuous administration of statins at levels actually prescribed for hyperlipidemia is more realistic than an intermittent administration schedule with higher doses. Since statin inhibition of the mevalonate pathway is implemented transiently but not permanently, longer exposure to statins may yield better activity. In this regard, a combination of statins with molecular targeting agents enables a reduction in statin concentrations corresponding to the doses that allow them to be administered for longer term, thereby extending the anticancer benefits. This further illustrates how to prevent statin-induced myopathy during a course of anticancer treatment.

Third, the optimal patient setting of statin use as anticancer agents remains to be determined. The antitumor effect of statins is currently being investigated among the patients with advanced or metastatic tumor. Given their growth inhibitory mechanisms of action rather than cytotoxicity, statins may be attractive agents to test in patients with the lowest tumor burden, as an adjuvant setting.

Taken together, these findings show that statins have multiple attributes that may be exploited for cooperation with molecular targeting therapies in the field of cancer treatment. Although statins effects on cancer risk are equivocal, recent meta-analyses have elucidated that statins *per se* have neutral or at least no positive effects on gastric [104] and colorectal [105] cancer development, suggesting that anticancer benefits of chemotherapies or molecular targeting therapies may not be nullified by statins. Therefore, statins will help widen considerably the anticancer therapeutic window in the near future in addition to the proven benefits in the management of hypercholesterolemia. The protocols of statin treatment need to be standardized with regard to which statin (e.g., lipophilic or hydrophilic), at what dose (e.g., higher or lower), or for how long (e.g., intermittent or continuous) to be used, as well as what with molecular targeting agents to be combined. Although our knowledge about statins as anticancer agents is still in its infancy, the plausible mechanisms of action to explain the antitumor effect of statins will

accelerate their testing in appropriately designed, prospective clinical trials.

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