

## REVIEW

# HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis

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The statin family of drugs target HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway, and have been used successfully in the treatment of hypercholesterolemia for the past 15 years. Experimental evidence suggests this key biochemical pathway holds an important role in the carcinogenic process. Moreover, statin administration *in vivo* can provide an oncoprotective effect. Indeed, *in vitro* studies have shown the statins can trigger cells of certain tumor types, such as acute myelogenous leukemia, to undergo apoptosis in a sensitive and specific manner. Mechanistic studies show bcl-2 expression is down-regulated in transformed cells undergoing apoptosis in response to statin exposure. In addition, the apoptotic response is in part due to the depletion of the downstream product geranylgeranyl pyrophosphate, but not farnesyl pyrophosphate or other products of the mevalonate pathway including cholesterol. Clinically, preliminary phase I clinical trials have shown the achievable plasma concentration corresponds to the dose range that can trigger apoptosis of tumor types *in vitro*. Moreover, little toxicity was evident *in vivo* even at high concentrations. Clearly, additional clinical trials are warranted to further assess the safety and efficacy of statins as novel and immediately available anti-cancer agents. In this article, the experimental evidence supporting a role for the statin family of drugs to this new application will be reviewed.

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**Keywords:** HMG-CoA reductase; statins; apoptosis; geranylgeranylation; bcl-2

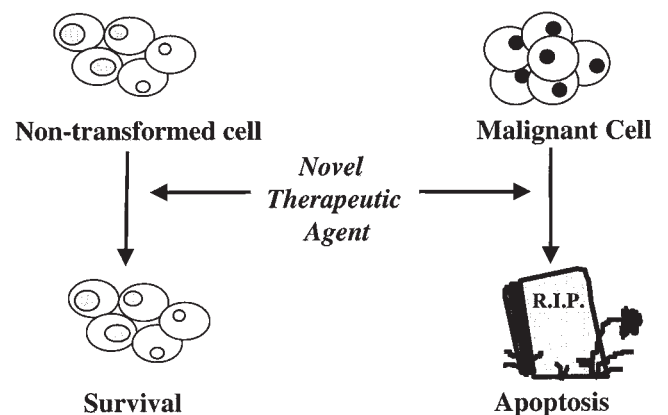
## Introduction

A new opportunity for the development of novel anti-cancer therapeutic agents has recently been realized with the discovery that cells are programmed with the potential to commit suicide through the molecular mechanism of apoptosis (for recent reviews see Refs 1–4). This apoptotic process is highly regulated at the cellular level by a multiplicity of independent and interdependent pathways.<sup>5–11</sup> Deregulation within the apoptotic network contributes to tumor development by allowing cells to evade signals to commit suicide,<sup>12</sup> yet paradoxically, transformed cells often retain the ability to undergo apoptosis. Proof of concept is provided by traditional chemotherapeutic agents that inhibit DNA synthesis or cellular replication, often leading to irreparable DNA breaks, cell cycle arrest and ultimately apoptosis of the tumor cells.<sup>13</sup> However, application of such agents is often limited by significant toxicity and a lack of specificity. Traditional cytotoxic agents affect both normal as well as tumor cells, and can result in toxic side-effects that significantly impact patient quality of

life.<sup>13</sup> Taken together, cancer eradication by chemotherapy is achieved by triggering tumor cells to undergo apoptosis; however, the stimuli need to be radically modified to target tumor cells in a more specific, less toxic manner (Figure 1). New approaches through molecular targeted therapies promise to fill this gap and provide the novel anti-cancer agents urgently required.

A novel molecular target with strong potential for rapid application to the clinic is the rate-limiting enzyme of the mevalonate pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.<sup>14</sup> The end products of the mevalonate (MVA) pathway are required for a number of essential cellular functions (Figure 2). These include sterols, such as cholesterol, involved in membrane integrity and steroid production; ubiquinone (coenzyme Q), involved in electron transport and cell respiration; farnesyl and geranylgeranyl isoprenoids involved in covalent binding of proteins such as the Ras family to membranes; dolichol, which is required for glycoprotein synthesis; and isopentenyladenine, essential for certain tRNA function and protein synthesis.<sup>14–18</sup> Importantly, inhibitors of this key enzyme, collectively known as statins, are well established and effective agents used in the treatment of hypercholesterolemia.<sup>19–22</sup> Thus, HMG-CoA reductase is a unique molecular target for anti-cancer therapy; it holds a pivotal role in the well-defined MVA pathway, and a specific family of inhibitors is available for immediate application in the cancer clinic.

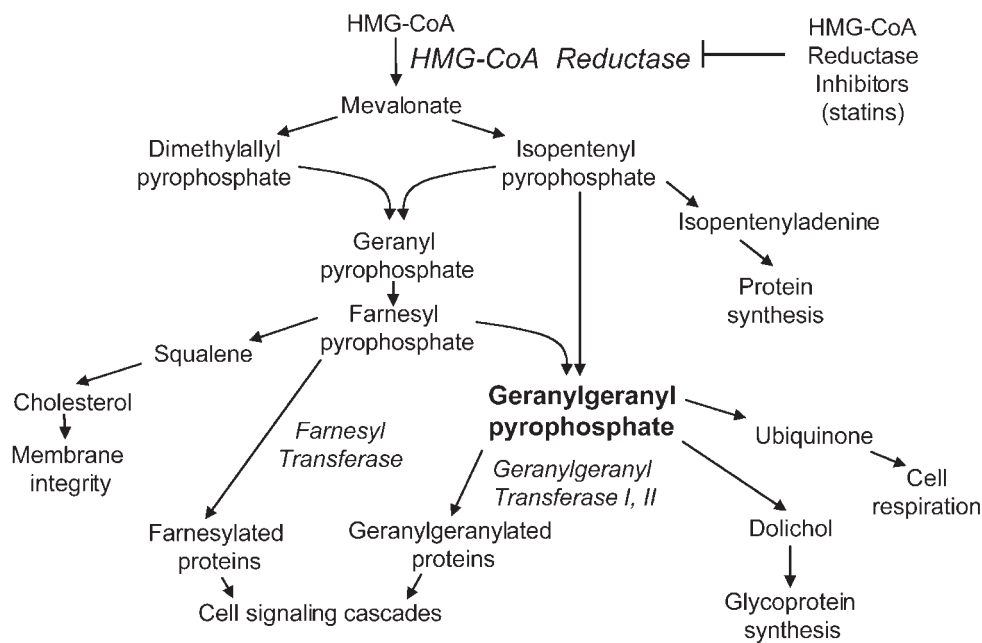
Recent evidence strongly suggests the MVA pathway holds an important regulatory role in cellular proliferation and transformation. For example, malignant cells appear highly dependent on the sustained availability of the end products of the MVA pathway.<sup>23–25</sup> Deregulated or elevated activity of HMG-CoA reductase has been shown in a range of different tumors



**Figure 1** Novel chemotherapeutic agents are required that induce apoptosis of malignant cells in a sensitive and specific manner.

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**Figure 2** The mevalonate pathway.

including hepatocellular carcinoma, leukemia, lymphoma, colorectal and lung adenocarcinoma.<sup>26–31</sup> Moreover, large retrospective analyses for drug safety and efficacy trials of statins in coronary artery disease have shown, that not only are these agents able to reduce cardiac disease-related mortality, but cancer incidence is also reduced by 28–33%.<sup>32,33</sup> These data further suggest these agents may have a role in cancer prophylaxis as well as therapy.<sup>19,32–35</sup> Indeed, recent analyses have demonstrated that inhibitors of HMG-CoA reductase can directly block tumor cell growth both *in vitro* and *in vivo*. In this review, we will focus on the antiproliferative activity of the statins, the mechanism of statin-induced apoptosis, and the application of statin therapy as an anti-cancer agent.

### The statin family of drugs

The statin family is composed of eight unique compounds that are naturally derived or chemically synthesized (Figure 3).<sup>22,36–39</sup> Statins derived from fungal fermentation include pravastatin, simvastatin, and lovastatin, whereas fluvastatin, atorvastatin, cerivastatin, rosuvastatin and pitavastatin<sup>NK-104</sup> are synthetic compounds.<sup>40–47</sup> The common structural characteristic of all statins is a side chain that exists either in a closed ring (inactive, lactone) or an open ring (active, acid) form (Figure 2).<sup>48,49</sup> The former undergoes activation *in vivo* by carboxyesterases in plasma and liver.<sup>50,51</sup> The open ring conformation of this drug blocks catalytically active HMG-CoA reductase by functioning as a molecular mimic of a reaction intermediate formed within the active site of this enzyme.<sup>49</sup> Statins are effective competitive inhibitors as they bind HMG-CoA reductase approximately 1000-fold more effectively than the natural substrate.<sup>36,49</sup>

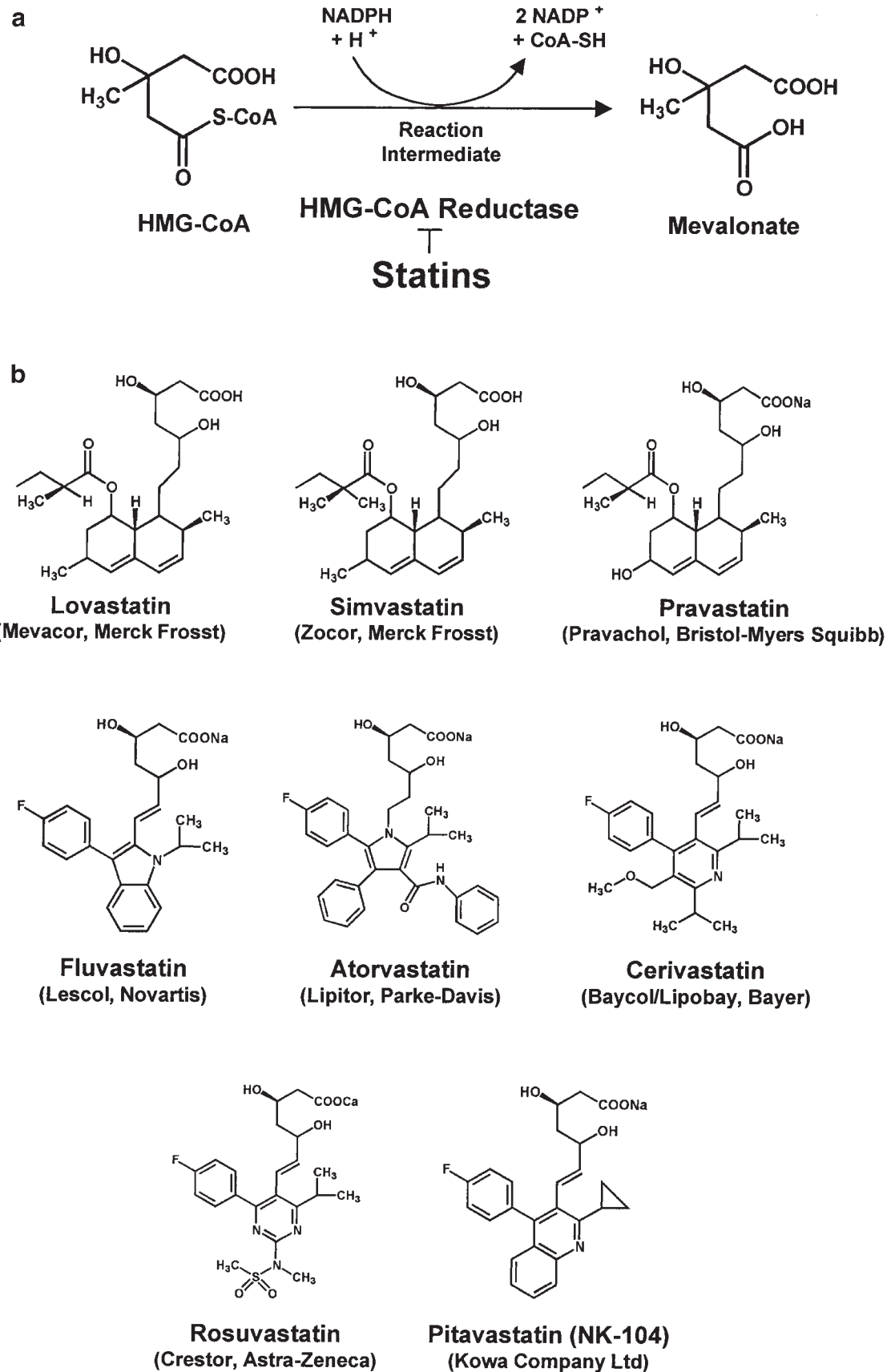
Each member of the statin family of drugs functions by a similar mechanism of action but maintains unique binding affinities, pharmacokinetics and dosing levels (Table 1). A detailed overview of these features is beyond the scope of this article, and the reader is referred to several reviews of this subject.<sup>36,39,40,46,47,52–55</sup> In brief, the binding affinities of the

inhibitors ( $K_i$ ) range from 0.1 to 2.3 nM,<sup>36,45–47</sup> whereas the  $K_m$  of the natural substrate, HMG-CoA is 4  $\mu$ M.<sup>56</sup> The pharmacokinetics are disparate and largely dictated by their lipophilic nature, acid or lactone form, and mechanism of cytochrome P450 metabolism in the liver, which is the primary site of action for cholesterol control.<sup>57,58</sup> Briefly, statin action for hypercholesterolemia leads to a decrease in intracellular hepatic cholesterol levels which then induces expression of cell surface low-density lipoprotein receptors, enabling cholesterol to be removed from the circulation and replenish intracellular cholesterol stores.<sup>59</sup> The safety of this family of drugs has been documented extensively and they are remarkably well tolerated.<sup>21,22,39,55</sup> Reports of minor adverse side-effects include constipation, flatulence, dyspepsia, nausea, gastrointestinal pain, and elevated serum transaminase levels.<sup>22,59</sup> The most serious adverse effect is myotoxicity including rhabdomyolysis which can be diminished with co-administration of ubiquinone.<sup>55,59</sup> Patients with hepatic insufficiency, cholestasis, or hepatic or renal diseases warrant careful monitoring when treated with statins.<sup>57,59</sup> In addition, drug:drug interactions must be thoroughly considered to ensure systemic concentrations are controlled. This is of particular importance with agents that are also metabolized by cytochrome P450 3A4 such as gemfibrozil.<sup>33,37,55,60–66</sup> Thus, the statins are functionally equivalent and the choice of drug is largely determined by individual patient needs and tolerability.

### Antiproliferative activities of statins

#### Growth arrest

It is well established that exposure of certain transformed cells to statins *in vitro* can lead to growth arrest at the G1/S phase boundary of the cell cycle.<sup>67,68</sup> Indeed, lovastatin is used routinely as an experimental tool to block G1 to S phase transition and to synchronize cells *in vitro*, by reversing the block with the addition of mevalonate.<sup>67</sup> This characteristic has been primarily exploited and studied in cell lines derived from



**Figure 3** The statin family of drugs block the conversion of HMG-CoA to mevalonate by inhibiting the rate-limiting enzyme of the mevalonate pathway, HMG-CoA reductase (a). The structural formulae of the statin family are shown in their open ring (active) form (b).

**Table 1** Characteristics of statins

Statin	Characteristic						
	Lipophilic	Form	Source	$K_1$ for HMG-CoA reductase (nM)	$IC_{50}$ for HMG-CoA reductase activity (nM) <sup>a</sup>	Major metabolism by P450	Dosage for cholesterol (mg/day)
Lovastatin	Yes <sup>55</sup>	Lactone <sup>57</sup>	Fungi <sup>57</sup>	0.6 <sup>36</sup>	20 <sup>40</sup>	3A4 <sup>39</sup>	20–80 <sup>165</sup>
Simvastatin	Yes <sup>55</sup>	Lactone <sup>57</sup>	Fungi <sup>57</sup>	0.12 <sup>36</sup>	18.1 <sup>46</sup>	3A4 <sup>39</sup>	10–80 <sup>166</sup>
Pravastatin	No <sup>55</sup>	Acid <sup>57</sup>	Fungi <sup>57</sup>	2.3 <sup>36</sup>	55.1 <sup>46</sup>	Minimal <sup>39</sup>	10–40 <sup>167</sup>
Fluvastatin	Yes <sup>55</sup>	Acid <sup>57</sup>	Synthetic <sup>57</sup>	0.3 <sup>36</sup>	17.9 <sup>46</sup>	2C9, 2D6 <sup>39</sup>	20–80 <sup>168</sup>
Atorvastatin	Yes <sup>55</sup>	Acid <sup>57</sup>	Synthetic <sup>57</sup>	NA	15.2 <sup>46</sup>	3A4 <sup>39</sup>	10–80 <sup>169</sup>
Cerivastatin	Yes <sup>55</sup>	Acid <sup>57</sup>	Synthetic <sup>57</sup>	1.3 <sup>45</sup>	13.1 <sup>46</sup>	3A4, 2C8 <sup>39</sup>	0.2–0.4 <sup>170</sup>
Rosuvastatin	No <sup>46</sup>	Acid <sup>46</sup>	Synthetic <sup>46</sup>	0.1 <sup>46</sup>	11.8 <sup>46</sup>	2C9, 2C19 <sup>37</sup>	5–80 <sup>37</sup>
Pitavastatin	Yes <sup>47</sup>	Acid <sup>47</sup>	Synthetic <sup>47</sup>	1.7 <sup>47</sup>	6.8 <sup>47</sup>	2C9, 2C18 <sup>47</sup>	4 <sup>47</sup>

<sup>a</sup>In rat liver microsomes.  
NA, not available.

mammary carcinomas but is also evident in other cell types.<sup>67,69–72</sup> At the molecular level, this p53-independent growth arrest response, is mediated by a down-regulation of cyclin dependent kinase (CDK) 2 activity with an associated up-regulation of CDK inhibitors p21<sup>Cip1</sup> and/or p27<sup>Kip1</sup>.<sup>69,71–73</sup> It has been recently suggested that this cytostatic activity can be mediated by the closed ring, pro-form of lovastatin or simvastatin by affecting proteasome function.<sup>74,75</sup> The precise inhibitory mechanism of statins on the proteasome function requires further clarification. Interestingly, these effects are reversible with mevalonate<sup>74–76</sup> and a role for the pro-form of lovastatin is not consistent with other results in the field. For example, cerivastatin, an active open ring statin, can induce the classical G1/S phase growth arrest with an associated increase in p21<sup>Cip1</sup> in malignant breast cells.<sup>77</sup> Moreover, we and others, have shown that the lactone ring is hydrolyzed to its active form when exposed to aqueous solution, including cell growth medium, strongly suggesting the pro-drug was activated in these *in vitro* studies.<sup>60,78,79</sup> Taken together, statins can growth arrest certain tumor sub-types by activating a well defined cell cycle checkpoint at the G1/S phase border by a mechanism that remains ill defined, but involves inhibition of HMG-CoA reductase.

### Apoptosis

In recent years it has become clear that inhibitors of HMG-CoA reductase can trigger a subset of tumor-derived cells to

**Table 2** Preliminary indications of tumor sensitivity to statin-induced apoptosis *in vitro*

Tumor type	Ref.
Acute myelogenous leukemia	80–82
Juvenile myelomonocytic leukemia	79
Squamous carcinoma of the head and neck	79
Squamous carcinoma of the cervix	79
Rhabdomyosarcoma	79
Medulloblastoma	79, 83
Mesothelioma	84
Astrocytoma	87
Pancreatic	85
Neuroblastoma	79, 86

undergo apoptosis (Table 2). Tumor cell types that undergo apoptosis upon exposure to lovastatin include acute myelogenous leukemia (AML), juvenile monomyelocytic leukemia, rhabdomyosarcoma, squamous cell carcinoma of the cervix and of the head and neck; medulloblastoma, mesothelioma, pancreatic carcinoma, neuroblastoma and astrocytoma.<sup>79–87</sup> Clearly, this list is not yet comprehensive. Further investigation is essential to fully evaluate which additional tumor types are sensitive to statin-induced apoptosis.<sup>72,88–90</sup> Sensitive tumor types show a consistent pronounced apoptotic response following statin exposure *in vitro*, suggesting these cancers may have a high-probability of sensitivity *in vivo*. The molecular features conferring sensitivity to statin-induced apoptosis remain unclear. Experimental evidence show cells must be proliferating to be sensitive to statin-induced apoptosis.<sup>91–94</sup> However, being engaged in the cell cycle is essential but not sufficient for statins to trigger an apoptotic response.<sup>73,79,82</sup> For example, proliferating tumor-derived cell lines that are not sensitive to statin-induced apoptosis *in vitro* include breast and prostate.<sup>79</sup> Further work delineating the molecular features conferring sensitivity to statin-induced apoptosis is a subject of intense investigation because of the therapeutic potential of statins to trigger tumor cells to undergo apoptosis *in vivo* (discussed below). Statin-induced apoptosis occurs due to the open-ring active drug blocking HMG-CoA reductase.<sup>79,95,96</sup> Cell lines that have been rendered resistant to lovastatin-induced apoptosis by exposure to increasing doses of statins show drug-resistance is due to amplification of the gene encoding HMG-CoA reductase.<sup>97,98</sup> In addition, the apoptotic response is abrogated by the addition of excess mevalonate to the sensitive cells.<sup>88,99–104</sup> Thus, cells of certain malignant transformations are sensitive to statin-induced apoptosis as a direct result of blocking HMG-CoA reductase and the mevalonate pathway.

Most importantly, statins can trigger apoptosis in a tumor-specific manner. The majority of both primary and established tumor cells derived from AML undergo apoptosis in response to lovastatin.<sup>81,82,105,106</sup> By contrast, myeloid progenitor cells derived from normal bone marrow or cord blood do not undergo apoptosis and retain their full proliferative potential.<sup>82,106</sup> Further evidence that non-transformed cells of hematopoietic origin are not damaged by exposure to statins originates from animal studies as well as both low- and high-dose

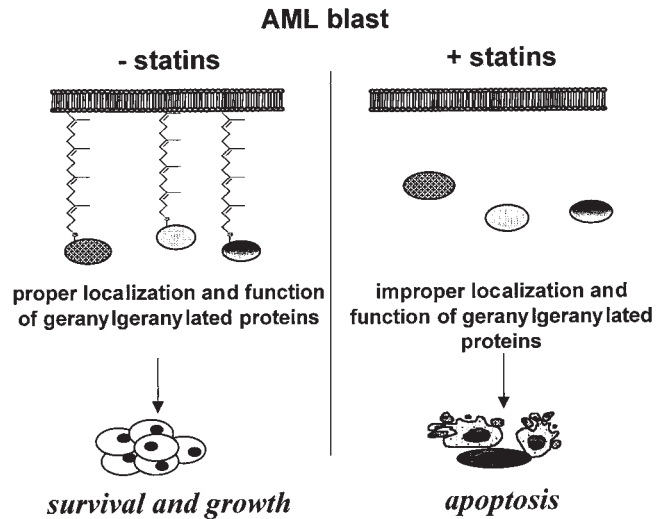
human clinical trials (discussed below).<sup>19,36,57,81,105–111</sup> Thus, despite the prevalence of HMG-CoA reductase in all cells, data to date suggests statins will possess a high therapeutic index (efficacy/toxicity) when used to target apoptosis-sensitive tumor sub-types *in vivo*.

### Molecular mechanism of statin-induced apoptosis

Understanding the mechanism of statin-induced apoptosis of tumor cells is at its infancy and further investigation is required to delineate the key features that dictate statin sensitivity. One of the distinguishing molecular characteristics of statin-sensitive AML and colon cells is the down-regulation of bcl-2 mRNA and protein, respectively.<sup>112,113</sup> Although basal bcl-2 mRNA levels are not associated with sensitivity to lovastatin-induced apoptosis, down-regulation of bcl-2 is a consistent feature of the lovastatin-sensitive AML cell lines.<sup>112</sup> Indeed, this molecular event contributes to the sensitivity of the apoptotic response as ectopic expression of bcl-2 can inhibit lovastatin-induced apoptosis.<sup>112,114</sup> The mechanism of bcl-2 down-regulation following exposure to lovastatin is unknown but is associated with a pronounced differentiation response in AML cells. For example, elevated expression of differentiation-specific cell surface antigens, CD11b and CD18 was detected in response to lovastatin. Interestingly, retinoic acid, a potent cell differentiating and growth inhibitory agent, regulated bcl-2 as well as CD11b and CD18 in a similar manner to lovastatin in the apoptosis-sensitive AML cell lines.<sup>112</sup> The relationship between lovastatin-induced differentiation and apoptosis are provocative and require further investigation. Statin regulation of Bcl-2 expression and function is consistent with statin-induced apoptosis employing the intrinsic mitochondrial pathway to effect cell death. Apoptosis in response to lovastatin is associated with release of cytochrome c, activation of caspase-3, and PARP cleavage in AML.<sup>115</sup>

The depletion of mevalonate is responsible for statin-induced apoptosis in sensitive tumor cells, suggesting that blocking the production of specific mevalonate metabolites is involved in this process. To determine which downstream product(s) of the mevalonate pathway could suppress this apoptotic response, add-back experiments were conducted. Of the many diverse downstream products of the mevalonate pathway, only geranylgeranyl pyrophosphate (GGPP) was able to inhibit apoptosis.<sup>88,102,104</sup> No effect was evident with other products including cholesterol, ubiquinone, isopentenyladenine and dolichol phosphate. Interestingly, farnesyl pyrophosphate (FPP), a molecule similar to GGPP, had little to no effect on statin-triggered apoptosis in a variety of cell systems.<sup>88,102,104</sup> GGPP and FPP serve as substrates for geranylgeranyl transferases (GGTase) and farnesyl transferase (FTase), respectively, which isoprenylate proteins to ensure proper localization within the cell.<sup>17</sup> The importance of geranylgeranylation in statin-induced apoptosis of AML cells was confirmed with inhibitors of geranylgeranyl transferase (GGTI-298) and farnesyl transferase (FTI-277).<sup>104</sup> GGTI-298 was as potent as lovastatin in triggering apoptosis, whereas FTI-277 showed little apoptotic activity.<sup>104</sup> Therefore, one possible model is that exposure to statins depletes GGPP causing improper localization and function of proteins which ultimately triggers the cell to commit suicide (Figure 4).

It remains unclear whether global loss of protein geranylgeranylation is key to apoptosis or whether loss of a restricted substrate(s) is responsible for the apoptotic response to statin



**Figure 4** One of many working models of the mechanism by which statins trigger tumor-specific apoptosis. Exposure to statins depletes the supply of geranylgeranyl pyrophosphate in the cell, leading to improper localization and function of geranylgeranylated proteins which may disrupt a critical survival pathway and ultimately induce apoptosis in the AML blast cell.

exposure. Approximately 0.5 to 1% of cellular proteins are geranylgeranylated yet only a small number of substrates have been identified.<sup>116</sup> Known target proteins include small GTP-binding proteins including K-Ras and N-Ras as well as the Rho family of proteins. Interestingly, statins have been shown to block metastasis at the level of cell attachment, migration and invasion in solid tumors.<sup>77,117–122</sup> Mechanistic studies strongly suggest geranylgeranylation is also key to the anti-metastatic properties of statins, and a pivotal role for RhoA in these activities.<sup>77,122</sup> It will be fascinating to delineate whether similar or different target proteins are responsible for the pro-apoptotic and antimetastatic properties of the statin family of drugs. To this end, direct analysis of the geranylgeranylated proteins in both apoptosis-sensitive and -resistant cells should begin to address the issue of target specificity and apoptotic response. Moreover, by this approach molecular markers to identify tumor cells that will undergo apoptosis in response to statin therapy may be achieved.

Analysis in three additional areas of research will further identify distinguishing features of tumor cells that are sensitive to statin-induced apoptosis. First, the nature and number of transforming events that contribute to the statin-induced apoptotic response remains relatively unknown.<sup>123–125</sup> Indeed, it has become clear in recent years that certain transforming events can significantly affect cellular apoptotic response. For example, cytostatic agents block proliferation of non-transformed cells, yet will trigger apoptosis in cells expressing an activated allele of the c-myc oncogene.<sup>126</sup> It will be instructive to learn which specific transforming events contribute to statin sensitivity. Secondly, cells of sensitive tumor types expressing P-glycoprotein (P-gp) have been shown to be further sensitized to the cytotoxic effects of lovastatin.<sup>86,127–129</sup> The mechanism of this remarkable characteristic has only recently been explored and requires additional investigation.<sup>62,63</sup> Finally, an important and often overlooked concept of apoptosis regulation, is the cell type-dependent response. For example, irradiation of T lymphocytes and fibroblasts leads to an induction of p53 expression that is similar at the molecular level in both cell types, but only the lymphocytes undergo

apoptosis.<sup>130</sup> Cell type differences clearly contribute to the multifunctional properties of statins. For example, statins can function as anti-inflammatory agents, antioxidants, immunomodulators, and angiogenic agents depending on the non-transformed cell type.<sup>131–139</sup> In addition, statins can block vascular smooth muscle cell proliferation as well as signal endothelial cell survival and progenitor cell expansion.<sup>140–144</sup> These results underscore the cell type-dependent effects of statins as well as the pleiotropic effects of these agents. Thus, the parameters that confer sensitivity to certain tumor cells to undergo statin-induced apoptosis require further investigation.

Complete mechanistic knowledge is key to optimal utilization of statins in the clinical management of cancer in combination with other anti-neoplastic agents. For example, insulin growth factor-1 (IGF-1) and nerve growth factor exposure of mouse colon cancer cells and neuronal cells, respectively, delayed the cytotoxic effects of lovastatin.<sup>94,145</sup> Similarly, growth factors, estradiol and IGF-1 have been shown to reverse the growth arrest phenotype triggered by lovastatin in breast and melanoma cells, respectively.<sup>146–148</sup> These data suggest that growth and survival pathways triggered by these factors can overcome the anti-cancer effects of statins. Identifying the modulators of statin activity within these signaling pathways may shed light on the mechanism of statin-directed cytotoxicity. This knowledge may provide an opportunity to further potentiate statin efficacy by combining inhibitors of these modulators with statin therapy *in vivo*.

### Preclinical evaluation of statins as anti-cancer agents

Analyses of cell culture and animal models of carcinogenesis have shown that statins can decrease tumor cell number alone and in combination with other anti-cancer agents. When administered as the sole agent in animal models statins can decrease tumor load of AML, melanoma, hepatoma, pancreatic, lung and neuroblastoma.<sup>107,117,149–152</sup> Importantly, there was little overt toxicity. However, it is unlikely that an agent will be effective in eradicating disease when administered by itself, hence multiagent cancer therapy is practised. In particular, lovastatin has been shown to potentiate antitumor activity of doxorubicin, TNF- $\alpha$ , carmustine (BCNU; N, N'-bis(2-chloroethyl)-N-nitrosourea) in mouse tumor models of lung, colon carcinoma, melanoma and astrocytoma, respectively.<sup>153–157</sup> Other statins, including lovastatin have been shown to potentiate apoptotic effects of cytosine arabinoside, phenylacetate, cisplatin, 5-fluorouracil, butyrate and non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac in AML, glioblastoma, and colon cancer cells.<sup>71,102,113,158–160</sup> Identifying agents that synergize with statins will aid in their proper application in the clinic and may also help elucidate the mechanism of statin-induced apoptosis.

### Clinical trials

Clinical trials investigating the possible value of the statins as chemotherapeutic agents have been recently conducted and suggest dosing and scheduling are important (Table 3). In the first phase I clinical trial lovastatin was administered at a dose of 25 mg/kg/day in four divided doses by the usual oral route for 1 week followed by 3 weeks off statin administration. Dose-related toxicities were minimal and consisted of gastrointestinal dysfunction, and musculoskeletal system complaints including myalgias and muscle weakness.<sup>109</sup> Supplementation

with ubiquinone reduced the severity but did not decrease the incidence of musculoskeletal toxicity or affect drug activity as a cholesterol agent.<sup>109</sup> Interestingly, at doses higher than 25 mg/kg/day, no direct correlation between the incidence of myotoxicity and the dose of lovastatin administered was evident.<sup>109</sup> Most importantly, the trial established the achievable plasma concentration at 0.10 to 3.92  $\mu\text{M}$  at a dose of 25 mg/kg/day, which corresponds to the dose range that can trigger apoptosis of sensitive tumor types *in vitro*.<sup>79,82</sup> Interpatient variability in achievable plasma concentration was evident and no direct relationship to the dose administered was noted.<sup>109</sup> In this phase I clinical trial, one minor response was seen at 30–35 mg/kg/day in a patient diagnosed with anaplastic astrocytoma.<sup>109</sup> There was no evidence of efficacy in patients with other tumor types including breast, prostate, ovarian and other primary central nervous system malignancies. However, the lack of efficacy in this trial may be because the tumor types under study did not correspond to those that are sensitive to lovastatin-induced apoptosis.

Two additional high-dose anti-cancer lovastatin trials have been recently reported. Using the same dosing schedule, a phase I–II trial targeted anaplastic astrocytoma and glioblastoma multiforme with lovastatin (20–30 mg/kg/day orally) alone or in combination with radiation treatment.<sup>110</sup> Of the nine patients treated with lovastatin alone, there was one stable, one minor and one partial response. Of the nine patients that were treated with both lovastatin and radiation, there were two minor and two partial responses as determined by standard clinical trial response criteria.<sup>110</sup> A phase II study of high-dose lovastatin (35 mg/kg/day orally) was conducted in patients with gastric adenocarcinoma.<sup>111</sup> Patients were treated for 1 week on and then were off drug for 3 weeks which resulted in one out of 14 patients with stable response.<sup>111</sup> In all three trials reported to date, the high dose was well tolerated with no neurological, hematological, liver or renal toxicity observed; however, tumor response was limited.

To evaluate the safety and efficacy of lovastatin in the control of AML blast counts, we initiated a trial of lovastatin in high-count, drug-refractory AML patients and administered an oral dose of 10–20 mg/kg/day for a 2 week dosing period followed by 2 weeks off. However, due to drug-related toxicities in these patients, including nausea and elevated levels of creatine phosphokinase, the full regimen could not be administered. An alternative approach to diminish these toxicity issues and to allow for an assessment of efficacy, was to administer a lower dose of lovastatin for a prolonged period of time. An elderly female presenting with relapsed AML, whose blast cells were sensitive to lovastatin-induced apoptosis *in vitro*,<sup>82</sup> was treated with twice the maximal recommended cholesterol dose of lovastatin 160 mg/day (~2 mg/kg/day) for 54 days.<sup>161</sup> This regimen was effective in managing blast counts during the period of drug administration.<sup>161</sup> Remarkably, despite halting the administration of drug, the decreased blast counts persisted for an additional 3 months.<sup>161</sup> Indeed, recent results of a clinical trial showed that administration of pravastatin to patients with hepatocellular carcinoma at the recommended cholesterol dose 40 mg/day (~0.5 mg/kg/day) in conjunction with 5-fluorouracil, doubled the median time of survival for these patients.<sup>108</sup> This suggests that the statins may be of value in disease control when combined with standard therapeutic approaches.<sup>162–164</sup> Moreover, efficacy may be improved when statins are administered in a low-dose regimen over an extended period of time. Further investigation is required to determine the best regimen of treatment for each tumor type

**Table 3** Summary of clinical trial results involving statins as anti-cancer agents

Trial	Statin	Dosing	Tumor types	Results
Thibault <i>et al</i> <sup>109</sup>	Lovastatin	2–45 mg/kg/day delivered for 1 week, then 3 weeks off	prostate, astrocytoma, glioblastoma, breast, colorectal, ovary, sarcoma, lung	Toxicity: low grade gastrointestinal dysfunction, musculoskeletal system, myalgia and muscle weakness at 25 mg/kg/day; no hematological toxicity Response: one of 12 patients with anaplastic astrocytoma at 30–35 mg/kg/day achieved 45% reduction in tumor size
Larner <i>et al</i> <sup>110</sup>	Lovastatin	30 mg/kg/day with and without radiation for relapsed patients; 20, 25, 30 mg/kg/day with partial brain radiation for newly diagnosed patients; dose delivered for 1 week, then 3 weeks off	glioma	Toxicity: no myalgia seen; no neurological, hematological, liver or renal toxicity observed Response: Lovastatin alone: 1 partial (decrease of 50% or more tumor volume), 1 minor, 1 stable (less than 25% increase or decrease in tumor volume) of nine patients; Lovastatin and concurrent radiation: 2 minor responses, 2 partial responses of nine patients
Kim <i>et al</i> <sup>111</sup>	Lovastatin	35 mg/kg/day for 1 week then 3 weeks off; supplemented with ubiquinone	gastric adenocarcinoma	Toxicity: gastrointestinal dysfunction, anorexia, mild nausea, myalgia and muscle weakness; muscle weakness reversed with ubiquinone supplementation; no hematological toxicity Response: one patient of 14 patients assessed, presented with stable disease for 16 weeks
Minden <i>et al</i> <sup>161</sup>	Lovastatin	40 mg twice daily (80 mg/day) for 12 days; 40 mg four times daily (160 mg/day) for 54 days	acute myelogenous leukemia	Toxicity: ulcerative lesions; no nausea Response: controlled blast counts for 3 months after taken off lovastatin
Kawata <i>et al</i> <sup>108</sup>	Pravastatin	40 mg/day with standard treatment of transcatheter arterial embolization and 5-fluorouracil	hepatocellular carcinoma	Toxicity: no change in liver or hematological function or frequency of muscle cramps compared to control group Response: significant increase in median survival from 18 months vs 9 months in control

whether it be administration of a low dose of statins over an extended period of time or a high dose of statins which is well-tolerated for shorter periods. Another approach may be to administer a statin with high specific activity in driving tumor cell death. Indeed, cerivastatin fulfills this criteria<sup>95,96</sup> and although it has been recently recalled from the market,<sup>66</sup> evaluating its efficacy as an anti-cancer agent *in vivo* may warrant its reinstatement. Taken together, further testing of the statins to fully evaluate their efficacy as a novel therapeutic agent alone and in combination with other agents is merited.

#### Future considerations

Clearly, understanding the molecular mechanism of statin's anti-cancer action remains outstanding. This knowledge is fundamental as it is critical to the clinical management of patients. To date, the depletion of GGPP is the pivotal signal that triggers sensitive tumor cell types to undergo apoptosis

following statin exposure. Delineating whether specific transforming events contribute to tumor sensitivity as well as identifying the geranylgeranylated substrate(s) and their downstream pathways essential for the cytotoxic effects of statins will mark a key advance. Moreover, further work to unravel the contribution of P-gp to tumor sensitivity and the mechanistic association of lovastatin-induced apoptosis and differentiation is essential. The outcome of such investigations will provide mechanistic insight into the growth arrest and apoptotic response upon exposure to statins and may uncover a novel molecular target for therapeutic intervention. In addition, molecular predictors of response may be identified allowing for more effective stratification of patients. Finally, with the mechanism well understood, a synergistic combination of agents can be designed to maximize statin efficacy *in vivo*.

Another major area of investigation in this field, is to evaluate and optimize the clinical utility of statins as anti-cancer agents. The tumor types that are sensitive to statin-induced

apoptosis, as opposed to growth arrest, will probably represent the most attractive therapeutic targets for tumor eradication. Furthermore, as statins possess low cytotoxicity toward non-transformed cells and high tumoricidal activity, the net result will be the recovery and survival of normal cells while transformed cells are eliminated. In comparison to other molecular targeted therapies that require local delivery, this agent can be delivered systemically to the patient, due to its tumor-specific apoptotic properties and minimal general toxicities.<sup>3</sup> The clinically achievable plasma concentration corresponds to the dose range that can trigger tumor-specific apoptosis *in vitro*. Experimental evidence suggests the exposure to statin therapy *in vivo* may be maximized by administering statins at a low dose for extended treatment times or at high doses for a limited period. Synergistic effects of statins in combination with traditional chemotherapeutic agents have been shown, warranting the addition of lovastatin to drug cocktails. This synergy may be due to statin down-regulation of bcl-2 expression which has been shown to potentiate therapeutic response with other agents that repress bcl-2 such as anti-sense bcl-2 and retinoic acid. Tracking this and other distinguishing features of statin-induced apoptosis *in vivo* will be mechanistically instructive. Finally, statins may be effective in cancer prevention and this aspect needs to be directly addressed. Taken together, HMG-CoA reductase inhibitors have a proven track record as safe and effective drugs and are readily available for application to the cancer clinic. Clearly, the efficacy of these well established inhibitors as novel anti-cancer therapeutic agents requires immediate evaluation through additional clinical trials.

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