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Hepatocellular Carcinoma and Statins

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Abstract

HMG-CoA reductase inhibitors (known as statins) are commonly prescribed worldwide for the management of coronary heart disease and the underlying dyslipidemia. This class of drugs

has been shown to infer significant decrease in the risk of cardiovascular morbidity and mortality. Only recently though, the potentially beneficial effects of statins in other diseases such as non-alcoholic steatohepatitis have been shown. Importantly also, multiple studies have revealed that statin use was associated with lower cancer-associated mortality across multiple types of cancers. This article aims at reviewing those studies with a particular focus on liver cancer. We also provide a review on the proposed mechanisms of actions describing how statins can induce chemo-preventive and anti-tumour effects.

ABBREVIATIONS

ASH, Alcoholic Steato-Hepatitis; cDDD, cumulative defined daily dose; CI, confidence interval; DEN, diethylnitrosamine; FDA, Food and Drug Administration; FPP, farnesylpyrophosphate; GGPP, geranylgeranyl pyrophosphate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HMG-CoA 3-hydroxy-3-methylglutaryl coenzyme A; Mcl-1, myeloid cell leukaemia-1; MVA, mevalonate ; NAFLD, non alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; SVR, *standard variable rate*; VEGF, vascular endothelial growth factor.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, accounting for more than 80% of primary liver tumours^{1, 2}. Globally, HCC is the fifth and seventh most frequent cancer in men and women, respectively¹. HCC also represents the third and sixth leading cause of cancer-related mortality in men and women, respectively³. Given its dismal prognosis, HCC associated mortality rates are almost identical to the frequency of new cases⁴. Liver cancer is normally diagnosed at an advanced stage, meaning that curative treatments (e.g., surgical resection, liver transplantation) may be applicable to only a small subset of patients⁵. Until recently, the only FDA approved first-line medications for HCC were sorafenib and regorafenib which increase the median survival merely by 10-12 weeks^{6, 7}. During the last few years, immune checkpoint inhibitors such as nivolumab and pembrolizumab (PD-1 inhibitors) gained approval in the second-line setting for patients with advanced HCC. On March 10, 2020, FDA granted accelerated approval to the combination of nivolumab and ipilimumab (a CTLA-4 inhibitor) as a second-line treatment of patients with HCC (FDA.org). The FDA approval was based on an early stage trial in which the objective response rate was 31%⁸. Given the lack of effective therapies for most patients and the fact that survival rates remain to be poor, there is an urgent unmet need to develop novel approaches to treatment.

Globally, HCC incidence continues to increase. Particularly, the incidence of HCC in developed countries with historically low rates such as the USA, Canada, Australia and Japan as well as Western Europe has been increasing markedly^{9, 10}. Indeed, the incidence of HCC in the USA alone has increased by approximately four fold over the past 40 years¹¹. This is partially a result of the growing incidence of metabolic syndrome and steatohepatitis^{12, 13}.

Multiple pre-clinical and clinical studies have shown that therapies targeting diabetes or hyperlipidaemia might be effective in ameliorating type 2 diabetes- and non-alcoholic

steatohepatitis (NASH)-related liver cancer^{14, 15}. For instance, the lipid lowering agent ezetimibe that inhibits the intestinal absorption of cholesterol, was also shown to improve hepatic inflammation and steatosis but not fibrosis in NASH patients in 2 pilot clinical trials¹⁶,¹⁷. Furthermore, statin use was found to be associated with protection from NASH, and fibrosis stage F2-F4, in a dose-dependent manner as reported in a clinical study including 107 patients¹⁸. Importantly also, multiple studies have revealed that statin use was associated with lower cancer-associated mortality across multiple types of cancers including HCC. This article aims at reviewing those studies with a particular focus on liver cancer. We then provide a review on the proposed mechanisms of action describing how statins can induce chemopreventive and anti-tumour effects.

Statins in oncological research

Statins are an important class of lipid lowering agents, acting through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme of cholesterol biosynthesis. Statins are commonly prescribed for the treatment of hyperlipidaemia and cardiovascular diseases and have been associated with the primary and secondary prevention of heart attack and stroke. More recently though, other therapeutic effects of statins are beginning to unfold. In particular, they have been shown to be associated with lower cancer-associated mortality rates. For instance, a large population study on patients from the entire Danish population who were diagnosed with cancer between 1995 and 2007 revealed that the use of statins before diagnosis was associated with a significantly lower overall cancer related mortality¹⁹.

This is in tandem with in vitro and animal studies showing chemopreventive properties of statins mediated by their proapoptotic, antiangiogenic, antiproliferative (arresting of cell-cycle

progression), immunomodulatory, metastasis inhibiting, and anti-infective effects and also possibly through targeting the cancer stem cell population^{20, 21, 22, 23}.

Statins and Liver cancer

Many studies have explored the association between statin use and the risk of liver cancer- some of which will be reviewed in this section and also summarized in Table 1.

Table 1. Statin use and risk of liver cancer

Statin	Initial pathology/setting	Patients/animal models	Effect on HCC risk	Reference
Statins ⁽¹⁾	Steatosis	Patient cohort	48-91 % reduction of HCC risk	Dongiovanni <i>et al.</i> (2015) ¹⁸
Statins	NASH	Patient cohort	38-76 % reduction of HCC risk	Dongiovanni <i>et al.</i> (2015) ¹⁸
Statins	Fibrosis stage F2-F4	Patient cohort	~ 50 % reduction of HCC risk	Dongiovanni <i>et al.</i> (2015) ¹⁸
Pitavastatin	Obesity and steatosis	Male C57BL/KsJ-db/db obese mice	Inhibition of the formation of hepatic premalignant lesions	Shimizu <i>et al.</i> (2011) ²⁴
Pravastatin	Advanced HCC treated with transcatheter arterial embolization & oral 5-FU with or without Pravastatin	Patient cohort	Extension of median survival from 9 to 18 months	Kawata <i>et al.</i> (2001) ²⁵
Pravastatin	HCC treated with chemoembolisation vs chemobolisation + Pravastatin	Patient cohort	Extension of median survival from 12 to 20.9 months	Graf <i>et al.</i> (2008) ²⁶
Statins	Diabetes	Diabetic patients	Marked reduction of HCC risk	El-Serag <i>et al.</i> (2009) ²⁷
Statins	HBV	HBV patients	Reduction of HCC risk	Tsan <i>et al.</i> (2012) ²⁸
Statins	HCV	HCV patients	Reduction of HCC risk	Tsan <i>et al.</i> (2013) ²⁹
Statins	Systematic review of five case-control observational studies	Meta-analysis	Reduction of HCC risk particularly in the case of Atorvastatin (OR 0.63, 95%CI 0.45-0.89) and Fluvastatin (OR 0.58, 95%CI 0.40-0.85)	Zhou <i>et al.</i> (2016) ³⁰

Statins	Liver cancer	Population-based case-control study	Reduction of liver cancer risk at <215.4 DDD *	Chiu et al. (2011) ²¹
Statins: lipophilic (atorvastatin, simvastatin, fluvastatin, lovastatin) vs. hydrophilic (pravastatin, rosuvastatin)	HCC with viral hepatitis	Cohort of patients with confirmed chronic HBV or HCV infection in Sweden.	Significant association of lipophilic statins with reduced HCC incidence and mortality, no association with hydrophilic statins	Simon et al. (2011) ³¹
Statins	Systematic review of observational and experimental studies	Meta-analysis	Reduction risk of HCC development	Islam et al. (2020) ³²
Statins	Cholesterol Treatment Trialists' (CTT) Collaboration Study	Meta-analysis	No reduction in the incidence or mortality rates	Armitage et al. (2019) ³³
Statins	Hyperlipidemia **	Population-based cohort study	No significant effect on liver cancer incidence	Friis et al. (2005) ³⁴

(1) Where the name of the statin is not mentioned, there have been multiple statins involved. Please refer to the original article for the full list of statins used in each cohort.

A few studies have shown no connection between statin use and the overall risk of liver cancer. For instance, a meta-analysis of 28 randomised controlled trials including 186854 participants conducted by the Cholesterol Treatment Trialists' Collaboration showed that statin therapy had no effect at any age on cancer incidence or death³³. On the other hand, multiple studies have described a significant decreased risk of developing HCC associated with the use of statins. For instance, in an experimental setting, pitavastatin was shown to reduce obesity- and steatosis-mediated hepatocarcinogenesis in male C57BL/KsJ-db/db obese mice²⁴. A randomised controlled clinical trial with 83 patients revealed that pravastatin suppressed tumour growth and prolonged the survival of patients with advanced HCC (extending median survival from 9 to 18 months)²⁵. Furthermore, another report has demonstrated that a combined therapy of chemoembolisation plus pravastatin enhanced the survival of patients with advanced HCC versus those receiving only chemoembolization (with a median survival of 20.9 months

vs. 12.0 months, respectively)²⁶. Multiple other studies have also reported a marked risk reduction for HCC with statin use in diabetic patients. For instance, a large, nested, matched, case-control study in patients with diabetes provided the first indication of a cancer-preventive effect for statins specific to HCC in this context²⁷. The study found a significant observed risk reduction ranging between 25% and 40%.

As for virus-related HCC, a large HBV cohort of 328,946 person-years with the overall incidence rate of 310.4 HCCs per 100,000 person-years revealed a significant negative association between statin use and the risk of HCC in those patients²⁸. The cumulative defined daily doses (cDDD) of 28–83, 84–365, and greater than 365 have been associated with a 44%, 53%, and 67% risk reduction for HCC, respectively, relative to no statin use reflecting a dose-dependent effect. Similarly, a large HCV study revealed a similar pattern of a significant dose-response relationship between statin use and HCC risk, reflecting the beneficial use of statins for the prevention of both HBV- and HCV- related HCCs³⁰.

Another comprehensive meta-analysis revealed that the use of statins (below 215.4 DDD) was associated with a 38% lower risk of liver cancer as compared with individuals who did not use statins²¹. Furthermore, a systematic review of five observational studies with a total of 87127 patients revealed that atorvastatin (OR 0.63, 95%CI 0.45-0.89) and fluvastatin (OR 0.58, 95%CI 0.40-0.85) significantly dropped the risk of liver cancer³⁰. In fact, the positive effect of statins in HCC patients has been observed in both Asian populations where chronic HBV was the underlying risk factor for HCC and also in Western populations with metabolic syndrome and NAFLD/NASH, as well as ASH (Alcoholic Steato-Hepatitis), being the major risk factors for developing HCC²⁷. This may suggest that statins improving liver cancer survival may not necessarily be dependent on their lipid lowering function or their effect on metabolic syndrome or fatty liver disease. Alternatively, this may also underline the possibility that targeting the lipid metabolism of liver cancer cells could be a promising therapeutic approach effective of

all types of HCC irrespective of the triggering conditions. In fact, it is well established that one of the most important metabolic hallmarks of cancer including HCC is the disruption of lipid metabolism in tumour cells. Indeed, HCC can represent the last stage of a liver disease where lipogenesis is enhanced, often resulting in the increase of free cholesterol. This aspect is reviewed more in detail by an accompanying review article by Alannan *et al.*

Statins anti-tumour effects and mechanism of action

While the mechanisms by which statins exert anti neoplastic effects are not fully elucidated yet, several reports have proposed multiple clues/hypotheses about the underlying molecular pathways that are often interconnected and will be briefly reviewed below and summarised in Figure 1 and Table 2.

Along with the inhibition of cholesterol biosynthesis, through the inhibition of HMG-CoA reductase and suppression of the conversion of HMG-CoA to mevalonate, statins inhibit the production of downstream products of the mevalonate pathway. Derivatives of the mevalonate pathway, primarily geranylgeranyl pyrophosphate (GGPP) and farnesylpyrophosphate (FPP) are necessary for post-translational prenylation and activation of various small G proteins, including small guanosine-5'-triphosphate binding proteins, such as Kras, and Rho family (discussed further by El-Serag *et al.*²⁷ and Chiu *et al.*²¹). These proteins are important mediators of cell growth, differentiation, motility, signalling, membrane integrity, intracellular vesicle formation and trafficking as well as nucleo-cytoplasmic transport and survival. Statins thereby disrupt the crucial effects of these growth signalling proteins and can result in pro-apoptotic, anti-proliferative, anti-invasive and anti-angiogenic effect³⁵.

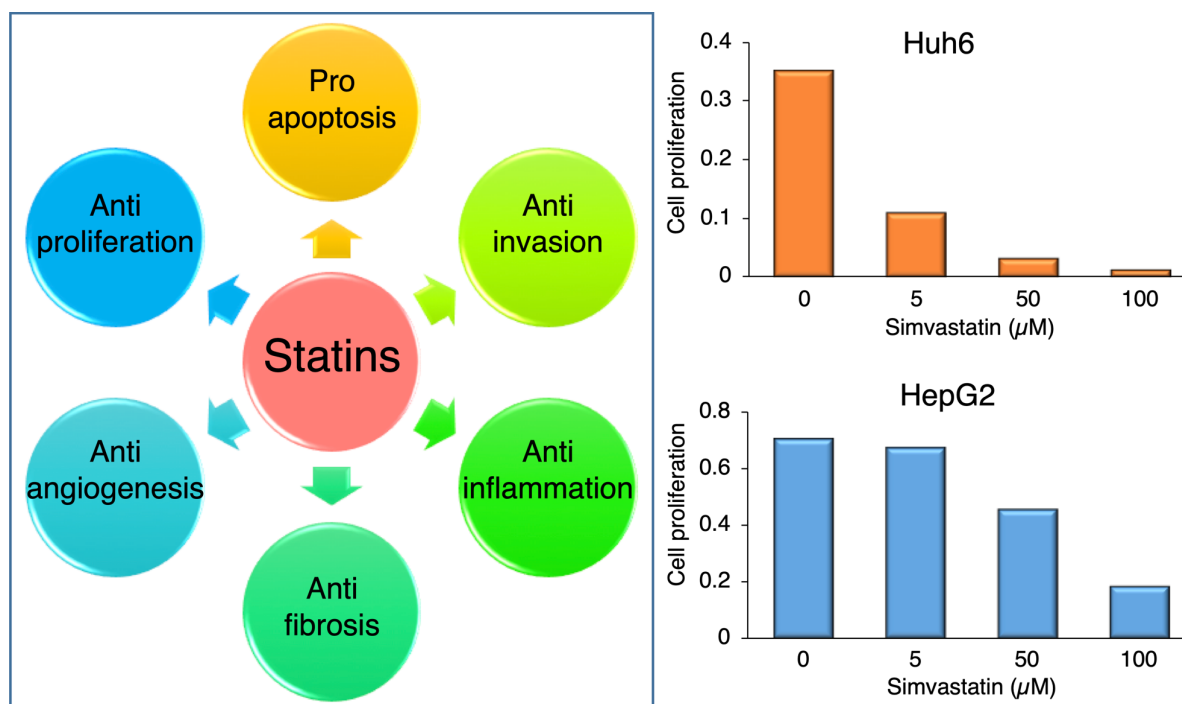


Figure 1. Potential mechanisms of action of statins in preventing hepatocellular carcinoma (see Table 2 for more details). Right graphs show dose dependent inhibition of liver cancer cell proliferation (Huh6 and HepG2) by simvastatin.

Table 2. Statins effects on cancer

Mechanism of action	Statin	Effect	Reference
Inhibition of proliferation	Cerivastatin	Blocking of Ras and Rhomediated cell growth	Denoyelle <i>et al.</i> (2001) ³⁶
	Lovastatin	Inhibition of the activation of the proteasome pathway, leading to p21 and p27 stabilisation	Rao <i>et al.</i> (1999) ³⁷
	Lovastatin	Cell cycle arrest by blocking of G1/S and G2/M transition	Naderi <i>et al.</i> (1999) ³⁸
	Simvastatin and lovastatin	Inhibition of the proliferation and collagen steady state levels in hepatic stellate cells	Rombouts <i>et al.</i> (2003) ³⁹
Induction of apoptosis	Fluva, Simva and Lovastatin	Downregulation of the MVA pathway and inhibition of prenylation of small G proteins	Kah <i>et al.</i> (2012) ⁴⁰

	Simvastatin	Non canonical regulation of RhoA and Rac1 GTPases through the downstream superoxidemediated activation of JNK pathway	Zhu <i>et al.</i> (2013) ⁴¹
	Lovastatin	Caspase activation; BCL-2 inhibition and Bax upregulation (regulation of MEKERK pathway)	Marcelli <i>et al.</i> (1998) ⁴² , Wu <i>et al.</i> (2004) ⁴³
	Atorvastatin	Activation of caspase9 and caspase3 (in hepatic stellate cells)	Aprigliano <i>et al.</i> (2008) ⁴⁴
	Simvastatin	Activation of Bax and downregulation of BCL-2	Spampanato <i>et al.</i> (2012) ⁴⁵
	Fluvastatin + celecoxib	Upregulation of cyclindependent kinase inhibitor p21(Waf1/Cip1), downregulation of pAkt, myeloid cell leukaemia1 (Mcl1) and survivin proteins	Gao <i>et al.</i> (2010) ⁴⁶
Impact on the adhesive capacity, angiogenesis and invasion of tumour cells	Cerivastatin and atorvastatin	Biphasic dose dependent effect:proangiogenic effect at low concentrations; antiangiogenic effect at higher concentrations	Weis <i>et al.</i> (2002) ⁴⁷
	Atorvastatin	Inhibition of angiogenesis and migration	Bayat <i>et al.</i> (2018) ⁴⁸
	Simvastatin	Inhibition of capillary formation (by blocking vascular endothelial growth factor (VEGF), Akt, and focal adhesion kinase signalling (FAK))	Park <i>et al.</i> (2002) ⁴⁹
	Simvastatin	Inhibition of tumour cell growth, attachment to endothelium and invasion (in HCC cell lines)	Relja <i>et al.</i> (2011) ⁵⁰
Impact on HCV pathogenesis	Lovastatin	Reduction of geranylgeranyl pyrophosphate, leading to the disruption of HCVRNA replication and reduction of viral load	Ye <i>et al.</i> (2003) ⁵¹
Suppression of the proliferation of embryonic stem cells	Simvastatin	Selectively blocking cytosoltomembrane translocalisation of RhoA small guanosine triphosphatebinding protein, decreasing Rhokinase (ROCK)2, downregulating ROCK activity	Lee <i>et al.</i> (2007) ⁵²
Inhibition of Myc phosphorylation and activation	Atorvastatin	Suppression of tumour initiation and growth transgenic in a model of Mycinduced HCC	Cao <i>et al.</i> (2011) ⁵³

Inhibition of proliferation

Through the inhibition of HMG-CoA reductase and subsequent to the reduction of isoprenoids, statins can inhibit the proliferation of cancer cells. Particularly, cerivastatin has been shown to block Ras- and Rho-mediated cell growth^{22, 23}.

The inhibition of cell proliferation by statins is not necessarily dependent on Ras function; Lovastatin was proposed to inhibit the activation of the proteasome pathway, resulting in p21 and p27 (both major cyclin-dependent kinase inhibitors that can hinder the growth of cancerous cells) stabilisation. Statins thereby can enhance the effect of these molecules in proliferation inhibition and retarding cancer cell mitosis³⁷.

Another study has also demonstrated that simvastatin and lovastatin inhibited the proliferation of hepatic stellate cells and their collagen steady state levels in a dose dependent manner³⁹. Pravastatin (10-20 mg/kg every other day) was shown to be associated with a lower risk of neoplastic hepatic nodules formation in a model of N-nitrosomorpholine induced hepatocarcinogenesis in sprague-dawley rats⁵⁴ and this was suggested to be due to the inhibition of p21ras isoprenylation and the subsequent inhibition of cell proliferation and induction of apoptosis in neoplastic lesions. Furthermore, lovastatin has been shown to induce cell cycle arrest by blocking G1/S and G2/M transition without the signs of apoptosis³⁸, projecting that statin-induced proliferation inhibition is not only dependent on its apoptosis inducing effects.

Induction of apoptosis

One of the mechanisms proposed for tumour suppressing effect of statins is the induction/deregulation of apoptosis. Statin mediated apoptosis is predominantly through downregulation of the mevalonate (MVA) pathway and the depletion of geranylgeranylated proteins. Kah et al. (2012), have demonstrated that the anti-tumour effect of statins was not

dependent on the inhibition of cholesterol production, but was based on the inhibition of prenylation, since restoration of mevalonate or geranyl-geranylation reversed the statin cytotoxicity in vitro⁴⁰. Statin-mediated depletion of mevalonate pathway product-modified proteins and its proapoptotic effect were suggested to involve non-canonical regulation of one of the most important geranylgeranylated proteins, Rho GTPases and to be mediated through the downstream superoxide-mediated activation of JNK pathway⁴¹.

There are also other mechanisms suggested for the pro-apoptotic effects of statins. Through HMG-CoA reductase inhibition and by activating caspases critically involved in apoptosis, as well as the inhibition of the antiapoptotic protein Bcl-2, combined with the upregulation of the proapoptotic protein Bax, lovastatin was shown to regulate RAF/mitogen-activated protein kinase 1/extracellular signal-regulated kinase (MEK-ERK) pathway and thereby induce proapoptotic functions^{42, 43}. Furthermore, atorvastatin was shown to significantly increase the protease activity of caspase-9 and caspase-3 and induce apoptosis in activated hepatic stellate cells⁴⁴. Spampanato *C. et al.*, demonstrated that simvastatin, (at 20 μ M for 24-72 h) induced the expression of Bax and inhibited Bcl-2 expression in several cancer cell lines (including breast cancer, gastric cancer and hepatic carcinoma), leading to enhanced DNA fragmentation. Interestingly, statin-mediated apoptosis was observed only in the cancer cells and the non-cancerous fibroblasts did not show any sign of apoptosis, even after 3 days of exposure to the drug⁴⁵. This reflects promising indications for statins in cancer. Both Bax and Bcl-2 are transcriptional targets for the tumour suppressor protein p53 which plays an important role in cell cycle arrest and apoptosis in response to DNA damage^{45, 55}. It has been shown that the anti-tumour activity of statins requires cell proliferation and is reduced by p53 overexpression. Indeed, the p53 over-expressing human hepatoma cell line Huh7 could be sensitised towards statin-mediated apoptosis by stable knockdown of endogenous p53⁴⁰. However, p53-independent mitochondrial-mediated apoptosis has also been reported following lovastatin

exposure in a mouse mammary carcinoma⁵⁶. These indicate the complexity of statins molecular mechanism of action which reflects the need for further elucidation.

Impact on the adhesive capacity, angiogenesis and invasion of tumour cells

Endothelial cell migration and proliferation play a critical role in angiogenesis. Several studies have previously shown that statins inhibit cell migration⁵⁷.

It has been shown that cerivastatin and atorvastatin have a biphasic dose dependent effect on angiogenesis, with probably a pro-angiogenic effect at low concentrations 0.005 - <0.05 $\mu\text{mol/L}$ (in vitro) or 0.5 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ (in vivo) and an anti-angiogenic effect at higher concentrations ≥ 0.05 $\mu\text{mol/L}$ (in vitro) or 2.5 $\text{mg/kg}\cdot\text{d}$ (in vivo) as shown in vitro (human dermal microvascular endothelial cells) and in vivo (a murine Lewis lung cancer model)⁴⁷. More recently, atorvastatin was demonstrated to inhibit angiogenesis and migration in an in vitro glioblastoma model in a dose dependent manner (studied in 1 to 10 μM concentrations)⁴⁸. Statins were also suggested to inhibit capillary formation by blocking vascular endothelial growth factor (VEGF), Akt, and focal adhesion kinase signalling (FAK)- which are RhoA-dependent pathways crucially involved in angiogenesis⁴⁹.

Overall, statins have been shown to impair the metastatic potential of tumour cells by inhibiting cell migration, adhesion to the extracellular matrix, and invasion of the basement membrane as observed in several cancer cell lines. However, only few studies have investigated this in the context of HCC. Relja *et al.*, (2011)⁵⁰ have demonstrated that simvastatin dose-dependently decreased tumour cell growth and impaired tumour cell adhesion to endothelial cell monolayers leading to reduced tumour cell invasion⁵⁰. The latter was associated with decreased expression of b1, b3 and a2 integrins and was reversed by exogenous mevalonate⁵⁰.

Impact on HCV pathogenesis

Statins are suggested to play a crucial role in the prognosis of HCV infection, which is currently a major risk factor for HCC and cirrhosis across the globe.

Statins have an anti-infective effect specific to HCV, the replication of which is believed to be at least partially dependent on geranylgeranylation of a host protein. High doses of statins can cause depletion of mevalonic acid, and consequently a reduction of cellular levels of the substrate for the geranylgeranyl-transferase, geranylgeranyl pyrophosphate. The decrease in geranylgeranyl pyrophosphate can lead to the disruption of HCV-RNA replication and therefore the reduction of the viral load and improvement of SVR in some patients^{51, 58}. In this regard, statins are suggested to improve the response to treatment with interferon- α plus ribavirin⁵⁹. Furthermore, the protective effect of statins in this population may be mediated through the amelioration of metabolic disturbances, as well as counteracting the HCV-mediated immune activation, inflammation, proliferation, and cell growth. As a result of these effects, statins could have a long term benefit for HCV patients by retarding the progression of liver fibrosis, and decreasing the risk of HCC incidence and cirrhosis^{60, 61}.

Other mechanisms of action

There are also other mechanisms that were proposed to be involved in the anti-tumour function of statins but these are less explored. These include anti-inflammatory and immunomodulatory effects, inhibition of cancer stem cells and Myc inhibition among others.

Statins were suggested to hinder the cell cycle inhibitor p27Kip1 and thereby enhance the proliferation of different types of stem cells, including endothelial progenitor cells⁶². On the other hand, another study has shown that through the inhibition of RhoA/ROCK-dependent cell-signalling, statins suppressed the proliferation of embryonic stem cells⁵².

In both human HCC-derived cell lines and a transgenic model of Myc-induced HCC, atorvastatin was demonstrated to inhibit Myc phosphorylation and activation, and to suppress tumour initiation and growth via HMG-CoA reductase-dependent pathway⁵³. Indeed, Myc activation is a critical step in hepatocarcinogenesis, and its inactivation has been shown to induce sustained regression of HCC⁶³.

Furthermore, statins are reported to have synergistic anti-tumour effects with cyclooxygenase-2 inhibitors⁶⁴. In a HCC mouse model, the combination of celecoxib and fluvastatin enhanced the level of cyclin-dependent kinase inhibitor p21(Waf1/Cip1), reduced p-Akt, myeloid cell leukaemia-1 (Mcl-1) and survivin proteins. This combination thereby increased the rate of apoptosis and enhanced the inhibition of tumour growth, tumour cell proliferation, and tumour angiogenesis compared with either of the treatments alone⁴⁶.

Statins side effects

In spite of being widely prescribed to lower blood cholesterol levels, discontinuation of treatment with statins may be advised in case of the development of several forms of toxicities and/or intolerance⁶⁵. Nonetheless, there is no universal agreement on the definition of statin toxicity or intolerance. This being said, the most frequently reported side effects are statin-associated muscle related side effects, accounting for up to 72% of all statin related adverse events⁶⁶. Other commonly reported side effects include the new-onset type 2 diabetes mellitus, and to a lesser extent, the neurological and neurocognitive manifestations, hepatotoxicity, renal toxicity, and others.

Although the mechanisms of all these toxicities are varied and linked to multiple pathways, the end result is a change in drug bioavailability and activity in different tissues. The fact that toxic myopathy is a more common condition associated with statin use, while myocardium is spared from its side-effects, may be related to tissue-specific pleiotropic effects of statins. This

is particularly relevant as some transporters of statins are expressed in skeletal muscles but are absent in cardiomyocytes⁶⁷.

As for hepatotoxicity, statins are considered a relatively hepato-safe class of drugs. However, there are reports showing that they can occasionally cause elevations in liver function tests in some patients. For instance, treatment with high doses of atorvastatin or simvastatin (80 mg/day) was associated with an increased risk of liver function test abnormalities⁶⁸. On the other hand, another study has shown that low-to-moderate doses of pravastatin, lovastatin, and simvastatin were not associated with a significant risk for abnormalities on liver function testing⁶⁹.

The molecular mechanisms underlying statin toxicities/intolerance remain poorly understood. Regardless, there is an urgent need to identify those at higher risk of developing side effects and to provide them with an adapted clinical management/treatment regimen.

Future perspectives

Statins are the bedrock of all international guidelines on hyperlipidaemia management and their role in the reduction of the risk of cardiovascular events in a range of patient with atherosclerotic cardiovascular diseases, diabetes mellitus, and hyperlipidaemia has been widely established.

Strong evidence from several observational studies and experimental studies support the benefits of statin use in chemoprevention, slowing the growth rate of HCC and increasing HCC patients' survival and thereby indicate the preventive and therapeutic potential of statins in this context.

Although several international organisations have identified statin side effects to be of major clinical importance, that may be outweighed by statins beneficial effects particularly in the context of a poor prognosis cancer. Similarly, the use of statins in NASH patients may also be

justified as they help improve hyperlipidaemia and metabolic syndrome which are commonly associated with NASH⁷⁰. Nevertheless, in case of the application of high doses, potential side effects have to be closely monitored.

Whilst a higher cumulative dose of statins is expected to have a higher chemopreventive effect than low doses²⁰, detailed data on the most effective statin type as well as the most compelling duration and dosage are lacking. More prospective interventional studies and comprehensive randomised controlled trials are therefore needed to confirm the effect of statins in the chemoprevention of HCC.

Finally, since one of the most important metabolic hallmarks of liver tumour cells is an enhanced overall lipogenesis, combining statins with other lipid metabolism inhibitors may emerge as a more effective therapeutic approach for liver cancer (see accompanying review by Alannan *et al.*).

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