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Controversy

The poor design of clinical trials of statins in oncology may explain their failure – Lessons for drug repurposing

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ABSTRACT

Statins are widely used to treat hypercholesterolaemia. However, by inhibiting the production of mevalonate, they also reduce the production of several isoprenoids that are necessary for the function of small GTPase oncogenes such as Ras. As such, statins offer an attractive way to inhibit an "undruggable" target, suggesting that they may be usefully repurposed to treat cancer. However, despite numerous studies, there is still no consensus whether statins are useful in the oncology arena. Numerous preclinical studies have provided evidence justifying the evaluation of statins in cancer patients. Some retrospective studies of patients taking statins to control cholesterol have identified a reduced risk of cancer mortality. However, prospective clinical studies have mostly not been successful. We believe that this has occurred because many of the prospective clinical trials have been poorly designed. Many of these trials have failed to take into account some or all of the factors identified in preclinical studies that are likely to be necessary for statins to be efficacious. We suggest an improved trial design which takes these factors into account. Importantly, we suggest that the design of clinical trials of drugs which are being considered for repurposing should not assume it is appropriate to use them in the same way as they are used in their original indication. Rather, such trials deserve to be informed by preclinical studies that are comparable to those for any novel drug.

Preclinical rationale for using statins in cancer patients

Statins are widely used to treat hypercholesterolaemia. They inhibit hydroxymethylglutaryl coenzyme A reductase (HMGCR) which is the rate-limiting step in the synthesis of mevalonate, a precursor for the biosynthesis of cholesterol (Fig. 1). In addition to their role in controlling cholesterol, there is also a solid scientific rationale to consider repurposing statins for use as anti-cancer agents [1]. Mevalonate also is a precursor for the isoprenoids farnesol and geranylgeraniol which are used to post-translationally modify several small GTPase oncogenes (e.g. Ras, Rac, Rho). In several cases, this modification has been shown to be necessary for the correct subcellular localization of the small GTPases [2]. Consequently, statins provide an elegant way to inhibit these oncogenes, which otherwise have been considered by many to be "undruggable". HMGCR itself is recognized as a metabolic oncogene [3], and its expression is increased by gain-of-function variants of the commonly mutated tumour suppressor *TP53* [4]. It is abundantly clear from numerous studies from several groups (reviewed [5]) that, in laboratory studies, statins have desirable anti-cancer effects on a broad range of cell lines representing many cancer types. Statins induce G_1 cell cycle arrest and apoptosis in cancer cells *in vitro* [5]. Statins may be classified as lipophilic or hydrophilic. As anti-cancer agents, lipophilic statins are significantly more potent than hydrophilic ones, presumably reflecting their superior membrane permeability [6]. Indeed, one statin which is considered to be hydrophilic, pravastatin, is only weakly active against many cancer cell lines. Relatively high concentrations of even the lipophilic statins are needed to kill cancer cells but we have shown that statins used at these concentrations retain an "on-target" mechanism and affect cancer cells through inhibition of HMGCR [7].

Brief summary of the available clinical data

The widespread use of statins has created a rich source of data to perform retrospective analyses of the incidence of cancer and death from cancer in patients using statins to control hypercholesterolemia (reviewed [5]). Although some studies have reported a reduction in cancer-related mortality among statin users, other studies have found no effect. This is perhaps not surprising because the dose and type of

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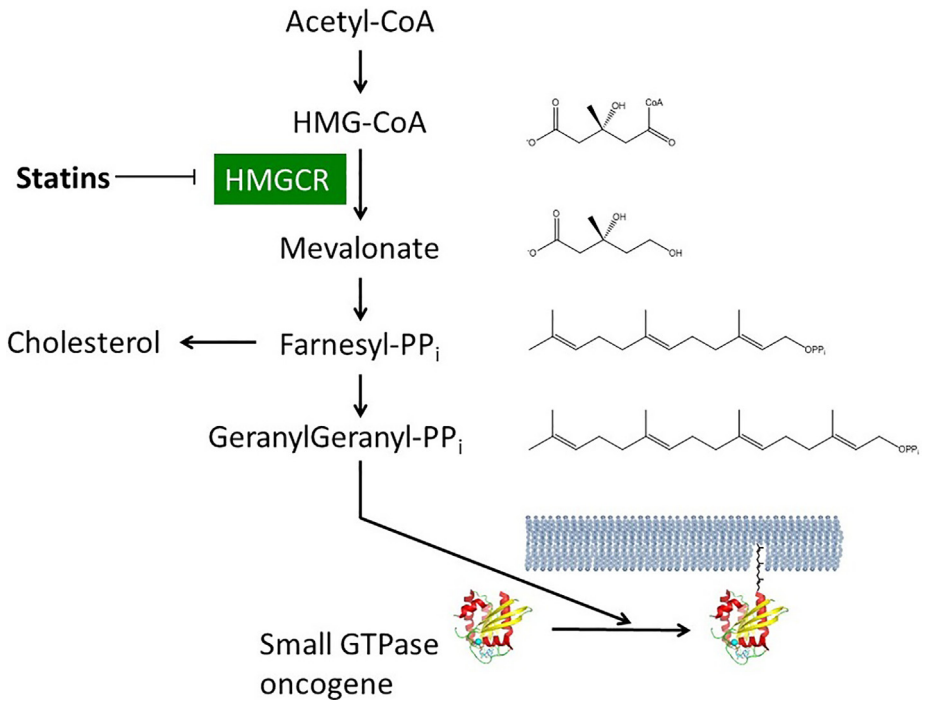

Fig. 1. The mevalonate pathway. Statins inhibit the synthesis of cholesterol as well as isoprenoids needed for the function of several small GTPase oncogenes.

statin varies between patients and other factors which determine cancer outcome, e.g. health status, may not be adequately balanced between statin users and non-users. Most importantly, these patients have received statins at a dose and frequency that is designed to reduce plasma cholesterol, not to have an anti-cancer effect. Thus, it is not clear that such studies would detect an anti-cancer effect of statins, even it were present. Controlled prospective trials, designed to evaluate an anti-cancer effect, are required.

Table 1 summarizes 27 trials which have prospectively evaluated statins for the treatment of cancer. A minority of trials (8/27) included an arm in which the patients received a placebo. The trials have evaluated statins across a broad range of cancers, mostly solid tumours but activity in AML and multiple myeloma has also been explored. The majority of trials (19/27) have evaluated simvastatin or lovastatin, both of which are lipophilic. Relatively few trials (5/27) evaluated statins as single agents.

Two placebo controlled trials [8,9] showed an impressive 8-month increase in survival of patients with hepatocellular carcinoma, but the lack of widespread adoption of this into clinical practice over the intervening 10 years raises concerns about the validity of these observations. A further encouraging trial found that pravastatin combined with idarubicine and cytarabine led to a 75% response rate in relapsed AML with 20 of 26 patient achieving complete remission [10]. Apart from these trials, the remaining 23 trials have been significantly less successful and reported at best a mixture of partial response or stable disease in a minority of trial subjects. In particular, a recent placebo-controlled trial [11] evaluating pravastatin in 410 SCLC patients found no improvement in overall survival or progression-free survival.

Why have statins not been successful so far?

These data create a paradox – despite a robust preclinical data and some encouraging clinical studies, most prospective studies have been disappointing. We believe that this can be explained by three crucial factors that must be considered for the effective use of statins in cancer and that lack of consideration of these has led to the unsatisfactory design of many clinical trials.

Dose

Firstly, the concentration of drug required to cause cell death is significantly higher (10-fold) than that achieved in patients following the doses normally used to treat hypercholesterolaemia [12,13], suggesting that relatively high statin doses are necessary. This has also been recognized previously by several researchers, and 11/27 clinical trials employed a dose of statin that is significantly higher than that used to treat hypercholesterolaemia (Table 1). However, the majority of clinical trials evaluated a dose of statin that is appropriate to treat hypercholesterolaemia and which affords a plasma concentration of statins significantly below that required to induce apoptosis in cancer cells [12].

Schedule and choice of statin

Secondly, in laboratory studies, we have found that continual inhibition of HMGCR is necessary to induce apoptosis; *in vitro*, repeated daily cycles of 12 h simvastatin interspersed with 12 h no-drug did not induce apoptosis, whereas robust cell death was observed if the statin was continuously present [12]. This implies that in patients receiving short half-life statins (e.g. simvastatin, $t_{½}$ = 2–3 h) once daily, HMGCR activity would recover between doses allowing resynthesis of isoprenoids and reactivation of small GTPases. A majority of clinical trials have used a dosing schedule that we consider to be inappropriate to treat cancer, instead apparently copying the schedule designed to treat hypercholesterolaemia. This problem is likely to have arisen in part for historical reasons. Lipophilic statins were developed before the hydrophilic ones and although they are more potent in the cancer setting, they have a shorter metabolic half-life in patients due to their ready uptake into the liver and subsequent metabolism by cytochrome P450 [14]. It is hard to conceive how such trials could ever work, now we know continual inhibition of HMGCR is necessary. The need to take into account the short half-life of lipophilic statins had been recognized by some researchers and 9/27 clinical trials increased the dosing frequency beyond that normally used to treat hypercholesterolaemia. A further two trials [15,16] used hydrophilic statins (atorvastatin, rosuvastatin) with relatively long half-lives that would improve drug exposure, but as