Statins and colorectal cancer

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Statins are naturally occurring compounds that inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase. Through their beneficial management of the body’s lipid metabolism, they are widely used medicinal drugs employed extensively in the primary and secondary prevention of cardiovascular disease. In addition, many studies to date have shown the therapeutic advantages derived from using statins in conditions such as endometriosis, osteoporosis, polycystic ovary syndrome and rheumatic disease. Due to the steady increase of cancer morbidity rates, as demonstrated by epidemiological data, the putative role of statins in treating or preventing cancer has been ever more frequently investigated; including for colorectal cancer. This paper attempts to bring together current knowledge/evidence on statin therapy targeted at the development, disease course and treatment of colorectal cancer, both in terms of epidemiological findings and clinical observations. Because of the reported link between metabolic disorders and the development of colorectal cancer, particular focus is given to the effects of statins on signalling pathways involving insulin-like growth factors (IGFs).

Key words: statins, pleiotropic effects of statins, colorectal cancer, epidemiology

Introduction

Statin compounds are naturally derived substances which have been introduced into medical practice for treating hypercholesterolemia and are also currently used in the primary and secondary prevention of cardiovascular disease; they are also regarded as being potentially effective for treating osteoporosis, endometriosis, polycystic ovary syndrome and rheumatic diseases [1]. The first statin was mevastatin, isolated in 1976 from the mould of Penicilum Citrinum with others being subsequently isolated, (e.g. lovastatin, pravastatin and simvastatin), until which time a method for chemical synthesis was developed, leading to chemical compounds of similar structure and properties such as fluvastatin, atorvastatin, pitavastatin, cerivastatin and rosuvastatin (Table I) [2].

These substances are biologically active, in that they inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, whereby HMG-CoA is not transformed into mevalonic acid [3]. Such blocking of the mevalonic pathway (Fig. 1) has numerous molecular consequences, described in the literature as pleiotropic effects of statins, which include the following: decreasing the endogenous synthesis of cholesterol coupled with increasing the number of LDL receptors on hepatocyte cell surfaces, reducing the prenylation of protein, decreased bile acid synthesis and their intermediates as well as other steroids (like vitamin D), modulating inflammatory responses, affecting adipokines release and having fibrinolytic activity [4].

Besides statins, interest in mevalonic pathway inhibitors that act further downstream, such as bisphosphonates, has increased following the discovery that a mutation in p53 protein, as found in many cancers, causes significant increases of mevalonic acid metabolism in tumour cells [5]. Of further importance is the ability of statins to block
post-translational prenylation of proteins, including proteins of the Rho and Ras family which amongst other things are responsible for initiating apoptosis in cancer cells [5, 6]. The immunomodulatory effects of statins should be stressed which also arise from arresting prenylation. Prenyl pyrophosphate activates the Caspase-1 pathway thereby impairing production/maturation of active interleukins 1 and 18. Statin treatment however effectively activates NK cells (natural killer), which constitute a first-line of defence against cancerous cells [5, 7]. Moreover, simvastatin stimulates production of IL-1, IL-2 and TNF protein by epithelial and dendritic cells [7, 8]. Such a plethora of effects, along with crossovers between intermediates from the mevalonic pathways which activate growth factors (such as IGF, VEGF, PDGF), has prompted much research on the role of HMG-CoA inhibitors in tumourigenesis [9].

In global terms, colorectal cancer is the third most commonly occurring cancer in men and the second found in women as well as being the fourth most common cause of cancer mortality. Since the 1980's, Poland has witnessed a steady rise in its incidence. Colorectal cancer morbidity mainly affects those aged over 50 years, where the risk increases with age; other epidemiological risk factors being diet (i.e. an unhealthy diet with a high, animal-derived fat content of animal origin and poor in fibre), the co-existence of the metabolic syndrome, cigarette smoking, alcohol abuse, and a sedentary lifestyle together with ethnic and geographical factors [10].

### Epidemiology

Over many years, taking regular statin medication/pharmacotherapy has been reported as a means for affording protection against colonic cancer development along with being used in those therapies designed to improve survival and treatment outcomes in patients already diagnosed with cancer. The beneficial effects of statins has been determined variously for lovastatin, cerivastatin, simvastatin and atorvastatin according to the study, where relative risks of contracting colonic cancer has been reduced; ranging from around a dozen up to 50% when compared with control groups [11–16]. Contemporary observations confirm such findings. Broughton et al. performed a retrospective analysis on approximately 200 subjects which found that using statins significantly reduced the risk of developing colonic cancer, where this effect was more pronounced the longer such therapy had been adopted [17].

A large group of subjects suffering from colonic cancer (n > 18,000) were investigated in a Danish study during 1995–2007, which found that the overall risk of death, as well as the risk of death from cancer became reduced through using inhibitors of HMG-CoA reductase [18]. A study by Lakha et al., however suggested that statin therapy lowers the risk of colonic cancer but has no effect on mortality in those patients diagnosed with cancer [19]. Nevertheless, a study by Cardwell et al. monitored 7,657 subjects with colonic cancer for over 9 years, which at the end found that the cancer mortality risk had decreased upon taking HMG-CoA inhibitors, with risk reductions being all the greater the longer such therapy had been undergone [20]. These conclusions were however challenged by Sendur et al., who pointed out that the analysis took no account of the oxaliplatin therapy regimen that had been introduced over the study period and, which of itself, most likely improved survival outcomes in the colorectal cancer patients receiving this treatment – regardless of the statin therapy [21].

A meta-analysis was undertaken in 2013 by Liu et al. which critically reviewed 42 such studies and ultimately concluded that, indeed, statins significantly reduced the
risk of developing colonic cancer of the colon [22]. An earlier meta-analysis from 2007 on 18 statin trials, encompassing in total 1.5 million patients, conducted by Bonovas et al. confirmed the link between using statins with the reduced risk of colorectal cancer in case-control studies, but not, however, in randomized clinical trials nor through cohort studies [23].

Other studies have also been less promising, which amongst various factors, found that mortality risks were not reduced in patients that had undergone statin treatment lasting more than five years [24–26]. These disparities are most probably due to the heterogeneity of the groups studied and the extensive effect of confounding factors, such as the coexistence of other diseases, polypharmacy, lifestyle, age and family history which often in themselves constitute independent risk factors for colorectal cancer.

**Experimental studies**

Numerous experimental studies have traced the effect of statins on the development of colorectal cancer through investigating individual components of localised growth processes and invasiveness. Statins regulate cellular proliferation and cell growth as demonstrated by studies on murine and human cell lines of colorectal cancer. When cell culture media contain statins, decreases in both cell viability and their proliferative potential are observed [27, 28]. Furthermore, the presence of statins in culture media enhances apoptosis, probably by regulating bcl-2 transcription and activating pro-apoptotic Bax protein, as confirmed by studies on cell lines of human colonic carcinomas (HT29) [28–30]. However, Al-Haidari et al. demonstrated in these same cell lines, after induction with CCL17, that simvastatin significantly affects the ability
of these cells to migrate without affecting their proliferation and apoptosis [31].

Colonic cancer tumours are part of those whose growth are stimulated, amongst others, through activation of IGF receptors. The occurrence of insulin resistance with the accompanying high levels of IGFS in obese patients are one of the causes of an increased risk of colorectal cancer for this group. McCarty et al. in 2001 demonstrated that inhibitors of HMG-CoA reductase are responsible for decreased IGF-1 receptors on the surface of colonic cancer cells [32, 33]. This effect may significantly limit the tumour’s growth potential because IGFS are in fact one of the most potent growth factors found in the human body. The effect of statins on subsequent stages of tumourigenesis and on tumour cell invasion of adjacent tissues has also been confirmed. This process is dependent, amongst others, on the activity of matrix metalloproteinases (MMPs) which, by degrading the matrix structure, facilitates tumour invasion of further areas. Metalloproteinases are actively produced by cancer cells as well as by stromal cells, which potentiate tumour invasion of the microenvironment [34]. Furthermore, MMPs regulate the bioavailability of other proteins, including adamalysins, that according to recent studies, also play a key role in tumourigenesis by activating signalling pathways associated with growth factors IGF, EGF, VEGF and likewise the TNF-α pathway [34].

Experiments on human cell lines of colonic cancer demonstrate that lovastatin has the potential to inhibit activities of MMP-1, 2, 3 and 9, whereas simvastatin does so only for MMP-9 [35–37]. Statins can also limit cell migration as well as the formation of distant metastases by restricting adhesion of tumour cells to capillary walls; this being one of the intermediate stages of the metastatic cascade. A study by Al-Haidari et al. [31] confirmed such cell migration restrictions on the HR-29 cell line. The effects of statins on cell cultures are a decrease in the expression of adhesion molecules ICAM-1, PECAM, VCAM-1 and 1-selectin on cell surfaces, thereby making difficult/confounding both adhesion to vascular endothelial cells and distant migration [38, 39].

Finally, another stage of tumour progression affected by HMG-CoA inhibitors is neoangiogenesis, which forms an essential part of further tumour growth at the point at which the tumour attains a size where further growth becomes untenable if only simple diffusion is relied upon for supplying oxygen and nutrients. Statins inhibit vascular proliferation through decreasing the expression of growth factors VEGF and PDGF which have been confirmed by studies on lovastatin, simvastatin and cerivastatin [33, 40].

In addition, Japanese studies have demonstrated that when pitavastatin was given to a studied Min-mouse strain, the numbers of polyps in the large intestine become significantly reduced together with a decreased expression of inflammatory cytokines in the colonic mucosa – suggesting that statins possess a high potential for prophylactic action [41].

Conclusions

The state of affairs as presented above, describes what is currently known from experimental and epidemiological studies. These have pinpointed inhibitors of HMG-CoA to be considered amongst those substances having potential anti-tumour effects in colorectal cancer. It should however be realised that a major proportion of the experimental studies have been performed on cell lines or animal models, where the beneficial effects so demonstrated have not been necessarily translated to, or confirmed by epidemiological studies on large patient groups. Nonetheless, there are some hopeful signs that statins are now more frequently being considered as having a role in adjunctive therapies used in oncology, because of their potentially synergistic effects with anticancer drugs, such as 5-FU or doxorubicin, that reduce the chemo-resistance of cancer cells to cytostatic treatments [42]. When cell lines of colorectal cancer are incubated with atorvastatin, the subsequently appearing drug resistance to doxorubicin is absent, when compared to cancer cell lines grown without statins [43].

But still a number of open questions remain, which can only be answered by wide-ranging and detailed clinical studies. Because most of the existing studies hitherto have covered rather short durations of applied statin therapy, it is thereby important that they are complemented by studies on patients that have been taking HMG-CoA reductase inhibitors for long periods of time.

Conflicts of interest: The authors declare no conflicts of interest.

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