Briefly about Anticancer Properties of Statins

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ABSTRACT

Statins (3-Hydroxy-3-Methylglutaryl-CoA Reductase Inhibitors) have been clinically used for the treatment of dyslipidemia / hypercholesterolemia for almost 40 years. This class of medications represents some of the most frequently prescribed drugs in the world and are the main players in pharmacologic primary and secondary prevention of atherosclerotic cardiovascular disease. Statins have gained much recent attention due to their antitumor effects. This mini review summarizes data about some potential anticancer properties of statins, putative mechanisms of their antitumor activity, and the challenges that have to be overcome in order to facilitate the introduction of these drugs in oncology practice.

Keywords: 3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA) Reductase Inhibitors; Statins; Cancer; Antitumor Activity

Introduction

Statins are potent competitive inhibitors of 3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA) reductase, a rate-limiting enzyme in the mevalonate pathway (cholesterol synthesis or isoprenoid pathway) by which HMG-CoA is converted to mevalonate. Mevalonic acid is the precursor in the biosynthesis of isoprenoid molecules such as cholesterol, dolichol, ubiquinone, Farnesyl Pyrophosphate (FPP) and Geranyl Geranyl Pyrophosphate (GGPP) [1,2]. Statins were initially identified as secondary metabolites of fungi [3]. The discovery of the first HMG-CoA reductase inhibitor (ML-236A) obtained from Penicillium citrinum was reported in 1976 [1,4]. As of 2013, there are seven statin drugs available: Atorvastatin (Lipitor and Torvast), Fluvastatin (Lescol), Lovastatin (Mevacor, Altocor, Altoprev), Pitavastatin (Livalo, Pitava), Pravastatin (Pravachol, Selekten, Lipostat), Rosuvastatin (Crestor), and Simvastatin (Zocor,Lipex) (http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm294358.htm). The pleiotropic effects of statins are well known. In addition to their potential to modify dyslipidemia (the most common application for this class of medications), statins affect some other key biological processes including inflammation, nitric oxide synthesis, coagulation cascade, etc. They have been recognized as potential candidates for the prevention / treatment of neurologic diseases, such as Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis [5].

Statins and Cardiovascular Diseases

Cardiovascular Diseases (CVD) accounts for >17 million deaths globally every year, and this number is predicted to rise to >23 million by 2030 [6]. Dyslipidemia has been shown to be a strong risk factor for CVD [7]. Statins are recognized as the most effective class of drugs for the treatment of lipid disorders. Randomized controlled trials and meta-analyses show the ability of statins to produce a significant reduction of incidental myocardial infarction, stroke, and death from atherosclerotic CVD in the patients. With more than 200 million people worldwide taking these drugs,
nowadays, statins are the most powerful pharmacologic weapon for the primary and secondary prevention of atherosclerotic CVD [8-11].

Safety
Statins have been documented to be well tolerated, and the risk of adverse symptoms is insignificant compared to the benefits. Toxicity is limited as HMG-CoA, the immediate precursor before the block, is water soluble and can be metabolised via alternative metabolic pathways, thus, preventing accumulation [12]. Muscle-associated symptoms including fatigue, weakness, and pain (possibly accompanied by elevated serum creatine kinase activity) are associated with statin use. Myalgia is the most common side effect of these medications (with documented rates of 1-10%) but is often mild and for most patients does not limit treatment. In others, reducing the dose or changing the medication may help. The withdrawal of the statin leads to resolution. Rhabdomyolysis is the most serious adverse effect of statins that affects only a tiny proportion of statin users (less than 0.1%).

Rhabdomyolysis may result in acute renal failure, disseminated intravascular coagulation, and death. Multiple risk factors for statin-induced myopathy have been established, including both patient-related (age, genetics, co-morbidities) and drug-related (statin metabolism via the CYP system, drug-drug interactions, and statin drug transport) factors. The most common risks among them are hypothyroidism, drug-drug interactions, and alcohol abuse [12-16]. Cervivastatin (Baycol, Lipobay) was withdrawn from the market in 2001 due to fatal rhabdomyolysis and kidney failure [17]. Statins have been found to exert a diabetogenic action, and the risk appears to increase among patients receiving higher doses [18,19]. Pitavastatin has not been associated with increased risk of diabetes [20].

Anticancer Activity of Statins
The anticancer properties of statins were reported in early 1990s. Their ability to express antiproliferative and proapoptotic effects have been documented in a wide range of cancer cell lines and animal tumor models [21,22].

The antitumor activity of statins can be related to various mechanisms of action some of which are listed below:

a) FPP and GGPP (by-products of mevalonate pathway) are essential substrates for posttranslational modification of rat sarcoma viral oncogene homologue (RAS) and RAS Homologue (RHO) – GTPases that are involved in the regulation of important biological processes in all eukaryotic cells and are associated with cell growth, proliferation, migration, and survival [23,24].

b) Ability of statins to synchronize tumor cells by blocking the transition of G1-S in the cell cycle, thus, increasing the sensitivity to treatment – it has been established that cells located in late G1 and G2-M phases of the cell cycle are the most susceptible to ionizing radiation-induced cell death, whereas cells located in the S phase are the most resistant [21,25].

c) The drugs (for instance lovastatin) have been shown to affect the so called Bcl-2 family rheostat [26] decreasing expression of the antiapoptotic protein Bcl-2 and increasing the expression of the proapoptotic protein Bax [21,27,28].

d) Statins exhibit anti-angiogenic effects through down-regulation of pro-angiogenic factors, such as vascular endothelial growth factor, suppression of endothelial cell proliferation, and inhibition of adhesion to extracellular matrix by blocking intercellular adhesion molecules [22].

e) HMG-CoA reductase inhibitors affect cell signaling pathways associated with the invasive and metastatic properties of cancer cells [21,27,29]. For instance, lovastatin has been reported to decrease CYR61 (Cysteine-rich angiogenic inducer 6) expression resulting in suppressed osteosarcoma cell invasion and altered epithelial-to-mesenchymal-transition-related protein expression [30]. Simvastatin has been documented to downregulate the production of Matrix Metalloproteinase -2 (MMP-2) [28].

f) Studies show that statins can interact additively or synergistically with some chemotherapeutic agents such as 5-fluorouracil, N, N’bis (2-choloroethyl)-N-nitrosourea, cisplatin, doxorubicin, and 1-β-d-arabinofuranosylcytosine [21]. A phase II study reported that simvastatin in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI regimen) chemotherapy was effective and feasible with no additive side-effects in patients with metastatic colorectal cancer [31].

g) The chemo-sensitizing [32,33] and radio-sensitizing [34] properties of statins have also been established.

h) The inhibition of the mevalonate pathway affects epigenetic regulation in cancer cells [35].

It has been shown that only lipophilic statins, such as simvastatin and lovastatin, show anticancer effect as they permeate the cell membrane [36-39].

The Antitumor Potential of Statins is Attractive for at Least Two Reasons: First, these drugs have been reported to possess anticancer properties against a wide variety of model systems in vitro and in vivo [21,22,27,40]; including cell cultures established from some of the most aggressive, lethal and socially important human malignancies for some of which currently there is limited number of treatment options, such as non-small cell lung cancer [41], triple negative breast cancer [28,42], pancreatic cancer [27,43], osteosarcoma [44], and glioblastoma multiforme [40,45]. Data shows that the combination of simvastatin and meclofenamic acid may be an effective strategy for the treatment of castration-resistant prostate cancer [46].

Second, the excessive cost and length of novelty drug discovery and development as well as the low rate of success motivates the repurposing of existing well-known and well-characterized (pharmacokinetics, pharmacodynamics, safety profile) non-cancer drugs for new application in oncology [47,48]. While antitumor activity of statins is widely reported in preclinical studies, the
Three main obstacles prevent successful clinical application of statins in cancer therapy:

a) These medications express their antitumor properties at relatively high doses (even 500 times higher than the ones used to treat hypercholesterolemia) that can induce serious side effects, including myopathy and rhabdomyolysis [52];

b) It is not possible to achieve such a high concentration of statins (upon oral intake) in the circulation because of their pharmacokinetic properties: short elimination half-lives (mostly 3 h or less) and low systemic bioavailability (below 20%), with the exception of pitavastatin, due to an extensive first pass effect at the intestinal and/or hepatic level [53,54]. Therefore, the efforts of biomedical research are focused on creating different strategies to overcome these challenges. One of the most promising among them is to deliver statins as proliposomes or liposomes [55-59].

c) In addition, not all tumor cell lines / tumors are sensitive to statins that can contribute at least partially to the results observed in clinical trials [60]. Reliable biomarkers are needed to predict sensitivity of tumors / patients to statin treatment. Transcriptome data from fourteen cancer cell lines and their statin concentration response data were used to prepare gene expression signatures able to identify statin sensitive and resistant cells. The validity of the identified biomarker profile was confirmed in additional experiments with an independent set of cell lines [61].

Conclusion

Statin are some of the most widely used medications in the world with significant input for primary and secondary prevention of cardiovascular diseases. The anticancer properties of these drugs have also been suggested and are attracting increasing interest among the biomedical society. However, further investigations are needed for an advanced clarification of the antitumor potential of statins (including particular cancer type(s), dosage and type of statin, treatment schedule and biomarkers to predict patient’s sensitivity to this class of medications, etc).

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