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Statins: A New Hope for Cancer Therapy

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Abstract 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is the key enzyme in cholesterol synthesis. Statins are used in treatment of hypercholesterolemia as inhibitors of HMG-CoA reductase. Cancer cells overexpress HMG-CoA reductase enzyme. Recent studies have demonstrated that statins may inhibit the proliferation of human breast cancer cells. Statins have proangiogenic effects in low therapeutic concentrations and angiostatic effects in higher concentrations. Statins induce apoptosis and reduce cell invasiveness in various cell lines, including malignant glioma, neuroblastoma and myeloid leukemia. The chemopreventive activity of statins against cancer is suggested to depend on inhibition of cholesterol synthesis together with their antioxidant and anti-inflammatory properties.

Keywords: *cholesterol, statins, cancer, HMG-CoA*

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1. Introduction

Cholesterol is the main structural component of mammalian cell membranes and is essential for cellular proliferation. Statins are a group of drugs used to lower cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which plays an important role in the production of cholesterol in the liver [1]. Statins inhibit the production of endogenous cholesterol and block protein prenylation, and statin use may therefore influence cell proliferation and migration. Increased cholesterol levels have been associated with cardiovascular diseases. Therefore, statins are used in the prevention of these diseases [2]. Large doses of statins have many adverse effects such as elevated hepatic transaminases and myopathy and many doctors believe that they are usually misused [1,3].

Cancer-cell proliferation is observed clinically as cancer growth and metastasis, and it often results in death of the patient. Reduction in the cholesterol availability could lead to decreased proliferation and migration of cancer cells [4]. Also, reduction in the products of the mevalonate pathway due to statin use had been associated with a reduced risk of cancer [5].

2. Statins as Chemotherapeutic Agents

Although there have been concerns that statins might increase cancer risk, several studies have found no relationship to cancer, the largest of which included nearly 87,000 participants [6]. Several case-control studies have found statins reduce cancer incidence, including one which showed that patients taking statins for over five years reduced their risk of colorectal cancer by 50% [6,7].

Moreover, recent evidences suggested that statins may act as chemotherapeutic agents against many types of cancers including gastric cancer, pancreatic cancer and colon cancer [8,9,10]. Statins reduce synthesis of non-sterol products which are essential for the isoprenylation of the intracellular second messenger mitogenic signaling proteins like Ras [9]. Many studies showed that blockade of mevalonate pathway induced cell cycle arrest and inhibited tumor cell growth [11,12]. However, the use of statins in cancer trials may be limited by their high-dose toxicity that was characterized by severe myopathy [13].

3. Antioxidant and Anti-inflammatory Effects of Statins

The antitumor effect of statins was attributed to its antioxidant, anti-inflammatory and cholesterol lowering properties. Atorvastatin was proved to induce apoptosis and slow tumor growth in mice [14]. Statins were found to improve the antioxidant status and have anti-inflammatory effects which may contribute to its anti-tumor effect [15]. Statins were proved to increase the activity of the antioxidant enzymes such as catalase and glutathione reductase and decrease the expression of tumor necrosis factor alpha in tumor cells. It was reported that the reduction in inflammation and oxidative stress was not attributed to the lipid-lowering effect of statins, indicating that statins had pleiotropic effects independent of their effects on the lipid profile [16].

At the cellular level, statins have been linked to the halting of cell-cycle progression and to increased radiosensitization in cancer cells. Thus, the regular use of statins before and after diagnosis of cancer could reduce cancer-related mortality. In large-scale trials of statins to reduce the risk of cardiovascular disease among persons

without cancer, statin use did not influence the incidence of cancer or related mortality [17].

4. Statins, Angiogenesis, Apoptosis and Metastasis

Statins had been reported to affect blood vessel formation, decrease vascular endothelial growth factor production and inhibit capillary tube formation [18]. Moreover, statins might induce up-regulation of proapoptotic protein expression (e.g., Bax protein), combined with decreased anti-apoptotic protein expression (e.g., Bcl-2). Statins also were shown to activate caspase proteases involved in programmed cell death [19]. Apoptosis was triggered in HepG2 hepatocellular carcinoma cell lines by fluvastatin, together with cell cycle arrest, and a down-regulation of the ERK1/2 and an up-regulation of the MAP kinase pathways [20]. Moreover, statins were suggested to impair the metastatic potential of the tumor cells by inhibiting cell migration, attachment to the extracellular matrix and invasion of the basement membrane [21]. Statins, by their anti-tumor effects, were shown to decrease melanoma cell metastasis [22].

5. Potential Carcinogenicity of Statins

On the other hand, various data suggesting a potential carcinogenicity and mutagenicity of statins were present. It was shown that statins may induce prometaphase retardation and chromosome lagging during cellular metaphase and anaphase leading to a mitotic disorder [19]. Moreover, lovastatin administration at high doses was associated with a higher incidence of hepatocellular carcinoma and pulmonary cancers. However, statin-associated carcinogenicity was limited to doses much higher than that commonly used to treat hypercholesterolemia in humans [23].

6. Synergism between Statins and other Chemotherapeutic Agents

It was proved that synergistic interactions are present between statins and chemotherapeutic agents such as cisplatin, methotrexate, 5-fluorouracil and doxorubicin [19]. Pretreatment with statins significantly increased cisplatin-induced apoptosis in colon cancer [24] and decreased the expression of P-glycoprotein responsible for resistance to chemotherapeutic agents [23,25]. Furthermore, statins enhanced the antitumor activity of doxorubicin in murine melanoma, colon and lung carcinoma [26]. In addition to increasing the antitumor effect, treatment with statins was associated with a lower risk for chemotherapy-associated cardiovascular adverse effects [19].

7. Conclusions

Statins have anti-tumor effects due to their antioxidant and anti-inflammatory properties together with interference with cholesterol synthesis in cancer cells, inhibition of new vessel formation, decreased resistance to chemotherapeutic agents and induction of apoptosis. As a whole, the benefits of the use of statins are much higher than their deleterious effects. Indeed, the current efforts should be directed to establish therapeutic benefits from statins in cancer therapy. It is of utmost importance to verify and validate statins as an adjuvant agent in different types of cancer.

Competing Interests

The authors have no competing interests.

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