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Statins in oncological research: From experimental studies to clinical practice

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Abstract

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors are commonly used drugs in the treatment of dyslipidemias, primarily raised cholesterol. Recently, many epidemiological and preclinical studies pointed to anti-tumor properties of statins, including anti-proliferative activities, apoptosis, decreased angiogenesis and metastasis. These processes play an important role in carcinogenesis and, therefore, the role of statins in cancer disease is being seriously discussed among oncologists. Anti-neoplastic properties of statins combined with an acceptable toxicity profile in the majority of individuals support their further development as anti-tumor drugs.

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The mechanism of action, current preclinical studies and clinical efficacy of statins are reviewed in this paper. Moreover, promising results have been reported regarding the statins' efficacy in some cancer types, especially in esophageal and colorectal cancers, and hepatocellular carcinoma. Statins' hepatotoxicity has traditionally represented an obstacle to the prescription of this class of drugs and this issue is also discussed in this review.

Keywords: Statins; Anti-tumor properties; Carcinogenesis; Cancer therapy; Cancer risk reduction; Chemoprevention

1. Introduction

A class of cholesterol-lowering drugs, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, have gained a great deal of attention because of their pleiotropic effects, which may be beneficial in various vascular diseases. The discovery of statins significantly changed the approach in dyslipidemic therapy and tremendously decreased morbidity and mortality from cardiovascular events. Statins had become a first choice in current prescribing practice and are pivotal in the primary and secondary prevention of cardiovascular disease (CVD) [1–4].

Recent findings unequivocally support statins for primary prevention in CVD. Taylor et al. [5] assessed the effects, both harms and benefits, of statins in people with no history of CVD. Eighteen randomized control trials were included (56,934 participants). Fourteen trials recruited patients with specific conditions (hyperlipidemia, diabetes, hypertension, microalbuminuria). Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people treated with statins. Recently, much debate has focused on the use of statins for primary prevention in relation to drug safety due to worsened hyperglycemia. Data from the Cholesterol Treatment Trialists' Collaborators demonstrated a 9% reduction in all-cause mortality and a 25% reduction in major vascular events even among low-risk patients. A 2013 Cochrane review corroborated these findings including a 14% reduction in all-cause mortality and a 25% reduction in cardiovascular disease events with statin therapy despite an 18% increase in incident diabetes. Statins effectively lowered atherogenic lipoproteins and resulted in clinically significant reductions in cardiovascular morbidity and mortality [6].

Statins are generally well-tolerated drugs and this was one of the reasons why they replaced previously used drugs in the treatment and prevention of cardiovascular events. The pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, anti-inflammatory properties, inhibition of cardiac hypertrophy, stabilization of atherosclerotic plaques, and inhibition of atherosclerotic process, thereby yielding potential benefits for patients at risk of cardiovascular disease, regardless of cholesterol levels [1–4].

Beyond cholesterol-reducing properties, statins exhibit many other biological activities which are responsible for their beneficial effects in organisms. As an essential step in biosynthesis of the mevalonate pathway statins affect the levels of cholesterol and also other downstream products (isoprenoids) which are important in key physiologic processes such as cell signaling, translation, post-translational modifications, proliferation, apoptosis, and differentiation [7,8]. These processes play an important role in carcinogenesis and, therefore, the anti-tumor properties of statins are intensively evaluated by investigators. The mechanism of action, in vitro and in vivo anti-neoplastic properties of statins, their use in cancer therapy and prevention, and possible adverse effects in cancer patients are the main topics of this review.

2. Statins in oncological research: evaluation of anti-tumor effects

Numerous in vitro experiments showed that statins demonstrate significant tumor-suppressive effects against various leukemia and solid tumor cells. The several conclusions were drawn from experimental studies. Firstly, different statins have apparent anti-proliferative and pro-apoptotic effects on various cancer cell lines. Secondly, the anti-neoplastic effects demonstrated only lipophilic statins. Fluvastatin, simvastatin, and lovastatin were cytotoxic against breast adenocarcinoma cells [7]; atorvastatin, simvastatin, lovastatin, and cerivastatin were cytotoxic against myeloma cancer cells [8] and simvastatin and lovastatin against ovarian cancer cells [9]. Thirdly, statins differ in their anti-neoplastic potential. Four acute myeloid leukemia cell lines using different statins were evaluated. Cell lines were most sensitive to cerivastatin, ten-fold less sensitive to lovastatin and fluvastatin, and only weakly sensitive to atorvastatin [10]. The observed differences in anti-neoplastic effects are explained by their different physicochemical characteristics (lipophilicity of statins is reflected to their potential to cross the cell membrane) and by their differential activation of specific receptors, such as for example nuclear pregnane X-receptor, farnesoid X-receptor and constitutive androstane receptor [11]. Fourthly, statin cytotoxicity may depend on the target tumor type. Dimitroulakos et al. have identified a subset of tumors (juvenile monomyelocytic leukemia, medulloblastoma, rhabdomyosarcoma, choriocarcinoma, and squamous cell carcinomas of the cervix, head and neck) that are sensitive to lovastatin-induced apoptosis and show HMG-CoA reductase as a potential therapeutic target of these cancers [12].