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ScienceDirect
Cancer Letters 260 (2008) 11–19
CANCER Letters
www.elsevier.com/locate/canlet

Mini-review

Statins in tumor suppression

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Received 26 September 2007; accepted 15 November 2007

Abstract

Statins are HMG-CoA reductase inhibitors with important cholesterol-lowering properties. The introduction of these agents in clinical medicine has had a major impact and has changed the natural history of coronary artery disease in humans. Beyond their cholesterol-lowering properties, statins exhibit important anti-inflammatory and antitumor activities. Extensive studies over the last few years have demonstrated that statins generate pro-apoptotic, growth inhibitory, and pro-differentiation responses on neoplastic cells of diverse origin. In addition, several cellular pathways activated by statins have been identified and key mechanisms involved in the generation of their antitumor effects have been characterized. Because of such *in vitro* effects, extensive efforts are underway to establish their utility in cancer prevention and their potential use in the treatment of certain malignancies, in combination with other agents. This review summarizes the documented effects of statins on different tumor cell types and discusses the cellular mechanisms of action of statins in malignant cells. The clinical-translational implications of the ongoing research efforts are also discussed.

Keywords: Statins; Cancer; Leukemia; Differentiation; Apoptosis; JNK; Erk; Kinase; MAPK; Malignanices; Antitumor

1. Introduction

Statins are synthetic HMG-CoA reductase inhibitors that are potent suppressors of cholesterol biosynthesis in humans [1–8]. There are at least eight known members of the statin family [1–8] with different hydrophatic profiles, ranging from very hydrophobic (e.g. cerivastatin) to partly hydrophobic (e.g., rosuvastatin) profiles [1–8]. The statins are structural analogs of HMG-CoA, and they compete for binding with the HMG-CoA reductase [7,8]. As the various statins have much higher affinity for the active site of HMG-CoA reductase, this results in inhibition of the activity of the enzyme and direct suppression of cholesterol biosynthesis [7–9]. Importantly, statin-treatment is also known to ultimately result to enhanced expression of low-density lipoprotein cholesterol receptors on hepatocytes [6,8,10], leading to accelerated/enhanced clearance of cholesterol from the blood [8,11]. The ability of various statins to reduce LDL cholesterol levels has led to extensive clinical trials that have established that these agents reduce progression of atherosclerosis in humans and decrease the incidence of cardiovascular episodes in patients with coronary artery disease (CAD) [12–22].

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doi:10.1016/j.canlet.2007.11.036

The relevance of the cholesterol-reducing properties of statins in the generation of beneficial effects on coronary artery disease (CAD) in humans has been clearly demonstrated over the years [12–21]. In fact, recent studies have shown that for patients with above-target LDL-c levels while on statin monotherapy, coadministration of another lipid-lowering agent, ezetimibe, further reduces the risk for coronary artery disease [22]. This has directly established that the ability of statins, alone or in combination with other agents, to reduce cholesterol levels is highly relevant and important for their beneficial effects in CAD.

Beyond their cholesterol-reducing properties, statins exhibit many other biological activities, and such statin-associated pleiotropy is responsible for many other beneficial effects of these drugs [23]. Statins have been previously shown to have important anti-inflammatory properties [24–26] and such statin-dependent decrease of inflammatory responses is associated with the remodeling response during stabilization of the atheromatic plaque [27]. Interestingly, this effect is independent of the cholesterol-reducing properties of statins [27]. The statins also induce a diverse range of other clinical responses when administered to humans. These include, among others, beneficial effects on non-ischemic heart failure [28], antihypertensive effects [29], reduction in the risk for various forms of dementia [30], antiplatelet effects [31], and a decrease in proteinuria and the rate of progression of kidney disease [32]. Altogether, the diverse effects of statins have raised the potential for the use in various disease states and have ignited extensive clinical trials to define their applications in clinical medicine.

2. Antitumor properties of statins

There is a plethora of experimental evidence by various research groups that statins exhibit antineoplastic effects *in vitro*. Such properties of statins appear to be generated either via effects on cell cycle and induction of growth suppression [33–37] or via induction of apoptosis of malignant cells [37–41]. The growth inhibitory and pro-apoptotic properties of statins *in vitro* may have important clinical implications, both in the prevention and treatment of certain malignancies and have led to clinical-translational efforts at various levels. Below we discuss recent work in the field and summarize the known effects of statins on various types of tumor cells.

2.1. Statins and leukemia

The effects of statins on cells of acute myelogenous leukemia (AML) origin is one of the most studied areas in malignancies, and have been documented in several reports [38,42–45]. Statins are potent inducers of apoptosis of various AML cell lines [44], while fluvastatin has been also shown to suppress the growth of primitive leukemic CFU-GM progenitors from patients with different subtypes of AML *in vitro* [45]. Although the precise mechanisms by which statins generated antileukemic responses remain to be defined, there is some evidence that statins kill AML cells and/or enhance their sensitivity to chemotherapy, by blocking adaptive cholesterol responses [43]. This is consistent with the fact that cholesterol levels are abnormally increased in the leukemic cells of many acute myeloid leukemia patients receiving chemotherapy [42], apparently via upregulation of mRNAs encoding 3-hydroxy-3-methylglutaryl coenzyme A reductase and the low-density lipoprotein (LDL) receptor [42]. Such an increase of cholesterol levels correlates with relative resistance to the effects of certain chemotherapeutic agents [42], suggesting that combined used of statins with chemotherapy may prove to be of clinical value. Interestingly, other studies have shown that blocking protein geranylgeranylation is essential for lovastatin-induced apoptosis of human AML cells [44]. Such studies have established that the geranylgeranyl transferase inhibitor (GGTI-298) mimics lovastatin-induced apoptosis, while the farnesyl transferase inhibitor, FTI-277, is much less effective at triggering apoptosis in AML cells [44]. Other studies have shown that statins can induce differentiation of the NB4 acute promyelocytic leukemia line that expresses the t [15,17] chromosomal translocation [45,46]. Importantly, recent work has established that atorvastatin or fluvastatin induce differentiation of NB4 variants or primary leukemia blasts that are resistant to ATRA, and reverse such ATRA-resistance [45]. In addition to reversing resistance to ATRA-dependent cell differentiation of NB4 variant cells, statins were also found to induce apoptosis and growth inhibitory responses in ATRA-resistant cells [45], raising the possibility that combined use of statins with ATRA may be a way to overcome the resistance that leukemic cells develop to their effects.