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REVIEW ARTICLE

The Anticancer Potential of Statins

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ABSTRACT

Background: Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are important medications for the treatment of lipid disorders. In primary and secondary prevention, they lower cholesterol levels and the risk of cardiovascular disease. Statins modulate signaling pathways to induce pleiotropic effects in numerous disorders, in addition to inhibition of cholesterol production. Because of their possible anticancer effects, statins have recently attracted a lot of attention. Key processes involved in cancer, such as suppression of proliferation, angiogenesis, and metastasis, seem to be inhibited by statins. **Aim**: to provide a brief insight about the promising role of statins as anticancer agents.

Conclusions: Lowering cholesterol levels and protection against cardiovascular diseases are the pharmacological effects of statins, which act through inhibiting the enzyme HMG-CoA reductase. The molecular processes behind statins' "pleiotropic" effects, which extend beyond lipoprotein reduction, have recently attracted attention. There area lot of preclinical studies that support statins' anticancer characteristics. We tried to represent a synopsis about the latest research on statins' anticancer mechanisms.

Key words: Dtatins; Anticancer activities; Signaling pathways.

INTRODUCTION

Research has demonstrated that statins, a class of medications used to lower blood cholesterol levels, can trigger cell death and cellular recycling [1].Hypercholesterolemia and coronary heart disease were the original indications for their development as therapeutic agents [2]. 3-hydroxy-3 methylglutaryl-CoA reductase is the rate limiting enzyme in the mevalonic acid (MVA) pathway, which these medications use to block cholesterol biosynthesis [3].

The importance of the mevalonate pathway in cell proliferation resided in the fact that many cancer cells have elevated HMG-CoA reductase activity.It is hypothesized that a novel cancer treatment could be developed by selectively inhibiting this enzyme. Some laboratory studies have demonstrated that statins can slow the proliferation of tumor cells [4].It is possible that the prevention of tumor cell growth is associated with the reduction of nonsteroidal isoprenoid substances, as shown by the achieved reduction of sterols synthesis by statins. Inhibiting Ras-dependent tumor cell proliferation, this action can affect Ras protein farnesylation. [5].

There are two main groups of statins: those derived from natural sources (such as pravastatin, lovastatin, mevastatin, and simvastatin,) and those made synthetically (such as pitavastatin, atorvastatin, fluvastatin as well as rosuvastatin) [6]. Statins are structurally composed of two parts: the pharmacophore moiety, which inhibits hydroxy-3 methylglutaryl-CoA reductase and can be a carboxylic acid chain in the active form or a lactone ring in the prodrug, and the ring system moiety, which varies for each kind of statin [6].Lovastatin and simvastatin are two exceptions to the rule that most statins are taken orally as active rings; instead, they are activated lactones [7]. Nevertheless, statins vary in how they work pharmacologically, how they dissolve in water, how quickly they are metabolized, and what kinds of metabolites are formed—active and inactive [8]. In terms of serious side effects,

statins are known to cause hepatotoxicity and rhabdomyolysis. [9,10].

We aimed a to provide a brief insight about the promising role of statins as anticancer agents.

Anticancer Mechanisms of Statins

1. The Mevalonate Pathway: There are distinct metabolic changes seen in cancer cells. Though it has always been challenging, discovering drugs that target different types of tumors and cancer-specific metabolic dependencies has not been easy. Polyol, ubiquinone, vitamin D, cholesterol, and lipoprotein production are all regulated by the MVA route, a signaling system that is both crucial and significant [11]. There is a growing evidence that the MVA pathway, which is essential for all cells, is increased in all malignant lesions [12].

Carcinogenesis is characterized by an increase in MVA demand, and tumor cells become more resistant as the availability of MVA pathway intermediates increases [13]. The MVA pathway is an attractive target for cancer treatment because to the availability of specific and well-tolerated inhibitors. It is possible to differentiate between effects produced by pathways mediated by cholesterol and those produced by mechanisms that do not involve cholesterol.

***2. Non-Cholesterol-Mediated Pathways*:** One way to make acetyl-CoA, a building block for MVA, is to decarboxylate pyruvate, which is the product of glycolysis. Three molecules of acetyl CoA are utilized inthe MVA pathway's rate-limiting step by hydroxy-3 methylglutaryl-CoA reductase (HMGCR) [14]. The conversion of MVA to isopentenyl pyrophosphate (IPP) by phosphorylation by MVA kinase exemplifies the central role of the MVA pathway in the reactions that geranylgeranyl pyrophosphate synthase (FDPS) catalyzes to generate FPP and GGPP [15]. One of the most important byproducts of the MVA pathway, squalene is made from FPP. Squalene is a precursor to cholesterol[16].

The cholesterol-regulating enzymes squalene epoxidase and squalene synthase are additional enzymes. The formation and upkeep of function as well the structure of cellular membranes are influenced by cholesterol. It also acts as a building block for bile a. This process is mediated by the enzymes geranyl transferases (GGTases) I and II and farnesyltransferase (FTase). The post-translational modification of many proteins and their prenylation are mediated by the enzymes GGTases I and II, which are farnesyltransferase (FTase) and geranyltransferase, respectively [17].

Anchoring, localization, and activity of several signaling proteins, steroid hormones, fatty acids, and vitamins are dependent on post-translational prenylation. Prenylation of numerous proteins, including small monomeric GTPases (guanosine-triphosphate hydrolase), as well as G-protein-coupled receptors (GPCRs) requires the synthesis of FPP and GGPP [14].

3. Cholesterol-Mediated Pathways: Publication from one hundred years ago provided the first evidence of a link between cancer and cellular cholesterol levels [18]. Since then, other studies have shown that tumors have increased cholesterol levels compared to normal tissues [19]. Researchers have found that tumor cells raise intracellular cholesterol levels by taking advantage of the lack of efficient feedback regulation related to LDL receptors [20]. Cell development, the cell cycle, and the S phase transition are all dependent on cholesterol, which is also essential for lipid metabolism. The demands of tumor-promoting cell signaling proteins are met by cancer cells with an increased cholesterol requirement and a greater lipid raft concentration compared to normal cells [21].

4. Statins Regulate Autophagy: Apoptosis as well as autophagy are two important biological processes that are involved in many different biological activities, such as cell development and differentiation. The function that cells perform is where autophagy and apoptosis diverge. In severe settings, autophagy mainly targets certain toxic components to ensure cell survival [22].

Autophagy is implicated in the progression of pathological disorders, including cancer, according to multiple investigations. Recent research has shown that blocking cancer cells' capacity to enter autophagy can either completely eradicate the disease or significantly lower its viability. Autophagy is likely involved in cancer progression [23].

Autophagy is a crucial step in the process of tumor suppression in the early stages of cancer progression. It regulates the destruction of damaged proteins or organelles, such as faulty mitochondria, and serves as a quality control mechanism to maintain genetic integrity [24]. To add to that, autophagy increases oncogene-induced senescence [25] and helps the immune system notice malignancy [26]. Autophagy mostly promotes tumor growth in the advanced stages of tumor development. Because cancer cells proliferate so rapidly, anabolic pathways have high nutritional requirements. Autophagy regulates cancer cell metabolism by recycling cellular

substrates [27]. Autophagy mitigates tumor hypoxia and endoplasmic reticulum stress, two conditions that promote cancer cell proliferation [28]. Where is the role of statins on autophagy????

5. Statins Induce Ferroptosis: Programed cell death (PCD) differs from necrosis,apoptosis, autophagy and pyroptosis[29]. The potential use of ferroptosis in cancer treatment has garnered interest, as it has been linked to numerous deadly diseases. Methods for blocking ferroptosis include scavenging reactive oxygen species (ROS), decreasing PUFA production, or storing free iron [30].

By regulating the GSH/GPX4 and FSP1/CoQ10/NAD (P) H axis, statins bring about ferroptosis via the MVA pathway. Both the synthesis of GPX4 and the creation of the CoQ10 backbone rely on the MVA pathway. One of the building blocks of CoQ10 is IPP, which is produced via the MVA pathway. An essential regulator in GPX4 development is Sec-tRNA, which is positively regulated by IPP. By inhibiting the activity of the rate-limiting enzyme in the mitochondrial VP-AKT pathway, statins reduce the efficiency of GPX4 translation, making cells more susceptible to ferroptosis [31].

6. Statins Target the Tumor Microenvironment: The term "tumor microenvironment" (TME) describes the noncancerous cells, substances, and activities that surround tumors. Cancer is known to be an ecological process involving the tumor microenvironment (TME) and cancer cells, which are known to interact in a dynamic and ongoing manner [32]. Tumor progression, metastasis, and treatment response are all profoundly impacted by the constant communication between tumor cells and the tumor microenvironment (TME). Oncogenic evasion of the immune system, prolonged proliferative signals, and other cancer markers are all aided by TME. The paradigm in cancer therapy has changed from being cancer-centric to being TME-centric as a result of improved understanding of the tumor microenvironment's crucial roles in tumor growth and treatment resistance. Some cancer treatments have focused on influencing specific parts of the tumor microenvironment [33]. What is role of statin here?

Statin Anticancer In Vivo Studies

Many types of tumors have been tested in published in vivo researches showing that simvastatin is effective against cancer. In these studies, simvastatin dosages were found to be supratherapeutic, in comparison to those utilized in individuals with hypercholesterolemia. As a result of statins' high clearance , rats require greater doses of the drug to get the same therapeutic effects as humans. Inhibiting hormone secretion by pituitary neuroendocrine tumors, simvastatin possesses antisecretory and antiproliferative properties. A concentration-dependent inhibition of tumor cell growth was observed in xenograft models of lung cancer and leiomyoma in mice, according to the researchers [34].

Statins and Autophagy

Regulating statin-mediated autophagy may involve multiple signaling pathways, one of which is the AMPK/mTOR (AMP-activated protein kinase/mechanistic target of rapamycin) system, while another is the AMPK/p21 pathway. Lastly, it has been proposed that statin-induced p53 increase can trigger autophagy. The prenylation of GTPase proteins, which are known as ATG proteins, is one of many molecular mediators involved in autophagy. These proteins include Rheb, Rabs, and RalB. Membrane subdomain development during maturation requires Rabs, which mediate vesicle transport and fusion and function as molecular switches [35].

The Role of Statin in the Microenvironment of Tumor Metabolism

Genomic instability, chronic inflammation (the root cause of cancers), and immune system escape are all linked to metabolic reprogramming, which is believed to be a feature of tumor cells. Statins influence the microenvironment of metabolism. A combination of simvastatin and monocarboxylate transporter 1 (MCT1) inhibitors has synergistic anti-tumor effects by changing tumor cells' metabolism, decreasing lactic acid generation, and increasing tumor sensitivity to both drugs [36].

CONCLUSIONS

As pharmacological effects, statins reduce cholesterol levels and protect against cardiovascular disease by inhibiting the enzyme HMG-CoA reductase. Recent years have seen an uptick in research into the molecular mechanisms behind statins' "pleiotropic" effects, which go beyond only decreasing lipoproteins.There have been a lot of preclinical studies that support statins' anticancer characteristics, so that's where most of the attention has gone. We have included a synopsis of the latest research on statins' anticancer mechanisms below. Mevalonate pathway is the first and most studied statin-induced anticancer mechanism. By blocking the activation and post-translational modification of small GTPases and the signaling pathways that follow, statins impact cell proliferation,

differentiation, apoptosis, and growth.Because of its function in controlling cellular cholesterol levels, the mevalonate pathway—which is essential for cholesterol production—has also been linked to cancer in multiple studies. We therefore investigated the mevalonate pathway's function in statin anticancer effects from two angles: the cholesterol-mediated and the non-cholesterol-mediated. Furthermore, we emphasized the most recent discoveries that provide light on anticancer mechanisms, including autophagy, ferroptosis, tumor microenvironment targeting, and statin pyroptosis.

Conflict of interest: None.

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