

From the Therapeutic Perspective: Effect of Statins-Use in Cancer

Olagunju AS^{1*}, Oladapo IP² and Kosemani SO¹

¹*Department of Biochemistry, University of Ibadan, Ibadan, Nigeria.*

²*Department of Zoology, University of Ibadan, Ibadan, Nigeria.*

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ABSTRACT

In the past, there were different concerns in regards to the association of statins with high prevalence of cancer and increased cancer-associated death; now, there are lot of evidences supporting the cytotoxic, cytostatic and anti-cancer efficacy this drug. Statins are confirmed competitive inhibitors of hydroxy-methylglutaryl (HMG)-CoA reductase enzyme, therefore regularly prescribed as cholesterol-lowering agents. Of recent, dysregulation of lipid metabolism has been confirmed as one of the hallmarks cancer cells. As a result, statins drugs have gained much attention towards its potential as therapeutic agents in cancer. Here, we discuss and summarize several observations on the anti- tumorigenic and angiogenic effect of the known mevalonate pathway inhibitor that is the statins drugs.

Keywords: Statins, Mevalonate, Cancer, HMG-CoA reductase, Hyperlipidemia

INTRODUCTION

Cancer is a complicated disease that ravages millions of people globally. The major available therapies are cytotoxic, while most cancers are incurable. Some clinical result trials recorded the probable effect of statins drug in cancer showing that statins can either increase or decrease the risk of carcinogenesis.

Ever since their endorsement in 1987 as an agent for hyperlipidemia reduction to prevent and manage cardiovascular diseases; statins, recognized cholesterol-lowering agents, is now one of the most commonly approved drugs globally, owing to their confirmed efficiency and good safety. Statins exert its main effect via the endogenous mevalonate pathway by binding and inhibiting the rate limiting enzyme that is HMG-CoA reductase enzyme in cholesterol and isoprenoids biosynthesis (**Figure 1**) [1]. The reversible inhibition, dose-dependent and competitive effects on 3-HMG-CoA reductase leads to the blocking of the 3-hydroxy-3-methylglutaryl CoA conversion to mevalonate, thereby inhibiting all other downstream intermediates and products such as isoprenoid and cholesterol metabolites.

With a significant pharmacological profile showed by Stains and accumulated data of their multiple effects apart from the know cholesterol-lowering for example neuroprotective effects, anti-inflammatory, anti-proliferative, encouraged research into their usefulness in a wide range of diseases including cancer.

EFFECT OF STATINS IN TUMORIGENESIS

Vital cellular metabolic adjustments were observed as a result of cell's high energy demands. These adjustments are known as the Warburg effect, which is a distinctive phenotypical feature of a cancer cell [3]. The mevalonate pathway for cholesterol biosynthesis and protein prenylation has been involved in several aspect of carcinogenesis. The oncoproteins such as the Ras protein family that is Ras and Rho-GTPase depends on post-translational and isoprenylation for their anchoring to the membrane and other activities as they are involved in a high fraction of human cancers incidence [4]. As a result, transformed malignant cells are highly dependent on the isoprenoid pathway for the synthesis of lipid moieties important for membrane integrity, cell proliferation, cell signaling and cell cycle progression [5-7]. Thus, with non-steroidal isoprenoid molecules as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) production inhibition, and therefore of oncoproteins prenylation, leads to their activity inhibition.

Corresponding author: A.S. Olagunju, Department of Biochemistry, University of Ibadan, Ibadan, Nigeria, Tel: +234-7068-528-329; E-mail: abolajisamson05@gmail.com; asolagunju@yahoo.com.

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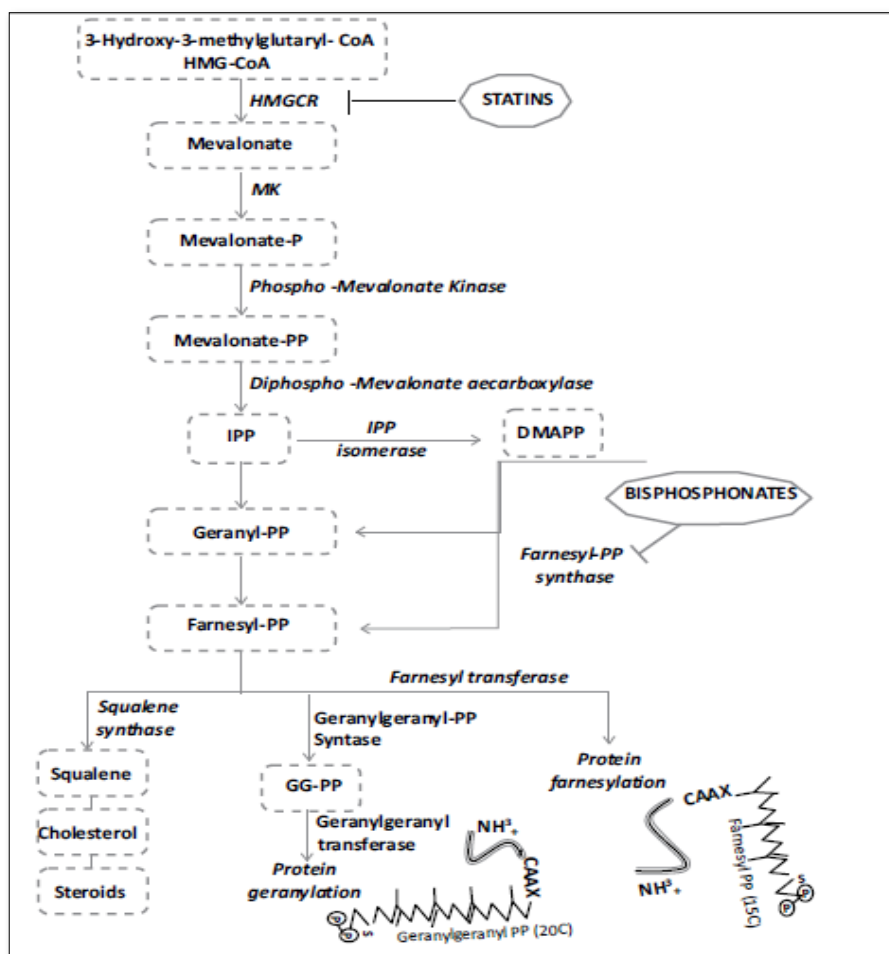


Figure 1. Mevalonate pathway and its principal inhibitor [2].

The likely mechanisms that result in increased lipid synthesis in tumor cells might be:

- (1) Availability of precursors for example acetyl-CoA, derived from hyper-activation of the glycolytic pathway [8]
- (2) Loss of HMG-CoA reductase feedback control or
- (3) Increase in expression and function HMG-CoA reductase.

Hence, cancer progression (for example in breast and liver) is promoted by the uncontrolled expression of HMG-CoA reductase collaborating with the Ras oncogene hypothesizing the role of HMGCR enzyme as a metabolic oncogene [8]. Surprisingly, breast cancer cells with mutant p53 have promoted mevalonate pathway activity. However, the system in which p53 mutant relates with sterol gene promoters through the sterol regulatory element binding protein (SREBP) transcription factors, may specifically be sensitive to inhibition by statins, this may reverse the malignant phenotype by inhibiting cancer cell invasive growth and survival (Freed-Pastor et al. [9].

Other enzymes in the mevalonate pathway have been shown to partake in tumor progression and resistance to

chemotherapy [10], for example, farnesyl diphosphate synthetase (FDPS), this enzyme catalyzes the formation of GPP and FPP which are key isoprenoid intermediates, utilized as substrates for protein prenylation.

Certainly, an increased farnesyl diphosphate synthetase (FDPS) expression and activity in human colon cancer has been established and has been shown to be involved in the pathology of some tumors [11]. Furthermore, the mevalonate pathway has been implicated in multidrug resistance (MDR), affecting the P-glycoprotein (P-gp) activity through hyper-activation of farnesyl diphosphate synthetase. The P-gp, a plasma membrane transporter plays a significant role in multidrug resistance (MDR) by enhancing the efflux of several drugs even chemotherapeutics.

Inhibition of farnesyl diphosphate synthetase (FDPS) effect by zoledronic acid which is a strong amino-biphosphonate, arrested Rho A and Ras activity preventing hypoxia inducible factor-1alpha (HIF-1α)-driven P-glycoprotein expression and returning the sensitivity of cancer cells to chemotherapy [12]. In lieu of these, increasing clinical and experimental data propose a novel promising therapeutic approach depending on

the inhibition of enzymes associated with the mevalonate pathway, as statins drugs, a likely candidate in cancer treatment strategies hinder tumor growth [13].

Statins mevalonate-dependent targets Rho A and C proteins, are involved in cancer cell proliferation and more significantly in invasion and migration [14]. It has been confirmed that statins inhibit migration, chemotaxis, and adhesion of acute lymphoblastic leukemia cell lines through

specific GTPases suppression [15]. Of note, statins could exhibit cytotoxic and anti-proliferative activity via the inhibition of HMG-CoA reductase and also against the natural killer cells. Similar to all lymphocytes, natural killer cell malignancies can increase leukemia [16]. The treatment with a particular statin drug (simvastatin) was able to inhibit the migration, proliferation and invasion of murine melanoma cells and shrink the tumor mass in mice (**Figure 2**) [17].

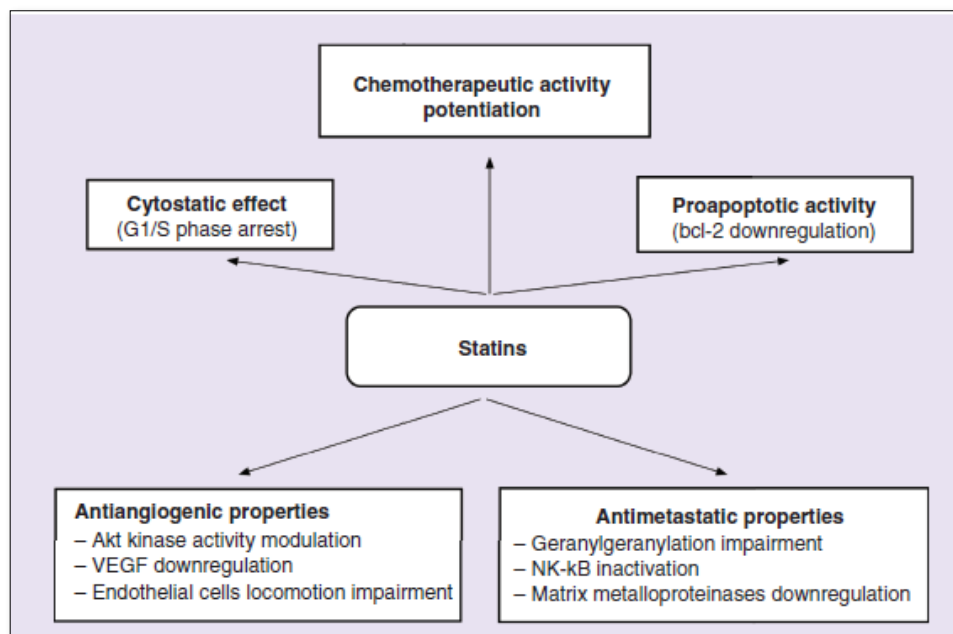


Figure 2. Relationship between statins therapy and cancer [18].

IMMUNO-MODULATORY EFFECT OF STATINS IN CANCER

Recently, there has been interplay between tumor cell and its microenvironment majorly the immune cells and the balance among these determines the development and inhibition of cancer cell. Furthermore, its contribution to tumor development and progression, activation of the isoprenoid pathway can represent an essential adaptive host response to stress, thus activating the anti-cancer immunity mechanism. Although the isoprenoid pathway is common and vital to cell survival, the mevalonate-deficient cells cannot be formed by selection induced mechanisms. Hence, making cells with modified isoprenoid pathway detection an optimal system for assessing the metabolic integrity of cells susceptible to modification, either during neoplastic conversion or during infection [19].

Recently, a study was conducted for the first time on the potential of an endogenous isoprenoid derivative of mevalonate pathway that is N-6-isopentenyladenosine (iPA) to selectively enlarge and directly target the human Natural

Killer cells (NKC) [20]. Also, it was reported that the pharmacological agents, amino-bisphosphonates that causes accumulation of the phosphorylated metabolites inhibiting farnesyl diphosphate synthetase enhancing *in vivo* and *in vitro* cancer cells to T cells, leading to a reduction in cancer development [21]. Similarly, inhibition of bisphosphonates, protein prenylation can also initiate caspase-1-dependent activation of the natural killer cells; together with T cells exert anti-tumor immune response [22]. For some years now, this huge therapeutic potential point to bisphosphonates (BPs) has the most promising method in inhibiting the mevalonate pathway in cancer cells to attain a protective anti-cancer response. Meanwhile statins drugs to which significant immuno-adjuvant characteristics have been ascribed shows a related positive mechanism. Effects of statins on the anti-tumor cell intrinsic barrier are well known, comprising of protein prenylation inhibition through decrease of downstream isoprenoid metabolites needed for essential cellular mechanisms [23] (**Figure 3**).

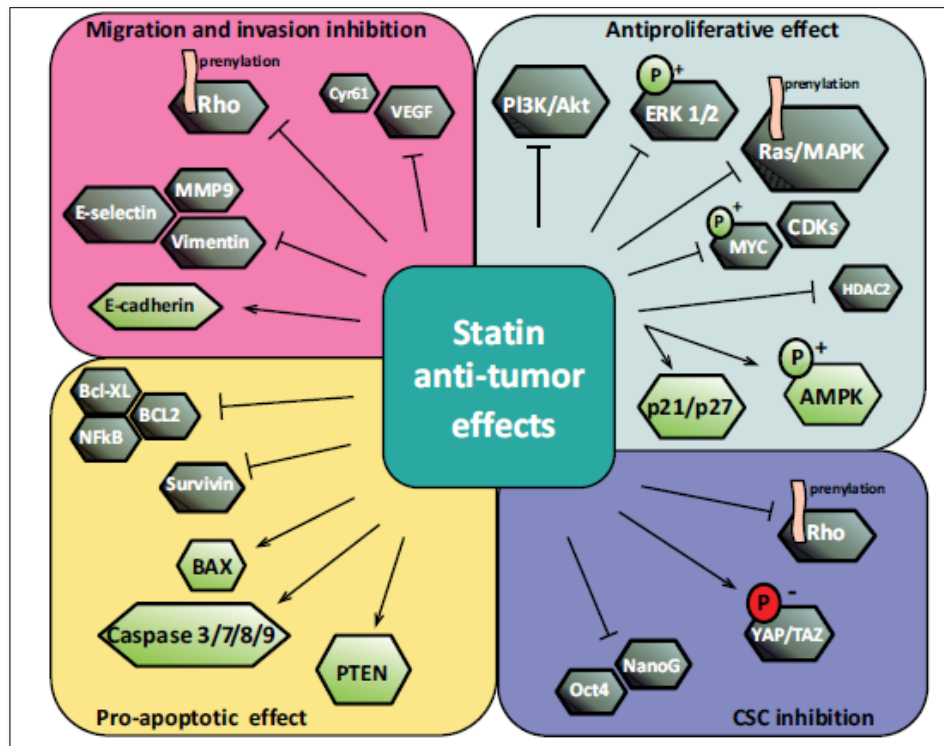


Figure 3. Cancer mechanisms and molecular targets affected by statins.

ANTI-METASTATIC PROPERTIES

It is worth of note that approximately 1% of cellular proteins are geranylgeranylated including the Rho proteins family, N-Ras, and K-Ras. Ras and Ras-homologous (Rho) Guanosine-5-triphosphate-ases (GTPases) are recognized as regulatory proteins, in which prenylation is vital for their normal intracellular function and localization. These proteins play a crucial role in several signal transduction pathways related to cell death, tumor progression and cell proliferation [28]. Statins have also been shown to exert anti-metastatic effects and geranyl geranylation is crucial to this mechanism. Many researches have connected the anti-invasive effect of statins (cerivastatin) therapy with RhoA delocalization from the cell membrane, leading to disorientation of actin fibres and removal of focal adhesion sites. Furthermore, inhibition of RhoA results in deactivation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to low expression of proteases involved in cell migration (urokinase and metalloproteinase 9) [29]. In particular, cerivastatin affects cell signaling pathways related with invasiveness and the metastatic attributes of extremely invasive cancer cells.

Statins could promote apoptosis by inhibiting GPP needed for ultimate Rho mediated cell proliferation. Statins can also up-regulate the pro-apoptotic proteins for example, Bim and Bax and down regulate anti-apoptotic proteins for example Bcl-2. Also, statins activate caspases involved in cell death. Thus,

showing many possible mechanisms for apoptosis [30] (Figure 4).

Statins consistently reduce the progression of liver fibrosis, mostly due to their ability to alleviate portal hypertension, immunomodulatory effect, and also enhances transcription factors with vasoprotective effects in the liver and inhibit stellate cells, hence possibly further decreasing fibrosis [31]. However, the zeal concerning statins potentials has been mitigated by fears about their safety profile in cirrhotic individuals due to their risk of dose-dependent hepatic injury [32].

In breast cancer, most of clinical evidence supports a protective potential of statins on reducing recurrence of breast cancer. The benefits of statins on reducing the recurrence of breast cancer appears shows strong effect in younger individuals, proposing a longitudinal effect of statin therapy. Another research established a 36% reduction in the risk of breast cancer recurrence in individuals on lipophilic statins therapy.

ANTI-ANGIOGENIC EFFECT OF STATINS

The mevalonate pathway metabolites dolichol through the inhibition of isoprenylation has been shown to have a stimulatory effect on DNA synthesis and regulate cell growth [33]. This action is significant in cancer cells, as there is an increase in G protein activity in many cancer types including, pancreatic, kidney, bladder, colorectal, thyroid, and

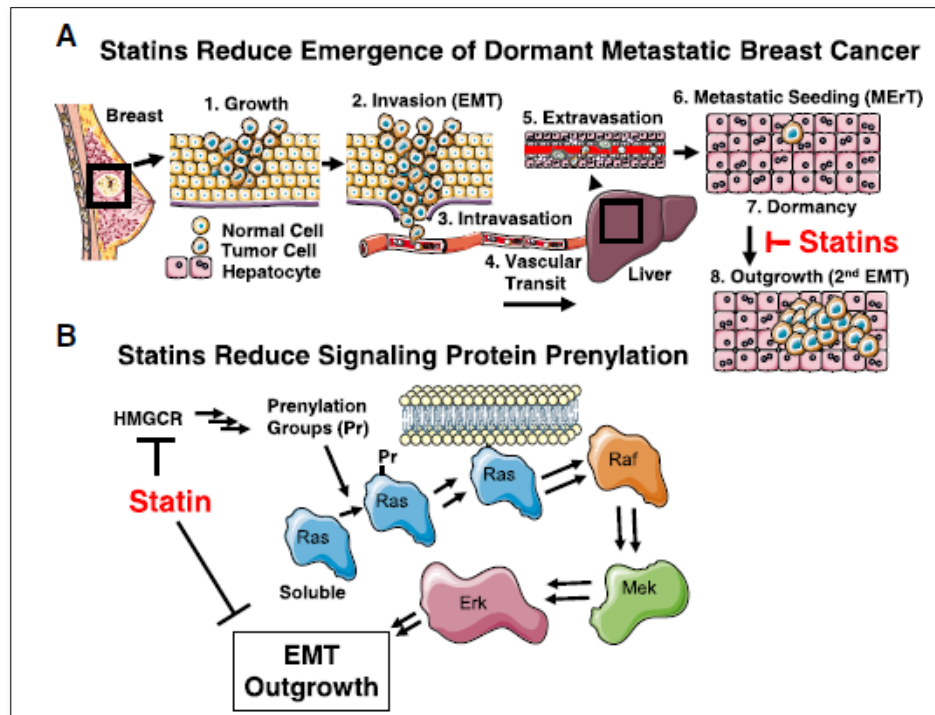


Figure 4. Proposed Mechanisms of action of Statins in Breast Cancer (SAS LLS 2018)

hepatocellular carcinomas, melanoma, and haematological malignancies [34]. Statins can also hinder cancer cell growth through upregulation of cell-cycle inhibitors, p21 and/or p27 and down-regulation of cell cycle-promoting mediators, for example cyclin-dependent kinases (CDKs). These effects increase factors to stop the cell proliferation [35].

Cancer cells need new vasculature (angiogenesis) to provide nutrients and oxygen as the mass increases; without enough supply, the tumor development can be hindered. Therefore, via angiogenesis inhibition, statins exert its anti-cancer effect. Hence, cancer promotes hypoxia to stimulate mediators for angiogenesis [36]. It inhibits formation of new blood vessels by inhibiting endothelial cell proliferation, stopping extracellular matrix adhesion and by decreasing the pro-angiogenic factors such as vascular endothelial growth factor (VEGF). Caveolin, a protein involved in the low expression and activity of endothelial nitric oxide synthase (eNOS) is essential for the inhibition of angiogenesis [37]. Hence, endothelial cell with low level caveolin might be more sensitive to the angiogenic effect of statins. Together with its angiogenic effect, statins may also exhibit anti-metastasis by inhibiting metastasis mechanisms such as cell adhesion, extravasation, breaking down of extracellular matrix (ECM), migration and also invasion of other tissues by decreasing endothelial adhesion molecules for example matrix metalloproteinase-9 and E-selectin [38].

CONCLUSION

Even though the potential anti-cancer effect showed by statins in preclinical models of several cancer types, only or in combination with other chemotherapeutic drugs, via the prevention of migration, invasion, induction of apoptosis and proliferation their actual efficacy in the clinical setting is not yet confirmed. Nevertheless, the likelihood to increase statins doses in cancer patients is narrow by the higher risk of side effects such as rhabdomyolysis and myalgia. A probable solution is to find appropriate favorable combinations of statins and standard chemotherapeutic agents or drugs, capable of having synergistic effects and therefore permit the use of lower effective doses both of the cytotoxic drug and statin, significantly decreasing side effects and promoting the quality of life of the patient.

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