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The balance between induction and inhibition of mevalonate pathway regulates cancer suppression by statins: A review of molecular mechanisms

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ABSTRACT

Statins are widely used drugs for their role in decreasing cholesterol in hypercholesterolemic patients. Statins through inhibition of Hydroxy Methyl Glutaryl-CoA Reductase (HMGCR), the main enzyme of the cholesterol biosynthesis pathway, inhibit mevalonate pathway that provides isoprenoids for prenylation of different proteins such as Ras superfamily which has an essential role in cancer developing. Inhibition of the mevalonate/isoprenoid pathway is the cause of the cholesterol independent effects of statins or pleotropic effects. Depending on their penetrance into the extra-hepatic cells, statins have different effects on mevalonate/isoprenoid pathway. Lipophilic statins diffuse into all cells and hydrophilic ones use a variety of membrane transporters to gain access to cells other than hepatocytes.

It has been suggested that the lower accessibility of statins for extra-hepatic tissues may result in the compensatory induction of mevalonate/isoprenoid pathway and so cancer developing. However, most of the population-based studies have demonstrated that statins have no effect on cancer developing, even decrease the risk of different types of cancer.

In this review we focus on the cancer developing "potentials" and the anti-cancer "activities" of statins regarding the effects of statins on mevalonate/isoprenoid pathway in the liver and extra-hepatic tissues.

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1. Introduction

Statins are amongst the most widely used drugs in the world for their impacts on cholesterol reduction as an effective treatment for hypercholesterolemia by inhibiting Hydroxy Methyl Glutaryl-CoA Reductase (HMGCR) and thereby reduction of cholesterol synthesis [1–4]. Meanwhile some studies showed other properties of statins and their possible effects on other diseases like different types of cancer [5–8].

Although several studies indicated that statins have no effect on cancer [9–14] or proposed a lower cancer incidence among statin users [5,15,16], some studies suggested statins can increase the risk of some types of cancers [17,18].

One of the main reasons of such controversial findings could be related to the type of the statin so that lipophilic and hydrophilic statins have different effects on extra-hepatic tissues [19,20]. This difference between these two types of statins leads to the different results of the studies on the effects of statins on cancer so that some studies showed lipophilic statins have anticancer effects [5,21–23] but not all statins [10,15,24]. On the other hand, the type of the cancer should be regarded as well [7,18,25–29].

Although most of the population-based case control studies have shown that statins decrease the risk of different types of cancer [16,21,22,30–33] such as gastrointestinal cancer [34–39], breast cancer [5,30,40], hepatocellular carcinoma [41–43], prostate cancer [44–46], lung cancer [47] and pancreatic cancer [48], there are other studies that concluded statins increase the risk of some cancers such as prostate [17] and both melanoma and non-melanoma skin cancer [18].

Regarding their different levels of penetrance to extra-hepatic tissues, in this review we aim to show the mechanisms of cancer developing/prevention by statins in the liver as the main target of statins and also in the extra-hepatic tissues.

2. Statins metabolism

Lipophilic statins with higher logD (distribution coefficient or 'partition coefficient' of the drug into octanol: water) can diffuse into all cells and hydrophilic ones with lower logD use a variety of membrane transporters (including organic anion transporting polypeptides) to gain access to cells other than hepatocytes [49]. Atorvastatin, Fluvastatin, Lovastatin, Simvastatin and Pitavastatin are categorized as lipophilic statins, while Pravastatin and Rosuvastatin are hydrophilic statins [50–52]. Simvastatin and Lovastatin are administered as a pro-drug, since they have a lactone ring which must be transformed into the biologically active form with an open acid in their structure while other statins are administered as the open acid, the active form [53,54]. Thus Simvastatin and Lovastatin are administered as a pro-drug, and other statins administered in the active form [55].

It is possible that opening of lactone via carboxenium ion formation primarily through nucleophile attack on carbon adjacent to ring oxygen and secondarily electrophile attack on ring oxygen activates the carbonyl oxygen. It seems the proton released from this opening may impose the quantum tunneling effect on the HMGCR.

Statins (except for Pravastatin, and partially Rosuvastatin) undertake a first pass liver metabolism. P-450 (CYP) is responsible for metabolizing of statins; however Pravastatin and Rosuvastatin undergo minimal degradation. An extensive first-pass extraction implies a low systemic bioavailability (see Table 1) [1,20,56].

Several members of the Organic Anion-Transporting Polypeptide (OATP) superfamily have been shown to be involved in hepatic uptake of statins; including OATP1B1, OATP1B3 and OATP2B1. Although OATP1B1 is thought to be exclusively expressed in the liver, OATP2B1 and OATP1B3 have been shown to express in different tissues (see Table 1) [54,57].

3. Regulation of the protein prenylation by statins

Consistent with the accessibility level of statins for extra-hepatic tissues, they may inhibit or induce mevalonate/isoprenoid pathway and so alter the synthesis of the isoprenoid units which serve as the precursor to the prenylation of Ras superfamily [44].

Isoprenoids as byproduct of mevalonate pathway play an important role in prenylation of the members of Ras superfamily and subsequent tethering of these proteins to cell membrane which is necessary for biological activity of these proteins [64]. Farnesyl pyrophosphate (FPP) and geranylgeranyl-pyrophosphate (GGPP) are the major isoprenoids involved in prenylation of proteins [34].

Members of the Ras superfamily consist of five major family: Ras sarcoma (Ras), Ras homologous (Rho), Ras-like proteins in brain (Rab), Ras-related Nuclear protein (Ran) and ADP-ribosylation factor (ARF) [56].

Farnesyl-transferase and geranylgeranyl-transferase I covalently attach farnesyl or geranylgeranyl isoprenoid units to the cysteine residue at the CAAX(C=Cys, A = aliphatic, X = any amino acid) motif at the C-terminal of Ras and Rho respectively and geranylgeranyl-transferase II attaches geranylgeranyl groups to a set of cysteine-containing C-terminal motifs of Rab family [65,66].

3.1. Rho family

In animals ten members have been identified for Rho family: RhoA-E, RhoG, Rac1 and -2, Cdc42, and TC10. RhoA, RhoB, and RhoC; Rac1, Rac2 and Cdc42 have been well disclosed [67].

Rho GTPases, Rac and Cdc42 are best known for their role in remodeling of cytoskeleton. These proteins regulate three independent signaling pathways and establish a link between cell membrane receptors and the assembly of distinct filamentous actin structures [68]; activation of these proteins induce specific short-term responses such as the formation of filopodia, lamellipodia,