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Could drugs inhibiting the mevalonate pathway also target cancer stem cells?

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ABSTRACT

Understanding the connection between metabolic pathways and cancer is very important for the development of new therapeutic approaches based on regulatory enzymes in pathways associated with tumorigenesis. The mevalonate cascade and its rate-liming enzyme HMG CoA-reductase has recently drawn the attention of cancer researchers because strong evidences arising mostly from epidemiologic studies, show that it could promote transformation. Hence, these studies pinpoint HMG CoA-reductase as a candidate proto-oncogene. Several recent epidemiological studies, in different populations, have proven that statins are beneficial for the treatment-outcome of various cancers, and may improve common cancer therapy strategies involving alkylating agents, and antimetabolites. Cancer stem cells/cancer initiating cells (CSC) are key to cancer progression and metastasis. Therefore, in the current review we address the different effects of statins on cancer stem cells. The mevalonate cascade is among the most pleiotropic, and highly interconnected signaling pathways. Through G-protein-coupled receptors (GRCP), it integrates extra-, and intracellular signals. The mevalonate pathway is implicated in cell stemness, cell proliferation, and organ size regulation through the Hippo pathway (*e.g.* Yap/Taz signaling axis). This pathway is a prime preventive target through the administration of statins for the prophylaxis of obesity-related cardiovascular diseases. Its prominent role in regulation of cell growth and stemness also invokes its role in cancer development and progression. The mevalonate pathway affects cancer metastasis in several ways by: (i) affecting epithelial-to-mesenchymal transition (EMT), (ii) affecting remodeling of

Abbreviations: ACAT, acetoacetyl-CoA transferase; acetyl-CoA, acetyl-coenzyme A; Arp2/3, actin-related protein 2/3 (actin polymerizing complex); BPs, bisphosphonates; CAMs, cell adhesion molecules; CDKIs, cyclin dependent kinase inhibitors; CSCs, cancer stem-like cells; CVD, cardiovascular diseases; EMT, Epithelial-to-mesenhymal transition; ESCs, embryonic stem cells; FPP, farnesyl pyrophosphate; FTase, farnesyl transferase; FTIs, farnesyl-transferase inhibitors; FZD7, frizzled family receptor 7; GAP, GTPase-activating protein; GDI, GDP-disassociation inhibitors; GEF, guanine nucleotide exchange factors; GGPP, geranylgeranyl pyrophosphate; GGTase, geranylgeranyl transferase; GGTIs, geranylgeranyl transferase inhibitors; GPP, geranyl pyrophosphate; GSLC, glioma stem-like cell; HA, hyaluronan; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGR, HMG-CoA reductase; HNSCC, head & neck squamous cell carcinoma; iPS, induced-pluripotent stem cells; GRCP, G-protein-coupled receptor; LDL, low-density lipoproteins; mDia, FH (formin homology) domain containing protein; MK, mevalonate kinase; MPP, mevalonate pyrophosphate; PCP, Wnt/planar cell polarity; PMK, phosphomevalonate kinase; MPPD, pyrophosphate decarboxylase; Oct4, octamer-binding transcription factor; RHAMM, Receptor for HA-mediated motility also known as HMMR, IHABP or CD168; RhoB-F, farnesylated RhoB; RhoB-GG, RhoB geranylgeranylated; RhoGDI, Rho-specific GDI; ROCK, Rho-associated protein kinase; SRE, Sterol regulatory element; SREBP, SRE-binding protein; WAVE, WASP (Wiskott-Aldrich syndrome protein) verprolin homologous; YAP, Yes-associated protein.

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the cytoskeleton as well as cell motility, (iii) affecting cell polarity (non-canonical Wnt/planar pathway), and (iv) modulation of mesenchymal-to-epithelial transition (MET). Herein we provide an overview of the mevalonate signaling network. We then briefly highlight diverse functions of various elements of this mevalonate pathway. We further discuss in detail the role of elements of the mevalonate cascade in stemness, carcinogenesis, cancer progression, metastasis and maintenance of cancer stem cells.

1. Introduction

Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-CoA (HMGCoA) reductase, form the basic class of hypolipidemic drugs used in both primary and secondary prevention of cardiovascular diseases (CVD). CVD are currently the leading cause of death in all Western countries. Nowadays CVD are considered a pandemic. A decrease in death from CVD observed during the last 40 years can be attributed in above 50% of patients due to a reduction in the intensity of risk factors, *e.g.* hypercholesterolemia, or their elimination such as smoking cessation (Di Chiara and Vanuzzo, 2009). Among 3 major risk factors, which could be controlled using drugs: hypercholesterolemia, arterial hypertension and obesity, hypercholesterolemia is the best controlled. The goal LDL-cholesterol level is achieved by 55% of patients, whereas BMI <25 is achieved by only 18% of patients. The best control of lipid disorders in CVD prevention could not be achieved without the use of statins. Nowadays statins are the most frequently used hypolipidemic drugs. They constitute a part of the golden standard "ABS" (aspirin, β-blocker and statin) in a treatment of patients after myocardial infarction. The introduction of statins was a milestone in CVD prevention (Taylor, 2012).

Osteoporosis is a disease causing bone loss resulting in a decrease in bone mineral density. It may occur in postmenopausal women, elderly people or as a serious side effect of corticosteroid therapy. Bisphosphonates are drugs used in the treatment of osteoporosis to improve mineral bone density and to prevent osteoporotic fractures. The introduction of bisphosphonates has made a great improvement in the treatment of osteoporosis.

There is a growing body of evidence suggesting antitumor activity of statins (Yeganeh et al., 2014). Preclinical studies suggest that bisphosphonates have anticancer activity, in particular nitrogen-containing bisphosphonates have the potential to improve prognosis. Some studies indicate that combination of statin and bisphosphonate can extend the lifespan of experimental animals bearing cancer (Tardoski et al., 2015; Van Acker et al., 2016; Zhao and Hu, 2015; Misra et al., 2015). These two drug classes, although registered to be used in different medical conditions, have also antitumor properties. They have one in common, they interact in the mevalonate pathway. Drug resistance is a serious problem in oncology. Researchers focus their efforts on better understanding of its mechanisms and overcoming it. New antifolates targeting various enzymes are being introduced into clinical use (Gonen and Assaraf, 2012). An intracellular metabolism of these drugs and enzymes involved in it are better understood (Assaraf, 2007; Wojtuszkiewicz et al., 2016). Cancer cells can develop various mechanisms of drug resistance, like fast efflux of anticancer drug mediated by multidrug resistance proteins, drug-accumulating lysosomes and highly acidic microenvironment of tumors (Taylor et al., 2015; Zhitomirsky and Assaraf, 2016). Scientists intensively try to develop new more effective strategies of anticancer therapies. Their efforts are focused either on improvement of efficacy of already existing agents, *e.g.* introducing nanovehicles enabling targeted delivery of a drug or finding new targets for new anticancer treatment (Livney and Assaraf, 2013). The mevalonate pathway seems to be a very promising new aim for the improvement of efficacy of anticancer pharmacotherapy.

In the current review we discuss the role of the mevalonate pathway focusing on cancer stem cells. We also discuss the role of this pathway in cancer development and anticancer treatment. Furthermore, targeting the mevalonate pathway in cancer, and in CSC in particular, has the potential to overcome anticancer drug resistance, a pleiotropic phenomenon that continues to be a primary hindrance to successful cancer therapy.

2. Biochemistry of the mevalonate pathway

The mevalonate pathway, previously known as cholesterol synthesis pathway, is a source of several important biochemical compounds and is implicated in key cellular processes (Yeganeh et al., 2014). This pathway converts acetyl-coenzyme A (acetyl-CoA) to mevalonate in three steps, and further through a series of intermediate steps into farnesyl pyrophosphate (FPP). FPP serves as a precursor in the biosynthesis of sterols including cholesterol, as well as ubiquinone, heme A and dolichols. Furthermore, FPP is converted into geranylgeranyl pyrophosphate (GGPP; Fig. 1). Both FPP and GGPP play a central role in the process of prenylation, where FPP or GGPP are post-translationally added to a protein to facilitate cell membrane anchoring (Ghavami et al., 2012a, 2014).

The pathway is initiated by acetoacetyl-CoA transferase (ACAT), which condenses two acetyl-CoA into acetoacetyl-CoA. Acetoacetyl-CoA is then condensed with an additional acetyl-CoA into 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase. The third step, catalyzed by HMG-CoA reductase (HMGR), converts HMG-CoA to mevalonate. The latter is the rate-limiting step in the mevalonate pathway, and the enzyme HMGR is highly regulated via transcription, phosphorylation and degradation (Goldstein and Brown, 1990). Furthermore, both HMG-CoA synthase and HMGR are regulated by feedback inhibition by the pathway product, cholesterol.

Mevalonate is converted to phosphomevalonate by mevalonate kinase (MK). However, although this step is not rate-limiting, it is highly controlled by feedback inhibition by geranylpyrophosphate, farnesylpyrophosphate and geranylgeranylpyrophosphate (Hinson et al., 1997). This is followed by phosphorylation- and decarboxylation steps, yielding first mevalonate pyrophosphate (MPP) and subsequently isopentenyl-5-pyrophosphate (IPP), and it is catalyzed by phosphomevalonate kinase (PMK) and mevalonate pyrophosphate decarboxylase (MPPD) (Bonetti et al., 2003).

Geranyl pyrophosphate synthase uses IPP and its isomer dimethylallyl-PP to synthesize the 10-carbon geranyl pyrophosphate (GPP). Further chain elongation is carried out by the addition of IPP via farnesyl synthase to yield the 15-carbon FPP. Following the synthesis of FPP, the pathway diverges into several different branches. FPP synthase is therefore a key enzyme as it catalyzes the final common step of the pathway. From FPP, the pathway diverges into numerous branches, mainly GGPP and cholesterol biosynthesis (Fig. 2) (Goldstein and Brown, 1990). The 20-carbon GGPP is synthesized by GGPP synthase from FPP and IPP, and is, together with FPP, an important factor in post-translational protein prenylation (Casey and Seabra, 1996; Novelli and D'Apice, 2012). In addition to its role in prenylation, GGPP is also a precursor for other isoprenoids including ubiquinone (Ghavami et al., 2012b). Along the