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Targeting the mevalonate cascade as a new therapeutic approach in heart disease, cancer and pulmonary disease

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ABSTRACT

The cholesterol biosynthesis pathway, also known as the mevalonate (MVA) pathway, is an essential cellular pathway that is involved in diverse cell functions. The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGCR) is the rate-limiting step in cholesterol biosynthesis and catalyzes the conversion of HMG-CoA to MVA.

Given its role in cholesterol and isoprenoid biosynthesis, the regulation of HMGCR has been intensely investigated. Because all cells require a steady supply of MVA, both the sterol (i.e. cholesterol) and non-sterol (i.e. isoprenoid) products of MVA metabolism exert coordinated feedback regulation on HMGCR through different mechanisms. The proper functioning of HMGCR as the proximal enzyme in the MVA pathway is essential under both normal physiologic conditions and in many diseases given its role in cell cycle pathways and cell proliferation, cholesterol biosynthesis and metabolism, cell cytoskeletal dynamics and stability, cell membrane structure and fluidity, mitochondrial function, proliferation, and cell fate.

The blockbuster statin drugs ('statins') directly bind to and inhibit HMGCR, and their use for the past thirty years has revolutionized the treatment of hypercholesterolemia and cardiovascular diseases, in particular coronary

Abbreviations: 15-epi-LXA$_4$, 15-epi-lipoxin A$_4$; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; ALI, acute lung injury; ALL, acute lymphoblastic leukemia; ARDS, acute respiratory distress syndrome; AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; AHR, airway hyperreactivity; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—lipid lower arm; NAC, N-acetylcysteine; ACQ, Asthma Control Questionnaire; ADMA, asymmetric dimethylarginine; AF, atrial fibrillation; BE, bronchial epithelial; BALF, bronchoalveolar lavage fluid; CV, cardiovascular; Cdc42, Cell Division Cycle-42; CCL, Chemokine (C–C motif) ligand; CARE, Cholesterol and Recurrent Events; CML, chronic myeloid leukemia; COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; JNK, c-jun NH$_2$-terminal kinase; CARDS, Collaborative Atorvastatin Diabetes Study; CAD, coronary artery disease; CRP, C-reactive protein; CF, cystic fibrosis; ED, emergency department; ER, endoplasmic reticulum; EMT, epithelial mesenchymal transition; ECM, extracellular matrix; FT, farnesyltransferase; FDP, farnesyl diphosphate; FPP, farnesyl pyrophosphate; FTase, farnesyltransferase; FTIs, farnesyltransferase inhibitors; GGPP, geranylgeranylpyrophosphate; GPP, geranyl pyrophosphate; GGTase, geranylgeranyltransferase; GGTIs, geranylgeranyltransferase inhibitors; GAPs, GTPase Activating Proteins; GDIs, guanine dissociation inhibitors; GEFs, Guanine Nucleotide Exchange Factors; GTPase, guanosine triphosphatase; HCC cells, hepatocellular carcinoma cells; HFL-1, human fetal lung fibroblast; HMEC-1, human microvascular endothelial cells; HC, hydroxycholesterol; HIDS, hyperimmunoglobulinemia D syndrome; ICS, inhaled corticosteroid; ICAM, inter-cellular adhesion molecule; IL, interleukin; ILD, interstitial lung disease; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LTB4, leukotriene B4; LPS, lipopolysaccharide; LIPID, long-term intervention with pravastatin in ischemic disease; LDL, low-density-lipoprotein; LFA1, lymphocyte function-associated antigen 1; MMP, matrix metalloproteinase; MVA, mevalonate; MVAK, mevalonate kinase; MM, multiple myeloma; MI, myocardial infarction; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; NOS, nitric oxide synthase; NO, nitric oxide; OR, odds ratio; OVA, ovalbumin; PCCs, pancreatic carcinoma cells; PM, particulate matter; PPAR, peroxisome proliferator activated receptor; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; PTase, prenyltransferase; PGE$_2$, prostaglandin E$_2$; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid lowering; ROCK, Rho GTPase and Rho kinase; SH, spontaneously hypertensive; SILI, statin-induced lung injury; T-ALL, T-acute lymphoblastic leukemia; TexCAPS, Texas Coronary Atherosclerosis Prevention Study; Th, T-helper; TSLP, thymic stromal lymphopoietin; TLR, Toll-like receptor; TGF, transforming growth factor; VEGF, vascular endothelia growth factor; VE, vascular endothelial; WOSCOPS, West of Scotland Coronary Prevention Study.

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heart disease. Initially thought to exert their effects through cholesterol reduction, recent evidence indicates that statins also have pleiotropic immunomodulatory properties independent of cholesterol lowering.
In this review we will focus on the therapeutic applications and mechanisms involved in the MVA cascade including Rho GTPase and Rho kinase (ROCK) signaling, statin inhibition of HMGCR, geranylgeranyltransferase (GGTase) inhibition, and farnesyltransferase (FTase) inhibition in cardiovascular disease, pulmonary diseases (e.g. asthma and chronic obstructive pulmonary disease (COPD)), and cancer.

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1. Introduction

Triacylglycerols (16%), phospholipids (30%), cholesterol (14%), cholesteryl esters (36%) and unesterified long chain fatty acids (4%) form the major component of plasma lipids. Cholesterol was extracted from gallstones for the first time (cholestrine: solid bile) in ancient Greece (Endo, 2010), yet the molecular formula of cholesterol was first established only in 1888.

Cholesterol and cholesteryl esters are major constituents of plasma lipids which are also widely distributed in all cells of the body especially in nervous tissue (Vance, 2012). Cholesterol is a major component of the cell plasma membrane and plasma lipoprotein structure. Cholesterol has significant effects on membrane fluidity and membrane ultrastructure, and its unique structure is necessary for steroid biosynthesis (Simons & Vaz, 2004).

Cellular cholesterol content is tightly regulated despite wide fluctuations in extracellular serum concentrations (Simons & Ikonen, 2000). 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGCR) is the rate-limiting enzyme in cholesterol biosynthesis, it catalyzes the conversion of HMG-CoA to MVA, and is ubiquitously expressed in all cells (Goldstein & Brown, 1984, 1990).

The MVA pathway in humans is indispensable for de novo synthesis of cholesterol and other molecules essential for many cellular functions (Goldstein & Brown, 1990). The cholesterol molecule consists of 27 carbons, which is synthesized in 30 enzymatic reactions [with all of the carbon atoms originally derived from acetate] (Goldstein & Brown, 1990; Gaylor, 2002; Kovacs et al., 2002). MVA itself is synthesized in an irreversible step from the HMG-CoA and is then further metabolized to the isoprenoids farnesyl diphosphate, a.k.a. farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP), precursors for a number of important metabolites including the sterols, dolichols, ubiquinones (Coenzyme Q), isoprenoids, and carotenoids. These molecules are required for membrane formation (cholesterol), protein N-glycosylation (dolichols), mitochondrial electron transport chain function (ubiquinone), protein–cell membrane anchoring (isoprenoids), and free radical scavengers (carotenoids) (Goldstein & Brown, 1990).

A schematic of the cholesterol biosynthesis pathway is shown in Fig. 1. Upstream of cholesterol in the MVA pathway, FPP and GGPP are substrates for the post-translational modification (a.k.a. isoprenylation) of proteins including the Ras and Rho family GTPases (i.e. monomeric, small G proteins), which play a role in numerous cellular mechanisms (Goldstein & Brown, 1990; Swanson & Hohl, 2006).

The MVA pathway and in particular cholesterol biosynthesis have been extensively studied and found to be associated with several diseases such as hypercholesterolemia, coronary artery disease, and stroke. HMGCR is the most important and proximal enzyme in this pathway, and serves as the rate-limiting step in cholesterol biosynthesis (Goldstein & Brown, 1984, 1990). It is one of the most highly regulated enzymes known and is located in the endoplasmic reticulum (Goldstein & Brown, 1990).

The human HMGCR is composed of 888 amino acids (339 membrane-associated and 548 soluble catalytic residues) (Liscum et al., 1985). Several studies have confirmed that both membrane and catalytic domains are highly conserved in different species (Luskey, 1988).

HMGCR plays a central role in cholesterol biosynthesis regulation and is regulated at different levels (Zammit & Easom, 1987) including HMGCR mRNA synthesis (Osborne et al., 1985), mRNA translation (Panini et al., 1989), HMGCR protein degradation (Gil et al., 1985), and HMGCR enzyme activity (Alberts et al., 1980) via complex hormonal regulation (Simonet & Ness, 1988).

Cholesterol itself inhibits HMGCR gene expression via negative feedback mechanisms (Goldstein & Brown, 1990). Membrane fluidity of the endoplasmic reticulum also regulates HMGCR activity (Goldstein & Brown, 1990). HMGCR activity may also be regulated via phosphorylation (inactive form) or dephosphorylation (active form) mechanisms which depend on the action of protein kinases (Goldstein & Brown, 1990).

A certain class of drugs, namely the statins, is capable of inhibiting the synthesis of endogenous cholesterol via competitive inhibition of HMGCR. Statins were originally discovered as *Penicillium citrinum*-derived metabolites with extremely potent inhibitory properties against HMGCR (Endo et al., 1976; Endo et al., 1985). From this discovery, lovastatin was developed and used to reduce endogenous cholesterol synthesis serving as a valuable pharmacologic treatment for patients with hypercholesterolemia (Alberts, 1988; Shepherd et al., 1995; Zhou & Liao, 2009; Montecucco et al., 2012; Raper et al., 2012).

Over the past decade it has become evident that the statins also exhibit immunomodulatory, anti-inflammatory, (Steffens & Mach, 2004; Greenwood et al., 2006) and neuroprotective (Kivipelto et al., 2005; Greenwood et al., 2006) effects.

Statins encompass a complex group of compounds, which differ from each other in their chemical structure, physiochemical and pharmacokinetic properties despite having similar biological activity. Statins can occur naturally as fermentation products of microorganisms