HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) (HMGR)

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Abstract: HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase, HMGCR) is the rate controlling enzyme (EC 1.1.1.88) of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. This enzyme is the target of the widely available cholesterol lowering drugs (statins). HMGCR is anchored in the membrane of the endoplasmic reticulum, and was long regarded as having seven transmembrane domains, with the active site located in a long carboxyl terminal domain in the cytosol. In humans, the gene for HMG-CoA reductase is located on the long arm of the fifth chromosome (5q13.3-14). Related enzymes having the same function are also present in other animals, plants and bacteria. [The Journal of American Science. 2008;4(3):62-64]. (ISSN: 1545-1003).

Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR) catalyzes the formation of mevalonate - converts HMG-CoA to mevalonic acid (Zhang, Wan et al. 2007). In many classes of organisms, this is the committed step leading to the synthesis of essential compounds, such as cholesterol. However, a high level of cholesterol is an important risk factor for coronary heart disease, for which an effective clinical treatment is to block HMGR using inhibitors like statins. Recently the structures of catalytic portion of human HMGR complexed with six different statins have been determined by a delicate crystallography study (Zhang, Wan et al. 2007).

HMGR inhibitors have been shown to upregulate GTP cyclohydrolase I (GTPCH-I), the key enzyme for tetrahydrobiopterin de novo synthesis and to normalize tetrahydrobiopterin levels in hyperglycemic endothelial cells (Wenzel, Daiber et al. 2008).

The liver is responsible for controlling cholesterol homeostasis in the body. HMGR and the LDL receptor (LDL-r) are involved in this regulation and are also ubiquitously expressed in all major tissues (Mutungi, Torres-Gonzalez et al. 2007).

Statin reduces cerebrovascular events independent of its cholesterol lowering effect. Reduction of cerebrovascular events by statins may be brought by the direct inhibition of atherosclerotic change (Tsuchiya, Nagotani et al. 2007).

Drugs inhit HMGR

Drugs which inhibit HMGR, known collectively as HMGR inhibitors (or "statins"), are used to lower serum cholesterol as a means of reducing the risk for cardiovascular disease. These drugs include lovastatin (Mevacor), atorvastatin (Lipitor), pravastatin (Pravachol), and simvastatin (Zocor), etc.

Vytorin is drug that combines the use simvastatin and ezetimibe, which blocks the formation of cholesterol by the body, along with the absorption of cholesterol in the intestines. Pravastatin is a typical drug that inhibits HMGR.

Hormones

HMGR is active when blood glucose is high. The basic functions of insulin and glucagon are to maintain glucose homeostasis. Thus, in controlling blood sugar levels they indirectly affect the activity of HMGR, but a decrease in activity of the enzyme is caused by an AMP-activated protein kinase which responds to an increase in AMP concentration, and also to leptin.

Importance

HMGR is a polytopic, transmembrane protein that catalyzes a key step in the mevalonate pathway which is involved in the synthesis of sterols, isoprenoids and other lipids. In humans, HMG-CoA reductase

is the rate-limiting step in cholesterol synthesis and represents the sole major drug target for contemporary cholesterol-lowering drugs.

The medical significance of HMGR has continued to expand beyond its direct role in cholesterol synthesis following the discovery that it can offer cardiovascular health benefits independent of cholesterol reduction. Statins have been shown to have anti-inflammatory properties, most likely as a result of their ability to limit production of key downstream isoprenoids that are required for portions of the inflammatory response. Notably, blocking of isoprenoid synthesis by statins has shown promise in treating a mouse model of multiple sclerosis, an inflammatory autoimmune disease.

HMGR is also an important developmental enzyme. Inhibition of its activity and the concomitant lack of isoprenoids that yields can lead to morphological defects. HMGR is a key enzyme in the sterol biosynthesis pathway, but its subcellular distribution in the Trypanosomatidae family is somewhat controversial (Pena-Diaz, Montalvetti et al. 2004).

Regulation of HMGCR

Regulation of HMGCR is achieved at several levels: transcription, translation, degradation and phosphorylation.

Transcription of the reductase gene

Transcription of the reductase gene is enhanced by the *sterol regulatory element binding protein* (SREBP). This protein binds to the *sterol regulatory element* (SRE), located on the 5' end of the reductase gene. When SREBP is inactive, it is bound to the ER or nuclear membrane. When cholesterol levels fall, SREBP is released from the membrane by proteolysis and migrates to the nucleus, where it binds to the SRE and transcription is enhanced. If cholesterol levels rise, proteolytic cleavage of SREBP from the membrane ceases and any proteins in the nucleus are quickly degraded.

Translation of mRNA

Translation of mRNA is inhibited by a mevalonate derivative which has been reported to be farnesol, although this role has been disputed.

Degradation of reductase

Rising levels of sterols increases the susceptibility of the reductase enzyme to proteolysis. Helices 2-6 (total of 8) of the HMG-CoA reductase transmembrane domain sense the higher levels of cholesterol and this leads to Lysine 248 being exposed. This lysine residue can become ubiquinated, and this serves as a signal for proteolytic degradation. The protease (SCAP, SCREBP Cleavage Activating Protein) that activates SREBP is also sensitive to levels of sterols.

Phosphorylation of reductase

Short term regulation of HMG-CoA reductase is achieved by inhibition by phosphorylation (of Serine 872, in humans). Decades ago it was believed that a cascade of enzymes control the activity of HMG-CoA reductase: an HMG-CoA reductase kinase was thought to inactivate the enzyme, and the kinase in turn was held to be activated via phosphorylation by HMG-CoA reductase kinase kinase. An excellent review on regulation of the mevalonate pathway by Nobel Laureates Joseph Goldstein and Michael Brown adds specifics: HMG-CoA reductase is phosphorylated and inactivated by an AMP-activated protein kinase, which also phosphorylates and inactivates acetyl-CoA carboxylase, the rate limiting enzyme of fatty acid biosyntheis. Thus, both pathways utilizing acetyl-CoA for lipid synthesis are inactivated when energy charge is low in the cell, and concentrations of AMP rise. There has been a great deal of research on the identity of upstream kinases which phosphorylate and activate the AMP-activated protein kinase. Fairly recently LKB1 has been identified as a likely AMP kinase kinase which appears to involve calcium/calmodulin signaling. This pathway likely transduces signals from leptin, adiponectin, and other signaling molecules.

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