Cholesterol Biosynthesis and Metabolism

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Summary. Cholesterol plays an essential role in cell membrane synthesis and in cell growth and differentiation. In mammalian cells, cholesterol can be synthesized from acetate precursors or taken up from dietary or exogenous sources. The major catabolic route for disposal of cholesterol involves conversion into excretable bile acids. The maintenance of cholesterol homeostasis is influenced and carefully controlled by multiple feedback mechanisms. The key regulatory targets of these feedback mechanisms are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in cholesterol biosynthesis, the low-density lipoprotein (LDL) receptor in cholesterol uptake, and cholesterol 7α-hydroxylase in cholesterol catabolism. The elucidation of regulatory mechanisms in cholesterol metabolism has been greatly facilitated by the discovery of a new class of lipid-lowering drugs, the HMG-CoA reductase inhibitors. In addition to proving therapeutically useful in the treatment of hypercholesterolemia, these drugs have revealed novel regulatory steps in cholesterol metabolism and several new targets for future drug development. This manuscript reviews recent developments in the cholesterol biosynthetic pathway and the regulatory mechanisms that maintain cholesterol homeostasis.

Key Words. cholesterol biosynthesis, autoregulation, homeostasis, 3-hydroxy-3-methylglutaryl coenzyme A, HMG-CoA

From a biochemical perspective, cholesterol is a necessary constituent for eukaryotic cell growth and development. The biosynthesis of cholesterol provides crucial building blocks for cell membranogenesis and membrane fluid regulation, and for the synthesis of sterol and nonsterol products that are important for normal cell function. Prevailing interest in cholesterol has revolved around its role in the development of atherosclerosis and cholelithiasis, and much research energy has been directed toward identifying mechanisms to decrease elevated serum cholesterol levels. More recent developments have underscored the essential nature of cholesterol in cell growth and development, and have begun to elucidate the mechanisms governing cholesterol homeostasis.

Cholesterol Metabolism

Cholesterol may be obtained for cellular metabolism either via uptake mediated by members of the low-density lipoprotein (LDL) receptor family or through biosynthesis. The uptake pathway involving the lipoprotein receptors may be further subdivided into an exogenous (dietary) pathway and an endogenous pathway (Figure 1). Although cholesterol uptake and biosynthesis are interdependent (i.e., changes in dietary cholesterol intake and cell requirements influence the rate of cholesterol biosynthesis through complex feedback mechanisms), cellular cholesterol requirements can be met equally well through either supply pathway.

Humans synthesize approximately 700–900 mg of cholesterol per day, while 300–500 mg are absorbed daily from dietary sources [2]. Normal daily cholesterol turnover is accounted for by excretion in the gastrointestinal tract (600 mg/day), conversion to bile acids (400 mg/day), sloughing skin (85 mg/day), and incorporation into membranes of actively dividing cells. Most mammalian cells are capable of endogenous cholesterol synthesis [3]. In all species examined to date, cholesterol synthesis occurs primarily in four organs: the liver, gastrointestinal tract, skin, and "carcass" (i.e., striated muscle and bone marrow). With the exception of the liver, these organs demonstrate high rates of cell turnover and use large amounts of cholesterol for synthesizing new membranes. In humans, the liver and ileum are the primary sites of cholesterol biosynthesis [3]. Although the human liver has a low rate of cell turnover, it nevertheless synthesizes and takes up large amounts of cholesterol for synthesizing new membranes. In patients who have undergone partial hepatectomy [4]. A diurnal variation in hepatic cholesterol synthesis (increased rate at night) has also been demonstrated in animals and humans [5,6].

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Quantitation of Cholesterol Biosynthesis

Several methods have been used to estimate the rate of endogenous cholesterol biosynthesis, including HMG-CoA reductase or mevalonate assays, sterol balance techniques, and determination of the plasma kinetics of radioactive cholesterol or LDL. Studies evaluating the correlation between HMG-CoA reductase levels and cholesterol biosynthesis in humans are just now being done [7] due to the difficulty in obtaining appropriate tissue samples. Sterol balance techniques are onerous because of the long observation periods and exquisite dietary control of cholesterol intake that are required [8].

Methods incorporating radiolabeled cholesterol precursors are most commonly used to quantitate cholesterol biosynthesis. The rate of substrate incorporation is measured in tissue after in vitro incubation with the substrate or by injection of the substrate followed by measurement [9]. Assays of the rate of incorporation of \[^{14}C\]substrates into cholesterol are useful only for determining the relative change in rates of cholesterol synthesis [2]. More recently, the use of radiolabeled water to measure cholesterol synthesis was shown to be superior to \[^{14}C\]substrates [8,10,11]. This technique has demonstrated that cholesterol synthesis in extrahepatic tissues is 5–20 times higher than previously thought, confirming that extrahepatic organs are self-sufficient with regard to cholesterol synthesis [2].

Cholesterol Biosynthetic Pathway

The initial step in cholesterol biosynthesis is the formation of acetoacetyl coenzyme A (CoA) from 2 moles of acetyl CoA. Condensation of a third mole of acetyl CoA results in the formation of the key intermediate, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) (Figure 2). The formation of HMG-CoA by the enzyme HMG-CoA synthase is one of several steps in the biosynthetic pathway that is regulated by feedback inhibition. HMG-CoA undergoes reduction by HMG-CoA reductase to form mevalonate in the most highly regulated step in the pathway [12–14]. It is this step that is inhibited by a new class of cholesterol-lowering drugs, the HMG-CoA reductase inhibitors (see be-