Functions of Cholesterol Metabolites

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Summary  Cholesterol is a major component of membrane lipids. Thus, adjusting the membrane cholesterol composition is essential for maintaining cellular homeostasis. Cholesterol biosynthesis and uptake by LDL receptors are tightly regulated at the transcriptional level through negative feedback control, which is mediated by sterol regulatory element-binding proteins (SREBPs). In particular, SREBP-2 is activated in a cholesterol-dependent manner and, thus, is significantly involved in regulating the expression of those genes associated with cholesterol metabolism. Cholesterol metabolites such as oxysterols are involved in regulating sterol metabolism by binding to the nuclear receptor, liver X receptor (LXR). Cholesterol catabolites, i.e., bile acids, are agonists for another nuclear receptor, farnesoid X receptor (FXR), and a bile acid receptor, TGR5. Activated FXR regulates bile acid metabolism and TGR5 improves glucose metabolism through the actions of glucagon-like peptide-1 (GLP-1).

Key Words  cholesterol, SREBP, LXR, FXR, TGR5

Cholesterol

Cholesterol is synthesized in cells from acetyl CoA through a series of more than 30 enzymatic reactions. Most extrahepatic cells acquire cholesterol from circulation in the form of LDL that is internalized by LDL receptors on a cell surface and hydrolyzed to free cholesterol in lysosomes. Because free cholesterol is one of the major components of membrane lipids, individual cells must balance these internal and external sources while simultaneously avoiding either a sterol shortage or an over-accumulation so as to maintain membrane lipid homeostasis. Both the biosynthetic and uptake pathways are well regulated by feedback control. When cells accumulate excess amounts of sterols, the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the biosynthetic pathway, declines by more than 90% and the number of LDL receptors also decreases (1). In contrast, when intracellular cholesterol is depleted, cells maintain a high activity level of this enzyme and also express a large number of LDL receptors on their surface.

SREBP Family

SREBPs were discovered as transcription factors that regulated the expression of most of the genes encoding the enzymes involved in cholesterol biosynthesis and aided in governing their negative feedback control (2, 3). The SREBP family members SREBP-1 and SREBP-2 are synthesized as membrane proteins in the endoplasmic reticulum (ER). Their N-terminal and C-terminal domains, each of which is about 500 amino acids in length, project into the cytoplasm and are linked by a pair of membrane-spanning domains. SREBP-2 is considered to be significantly involved in regulating cholesterol metabolism. Several gene promoter analyses revealed that the expression of most of the genes for cholesterol biosynthetic enzymes, squalene synthase in particular, was largely regulated by SREBP-2 (4, 5). SREBPs that are synthesized as ER membrane proteins are subjected to proteolytic cleavage through the same processing pathway to become transcriptionally active forms, including the N-terminal bHLH-Zip domain (Fig. 1).

SCAP as a Transporter and Cholesterol Sensor

Both SREBP-1 and -2 associate and form a complex with another ER membrane protein, SREBP cleavage-activating protein (SCAP). When cells become loaded with cholesterol, which results in an increase in its concentration in the ER membrane, a conformational change occurs in SCAP and initiates SCAP binding to another ER membrane protein, Insig (6). This association hinders the ER-to-Golgi transport of the SREBP/SCAP complex, which results in a reduction in the proteolytic activation of precursor SREBP in the Golgi apparatus so as to generate its N-terminal transcriptionally active domain.

Oxysterols

Intracellular cholesterol is enzymatically or spontaneously oxidized and is subsequently utilized as an agonist of LXR, which induces the expression of those genes associated with sterol extracellular efflux. These include the genes ABCA1, ABCG1, and Idol, which are thought to be involved in reducing intracellular cholesterol levels. Three known oxysterol biosynthetic enzymes, cholesterol 24-hydroxylase, cholesterol 25-hydroxylase, and sterol 27-hydroxylase, are involved in producing 24-hydroxy, 25-hydroxy, and 27-hydroxycholesterol, respectively (7). Among these oxysterols, 25-hydroxy-
cholesterol is the least potent LXR agonist. Another cholesterol metabolite that is a potent LXR agonist is 24,25-epoxycholesterol.

Because intracellular oxysterol levels theoretically increase with an increase in cholesterol levels, it is reasonable to assume that the increased expression of genes associated with sterol efflux are induced by LXR. Furthermore, 25-hydroxycholesterol is a potent inhibitor of SREBP activation. This oxysterol binds to Insig, another ER membrane protein. Oxysterol-bound Insig induces a tight interaction with cholesterol-binding SCAP and prevents the SREBP/SCAP complex from moving to the Golgi, thereby hindering SREBP proteolytic activation (8, 9).

Bile Acids

The liver is the only organ that can remove excess amounts of cholesterol by converting it to bile acids through several enzymatic processes and excreting these into bile. After a meal is consumed, the gallbladder contracts so as to expel bile into the intestine, where bile acids act as solubilizers to facilitate the absorption of lipids and fat-soluble vitamins. Most bile salts (>90%) are reabsorbed in the lower small intestine through a bile acid transporter and are then transported back to the liver. It has been estimated that bile acids are recycled more than 10 times before they are finally eliminated.

In the small intestine and liver, bile acids can activate the nuclear receptor FXR and exert a direct effect on gene expression (10). FXR augments the expression of the gene for fibroblast growth factor 15/19 (FGF15/19) in intestinal epithelial cells. FGF15/19 secreted from the small intestine interacts with FGF15/19 receptors in the liver and subsequently suppresses the expression of CYP7a1, a rate-limiting enzyme for bile acid synthesis (11).

A G protein-coupled receptor, TGR5, which comprises 330 amino acid residues, was found to be responsive to bile acids as a cell-surface receptor. In humans, TGR5 is expressed in various tissues, such as heart, spleen, skeletal muscle, kidney, liver, small intestine, placenta, lung, and peripheral blood leukocytes, and binds to both free forms of bile acids and taurine- and glycine-conjugated forms (12, 13). Bile acids induce GLP-1 secretion from intestinal enteroendocrine cells by a mechanism that depends on TGR5 activation and the subsequent elevation of intracellular cAMP levels (14). GLP-1 regulates glucose homeostasis by stimulating insulin secretion and by inhibiting glucongen secretion, suppresses gastric emptying and reduces food intake. Thus, TGR5 may be a promising target for therapeutic or nutriceutical management of type 2 diabetes and obesity (15).

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