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Cholesterol homeostasis: How do cells sense sterol excess?

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ABSTRACT

Cholesterol is vital in mammals, but toxic in excess. Consequently, elaborate molecular mechanisms have evolved to maintain this sterol within narrow limits. How cells sense excess cholesterol is an intriguing area of research. Cells sense cholesterol, and other related sterols such as oxysterols or cholesterol synthesis intermediates, and respond to changing levels through several elegant mechanisms of feedback regulation. Cholesterol sensing involves both direct binding of sterols to the homeostatic machinery located in the endoplasmic reticulum (ER), and indirect effects elicited by sterol-dependent alteration of the physical properties of membranes. Here, we examine the mechanisms employed by cells to maintain cholesterol homeostasis.

1. Introduction

Cholesterol is essential for mammalian cell viability and proliferation. It is a structural component of cell membranes, maintaining both membrane fluidity and rigidity and mediating cell signalling through the formation of rigid subdomains (Simons and Ikonen, 1997), while also functioning as a precursor for steroid hormones and bile acids. Mammals have evolved intricate regulatory networks to maintain cholesterol homeostasis and ensure that adequate levels of this vital molecule are readily available when required (Maxfield and van Meer, 2010). However, excess cholesterol can be toxic to cells. Therefore, the cholesterol homeostatic machinery must also be able to shut down cholesterol synthesis and rapidly increase efflux in conditions of sterol excess. Dysregulation of cholesterol homeostasis is associated with a number of human disease states. These include atherosclerosis, which is associated with high cholesterol levels (Lewington et al., 2007), and several developmental disorders that result from abnormally low cholesterol levels, notably Smith-Lemli-Opitz syndrome (Tint et al., 1994).

Here we review our current knowledge of cholesterol homeostasis with a focus on how cells sense and respond to changing sterol status.

2. The major players in cholesterol homeostasis

The regulation of cholesterol homeostasis involves a complex interplay between a growing list of proteins that act to sense and respond to changing levels of cellular cholesterol. These proteins may be regulated by cholesterol itself or by certain cholesterol intermediates or derivatives.

While the majority of cellular cholesterol resides in the plasma membrane, most of the cholesterol homeostatic machinery is located in the endoplasmic reticulum (ER[1]). Among these are the sterol regulatory element-binding proteins (SREBPs), the master transcription factors (TFs) in cholesterol homeostasis, and their associated regulatory proteins. These include Scap (SREBP cleavage-activating protein), which complexes with SREBP in the ER membrane when cholesterol levels are low and escorts it to the Golgi for proteolytic activation; Insig (insulin-induced gene), which retains Scap in the ER when cellular cholesterol levels are sufficient or in excess; and erlin-1 and -2, which interact with Insig to help retain the Scap/SREBP complex in the ER in high cholesterol

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[1] Abbreviations used: ACAT, acyl-CoA:cholesterol acyltransferase; ABC, ATP binding cassette; CRAC, cholesterol recognition amino acid consensus; ER, endoplasmic reticulum; ERAD, ER-associated degradation; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Insig, insulin-induced gene; LDL, low density lipoprotein; LDLR, LDL receptor; LXR, liver X receptor; MARCH6, Membrane-Associated Ring Finger (C3HC4) 6; MvINS, mycobacterium Insig homologue; Scap, SREBP cleavage-activating protein; SM, squalene monooxygenase; SPFH, stomatin/prohibitin/flotillin/HflK/C; SREBP, sterol regulatory element-binding protein; TF, transcription factor.

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conditions. Most cholesterol synthesis enzymes, including the two rate-limiting enzymes 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and squalene monooxygenase (SM), also reside in the ER, as well as the cholesterol esterification enzyme acyl-CoA:cholesterol acyltransferase (ACAT), which esterifies excess cholesterol for storage.

However, the plasma membrane and several plasma membrane proteins also play vital roles in regulating cholesterol homeostasis. The plasma membrane, which accommodates the vast majority of cellular cholesterol, regulates the levels of cholesterol in the lipid-poor ER membrane (Section 8). The low density lipoprotein receptor (LDLR) imports exogenous cholesterol from low density lipoproteins (LDL) when cellular cholesterol levels are low, whereas the ATP binding cassette (ABC) transporters ABCA1 and ABCG1 export excess cholesterol when cellular cholesterol levels are high. Additionally, the nuclear liver X receptor (LXR) upregulates expression of ABCA1 and ABCG1, as well as Idol, an E3 ubiquitin ligase that mediates the degradation of LDLR. The interactions of these key players in cholesterol homeostasis are illustrated in Fig. 1 and are described in detail in later sections.

3. The SREBP pathway

At the centre of cholesterol homeostasis are the SREBPs, a family of TFs anchored in the ER membrane. There are three known isoforms of SREBP: SREBP-1a and -1c, which are alternatively spliced from the same gene, and SREBP-2, which is encoded by a different gene (Hua et al., 1995). SREBP-2 is responsible for maintaining cholesterol homeostasis, acting to increase cholesterol synthesis and uptake in response to cholesterol depletion, whereas SREBP-1c upregulates fatty acid synthesis (Horton et al., 2003). SREBP-1a regulates both cholesterol and fatty acid synthesis (Shimano et al., 1996). SREBPs constitutively bind to Scap immediately after they are synthesised in the ER via an interaction between SREBP's C-terminal regulatory domain and the WD40 repeat domains at the C-terminus of Scap (Sakai et al., 1997). A recent crystal structure of the WD40 domain of a yeast homologue suggests a lysine/arginine rich domain (R/K patch) is responsible for the interaction (Gong et al., 2015).

Scap is anchored to the ER membrane by eight transmembrane helices and contains a 'sterol-sensing' region spanning transmembrane domains two to six (Brown et al., 2002; Radhakrishnan et al., 2004). Although Motamed et al. (2011) found evidence to suggest

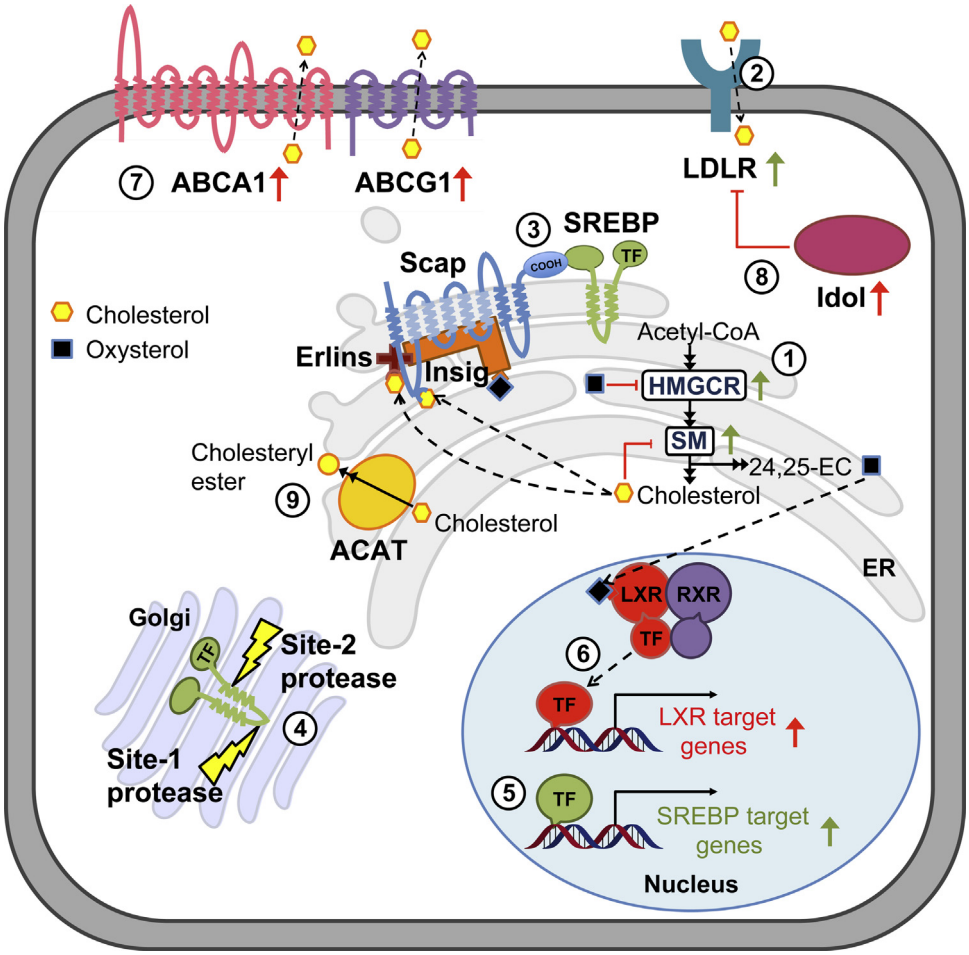

Fig. 1. Interplay of cholesterol homeostatic machinery. Cholesterol (yellow hexagon) is synthesised from acetyl-CoA in the ER (1) or taken up through the LDLR (2). When sterol levels are low, Insig (orange) dissociates from Scap (blue), enabling Scap to escort SREBP (green) (3) to the Golgi for processing by Site-1 and Site-2 proteases (4). This releases an SREBP TF that translocates to the nucleus and upregulates SREBP target genes (5). These include HMGCR, SM and LDLR (indicated by green arrows). When sterol levels are high, cholesterol negatively regulates SM and oxysterols (black squares) negatively regulate HMGCR (indicated by the red barred lines), causing their degradation. Cholesterol binds to Scap and erlins -1 and -2 (maroon), and oxysterols bind to Insig, causing the retention of Scap/SREBP in the ER. Oxysterols, such as 24(*S*), 25-epoxycholesterol (denoted 24,25-EC), also act as ligands for the LXR (bright red)-retinoid X receptor (RXR, purple) heterodimer, releasing the LXR TF and upregulating transcription of LXR target genes (indicated by red arrows) (6). These include ABCA1 and ABCG1, which synergise to export cholesterol from the cell (7), and Idol (pink), which mediates degradation of LDLR (indicated by the red barred line) (8). Excess cholesterol can also be esterified by ACAT (light orange) for storage in an inactive form (9). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)