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Cholesterol homeostasis in cardiovascular disease and recent advances in measuring cholesterol signatures

Hong Seog Seo [a,b], Man Ho Choi [c,*]

[a] Cardiovascular Center, Korea University Guro Hospital, Seoul 152-703, South Korea
[b] Korea University-Korea Institute of Science and Technology Graduated School of Converging Science and Technology, Seoul 152-703, South Korea
[c] Materials and Life Science Research Division, Korea Institute of Science and Technology, Seoul 136-791, South Korea

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ABSTRACT

Despite the biochemical importance of cholesterol, its abnormal metabolism has serious cellular consequences that lead to endocrine disorders such as cardiovascular disease (CVD). Nevertheless, the impact of blood cholesterol as a CVD risk factor is still debated, and treatment with cholesterol-lowering drugs remains controversial, particularly in older patients. Although, the prevalence of CVD increases with age, the underlying mechanisms for this phenomenon are not well understood, and metabolic changes have not been confirmed as predisposing factors of atherogenesis. The quantification of circulating biomarkers for cholesterol homeostasis is therefore warranted, and reference values for cholesterol absorption and synthesis should be determined in order to establish CVD risk factors. The traditional lipid profile is often derived rather than directly measured and lacks a universal standard to interpret the results. In contrast, mass spectrometry-based cholesterol profiling can accurately measure free cholesterol as a biologically active component. This approach allows to detect alterations in various metabolic pathways that control cholesterol homeostasis, by quantitative analysis of cholesterol and its precursors/metabolites as well as dietary sterols. An overview of the mechanism of cholesterol homeostasis under different physiological conditions may help to identify predictive biomarkers of concomitant atherosclerosis and conventional CVD risk factors.

1. Introduction

Cardiovascular disease (CVD) is a major class of morbidity and mortality worldwide. The disease involves the development of atherosclerosis, which presents as deposition and accumulation of lipid molecules and macrophage foam cells in the artery wall [1]. Although patients with coronary artery disease often become symptomatic in their mid-forties, atherosclerotic conditions in the blood vessels are generally initiated earlier in life [2,3]. The prevalence of the disease varies from 17% (<20 years old) to 85% (≥50 years old), regardless of the presence of risk factors [4]. The development of clinical atherosclerotic vascular disease is associated with risk factors such as hypertension, hypercholesterolemia, diabetes, and others [5], but the atherosclerotic process is not yet fully understood. Among the atherosclerotic vascular diseases, the acute coronary syndromes (ACS) may lead to unstable angina, acute myocardial infarction, and coronary sudden death. Most ACS conditions have been known to result from luminal thrombosis associated with calcified nodules and coronary plaque rupture/erosion [6]. Although recent advances in the understanding of CVD pathology and treatment have been made, the prevalence of the disease is still on the rise.

Cholesterol is a lipid that is synthesized in the body (Fig. 1) and is also consumed as part of the daily diet. It plays important biochemical roles in the body, but excessive cholesterol levels and abnormal metabolism can lead to the development of health problems [7]. In recent years, high- and low-density lipoproteins (HDL and LDL) have been established as indicators for the risk of heart disease [8], where HDL is regarded as “good cholesterol” and LDL as “bad cholesterol.” A high HDL/LDL ratio is associated with a reduced risk of heart disease, and may therefore be considered a more suitable biochemical indicator than total cholesterol. It should be noted that both lipoproteins do not themselves constitute cholesterol, but rather serve as transfer molecules for cholesterol transport throughout the body. LDL transfers cholesterol from the liver to the peripheral cells, while HDL returns cholesterol from the blood vessels back to the liver where it can be excreted through bile acid metabolism. Cholesterol levels in the normal metabolic condition can fluctuate as much as 10% from one

* Corresponding author at: Materials and Life Science Research Division, KIST 39-1 Hawolkok-dong, Seoul 136-791, Korea. Tel.: +82 2 958 5081; fax: +82 2 958 5059.
E-mail address: mh_choi@kist.re.kr (M.H. Choi).

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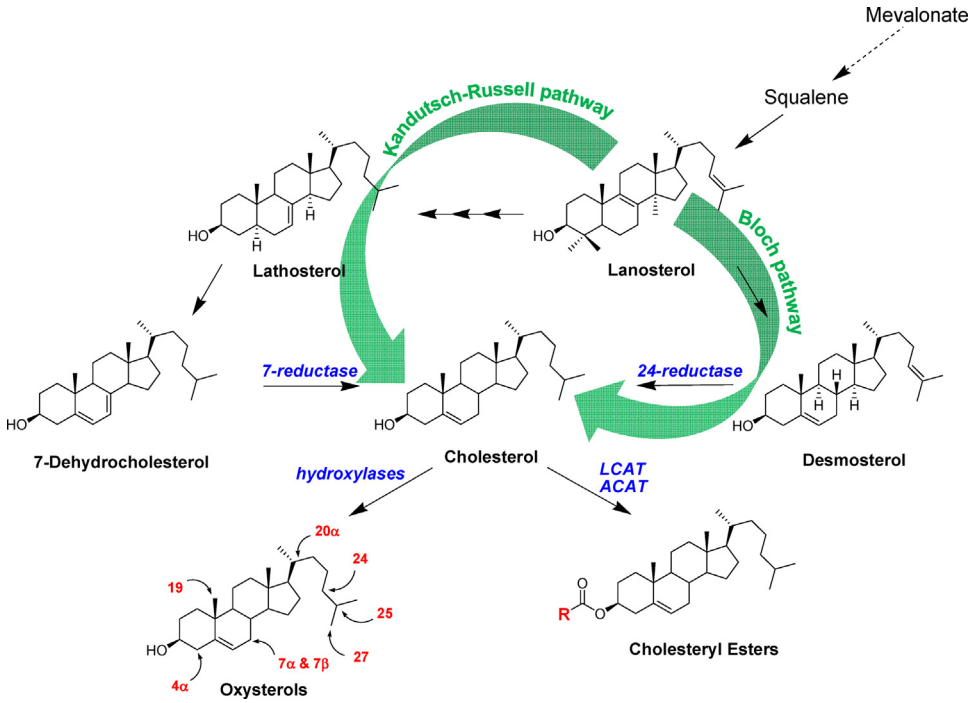

Fig. 1. Overview of cholesterol metabolism. The physiological requirements for cholesterol are provided mostly through *de novo* synthesis which is directly regulated by the mevalonate pathway *via* lanosterol. Lanosterol is then converted to cholesterol through 2 distinct pathways *via* formation of lathosterol and 7-dehydrocholesterol (*Kandutsch-Russel pathway*), or *via* desmosterol (*Bloch pathway*). Cholesterol is further metabolized to cholesterol esters (CEs) and hydroxycholesterols to prevent over-accumulation and maintain homeostasis. The enzymes 24-reductase and 7-reductase generate cholesterol from desmosterol and 7-dehydrocholesterol, respectively. Cholesterol forms CEs with fatty acids *via* action of lecithin:cholesterol acyltransferase (LCAT) and acyl CoA:cholesterol acyltransferase (ACAT); it may also form hydroxycholesterols (OHCs) by action of various hydroxylases or non-enzyme-derived hydroxylation at the C-4, C-7, C-19, C-20, C-24, C-25, and C-27 positions. Data modified from Son et al. (2015).

month to another; however, unexpected risk assignment or therapeutic intervention should be considered as factors that influence cholesterol metabolism [9]. Other factors such as diet, seasonal variations, physical activity, and hormones may contribute to the fluctuation of cholesterol levels as well.

The role of cholesterol as a risk factor of heart disease remains controversial, and it may in fact be a very poor predictor at best [10,11] even for longevity [12,13]. It is therefore necessary to obtain a "bird's-eye view" of cholesterol metabolism, in contrast to the traditional lipid profile, which can only offer a less comprehensive assessment. Intracellular cholesterol levels are regulated by cholesterol biosynthesis and the efflux/influx of lipoprotein-bound cholesterol. Understanding cholesterol homeostasis may change current perspectives and help to elucidate disease-causing mechanisms as a result of altered cholesterol levels, such as in atherosclerosis. In addition, the proportion of free cholesterol

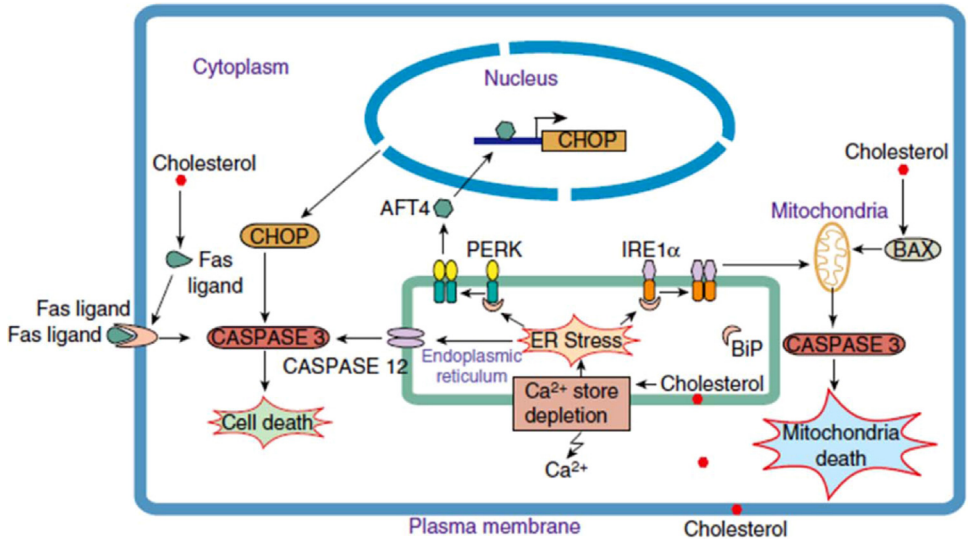

Fig. 2. Cholesterol-induced cytotoxicity in the signaling unfolded protein response (UPR)-mediated cell death. Free cholesterol depletes calcium in the ER stores causing ER stress, which results in activation of the UPR transducers, PERK and IRE1, by release of the ER chaperone BiP. Activation of PERK causes translation of the transcription factor, ATF4, which induces expression of the pro-apoptotic factor CHOP. Activated IRE1 elicits activation of the mitochondria-dependent caspase cascade. ER stress also promotes cleavage and activation of caspase-12 to initiate caspase activation, resulting in apoptosis. In addition, free cholesterol can trigger apoptosis *via* the Fas pathway and mitochondrial apoptosis through increasing levels of the pro-apoptotic protein, Bax. Data taken from Zhang (2003).

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