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Mathematical analyses of two-compartment model of human cholesterol circulatory transport in application to high blood cholesterol prevention, diagnosis and treatment

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ABSTRACT

Cholesterol plays a vital role in human body and thus its unbalanced homeostasis leads to health problems. Elevated blood cholesterol levels are now considered a classic coronary risk factor and are suspected to lead to coronary artery diseases, causing 2.6 millions of deaths each year. However, many of the mechanisms behind cholesterol-related processes remain unknown. Mathematical and computational models can aid investigation of complex biological phenomena, yet cholesterol-focused models remain rare. Here, we develop a two-compartment mathematical model to investigate cholesterol transport in the human circulatory system. We focus on the key aspects of cholesterol circulatory transport in the lipoproteins, its *de novo* synthesis and bile recycling and represent them by two simultaneous linear differential equations. The solutions yield changes over time of the cholesterol levels in the liver (compartment I) and bloodstream (compartment II). Drawing from the current clinical practice, we show the application of the model to personalized high blood cholesterol prevention, diagnosis and treatment.

1. Introduction

Cholesterol plays vital structural and functional roles in human body. It is an essential building component of cell membranes where it modulates membrane permeability and fluidity over a range of physiological conditions [1,2]. In addition, it stabilizes proteins that perform a wealth of cellular function, including transporting substances into and out of cell, attaching to and communicating with other cells or responding to endocrine hormones [3,4]. On functional level, cholesterol is involved in the modulation of intracellular transport, cell signaling and nerve conduction [5,6] and is acting as an essential precursor molecule in biosynthesis of steroid hormones, bile acids and vitamin D [7,8].

To provide sufficient amount of cholesterol in the human body, ca. 1 g of cholesterol is *de novo* synthesized daily in the human liver and ca. 2–3 g are obtained from food (dietary cholesterol) [9]. As cholesterol is almost insoluble in water it cannot freely travel in the bloodstream. To maintain its adequate and targeted delivery to tissues and cells, cholesterol is transported in the circulatory system encapsulated in the lipoprotein complexes that are made of hydrophobic lipids core

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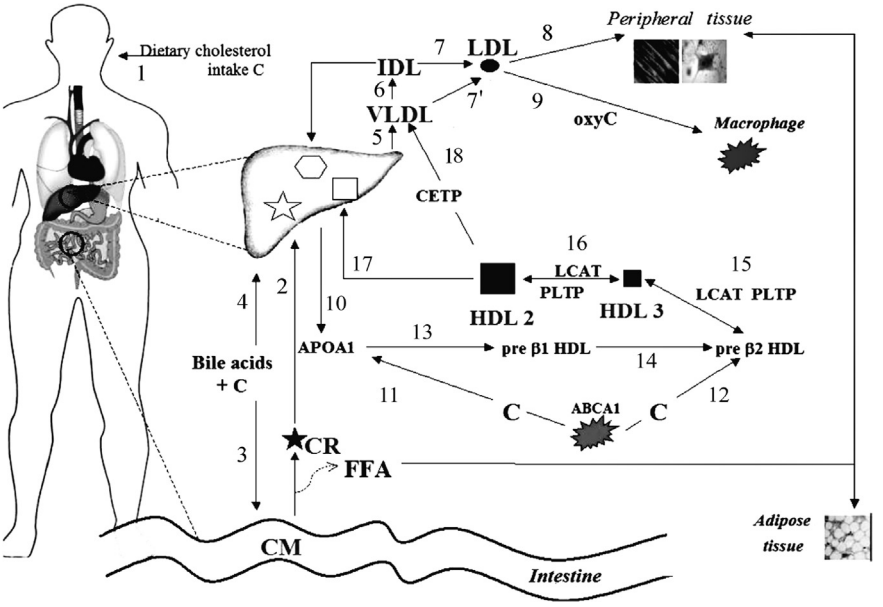

Fig. 1. Overview of the keys biochemical processes behind cholesterol transport by lipoproteins. Dietary and *de novo* synthesized cholesterol is redistributed to muscles and peripheral tissues (LDLs) as well as removed from the bloodstream (HDLs) to maintain cholesterol homeostasis.

surrounded by a shell of more-polar lipids and proteins [10] (Fig. 1). The body regulates the transport and amount of cholesterol present using various levels of control. Among others, the increased intake of dietary cholesterol is compensated by the decreased *de novo* cholesterol synthesis by the feedback regulation of the amount and activity of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), an important intermediate of the cholesterol biosynthesis pathway [7,11].

Unbalanced cholesterol homeostasis leads to health problems. In particular, elevated blood cholesterol levels have been established as a classic coronary risk factor and are suspected to lead to the third of the coronary artery disease causing 2.6 millions of deaths each year (World Health Organization). It has been hypothesized that in coronary artery disease, LDLs ('bad cholesterol') promotes plaques formation, which build up along the inner walls of the arteries of the heart, narrowing them and reducing blood flow to the heart [12,13]. However, the exact mechanisms of plague formation remain unclear, so does other aspects involving high blood cholesterol and its treatment.

Developing mathematical modeling of the cholesterol circulatory transport could help gaining further insight into the underlying mechanisms of cholesterol homeostasis disturbance. As cholesterol molecular and physiological processes are complex, this is not an easy task, with previous work in this area being rather limited. Existing models addressed lipoprotein dynamics such as the model of the fluid dynamics of lipid accumulation on the arterial walls [14] and chemical kinetics of LDL oxidation [15]. Model of lipoprotein metabolism was also proposed [16]. Here, we focus on the key aspects of the cholesterol circulatory transport to develop a mathematical model applicable to high blood cholesterol prevention, diagnosis and treatment.

2. Material and methods: modeling cholesterol circulatory transport

2.1. Overview of the current knowledge

Based on the literature search, we have identified the key aspects of the current knowledge of cholesterol circulatory transport in the lipoproteins (Fig. 1 and [17]). Briefly, cholesterol C obtained from the diet, *de novo* synthesized in the liver and reabsorbed from the small bowel is carried out in the circulatory system encapsulated in five main types of lipoproteins. These are classified according to increasing density as chylomicrons, chylomicron remnants, very low density lipoproteins (VLDLs), intermediate-density lipoproteins (ILDs), low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs) [18]. LDLs are the major carrier of cholesterol in the blood and their role is to transport cholesterol to the peripheral tissues and regulate *de novo* cholesterol synthesis at these sites. HDLs, on the other hand, bind the free and esterified cholesterol released from the peripheral tissues and transport it back to the liver for the synthesis of bile and steroid hormones [7,18]. The body tries to maintain cholesterol homeostasis by regulating *de novo* cholesterol synthesis, re-absorption and secretion. Various chemical reactions are catalyzed by enzymes and regulated by proteins: ABCA1, cholesterol efflux regulatory protein; CEPT, cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase; LIPC, hepatic lipase; LIPG, endothelial lipase; LPL, lipoprotein lipase; LIPC, hepatic lipase and PLTP, phospholipid transfer protein.