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Review

Cross-talk between liver and intestine in control of cholesterol and energy homeostasis

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ABSTRACT

A major hurdle for organisms to dispose of cholesterol is the inability to degrade the sterol nucleus which constitutes the central part of the molecule. Synthesis of the sterol nucleus requires a complex, energy costly, metabolic pathway but also generates a diverse array of intermediates serving crucial roles in cellular energy metabolism and signal transduction. This may be the reason why this complex pathway has survived evolutionary pressure. The only way to get rid of substantial amounts of cholesterol is conversion into bile acid or direct excretion of the sterol in the feces. The lack of versatility in disposal mechanisms causes a lack of flexibility to regulate cholesterol homeostasis which may underlie the considerable human pathology linked to cholesterol removal from the body. Export of cholesterol from the body requires an intricate communication between intestine and the liver. The last decade this inter-organ cross talk has been focus of intense research leading to considerable new insight. This novel information on particular the cross-talk between liver and intestine and role of bile acids as signal transducing molecules forms the focus of this review.

Contents

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1. Introduction

Cholesterol is essential for the maintenance of life in vertebrates (Maxfield and van Meer, 2010). It is a structural component of cell membranes, and cholesterol metabolites, such as bile salts (BS), steroid hormones and oxysterols, fulfill a wide variety of important biological functions (Rezen, 2011; Rezen et al., 2011). Stringent regulation of cellular and whole body cholesterol homeostasis is essential because both a shortage and an excess of cholesterol can be harmful. Hypercholesterolemia, i.e., high plasma levels of cholesterol, promotes the development of atherosclerosis and thereby represents a major risk factor for cardiovascular disease (Kannel et al., 1979; Liu et al., 2006). Low plasma levels of plasma cholesterol have been linked to suicide (Zhang, 2011) and inborn defects in cholesterol synthesis lead to severe clinical phenotypes while absence of the key enzyme in cholesterol synthesis HMGCoA reductase is not compatible with life (Ohashi et al., 2003). The liver controls plasma cholesterol levels via an intricate metabolic network of lipoprotein receptors; sterol transporters and nuclear receptors that translates signals evoked by altered cholesterol status into selective transcriptional control of gene expression. The LDL receptor- as well as the LXR- and SREBP-controlled pathways that play a crucial role in this network have extensively been reviewed (Sato, 2010; Raghow et al., 2008; Tontonoz, 2011; Ye and DeBose-Boyd, 2011; Zhao and Dahlman-Wright, 2010; Go and Mani, 2012) and will therefore not be covered here.

Next to the liver, the intestine is important in regulation of many aspects of cholesterol metabolism. In retrospect, the crucial role of the intestine in the maintenance cholesterol homeostasis can be considered as rather obvious because it is evidently the main site for cholesterol absorption and excretion, i.e., the location where input and output of this non-degradable molecule can be controlled. Yet, it is important to realize that the balance between cholesterol uptake, synthesis and excretion requires extensive cross-talk between liver and intestine at a multiscale level. The different scales of interaction underlying this cross-talk will be discussed in this review. It starts with a condensed summary of the pathways that cholesterol takes when traveling through the body to finally end up in the feces, either as a neutral sterol or as a BS. The conversion of cholesterol into BS has considerable consequences: on the one hand it constitutes a major route for sterol removal from the body while, on the other hand, BS have been found to fulfill a variety of functions in signal transduction pathways as well as in control of energy metabolism. The physiological role of this important cholesterol metabolite will be discussed. Disturbance in cholesterol processing by the liver may be cause or consequence of cholestasis, which strongly impacts on the efficiency of the cross-talk between liver and intestine. The consequences of cholestasis on cholesterol metabolism and BS signaling will be discussed in the last part of this review.

2. Cholesterol synthesis and transport

Cholesterol belongs to the category of the so called "polar lipids class I: insoluble non-swelling amphiphiles" (Verkade and Tso, 2001). When exposed to water or, in general, to an aqueous environment, cholesterol is virtually insoluble, but can form a stable monolayer at the fluid-air surface. Within the body, physiology overcomes the insolubility of cholesterol by its incorporation into phospholipid membrane structures (either as mono- or as bilayer), or, after its acylation, into hydrophobic cores of fat droplets or lipoproteins. Cholesterol is essential in all mammalian cells (Spady and Dietschy, 1983; Dietschy et al., 1993) as reflected by the fact that synthesis of the sterol can occur in almost all cells of the body. Yet, as demonstrated in several studies that date back to the mid 1990's, the liver is the major site of synthesis in most mammals (Dietschy et al., 1993; Turley et al., 1995). The intricate pathway involving 25 enzymatic steps by which C2 acetate moieties are converted to a C27 cholesterol molecule (Goldstein and Brown, 1990); with the conversion of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) into mevalonate by HMGCoA reductase as the first committed and rate-controlling step, has been subject of extensive reviews and will not be covered in detail here (Mazein et al., 2013). Cholesterol synthesis is a rather costly process: the process takes at least 18 ATP and 16 NADPH units per cholesterol molecule (Bloch, 1965). From an evolutionary point of view, this may be a reason why mammalian cells do not degrade the cholesterol molecule. The only way to dispose of the sterol from the body is through excretion into the intestine, either as such or after conversion into a BS molecule Russell, 2003). Yet, it should be realized that cholesterol is not the only valuable product of the extremely complex "mevanolate pathway".

As depicted in the scheme in Fig 1, ubiquinone ("Coenzyme Q") (Fosslien, 2001) is one of these products and plays a primary role in electron transfer in mitochondrial oxidative phosphorylation. Intermediates such as farnesyl and geranyl–geranyl (Edwards and Ericsson, 1999) play essential roles in signal transduction pathways by providing hydrophobic anchors to connect proteins with specific membrane domains, a process that is called prenylation. Dolichols are of central importance in N-linked glycosylation of proteins. All these pathways are of pivotal importance for cellular metabolism. It is therefore not surprising that deletion of HMG-CoA reductase, the key enzyme in the mevanolate pathway, is not compatible with life (Ohashi et al., 2003). A liver-specific HMG-CoA reductase knock-out mouse also dies shortly after birth (Nagashima et al.,

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