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Review

Bile acids: From digestion to cancers☆

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ABSTRACT

Bile acids (BAs) are cholesterol metabolites that have been extensively studied these last decades. BAs have been classified in two groups. Primary BAs are synthesized in liver, when secondary BAs are produced by intestinal bacteria. Recently, next to their ancestral roles in digestion and fat solubilization, BAs have been described as signaling molecules involved in many physiological functions, such as glucose and energy metabolisms. These signaling pathways involve the activation of the nuclear receptor FXRα or of the G-protein-coupled receptor TGR5. These two receptors have selective affinity to different types of BAs and show different expression patterns, leading to different described roles of BAs. It has been suggested for long that BAs could be molecules linked to tumor processes. Indeed, as many other molecules, regarding analyzed tissues, BAs could have either protective or pro-carcinogen activities. However, the molecular mechanisms responsible for these effects have not been characterized yet. It involves either chemical properties or their capacities to activate their specific receptors FXRα or TGR5. This review highlights and discusses the potential links between BAs and cancer diseases and the perspectives of using BAs as potential therapeutic targets in several pathologies.

1. Introduction

1.1. Physico-chemical function and biosynthesis: old stories…

With cholesterol, phospholipids and bilirubin, bile acids (BAs) are the main component of bile. Present in digestive tract during the meal, they ensure fat solubilization and emulsification and thus promote digestion [1]. This property is mainly due to their amphipathic nature.

In adult human, around 500 mg of cholesterol are converted into BAs per day. Their synthesis takes place in liver and involves a series of enzymatic modifications of cholesterol at both sterol ring and lateral side chain. There are two different synthetic pathways. The first one, known as classical pathway, involves CYP7A1 and CYP8B1, the second named alternative pathway, involves cytochromes CYP27A1 and CYP7B1. Both syntheses lead respectively to production of so-called primary BAs: cholic acid (CA) and chenodeoxycholic (CDCA) [2] (Fig. 1). BAs greatly differ between species. It has to be noticed that mice present muricholic acids derived from chenodeoxycholic acid which is more hydrophobic and less toxic for cells than CDCA.

During the entero-hepatic cycle, in distal ileum as well as in colon, small part of BAs could be deconjugated and enzymatically modified by intestinal microflora [3]. These transformations lead to secondary BA, namely deoxycholic acid (DCA) and lithocholic acid [4], respectively originating from CA and CDCA [4]. By the end, conjugated BAs represent 98% of the pool.

In liver, primary and secondary BAs are coupled with amine residues (glycine or taurine) leading to production of amphipathic bile salts tauro- and glyco-conjugated and stored in gallbladder. After meal BAs and their conjugates are delivered in duodenum to facilitate digestion and absorption of fats and liposoluble vitamins in the intestine throughout the enterocyte barrier (Fig. 2). Indeed, BAs are transported from apical surface into enterocytes by the

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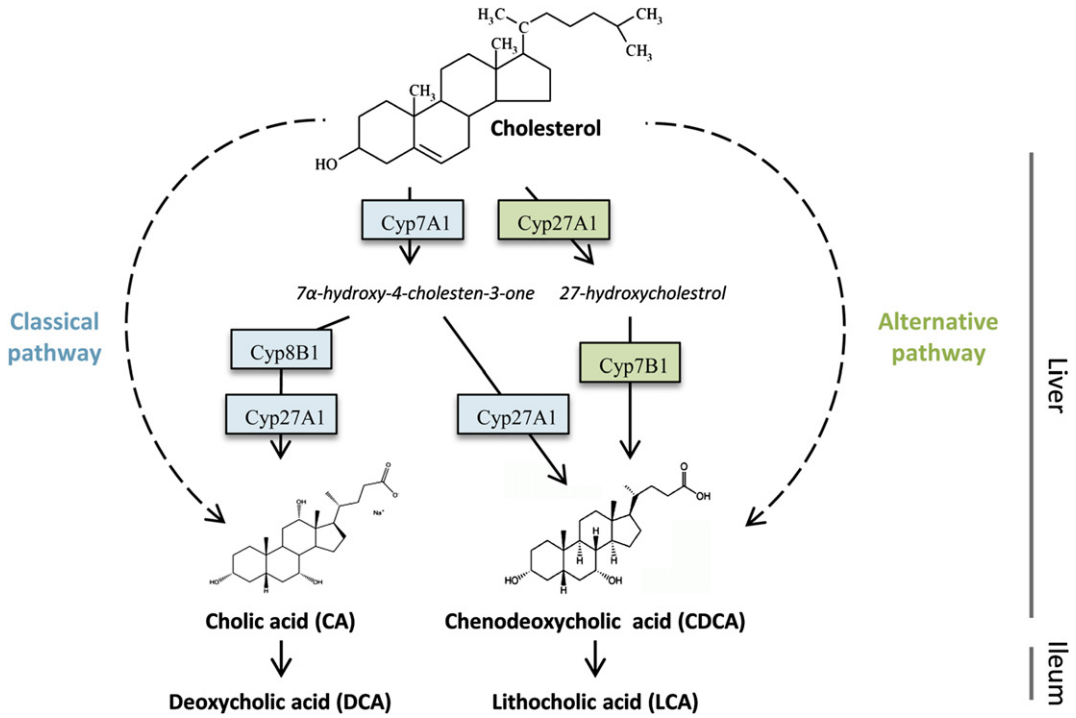

Fig. 1. Schematic representation of pathways of BA synthesis. BA synthesis takes place in the liver. They are formed from cholesterol. The classical pathway involves among other cytochromes CYP7A1, CYP27A1 and CYP8B1; alternative pathway involves cytochromes CYP27A1 and CYP7B1. Both lead to the production of primary BAs, cholic acid (CA) and chenodeoxycholic (CDCA). Then, they are converted into secondary BAs by bacterial flora in the ileum: deoxycholic acid (DCA) and lithocholic [4], respectively.

apical sodium-dependent BAs transporter ASBT (Apical Sodium-Dependent Bile Acid transporter). Then, BAs are bound to the ileal BA binding protein IBABP, transported across cell to basolateral membrane, and exported by the heterodimeric organic solute transporter OSTα/β [5].

In ileum and colon, the majority of BAs (95%) is reabsorbed and recycled in liver. Thus, neo-synthesized BAs can be excreted again, 20–40 times during digestion. This recycling mechanism, called entero-hepatic cycle, involves a system of tightly regulated transporters ensuring not only the maintenance of BAs metabolism, but also the control of cholesterol homeostasis from which they are derived [6].

1.2. BAs as cell signaling molecules: a new story begins…

In addition to their mechanical role, BAs have been described as signaling molecules binding two specific receptors: the nuclear receptor Farnesol-X-receptor (FXRα, NR1H4) and G-protein-coupled receptor TGR5 (GPBAR1, G-protein-coupled bile acid receptor).

1.2.1. The nuclear receptor for bile acids: FXRα

Identified in liver, intestine, or kidney, FXRα belongs to nuclear receptor superfamily [7]. More potent ligands for FXRα are CDCA and its conjugated forms [8]. It acts as an obligatory heterodimer with retinoid X receptor (RXR). This heterodimer binds to specific IR1 (inverted repeat-1) sequences on target gene promoters and then regulates their transcription. FXRα has been involved in regulation of many physiological functions. Among them, mouse model invalidated for *Fxrα* gene (Fxrα−/−), allows to highlight its involvement in regulating BAs biosynthesis and entero-hepatic cycle [9]. Fxrα−/− mice exhibit high BA plasma levels associated with abnormal hepatic biosynthesis, due to an alteration of FXRα-mediated negative feed-back on BA biosynthesis. The molecular mechanisms involved have been described (Fig. 3). In liver, FXRα represses *Cyp7a1* gene expression, a key enzyme of BA biosynthesis. At molecular level, in mouse models, this pathway involves several other members of nuclear receptor superfamily, such as SHP (Small heterodimer partner, NR0B2), LRH1 (Liver receptor homolog-1, NR5A2), or LXRα (Liver X Receptor α, NR1H3) [10]. It is interesting to note that in human, the regulation of Cyp7a1 doesn't not exist, what highlights the differences between species [11]. In parallel, FXRα protects liver from toxic effects of accumulated BAs. In hepatocytes, FXRα decreases BA uptake *via* repression of Na+-taurocholate cotransporting polypeptide (NTCP), organic anion-transporting polypeptide (OATP)-1 and OATP-4 expressions [12]. It also promotes BA excretion in bile ducts through transcriptional induction of the specific BA transporter BSEP (Bile salt export pump) in hepatocytes [6]. This effect is related to BA decreased excretion in digestive tract of *Fxrα* mutant mice [9].

FXRα is also involved in controlling lipid and glucose homeostasis as suggested by high plasma triglycerides concentrations in FXRα−/− mice [13] (Fig. 3). *Via* a SHP-dependant pathway, FXRα limits triglyceride synthesis. Indeed, it inhibits the expression of enzymes involved in triglyceride synthesis such as sterol-regulatory-element-binding (SREBP1-c), fatty-acid-synthase (FASN) and stearoyl coenzyme A desaturase-1 (SCD-1) [14]. In parallel, FXRα controls blood glucose by lowering expression of phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme of gluconeogenesis, and glucose-6-phosphatase (G6P) involved in glycogenolysis reactions [15] (Fig. 3).

1.2.2. G-protein-coupled receptor for BAs: TGR5

TGR5 is a member of G-protein-coupled receptors family with seven transmembrane domains. It has been recently recognized as BA receptor [16] more particularly for LCA and DCA [17]. TGR5 agonist activates protein kinase-A (PKA) pathway leading to cAMP-responsive-element-binding protein (CREB) phosphorylation which induces expression of its target genes, even though most of these transcriptional targets need to be identified (Fig. 4).

Expressed predominantly in liver, intestine or brown adipose tissues, TGR5 has been implicated in regulation of multiple