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REVIEW

The human gut sterolbiome: bile acid-microbiome endocrine aspects and therapeutics

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Abstract The human body is now viewed as a complex ecosystem that on a cellular and gene level is mainly prokaryotic. The mammalian liver synthesizes and secretes hydrophilic primary bile acids, some of which enter the colon during the enterohepatic circulation, and are converted into numerous hydrophobic metabolites which are capable of entering the portal circulation, returned to the liver, and in humans, accumulating in the biliary pool. Bile acids are hormones that regulate their own synthesis, transport, in addition to glucose and lipid homeostasis, and energy balance. The gut microbial community through their capacity to produce bile acid metabolites distinct from the liver can be thought of as an "endocrine organ" with potential to alter host physiology, perhaps to their own favor. We propose the term "sterolbiome" to describe the genetic potential of the gut microbiome to produce endocrine molecules from endogenous and exogenous steroids in the mammalian gut. The affinity of secondary bile acid metabolites to host nuclear receptors is described, the potential of secondary bile acids to promote tumors, and the potential of bile acids to serve as therapeutic agents are discussed.

Abbreviations: APC, adenomatous polyposis coli; BA, bile acids; BSH, bile salt hydrolases; CA, cholic acid; CDCA, chenodeoxycholic acid; COX-2, cyclooxygenase-2; CRC, colorectal cancer; CYP27A1, sterol-27-hydroxylase; CYP7A1, cholesterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; DCA, deoxycholic acid; EGFR, epidermal growth factor receptor; FAP, familial adenomatous polyposis; FGF15/19, fibroblast growth factor 15/19; FXR, farnesoid X receptor; GABA, γ-aminobutyric acid; GPCR, G-protein coupled receptors; HMP, Human Microbiome Project; HSDH, hydroxysteroid dehydrogenase; LCA, lithocholic acid; LOX, lipooxygenase; MetaHIT, Metagenomics of the Human Intestinal Tract; NSAIDs, non-steroidal anti-inflammatory drugs; PKC, protein kinase C; PSC, primary sclerosing cholangitis; PXR, pregnane X receptor; UDCA, ursodeoxycholic acid; VDR, vitamin D receptor

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1. Introduction

The "omics" revolution and the systems biology approach are fundamentally reshaping thought about the human body. Microbiome specialists now regard the epithelial surfaces of body (skin, oral and gastrointestinal, respiratory, and reproductive tract) as an interconnected network of ecosystem harboring all three domains of life, the eukarya, the prokarya, and the archaea. The gut microbiome is now regarded as a virtual organ[1]. It is unique among organs as it is composed of hundreds of species and thousands of strains of prokaryotes and their viruses[2]. The Human Genome Project is only part of the metagenome that comprises the human ecosystem. Indeed, work on the "second human genome"[3] has been undertaken by the Human Microbiome Project (HMP) in the United States, and by Metagenomics of the Human Intestinal Tract (MetaHIT) in Europe[4,5]. A major goal of much of this research is to understand the structure and function of the gut microbiome, and how diet, antibiotics, and pharmaceuticals perturb it. These studies also aim to uncover fundamental host-microbe interactions.

Research over the past several decades highlights the expanding role of bile acids (BAs) as hormones regulating lipid, glucose, lipoprotein, energy metabolism in addition to inflammatory responses[6,7]. BAs are also known to fundamentally shape the gut microbiome and vice versa. We will argue here that our gut microbiome should now be thought of as an "endocrine organ"[8,9] and we will focus on BAs, although this concept applies to many other classes of molecules including catecholamines[9], short-chain fatty acids[9], amino acids (GABA, γ-aminobutyric acid)[10] and steroid hormones[11].

2. Prokaryote-eukaryote influences on BA pool

Host primary BAs are synthesized in the liver from cholesterol and modified by prokaryotes in the gut[12] (Fig. 1). In humans, there are two separate pathways forming two primary BAs. The neutral pathway is thought to be the major pathway of BA synthesis under healthy conditions in humans. The liver is the only organ capable of producing the 14 enzymes which facilitate *de novo* synthesis of the dihydroxy BA chenodeoxycholic acid (CDCA; 3α, 7α), and the trihydroxy BA cholic acid (CA; 3α, 7α, 12α)[13]. The rate-limiting step of BA synthesis from cholesterol is initiated by cholesterol 7α-hydroxylase (CYP7A1). The synthesis of CA and the ratio of CA/CDCA are regulated by sterol 12α-hydroxylase (CYP8B1)[6]. Both CYP7A1 and CYP8B1 are tightly regulated by BAs through feedback repression mediated by farnesoid X receptor (FXR)-dependent induction of fibroblast growth factor 15/19 (FGF15/19) in the intestines[14]. FGF15/19 binds to FGF receptor 4/β-Klotho complex in hepatocytes which in turn activates the JNK1/2 and ERK1/2 signaling cascades, down-regulating *CYP7A1* mRNA expression in the liver[15–17].

The acidic pathway is initiated by mitochrondrial sterol-27-hydroxylase (CYP27A1) in the inner mitochondrial membrane[13]. CYP27A1 is expressed extra-hepatically in numerous tissues. The acidic pathway is thought to be a minor pathway for BA synthesis under the normal physiological state, but appears to predominate in patients with cholestatic liver disease as CYP7A1 is down-regulated by the inflammation produced as a consequence of small bowel overgrowth in these patients[18].

The BA pool of rodents, in addition to CA, converts a significant quantity of CDCA to muricholic acids by 6β-hydroxylation. Rodents, unlike humans, are capable of making 7α-hydroxylating secondary BAs return to the liver during enterohepatic circulation, thus maintaining a highly hydrophilic biliary pool. By contrast, secondary BAs can predominate in some humans approaching 60% of the biliary pool[12].

As bile salts enter the terminal ileum and the proximal colon, they are rapidly deconjugated by prokaryotic enzymes known as bile salt hydrolases (BSH)[12,19]. BSH have different affinities for

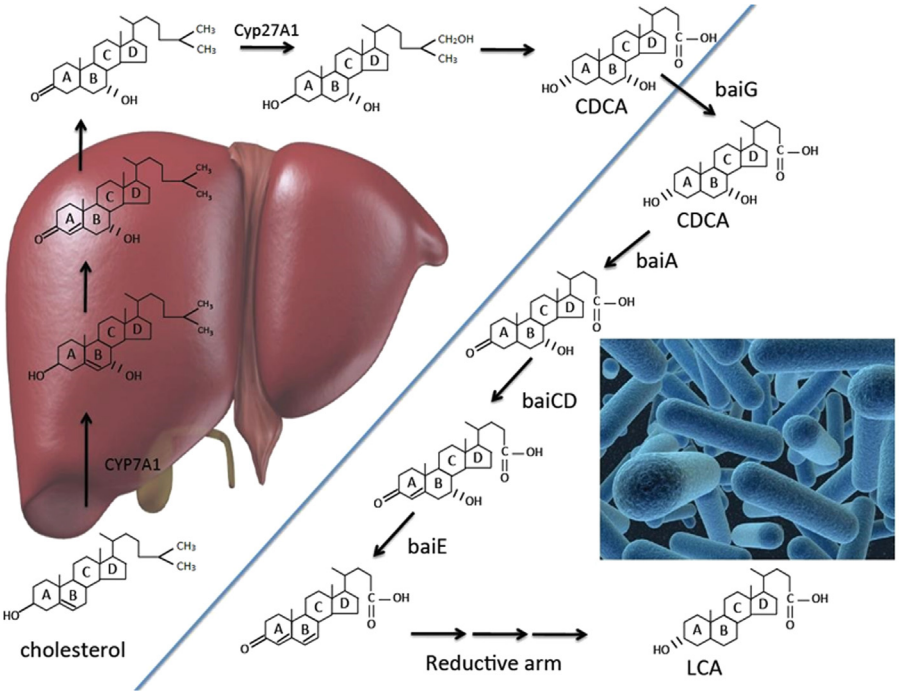

Figure 1 Pathway from cholesterol to lithocholic acid in the human ecosystem. CDCA is synthesized in the liver *via* the neutral pathway through a series of oxidative steps. LCA is produced by members of the gut microbiome through a multi-step biochemical pathway, the first half of which is oxidative followed by a net 2 electron reduction.