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# Interactions between gut bacteria and bile in health and disease

Sarah L. Long [a, b], Cormac G.M. Gahan [a, b, c, *], Susan A. Joyce [a, d]

[a] APC Microbiome Institute, University College Cork, Cork, Ireland
[b] School of Microbiology, University College Cork, Cork, Ireland
[c] School of Pharmacy, University College Cork, Cork, Ireland
[d] School of Biochemistry and Cell Biology, University College Cork, Cork, Ireland

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ABSTRACT

Bile acids are synthesized from cholesterol in the liver and released into the intestine to aid the digestion of dietary lipids. The host enzymes that contribute to bile acid synthesis in the liver and the regulatory pathways that influence the composition of the total bile acid pool in the host have been well established. In addition, the gut microbiota provides unique contributions to the diversity of bile acids in the bile acid pool. Gut microbial enzymes contribute significantly to bile acid metabolism through deconjugation and dehydroxylation reactions to generate unconjugated bile acids and secondary bile acids. These microbial enzymes (which include bile salt hydrolase (BSH) and bile acid-inducible (BAI) enzymes) are essential for bile acid homeostasis in the host and represent a vital contribution of the gut microbiome to host health. Perturbation of the gut microbiota in disease states may therefore significantly influence bile acid signatures in the host, especially in the context of gastrointestinal or systemic disease. Given that bile acids are ligands for host cell receptors (including the FXR, TGR5 and Vitamin D Receptor) alterations to microbial enzymes and associated changes to bile acid signatures have significant consequences for the host. In this review we examine the contribution of microbial enzymes to the process of bile acid metabolism in the host and discuss the implications for microbe-host signalling in the context of *C. difficile* infection, inflammatory bowel disease and other disease states.



## 1. Introduction

Bile acids are the major functional components of bile. They are synthesized from cholesterol in hepatocytes, stored in the gall bladder and are subsequently released into the small intestine (Joyce and Gahan, 2016). The host enzymes involved in bile acid synthesis have been well characterised, and there is significant information available concerning the pathways that are central to bile acid synthesis (Li and Chiang, 2014). Significantly, bile acids are further modified by unique microbial enzymes that are encoded within the gut microbiome. These enzymes are as important to the host metabolism of bile acids as the liver cytochrome P450 enzymes that are encoded within the host genome. Indeed, the relationship between host and microbe-mediated bile acid metabolism represents an excellent exemplar of the symbiotic reliance upon microbial enzymes to complete functions that are essential to homeostasis in the host. Without a microbial contribution to bile acid metabolism the host bile acid signature is perturbed with resultant impacts upon a range of host physiological processes (Joyce et al., 2014a; Sayin et al., 2013; Swann et al., 2011). The basic microbial enzymes that contribute to bile acid metabolism include bile salt hydrolase (BSH) and bile acid dehydratase enzymes that generate unconjugated and secondary and tertiary bile acids (see Fig. 1).

A major function of bile acids is to facilitate the emulsification of dietary fats and to aid intestinal absorption of lipids and lipophilic vitamins (Begley et al., 2005a). However much recent work has also shown that bile acids represent signalling molecules in the host with the capacity to regulate cellular and metabolic activities through interaction with host bile acid receptors (Li and Chiang, 2014; Vitek and Haluzik, 2016). These receptors include the ligand-activated nuclear receptors such as the farnesoid-X-receptor (FXR) and the vitamin D receptor (VDR) as well as the cell surface-located G protein-coupled bile acid receptor TGR5 (Li and Chiang, 2014). Importantly different receptors have differing affinity for individual bile acids. For instance the most potent agonists of the

* Corresponding author. School of Microbiology, University College Cork, Cork, Ireland.
*E-mail address:* c.gahan@ucc.ie (C.G.M. Gahan).

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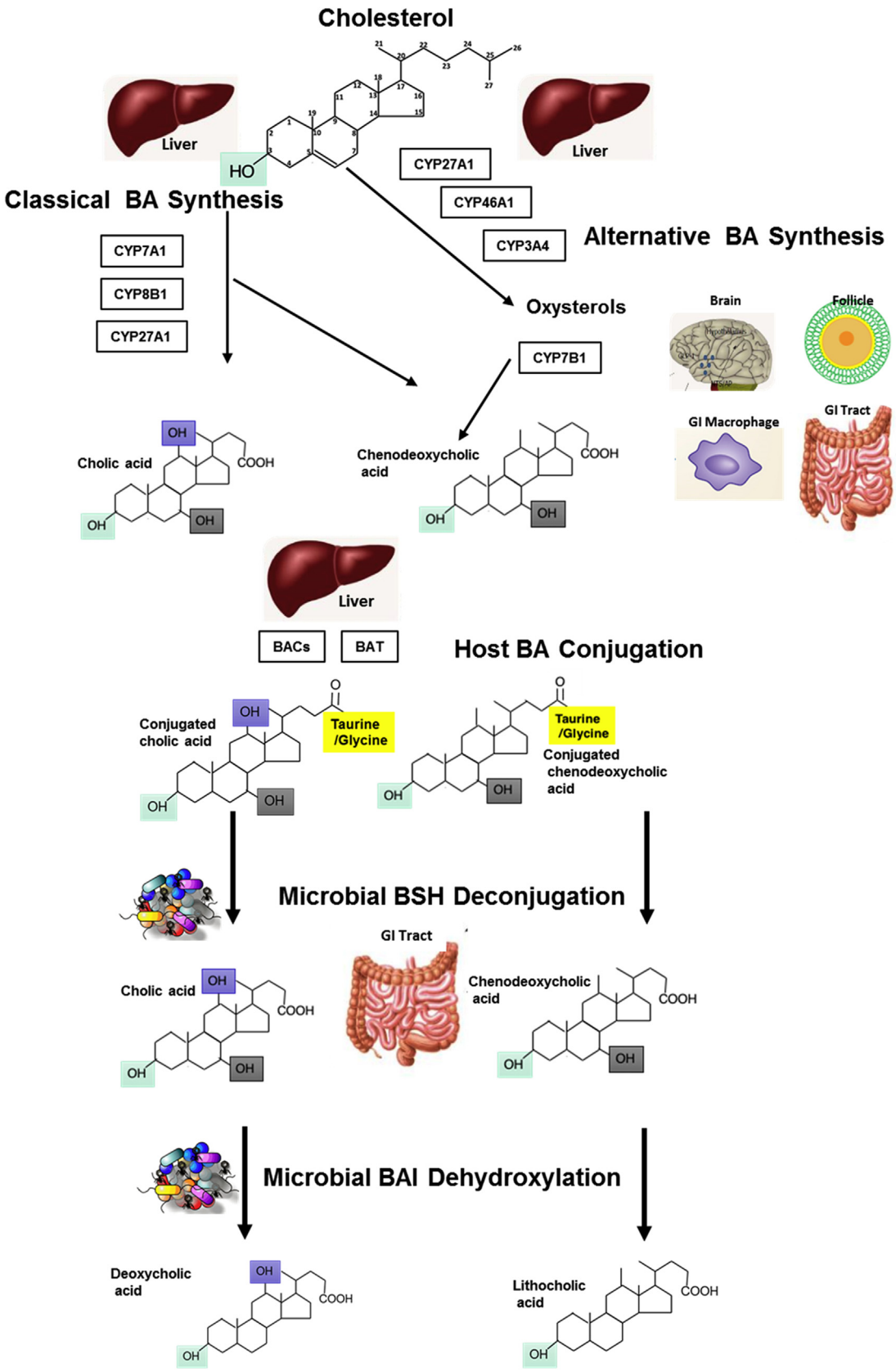


**Fig. 1.** Host and microbial bile acid metabolism: Synthesis from cholesterol in the liver by host Cytochrome P450 enzymes (boxed) through the classical and alternative bile acid synthetic pathways. Bile acid conjugation is a host process that occurs in the liver however microbes in the GI tract modify BA moieties through deconjugation by bile salt hydrolases releasing free primary bile acids that are now susceptible to a range of microbial modifications to produce a range of bile acids (for simplicity only two are shown here).