Molecular Aspects of Medicine xxx (2017) 1–12

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Interactions between gut bacteria and bile in health and disease

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ARTICLE INFO

Article history:
Received 30 December 2016
Received in revised form
26 May 2017
Accepted 7 June 2017
Available online xxx

Keywords:
Bile salt hydrolase (BSH)
Bile acid inducible (BAI)
Microbiome
Microbiota
Lactobacillus

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

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http://dx.doi.org/10.1016/j.mam.2017.06.002
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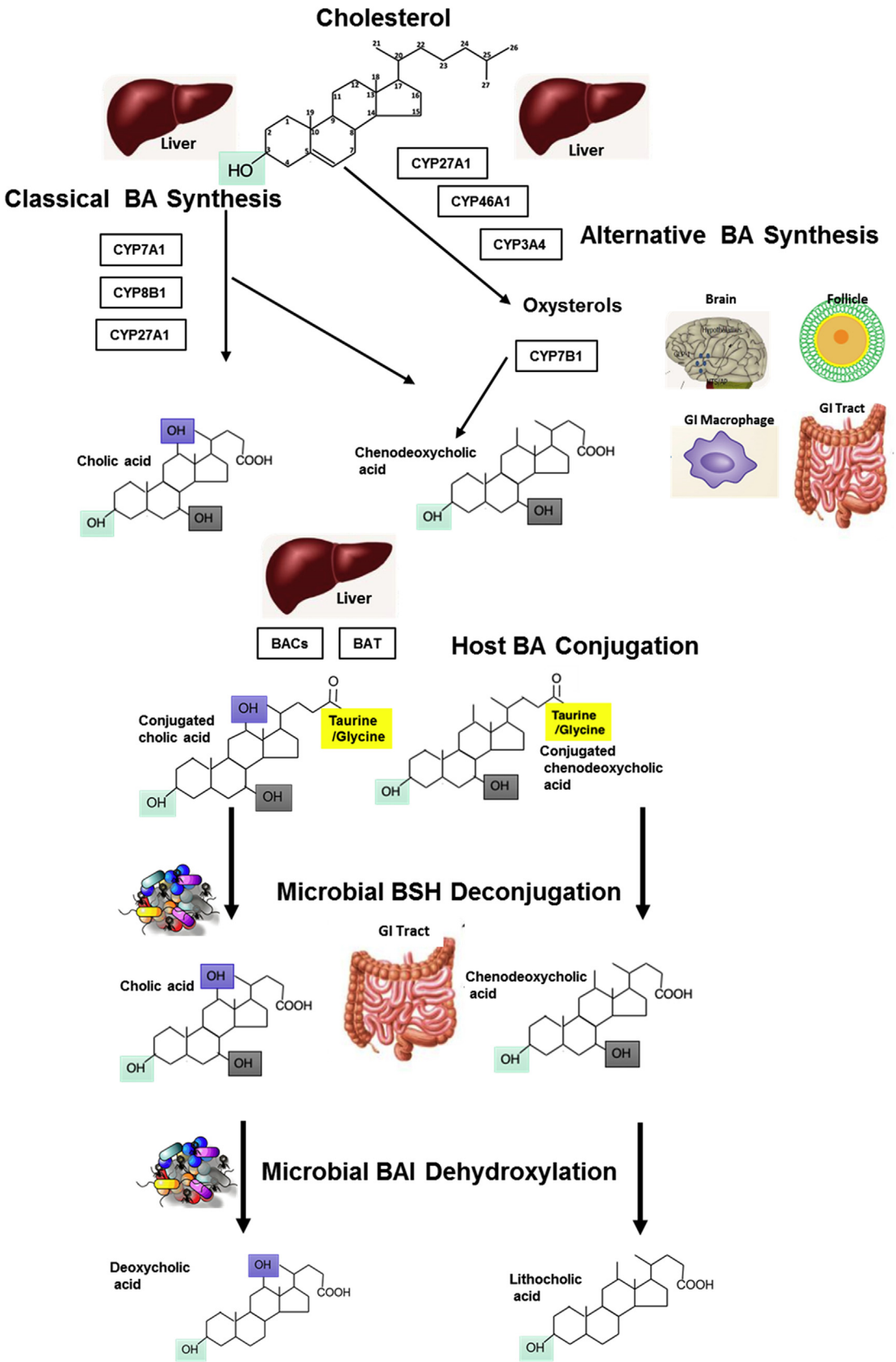

Fig. 1. Host and microbial bile acid metabolism: Synthesis from cholesterol in the liver by host Cytochrome P450 enzymes (boxed) through the classical and alternative bile acid synthetic pathways. Bile acid conjugation is a host process that occurs in the liver however microbes in the GI tract modify 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).

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FXR (in rank order of potency) are CDCA > LCA = DCA > CA with both conjugated and unconjugated moieties capable of activating the FXR (Parks et al., 1999; Zhou and Hylemon, 2014). TGR5 recognises both conjugated and free bile acids with a preference for TLCA followed by TDCA > TCDCA > TCA (Joyce and Gahan, 2016; Li and Chiang, 2014). This implies that subtle variations to the local or systemic bile acid signature may alter the signalling properties of the bile acid pool with a resultant physiological impact upon the host. Given that the gut microbiota has a major influence upon this bile acid signature, perturbations to the gut microbial community structure will have significant consequences for the signalling properties of bile acids in the host. This is most likely to occur in disease states where alterations of the gut microbiota are exaggerated.

In the current review we examine the role of specific microbial enzymes upon bile acid metabolism in the host and outline how perturbations to the microbiota may influence systemic bile acid profiles with an emphasis upon disease states. For in-depth reviews on the biochemical signalling effects of bile acids the reader is referred to excellent reviews by Li and Chiang (2014) and Zhou and Hylemon (2014) (Li and Chiang, 2014; Zhou and Hylemon, 2014).

2. Host synthesis of bile acids

Bile acids are products of steroid cholesterol and are generated through either the classical or alternative pathway primarily in hepatocytes (see Fig. 1). The host enzymes responsible for bile acid synthesis are cytochrome P450 family enzymes. Over 200 potential cytochrome P450 enzymes are encoded by the human genome, 57 of which have an assigned function either as hydroxylases or as oxidases involved in many cellular processes including cholesterol biosynthesis, steroid hormone biosynthesis, drug/xenobiotic metabolism, eicosanoid metabolism, and vitamin D metabolism (Nebert and Dalton, 2006; Rodriguez-Antona and Ingelman-Sundberg, 2006). Of these 14 are assigned to the multiple steps involved in bile acid synthesis. The chemical processes responsible for the host synthesis of bile acids have been extensively reviewed elsewhere (Li and Chiang, 2014) and are briefly described below.

The classical pathway for bile acid synthesis is regulated by the cytochrome monooxygenase enzyme cholesterol 7α-hydroxylase, CYP7A1. It is the rate limiting step in pushing cholesterol towards bile acid synthesis through the intermediate, 7α-hydroxycholesterol. The latter either undergoes 12α-hydroxylation of the steroid ring (CYP8B1) to ultimately produce cholic acid (CA) or CYP27A1 aids its conversion to chenodeoxycholic acid (CDCA). In addition, the alternative pathway contributes between 9% and 25% of the total bile pool and produces only CDCA (de Aguiar Vallim et al., 2013). The alternative pathway is a mitochondrial-based process, all cells and tissues therefore have the potential to produce CDCA. Indeed, the enzyme CYP27A1 can initiate the alternative pathway both in the liver and in macrophages (Chiang, 2009). The brain is also a potential site of bile acid synthesis and a recent study in rats (Zheng et al., 2016) detected a range of 20 bile acids and oxysterols in regions of the brain, supporting the potential for CYP8B1 and CYP7A1 expression in this tissue (Bjorkhem et al., 1999; Cali et al., 1991; Ogundare et al., 2010). Whilst further research is necessary, this opens the possibility that bile acids can be synthesized in a number of tissues with the potential to subsequently influence local host signalling events.

The final step prior to secretion of bile moieties is the conjugation of bile acids to either glycine or taurine, a process that increases their solubility for secretion into biliary fluid. The process is carried out by bile acid cholyl-CoA synthetase (BAC) activity and amidation at C24 to either glycine or taurine by the enzyme bile acid-CoA:amino acid *N*-acyltransferase (BAT). As a result of this activity the majority of bile acids excreted from the liver are conjugated (Gerard, 2013).

Feedback regulation of specific enzymes in the system results in alterations to the ratio of individual bile acids in the bile acid pool. For instance, sterol 12 α-hydroxylase (CYP8B1) controls the chemical diversity of the bile acid pool by adjusting the ratio of CA and CDCA in the classical pathway. Overall regulation of bile acid synthesis is through feedback inhibition of CYP7A1. Direct interaction between bile acids and the FXR results in regulation of numerous processes in hepatocytes including downregulation of *CYP7A1* gene expression. In the liver FXR activates another layer of transcriptional regulation through transcription factor MafG, (Musculoaponeurotic Fibrosarcoma Oncogene Homolog G) which represses both the classical (effective targeting of *Cyp8B1*) and the alternative (weaker targeting of *Cyp7B1*) pathways (de Aguiar Vallim et al., 2015). Alternatively, engagement of FXR in enterocytes locally by bile acids results in gut expression of the regulatory hormone FGF19 (designated as FGF15 in mice) which enters the circulation and can repress *CYP7A1* activity in hepatocytes through interaction with a specific cellular receptor (FGFR4). FGF15/19 has a myriad of other effects including regulation of glucose metabolism, lipogenesis and metabolic rate (Li and Chiang, 2014). Therefore engagement of FXR by bile acids in hepatocytes or in enterocytes (with resultant FGF15/19 expression) regulates a significant number of physiological processes in the host (including cellular gluconeogenesis, cholesterol metabolism and triglyceride metabolism) and ultimately feeds back to regulate further bile acid biosynthesis (reviewed in (Li and Chiang, 2014)).

In adults, the relative ratio of glycine to taurine conjugates in the bile acid pool is approximately 3:1, but increased taurine dietary intake can alter these levels (Sjovall, 1959). Bile salts synthesised in the liver are immediately secreted into bile, they are released from the gall bladder post-prandially to facilitate nutrient digestion and absorption and they are reabsorbed in the intestine and transported back to the liver. The enterohepatic circulation of bile acids and salts is very efficient with 95% of bile acids actively reabsorbed through packaging in lipid micelles at the brush border membrane of the terminal ileum and secretion into the portal blood circulation to the liver (Chiang, 2013). Also, passive diffusion of free hydrophobic bile acids along the GI tract contributes to portal bile acid levels. The cycle occurs several times each day with approximately 5% of bile salts lost to the human colon while the remainder are recycled (Joyce and Gahan, 2016).

3. Microbial modifications of bile acids

Host synthesis of bile acids represents the origin of bile acids in the bile acid pool. However, the chemical composition of bile acids is significantly influenced by the gut microbial community and therefore the microbiota should be considered as an essential factor in bile acid homeostasis in the host (Fig. 1). Here BSH enzymes deconjugate bile acids to unconjugated forms which are then subject to further modifications. The key enzymes involved in these biochemical conversions are outlined below. As the gut microbiota plays such a central role in bile acid metabolism any perturbation of the microbiota has the potential to disrupt bile acid homeostasis and impact host physiological processes (see below).

3.1. Microbial bile acid deconjugation through bile salt hydrolase activity

3.1.1. Bacterial bile salt hydrolase (BSH) enzymes

Bile salt hydrolases (BSH; E.C.3.5.1.24), are microbial enzymes which belong to the Ntn-hydrolase superfamily of proteins. Discovered as recently as 1995 (Artymiuk, 1995; Brannigan et al.,

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1995), all proteins which belong to this large family of enzymes hydrolyse amide bonds but vary in their substrate specificity (Oinonen and Rouvinen, 2000). Bile salt hydrolases in particular cleave the amide bond between the glycine and taurine moiety conjugated to the steroid nucleus of bile salts. Their action liberates bile acids (deconjugation) and is the crucial first step for further bile acid alterations by microbes within the gut environment (Begley et al., 2006).

3.1.2. Distribution of BSH enzymes in bacteria

BSH enzymes are represented in various microbial species across most phyla. With a focus on commensal gut microbes BSH activity has been reported in *Lactobacillus* (Chae et al., 2013; Corzo and Gilliland, 1999; Elkins et al., 2001; Gu et al., 2013; Jayashree et al., 2014; Lambert et al., 2008a; McAuliffe et al., 2005; Ren et al., 2011; Wang et al., 2012), *Bifidobacterium* (Grill et al., 1995a, 1995b; Kim et al., 2004a, 2005, 2004b; Tanaka et al., 2000), *Enterococcus* (Franz et al., 2001; Wijaya et al., 2004), and *Clostridium* spp (Coleman and Hudson, 1995; Gopal-Srivastava and Hylemon, 1988; Rossocha et al., 2005) all of which are gram positive bacteria. BSH has also been detected in some commensal gram negative *Bacteroides* spp (Kawamoto et al., 1989; Stellwag and Hylemon, 1976). Given the specific role of BSH, the majority of studies focus on gut-resident and related microbes. For instance, the gastrointestinal pathogen *Listeria monocytogenes* is BSH active, a feature which aids its gut persistence during infection (Begley et al., 2005b; Dussurget et al., 2002). It is understood that BSH activity is generally confined to gut-associated bacteria (Jones et al., 2008), but it has been found in *Xanthomonas maltophilia* isolated from soil (Dean et al., 2002; Pedrini et al., 2006) and thermophilic *Brevibacillus* sp isolated from hot springs (Sridevi and Prabhune, 2009; Sridevi et al., 2009). This indicates that this function may indeed be a more widespread feature of bacteria adapted to different environments.

Interestingly the numbers of BSH alleles in any given strain can vary, with up to 4 different alleles in certain isolates (Lambert et al., 2008a). There is evidence of horizontal transmission of BSH amongst gut bacteria suggestive of strong evolutionary selection for this activity (Jones et al., 2008). Focusing on the species *Lactobacillus* four different BSH enzymes have been reported in two strains of *L. plantarum* (Lambert et al., 2008a; Ren et al., 2011). The strain *L. johnsonii* PF01 contains 3 distinct BSH's (Chae et al., 2013). Two BSH enzymes were found in the strain *L. acidophilius* NCFM, each of which was found to have different substrate specificities confirmed by targeted inactivation (McAuliffe et al., 2005). Two *bsh* genes were also found in the *L. salivarius* strains JCM1046 and UCC118 designated BSH1, BSH2 in both cases but through further analysis *L. salivarius* UCC118 BSH2 was reclassified as encoding a penicillin V acylase (PVA) enzyme (Fang et al., 2008, 2009).

We previously examined the function, distribution and abundance of BSH within the human gut microbiome using a functional metagenomics approach (Jones et al., 2008). Functional *bsh* coding sequences were evident across both domains of life in the gut (Bacterial and Archaeal) and among all the major bacterial phyla. The wide distribution of the activity across gut bacteria is strongly suggestive of host-driven selection. Furthermore, the BSH alleles detected in the human microbiome were markedly different in other environments such as the murine gut. Whilst much further investigation is required, this suggests host species-specific selection of microbial BSH activities which may be driven by species specific differences in host bile acid pools and which may indicate host-species specific functional differences in BSH activity (Jones et al., 2008).

3.1.3. BSH enzyme structure

BSH proteins show high similarity to a closely related family of enzymes known as Penicillin V acylases. These enzymes comprise the Ntn-CBAH hydrolase family. Both contain conserved amino acids within the active centre and cleave amide bonds but they are significantly different when it comes to their substrates (bile acids for BSH and penicillin V for PVA) (Jones et al., 2008; Kumar et al., 2006). The high level of homology between these two proteins has resulted in confusion in the annotation of genes encoding these enzymes. In recent years characterization of the enzyme binding site and enzyme substrate specificity along with phylogenetic analysis has improved differentiation and annotation of both BSH and PVA (Lambert et al., 2008b; Panigrahi et al., 2014).

BSH enzymes are synthesised as pre-proteins. These inactive precursor proteins are proteolytically processed by post-translational machinery within the cell which results in the formation of a mature catalytically active enzyme. Activation of BSH requires the catalytic cleavage of the N-terminal formylmethionine residue resulting in the exposure of a new N-terminal amino acid, usually cysteine, which acts as a nucleophile and a proton acceptor (Duggleby et al., 1995; Kumar et al., 2006; Oinonen and Rouvinen, 2000). Exposure of this Cys2 residue is crucial for the catalytic activity of the mature protein and this has been confirmed through site-directed mutagenesis (Kumar et al., 2006).

Members of this family of proteins share a conserved αββα core (Fig. 2): 2 anti-parallel β-sheets covered by a layer of anti-parallel α-helices (Oinonen and Rouvinen, 2000). Despite the large diversity of *bsh* alleles described within the gut environment (Jones et al., 2008), the crystalline structure of BSH has been reported for only three distinct microbial species: *Clostridium perfringens* (Rossocha et al., 2005), *B. longum* (Kumar et al., 2006) and most recently *L. salivarius* (Xu et al., 2016). All three structures confirm the αββα fold and all three contain the catalytically active Cys2 residue (Fig. 2). The main difference between these three strains is the amino acid sequence within their binding pockets: loop I and loop II (Xu et al., 2016). This may account for the difference in substrate specificities associated with each strain. *C. perfringens* BSH can metabolise both glyco- and tauro-conjugated bile acids as can *L. salivarius* BSH which also is reported to exhibit broad range substrate affinity (Rossocha et al., 2005; Wang et al., 2012). *B. longum* however shows a preference towards glyco-conjugated bile acids only (Kumar et al., 2006).

BSH proteins tend to form dimeric or more complex multimeric arrangements. The BSH from *L. salivarius* exists as a dimer but can be stable as a dimer or a tetramer in solution (Krissinel and Henrick, 2007). The crystalline structure of *C. perfringens* and *B. longum* BSHs confirm that these enzymes have a native tetrameric structure (Kumar et al., 2006; Rossocha et al., 2005). BSH trimers have been reported in *L. johnsonii* 100-100 (Elkins et al., 2001; Lundeen and Savage, 1990), hexamers in *Bif. longum* BB526 (Grill et al., 1995a), octomers in *B. fragilis* and dimers in the strains *Xanthomonas maltophilia* (Dean et al., 2002) and *Brevibacillus* sp (Sridevi et al., 2009).

3.1.4. Functional role of BSH in microbes

Conjugated bile acids in the gut are known to be toxic to bacteria, particularly at low pH, and are proposed to influence the growth of bacteria in different regions of the GI tract (Islam et al., 2011). The presence of BSH can confer a protective effect for some bacterial species through bile acid deconjugation and numerous studies show that BSH is also advantageous for bacterial colonisation (Bateup et al., 1995; Begley et al., 2005b; De Smet et al., 1995; Delpino et al., 2007; Dussurget et al., 2002; Grill et al., 2000; Jones et al., 2008). BSH activity liberates amino acids (glycine or taurine) which some bacteria may be able to use as an energy source. Glycine can be metabolised to ammonia and carbon dioxide

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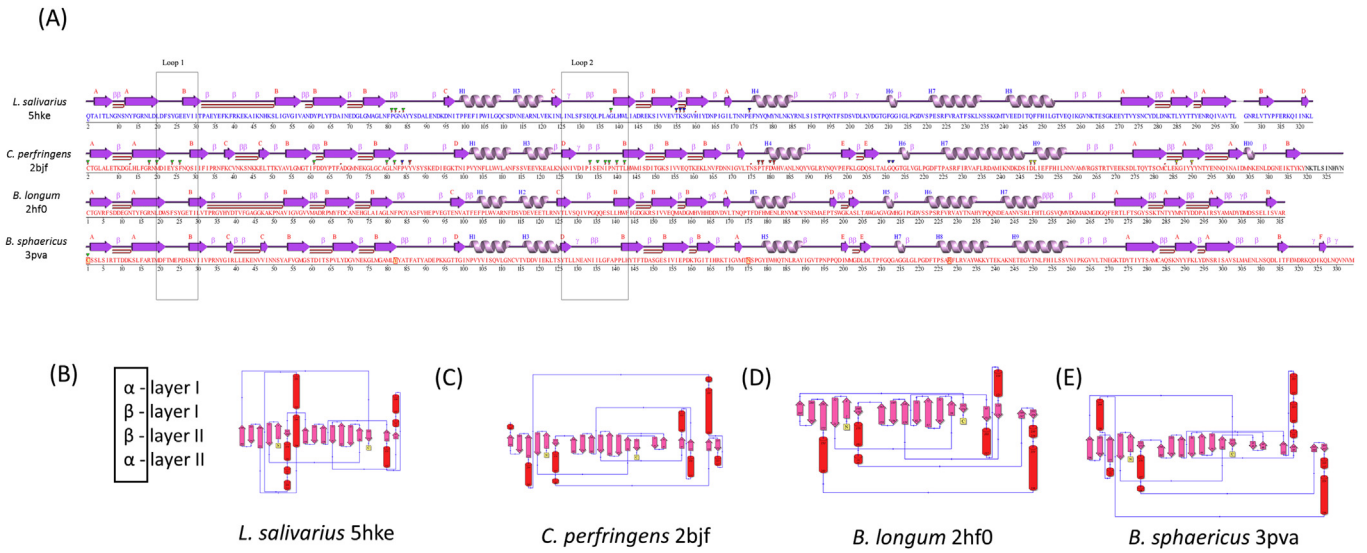

Fig. 2. (A) Secondary structure elements of BSH proteins, *L. salivarius* BSH (PDB entry 5hke), *C. perfringens* BSH (PDB entry 2bjf), *B. longum* BSH (PDB entry 2hf0) and *B. sphaericus* penicillin V acylase (PDB entry 3pva). Diagrams generated using the PDBSum tool (Laskowski 2009). Structures such as α-helices are labelled H1, H2 and β-strands are labelled according to their sheets A, B. Various structural motifs such as β- and γ-turns, and β-hairpins are also highlighted. Catalytic residues are highlighted with a yellow box and red boxes above amino acids indicate residues that interact with bound ligands. Topology diagrams (B) 5hke, (C) 2bjf, (D) 2hf0 and (E) 3pva show that even though the amino acid sequence of all proteins are different, when packaged into their secondary structures they all share the unique αββα core. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and taurine can be metabolised to produce ammonia, carbon dioxide and sulphate all of which can be utilised as carbon and nitrogen sources (De la Puerta et al., 2010; Gopal-Srivastava and Hylemon, 1988; Wang et al., 2013). Furthermore it has been proposed that BSH may play a role in the regulation of intracellular pH in the bacterial cell and thereby aid in resistance to bile acids at low pH (reviewed in (Begley et al., 2005b)). As BSH is associated with a greater capacity to survive gut transit, BSH activity is regularly included within the selection criteria for probiotics (Jones et al., 2008; Vizoso Pinto et al., 2006).

3.1.5. Impact of BSH activity on the host

3.1.5.1. Cholesterol lowering. Hypercholesterolemia is defined by high levels of circulating cholesterol accompanied by elevated low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL). This abnormal lipid profile in patients is considered a major risk factor for the development of cardiovascular disease (CVD), a major cause of death globally. One alternative preventative measure to modulate serum cholesterol is the administration of probiotic bacteria, and a number of potential probiotic species have been shown to significantly reduce circulating cholesterol levels (De Smet et al., 1998; Smet et al., 2011; Tannock et al., 1989). There have been multiple different mechanisms proposed which include; the ability of BSH activity to deconjugate bile salts and decrease micellular fat and cholesterol reabsorption (Liong and Shah, 2005); assimilation of cholesterol by the bacteria themselves (Gilliland et al., 1985; Pereira and Gibson, 2002; Tomaro-Duchesneau, 2014); production of ferulic acid (Tomaro-Duchesneau et al., 2012a, 2012b); short chain fatty acid fermentation to increase gut health and cholesterol conversion to 5β-coprostanol (Bull et al., 2002).

As previously mentioned, approximately 5% of bile acids escape recycling daily. This is due, in part, to bacterial deconjugation occurring in the colon. These unconjugated bile acids are more hydrophobic and are therefore inefficiently absorbed (by passive diffusion), whereas conjugated bile acids are actively taken up by IBAT/ABAT transporters (Craddock et al., 1998; Dietschy and Turley, 2002). As a consequence, the rate of excretion of bile acids in the faeces can increase. This, in turn may induce the demand for *de novo* bile acid synthesis from cholesterol or indeed reverse cholesterol transport to the liver leading to a reduction in serum levels (Begley et al., 2006). A study carried out by our group (Joyce et al., 2014a) in a mouse model showed that expression of BSH1 from the *L. salivarius* strain JCM1046 significantly reduced LDL cholesterol and serum triglycerides. Other studies have correlated lowering of cholesterol with elevated BSH activity in animal models (Begley et al., 2006; Damodharan et al., 2015; De Smet et al., 1998; Gu et al., 2014).

Human trials investigating the effects of BSH-active probiotic strains on cholesterol metabolism have also been reported. Ooi et al. (2010) performed a randomized, placebo-controlled clinical trial with a synbiotic capsule which contained a BSH- active strain of *L. acidophilus* combined with inulin. After 6 weeks of treatment with the synbiotic they also found that plasma levels of both total cholesterol and LDL-cholesterol were significantly reduced compared to levels seen in the control group (Ooi et al., 2010). Another probiotic strain, *L. reuteri* NCIMB 30242 was also characterised in vitro and in vivo for its cholesterol-lowering ability. A comprehensive in vitro characterisation of this strain confirmed the presence of an active BSH. A number of randomised control trials were carried out in order to determine the probiotic safety and tolerance via both capsule and yoghurt formulations. *L. reuteri* NCIMB 30242 capsules taken over a 9 week period significantly reduced LDL-C and total cholesterol compared to volunteers receiving the placebo. They also found that plasma deconjugated bile acid levels were elevated relative to the placebo group suggesting that the bacterial BSH is active in this setting (Branton et al., 2011; Jones et al., 2012a, 2012b, 2012c).

3.1.5.2. Weight gain & lipid metabolism. We demonstrated that the expression of a single cloned BSH in a controlled setting significantly reduced weight gain in conventionally raised animals. This indicated a potential role for microbial BSH activity in weight gain and suggested that BSH may be a possible intervention target in the

area of obesity and metabolic disease (Joyce et al., 2014a).

The concept of BSH-associated alterations in weight gain has also been explored in the agricultural sector in a search to find alternatives to antibiotic growth promoters (AGP) for livestock. Antibiotics have long been used as food additives in the animal food industry and lead to weight gain as a result of alteration of the gut microbiota. Weight gain mediated by AGP is hypothesised to be a result of a reduction in BSH positive bacteria such as *Lactobacillus* spp (Guban et al., 2006). This has prompted the identification of specific BSH inhibitors for use as alternatives to AGPs for animal husbandry. Numerous BSH inhibitory compounds have been identified through chemical screens, including riboflavin and phenethyl caffeate, which will now be tested in vivo (Smith et al., 2014; Wang et al., 2012). Interestingly, a recent longitudinal study in humans supports an association between BSH and weight gain (Korpela et al., 2016). Analysis of microbial populations in children aged between 2 and 7 demonstrated a correlation between the use of macrolide antibiotics, a prolonged reduction in overall *bsh* abundance and weight gain (Korpela et al., 2016).

In contrast to the evidence outlined above, some recent studies indicate that an increase in BSH activity may drive an increase in weight gain through FXR-mediated mechanisms. Li et al. 2013 found that the anti-oxidant compound Tempol prevented obesity in mice as a consequence of lowering BSH activity. Administration of Tempol resulted in alterations to the microbiota, including significant reductions in the number of *Lactobacillus* and *Clostridium* species which are key BSH-containing bacteria. This resulted in altered levels of metabolites with a notable increase in the taurine-conjugated bile acid, tauro-beta muricholic acid (TβMCA). TβMCA has been previously identified as a potent inhibitor of the nuclear receptor FXR which regulates lipid metabolism (Sayin et al., 2013). This mechanism is responsible for the anti-obesity effects observed in Tempol treated mice (Li et al., 2013). *In vivo* studies using $FXR^{-/-}$ mice further support these data (Gonzalez et al., 2016; Li et al., 2013; Parséus et al., 2017).

Overall these studies show that there are links between microbial BSH activity and lipid metabolism in the host with an impact upon body weight, but differences in the model systems used have made direct comparisons difficult. Absolute levels of BSH activity, location of BSH activity in the gut and subtle differences in resultant bile acid signatures may potentially influence the phenotypic outcome. As outlined above evidence suggests that engagement of the FXR results in an increase in body weight in mice (Parséus et al., 2017). However recent studies have indicated that high level BSH expression by probiotics may blunt the FXR response in mice (Degirolamo et al., 2014; Kim et al., 2016). In addition, engagement of another bile acid receptor, TGR5, can reduce body weight (Watanabe et al., 2006) and indicates a subtle interplay between FXR and TGR5 that is deserving of greater study.

3.1.5.3. Other host effects of microbial BSH activity. Gut colonization of gnotobiotic mice with highly active BSH-producing bacteria was used to generate a roadmap of the host transcriptional response which accompanies elevated BSH activity (Joyce et al., 2014a, 2014b). In addition to pathways involved in cholesterol and lipid metabolism the study revealed that elevated BSH activity influences a number of physiological processes in the host including an impact upon host circadian rhythm (Govindarajan et al., 2016), expression of factors influencing epithelial cell homeostasis (such as RegIIIγ and EGFr) and factors influencing local immune function in the gut (reviewed in (Joyce et al., 2014b)). Given that BSH activity significantly impacts the bile acid signature it is highly likely that this microbial activity influences immune and barrier function in the gut through bile acid receptors including FXR, VDR and TGR5 (Barbachano et al., 2016; Ichikawa et al., 2012; Li and Chiang, 2014).

3.2. Microbial modification of bile acids to generate secondary and tertiary bile acids

Once BSH enzymes have liberated bile salts from the C24 taurine or glycine amide they are now accessible to microbial enzymes for further metabolism. For the most part, reactions are carried out on freed bile acids that escape ileal uptake into enterohepatic recirculation. These bile acid modifications are performed mainly by anaerobes in the lower intestine and they include re-amidation (Ridlon and Hylemon, 2012), oxidation-reduction reactions (Ridlon et al., 2006) and esterification and desulfatation reactions (Lepercq et al., 2004; Tazuke et al., 1998). Bile acid ethyl ester formation allows bile acid oligomerization. Moreover, large amounts of deoxycholic acid oligomers, formed by esterification of the C-24 carboxyl group of one molecule with the 3α-hydroxy group of the next, are detected in human feces (Bokkenheuser et al., 1977; Eriksson and Gustafsson, 1970; Graef et al., 1977; Kelsey and Sexton, 1976; Macdonald et al., 1983). Esterification of bile acids is currently associated with relatively few bacterial genera including *Lactobacillus, Eubacteria* and *Bacteriodetes* (Edenharder and Schneider, 1985) although this list is likely to expand with further functional genetic investigations.

Sulfonation of bile acids is mediated by host enzymes induced through engagement of the VDR, to target toxic bile acids and xenobiotics (Chatterjee et al., 2005). However microbial desulfation of bile acids can also occur to prevent bile acid excretion in the urine and the faeces (reviewed in (Alnouti, 2009)). This activity is associated with the bacterial genera *Peptococcus, Clostridium*, *Pseudomonas* and *Fusobacterium* and it allows certain hydrophobic BA to accumulate to potentially toxic levels in both the gut and the liver (Eyssen et al., 1985; Huijghebaert et al., 1982; Van Eldere et al., 1990).

Oxidation, epimerization and dehydroxylation of bile acids can be performed by bacterial stereospecific hydroxysteroid dehydrogenases (HSDH). These modifications produce bile acid epimers and iso bile acids at C3 and C12 respectively which are usually recycled to the liver and repaired there before entry back into bile (Hofmann, 2009). 7α-dehydroxylation or removal of an hydroxyl (OH) group at the C7 position is critical for secondary bile acid formation and leads to the generation of deoxycholic acid (DCA) from cholic acid (CA), while chenodeoxycholic acid (CDCA) is converted to lithocholic acid (LCA) (Fig. 1) (Bennett et al., 2003).

In the hepatocyte, secondary bile acids may have different fates; DCA and LCA may be conjugated to glycine or taurine and allowed to circulate with other conjugated primary bile acids, otherwise LCA can be altered by CYP3A4 to generate hyodeoxycholic acid (HDCA) (Xie et al., 2001). Alternatively LCA can induce VDR in the GI tract for phase II catabolism and sulfation directing it for excretion in faeces and urine (Runge-Morris et al., 2013). CDCA may also be converted by *Clostridium* species including *Clostridium absonum* (Ferrandi et al., 2012; Macdonald et al., 1981) and *Clostridium baratii* in a 2 step reaction (7α-hydroxyl group oxidation by a 7α-HSDH followed by reduction of the 7-keto by a 7β-HSDH) to the beneficial hydrophilic bile acid ursodeoxycholic acid (UDCA) (Hofmann and Hagey, 2008; Lepercq et al., 2004).

Interestingly, although HDCA can be synthesized in the liver from LCA, it can also be synthesized in the GI tract by an uncharacterized strictly anaerobic bacterium designated as HDCA-1. The reaction occurs only through syntrophy with *Ruminococcus productus* and can proceed from a range of bile acids as substrates, including α, β or ω muricholic acid (MCA) as well as hyocholic acid (HCA) (Eyssen et al., 1999). Proposed reactions include both 7α and 7β dehydroxylation followed by epimerization. Indeed, HDCA of either hepatic or bacterial origin may act as a substrate to generate ωMCA by further hepatic modification (Bock and Lammert, 2002).

Please cite this article in press as: Long, S.L., et al., Interactions between gut bacteria and bile in health and disease, Molecular Aspects of Medicine (2017), http://dx.doi.org/10.1016/j.mam.2017.06.002

ωMCA is also the product of microbial βMCA metabolism, again in syntrophy with other strains: *Clostridia* Type II uses βMCA with *Veillonella* species (Sacquet et al., 1979) and *Eggerthella lentum* (formerly *Eubacteria lentum*) produces ωMCA in cooperation with 2 *Fusobacteriua* spp. (Eyssen et al., 1983).

CA can also be converted to UDCA, in a 2 step process involving C7α to β epimerization and 12αHSDH oxidation. These activities are distinct to some members of the *Clostridia*, *Bacteroides,* certain *E. coli* strains and *Xanthomas* species for 7αHSDH and *Clostridia* species for 12αHSDH (Braun et al., 2011). *Acinetobacter calcoaceticus* var. *lwoffii* harbours both enzymes required to produce UDCA from CA (Giovannini et al., 2008).

Kisiela and coworkers (Kisiela et al., 2012) performed an *in silico* analysis for the presence of 3αHSDHs, 7αHSDHs and 12αHSDHs in bacteria. They examined 3 classes of 7αHSDHs that featured among both gut representatives and environmental isolates. Class I enzymes were highly represented among known environmental isolates, pathogens and some commensals particularly within the phylum Proteobacteria. The homologues of Class II 7αHSDH were mainly represented amongst the Bacteriodetes and Actinobacteria. The third class was mainly comprised of Firmicutes, specifically gut-associated *Clostridia* species including *C. scindens* where functionality has already been tested and assigned (Ridlon and Hylemon, 2012). Using *C. hylemonae* 12αHSDH as a driver sequence homologues were predominantly limited to the intestinal anaerobic Firmicutes, *Clostridium* spp. and also to *Collinsella* and *Coprococcus* spp. Archaeal 12αHSDH representation was also detected in *Methanobrevibacter*, a gut associated microbe known to also carry BSH activity (Jones et al., 2008).

3.2.1. The bai operon in Clostridium species and bile acid metabolism

Only a small number of species of intestinal anaerobic bacteria can complete bile acid 7α-dehydroxylation (Masuda et al., 1984). Mallonee et al. (1990) were first to characterize the bile acid-inducible *bai* operon (*bai*BCDEAFGHI) which facilitates 7α alterations to bile acids. A second associated operon (*bai*JKL) which catalyses 7β alterations was discovered by Ridlon and Hylemon (2012). The workings of this system have been biochemically, genetically and functionally characterised in a number of *Clostridium* species (including *C. scindens* VPI 12708, *C. hiranonis* DSM13275 and *C. hylemonae* DSM 15053) and partially characterized in *C. sordelli* VPI9048 (Coleman et al., 1987; Dawson et al., 1996; Kang et al., 2008; Mallonee et al., 1990, 1992; Mallonee and Hylemon, 1996; Ridlon et al., 2010). The pathway is critical for secondary bile acid formation and leads to DCA production from CA, while CDCA is converted to LCA. This multi-step *bai* encoded pathway involves bile acid import, modification and export from bacterial cells and it is one of the most physiologically relevant transformations of bile acids in the gut. This is due to the fact that the activity of these bacterial enzymes can significantly alter the signalling properties of the bile acid pool with consequences for interaction with cellular bile acid receptors (Li and Chiang, 2013, 2014).

Transport of free primary bile acids into the bacterial cell is the first step in the process and it is mediated by the proton-dependent bile acid transporter BaiG. It should be noted that a different transporter (unidentified) is used for export, from the cell, post-modification (Wells and Hylemon, 2000). Once inside the cell, the primary bile acid is ligated to CoA in a Mg^{2+}- and ATP-dependent reaction by CoA ligase, the product of the *baiB* gene (Ridlon and Hylemon, 2012). The ligation requires a free carboxyl group on C_{24} bile acids and it functions to both sterically hinder the constitutive 7α-hydroxysteroid dehydrogenases (7α-HSDHs), committing the bile acid to 7α-dehydroxylation and serving to retain the bile acid inside the cell (Ridlon et al., 2006). The bile acid-CoA thioester is then oxidised at the 3-hydroxy group by an NAD^+(P)-dependent 3α-hydroxysteroid dehydrogenase (3α-hydroxysteroid) by the product of *baiA* which is specific for bile acid-CoA conjugates (Ridlon et al., 2010). In fact, three *baiA* genes have been cloned from *C. scindens* with the *baiA1* and *baiA3* genes being monocistronic and the *baiA2* gene being part of the polycistronic *bai* operon. There is no clear understanding of the physiological significance of multiple *baiA* genes but they are 92% similar in identity implying potential redundancy of function (Ridlon et al., 2006).

3-dehydro-Δ^4-CDCA or 3-dehydro-Δ^4-CA and 3-dehydro-Δ^4-UDCA can then be made by the action of NAD-dependent flavoproteins, encoded by the *baiCD* or *baiH* genes, respectively (Kang et al., 2008; Ridlon et al., 2010). 7α-dehydratase (BaiE) catalyses irreversible 7α-dehydration (the rate limiting step) (Ridlon and Hylemon, 2012). A 3-oxo-$\Delta^{4,6}$ intermediate is formed from the 7α-dehydration of the 3-oxo-Δ^4-7α-hydroxy bile acid. The intermediate is then reduced in three steps to form DCA (Dawson et al., 1996).

The *baiI* gene is thought to encode a bile acid 7β-dehydratase with 40% similarity to the *baiE* gene (20% at the amino acid level) (Kang et al., 2008). Two bile acid CoA transferases are encoded near the operon and are part of a 3 gene transcription (*baiJKL*) unit in *C. scindens* and in *C. hylemonae*. BaiF shows broad bile acid substrate specificity and BaiK may encode a type III CoA transferase (Ridlon and Hylemon, 2012). The *baiL* gene is predicted to encode a short chain pyridine nucleotide-dependent alcohol/polyol oxidoreductase which belongs to the same family as the *baiA* gene (Ridlon and Hylemon, 2012).

While function is assigned to the majority of components of the *bai* operon the enzymes responsible for the final reductive processing to mature DCA have not been identified. The secondary BA exporter protein or system has also not yet been isolated. There are apparent species-specific differences in the distribution of particular *bai* genes. *C. hiranonis* carries *bai*BCDEA2FG, *bai*H, *bai*J and 7α-HSDH while *C. sordellii* VPI 9048 carries only *bai*CD, *bai*A2, *bai*H, *bai*E, and 7α-HSDH and this could potentially denote the minimal *bai* representation for secondary BA production. In high fat diet-fed animals *C. sordelli* was seen to bloom and DCA levels were elevated, correlating with increased incidence of liver disease (Yoshimoto et al., 2013).

The true distribution of *bai* genes across bacterial species in the gut remains to be elucidated and the minimum *bai* gene set required for secondary bile acid synthesis is unclear. Furthermore, the evolutionary advantage of the *bai* system is also the subject of speculation. One advantage for microbes is that the process generates reduced (NAD(P)H) which is capable of driving other anabolic reactions as well as contributing to proton motive force to drive oxidative phosphorylation to produce chemical energy.

4. Perturbation of microbial populations and effects upon bile acid metabolism

Changes to the gut microbial community which alter the copy number or expression levels of BSH or BAI enzymes will influence the detergent and signalling properties of the bile acid pool in the host. This is most clearly evidenced by the significant differences in the bile acid pool that exist when germ free or antibiotic treated animals are compared to their conventionally raised counterparts (Sayin et al., 2013; Swann et al., 2011). In healthy subjects subtle changes to the microbial community structure occur throughout the circadian cycle and are influenced by consumption of food (Leone et al., 2015; Thaiss et al., 2014). Such daily changes to the microbiota have a profound influence upon diurnal fluctuations in host transcriptional profiles and significantly impact host

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physiology (Thaiss et al., 2016). More dramatic and pervasive changes to the microbiota are likely to occur in disease states (Joyce and Gahan, 2014, 2016). For instance analysis of the microbiota by 16s rDNA or shotgun sequencing analysis has revealed that a reduction in species richness and diversity correlates with frailty in the elderly (Claesson et al., 2012), inflammatory bowel disease (Duboc et al., 2013) and risk of type two diabetes and metabolic disease (Karlsson et al., 2013; Le Chatelier et al., 2013). A selection of studies are highlighted below which examine how microbial changes affect the bile acid pool during disease.

4.1. Bile acids impact the structure of the gut microbial community

There is a dynamic interplay between host bile acids and the microbial population in the gut. Feeding of CA to rats significantly altered the microbiota at the phylum level, resulting in an increase in the Firmicutes and a concomitant reduction in the Bacteroidetes. Within the phylum Firmicutes bacteria of the classes Clostridia and Erysipelotrichia were significantly increased along with an increased conversion of CA to DCA (Islam et al., 2011). The study indicated the potential for bile acids to select for populations of bacteria in the gut with resultant impacts upon bile acid signatures (Yokota et al., 2012). Another study demonstrated a link between diet, bile acids and outgrowth of bacteria in the gut that potentially contribute to inflammatory disease. Feeding of a diet high in saturated milk-derived fats to IL-10 knock-out mice led to enhanced synthesis of taurine-conjugated bile acids which promoted the outgrowth of *Bilophila wadsworthia*, a potential pathobiont associated with immune inflammation in the gut. The effect was not seen in mice fed a diet rich in vegetable derived fats. The authors suggested that taurine metabolism contributes to the elevated availability of organic sulphur which promotes the growth of sulphite-reducing bacteria such as *B. wadsworthia* (Devkota et al., 2012).

4.2. Bile acids influence Clostridium difficile infection (CDI)

Bile acids play a significant role in the pathogenesis of *C. difficile*, a spore-forming pathogen which predominates in the gut of susceptible individuals following treatment with broad spectrum antibiotics. Pathogenesis of *C. difficile* is dependent upon gastrointestinal outgrowth of spores into vegetative cells which are capable of producing potent enterotoxins that act upon mammalian G proteins resulting in cellular damage, inflammation and diarrhea (Abt et al., 2016). Bile acid signatures in the intestine influence the process of spore germination and resultant pathogenesis as certain bile acids (notably TCA) activate germination through interaction with specific spore receptors (Francis et al., 2013). In contrast CDCA is a high-affinity competitive inhibitor of *C. difficile* germination, a finding which suggests that germination inhibitors may provide the basis for novel therapeutics against CDI (Sorg and Sonenshein, 2010).

In addition to controlling spore germination, bile acids appear to directly inhibit vegetative cells of *C. difficile*. In particular, there is significant evidence that secondary bile acids are direct inhibitors of CDI. In mice there is a clear association between the presence of *C. scindens* in the gut microbiota and resistance to CDI. *C. scindens* contributes significantly to secondary bile acid synthesis which is proposed as the mechanism by which CDI is inhibited in these animals (Buffie et al., 2015). The work suggests an approach towards improved therapeutics against CDI which incorporates rationally selected microorganisms for precision microbiome reconstitution (Buffie et al., 2015).

In addition, patients with severe CDI display low to undetectable levels of faecal secondary bile acids and reduced abundance of bacteria of the families Lachnospiraceae and Ruminococcaceae that are most likely to be responsible for the bioconversion of primary bile acids to secondary bile acids (Weingarden et al., 2014). Following faecal microbial transplantation (FMT) in these patients bacterial community structure is restored, secondary bile acid profiles are normalised and resistance to CDI increases (Weingarden et al., 2014). Bile acid profiles mimicking those found in patients pre-FMT have been shown to enhance *C. difficile* spore outgrowth and permit growth of vegetative cells. In contrast bile acid profiles from patients post-FMT inhibit outgrowth of spores and growth of vegetative cells (Weingarden et al., 2016). Interestingly the influence of bile acids on the behaviour of individual strains of *C. difficile* can vary significantly (Weingarden et al., 2016) and may be a factor dictating strain-to-strain variation in virulence potential. In support of this hypothesis, a recent study demonstrated that *C. difficile* strains with a high disease score in mice are most likely to show resistance to LCA (Lewis et al., 2016).

4.3. Bile acid metabolism, microbiota and disease

Altered bile acid metabolism occurs in parallel with a number of increasingly common gastrointestinal diseases and disorders. Aberrant bile acid profiles may reflect alterations to the gut microbial community. It is difficult to determine whether the changes in bile acid profiles are directly linked to disease pathogenesis or are a result of the effects of disease onset upon the microbiota. In irritable bowel syndrome (IBS) alterations to the gut microbiota have been noted relative to healthy controls (Dior et al., 2016; Giamarellos-Bourboulis et al., 2015). Patients with diarrhea-predominant IBS (IBS-D) have been shown to have elevated levels of primary bile acids in the faeces, suggestive of bile acid malabsorption which may contribute to the diarrhea symptoms (Dior et al., 2016; Duboc et al., 2012). Patients with constipation-predominant IBS also had altered bile acid profiles with a correlation between bile acid profiles and abdominal pain score (Dior et al., 2016).

Patients with inflammatory bowel disease (IBD) have an altered gut microbiota which exhibits relatively reduced overall diversity, reduced levels of bacteria in the phylum Firmicutes and a reduction in levels of the anti-inflammatory bacterium *Faecalibacterium prausnitzii* (Duboc et al., 2013; Matsuoka and Kanai, 2015). Bile acid profiles in patients with IBD were determined to differ from healthy controls with changes most evident during active disease (flare) (Duboc et al., 2013).

Surgical resection of the gut also alters gut microbiota and host bile acid profiles. Bariatric surgery to bypass or remove the stomach results in alterations to host bile acid profiles and to the gut microbiota. Surgery in patients or in animal models results in increased bile acid levels and weight loss is associated with the FXR (Ryan et al., 2014; Sweeney and Morton, 2014). It is interesting to note that transplant of the microbiota from surgically resectioned (gastric bypass) mice to recipient animals results in weight loss in the recipient (Liou et al., 2013). This suggests that the phenotype of weight loss is closely associated with the microbiota.

Similarly, recent studies have indicated disruption of the gut-liver bile axis in short bowel syndrome (SBS), a syndrome that arises through congenital disease or resection of the small intestine giving rise to nutritional malabsorption, diarrhea or steatorrhea. A recent study utilising a piglet model of SBS demonstrated alteration of the gut microbiota in animals with short bowel resection with attendant alterations to bile acid profiles (Pereira-Fantini et al., 2014, 2016). The study suggested aberrant FXR signalling following resection and elevated bile acid synthesis associated with SBS in the porcine model (Pereira-Fantini et al., 2014).

Altered bile acid metabolism has also been associated with a

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number of diseases that manifest outside of the GI tract. As bile acids are efficiently reabsorbed in the distal small intestine, altered bile acid metabolism and gut microbiota has the potential to influence the gut-liver axis as well as other body systems (Swann et al., 2011). For instance, a recent study examined bile acid profiles and microbiota community structure in a mouse model of primary sclerosing cholangitis (PSC) and demonstrated that the disease severity was exacerbated in germ free mice (Tabibian et al., 2016). Cholangiocyte senescence (a hallmark of the disease) could be reduced in vitro by administration of the bile acid UDCA. The work suggests a role for the microbiota and bile acids in protecting against biliary injury in PSC (Tabibian et al., 2016).

A number of studies have suggested links between the gut microbiota, bile acids and risk of cardiovascular disease (Jones et al., 2013; Joyce and Gahan, 2016). Notably studies have demonstrated that a microbial metabolite (trimethylamine-*N*-oxide (TMAO)) derived from a meat-based diet rich in carnitine is associated with elevated cardiovascular disease risk (Koeth et al., 2013). Feeding mice TMAO decreases primary bile acid synthesis (through down-regulation of Cyp7A1) and ultimately reduces expression of a cholesterol homeostatic mechanism (reverse cholesterol transport), resulting in elevated disease risk (Koeth et al., 2013).

Finally, an intriguing recent study examines links between the microbiota in early life and asthma risk and implicates bile acids as potential markers of disease risk. The longitudinal study found that infants predisposed to developing asthma later in life have low levels of specific gut bacteria with concomitant alterations to urinary bile acids (Arrieta et al., 2015). The work identifies a number of biomarkers of asthma risk and suggests preventative regimens that could be put in place to ensure a reduction in disease risk in susceptible infants (Arrieta et al., 2015).

5. Conclusions

Whilst bile acids are synthesized within the host liver, the significant diversity of the bile acid pool is ultimately generated by the gut microbiota through microbial conversions of primary bile acids to unconjugated and secondary bile acids. This is an aspect of bile acid metabolism that is missing in germ free animals and is a good example of the interplay between gut microbes and the host that is essential for homeostasis (Joyce et al., 2014a; Sayin et al., 2013; Swann et al., 2011). Given the potential for secondary bile acids to act as strong ligands for bile acid receptors in the host, the final conversion of primary bile acids to secondary bile acids by anaerobic bacteria is likely to be important for bile acid signalling in both health and disease. As the ability to convert primary bile acids to secondary bile acids is present in only a limited number of bacterial species any perturbation in these species is likely to have physiological consequences for the host. The clearest example of this seen in *C. difficile* infection where susceptibility correlates with low levels of secondary bile acids and the species that produce them (Buffie et al., 2015; Weingarden et al., 2014). In contrast, high levels of specific secondary bile acids have been associated with increased cancer risk with a link to both diet and microbiota (O'Keefe et al., 2015; Yoshimoto et al., 2013). Understanding the fine balance that exists between homeostasis and disease with respect to secondary bile acid levels will be a challenge for future research.

Furthermore, there is strong host-driven selection for bacteria expressing BSH enzymes that carry out the essential bile acid deconjugation reaction, and this trait is found across numerous bacterial phyla in the gut (Jones et al., 2008). Undoubtedly BSH activity plays a role in regulation of homeostasis in the host and the activity is likely to play a key role in gut barrier and immune function as well as the regulation of host lipid and cholesterol metabolism (Joyce et al., 2014a). The activity may also provide an input into the peripheral circadian clock (Govindarajan et al., 2016), an aspect that may ultimately be linked to food intake. However significant future work is required to understand the subtle interplay between microbe-generated bile acid signatures and host bile acid receptors that may ultimately act as molecular switches to drive health or disease in the host.

Acknowledgements

The authors acknowledge the funding of the APC Microbiome Institute by the Science Foundation of Ireland Centres for Science, Engineering and Technology (CSET) programme (Grant Number SFI/12/RC/2273). The authors declare no conflict of interest.

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Please cite this article in press as: Long, S.L., et al., Interactions between gut bacteria and bile in health and disease, Molecular Aspects of Medicine (2017), http://dx.doi.org/10.1016/j.mam.2017.06.002

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Please cite this article in press as: Long, S.L., et al., Interactions between gut bacteria and bile in health and disease, Molecular Aspects of Medicine (2017), http://dx.doi.org/10.1016/j.mam.2017.06.002

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Please cite this article in press as: Long, S.L., et al., Interactions between gut bacteria and bile in health and disease, Molecular Aspects of Medicine (2017), http://dx.doi.org/10.1016/j.mam.2017.06.002