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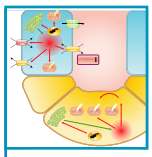
GUTS AND GALL: BILE ACIDS IN REGULATION OF INTESTINAL EPITHELIAL FUNCTION IN HEALTH AND DISEASE

Peter Hegyi, Jozsef Maléth, Julian R. Walters, Alan F. Hofmann, and Stephen J. Keely

Momentum Translational Gastroenterology Research Group, Hungarian Academy of Sciences–University of Szeged, Szeged, Hungary; Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; Momentum Epithelial Cell Signalling and Secretion Research Group and First Department of Medicine, University of Szeged, Szeged, Hungary; Division of Digestive Diseases, Department of Gastroenterology, Hammersmith Hospital, Imperial College London, London, United Kingdom; Division of Gastroenterology, Department of Medicine, University of California, San Diego, La Jolla, California; and Department of Molecular Medicine, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland



Hegyi P, Maléth J, Walters JR, Hofmann AF, Keely SJ. Guts and Gall: Bile Acids in Regulation of Intestinal Epithelial Function in Health and Disease. *Physiol Rev* 98: 1983–2023, 2018. Published August 1, 2018; doi:10.1152/physrev.00054.2017.—Epithelial cells line the entire surface of the gastrointestinal tract and its accessory organs where they primarily function in transporting digestive enzymes, nutrients, electrolytes, and fluid to and from the luminal contents. At the same time, epithelial cells are responsible for forming a physical and biochemical barrier that prevents the entry into the body of harmful agents, such as bacteria and their toxins. Dysregulation of epithelial transport and barrier function is associated with the pathogenesis of a number of conditions throughout the intestine, such as inflammatory bowel disease, chronic diarrhea, pancreatitis, reflux esophagitis, and cancer. Driven by discovery of specific receptors on intestinal epithelial cells, new insights into mechanisms that control their synthesis and enterohepatic circulation, and a growing appreciation of their roles as bioactive bacterial metabolites, bile acids are currently receiving a great deal of interest as critical regulators of epithelial function in health and disease. This review aims to summarize recent advances in this field and to highlight how bile acids are now emerging as exciting new targets for disease intervention.

I.	INTRODUCTION	1983
II.	BILE ACID PHYSIOLOGY	1984
III.	EPITHELIAL CELL PHYSIOLOGY	1986
IV.	BILE ACIDS AND EPITHELIAL SIGNALING	1989
V.	BILE ACIDS AND EPITHELIAL FUNCTION	1992
VI.	PATHOLOGICAL EFFECTS OF BILE ACIDS	1999
VII.	THERAPEUTIC TARGETING OF …	2005
VIII.	CONCLUSIONS	2008

I. INTRODUCTION

Bile acids, classically known for their roles in facilitating the digestion and absorption of dietary lipids, are now also appreciated as a family of enteroendocrine hormones that have important roles in regulating many aspects of mammalian physiology, both within and outside the intestinal tract. Driven largely by the discovery of two new bile acid receptors at the turn of the millennium, the past two decades have seen a renaissance in research activity that has firmly placed bile acids as being central to maintenance of our overall health. Disruptions to the processes that control the synthesis, recycling, and excretion of bile acids are associated with the onset of many diseases that can affect the intestine, its accessory organs, and beyond. Significant progress has been made in understanding various molecular mechanisms involved, and there is a rapidly growing interest in developing our capacity to target such pathways for disease treatment. Such an idea can hardly be considered as being new, given that as long as 2500 yr ago, bile was considered as comprising two of the four "humors" (black bile and yellow bile) upon which Hippocrates established his long-held system of human medicine (510), while animal gall has been used for centuries in Traditional Eastern Medicine to treat many different ailments (483). However, along with the discovery of new receptors for bile acids, recent years have also seen a growing appreciation of how important these molecules are to human physiology in health and disease. This appreciation has sparked renewed interest in the potential use of bile acids as therapeutic agents.

Central to developing our understanding of how bile acids can be therapeutically exploited is an understanding of how they interact with epithelial cells throughout the intestinal tract. These cells line the entire gut and its accessory organs

and, as the interface between the body and the luminal contents, they are primary effectors of bile acid-induced responses, whether they be intestinal, hepatic, or metabolic. While other reviews have covered recent developments with respect to bile acids in regulation of hepatic and metabolic function (97, 111, 151, 252, 370, 463), the current manuscript aims to provide an overview of how luminal bile acids interact with gastrointestinal epithelial cells, the implications of such interactions for our physiology, and how we can ultimately target these fascinating molecules for the treatment of disease.

II. BILE ACID PHYSIOLOGY

A. Bile Acid Synthesis and Metabolism

Since this review is primarily concerned with the physiological effects of bile acids on extrahepatic epithelia, we aim to include only a broad overview of the processes involved in their biosynthesis and metabolism. For more detail, readers are directed to excellent reviews previously published on this topic (328, 390). Essentially, epithelial cells along the intestinal tract can come into contact with either primary and/or secondary bile acids, which are either in their conjugated or unconjugated forms. Primary bile acids are synthesized from cholesterol by hepatocytes in the liver through complex enzymatic pathways, with the rate-limiting step being the enzyme CYP7A1. In humans, the primary bile acids are cholic acid (CA) and chenodeoxycholic acid (CDCA). However, it should be noted that other primary bile acids are synthesized in different species, such as muricholic acid in mice and hyocholic acid in pigs (168), and that these bile acids can have dramatically different bioactivities from those of CDCA and CA. Thus it is important to keep this in mind when translating experimental data from animal models into humans.

After their biosynthesis, primary bile acids are conjugated to either taurine or glycine. In most vertebrates, conjugation is with taurine, but in humans, glycine conjugation predominates. Glutathione conjugates have also been identified in bile, but only in trace amounts (303). Conjugation involves formation of a bile acid coenzyme A ligase (which activates the carboxyl group) and an amino transferase, in which the CoA thioester links the carboxyl group of the bile acid to the amino moiety of taurine or glycine to form a stable amide bond. Conjugation lowers the pK_a of bile acids and therefore has important consequences for their physicochemical properties and their biochemical and physiological actions, making them fully ionized at the pH of luminal contents of the proximal small intestine (170, 385). Thus, unless a transporter is present, conjugated bile acids are impermeable to epithelial cell membranes, permitting high luminal concentrations to be achieved in the biliary tract and proximal small intestine, thereby enabling micellar solubilization of dietary lipids to occur (409).

Within the intestinal lumen, particularly in the colon, primary bile acids are extensively metabolized by the resident microbiota into secondary bile acids, first by hydrolysis of their amide bond and subsequently by modifications to the hydroxy groups on their steroid nucleus (383). Deconjugation is the gateway reaction to further bile acid metabolism and is carried out by bile salt hydrolases (BSH), enzymes that are widely expressed by gram positive, and some gram negative, bacteria within the gut lumen. Several isoforms of BSH exist which differ in their substrate specificities but which tend to have a higher affinity for glycine-conjugated bile acids (58, 200, 265). Resistance to bile acid toxicity is an important characteristic enabling bacterial survival within the gut lumen, and different species have different sensitivities to conjugated and deconjugated bile acids. Therefore, the pattern of expression of BSHs plays a vital role in shaping the makeup of the luminal microbiota, while at the same regulating the capacity of bile acids to penetrate epithelial membranes, activate their receptors, and induce biological responses.

Upon deconjugation, the hydroxyl groups at positions 3, 7, and 12 of the steroid nucleus can then be subjected to metabolism by a number of bacterial enzymes, including dehydroxylases, dehydrogenases, and epimerases. For example, CA is dehydroxylated at position 7, to yield DCA, a dihydroxy bile acid, whereas 7-dehydroxylation of CDCA yields LCA, a monohydroxy bile acid. DCA and LCA are normally the two most common of the colonic bile acids in humans (152). The 7-hydroxy group of CDCA can also by epimerized (7α-hydroxy to 7β-hydroxy) to yield UDCA, which compared with other dihydroxy bile acids is relatively hydrophilic and has very distinct biological properties. However, UDCA is normally present at relatively low levels since epimerization at C-7 is mediated by only a few bacterial species and it is also rapidly metabolized by bacterial hydroxysteroid dehydrogenases to LCA, a reversible reaction with 7-keto-LCA being an important intermediate. Bile acids can also undergo epimerization at the C-3 hydroxyl group during transit through the intestine, with such 3β-hydroxy bile acids being termed "iso" bile acids; isoCDCA, isoDCA, and isoLCA are present in the colon but upon reabsorption and recirculation to the liver, they undergo re-epimerization to their 3α-hydroxy counterparts (169). The bacterial enzymes mediating alterations to bile acid hydroxyl groups are less widely expressed than BSHs, but their actions are also critically important in determining their membrane permeability, cytotoxicity, and receptor selectivity. Readers wishing to learn more detail of bile acid metabolism and nomenclature are directed to previously published reviews (172, 383).

B. Enterohepatic Cycling of Bile Acids

The enterohepatic circulation (EHC) of bile acids is an extremely complex and elegant process that includes their

synthesis in the liver, storage in the gallbladder, transit through the intestinal tract, bacterial metabolism, reabsorption from the small intestine and colon, transport via the portal circulation to the liver, and reuptake into hepatocytes **(FIGURE 1)**. In the liver, recirculated bile acids can be further metabolized by hepatic enzymes and reconjugated to glycine and taurine after which they are then secreted into the bile and recirculated to the gallbladder for storage. Efficient enterohepatic cycling ensures that a relatively constant-sized pool of bile acids is available to facilitate lipid digestion and absorption, rather than de novo synthesis being required each time food is ingested. The amount of bile acids in the EHC can be calculated by isotope dilution (261) and in humans is in the range of 2,000–3,000 mg, which is approximately six times the daily synthesis rate (300–500 mg/day). Normally, the size of the circulating bile acid pool is kept relatively constant with fecal loss being balanced by hepatic synthesis.

After bile acids enter the small intestine, they perform their classical functions in aiding the digestion and absorption of fats. Absorption of bile acids themselves from the intestinal lumen occurs by several mechanisms. Glycine-conjugated dihydroxy bile acids (glyco-DCA and glyco-CDCA) are relatively hydrophobic and can undergo passive absorption from the duodenum when luminal contents are transiently acidic. These glycine-dihydroxy bile acids can also be absorbed from the jejunum via organic anion transporting polypeptide (OATP) transporters (144). Postprandial levels of CDCA conjugates increase ahead of cholyl conjugates, indicating the CDCA conjugates are more efficiently absorbed in the proximal small intestine (398).

Although reabsorption in the proximal small intestine contributes to the EHC of bile acids, the most important reabsorptive process occurs in the terminal ileum, where epithelial cells express the apical sodium-dependent bile acid transporter, ASBT (also known as the ileal bile acid transporter, IBAT). In contrast to other transporters involved in the EHC (e.g., OSTα/OSTβ, NTCP, BSEP) which can transport non-bile acid molecules, ASBT transports only bile acids and has a greater affinity for those that are conjugated over those that are not. Thus it is ASBT which confers the specificity of the EHC for bile acids (89, 91).

Following uptake by ASBT, bile acids traverse the cytoplasm of the epithelial cells bound to ileal bile acid binding protein (IBABP) and exit the basolateral domains of the enterocyte via the heterodimeric protein, OSTα/OSTβ, a facilitated diffusion transporter that is present throughout the small intestine (89, 90). Once in the interstitium, it is unclear how conjugated bile acids enter villus capillaries to gain access to the portal circulation. However, as capillary endothelial cells are fenestrated, similar to hepatic endothelial cells, entry of bile acids into the capillary plexus likely occurs by a passive process. Once in the portal venous blood, bile acids are transported bound to albumin, with dihydroxy conjugates binding more tightly (>90%) than conjugates of cholic acid (60–80%) (337).

Upon deconjugation in the terminal ileum and colon, bile acids become more hydrophobic and are primarily reabsorbed by passive diffusion across the epithelium. Absorption of DCA is 20–50% of that formed (462), while that of lithocholic acid is less, presumably because its hydrophobicity promotes binding to unabsorbed dietary constituents

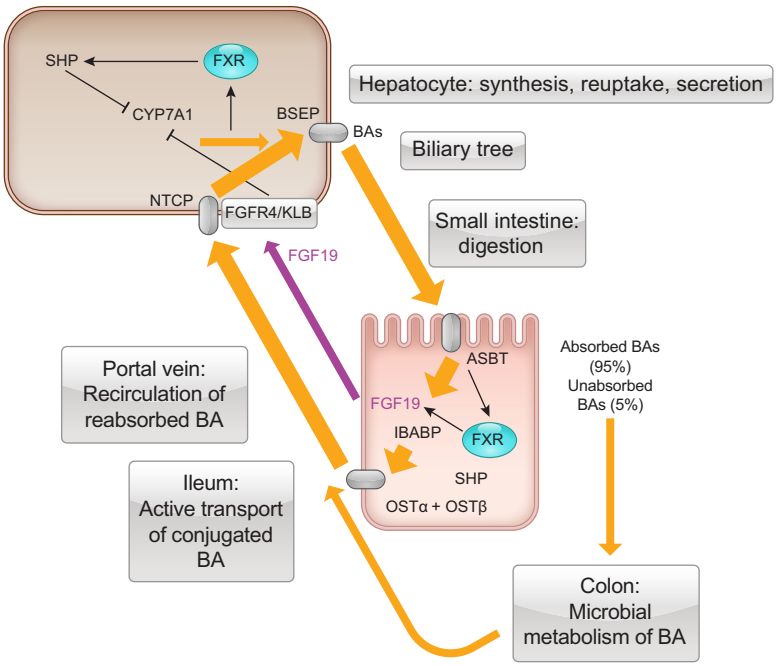


FIGURE 1. Enterohepatic circulation of bile acids. Bile acids (BAs) are synthesized in the liver with the enzyme, CYP7A1, being the initial step. They are transported from the liver by the bile salt export pump (BSEP) and travel via the biliary tree to the gallbladder for storage. Upon ingestion of a meal, bile acids are ejected into the small intestine, where they facilitate lipid digestion and absorption. In the ileum, active reuptake of conjugated bile acids occurs via the apical bile salt transporter (ASBT), expressed in the brush border of terminal ileal epithelial cells. In the cytoplasm, bile acids bind to ileal bile acid binding protein (IBABP) and are transported from the ileal enterocyte via the basolateral heterodimeric protein OST α/β. Bile acids enter the portal venous circulation and return to the liver, where reuptake takes place via the Na^+-taurocholate polypeptide (NTCP). In both enterocytes and hepatocytes, BAs bind to FXR in the nucleus, stimulating transcription of proteins including SHP and FGF19. Approximately 5% of ileal BAs are not absorbed and enter the colon where they are metabolized into secondary bile acids by the microbiota, with some being reabsorbed and recycled.

(79). When these unconjugated bile acids return to the liver, they are reconjugated with glycine or taurine and secreted into canalicular bile. In some species, deoxycholic acid undergoes 7-hydroxylation to form cholic acid which is then conjugated with taurine or glycine. Additionally, in humans but not in rodents, a major fraction of lithocholic acid is esterified with sulfate after reconjugation. Such sulfolithocholyl amidates are secreted into the bile but cannot be absorbed from the small intestine, with the result that LCA is rapidly eliminated from the body. Thus LCA constitutes <5% of biliary bile acids, with higher proportions being associated with hepatotoxicity, at least in animals.

Hepatic uptake of bile acids remains constant during meals, and under normal circumstances of feeding and fasting, it is likely to remain far below its V_{max}. Uptake of bile acids is greatest in the periportal hepatocytes and is more efficient for conjugated than unconjugated molecules (337). Conjugated bile acid uptake is mediated mostly by the sodium/taurocholate cotransporting polypeptide (NTCP, gene name *SLC10A1*), which has considerable homology to ASBT, and like ASBT, uses the transepithelial sodium gradient to drive uptake. After they have been taken up into the liver, bile acids are then secreted into the bile via an ATP-driven transporter, known as the bile salt export pump (BSEP). This protein is present in the canalicular membrane of hepatocytes and transports bile acids against a steep concentration gradient. The importance of NCTP and BSEP in the EHC is underscored by congenital disorders in which they are dysfunctional, with absence of NCTP causing markedly elevated plasma levels of bile acids (468), and inborn errors of BSEP being characterized by bile acid retention, hepatocyte death, and inflammation (187).

Each stage of the EHC, from hepatic synthesis, to intestinal reabsorption, and reuptake into hepatocytes, is intricately regulated by complex pathways of cellular and molecular communication along the gut-liver axis. Importantly, bile acids themselves play a major role in regulating this process, primarily through their actions on farnesoid X receptor (FXR) expressed in hepatocytes and epithelial cells lining the intestinal lumen. FXR reversibly binds bile acids, with CDCA being the most active natural agonist (273, 345). When activated by bile acids, FXR forms a dimer with the retinoic acid receptor (RXR) and binds to specific FXR-responsive elements in target genes, several of which are involved in bile acid metabolism and transport. In the liver, a major FXR target gene that regulates CYP7A1 expression is short heterodimer partner-1 (SHP). SHP itself does not bind DNA but instead inhibits the activity of liver receptor homolog 1 (LRH-1), thereby reducing CYP7A1 expression and bile acid synthesis (140).

A number of other FXR-dependent pathways are also involved in regulating bile acid synthesis and transport in the liver and have been reviewed elsewhere (69, 88, 229) In humans, ileal ASBT expression is downregulated by activation of FXR, whereas IBABP and the basolateral transporters, OSTα and OSTβ, are upregulated, effects that decrease the concentration of bile acids within the ileal enterocyte (125, 284, 519). However, the most prominent and best-characterized of the FXR responsive genes in the ileum is fibroblast growth factor 19 (FGF19), and its homolog FGF15 in rodents. These are proteins of ~24 kDa that are secreted from the basolateral aspect of ileal enterocytes into the portal venous blood. FGF15/19 then travels to the liver where it binds to FGF receptor 4 (FGFR4) and its co-receptor, Klotho-beta, on hepatocytes to inhibit CYP7A1 via a MAPK-dependent signaling mechanism (424). This provides an elegant system of negative-feedback regulation of bile acid synthesis, whereby bile acid reabsorption in the ileum signals through the gut-liver axis to inhibit de novo synthesis in the liver. FGF19 levels peak in blood several hours after a meal and are inversely related to those of the bile acid precursor C4 (267), the plasma levels of which increase in direct relationship to the rate of bile acid synthesis. Under pathological conditions, such as those causing bile acid diarrhea, defective production of FGF15/19 leads to a loss of this negative-feedback loop, with increased synthesis resulting in epithelial cells along the upper and lower intestinal tract being exposed to considerably higher levels of bile acids (482).

Other pathological conditions can also lead to disruptions in the EHC with the consequence that epithelial cells, both within and outside of the intestinal tract, become exposed to bile acids. For example, conditions associated with malabsorption of bile acids in the terminal ileum (e.g., Crohn's disease) cause their increased delivery into the colon. On the other hand, in gastroesophageal reflux disease (GERD), the EHC leaks upwards with the result that cells of the esophagus and airways can become exposed to bile acids. Similarly, common channel obstruction can cause bile acids to enter the pancreas where they come into contact with the epithelial cells lining the ducts and acini. Not surprisingly, such conditions can dramatically alter the physiology of these cells leading to the onset of disease.

III. EPITHELIAL CELL PHYSIOLOGY

Before we consider how they are regulated by bile acids, in this section we review the basic functions and physiological characteristics of intestinal epithelial cells. These cells, lining the surfaces of the entire intestinal tract and its accessory organs, are exposed to constantly changing luminal conditions and must have the capacity to adapt appropriately. For example, in the intestine, the epithelium must be able to evoke rapid responses upon ingestion of a meal. This is achieved through the release of hormonal messengers, secretion of digestive enzymes, and expression of transport proteins that enable the uptake of fluid and nutrients from the lumen. At the same time, the epithelia must also act as

barriers that protect against the entry of harmful substances, whether they originate endogenously (e.g., gastric acid, digestive enzymes, bile acids) or are ingested (e.g., bacteria, viruses, fungi, and their toxins). Given the widely diverse functions of different intestinal regions and the different stimuli to which they are exposed, it is not surprising that epithelial cells express regional and organ-specific characteristics. However, throughout the intestine, epithelial cells also have common characteristics that are essential to their fundamental barrier and transport functions **(FIGURE 2)**.

Epithelial cells in the intestinal tract originate from stem cells located near the base of crypts. Stem cells give rise to progenitor cells which, in turn, develop into one of the four main types of epithelial cell; enterocytes, goblet cells, and enteroendocrine cells migrate upwards from the stem cell niche, while Paneth cells migrate downwards towards the crypt base. Enterocytes are the most common of the intestinal epithelial cells and are responsible for the surface hydrolysis and uptake of nutrients, absorption and secretion of electrolytes and fluids, and the conservation of bile acids. Goblet cells secrete mucus which promotes intestinal barrier function, protecting against pathogen invasion and physical damage due to peristalsis (288). Paneth cells secrete antibacterial peptides, most notably defensins and lysozyme, which are important in intestinal defense against bacterial infection. Paneth cells are also important in maintenance of the stem cell niche (75). Enteroendocrine cells serve to "taste" the luminal contents and release hormones and neurotransmitters that enable coordination of both local and systemic responses to the presence of nutrients in the intestine (270). A subset of enteroendocrine cells, the L cells, can also sense bile acids in the gut lumen through their expression of TGR5 and FXR, with signals from these receptors regulating the expression of the incretin hormone, glucagon-like peptide-1 (GLP-1). Such actions link changes in luminal bile acids to changes in our metabolism and energy expenditure and are the basis for a great deal of ongoing research into the potential for targeting bile acids in treatment of metabolic diseases, such as diabetes and obesity. This exciting and complex area of research is beyond the scope of the current review, and we direct the reader to several recent publications for further information (47, 146, 344, 431, 450, 464).

The ability of epithelial cells to form barriers and to vectorially transport nutrients, fluid, and ions is dependent on

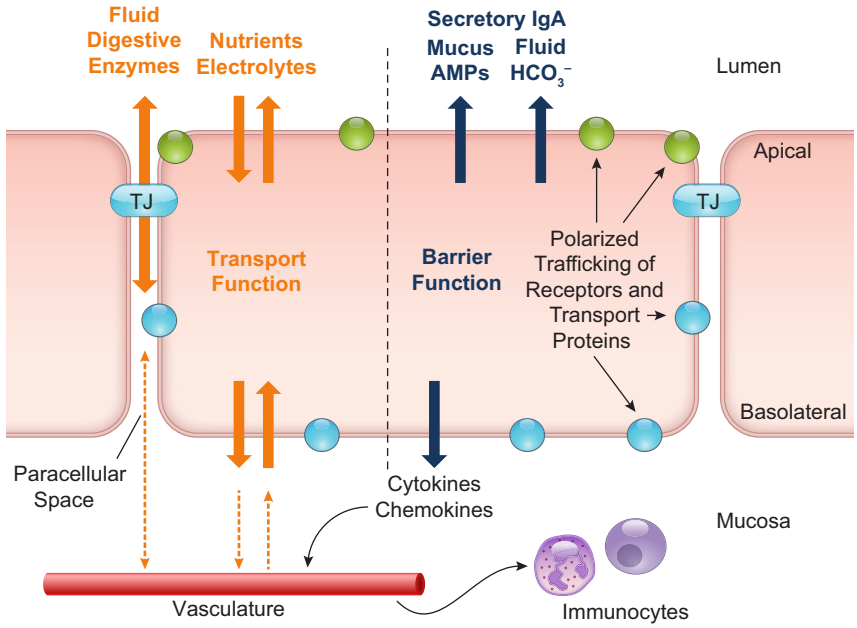


FIGURE 2. General characteristics and functions of intestinal epithelial cells. The primary functions of epithelial cells throughout the intestinal tract are to transport nutrients, electrolytes, digestive enzymes, and fluid to and from the lumen, while at the same time acting as a protective barrier to prevent the entry of harmful pathogens and toxins. Transport of substances between the luminal contents and the body is enabled by two specific epithelial properties. First, the polarized expression of transport proteins on the apical and basolateral membranes allows for the vectorial movement of solutes in the luminal or mucosal direction. Second, the capacity of epithelial cells to form ion-selective tight junctions (TJs) with one another enables them to create selectively permeable monolayers across which electrical and osmotic gradients can be established. Barrier function is comprised of the physical barrier posed by the epithelial cells themselves and their associated TJs along with a number of factors secreted across the apical membrane, including mucus, antimicrobial peptides (AMPs), acid-neutralizing HCO_3^-, and fluid. Secretion of cytokines and chemokines across the basolateral membrane into the mucosa regulates the recruitment of innate immune cells that augment the barrier properties of the epithelium.

their ability to form tight junctions and to undergo functional polarization. Functional polarity refers to the ability of epithelial cells to differentially express proteins on their apical and basolateral surfaces. Such differentially expressed proteins include the transport proteins that facilitate the vectorial movement of substances across the epithelial layer and the receptors that are involved in their regulation. Tight junctions are an essential feature in the development and maintenance of functional polarity, dividing the membrane into distinct apical and basolateral domains and providing a focal point from which membrane proteins are sorted to each domain (278, 491). At the extracellular side, tight junctions make contact with each other through homotypic binding of their structural transmembrane components, occludin, claudins, and junctional adhesion molecule. Tight junctions form paracelluar pores through which solutes and water can flow, the permeability of which is determined primarily by the particular claudins expressed within the junctions (237, 456). Tight junctions are not static but open and close in response to many endogenous and exogenous stimuli, thereby controlling the paracellular passage of fluid and solutes to and from the lumen.

A. Epithelial Fluid and Electrolyte Transport

One of the most important functions of epithelial cells is to regulate water movement across the various surfaces of the intestinal tract and its accessory organs. From beginning to end, water secretion is necessary for a number of vital processes in the intestine, including providing a liquid medium for digestion and diffusion of enzymes and nutrients, for lubricating and protecting the mucosal surface, and for diluting potentially harmful substances, for example, digestive enzymes in the pancreatic ductules. On the other hand, the ability of epithelial cells to absorb water is also critical since this is required not only to prevent dehydration but also in processes that require concentration of the luminal contents, for example, in the formation of bile. The volumes of fluid that are moved across intestinal epithelial surfaces on a daily basis are great. Each day ~9 liters of fluid enters the proximal small intestine, comprised of ~2 liters of ingested fluid and 7 liters of digestive secretions arising from the stomach, duodenum, pancreas, and liver. It is remarkable that of this fluid load, <200 ml are normally lost in the feces, illustrating the extraordinary efficiency with which the intestine handles fluid.

Fluid movement across epithelial cells occurs passively in response to the osmotic gradients established by active solute transport. In turn, solute transport is governed by the activity of various transport proteins that are arranged into pathways specific to the location and function of the particular epithelial cell. For example, the organization of transport proteins in pancreatic and biliary ductal cells, which secrete a HCO_3^--rich fluid, is quite distinct from that of the surface cells of the colon, which avidly absorb Na^+.

1. Secretory pathways

In the intestine, fluid secretion occurs predominantly from the crypts and is driven by electrogenic Cl^- secretion. The molecular process of Cl^- secretion involves the concerted activity of several basolateral transport proteins, including Na^+-K^+-ATPase pumps, the $Na^+/K^+/2Cl^-$ cotransporter NKCC1, and the K^+ channels KCNQ1 and KCNN4 (34). Together the activity of these transporters serves to elevate intracellular levels of Cl^- above its electrochemical equilibrium, creating a gradient for its exit when channels in the apical membrane open. The cystic fibrosis transmembrane conductance regulator (CFTR), a Cl^- channel that opens in response to phosphorylation by cAMP-dependent protein kinase A, is the primary exit pathway for Cl^- in intestinal epithelia. A Ca^{2+}-dependent Cl^- channel, TMEM16A, is also expressed (319), although its contribution to transepithelial water transport is not well defined.

While Cl^- secretion is the main driving force for fluid secretion in the distal intestine, HCO_3^- secretion predominates in more proximal regions, such as the duodenum. Here, HCO_3^- secretion serves to neutralize acid entering the small intestine from the stomach. HCO_3^- secretion occurs either through an electrogenic pathway which involves its exit across the apical membrane through CFTR or an electroneutral pathway involving the Cl^-/HCO_3^- exchangers DRA and PAT-1 (405).

2. Absorptive pathways

In the ileum and colon, fluid absorption normally predominates and is driven by cation absorption, most notably that of Na^+, through three main processes. In the small intestine, Na^+-nutrient cotransporters, including SGLT-1 and Pept1, are primarily responsible for fluid absorption after eating a meal (504). Electroneutral Na^+ absorption, a process mediated by coordinated activity of the sodium-hydrogen exchangers, NHE3 and NHE2, and the chloride bicarbonate exchangers, DRA and PAT1 (211), occurs throughout the small and large intestine and is responsible for fluid absorption in interdigestive periods. Electrogenic Na^+ absorption occurs in the colon through Na^+ channels known as ENaC (176). The energy for each of these processes is derived from the activity of basolateral Na^+-K^+-ATPase pumps which maintains intracellular Na^+ at low levels, thereby facilitating its influx through apically expressed SGLT1, NHE3, and ENaC.

B. Epithelial Barrier Function

While they are carrying out their roles in fluid, nutrient, and electrolyte transport, intestinal epithelia must also form a barrier to prevent mucosal damage from harmful luminal contents, such as acid, proteases, and invading pathogens. There are two main components to this physical barrier: the

epithelial cells themselves and the tight junctions which hold them together. Normally, there is a tightly regulated balance between epithelial proliferation and programmed cell death by apoptosis, ensuring the integrity of the barrier. However, should this balance become dysregulated, for example, as a consequence of increased apoptosis in the setting of inflammation, then barrier function can become compromised allowing access of the luminal contents to the mucosa. The permeability of tight junctions can also be affected in disease conditions, where alterations in the phosphorylation or expression of tight junction proteins can lead to opening of the paracellular pores.

In addition to the physical barrier posed by epithelial cells themselves, there are several other innate factors that are crucial in augmenting barrier function. These include water secretion, whether it is driven by HCO_3^- or Cl^-, mucus secretion from goblet cells, defensin secretion from Paneth cells, and secretory IgA secretion. Together these components create a protective layer overlying the epithelium which protects against erosion and prevents entry of pathogens and their toxins. Furthermore, epithelial cells also produce an array of cytokines and chemokines, conferring them with the ability to recruit immune cells, such as monocytes and neutrophils, to enhance barrier function in times of infection or inflammation.

C. Regulation of Epithelial Transport and Barrier Function

To function effectively, intestinal epithelia must be able to adapt to the constantly changing environment of the lumen. The activity and expression of proteins involved in maintenance of barrier and transport function are closely regulated by integrated signals arising from the luminal contents, the enteric nervous system, the mucosal immune system, blood-borne hormones, the resident microbiota, and the epithelium itself (34, 87, 121, 145, 219, 412, 502). In the short term, rapid changes in epithelial function occur by posttranslational modifications or altered cell surface trafficking of proteins that constitute tight junctions and transport pathways. In the longer term, transcriptional mechanisms regulate the cellular expression of these proteins. Often, changes in junctional and transport proteins occur simultaneously, enabling the coordination of epithelial permeability to fluid, nutrient, and electrolyte transport.

IV. BILE ACIDS AND EPITHELIAL SIGNALING

Whether in the small or large intestine, the gallbladder, or the liver, epithelial cells of the lower intestine and biliary tract are constantly exposed to bile acids. However, the levels and types of bile acids to which they are exposed vary considerably from tissue to tissue. Furthermore, pathological conditions, notably cholestasis or GERD, can result in epithelial cells of the pancreas, upper gastrointestinal tract, or the airways coming into contact with bile acids. With this in mind, it is perhaps not surprising that bile acids have emerged as important regulators of epithelial physiology and pathophysiology and, indeed, studies from more than 100 yr ago were already reporting how bile acids contribute to the pathogenesis of diseases, such as gastric ulcers and pancreatitis (122, 301, 335). Since then bile acids have been found to have the capacity to modulate many aspects of epithelial function and to play important roles in disease pathogenesis. With the discovery of nuclear and cell surface receptors for bile acids, the past decade has perhaps seen the greatest advances in our understanding of how bile acids exert their effects on epithelial cells, and with these advances, we have begun to truly appreciate the critical roles that they play in intestinal homeostasis.

A. Epithelial Sensing of Bile Acids

Although bile acids have been known for many decades to alter levels of intracellular second messengers and activate signaling cascades, our knowledge of how they initially interact with epithelial cells to trigger such responses has only slowly evolved. However, at the turn of the millennium, the discovery of the first "dedicated" bile acid receptors stimulated an exciting new era of research in the field. Our understanding of how these molecules exert their physiological and pathological effects has since been rapidly growing.

1. TGR5: the cell surface bile acid receptor

TGR5, a member of the G protein-coupled receptor (GPCR) superfamily, was discovered as a plasma membrane receptor for bile acids in 2002 (213, 282). The coding sequence of the TGR5 gene contains 993 base pairs, encoding 330 amino acids with the 7 putative transmembrane domains characteristic of GPCRs (213). In humans, the TGR5 gene is located on chromosome 2q35, and mapping of TGR5 mRNA expression shows that it is widely distributed, being present in the immune system, adipocytes, muscle, and endocrine organs (213). TGR5 is expressed on enteric nerves, innate immune cells, and epithelial cells throughout the intestinal and biliary tracts (47, 173, 220, 221, 234, 488). TGR5 is characterized as a G_sPCR, and its activation stimulates increases in levels of intracellular cAMP and activation of protein kinase A, leading to phosphorylation of target proteins. Activated effector proteins can then alter cellular function either in the short term, or more chronically, through regulating the activity of transcription factors, such as cAMP response element binding protein (CREBP) or C/EBPβ (213, 322, 363). TGR5 was first recognized for its roles in energy homeostasis, through its actions on energy expenditure in brown adipose tissue and its enhancement of insulin sensitivity, thereby improv-

ing glucose metabolism (212, 490). Based on such actions, TGR5 is currently receiving a great deal of research interest as a new target to treat liver, cardiovascular, and metabolic diseases (108, 238, 364, 370, 397). However, given its widespread expression throughout the body, consequences of TGR5 activation are now known to be much broader (50). In particular, TGR5 receptors on enteric neurons are now known to be important in regulation of intestinal motility (8), while receptors expressed on innate immune cells appear to dampen inflammatory responses (181, 291). The most powerful known endogenous agonists of TGR5 are bile acids with the rank order of potency of lithocholic acid $\geq$ deoxycholic acid $>$ chenodeoxycholic acid $>$ cholic acid (213). Taurine-conjugated bile acids are more potent than unconjugated bile acids, which, in turn are more potent than glycine-conjugated bile acids. Semi-synthetic agonists of TGR5 have also been developed, the most potent of which, to date, is 6α-ethyl-23(S)-methyl cholic acid (S-EMCA; INT-777), synthesized by Pellicciari et al. (354). Another modified bile acid derivative, INT-767, a C_{24} bile alcohol sulfate, activates both TGR5 and FXR (384).

2. Nuclear bile acid receptors

Although first discovered as an "orphan" receptor that is weakly responsive to farnesoids (124), FXR was subsequently identified as a primary nuclear receptor for bile acids in 1999 (273, 484). FXR is one of the 48 members of the nuclear receptor superfamily and contains a DNA binding domain (DBD), a ligand binding domain (LBD), and additional activation domains. In its ligand-free state, FXR exists as a heterodimer with RXR and is bound to specific FXR response elements (FXREs) on target genes (206). Upon ligand binding, FXR undergoes a conformational change which induces the release of co-repressor proteins and the recruitment of co-activators, such as SRC-1, PGC1α, and PRMT-1 (224). Although two genes encoding FXR, FXRα and FXRβ, exist, FXRβ is not functional in humans, while FXRα exists as four isoforms (FXRα1–4) that can differentially drive the activation of FXREs on different genes (175, 521). FXR is expressed in tissues and organs throughout the body but is at particularly high levels in tissues involved in regulating bile acid homeostasis, such as the liver, intestine, and kidneys (41, 124, 175, 273, 360). FXR is also expressed on epithelial cells of the small intestine, stomach, colon, esophagus, biliary tree, and pancreas (92, 162, 201, 234, 257). It is also found on enteroendocrine L cells (449). FXR was first recognized as being a critical contributor to intestinal/hepatic crosstalk in regulation of bile acid biosynthesis and transport (266, 273) but, similar to TGR5, was soon found to be also important in controlling metabolic homeostasis (55, 210, 419). Currently, FXR is receiving a great deal of interest for its potential in treating liver diseases, such as non-alcoholic steatohepatitis (NASH) and primary biliary cirrhosis (PBC), and metabolic disorders, particularly diabetes and obesity. These important applications of FXR agonists have been reviewed extensively elsewhere (3, 257, 326, 370). The structure-activity relationship for bile acids in activating FXR differs considerably from that of TGR5 with a rank order of potency of: CDCA $>$ DCA $>$ LCA $>$ CA (484). Several specific steroidal and nonsteroidal FXR agonists have been developed, including GW4064, obeticholic acid (OCA), fexaramine, and GSK2324 (408). These agonists have proved to be important tools for developing our understanding of the roles of FXR in health and disease. To date, the most clinically advanced of these agonists is OCA, which is the first specific FXR agonist to receive Food and Drug Administration (FDA) approval for use in humans (166).

In addition to FXR, there are other nuclear receptors that can be activated by bile acids. For example, the pregnane X receptor (PXR) is highly expressed in the liver and intestine and is best known for its roles in detoxification of drugs and xenobiotics (57). However, PXR is a very promiscuous receptor and can also be activated by numerous endogenous substances, including bile acids. It was first identified as a receptor for LCA in 2001, with its activation (in mice) inducing the expression of proteins required for its detoxification (by additional hydroxylation or sulfation), transport, and excretion of this toxic bile acid from the body (432). While PXR is activated by LCA, its oxidized metabolite, 3-keto-cholanoic acid, and also by UDCA, it is only weakly responsive to CDCA, DCA, CA, and conjugated bile acids, making its sensitivity to bile acids quite distinct from that of FXR (401). Recent years have seen considerable advances in our understanding of the physiology and pathophysiology of PXR, and it is now known that in addition to its detoxifying roles it also exerts potent cytoprotective and anti-inflammatory effects on intestinal epithelial cells (65, 296, 445, 524).

The vitamin D receptor (VDR) is another nuclear receptor that is widely expressed throughout the body in tissues such as bone, kidney, intestine, and innate immune cells. VDR controls numerous physiological processes, including bone and calcium metabolism, inflammatory responses, and cell growth, survival, and differentiation (71, 258, 391). While the classical endogenous ligand of VDR is 1,25-dihydroxyvitamin D_3, studies have shown that it can also be activated by LCA and that, similar to PXR, it regulates genes involved in metabolism and transport of that bile acid (272). Furthermore, VDR activation stimulates ileal epithelial secretion of FGF15, leading to subsequent repression of hepatic CYP7A1. This suggests that the VDR plays a complementary role to the FXR in regulating the synthesis and EHC of bile acids (153). Meanwhile, other studies have shown that, similar to PXR and FXR, activation of VDR exerts cytoprotective and anti-inflammatory actions in the intestine (51, 258).

Finally, the glucocorticoid receptor (GR) is another nuclear receptor that has the capacity to mediate responses to bile acids, particularly UDCA. In several experimental systems, UDCA has been shown to induce nuclear translocation of the GR and activation of GR-dependent genes that modulate immune responses (441, 443, 496). Interestingly, the effects of UDCA appear to be mediated through its binding to a region of the GR LBD that is distinct to that bound by the classical GR agonist dexamethasone, in turn leading to the regulation of a distinct subset of GR-dependent genes (304).

3. Receptor crosstalk

In addition to directly binding to and activating their cognate receptors, bile acids can also induce cellular responses by recruiting "non-bile acid" receptors. For example, recent studies have shown that TGR5 can transactivate the epidermal growth factor receptor (EGFr), thereby enabling the recruitment of tyrosine kinase-dependent signaling pathways to regulate cell growth (190, 380, 511). Studies by Cheng and Raufman (66) have demonstrated that taurine and glycine conjugates of LCA and DCA can also induce EGFr transactivation, but in this case, through their actions as partial agonists of the muscarinic M_3 receptor. Further studies suggest that such bile acid-induced GPCR/EGFr crosstalk is mediated by metalloprotease-induced shedding of EGFr ligands from the cell membrane (14, 67, 297, 317, 497) and inhibition of EGFr degradation (56). However, although it is clear that EGFr activation plays an important role in mediating epithelial responses to GPCRs activated by bile acids, such responses are also likely to be tempered by their activation of FXR, which has been shown to inhibit EGFr-dependent signaling in intestinal epithelial cells (105, 357). Studies from mammary epithelial cells indicate that FXR activation may also inhibit EGFr-dependent signaling by downregulating expression of other members of the ErbB receptor family with which it heterodimerizes (135). Interestingly, GR and VDR activation have also both been shown to be coupled to inhibition of EGFr signaling and expression, suggesting that bile acids may also have the capacity to influence growth factor-dependent signaling through these pathways (290, 382). Understanding how such complex mechanisms of crosstalk between bile acid and growth factor receptors ultimately impact intestinal epithelial physiology should be an important area of research focus in the coming years.

4. Membrane perturbations

Finally, in addition to activating specific cell surface GPCRs and intracellular nuclear receptors, bile acids can also initiate signaling in epithelial cells by causing perturbations in the plasma membrane. Studies have shown that treatment of colonic epithelial cells with hydrophobic bile acids cause a redistribution of membrane cholesterol and phospholipids, leading to alterations in caveolin expression and membrane fluidity within distinct microdomains (189). Interestingly, such effects also bring about transactivation of the EGFr but, in contrast to TGR5- and M_3R-mediated responses, they appear to do so independently of EGFr ligand shedding (5, 189). While further investigation is required, it is tempting to speculate that such distinct mechanisms of EGFr transactivation would lead to different patterns of receptor phosphorylation, differential recruitment of downstream effector pathways, and ultimately, different cellular responses to different bile acids.

B. Intracellular Signaling by Bile Acids

Bile acids can alter epithelial function both in the short and long term. Rapid responses to bile acids involve changes in the levels of intracellular second messengers, such as Ca^{2+}, cAMP, and reactive oxygen species subsequent to activation of cell surface receptors or induction of membrane perturbations. These second messengers can then alter cell physiology either through direct interactions with effector proteins or indirectly through the activation of signaling cascades that alter the phosphorylation and activity of downstream effectors. Kinase cascades commonly reported to be involved in mediating the actions of bile acids include protein kinase C (PKC), protein kinase A (PKA), ERK, JNK and p38 mitogen-activated protein kinases (MAPKs), to name but a few (19, 139, 250, 305, 394, 438). The lipid kinase phosphatidylinositol 3-kinase (PI3K) has also been shown to be an important mediator of bile acid actions in many different systems (19, 425). Another type of post-translational modification that can rapidly alter cell function in response to bile acids is ubiquitination, leading to proteosomal degradation of effector proteins (13, 306). Degradation of proteins can also occur by the process of autophagy, and recent studies suggest that bile acids are also important regulators of this process in hepatocytes, enterocytes, and pancreatic epithelial cells (45, 275, 351, 508). Rapid alterations in the trafficking of proteins to and from the cell surface can also occur in response to bile acids through regulating their internalization by endocytosis (202, 400). More long-term changes in epithelial phenotype can be brought about through altering the expression of proteins that contribute to barrier and transport function. Such changes can occur in response to the activation of transcription factors (e.g., NFκB, AP-1, CREB) downstream of intracellular second messengers, or by activation of nuclear receptors (e.g., FXR, PXR, VDR). Bile acids can also alter the expression of effector proteins through regulating miRNA production (64, 120, 507), or by epigenetic mechanisms, involving DNA methylation or histone deacetylation (228, 262). A summary of bile acid-induced epithelial signaling mechanisms is shown in **FIGURE 3**.

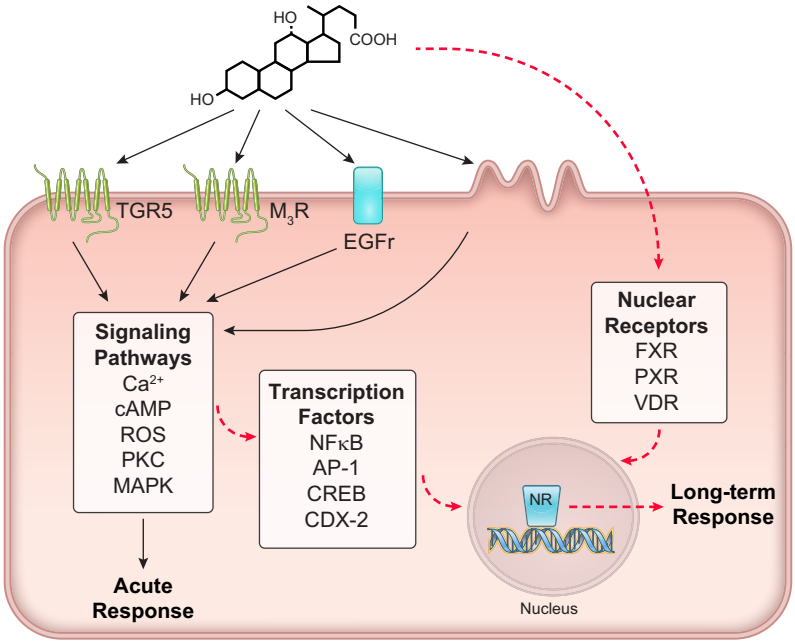


FIGURE 3. Intracellular signaling in response to bile acids. Bile acids induce acute responses (solid black arrows) in epithelial cells through the activation of multiple receptor types on the cell surface or through induction of membrane perturbations. This leads to the generation of numerous intracellular second messengers and the activation of signaling cascades. Such signaling pathways can also lead to more long-term changes in cellular function through the activation of transcription factors and regulation of gene transcription (dashed red arrows). Changes in gene transcription and protein expression can also be brought about by the activation of several nuclear receptors, including farnesoid X receptor (FXR), pregnane X receptor (PXR), and vitamin D receptor (VDR).

C. Bile Acids and the Microbiota

One of the primary determinants of the bioactivity and bioavailability of bile acids in the intestine is their metabolism by resident microbes The colon is home to a population of trillions of bacteria, comprised of hundreds of different species, many of which have the capacity to metabolize bile acids. Normally, through deconjugation and dehydroxylation, the colonic microbiome converts conjugated bile acids, which have failed to be absorbed via the ASBT in the small intestine, into more hydrophobic molecules. Since there are no reports of ASBT being expressed on the apical membrane of colonic epithelial cells, increased hydrophobicity and decreased ionization enables bile acid reabsorption by passive diffusion across the cell membrane.

The most rate-limiting step in bacterial metabolism of bile acids is deconjugation of glycine or taurine by the action of bile salt hydrolases (BSH). This reaction dramatically changes the physicochemical properties of the bile acids, making them more lipophilic and partially protonated and thereby enabling further metabolism by dehydroxylases and epimerases (200, 256). The past two decades have seen enormous advances in our understanding of how the microbiome influences human health, not only in the intestine (348), but also through its roles in regulating energy expenditure, metabolism, and cardiovascular function (46, 154, 503). By way of the gut-brain axis, the microbiome is now becoming recognized as an important regulator of higher central functions, including emotional state and appetite (6, 82, 117). It even regulates our circadian rhythms (199, 447).

The microbiome is highly dynamic and its composition depends on many factors, including diet, environment, age, fitness level, and psychological state, to name but a few (73, 264, 269, 333). It is also clear that dramatic changes in the microbiome can occur in many disease states, and being at the dividing line between the human and microbial worlds, the epithelium has a critical role to play in mediating the effects of such changes. Understanding how bacteria and epithelial cells communicate with one another under normal and disease states is a critically important area of research that is advancing rapidly. Bile acids clearly have an important role to play in this communication network, since changes in the microbiome lead to changes in bile acid metabolism and, consequently, changes in the hydrophobicity/hydrophilicity ratio of the colonic bile acid pool (107, 205). Thus the precise levels of different bile acids in the colon, i.e., the "colonic bile acid signature" is determined by the makeup of the microbiota. In turn, each individual's bile acid signature determines what contributions TGR5, FXR, VDR, PXR, M3R, GR, EGFr, and membrane disruptions make in setting the overall tone of epithelial function at any given time. A summary of how microbiota/bile acid interactions impact on intestinal physiology in health and disease is shown in **FIGURE 4**.

V. BILE ACIDS AND EPITHELIAL FUNCTION

As discussed above, the two primary functions of intestinal epithelial cells are to transport fluid electrolytes and nutrients to and from the luminal contents and to act as a barrier to prevent the entry of harmful substances from the intestinal lumen to the mucosa. In their capacity as signaling molecules, bile acids play important roles in regulating both of these aspects of epithelial function.

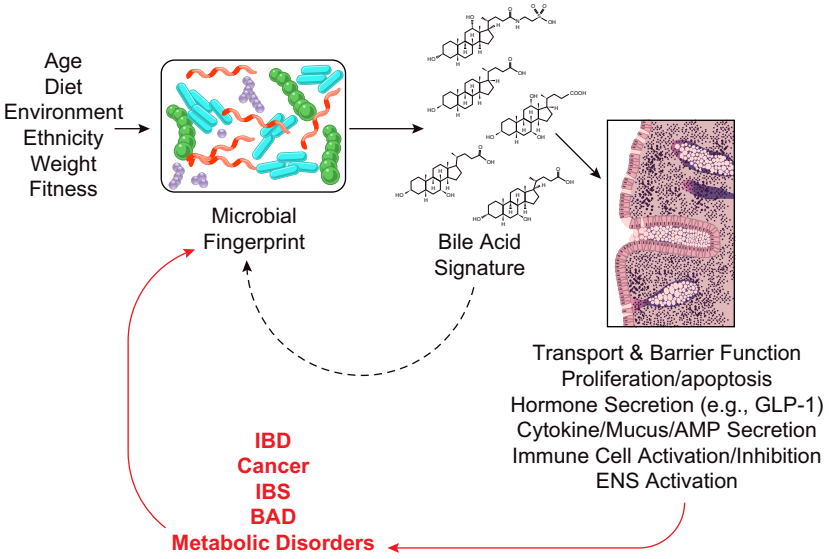


FIGURE 4. Bile acid/microbial interactions in regulation of intestinal physiology and pathophysiology. Environmental and genetic factors contribute to determining the nature of the microbial fingerprint that exists within the intestinal lumen which, in turn, determines the makeup of our intestinal bile acid signatures. Luminal bile acids regulate many different aspects of mucosal physiology, from epithelial transport and barrier function to immune cell and neuronal activation in the lamina propria. Bile acids also play an important feedback role in shaping the microbial fingerprint. Dysregulation of microbial/bile acid interactions can negatively impact mucosal function, contributing to the onset of intestinal and metabolic disorders (red arrows). In turn, disease progression can also impact the intestinal flora, making it difficult to determine whether changes in the microbial fingerprints and bile acid signatures are a cause or consequence of disease.

A. Bile Acids in Regulation of Epithelial Fluid and Electrolyte Transport

There has long been an association between bile acids and intestinal fluid homeostasis. The first reports of the bile acid binding resin cholestyramine being useful in treating diarrhea were published in the late 1960s (171, 387), and soon afterwards a landmark study by Mekhjian et al. (295) directly demonstrated that instillation of bile acids at high concentrations into the colons of healthy volunteers induced fluid secretion. Subsequent studies in animal models and cultured epithelial cell lines have revealed that the effects of bile acids on luminal fluid accumulation are due to both inhibition of Na^+ absorption and stimulation of Cl^- secretion (40, 141, 294, 395). Although there can be quite a degree of variation in their concentration dependence in different models, it is clear that in most species, including humans, only pathophysiologically high levels of bile acids induce colonic fluid secretion. There is also a marked structural specificity for bile acids in exerting their actions, with only the dihydroxy bile acids, CDCA and DCA, having prosecretory effects (141, 217, 444). UDCA, the 7β-OH epimer of CDCA, is a notable exception in that it has been shown to be devoid of prosecretory activity and, in fact, has antisecretory actions (130, 223). Conjugation to glycine or taurine is also an important factor in determining bile acid actions on intestinal fluid transport. Since colonic epithelial cells do not express apical transporters for bile acids, they must first be deconjugated, to become more lipophilic and partially protonated before they can passively cross the cell membrane. However, if levels of luminal conjugated bile acids increase sufficiently, loss of tight junction integrity occurs, allowing bile acids to gain access to the basolateral side where they can then be transported into the cell to exert their effects (102, 217). Thus the colonic microbiome, through its deconjugating, dehydroxylating, and epimerizing activities, is a crucial regulator of intestinal transport responses to bile acids. While the physiological basis for such cathartic actions of bile acids in the colon is still not certain, it is thought they have likely evolved as an innate defense mechanism to protect the mucosa at times when colonic delivery of bile acids is abnormally high. Under such conditions, bile acid-induced secretion dilutes colonic content and causes rapid elimination from the body, thus preventing damage to the epithelial barrier.

The molecular mechanisms by which intestinal epithelial transport function is altered by bile acids are still not fully elucidated. However, in vitro studies in cell culture models clearly show that they can exert their effects, at least in part, through direct actions at the epithelium itself (101, 102, 217). Such direct effects of bile acids are mediated primarily by elevations in intracellular Ca^{2+}, leading to activation of basolateral KCNN4 channels, thereby creating the electrical driving force for Cl^- secretion into the lumen. Such Ca^{2+}-dependent prosecretory effects of bile acids have also been reported in colonic tissues from animal models (286, 311). Studies on isolated colonic epithelial cells have shown that bile acid-induced increases in intracellular Ca^{2+} also inhibit the activity of Na^+/H^+ and Cl^-/HCO_3^- exchangers in the apical membrane of surface cells. In vivo, such an effect would result in reduced salt and water absorption from the lumen (11, 339). Recent studies in rats also suggest that changes in epithelial expression of aquaporins occur upon exposure to bile acids, although the contribution that these channels make to intestinal fluid secretion is still unknown (512).

While it is clear that elevations in intracellular Ca^{2+} are important in mediating bile acid actions, the upstream mechanisms involved have yet to be elucidated. The strict structure-activity relationship for bile acids in regulating epithelial transport function suggests that a receptor may be involved, but if this is so, its identity has yet to be revealed.

Our own studies suggest that the cell surface bile acid receptor TGR5 is not involved since, even though the receptor is expressed on colonic epithelial cells, its activation with the TGR5 specific ligand INT-777 inhibits, rather than stimulates, Cl^- secretion in rat colonic tissue (488). Meanwhile, the rapidity with which bile acids induce epithelial secretion (i.e., within seconds) rules out a role for nuclear receptors. An alternative possibility to the involvement of a specific receptor could be that hydrophobic bile acids cause membrane perturbations, either at the plasma membrane or within intracellular organelles, such as mitochondria and the ER, leading to the emptying of intracellular Ca^{2+} stores and increased influx from the extracellular milieu (255, 453).

In addition to their direct effects on epithelial cells, bile acids can also alter intestinal fluid and electrolyte transport through indirect mechanisms. In an important series of studies carried out by Lundgren and co-workers at the University of Gothenburg, the involvement of intrinsic neural reflexes in bile acid-induced fluid secretion in the small intestine was defined (208, 209). Subsequent studies revealed that this reflex arc is initiated by enterochromaffin cells which, in the presence of high luminal bile acid levels, release 5-HT to activate intrinsic afferent neurons (358). The efferent arm of the reflex arc appears to be mediated by both cholinergic and noncholinergic, nonadrenergic nerves that release their neurotransmitters into the neuroepithelial junction.

In addition to recruitment of the ENS, bile acids can also stimulate intestinal secretion through the activation of immune cells present in the lamina propria. For example, in guinea pig colon, CDCA-induced secretory responses are mediated, at least in part, by activation of mast cells and the release of histamine, which then acts at epithelial H_1 receptors to induce secretion (130). Other mediators released from activated mast cells, such as adenosine and prostaglandins, are also likely to be involved, although this remains to be investigated. It should also be kept in mind that mast cells and nerves exist in close apposition to each other within the intestinal mucosa and engage in bidirectional communication (94). Such neuroimmune interactions are also likely to be important in regulating the full expression of bile acid-induced intestinal transport responses.

While most studies to date have focused on how bile acids acutely induce fluid and electrolyte secretion when they are present at high levels in the colon, in more recent studies we have begun to address possible roles they may play under more physiological circumstances. It was found that chronic exposure of isolated epithelial cells or rat colonic tissue to relatively low DCA concentrations (10–200 μM), which by themselves do not induce secretion, inhibited subsequent responses to both Ca^{2+} and cAMP-dependent secretagogues. This effect was slow in onset and was not associated with alterations in secretagogue-induced increases in intracellular second messengers (215). In subsequent studies it was found that such anti-secretory actions are likely mediated by the nuclear bile acid receptor FXR, since agonists of this receptor mimicked the antisecretory actions of DCA and CDCA in cultured epithelial cells and ex vivo sections of mouse colon. Actions downstream of FXR activation appear to involve inhibition of the activity at least two key components of the Cl^- secretory pathway, apical CFTR channels and basolateral Na^+-K^+-ATPase pumps (313). It was proposed that such antisecretory actions of bile acids may serve a physiological role by dampening basal fluid secretion and thereby promoting the normal absorptive function of the colon. Such dual actions of bile acids in acutely promoting and chronically inhibiting fluid secretion at high and low levels, respectively, suggests that they may have a role as colonic "osmosensors" that serve to dynamically regulate luminal fluid levels. A summary of our current understanding of how bile acids regulate colonic secretion under normal and pathological circumstances is depicted in **FIGURE 5**.

B. Bile Acids in Regulation of Epithelial Barrier Function

The intestinal epithelial barrier is comprised of the physical barrier posed by the epithelial cells themselves, augmented by a number of secreted factors, including antimicrobial peptides, mucus, cytokines, and immunoglobulins. This barrier is by no means static but is in a constant state of flux as the cells which comprise it are continuously undergoing proliferation, migration, and differentiation. At the same time, the barrier retains the plasticity to rapidly respond to changes in the luminal environment, such as the passage of food or the presence of pathogens. The epithelium is exposed to a myriad of endogenous and exogenous stimuli, many of which have the capacity to alter one or several aspects of barrier function. In the following sections we discuss the role that bile acids play in this vital aspect of epithelial function.

1. Cell death and survival

Epithelial cells, particularly those of the intestinal tract, are being constantly renewed. This regeneration process requires programmed elimination of damaged cells, usually via the apoptotic cell death pathway, balanced with a constant source of newly dividing cells. This finely-tuned balance between epithelial regeneration and death can become disturbed in various pathophysiological conditions, leading either to loss of barrier and transport function on the one hand, or to the development of cancer on the other. The roles of bile acids in regulating cell death and survival have been widely investigated in different epithelial cell types along the gastrointestinal tract, including those from the small and large intestine, the liver and biliary tree, and the

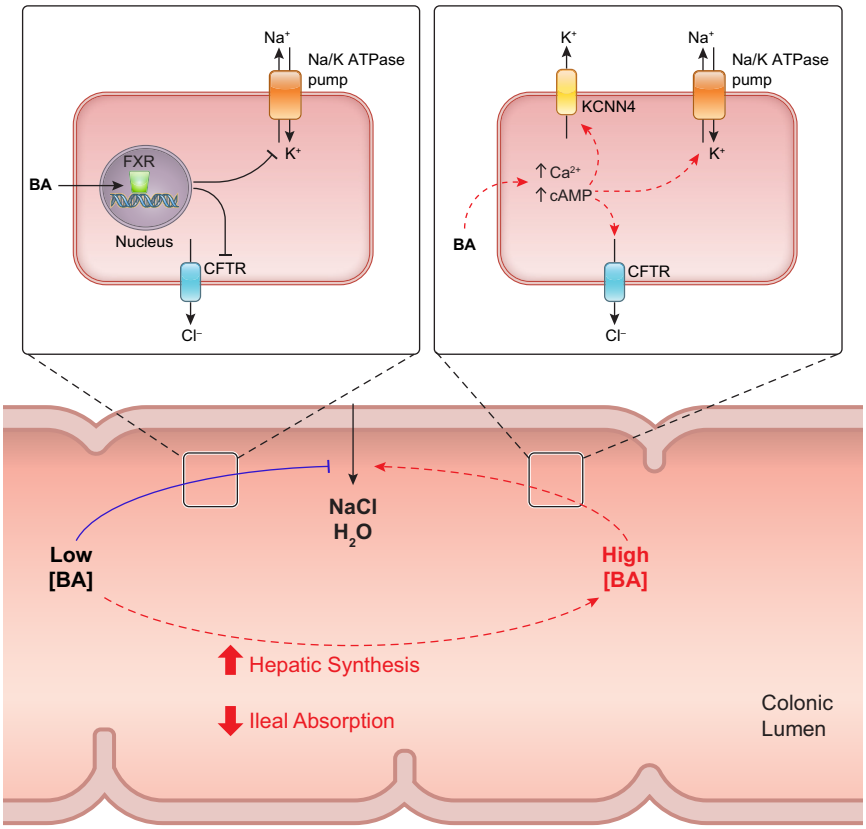


FIGURE 5. Bile acids in regulation of colonic epithelial Cl^- secretion. Under normal circumstances bile acids (BA) are present in the colon at relatively low concentrations where they inhibit Cl^- and fluid secretion, thereby promoting normal colonic absorptive function. This effect is mediated by farnesoid X receptor (FXR)-induced downregulation of cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel expression and Na^+-K^+-ATPase pump activity. Pathological conditions (depicted by red arrows) that cause bile acid malabsorption in the ileum or increased hepatic synthesis lead to increased delivery of bile acids to the colon where they can act directly on the epithelial cells to elevate levels of the prosecretory second messengers, Ca^{2+} and cAMP. In turn, these second messengers rapidly stimulate the activity of the proteins that comprise the Cl^- secretory pathway and the consequent fluid secretion into the lumen causes diarrhea. Such fluid secretory responses to bile acids are amplified by recruitment of the mucosal immune system and activation of enteric nervous reflexes and are accompanied by concommitant inhibition of fluid absorption (see text for details).

pancreas. While there is still much to learn, it is clear that the response of epithelial cells from different tissues and organs depends both on the bile acids to which they are exposed and on the complement of receptors and signaling pathways expressed.

Several studies have shown that DCA, a major secondary bile acid, induces epithelial proliferation at concentrations that would be expected to occur under normal conditions in the colonic lumen. The molecular pathways involved are complex and in various systems have been shown to involve recruitment of the EGFr, with consequent activation of extracellular signal-regulated kinase (ERK). ERK then induces the upregulation of cyclooxygenase-2 and the basolateral release of prostaglandins, which stimulate mitogenesis (66, 297). Proliferative actions of bile acids have also been shown to be mediated by PKC (410), which can also be activated downstream of the EGFr or through bile acid-induced membrane perturbations (5). Indeed, ligand-dependent transactivation of the EGFr appears to be a common pathway underlying proliferative actions of bile acids throughout the intestine (26, 317, 380). Furthermore, such mitogenic actions of bile acids appear to be antagonized by an FXR-mediated pathway which inhibits EGFr-dependent signaling and cell proliferation (105, 357). Studies from mammary epithelial cells indicate that FXR activation may also inhibit EGFr-dependent signaling by downregulating expression of other members of the ErbB receptor family with which it heterodimerizes (135). Interestingly, GR and VDR activation have also both been shown to be coupled to inhibition of EGFr signaling and expression, suggesting that bile acids may also have the capacity to influence growth factor-dependent signaling through these pathways (290, 382).

While bile acids clearly have important roles in controlling the rate at which cells proliferate, they are also equally important in determining how long cells survive through their actions in modulating apoptotic pathways. Apoptosis is a highly regulated process of programmed cell death, necessary for normal homeostasis of epithelial cells along the crypt-villus axis (148). The complex molecular mechanisms underlying apoptosis have been extensively reviewed elsewhere, and only a brief overview is provided here (33, 61, 114). Apoptosis typically occurs in response to cellular stresses, including a range of intracellular and extracellular stimuli, such as inflammatory mediators, pathogens, reactive oxygen species (ROS), and endoplasmic reticulum (ER) stress, to name but a few, and can be divided into two interrelated pathways, extrinsic and intrinsic. The intrinsic pathway, as the name suggests, arises from intracellular signals that ultimately lead to Bax-mediated increases in mitochondrial membrane permeability (MMP) and release of cytochrome *c* and other regulatory proteins, such as XIAP and Smac/Diablo. Cytochrome *c* activates apoptotic

protease activating factor (APAF1) which binds caspase 9, leading to formation of the apoptosome, and subsequently activation of caspases 3, 6, and 7, which function as executioners. In contrast, the extrinsic pathway is initiated by extracellular signals, such as tumor necrosis factor-α (TNF-α). These ligands activate the Death Receptors, which are members of the TNF receptor family, including TRAILR1, TNFR1, and FAS/CD95. Binding of TNF-α to TNFR1 leads to recruitment of TRADD (or FADD in the case of FAS/CD95 activation) and procaspase 10, in turn leading to activation of caspase 8, and subsequent activation of the executioner caspases. Importantly, the two pathways do not function independently with the extrinsic pathway having the capacity to recruit the intrinsic pathway through elevating levels of the cytosolic protein BID. Ultimately, whether it is by the intrinsic or extrinsic pathways, activation of caspases leads to cleavage of poly-(ADP ribose) polymerase (PARP), disruption of the cellular cytoskeleton and nuclear matrix proteins, DNA fragmentation, membrane blebbing, and finally disintegration of the cell into apoptotic vesicles.

The effects of bile acids on pro- and anti-apoptotic pathways in epithelial cells are complex and appear to be highly dependent on context. On the one hand, depending on the particular cell type and levels of bile acids present, inhibition of apoptosis can occur, and this is thought to augment proliferative responses to bile acids (292). Notably, activation of the bile acid receptors PXR, VDR, and TGR5 have all been shown to prevent apoptosis in various epithelia from the intestine and biliary tree (137, 258, 380, 524). In contrast, activation of FXR has been reported to promote apoptosis of transformed cells (308), thereby complementing its antiproliferative and tumor suppressor activity described above. Thus the relative expression and activation of different bile acid nuclear receptors is likely to be an important factor in determining epithelial cell fate.

Many studies have focused on investigating the effects of bile acids in pathological conditions when epithelial cells of intestine are exposed to abnormally high levels of bile acids (150). Under these conditions, increased apoptotic cell death is thought to contribute to associated losses of epithelial barrier and transport function (33). There is a considerable amount of evidence showing that there is a correlation between increasing bile acid hydrophobicity and induction of apoptosis. Thus hydrophobic bile acids, such as CDCA, DCA, and LCA, are generally thought be pro-apoptotic, while the relatively hydrophilic bile acid UDCA is anti-apoptotic (33, 433). The mechanisms involved in the pro-apoptotic effects of hydrophobic bile acids in enterocytes appear to differ from those that occur in hepatocytes during cholestasis. Whereas in the liver, both intrinsic and extrinsic pathways are important, in the intestinal epithelium bile acid-induced apoptosis appears to occur mainly by the intrinsic pathway (33, 399, 477). Thus, in various in vitro and in vivo models, apoptosis in response to hydrophobic bile acids has been shown to involve oxidative stress-mediated activation of Bax, disruption of the MMP, release of cytochrome *c*, apoptosome formation, and ultimately the activation of executioner caspases 3, 6, and 7 (182, 477, 515). Interestingly, while it is clear that bile acids can promote epithelial apoptosis when they are present at high levels, prolonged exposure can lead to the development of apoptosis resistance and promotion of proliferation (110, 411). This may, at least in part, underlie the correlations that have been reported between elevated levels of luminal bile acids and increased probability of colon and esophageal cancer (see sect. VI).

In summary, whether exposure of epithelial cells to bile acids promotes their survival, proliferation, or death depends on many interrelated factors but probably most importantly the pattern of receptors that are expressed and the concentrations/types of bile acid to which the cells are exposed **(FIGURE 6)**. This is not surprising given that epithelial cells in different regions of the intestine encounter bile acids under very different contexts. For example, we would expect that in cholangiocytes and gallbladder epithelium, which are exposed to high monomeric concentrations of conjugated bile acids (1–3 mM), responses would differ from those of enterocytes lining the colonic lumen, where bile acids are normally deconjugated and levels are relatively low ($<$500 μM). Elucidating the complex mechanisms involved in these processes is as important as it is challenging.

2. Bile acids and tight junctions

As described above, the ability of neighboring epithelial cells to form tight junctions (TJs) with one another is critical to the formation and maintenance of the intestinal barrier. TJs are highly regulated and dynamic structures which provide a "gatekeeper" function to control the movement of nutrients, fluid, electrolytes, microbes, and their toxins from the luminal contents into the mucosa. As such, changes in levels of endogenous or exogenous factors that regulate the expression and activity of TJ proteins can have dramatic consequences for intestinal health and disease pathogenesis. Several studies have demonstrated that TJ function is regulated by luminal bile acids. For example, incubation of cultured Caco-2 cell monolayers or human colonic biopsies with dihydroxy bile acids reversibly decreases transepithelial resistance (TER) and induces phosphorylation and redistribution of the TJ junction protein occludin (315, 375). The mechanisms underlying such actions have not been well-elucidated but appear to involve recruitment of the EGFr and generation of ROS (19, 375). Other studies in esophageal epithelial cells have demonstrated that treatment with a combination of bile acids, in the presence of acid, decreases TER by modulating the expression of claudins 1 and 4 (63).

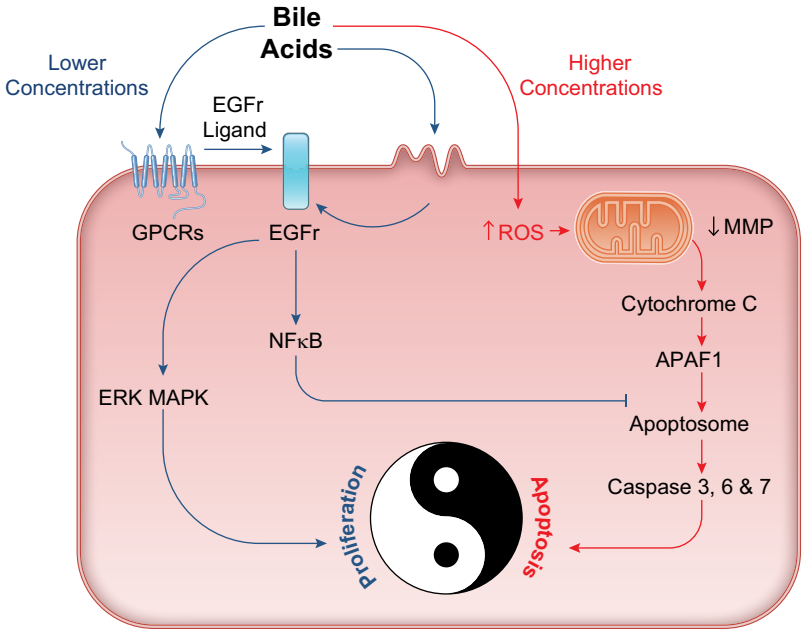


FIGURE 6. Bile acids in regulation of epithelial cell proliferation and death. Bile acids can induce epithelial proliferation through recruitment of epidermal growth factor receptor (EGFr)-dependent signaling mechanisms (blue arrows). Transactivation of the EGFr occurs through activation G protein-coupled receptors (GPCRs), such as the muscarinic M_3 receptor and TGR5. GPCR activation leads to EGFr activation through the release of ligands, such as amphiregulin or transforming growth factor (TGF)-α. Bile acid-induced membrane perturbations can also lead to EGFr activation but in a ligand-independent fashion. Activation of EGFr leads to induction of a pro-proliferative pathway, involving downstream activation of ERK mitogen-activated protein kinases (MAPKs). EGFr activation also leads to stimulation of nuclear factor κB (NFκB) which prevents apoptosis, thereby promoting cell survival and proliferation. Conversely, bile acids also have the capacity to stimulate epithelial apoptosis (red arrows). This occurs, least partly, through bile acid-induced accumulation of reactive oxygen species (ROS), leading to cellular cytotoxicity, loss of mitochondrial membrane potential (MMP), release of cytochrome *c*, and consequent activation of the intrinsic apoptotic pathway. The balance between proliferation and apoptosis is closely regulated and is largely dependent on epithelial cell type and the concentration and hydrophobicity of the bile acids present.

A role for bile acids in regulating TJ permeability is also supported by in vivo studies in animal models. For example, studies in mice fed a high-fat diet have shown that increases in epithelial permeability and decreased expression of the TJ proteins ZO-2 and JAM-A are associated with increased colonic bile acids (316). Studies in mouse and rat bile duct ligation models, where intestinal delivery of bile acids is ablated, also reveal increased gut permeability and bacterial translocation associated with decreased expression of occludin and claudin-2 (184, 470). Interestingly, FXR activation decreased the severity of intestinal inflammation in these models, an effect that was associated with increased expression of occludin and claudin-1, normalized permeability, and reduced bacterial translocation. While it remains to be determined if such actions are due to direct effects of FXR activation on TJ protein expression, or if they are indirect actions resulting from altered immune cell recruitment to the mucosa, these studies suggest an important protective role for FXR in preventing dysregulation of the intestinal barrier (470). In addition to FXR, TGR5 has also been identified as a regulator of TJ function, since TGR5$^{-/-}$ mice display altered expression of TJ proteins, particularly ZO-1 and occludin, have increased intestinal permeability to macromolecules, and are more susceptible to the development of experimental colitis compared with wild-type controls (72).

3. Bile acids and the mucus layer

Epithelial cells of the intestine secrete a number of factors that serve to enhance the physical barrier posed by the cells themselves and their TJs. Perhaps most important of these is the mucus layer which overlies the epithelium and which serves to maintain hydration of the mucosal surface, prevent abrasion by digested food particles as they move through the lumen, and protect against invasion by pathogens. Mucus is primarily produced by goblet cells along the intestinal tract, but transporting enterocytes also have the capacity to synthesize and secrete mucins. The organization of the protective mucus layer is not constant along the intestinal tract, with the small intestine being covered by a single nonattached layer and the stomach and colon having two layers, a dense inner layer that is firmly attached to the epithelium and a looser outer layer derived from proteolytic cleavage of the inner layer (193, 352). The inner layer is normally impenetrable to bacteria, while the outer layer provides an environment in which commensal bacteria reside (192, 193). The primary component of mucus in the

stomach is MUC5AC and in the ileum and colon is MUC2, both of which are secreted from goblet cells. However, enterocytes of the small intestine and colon also produce transmembrane mucins, such as MUC3 and MUC7, that not only contribute to the mucosal barrier but also have important signaling roles in regulation of growth, differentiation, and inflammation (352, 465). Mucins are highly glycosylated with the attached sugar moieties acting as attachment sites and providing nutrients for the resident microbiota (21).

Studies in rat and rabbit colon have demonstrated that pathologically high (i.e., mM) concentrations of unconjugated bile acids, including DCA and CDCA, promote mucus secretion, while their corresponding conjugated derivatives are less effective (32, 53, 388). Such findings suggest that mucus secretion, coordinated with fluid secretion, is likely to be a protective mechanism that prevents epithelial damage when concentrations of bile acids in the lumen are abnormally high. Induction of mucus secretion by bile acids has also been proposed to protect against bacterial infection (452). Recent studies have also shown that the protective effects of the taurine conjugate of UDCA (TUDCA) in experimental colitis in vivo are also associated with increased colonic mucus secretion (245). Studies in cultured epithelial cells from the stomach or colon also support a role for unconjugated bile acids in promoting the secretion of MUC2 (250), an effect that is mimicked by synthetic agonists of FXR (506).

Interestingly, some studies have shown that relatively low, physiologically occurring, concentrations of DCA are sufficient to induce MUC2 expression in cultured colonic epithelial cells (230, 426), while others showed that chronic (i.e., 7 days) exposure to physiologically relevant levels of DCA inhibited colonic epithelial mucus production (414). Thus, while it seems likely that luminal bile acids contribute to regulation of barrier function through their effects on mucus secretion, there is still much work to be done to understand the molecular mechanisms involved and the physiological/pathophysiological consequences of changes to the mucus layer induced by different bile acids.

When considering how bile acids regulate mucus secretion, one must also consider how they affect the production of various epithelial-derived substances that serve to enhance its barrier properties. For example, antimicrobial peptides (AMPs) are secreted into the mucus layer where they act to prevent bacterial penetration to the epithelium (16). Among the AMPs expressed throughout the intestine are cathelicidin and the defensins, of which there are several types broadly divided into those secreted from ileal Paneth cells, the α-defensins, and those which are produced by enterocytes [i.e., the β-defensins (HβDs)] (493, 494). AMPs play critical roles at the interface of microbial/epithelial communication in that they help to maintain sterility of the inner mucus layer, and they contribute to determining the makeup of the microbiome, regulate epithelial wound healing, and induce recruitment of immune cells to the mucosa. Despite such a central role in mediating crosstalk between the microbiota and the host, there is still little known of the role that bile acids play in their regulation. However, that such actions are likely to be important is evidenced by a number of experimental studies in vitro and in vivo. For example, in hepatic epithelial cells, CDCA, via FXR activation, promotes cathelicidin expression (83), while LCA, via activation of the VDR, has been shown to induce expression of this AMP in cultured colonic epithelial cells (446). In vivo studies using a mouse model of cirrhosis have shown that FXR activation upregulates ileal α-5-defensin in association with improved barrier function (457). Furthermore, a direct association between bile acids, the microbiome, and AMP production was demonstrated in recent studies by Joyce et al. (199), where changes in expression of microbial bile salt hydrolase, with concomitant increases in levels of unconjugated bile acids, led to increased ileal expression of the antibacterial protein RegIIIγ. Our own studies of colonic epithelial cells show that secondary bile acids differentially regulate the expression of HβDs in colonic epithelial cells, with DCA promoting both HβD1 and HβD2 secretion and UDCA having antisecretory effects (242). However, much more work is needed to understand how different microbial populations in the gut alter the intestinal bile acid pool to regulate defensin secretion, and more importantly, how these interactions impact on intestinal health.

Another important protein secreted into the mucus layer by the epithelium is secretory immunoglobulin A (sIgA). Synthesized in Peyer's patches, sIgA is transported across the epithelium and secreted into the lumen, where it plays critical roles in promoting barrier function through blocking bacterial penetration of the mucus, altering epithelial signaling responses to commensal bacteria, and promoting the activation of mucosal immune cells (276, 283). While the microbiome is known to be an important regulator of epithelial IgA secretion (155), whether bile acids also have roles to play in this regard is an important area of research that is yet to be addressed.

4. Bile acids and epithelial secretion of cytokines

If luminal pathogens evade the defense mechanisms posed by the mucus layer, a second line of defense, the innate immune response, is triggered in an attempt to clear the invading species. Again, through the regulated release of a range of mediators, chemokines, and cytokines, the epithelium plays a key role in initiation of this response. These messengers have diverse physiological actions within the intestine and beyond, but essentially, they serve to recruit, differentiate, and activate innate immune cells to the mucosa. In turn, these cells engulf

invading pathogens and release additional mediators that promote inflammation, tissue remodeling, edema, and recruitment of the acquired immune response. The peptide, protein, lipid, and chemical mediators released by the epithelium to control mucosal inflammation are vast in number and have been extensively reviewed elsewhere (186, 203, 359). However, particularly important are thought to be cytokines, such as TNF-α, interleukin (IL)-8, and interferon (IFN)-γ, which contribute to the recruitment and activation of immune cells, while anti-inflammatory cytokines, such as IL-10, and other factors, including resolvins and lipoxins, serve to dampen or switch off the inflammatory response (116, 498).

There is little doubt that the release of cytokines and other mediators from epithelial cells is key to regulating inflammatory responses that occur in various conditions associated with elevated levels of luminal bile acids (107, 204, 249, 434). Numerous studies on cells and tissues derived from the liver, intestinal tract, and pancreas have also shown that bile acids can act directly on epithelial cells to modulate production of proinflammatory cytokines, such as IL-8, IL-1β, and IL-6 (18, 246, 314, 356, 437). Furthermore, how epithelial cells respond depends on the bile acid in question. For example, DCA and its taurine conjugate, TDCA, both stimulate NFκB-dependent IL-8 release from colonic epithelial cells, although considerably higher levels of TDCA are required to induce a response (314), In contrast, UDCA and its conjugated derivative, TUDCA, have been shown to inhibit cytokine release from cultured epithelial cells in vitro and reduce mucosal accumulation of TNF-α and IL-1β in vivo (245, 280, 392). In addition to cytokines, epithelial production of other inflammatory mediators, such as prostaglandins (36, 76, 439), leukotrienes (103), nitric oxide (185), and ROS (19, 80), have also been shown to be increased in response to bile acids in various different models.

Finally, it should also be noted that in addition to regulating mucosal immune cells indirectly through epithelial cytokine release, bile acids can also exert direct actions on the immune cells themselves. For example, dihydroxy bile acids have shown to activate and degranulate mast cells causing local histamine release (130, 373). In contrast, activation of FXR or TGR5 on innate immune cells, such as macrophages, monocytes, and dendritic cells, appears to suppress expression of various pro-inflammatory cytokines (128, 181, 364, 513). Bile acids also appear to suppress the proliferation of lamina propria lymphocytes (115). Thus how alterations in the levels of luminal bile acids influence gut function, both under normal circumstances and under conditions of infection or inflammation, ultimately depends on a complex interplay of pro- and anti-inflammatory mediators released from both epithelial and immune cells.

VI. PATHOLOGICAL EFFECTS OF BILE ACIDS

From the preceding sections, it is clear that in addition to their digestive functions, bile acids have crucial roles to play in normal regulation of intestinal homeostasis. Alterations in either the size or composition of the bile acid pool can have a dramatic impact on intestinal function, and thus the enterohepatic circulation is a tightly regulated process, under the control of numerous intrinsic and extrinsic factors (91, 167). Normally, most of the circulating bile acids (90–95%) are reclaimed in the distal ileum and returned to the liver, with only a small fraction entering into the colon (see sect. I for details). However, if the EHC becomes dysregulated, this can lead to significant alterations, not only in the size and makeup of the bile acid pool, but also in the range of tissues and organs exposed to these molecules **(FIGURE 7)**. For example, malabsorption in the ileum can lead to greatly increased levels of bile acids entering the colon, impaired FGF19 secretion can produce greater bile acid pool size with greater loss into the colon, cholestasis can result in bile acids entering the pancreas, whereas GERD can be accompanied by bile acids entering the esophagus, and from there into airways. In each of these pathological scenarios, dysregulated epithelial cell function has been well-established to be a central aspect of disease progression.

A. Bile Acids in Chronic Diarrhea and Constipation

As discussed in earlier sections, increased delivery of bile acids to the colon can occur either as a consequence of ileal resection or dysfunction or because of defective FGF19 release from ileal enterocytes. In either case, increased levels of deconjugated bile acids in the colon can have profound actions on epithelial function, inhibiting Na^+ absorption, stimulating Cl^- secretion, and enhancing permeability. The resulting accumulation of fluid in the colonic lumen leads to the onset of what has become known as bile acid diarrhea (BAD) (218, 312, 334)]. In addition, elevated levels of luminal bile acids are also well-established to promote intestinal motility through neuronally mediated pathways (123, 355, 422), effects that are now known to be mediated by neuronal TGR5 (8, 216, 369). Thus, in conditions of BAD, intestinal transit is also accelerated, thereby contributing to the onset of diarrhea in these patients. Indeed, a recent study of irritable bowel syndrome with diarrhea (IBS-D) patients shows that even in the absence of overt bile acid malabsorption, by virtue of their prokinetic effects, modest increases in stool bile acids can be an underlying factor in the onset of diarrhea (353).

When BAD is due to malabsorption of bile acids in the ileum, whether this is due to congenital absence of bile acid transporters, ileal inflammation, or surgical resection, it is classified as being type I (or secondary) BAD. On the other

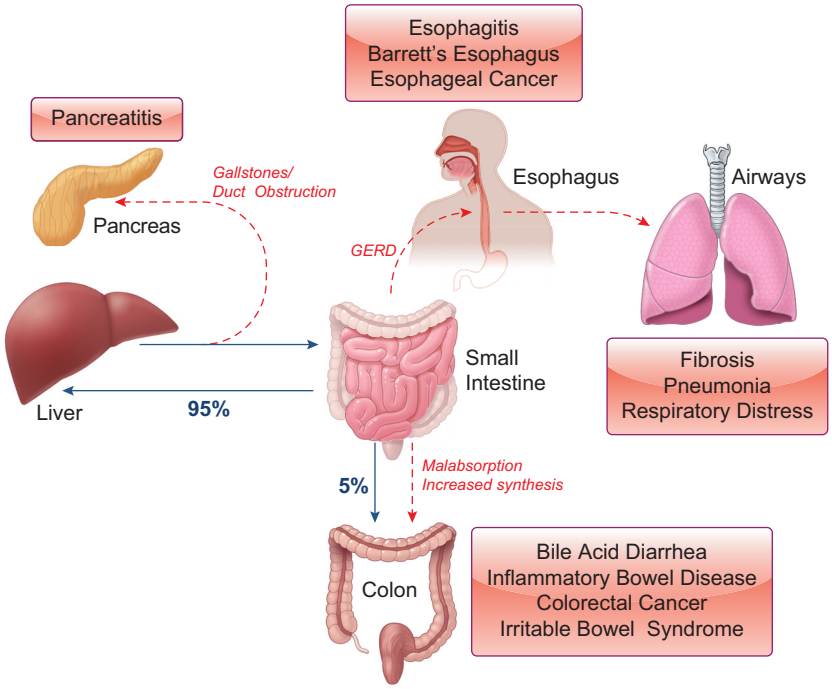


FIGURE 7. Pathological consequences of enterohepatic circulation (EHC) dysregulation. Blue solid lines depict the normal EHC, where bile acids are released from the liver into the small intestine to facilitate lipid digestion and absorption. Approximately 95% of released bile acids are reabsorbed from the small intestine and are recycled to the liver through the EHC. A small proportion (~5%) normally enters the colon where bacterial metabolism, followed by either passive reabsorption or excretion in the feces, occurs. Red dashed lines depict conditions associated with dysregulation of the EHC. Malabsoprtion or increased biosynthesis of bile acids results in their increased delivery to the colon, causing bile acid diarrhea or contributing to the pathogenesis of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colorectal cancer (CRC). Blockage of bile flow to the small intestine can result in reflux into the pancreas, contributing to the onset of pancreatitis. In gastroesophageal reflux disease (GERD), bile refluxes into the esophagus, causing esophagitis and progressing to Barrett's esophagus and cancer. From the esophagus, aspiration of bile acids into the airways can lead to the development of fibrosis, pneumonia, and respiratory distress syndrome.

hand, BAD in the absence of ileal pathology is classified as being type II (or primary) disease. Although primary BAD (pBAD) has long been considered an idiopathic disease, recent years have seen great advances in our understanding of its prevalence and pathogenesis. Recognition of its high prevalence has been obtained by SeHCAT testing, a diagnostic tool which uses a ^{75}Se-tagged radionuclide bile acid homologue to monitor turnover of the bile acid pool. Studies with this test have shown that at least 30% of patients, who would normally be diagnosed as having IBS-D, actually suffer from pBAD (239, 421, 492). The condition is highly prevalent, affecting at least 1% of the population of Western societies.

It is now known that pBAD occurs due to a defect in FXR/FGF19/FGFR4 axis in regulation of the EHC. Under normal circumstances, bile acid uptake at the apical surface of ileal enterocytes via ASBT activates intracellular FXR and induces transcription of FGF19. FGF19 is then secreted via the basolateral membrane of the enterocyte into the EHC and travels to the liver where it downregulates bile acid biosynthesis by inhibiting CYP7A1 expression (cf. **FIGURE 1**) (424, 482). In pBAD, FXR induction of FGF19 expression is impaired, resulting in an increase in bile acid biosynthesis, increased colonic delivery, and consequently the onset of diarrhea. Studies have shown that, in patients with pBAD, ileal bile acid uptake is unaltered and there is a larger bile acid pool. This contrasts with an expected reduction if ileal malabsorption rather than increased hepatic synthesis was the predominant pathology. Current research in this area is focused on the identification of biomarkers for pBAD and in determining the causative factors leading to reduced FGF19, which are likely to be multiple (185, 479). Some patients have hypertriglyceridemia, and patterns of impaired/meal-stimulated FGF19 responses can be found. While no clear causative genetic variants of FXR, FGF19, or the bile acid transporters are apparent, allelic variants of the FGF19 receptor FGFR4 or the co-receptor Klotho-beta may be present in a subset of pBAD patients, resulting in hyporesponsiveness to the hormone in the liver (194).

As noted previously, the diarrhea associated with increased colonic bile acids may represent an innate protective mechanism, whereby luminal fluid accumulation dilutes potentially cytotoxic bile acids, such as DCA and LCA, before they can achieve levels that cause epithelial damage and loss of function. This idea is supported by observations that, despite elevated levels of colonic bile acids, BAD is not associated with significant changes in mucosal histology (403). However, BAD is a chronic disease, and the quality of life for patients suffering with the condition is severely impacted due to fecal incontinence, urgency, abdominal pain, and often anxiety and depression (31). Despite its prevalence, BAD remains underdiagnosed and treatment options are limited. Bile acid binding resins, such as cholestyramine, can be of benefit, but their use is limited by poor patient tolerance, bloating, mucoadherence, and drug-drug interactions (52, 481). A new bile acid sequestrant that binds bile acids more efficiently, colesevelam, is available in tablet form and appears to have less adverse effects. A proof-of-concept study suggests that FXR agonists, by stimulating FGF19 production, could also have a future role in the therapy of this disorder (see below) (455).

Just as the delivery of abnormally high levels of bile acids to the colon is an underlying cause of diarrhea, so too can

abnormally low levels be involved in the pathogenesis of chronic constipation. A recent retrospective study by Camilleri and co-workers has shown that ~15% of patients with irritable bowel syndrome with constipation (IBS-C) have decreased levels of bile acids in their feces and that this correlated with increased colonic transit time (471). Decreased biosynthesis in the liver, as indicated by elevated FGF19 and reduced C4 in the serum, appears to be a factor underlying reduced fecal bile acids in these patients. Indeed, simply restoring levels of luminal bile acids by oral administration of CDCA appears to be an effective treatment for patients diagnosed with either IBS-C or chronic constipation (37, 377). An alternative approach currently under investigation for increasing colonic bile acids in treatment of constipation is the use of ASBT inhibitors, such as elobixibat, that prevent bile acid absorption in the terminal ileum (2) (see sect. VI). In addition to their reduced colonic delivery, altered bile acid metabolism may also contribute to constipation in some patients. For example, patients with IBS-C have been shown to have reduced amounts of prosecretory bile acids, such as DCA and CDCA, in their feces (416), while in a subset of pediatric patients with chronic constipation the predominant fecal bile acid is 3-sulfo-CDCA, which unlike CDCA does not stimulate intestinal fluid secretion (169).

B. Bile Acids and IBD

Inflammatory bowel diseases are a group of conditions associated with chronic recurring inflammation of the intestinal mucosa. The most common of these conditions are ulcerative colitis (UC) and Crohn's disease (CD), which are estimated to affect 0.5–1% of the population of Western societies and which are associated with symptoms of abdominal pain, diarrhea, fatigue, rectal bleeding, and weight loss (1, 207). Patients suffering from IBD also experience psychological comorbidities due to increased prevalence of anxiety and depression (300, 321) and have an increased risk for the development of colorectal cancers (126, 386). There is currently no cure for IBD, and treatment aims primarily to induce, and then maintain, remission through the use of anti-inflammatory drugs, such as 5-aminosalicylates, steroids, immunosuppressants, and biologics targeting TNF-α (323, 367). However, since such drugs can be expensive, may have severe side effects, and are often ineffective, new treatment options are urgently required.

While the triggers for IBD are still not fully understood, both genetic and environmental factors appear to be important in leading to dysregulated mucosal immune responses (96, 486). Hallmark features of the disease also include enhanced epithelial permeability and alterations to the resident microbiota (15, 298, 374), although whether these are a cause or consequence of the disease is still not certain. Studies showing that asymptomatic relatives of IBD patients also have enhanced epithelial permeability and distinct microbial fingerprints suggest that such alterations may be necessary, but not sufficient, for disease progression (136, 142, 156, 225). Furthermore, changes in the profile of luminal bile acids have also been closely associated with IBD progression. Such changes can occur as a consequence of a dysregulated enterohepatic circulation, leading to increased delivery of bile acids to the colon (188, 327, 378, 473). Changes in the luminal bile acid profile in IBD have also been closely linked to changes in the microbiota (107, 327, 473). For example, recent studies by Duboc et al. (107) have demonstrated that altered enzymatic activity within the microbiota of IBD patients alters the colonic bile acid profile towards increased levels of conjugated and sulfated bile acids. Other studies in mouse models indicate that consumption of a high-fat diet shifts hepatic conjugation of bile acids from glycine to taurine, resulting in enhanced generation of sulfur in the colonic lumen. In turn, this promotes growth of bile-tolerant bacteria, most notably *Bilophila Wadsworthia*, which promote Th-1-mediated mucosal immune responses (100). Still further studies suggest that dysregulated signaling via bile acid receptors may also have a role to play in disease progression, given that SNPs in FXR and altered receptor expression and activity have been shown to be associated with CD and UC (25, 325). Given their crucial roles in regulating intestinal epithelial apoptosis and proliferation, TJ permeability, and water, cytokine, and mucus secretion (cf. sect. IV), it is perhaps not surprising that alterations in luminal bile acids contribute to pathogenesis of intestinal inflammation. Indeed, studies have demonstrated that bile acids may underlie the enhanced epithelial permeability associated with disease progression (434). However, the precise roles that bile acids play in IBD pathogenesis is still uncertain and whether they act as promoters or inhibitors of inflammation likely depends on several factors, including their concentration, physicochemical properties, and the resident microbiota (350). For example, DCA, when present at abnormally high levels, has been shown to enhance inflammation in an animal model of colitis through NLRP3 inflammasome activation (523). In contrast, feeding with CDCA has been shown to prevent inflammation in the DNBS model of colitis (143), an effect which may be due to colonic generation of the CDCA metabolite UDCA, which has well-established anti-inflammatory and cytoprotective actions. Despite our still limited understanding of complex roles that bile acids play in regulating intestinal inflammation, studies in animal models which demonstrate protective actions of synthetic FXR and TGR5 agonists provide great promise for the development of new bile acid-based therapeutics for IBD in the future (28) (cf. sect. VI below).

C. Bile Acids and Cancer

Colorectal cancer (CRC) is the third most common form of cancer in Western countries and is responsible for ~700,000 deaths worldwide each year (22). While there are undoubt-

edly genetic and environmental components to disease development, relationships between diet, the resident microbiota, and bile acids have also long been suspected as important contributing factors (20, 163, 368, 379). Early epidemiological studies showed strong correlations between CRC occurrence and levels of fecal bile acids, while studies in animal models demonstrated that increased levels of bile acids, whether they are due to ileal bypass surgery or direct colonic instillation, promote tumor formation (164, 231, 404, 500). In contrast, a long-term study of human patients with ileal bypass reported no overall increase in cancer deaths over a 25-yr followup period (48). It should be noted however that the latter study did not specifically report on the incidence of CRC in these patients. Nevertheless, evidence has continued to accumulate to support the hypothesis that interactions between diet, the microbiota, and bile acids are key contributors to CRC development (331), while our understanding of the molecular pathways by which bile acids regulate epithelial cell death and survival in the colon has grown steadily (cf. sect. IV).

Factors that increase delivery and that shift the colonic pool of bile acids towards a more hydrophobic profile (i.e., deconjugated and dehydroxylated) are associated with increased risk of CRC development. Thus the Western diet, which is rich in fat and low in fiber, leads to alterations in the enterohepatic circulation leading to increased synthesis and colonic delivery of bile acids (263, 316). At the same time, alterations to the colonic microbiota, or dysbiosis, cause a shift towards increased dehydroxylation and deconjugation, leading to the generation of secondary bile acids, such as DCA and LCA (4, 161, 198, 338, 454). Elevations in the levels of secondary bile acids in this way are believed to increase epithelial permeability (316, 434), leading to enhanced bacterial translocation and prolonged low-grade mucosal inflammation, ultimately contributing to cancer development. As discussed above, such increases in epithelial permeability brought about by secondary bile acids likely involve epithelial apoptosis, with cytotoxicity being directly proportional to the lipophilicity of the luminal bile acid pool (372). Interestingly, while increased apoptosis might contribute to disruptions in epithelial barrier function, such actions would also be expected to prevent tumor growth. However, it is thought that prolonged exposure of the colonic epithelium to pathophysiological levels of lipophilic bile acids ultimately leads to overactivation of NFκB and development of apoptosis resistance, thereby promoting tumor development (81, 411).

Another important way in which bile acid signaling appears to be involved in the development of intestinal cancer is through the nuclear receptor FXR, which has been shown to be downregulated in tissues from patients with the disease (93, 247, 448) **(FIGURE 8)**. The role of FXR has been mostly studied in CRC, where in mouse models loss of FXR expression is associated with increased size and number of

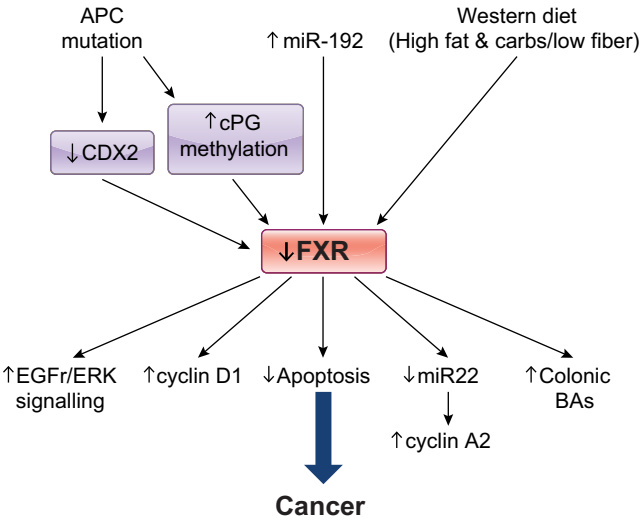


FIGURE 8. Farnesoid X receptor (FXR) downregulation in the pathogenesis of colorectal cancer. The expression of FXR decreases in colorectal cancers, an effect that has been proposed to be linked to multiple factors, including the acquisition of mutations in the tumor promoter, adenomatous polyposis coli (APC), expression of miRs, and the consumption of a high-fat western diet. Downregulation of FXR expression is thought to contribute to the pathogenesis of colorectal cancers by multiple mechanisms, including alterations in cell cycle proteins, activation of EGFr-dependent signaling, decreased apoptosis, and increased levels colonic bile acids. Reactivation of FXR in colon cancers has been shown to prevent the growth and development of tumors.

adenocarcinomas. Such effects appear to be multifactorial and are related to enhanced Wnt signaling, expression of cell cycle proteins, increased proliferation, and downregulated apoptosis (277, 308). Given the importance of NFκB in development of apoptosis resistance to bile acids, recent findings that FXR and NFκB are reciprocally regulated may provide an important insight into disease pathogenesis (127, 467). While upregulation of NFκB activity appears to dampen FXR expression in cancer, other mechanisms are also likely to be involved, including enhanced expression of FXR-modulating miRNAs (235, 520). Acquired mutations in the tumor suppression gene adenomatous polyposis coli are also an important factor, leading to enhanced methylation of the FXR promoter and downregulation of CDX2, a transcriptional regulator of FXR (30, 307, 406).

Interestingly, while FXR appears to play a protective role against the development of CRC and gastric cancer (106), the same is not true for all gastrointestinal cancers. For example, in the esophagus, expression of FXR is poorly correlated with disease outcome, and in direct contrast to its actions in the colon, it prevents apoptosis in these tissues (92, 147). Similarly, overexpression of FXR in other organs, such as the pancreas or gallbladder, is a poor prognostic factor where it appears to promote tumor growth and metastatic potential (174, 251). Thus, while FXR is now emerging as an important factor in the development of cancer throughout the intestinal tract, its roles appear to be

tissue specific, and there is still much work to be done in its development as a new target for chemotherapeutic interventions.

D. Bile Acids and Pancreatitis

Acute pancreatitis is the most common cause for hospitalization among nonmalignant gastrointestinal disorders (244, 254, 271). In severe cases, the mortality of the disease can reach 20–30% (346). Gallstones are the most common etiological factors in acute pancreatitis in the Western world. Small gallstones entering the common bile duct and settling at the papilla of Vater can simultaneously block the outflow of bile and pancreatic juice (158). The exact pathogenesis of acute biliary pancreatitis is still a matter of debate, with two theories predominating (253). According to the common channel theory, bile acids reflux into the pancreatic ductal tree, whereas the duct obstruction theory emphasizes the role of increased pressure and outflow blockage. Whatever the cause, studies from in vivo models suggest that bile acids are likely to play a pivotal role, since pancreatic duct ligation evokes only mild pancreatitis (309), whereas simultaneous ligation of the bile duct significantly increases disease severity (407). Furthermore, infusion of the bile acid taurolithocholic acid 3-sulfate (TLC-S) into the pancreatic ducts of anesthetized mice has been shown to induce acute necrotising pancreatitis, which is likely in part due to increased NFATc3 activity, an enzyme responsible for trypsinogen activation, inflammation, and pancreatic tissue damage (27, 362). Interestingly, TGR5 knockout mice are protected against the onset of pancreatitis in this model, suggesting an important role for the receptor in disease pathogenesis (361). Such protective effects are associated with an attenuation of bile acid-induced Ca^{2+} signals, intracellular activation of digestive zymogen granules, and cell injury as demonstrated in vitro on isolated TGR5 knockout pancreatic acinar cells.

Key to mediating the toxic effects of bile acids on acinar cells are changes in intracellular Ca^{2+} levels **(FIGURE 9)**. TLC-S induces sustained elevations in cytosolic Ca^{2+} due to stimulation of Ca^{2+} release from the ER and acidic Ca^{2+} stores (131, 474), along with simultaneous inhibition of its reuptake into the ER via SERCA pumps (227). Depletion of Ca^{2+} stores subsequently induces Ca^{2+} influx from the extracellular space via store-operated Ca^{2+} entry channels (268), thereby maintaining cytosolic intracellular Ca^{2+} concentration at high levels. In turn, such sustained increases in intracellular Ca^{2+} trigger damage to the mitochondrial membrane, intra-acinar trypsinogen activation, and aberrant enzyme secretion, leading to acinar cell damage and, ultimately, pancreatitis (104, 236, 415). Ca^{2+}-independent mechanisms may also be involved in mitochondrial toxicity when higher (100 μM) concentrations of bile acids are present (475, 476). Schulz et al. (402) demonstrated that, at such concentrations, bile acids can damage the mitochondrial membrane, leading to decreased mitochondrial membrane potentials and cellular damage.

Bile acid actions on cells other than acinar cells are also important in development of pancreatitis. For example, pancreatic stellate cells (PSCs) are found in close apposition to acinar cells and normally function in the maintenance of the ECM through a balanced production and degradation of ECM proteins (157). During tissue injury, excessive activation of stellate cells induces increased production of ECM proteins, leading to tissue fibrosis (149). Recent studies of mouse and human PSCs demonstrate that treatment

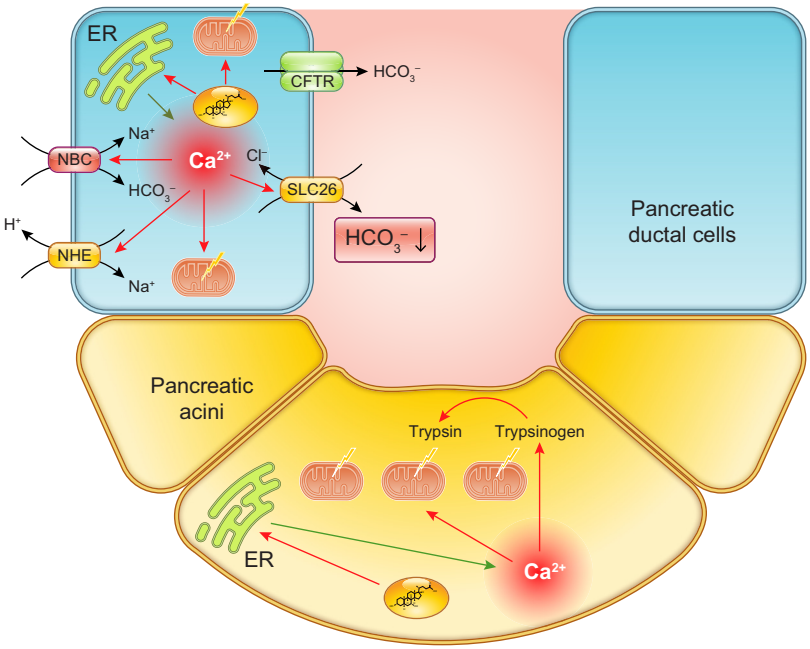


FIGURE 9. Role of bile acids in pathogenesis of acute pancreatitis. Although the pathogenesis of acute biliary pancreatitis is still elusive, bile acids have been shown to induce significant damage in the exocrine pancreas. In both pancreatic acinar and ductal cells, bile acids induce Ca^{2+} release from the endoplasmic reticulum (ER), leading to sustained intracellular Ca^{2+} overload. Elevated intracellular Ca^{2+} can, in turn, induce mitochondrial damage, thereby decreasing intracellular ATP levels. In pancreatic acinar cells, elevated Ca^{2+} can promote auto-activation of trypsinogen to trypsin, whereas in ductal cells, sustained intracellular Ca^{2+} overload inhibits ion and fluid secretion. Ultimately, these actions result in autodigestion of the tissue and necrosis, which are hallmarks of pancreatitis.

with cholate or taurocholate induces large, sustained, increases in intracellular Ca^{2+} leading to necrosis (119). Interestingly, TLC-S had only a minor effect on Ca^{2+} signaling in PSCs, indicating a distinct responsiveness to bile acids compared with their neighboring acinar cells.

Studies from the Hegyi group indicate that bile acids also act on the epithelial cells of the ducts during pancreatitis. At relatively low concentrations, the nonconjugated bile acid CDCA stimulates pancreatic ductal HCO_3^- secretion via inositol trisphosphate-mediated Ca^{2+} release and induction of Cl^-/HCO_3^- exchange activity, a response that may serve as a protective mechanism against the presence of toxic bile acids (183, 469). In contrast, when present at high concentrations, ductal CDCA causes mitochondrial damage and a Ca^{2+}-independent inhibition of bicarbonate secretion (274, 469). In turn, this leads to intraluminal acidification, increased autoactivation of trypsinogen, and generation of trypsin, which then acts at PAR-2 receptors to downregulate HCO_3^- exchange and CFTR (340, 341, 440). Recent clinical studies, showing that intraluminal pH is significantly lower in patients with acute biliary pancreatitis than in controls, further support these observations.

E. Bile Acids and GERD

GERD is a highly common chronic condition associated with esophageal mucosal inflammation, which can progress to ulceration and metaplasia of the epithelium and increase the likelihood of developing esophageal adenocarcinoma (EA) (428, 487). First described in the 1800s, esophagitis was even then assumed to be a condition caused by reflux of stomach acid into the lower esophagus, causing intense pain, the appearance of gastric-like ulcers, and ultimately leading to esophageal perforation and death [reviewed in Barrett, 1950 (35)]. Bile acids became appreciated for their role in disease development in the early 1970s, with subsequent decades seeing much progress in understanding the cellular and molecular mechanisms involved (159). Similar to their actions in the lower intestine, the presence of bile acids in the esophageal lumen induces alterations in the expression of TJ proteins, such as claudin-1 and claudin-4 and induction of apoptosis, thereby contributing to the enhanced permeability and loss of barrier function associated with GERD (42, 63, 132, 343). However, in addition to dysregulated EEC barrier function, other studies suggest that immune-mediated mechanisms are also likely to be important and may even precede loss of epithelial barrier function (429). Furthermore, several studies suggest that bile acids are likely to contribute to this immune-driven response, since exposure of esophageal squamous epithelial cell lines and ex vivo mucosal tissues to bile acids significantly increases expression of cyclooxygenase-2 and inducible nitric oxide synthase, and secretion of the proinflammatory cytokines IL-8 and IL-1β, leading to enhanced migration of T cells and neutrophils into the mucosa (191, 293, 417, 429). Increased expression of FXR in the epithelium appears to be involved in mediating such responses (54, 92, 460), and a combination of acidic media with bile acids seems to be important. Interestingly, cytokine release from human esophageal epithelial cells can be prevented by the proton pump inhibitor omeprazole, an effect which may contribute to the therapeutic actions of the drug in patients with GERD (180).

A significant risk associated with GERD is development of Barrett's esophagus (BE), a condition estimated to affect ~6% of adults in the United States, in which the normal stratified squamous epithelium differentiates into an intestinal-type columnar epithelium (336, 430). BE is more common in Caucasians than other ethnic groups, and it has been proposed the condition occurs when both genetic and environmental factors combine to cause abnormal defensive responses to esophageal refluxate (376, 381). Although molecular events underlying the pathogenesis of Barrett's metaplasia are not yet fully understood, it is clear that they are multifactorial involving complex interactions among developmental signaling pathways, morphogenetic factors, and caudal homeobox (CDX) genes (134). CDX genes are normally expressed in epithelial cells of the lower intestine but not in the esophagus. However, in patients with esophagitis, CDX1 expression increases, subsequently leading to expression of CDX2, a transcription factor known to be a critical regulator of epithelial differentiation (77, 113, 178, 214). Conditional deletion of CDX2 in the intestine of mice leads to the formation of a squamous epithelium (129), whereas ectopic expression of the protein in the esophagus leads to the formation of a transitional epithelium, intermediate of squamous and columnar epithelia, with reduced proliferation and compromised barrier function (232). Furthermore, studies have shown that exposure to bile acids can promote such "transcommitment" of normal esophageal epithelial cells through repression of transcription factors, such as SOX2, that establish their normal squamous phenotype and enhancing expression of those, such as CDX2, that drive an intestinal columnar phenotype (62, 98, 179, 302, 442). Multiple upstream signaling mechanisms appear to be involved in mediating bile acid-induced effects on CDX2 expression, including ROS production via activation of NADPH oxidase NOX5-S, EGFr activation, activation of NFκB, induction of cytokine secretion, and upregulation of trefoil factors (23, 178, 240, 423). The development of BE is also associated with altered epithelial transport function leading to a dysregulated acid/base balance and intracellular acidification (138).

BE is the main predisposing factor for the development of EA, a condition with very low 5-yr survival rates and a rapidly increasing worldwide incidence (12). Development of EA from BE occurs progressively from low-grade dysplasia to high-grade dysplasia and ultimately to invasive EA. However, the incidence of BE progression to EA is very low,

occurring in only ~0.5% of patients, and although the factors involved in driving this transition are still not well-defined, they are multifactorial (74). Bile acids appear to play an important role through induction of ROS production, DNA damage, and persistent NFκB activation, leading to apoptosis resistance (177). Although FXR expression decreases during the transition from BE to EA, levels remain elevated with respect to normal esophageal epithelial cells, with expression of the receptor being reported as a poor prognostic factor. Interestingly, in contrast to its pro-apoptotic actions in CRC (cf. sect. IV), FXR appears to prevent apoptosis of EA cells, thereby promoting tumor growth, while at the same time it downregulates expression of CDX2, contributing to tissue dedifferentiation (92, 147, 285). Expression of TGR5 also increases as BE cells become increasingly dysplastic and may contribute to cancer development through induction of NOX-5S expression and generation of ROS (255, 279, 342).

F. Bile Acids and the Airways

Another important consequence of GERD is that refluxate in the esophagus can enter the airways by aspiration, resulting in bile acids, acid, and digestive enzymes coming into contact with the respiratory epithelia. One particular condition of which this is a feature is cystic fibrosis where up to 60% of patients have been shown to have bile acids present in their airways, with their presence being directly correlated with inflammatory indexes and decreased lung function (43, 349). Patients that have undergone lung transplantation are also at increased risk for bile acids entering the airways where they may contribute to the development of bronchiolitis obliterans syndrome (BOS), a common cause of organ rejection (43, 84, 85). Bile acids have been also associated with a poor prognosis in other conditions, such as ventilator-associated pneumonia (505), idiopathic pulmonary fibrosis (396), and respiratory distress syndrome (516). The latter can be particularly important in the setting of intrahepatic cholestasis of pregnancy (ICP), a condition which typically occurs in the third trimester of up to 1% of pregnancies in Western countries (347). Several factors contribute to the onset of ICP, including genetic, environmental, and hormonal influences, leading to dysregulation of the enterohepatic circulation with a marked increase in levels of maternal serum bile acids. As a consequence, bile acids accumulate in the amniotic fluid and can contribute to the onset of premature labor, infant respiratory distress, and stillbirth. Several studies have demonstrated increased levels of bile acids in the serum and bronchoalveolar lavage fluid (BALF) of neonates with ICP-associated respiratory distress (160, 514, 517, 518), while bile acids have also been shown to be elevated in BALF of infants after sudden infant death syndrome (165).

Despite these important clinical observations, until recently bile acids have been mostly considered only as biomarkers for aspiration of GERD, and their possible roles in modulation of airway physiology has been largely neglected. However, recent studies have begun to give significant insights into the detrimental actions of BAs in the airways, where they are proposed to promote damage through induction of cytokine release (7, 365), increased alveolar permeability (438), fibrosis (60), degradation of surfactant (95), and apoptosis (522). Furthermore, the presence of bile in the airways can lead to biofilm formation by cystic fibrosis-associated respiratory pathogens, which may be an important factor contributing to airway colonization by opportunistic microorganisms (458). The molecular pathways by which bile acids exert their actions in the airways are still poorly defined, although recent studies have implicated FXR in mediating their effects on airway epithelial survival, epithelial-mesenchymal transition, and activation of fibroblasts (59, 485). However, other studies demonstrating protective actions of FXR against airway inflammation and fibrosis suggest that there is still much to be learned of how this, and indeed other bile acid receptors, contribute to airway health and disease (78).

VII. THERAPEUTIC TARGETING OF BILE ACIDS IN INTESTINAL DISEASE

Given that bile acids perform so many critical roles in regulating intestinal physiology and pathophysiology, they provide excellent targets for development of new therapeutic interventions. Exploitation of bile acid-dependent regulatory mechanisms can be achieved either by the use of pharmaceuticals that target bile acid receptors and transporters, or alternatively, by indirect approaches that alter the luminal bile acid signature. In this final section, we briefly review the state of the art with respect to therapeutic targeting of bile acids which, at least at the time of writing, provides an index of how bile-acid-directed therapeutics may look in the future.

A. Bile Acid Receptor Modulators

The discovery of the FXR and TGR5 as nuclear and cell surface receptors for bile acids at the turn of the millennium represented a huge step forward in our ability to therapeutically manipulate bile acid-dependent regulatory mechanisms. Since its discovery, the crystal structure of FXR has been resolved, giving medicinal chemists the opportunity to apply rational drug design approaches in development of new receptor ligands (299, 413). A number of specific agonists have so far been developed, such as GW4064, PX-102, LJN452, and Ec001, but with only one to date having made its way into clinical use. In 2016, obeticholic acid (OCA), the 6α-ethyl derivative of CDCA, became the first synthetic bile acid to be approved by the FDA for use in patients. Marketed as Ocaliva, OCA is currently used in combination with UDCA for treatment of primary biliary cholangi-

tis (10) and is also in clinical trials for other liver diseases, including NASH and primary sclerosing cholangitis (9, 248, 499). However, given the central role that FXR plays in regulation of many extrahepatic aspects of human physiology, it is likely that agonists of the receptor will find additional therapeutic uses in the future. Based on its important roles in cholesterol, lipid, and carbohydrate metabolism, FXR agonists are also currently under investigation for metabolic disorders, such as obesity, diabetes, and cardiovascular disease (24, 257, 310, 408). With respect to intestinal diseases, preclinical studies in the DSS model of intestinal inflammation in mice suggest that FXR agonists might also be of use in treatment of IBD (128, 435). Based on our own studies demonstrating that FXR agonists inhibit fluid secretion into the gut (313), it is possible that such drugs may also have a future role in the treatment of diarrheal diseases. Patients with BAD could be expected to particularly benefit from the use of FXR agonists, since such drugs would be expected not only to inhibit colonic fluid secretion but also to reduce bile acid biosynthesis and the amounts of bile acids entering the colon (218). Indeed, a recent phase II clinical trial at Imperial College London demonstrated OCA to be effective in increasing serum FGF19 levels and alleviating diarrheal symptoms in BAD patients (480).

The crystal structure of TGR5 has not yet been resolved with the result that the identification and development of agonists for this receptor is currently lagging somewhat behind that of the FXR. Leading the way is INT-777, a semi-synthetic agonist which displays an affinity of 0.8 μM for TGR5 compared with >100 μM for FXR in cell-based assays (354). Work in preclinical models suggests that, similar to FXR agonists, drugs which target TGR5 have great promise for treatment of hepatic and metabolic disorders (70, 259). In the intestine, TGR5 appears to have important roles in regulating motility, secretion, and mucosal inflammatory responses (8, 50, 72, 109, 393, 488), suggesting that drugs targeting the receptor may find future uses in treatment of intestinal disorders, such as IBS and IBD. However, with first-in-man studies of TGR-5 targeted drugs still lacking at the time of writing, it would seem that such therapeutics are still some way off.

B. UDCA

As the primary component of bear bile, UDCA has been in use in Traditional Chinese Medicine for centuries to treat a range of maladies, including liver and intestinal disorders, poor vision, convulsions, and impotency, to name but a few (118). In Western medicine, UDCA has been in use for many years in the treatment of liver diseases, especially PBC (97). It has also been closely studied for its potential in preventing the development of CRC associated with primary sclerosing cholangitis and IBD. In this respect, low-dose UDCA has been reported to exert chemopreventive actions (38, 420), while its use at high doses over prolonged periods of time may actually increase the incidence of CRC (112). In clinical and preclinical studies, UDCA has shown promise in treatment of numerous extrahepatic conditions, including IBD (466). In various animal models of IBD, UDCA or its taurine-conjugated derivative reduces disease activity, attenuates mucosal cytokine levels, inhibits release of antimicrobial peptides, and prevents apoptosis (245, 280, 461, 509). UDCA also acts on mucosal immune cells to dampen their activation and the release of proinflammatory cytokines (330). Interestingly, although the primary metabolite of UDCA, LCA, is typically regarded as the most toxic of the colonic bile acids, our recent studies suggest that metabolism to LCA may, in fact, be required for the full expression of the protective effects of UDCA in intestinal inflammation (489). It is clear that considerable work is still required to elucidate relationships between UDCA, its metabolites, the microbiota, and mucosal inflammatory responses.

C. ASBT inhibitors

Chronic idiopathic constipation (CIC) is an extremely common condition, which affects ~25% of the general population and for which currently available treatments are often unsatisfactory (478). A new approach to therapy currently in clinical trials involves inhibition of the ileal ASBT. ASBT is localized on the apical membrane of enterocytes in the terminal ileum and plays a central role in absorption of conjugated bile acids from the intestinal lumen (90). Inhibition of ASBT reduces ileal absorption of bile acids resulting in increased hepatic synthesis and increased delivery to the colon, where they promote fluid secretion and motility (2). Elobixibat is a potent and selective inhibitor of IBAT, which has been shown in clinical trials to reduce colonic transit time, increase the number of spontaneous bowel movements, and improve stool consistency (68, 418, 501). Elobixibat has limited systemic bioavailability, thereby reducing the potential for side effects and drug interactions. The use of elobixibat may also have potential added benefits in patients with metabolic disorders, since inhibition of ileal bile acid reabsorption decreases activation of the FXR/FGF19 axis, consequently upregulating bile acid synthesis and reducing serum cholesterol. At the same time elobixibat also increases plasma levels of the incretin GLP-1, an effect that is likely due to luminal bile acids activating TGR5 on enteroendocrine L-cells (389). Such metabolic sequelae of ASBT inhibition suggest that drugs, such as elobixibat, may be of particular benefit to patients with either dyslipidemia or diabetes mellitus, both of which can be comorbidities of chronic constipation.

D. Bile Acid Sequestrants

Bile acid sequestrants (BAS; e.g., cholestyramine, colestipol, and colesevelam) are anionic nondigestible resins which

bind bile acids in the intestine, forming insoluble complexes which are then excreted in the feces. Originally developed for treatment of hypercholesterolemia, cholestyramine acts by disrupting the EHC, resulting in increased conversion of cholesterol to bile acids in hepatocytes, thereby lowering plasma LDL-C (287). BAS are also effective in improving glucose homeostasis through induction of TGR5-mediated GLP-1 release in the distal intestine (371, 427). As a consequence of these metabolic effects, BAS are currently receiving a great deal of interest for their potential as new treatments for obesity and type 2 diabetes (257, 431). Given that they bind luminal bile acids, one might expect that BAS should also be useful in treating bile acid diarrhea, and indeed, this is the case, as demonstrated by several clinical studies (reviewed in Refs. 52, 481). BAS have also been found to be of benefit in treating diarrhea associated with *Clostridium difficile* infection, microscopic colitis, and CD (29, 289, 329). BAS are generally safe to use, but cholestyramine and colestipol are often poorly tolerated due to poor palatability and frequent gastrointestinal side effects, such as constipation, abdominal pain, bloating, and flatulence (260). In contrast, colesevelam is available in tablet form and has only mild gastrointestinal adverse effects. Nonetheless, BAS can have significant drug-drug interactions which limits their therapeutic usefulness. To overcome some of these issues, a colonic release formulation of cholestyramine, known as A3384, has been recently developed and in clinical trials was found to be well-tolerated and efficacious in reducing diarrhea (17).

E. Dietary Manipulation

The saying that "you are what you eat" is certainly true when it comes to the makeup of our colonic bile acid signature. The Western high-fat/high-sugar/low-fiber diet, which is associated with the development of many diseases, including CRC, IBD, IBS, obesity, and diabetes, is also associated with a significantly altered bile acid signature. These changes occur, at least partly, as a consequence of increased hepatic bile acid biosynthesis in response to the high intake of fat and partly to their altered metabolism due to the presence of a "Westernized" microbiota in the colon (i.e., a high firmicutes-to-bacterioidetes ratio) (86, 318, 455, 472). Thus studies in mice have shown that consumption of a high-fat diet results in enhanced gut permeability, associated with increased levels of luminal bile acids, along with an increase in the ratio of DCA to UDCA (39, 316, 433, 434). Furthermore, studies suggest that Western diets, with their high meat intake, favor taurine rather than glycine conjugation of bile acids, leading an increase in taurine-metabolizing bacteria in the colon, such as *B. Wadsworthia*. In turn, increased production of hydrogen sulfide has been implicated in the pathogenesis of CRC and UC (100, 383). Thus avoidance of a Western diet in favor of one containing less fat and more fiber appears to be the simplest approach to modulate the intestinal bile acid signature for prevention of intestinal diseases (332, 383, 459).

F. Probiotics

Another way in which the luminal bile acid signature can be manipulated to treat or prevent disease is through the use of neutraceuticals, such as probiotics (197). To date, this approach has been most studied in the context of metabolic diseases, with probiotics, such as *L. rhamnosus GG* and *L. Reuteri*, being shown to prevent hypercholesterolemia and obesity in various preclinical and clinical settings (195, 281). Key to the positive effects of probiotics on lipid and cholesterol metabolism appears to be their expression of BSH enzymes, associated changes in conjugation/deconjugation of the bile acid signature, with consequent alterations in the ileal FXR/FGF19 axis (99, 196, 199). Thus, while there is still a great deal to be learned of the mechanisms and pathways involved, there appears to be some potential in employing probiotics as an approach to modulate the luminal bile acid signature to drive a more positive metabolic phenotype. Studies in animal models suggest that such an approach may also be useful for the treatment of intestinal diseases. For example, the BSH activity of *Lactobacillus johnsonii* La1 has been shown to prevent Giardia growth by producing secondary bile acids that are toxic to the parasite (451), while the 7α-dehydroxylating activity of *Clostridium scindens* creates a bile acid signature in mice that prevents *C. difficile* infection (49). Whether probiotic-driven alterations in luminal bile acid composition might be beneficial in patients with IBD remains to be determined, but available evidence would suggest that this should be the case. Bile acid modifying genes, including BSHs and 7α-dehydroxylases, are significantly altered in the microbiota of patients with UC and CD, likely underlying the generation of bile acid signatures with high levels of primary, conjugated, and sulfated bile acids (107, 241). While systematic analysis of clinical trials suggests that probiotics can have varying degrees of efficacy in alleviating IBD symptoms (133), studies employing bacterial strains specifically selected for their BSH or 7α-dehydroxylating activities are still required. Another exciting approach that is likely to be an area of increasing research interest in the coming years is the use of prebiotics (e.g., rice bran) to modulate the microbiota and bile acid signature for therapeutic purposes (299a, 320, 324).

G. Fecal Microbial Transfer

Fecal microbial transplantation (FMT) is defined as the transfer of fecal material containing bacteria from a healthy donor into a diseased recipient. Although used for centuries in traditional Eastern medicines, FMT is only recently gaining acceptance as an approach to therapy in Western societies (243, 366). FMT has been shown to be highly effective in treatment of recurrent *C. difficile* infection (CDI), with a "clinical cure" rate of >90% in most studies conducted to date (222, 226, 233). As might be expected, FMT dramatically alters the bile acid signature in CDI recipients from

one which contains high concentrations of primary bile acids, to one which contains predominantly secondary bile acids (495). Furthermore, recent studies suggest that FMT-induced changes in the colonic bile acid signature alone are sufficient to prevent *C. difficile* growth (495). These data clearly demonstrate the potential for using FMT as a therapeutic tool to manipulate luminal levels of bile acids in disease treatment. As a consequence of its success in CDI, FMT is currently under investigation for numerous other intestinal disorders, including IBD, IBS, and pancreatitis. As these studies progress, it will be critically important to monitor the role of bile acids in mediating any beneficial actions that are observed. Indeed, the potential for orally administered bile acids as an alternative to FMT is supported by a recent study demonstrating that UDCA inhibits the germination of *C. difficile* spores in vitro and effectively induced and maintained remission from recurrent CDI in a human subject (495). Further studies suggest that such a therapeutic approach could also be taken a step further through the development of synthetic bile acid analogues that prevent *C. difficile* growth but which are restricted to the gut lumen (436).

VIII. CONCLUSIONS

In this review we set out to describe some of the exciting advances that have been made over the past two decades with respect to our understanding of how bile acids regulate intestinal epithelial physiology in health and disease. Driven by the discovery of new receptors for bile acids, our knowledge of how epithelial cells sense changes in luminal bile acid signatures and the molecular pathways that are consequently activated is rapidly developing. At the same time, the endogenous and exogenous factors that bring about changes in the size and makeup of the bile acid pool are becoming increasingly understood. However, there is still much to be learned. The growing appreciation of the role that bile acids play in health and disease, along with increasing interest within the Pharma sector for exploiting bile acids in treatment of intestinal and extraintestinal disorders, ensures that this will remain an area of intense research activity for years to come. Particularly important, and equally challenging, is the development of our understanding of how bile acids act as signaling intermediates between us as humans and the microbes that colonize our guts. Cracking the code of this intra-kingdom dialogue and how epithelial cells integrate and transduce these signals into biological responses will be sure to provide valuable new targets for therapeutic intervention. It seems certain that whether it be through the use of receptor selective drugs, dietary manipulation, pre/probiotics, or fecal transplants, the coming years will see the emergence of new approaches to manipulate luminal bile acid signatures and associated epithelial signaling pathways in treatment and prevention of disease.

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Address for reprint requests and other correspondence: S. Keely, Dept. of Molecular Medicine, RCSI Education and Research Centre, Smurfit Building, Beaumont Hospital, Dublin 9, Ireland (e-mail: skeely@rcsi.ie).

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