Curr Treat Options Gastro (2019) 17:378–393
DOI 10.1007/s11938-019-00241-6

Colon (JC Anderson, Section Editor)

Interplay of Liver Disease and Gut Microbiota in the Development of Colorectal Neoplasia

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Published online: 20 July 2019

This is part of the Topical Collection on *Colon*This is part of the Topical Collection on *Colon*

Keywords Colorectal neoplasia · Liver disease · Bile acids · Gut microbiota · Inflammation · Dysbiosis · Colorectal adenoma

Abstract

Purpose of the review Liver disease, colon cancer, and the gut microbiome are intimately interrelated; however, the connections linking liver disease and colorectal neoplasia via the gut microbiota remain poorly understood and rarely addressed in a single space. The goal of this review is to take a broad perspective on the clinical problem of colorectal neoplasia in the liver disease population, recognize the significance of the clinical study findings, and delve into the evidence supporting putative molecular mechanisms connecting dysbiosis in the progression of liver disease to the development of colorectal neoplasia.

Recent findings Clinical studies have recently reported increased risk of colorectal neoplasia in patients with fatty liver disease, and risk increases with liver disease severity. Concurrently, the evolution of -omics technology has shown dysregulation of the gut microbial community, termed dysbiosis, in the progression of liver disease. Specific microbes enriched in the gut flora of liver disease patients have been linked to colon cancer and adenomatous precursor lesions.

Summary The gut microbiome of liver disease patients generates a pro-neoplastic environment, mediated via altered bile acid signaling and a dysregulated inflammatory response that suppresses immune surveillance. Research focused on the mechanisms linking liver disease to colorectal neoplasia via the gut microbiome is needed to help us

prepare for the rising tide of colon cancer in young patients with an increasing prevalence of liver disease.

Introduction

In the early 1940s, investigators observed hepatic dysfunction commonly accompanied gastrointestinal malignancy. These researchers noted significant decrease in vitamin A levels, hypoalbuminemia, impaired clearance of bilirubin, and impaired coagulation in the absence of clear metastasis to the liver. They postulated hepatic dysfunction was a consequence of gastrointestinal malignancy that would resolve upon removal of the tumor, noting patients who had survived surgical resection of their GI tumors did not bear evidence of ongoing liver compromise [1]. Investigators in the 1950s noted the common occurrence of three forms of liver disease in patients with ulcerative colitis including fatty change, portal inflammation, and cirrhosis of the biliary type [2]. Only later did a connection between liver inflammation and ulcerative colitis become more clear [3, 4]. Careful epidemiologic investigation and clinical observations in the field of inflammatory bowel disease ultimately guided investigators to link colorectal malignancy back to liver disease. Several teams in the 1980s documented the increased risk of colorectal neoplasia in patients with inflammatory liver disease, specifically recognizing the powerful neoplastic potential of primary sclerosing cholangitis associated with ulcerative colitis [5, 6]. Indeed, IBD patients suffering from the autoimmune liver disease primary sclerosing cholangitis (PSC) have the highest risk of colorectal malignancy in IBD and need regular endoscopic surveillance [7, 8]. There could be no better time than now to look broadly at the link between liver disease and colorectal malignancy given the rising tide of fatty liver disease globally.

Non-alcoholic fatty liver disease (NAFLD) is reaching epidemic proportions in the USA, and its prevalence, if accompanied by even a modest risk for colorectal neoplasia, could substantially alter the landscape of colorectal cancers. In support of this, several recent clinical investigations have helped better define the risk for fatty liver disease-associated CRC and precursor lesions [9–11]. This trend may preferentially hit younger patients, as we see dramatic increases in fatty liver disease and rising rates of colorectal cancer in these same patients [12, 13]. Hepatic steatosis is not alone—autoimmune liver diseases, viral hepatitis, and alcoholic liver disease have been shown to confer increased overall risk of colorectal neoplasia [14].

Mechanisms linking liver disease to colorectal neoplasia have been challenging to dissect. Fortunately, we now have improved tools to both measure the many components involved that may be driving neoplasia forward in the setting of an ill liver. The evolution of -omics technologies have enabled microbial ecologists to identify patterns of gut microbiota associated with colorectal neoplasia. Indeed, specific organisms have been associated with colon cancers and precursor lesions. These same technologies have also helped us learn how the gut microbiome evolves over the course of liver disease [15••]. Observations made in these two arenas share concerning overlap at both the microbe and molecular levels. These parallels support the possibility that the gut microbiota may in fact serve as a critical link transducing gut-liver axis signals.

At the center of this hypothesis is the epithelial interface of self and the lumen of the bowel, where the collective gut microbiome interacts directly with epithelia and mucosal immunity. Mucosal immune cells are differentially recruited and their function directly influenced by the microbes present as well as by the health of the host liver. This is a three-way conversation with gut, liver, and microbiota communicating via bile acid signaling, microbe-derived organic compounds including short chain fatty acids, liver-derived immune active retinoids, and

non-coding RNA molecules [16–18]. This review serves as a brief overview of the recent literature that looks at the interconnectedness of liver disease, gut microbiota, and colorectal neoplasia.

Liver disease and colorectal neoplasia: clinical associations

Fatty liver disease

As the new world leader of chronic liver diseases, fatty liver disease demands first evaluation and has been the focus of most recent studies. The prevalence of NAFLD in the general population is sobering. In the recently released practice guideline from the American Association for the Study of Liver Disease (AASLD), the summarized prevalence estimate, gleaned from our best studies to date, is approximately 20% [19]. Some of the more troubling individual studies referenced include the Dallas Heart Study, where MR spectroscopy identified NAFLD in 31% of the urban population screened, and the report from Lee et al. (South Korea), where 51% of liver biopsies taken from potential living donors were found to have evidence of NAFLD [20, 21]. The fatty liver disease epidemic parallels the rise of obesity in our patients and the separate contributions of these conditions to colorectal neoplasia are being aggressively investigated.

Two meta-analyses surveyed the landscape linking fatty liver disease and non-alcoholic steatohepatitis (NASH) to colorectal neoplasia prior to 2017. Understanding the limitations of the measurements taken in these large screening database studies (fatty liver disease assessed most frequently by a somewhat subjective interpretation of an imaging study—most commonly ultrasound, only infrequently with biopsy), the summary conclusions in each case identified a clear association of NAFLD with the presence of colorectal adenomas found on screening colonoscopy [9, 10]. A more recent meta-analysis and systematic review published in the latter half of 2018 reinforced these findings. The authors concluded that in the studies reviewed, encompassing a total of 91,124 asymptomatic adults (of which 32.1% had NAFLD) harboring 14,911 colorectal adenomas and 1684 cancers, NAFLD was independently associated with a moderate increase in prevalence and incidence of colorectal adenomas and colon cancers. The studies reviewed in this synthesis came from screening efforts in predominantly Asian populations. The strength of the association was modest in the studies that used imaging to define fatty liver disease, with odds ratio for prevalent disease of OR = 1.28 (CI 1.11–1.48) for colorectal adenomas and OR 1.56 (CI 1.25–1.94) for cancers. In a small study reviewed by the authors as part of their meta-analysis, liver biopsy-proven NAFLD conferred a more substantial risk of prevalent colorectal neoplasia: OR of 3.04 for prevalent cancer (CI 1.29–7.18). The calculated risks in this meta-analysis were independent of age, sex, smoking, body habitus, metabolic syndrome, and diabetes [22].

Fatty liver disease encompasses a wide range of disease, from seemingly benign fat infiltration of the liver without evidence of steatohepatitis to NASH

cirrhosis. Two smaller studies have attempted to characterize risk in the setting of liver disease severity, utilizing fibrosis risk scores to stratify patients in order to define colorectal neoplasia risk across the spectrum of disease. In both reports, worsening NAFLD severity drove increased burden of colorectal neoplasia, although at the lowest end of the diagnosis, steatosis without serum evidence of fibrosis or tissue injury did not confer an appreciable risk of increased colorectal adenomas [11, 23].

A more recent study undertaken by Ahn and colleagues in South Korea, explored the relationship of NAFLD to prevalent colorectal neoplasia in a cross-sectional study of patients participating in a "comprehensive health check-up program" at the Health Promotion Center of Samsung Medical Center in Seoul, South Korea between 2003 and 2012 [24]. Patients aged 18 and over underwent first-time screening colonoscopy as well as an abdominal ultrasound as part of the program. The study sample size was 26,540 patients. NAFLD severity was stratified with the use of fibrosis scoring systems using the aspartate aminotransferase to platelet ratio (APRI) score, fibrosis-4 (FIB-4) score, and NAFLD fibrosis score. Results were adjusted to address potential confounders of age, sex, smoking, alcohol, family history of CRC, aspirin use, and metabolic data (BMI, fasting blood glucose, use of diabetic medication, cholesterol, systolic blood pressure, use of anti-hypertensives).

NAFLD prevalence in their study was 35.8%. Colorectal neoplasia was found in 32.1% with advanced colorectal neoplasia found in 2.2% of patients screened. Prevalent colorectal neoplasia was higher in the NAFLD population (38.0 vs. 28.9%), and advanced neoplasia was likewise higher in the NAFLD patients (2.8% vs. 1.9%). Importantly, advanced fibrosis increased the burden of colorectal neoplasia; those with NAFLD fibrosis scores > – 1.455 (predictive of Metavir F2 fibrosis or greater) had an odds ratio of 1.66 (1.51–1.81) for any colorectal neoplasia and an odds ratio of 2.26 (1.75–2.92, $P < 0.001$) for advanced neoplasia.

Despite the strength of the associations proposed here, including an apparent dose effect of rising adenoma burden with increasing liver disease severity, the limitations of observational studies still remain. The authors of the meta-analysis work in this area call for more studies to establish risk associations, especially prospective analyses [10, 22].

Independent studies of small unique patient populations have likewise supported the association of colorectal neoplasia in patients with NAFLD/NASH. Patients undergoing liver transplant evaluation at a transplant center in the Northeast USA underwent colonoscopy as part of the transplant work-up. In this study, the authors found the highest prevalence of colorectal adenomas in patients with end-stage liver disease due to NAFLD/NASH and in those with a history of heavy alcohol exposure. They noted that the population of patients evaluated for liver transplant had a higher overall burden of colorectal neoplasia when compared with the non-transplant population [25].

Alcoholic, viral, and autoimmune liver disease

As reviewed above, colorectal neoplasia was more prevalent in liver-sick patients undergoing evaluation for liver transplant. Alcohol exposure is

known to drive the development of advanced neoplasia and intriguingly, patients transplanted for alcoholic liver disease retain a higher risk of developing colorectal neoplasia following transplant [26, 27]. Chronic viral hepatitis patients have likewise demonstrated an increased risk of developing colorectal neoplasia [28]. The link to autoimmune liver disease is strongest with PSC, and while autoimmune hepatitis and PBC patients harbor increased overall risk of cancer, the specific association with colorectal neoplasia is less well studied [29, 30].

Studies of the link between primary sclerosing cholangitis and colorectal neoplasia provide some intriguing insights into the mechanisms linking liver to gut and gut pathology. Formerly a first-line treatment option for PSC, the synthetic bile acid ursodeoxycholic acid (UDCA), is now no longer recommended for the management of this condition. However, studies of the use of ursodiol in PSC during its heyday bore interesting results. In a systematic review and meta-analysis, Singh and colleagues identified a data trend that suggested low-dose UDCA reduced the risk of advanced colorectal neoplasia in patients with PSC-IBD [31]. This suggests that modulation of the pro-neoplastic liver-bile-gut microbiota-colon epithelia circuit in PSC by an alternative bile acid produced a reduction in colorectal malignancies. Intriguingly, the gut-liver axis in the PSC patient remains problematic following liver transplantation, as multiple studies have shown OLT does not alter the CRC risk in these patients [32]. This suggests the liver is not the sole driver of cancer risk in these patients. Liver disease as well as colorectal cancer is propagated in these example patients by incompletely understood processes that include the gut microbiota, a previously unrecognized powerful factor.

Molecular and cellular events potentiating colorectal neoplasia—links to microbiota and liver disease

Immune system activation and chronic inflammation in the bowel lead to a loss of homeostasis between gut microbiota and the host epithelium. Disruption of the gut barrier leads to enhanced immune activation in the lamina propria by host gut microbes, potentiating a pro-neoplastic environment. Several immune activation pathways are upregulated both in IBD-associated as well as spontaneous colorectal adenomas and adenocarcinomas, including NF-κB, cyclooxygenase 2 (COX-2), TNF-α, and the pro-inflammatory cytokine IL-6 [33, 34]. Importantly, these pathways are chronically activated in the gut epithelia of patients with fatty liver disease, non-alcoholic steatohepatitis, viral hepatitis, and alcoholic liver diseases, in each case commonly associated with dysbiosis [35–38, 39••].

Specific immune cell components of the mucosa can play a central role in either the suppression or promotion of colorectal neoplasia. Bone marrow-derived myeloid cells play an active role in the production of an immune-suppressive and pro-inflammatory environment that can spur neoplasia forward while suppressing T cell immune surveillance and the appropriate elimination of tumor cells [40, 41•]. These bone marrow-

derived cells, termed "Myeloid Derived Suppressor Cells" (MDSCs) have been shown in animal models to be directly recruited to adenomas or adenocarcinomas by specific microbes, potentiating immunosuppression via modulation of the microenvironment. Microbes associated with colorectal lesions have been shown to spur cytokine and prostaglandin alterations in colonic epithelia that drive neoplasia forward unchecked by inhibiting effective host immunity [42]. Global shifts as well as specific microorganisms are associated with the development of colorectal neoplasia (summarized in Table 1). Several studies using phylogenetic analyses of patient samples have revealed altered microbial communities of

Table 1. Gut bacteria associated with colorectal neoplasia

Tissue	Overall diversity	Lower (reduction/loss)	Higher (gain/enrichment)	References
Healthy tissue	Normal	Bacteroidetes: Porphyromonadaceae Prevotellaceae Proteobacteria: Enterobacteriaceae Alcaligenaceae	Firmicutes: Lachnospiraceae Actinobacteria	[43]
Hyperplastic polyps	Normal	Lachnospiraceae Gammaproteobacteria: Enterobacteriales	Lactobacillus zeae Anaerostipes	[44]
Tubular adenoma	Reduced	Lactobacillus spp. Roseburia spp. Bifidobacterium spp.	Fusobacterium nucleatum Enterococcus feacalis *Streptococcus bovis* Enterotoxigenic *B. fragilis* Porphyromonas	[45]
Sessile serrated adenomas	Reduced	Erysipelotrichi	Fusobacteria	[44, 46]
Colorectal adenocarcinoma	Greatly reduced	Fecalibacterium Bifidobacterium Blautia	Lactobacillales Fusobacterium Porphyromonas Peptostreptococcus Mogibacterium Erysipelotrichaceae Prevotellaceae Coriobacteriaceae	[43, 47]
		Ruminococcaceae Clostridiaceae Lachnospiraceae	Proteobacteria: Alcaligeneaceae Enterobacteriaceae Porphyromonadaceae Prevotellaceae *Streptococcus gallolyticus* *Enterococcus faecalis* *Bacteroides fragilis* Fusobacterium nucleatum	[43]

patients harboring colorectal adenomas or adenocarcinomas. The principle changes observed include loss of diversity and outgrowth of specific microbes [41•, 48, 49].

Gut microbiota changes associated with colorectal neoplasia

Inflammatory diseases including chronic liver disease and inflammatory bowel disease (IBD) share a trend towards this loss of diversity in the gut microbiome [47, 48]. In the setting of colorectal neoplasia, loss of representatives in the Firmicutes phylum (esp. family Lachnospiraceae: Anaerostipes, Blautia, Dorea, Eubacterium hallii, Pseudobutyrivibrio) is detrimental while outgrowth of pro-carcinogenic Porphyromonads, Prevotellaceae, Enterobacteriaceae, and Alcaligenaceae of the phylae Bacteroidetes and Proteobacteria appears to be harmful [43]. Beyond global shifts in phyla, certain specific organisms have been identified as likely pro-oncogenic.

The gram-negative bacterium *Fusobacterium nucleatum* has been directly implicated in the development of colorectal neoplasia. *F.nucleatum* is a common component of periodontal plaque and is most commonly found associated with dental disease but has also been impugned in squamous cell carcinoma of the oral cavity [40, 50]. Using deep-sequencing techniques, several laboratories identified *Fusobacterium nucleatum* enrichment in colorectal adenomas and adenocarcinomas compared with normal colon tissue from the same host [51–53]. Rarely seen in healthy patient gut microbiome, *F. nucleatum* is more commonly found in the intestinal flora of IBD patients and *Fusobacteria* spp. are likewise enriched in the gut microbiota of cirrhotic patients [54, 55]. Global breakdown of mucosal barriers with dysbiosis in both the gut and oral cavity is observed in the progression of liver disease to cirrhosis and in the transition from compensated cirrhosis to decompensated disease [55, 56]. This breakdown of mucosal integrity may allow the propagation of oral microbes throughout the GI tract in the setting of liver disease, producing a microbial environment primed to support or initiate colorectal neoplasia in patients with hepatic dysfunction [57].

Other organisms more classically associated with colorectal neoplasia include *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*). *S. gallolyticus*/*S. bovis* bacteremia in the hospitalized patient inevitably prompts a hunt for a colorectal cancer, and the interaction of this organism with host gut epithelial and immune components has recently been better defined. In similar fashion to *F. nucleatum*, *S. gallolyticus* appears to recruit myeloid cells to the tumor tissue inducing a feed-forward inflammatory profile with IL-6, COX-2, and TNFα production that promotes neoplasia and suppresses T cell function [40, 58]. Globally, these organisms are enriched in both precursor lesions as well adenocarcinomas of the colorectum [44, 45]. A summary of reported observed trends in microbiota populations associated with colorectal neoplasia is provided in Table 1.

At the gut mucosa boundary, microbe-microbe and microbe-epithelial interactions can regulate intestinal permeability and intestinal inflammation, potentiating the environment in which colorectal cancer may arise [59]. Many

inputs into this local system influence the composition and metabolic activity of bacteria in both the luminal and mucus boundary layer niches. Food, alcohol, and medications are principle drivers. Antibiotic therapy potently predisposes to dysbiosis. Epidemiologic analyses demonstrate antibiotic exposure increases the risk of de novo IBD, fatty liver disease, and colorectal neoplasia in a dose-dependent fashion [60–65]. Once disrupted, dysbiosis initiates a cascade leading to sustained inflammation in both liver and gut, potentiating neoplasia in both locations. Importantly, the flow of information and signals in the enterohepatic circuit works in both directions. The liver is directly influenced by gut permeability and intestinal inflammation. Increased permeability leads to a larger burden of bacterial products including Toll-like receptor (TLR) ligands in the portal circulation. The liver in turn then exerts a direct effect on the bowel via the immunomodulatory properties of bile and secretion of cytokines into the systemic circulation [66]. Independent of the changes observed in the CRC and adenoma research fields, distinct shifts in the gut microbiome accompany the progression of liver disease.

Gut microbiota changes associated with liver diseases

Gut microbiota composition in both chronic liver disease and colorectal neoplasia follow common patterns. As detailed above, loss of diversity in the gut microbial community is a hallmark of patients with colorectal neoplasia. In some of the earliest analyses that identified this trend, diversity between patients and within CRC tissue was assessed [47]. CRC tissue exhibited a loss of diversity and specific enrichment in certain organisms such as *Fusobacterium nucleatum* [41•, 53]. In parallel, studies assessing the structure of the gut microbiota with liver disease have likewise demonstrated a shift towards reduced diversity [67]. As liver disease progresses, the structure of the gut microbiome shifts from a Bacteroidetes–phyla dominated profile towards a profile enriched with microbes from the Firmicutes phylum [35]. When this pattern is seen, it is often associated with a trend towards increased intestinal permeability, aberrant immune activation in the gut epithelium, and altered metabolic function of the new community of gut microbes [68–70].

Liver disease shifts in gut microbiota are therefore characterized by loss of diversity, enrichment of facultative anaerobes, and subsequent immune activation in the intestinal epithelium. Specifically, aberrant activation of mucosal immunity towards a pro-inflammatory state is thought to potentiate the comorbid disease associations with NAFLD including malignancy and cardiovascular disease [71]. This inflammatory change is linked to shifts in the structure of the gut microbiota towards the Firmicutes-dominant profile [72]. As with colorectal neoplasia, individual organisms have been identified in the microbial communities of liver disease patients that appear to associate with advancing disease. In a recent observational study, outgrowth of *Enterococcus* sp. (oral microbes) in the gut microbiota was identified as a driver for the progression of liver disease. Interestingly, proton-pump inhibitor use allowed propagation of oral microbiota into the proximal bowel in their patient cohort effectively spurring on liver disease by altering the gut microbiota community [15••]. The observational data across both fields of liver disease and colorectal

neoplasia has demonstrated global shifts in the gut microbiome with a reduction in diversity and outgrowth of specific organisms associating with disease states. Subsequent skewing of mucosal immunity towards a pro-inflammatory and tumor permissive state is proposed as a key piece of the mechanism linking dysbiosis to malignancy. Continued investigations are needed to elucidate the molecular pathways involved in this circuit, but some compelling observations in the fields of bile acid signaling and microbial fatty acid metabolism have provided interesting leads.

Bile and short-chain fatty acid metabolism and signaling: linking liver to gut

A critical component of the enterohepatic circuit, the bile acid pool is made up of primary bile acids, which are produced by the host, and secondary bile acids that are products of bacterial modification of those molecules. Humans make two principle bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), via oxidation of cholesterol. These are then conjugated to either glycine or taurine by hepatic enzymes to produce glycocholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid, which are secreted into the bile canaliculus via the action of the bile salt export pump (BSEP). Separately, CA and CDCA can also undergo sulfation or glucuronidation prior to glycine or taurine conjugation and are then exported to the bile flow via the multidrug resistance-associated protein 2 (MRP2).

Gut microbiota biotransform intestinal bile acids to bioactive forms that activate bile acid signaling receptors. Several gut bacteria participate in this process to produce bioactive secondary bile acids (Table 2). These microbes generate secondary bile acids via step-wise bile-salt hydrolase deconjugation, C-7 epimerization, and 7α-dehydroxylation (reviewed in [75]). The most abundant bile acids in mammals include the principle primary bile acids CA

Table 2. Gut microbiota production of secondary bile acids; examples of contribution to colorectal neoplasia

Organisms	Pathway	Products	Oncogenic	Reference
Bacteroides Clostridium Lactobacillus Bifidobacterium Listeria	Bile salt hydrolysis; deconjugation	CA CDCA	Precursor to DCA	[16]
Bacteroides Clostridium Escherichia Eubacterium Peptostreptococcus Ruminococcus	C-7 epimerization, 7α-dehydroxylation	DCA LCA	++	[73]
Bilophila	Taurine respiration (from taurine-conjugated bile acids)	H_2S	++	[74]

and CDCA and the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA). Importantly, bile acids are active signaling molecules, serving as ligands for nuclear receptors including the farnesoid X receptor (FXR), G protein-coupled bile acid receptor (TGR5), pregnane X receptor, the vitamin D_3 receptor, and the constitutive androstane receptor (CAR). Intriguingly, bile acid signaling has been directly linked to hepatic carcinogenesis. In one elegant example, increased DCA production from dysbiosis drove hepatocellular carcinoma in an obesity-associated HCC mouse model [76]. Colorectal neoplasia has likewise been linked to a Western diet that induced increases in secondary bile acids DCA and LCA, which increase oxidative damage, activate NF-κB, and stimulate colonocyte proliferation [73, 77]. Animal models have furthered this line of investigation with researchers recently demonstrating DCA-driven colon carcinogenesis linked to dysbiosis [78•, 79]. Other investigators have linked bacterial metabolism of taurocholic acid (enriched in Western diets replete with red meat) to the development of colorectal neoplasia via the combined effect of its bacterial deconjugation to hydrogen sulfide (oxidant) and deoxycholic acid (a potent genotoxin) [74].

Many steps in the bile acid generation and recirculation pathway may alter the quantity of secondary bile acids passing into the colon. High levels of intracellular bile acids are toxic in either liver cells or intestinal cells. Consequently, both ileal enterocytes and hepatocytes have negative feedback loops in place to regulate bile acid uptake and enterohepatic recirculation. Under normal physiologic conditions, FXR signaling in the ileum downregulates the apical sodium-dependent bile acid transporter from the brush border. FXR signaling in the ileum induces expression of the ileal bile acid binding protein which then facilitates bile acid transport across the basolateral membrane of the enterocyte into the portal vein. Once in the liver, bile acids are taken up by the sodium/taurocholate co-transporting polypeptide (NTCP). The brakes on bile acid production get applied in the hepatocyte where FXR engagement by bile acids suppresses de novo synthesis. Via these regulatory mechanisms, 90–95% of the bile acid pool recirculates and only a small amount of bile acids are generated each day to compensate for losses in the lumen of the bowel [16]. Inflammation in the mucosa, be it in the setting of IBD, or low-grade inflammation from underlying liver disease, can disrupt this equilibrium, leading to increased local concentrations of secondary bile acids in the intestine. TGR5 expressed on intestinal macrophages can then be activated leading to a net induction of immunosuppressive "M2"-like polarization of the macrophage population with the potential to reduce immune surveillance for epithelial neoplasia [80]. Altered bile acid pools, augmented by dysbiosis, affect both liver and gut mucosa. In the small bowel and colon, these changes produce a shift in mucosal immune cell populations and function. In the liver, bile acids shift the inflammatory environment of the sinusoid, potentiating activation of stellate cells and inflammatory cytokine production in hepatocytes [81].

The link between colorectal neoplasia and chronic liver disease is strengthened by recognition of this putative mechanistic connection: bile acids can directly influence mucosal immunity, alter inflammation in the liver, and also potentiate colorectal neoplasia. As with gut microbiota dysbiosis, significant research in the bile signaling realm has revealed substantial changes in the bile acid profiles in chronic liver disease. High-quality studies have identified altered bile acid composition in the gut, peripheral circulation, or urine in

autoimmune liver diseases, fatty liver disease, viral hepatitis, and liver disease driven by alcohol consumption [82–86].

Paralleling the work in bile acid metabolism and signaling by gut microbiota, several recent studies have demonstrated shifts in short chain fatty acid (SCFA) metabolism by the gut microbiome can potentiate both liver disease and colorectal malignancy. Butyrate has long been recognized as an important microbe-derived nutrient for colonocytes, and butyrate enemas are used in the treatment of diversion colitis [87]. In the example of diversion colitis, the gut microbiota in the diverted colon are starved of dietary fiber, which in turn deprives colonocytes of the needed short-chain fatty acid produced. Butyrate is one of several short-chain fatty acids, synthesized by gut microbiota during fermentation of non-digestible carbohydrates such as non-starch polysaccharides and resistant starches. Formate, acetate, and priopionate along with butyrate make up the principle pool of bacterial-derived metabolic products [88]. Butyrate, in addition to its anti-inflammatory effects, has demonstrated anti-neoplastic properties via direct inhibition of colorectal cancer cells and immune-modulation of the T cell compartment [89–91]. Importantly, cirrhotic patients and patients with advanced fibrosis have reduced butyrate production in their colons and instead demonstrate an increase in formate and acetate [92, 93]. This reduced capacity of the liver-disease microbiota to produce SCFAs that

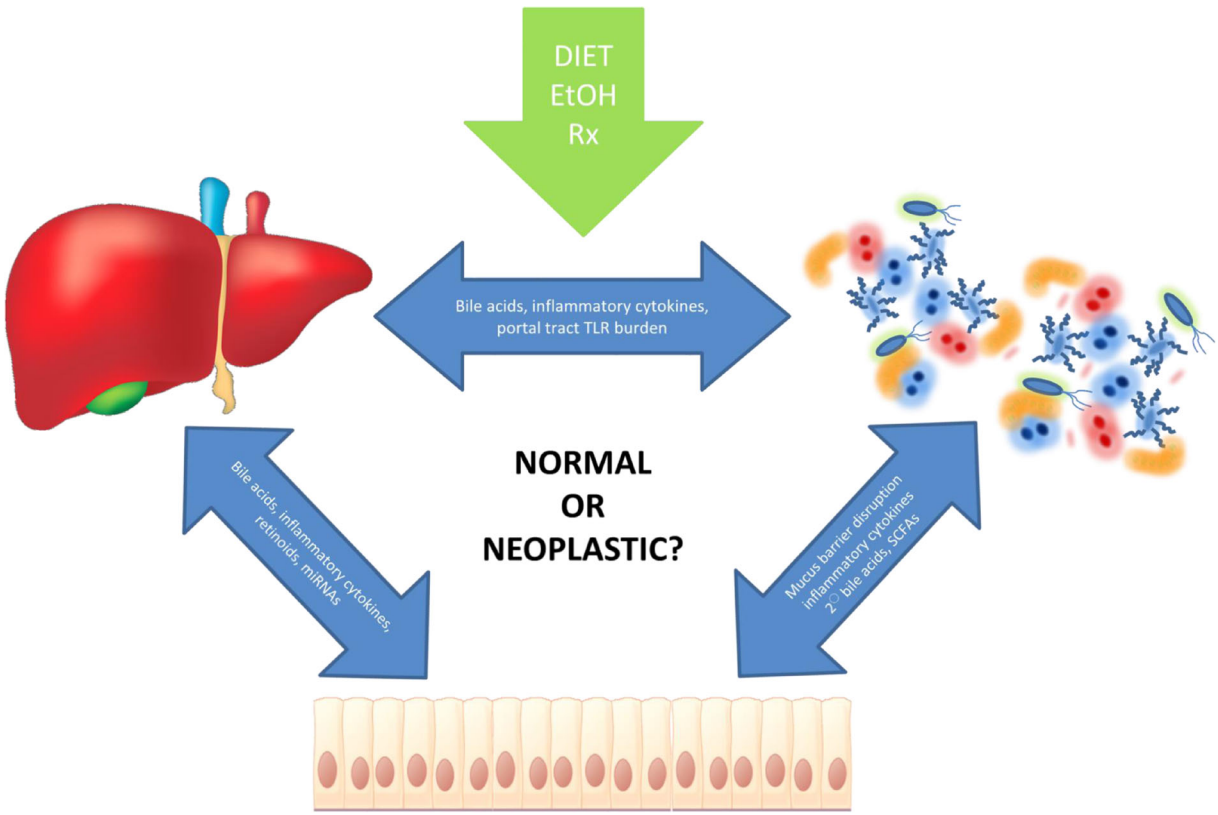

Fig. 1. Multi-faceted interactions between liver, mucosal epithelium, and the gut microbiome can protect against or potentiate neoplasia.

can promote colon integrity and quell inflammation in the gut contributes directly to the process of neoplasia in liver disease (Fig. 1).

Conclusion

The interwoven connections of liver disease, the gut microbiome, and colorectal neoplasia are dynamic and remain only poorly understood. Disruption of the balanced circuit leading to dysbiosis, aberrant bile signaling, altered SCFA profiles, and inflammation can and will drive colorectal neoplasia forward. Dissecting the many processes linking liver disease to colorectal neoplasia will shed light on the basic mechanisms of barrier function, immune tolerance, and immune surveillance of cancer in the complex ecology that is the gut-liver environment. There is an explosion of obesity and fatty liver disease in our patients and a troubling rise in colon cancers in the young. As providers, we need to be cognizant of the underlying drivers of dysbiosis that contribute to the diseases we treat. Acid suppression and antibiotic prescriptions are important tools in our medical armamentarium, but recognition of the potential downstream unintended consequences will be required. Counseling our patients to stop drinking, lose weight, and eat more fiber is more urgent than ever before.

To truly prepare for the burden of disease ahead, we need to better understand the mechanisms linking liver disease to colorectal neoplasia. This will require many layers of investigation including careful epidemiologic work linking features of dysbiosis to disease and cancer risk along with mechanistic studies that delve into the biology of these processes. Fatty liver disease now leads as the principle driver of liver disease complications. We need to discover ways to predict, identify, and intervene in the surge of colorectal malignancy that will follow the fatty liver disease tsunami.

Compliance with Ethical Standards

Conflict of Interest
Dr. Gleeson declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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