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Cruel to Be Kind: Epithelial, Microbial, and Immune Cell Interactions in Gastrointestinal Cancers

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Abstract

A plethora of experimental and epidemiological evidence supports a critical role for inflammation and adaptive immunity in the onset of cancer and in shaping its response to therapy. These data are particularly robust for gastrointestinal (GI) cancers, such as those affecting the GI tract, liver, and pancreas, on which this review is focused. We propose a unifying hypothesis according to which intestinal barrier disruption is the origin of tumor-promoting inflammation that acts in conjunction with tissue-specific cancer-initiating mutations. The gut microbiota and its products impact tissue-resident and recruited myeloid cells that promote tumorigenesis through secretion of growth- and survival-promoting cytokines that act on epithelial cells, as well as fibrogenic and immunosuppressive cytokines that interfere with the proper function of adaptive antitumor immunity. Understanding these relationships should improve our ability to prevent cancer development and stimulate the immune system to eliminate existing malignancies.

Keywords

immunity; inflammation; gut-liver axis; microbiome; immunotherapy

I must be cruel only to be kind; Thus bad begins, and worse remains behind.

—William Shakespeare, *Hamlet*

INTRODUCTION

A century and a half ago, the founding father of modern pathology, Rudolph Virchow, suggested that chronic irritation (inflammation) can lead to cancer. Very little was understood about cancer or inflammation at the time, but certain aspects of that prediction have been verified using the tools of modern molecular biology. In fact, inflammation has been recognized as one of the key enablers of the malignant state (1), contributing to cancer

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initiation, progression, and response to therapy (2). Oddly, Virchow's academic nemesis was Robert Koch, a pioneer of modern microbiology who came up with the bacterial theory of disease, which Virchow was reluctant to acknowledge. Now we know that bacteria and their products are key drivers of inflammation, not only in the context of infectious disease but also in cancer and premalignant conditions. In this review, we cover recent advances in understanding the origin of tumor-elicited inflammation and the myriad of different mechanisms by which it affects cancer initiation and progression. As the topic of inflammation and cancer has been amply reviewed in the recent past (3, 4), we focus this review on gastrointestinal (GI) malignancies, those that arise along the GI tract, the liver, and the pancreas. Our decision to focus on GI cancer is based not only on our own research interests but also on the fact that the initial human epidemiological studies that provided important support for the role of inflammation were conducted on GI malignancies (5–8). Furthermore, the origin of tumor-promoting inflammation in GI cancer is fairly well understood, and much of it can be attributed to loss of epithelial barrier integrity. Once the barrier is compromised, commensal microbes and their products lead to activation of the major inflammation-activated transcription factor NF-κB, which through induction of IL-6, TNF, and other cytokines can accelerate the development of colon (7), liver (9), and pancreatic (10) cancers.

Although cancer is a disease of uncontrolled cell proliferation, it should be realized that the healthy human liver or pancreas hardly contains any proliferating cells, especially not at the age at which most cancers are detected. Also, the large intestine, encompassing the colon and rectum, the two sites at which most intestinal cancers are commonly initiated, exhibits lower rates of cell proliferation than the small intestine, at which primary cancer is hardly detected. In the adult liver, it is quite clear that cell proliferation only occurs as a response to necroinflammatory injuries triggered by chronic hepatitis B and C viral (HBV and HCV, respectively) infections, excessive alcohol consumption, fat accumulation, or exposure to certain toxicants. Such injuries trigger chronic inflammation (hepatitis) that stimulates proliferation of periportal hybrid hepatocytes, cells that hardly ever give rise to cancer (11), and fully differentiated zone 3 hepatocytes that have been implicated in the initiation of hepatocellular carcinoma (HCC), the major type of liver cancer (12). In the pancreas, chronic tissue damage gives rise to inflammation (pancreatitis), which converts fully differentiated acinar cells to ductal progenitors, which have higher proliferative capacity through acinar-to-ductal metaplasia (ADM) (13, 14). In colorectal cancer (CRC), however, the relationship between cell proliferation and tumor initiation is more complex, as the colon contains a population of true stem cells (whose existence in the mature liver remains controversial, although it is generally agreed that adult tissue stem cells are not part of the pancreas) that are in charge of maintaining mucosal layer integrity (15). However, the rate of cell division in the healthy colonic mucosa is considerably lower than that in the small intestinal mucosa. Since inflammatory bowel disease (IBD) affects either the large intestine (ulcerative colitis) or both small and large intestines (Crohn disease), the key difference in cancer rates between these two parts of the GI tract is unlikely to reside in their ability to develop inflammation. Instead, the colon and rectum host a much larger population of commensal microbes, with colonic bacteria accounting for 70% of all bacteria in the human body (16). As discussed below, loss of intestinal barrier integrity and the

ensuing translocation of commensal microbes or their products is the key contributor to tumor-elicited inflammation in the colon (17). More surprisingly, loss of gut barrier integrity has also been implicated in some of the key inflammatory conditions that give rise to HCC, pancreatic ductal adenocarcinoma (PDAC), and bile duct cancer, which are some of the most aggressive and treatment-refractory malignancies (18), and for which an influential role of the microbiome has been recognized (19). Moreover, barrier disruption and the ensuing inflammatory response profoundly affect and modulate both natural immunosurveillance and drug-induced antitumor immunity.

THE GUT BARRIER AND ITS CONNECTION TO THE LIVER AND PANCREAS

Given the important role of gut barrier disruption in the initiation of most GI malignancies, we discuss key features of the intestinal epithelial barrier and its relationship with the mucosal immune system (Figure 1). The GI tract represents a unique challenge to the immune system, which must tolerate gut microbiota and maintain homeostatic conditions that prevent microbial dysbiosis and overproliferation of facultative pathogens. While not responding to food products and microbial components, the immune system needs to protect the host from invading bacteria and potentially harmful ingested antigens. The intestinal epithelium, composed of a single-cell layer, is crucial for preserving gut homeostasis and acts as not only a physical barrier but also a source for antimicrobial peptides and proteins, such as α-defensins, lysozyme, and different RegIII isoforms (20). Small intestinal villi and crypts and large intestinal crypts undergo constant cycles of intestinal epithelial cell (IEC) replenishment and renewal, and under homeostatic conditions, an entire crypt is replaced every four to five days. A crypt consists of enterocytes, the most prominent cell type of the intestinal epithelium that is responsible for nutrient and water absorption; mucin-secreting goblet cells; hormone-secreting enteroendocrine cells; Paneth cells that release antimicrobial factors/peptides (AMPs); and intestinal stem cells. Paneth cells are unique to the small intestine; they are the major sources of α-defensins, lysozymes, ribonucleases (like angiogenin 4), and secretory phospholipase A2. However, although Paneth cells are unequally distributed along the GI tract, enterocytes can also express different AMPs like REG3γ and REG3β, and in the large intestine β-defensin and cathelicidins are produced by IECs. Goblet cells, which are more abundant in the large intestine, express AMPs like RELMβ, ANG4, REG3γ, and REG3β (21). All of these cells express tight junction proteins (TJPs), including occludins, claudins, zonula occludens, and junctional adhesion molecules (JAMs) that provide a tight but highly regulated seal that allows passage of essential molecules but restricts entry of harmful substances and bacteria. Tight junctions are regulated by extracellular stimuli, including cytokines, via small GTPases and protein kinases, although the exact mechanism and function of individual TJPs remain elusive (22). Tight junctions form two types of barriers: the paracellular and intramembrane barriers, the first of which regulates selective paracellular permeability, which is the passive transport of molecules across the tissue and between distinct compartments of the body. The intramembrane barrier restricts the exchange of membrane components between the apical and basolateral cell surface domains (fence function) (22). IECs are in direct contact with the microbiota and express a variety of pattern recognition receptors (PRRs), like Toll-like

receptors (TLRs) that signal via MyD88 and TRIF to activate NF-κB and IRF signaling and also promote NLRP3 inflammasome activation (23, 24).

Under homeostatic conditions, RORγt-expressing lymphoid cells, including $CD4^+$ T helper type 17 (Th17) cells, γδ T cells, and innate lymphoid cells (ILCs), support host defense and tissue repair (25, 26). IL-10-secreting T regulatory cells (Tregs) are abundantly represented in the healthy tissue and are responsible for preventing excessive inflammation. IgA-producing B cells (which are described in more detail below) maintain microbial homeostasis and prevent overproliferation of inflammation-causing bacteria (27, 28). Virulent pathogens, like *Citrobacter rodentium*, can induce an IgG response, which is not elicited by commensals or avirulent pathogens (29). Under inflammatory conditions (Figure 2), however, translocating bacteria or microbial products activate local myeloid cells to produce IL-23, promote IL-17-related inflammatory responses (30), and inhibit Treg generation (25, 31). These alterations not only lead to chronic gut inflammation but also influence systemic, liver, and pancreatic inflammation. The so-called gut-liver axis, which is based on the anatomical and physiological connection between the liver and gut through the biliary tract and portal vein, allows delivery of liver-produced bile acids to the GI tract, while lipid-rich and endotoxin-containing blood is received from the small intestine to be filtered in the liver. Since most bacterial metabolites and food antigens are cleared in the liver, the liver and intestine share some common immunological features. Given that the GI tract contains a larger mass of immune cells than any other organ system, many of these cells also reach the liver. Importantly, both tissues need to work together to maintain a delicate balance between immune reactivity and tolerance, which probably makes them more susceptible to chronic inflammatory diseases (32).

Nonparenchymal liver cells are thought to be responsible for establishment of tolerance, including resident dendritic cells (DCs), plasmacytoid DCs, liver sinusoidal endothelial cells, and Kupffer cells, as well as hepatic stellate cells (HSCs), Tregs, and IgA^+ plasmocytes (33, 34). These cells mediate immunosuppression via expression of anti-inflammatory cytokines such as IL-10 and TGF-β, as well as the negative costimulatory molecule programmed cell death ligand 1 (PD-L1). The close interaction between the liver and gut enables them to influence and modulate each other's fate during disease conditions. For example, a relatively common extraintestinal manifestation of IBD is hepatic steatosis. Furthermore, hypernutrition, fructose consumption, and alcohol abuse promote the development of steatohepatitis, in part through barrier disruption, dysbiosis, and perturbation of gut immune homeostasis. Interestingly, nonalcoholic fatty liver disease (NAFLD) is often associated with presence of colorectal adenomas (35, 36). Although the detailed mechanisms remain elusive, the balance between inflammation and tolerance induction seems to contribute to all of these pathologies, with inflammation due to barrier disruption playing a cardinal role, as discussed below.

INFLAMMATION IN COLORECTAL CANCER

Early studies of inflammation and its role in colorectal tumorigenesis were mostly focused on colitis-associated cancer (CAC), a specific form of CRC that is likely to appear in IBD patients. CAC accounts for only 2% of all CRCs, although it is responsible for 15%

of all causes of death among IBD patients; but unlike sporadic CRC, its connection with inflammation was obvious, hence the early interest in this particular malignancy (37–41). Comparison between CRC and CAC is provided in Table 1. Of note, CAC risk increases with the length and severity of the disease. In ulcerative colitis, around 2% of patients develop cancer after 10 years, 8% after 20 years, and 18% after 30 years. Approximately 8% of Crohn disease patients develop precancerous lesions or CAC after 30 years (42, 43). One of the most popular mouse models of CRC—the azoxymethane (AOM) plus dextran sulfate sodium (DSS) model—is based on a combination of DSS-induced experimental colitis with carcinogen (AOM) exposure. The key differences in the mutational mechanisms that give rise to CAC on one hand and sporadic and familial CRC on the other have been amply discussed (41, 44–48). Although loss or inactivation of the tumor suppressor *Adenomatous polyposis coli* (*APC*) gene is the first genetic event in sporadic and familial CRC, followed by *SMAD* and *TP53* mutations, next-generation sequencing has identified *TP53* loss-of-function mutations and recurrent loss- or gain-of-function mutations in *KRAS*, *APC*, *EGFR2*, *MLL*, and *EP300* in CAC (49–51). Most importantly, recent evidence also implicates inflammation in the initiation of sporadic and familial CRC (52, 53), making them less different from *APC*-independent CAC than previously thought. Life style factors, including obesity, cigarette smoking, and sedentary lifestyle, have been described to support CRC, probably by inducing or contributing to inflammation (8, 54). We, for instance, found that activation of NF-κB in murine IECs, which also takes place in both CAC and sporadic/familial CRC, results in induction of NO synthase (iNOS), which gives rise to nitrosatively damaged DNA (55). When this takes place in mouse IECs that harbor a single *Apc* allele, iNOS-induced DNA damage accelerates loss of the remaining *Apc* allele, giving rise to aberrant crypt foci (ACFs), the preneoplastic lesions that precede colonic adenomas. Exactly how DNA damage accelerates loss of heterozygosity is not entirely clear, but one plausible mechanism is recombination-based DNA repair. However, nitrosative DNA damage in IECs that harbor wild-type *APC* may result in acquisition of different oncogenic mutations.

The origin of inflammation in human CAC can be either autoimmunity, as is the case of ulcerative colitis or Crohn disease, which, although not a typical autoimmune disease, is characterized by uncontrolled activation of immune cells, particularly T cells. Both diseases are associated with dysregulated production of TNF and other inflammatory cytokines, such as IFN-γ and IL-17 (26, 56–58). In DSS-treated mice, however, inflammation is initiated by barrier disruption and enhanced translocation of microbes or microbial products, such as endotoxins and nucleic acids, that activate TLR signaling in mucosal macrophages (53, 59). On NF-κB and NLRP3 inflammasome activation, these macrophages produce several tumor-promoting cytokines, including TNF, IL-6, and IL-1β (44). Beyond endotoxin and nucleic acids, commensal-IgG immune complexes also activate NF-κB and NLRP3 inflammasomes via Fcγ receptors (FcγRs) (31). Moreover, IgG immune complex cross-linking of neonatal Fc receptor (FcRn) in DCs promotes Th1/Tc1 cytokine secretion and shows protective immunity against CRC in mice (60). Much of the early work on the DSS-AOM model had focused on the role of IL-6, which activates STAT3 to increase the survival and proliferation of IECs that harbor AOM-induced oncogenic mutations (7, 61). Another cytokine that contributes to STAT3 activation in CAC is IL-11, which unlike IL-6 is mainly produced by activated stromal fibroblasts (62). Another model used for deliberate

induction of oncogenic colonic inflammation is infection with *Helicobacter felis* (63). In addition to macrophages, both DSS and *H. felis* activate ILCs that produce IL-22 (64). IL-22 is a regeneration-inducing cytokine that activates intestinal stem cells (65). IL-22, however, is not the only regeneration-inducing cytokine, as IL-6 appears to be even more critical for postinjury barrier restoration (61). In addition to STAT3, the regenerative activity of IL-6, and probably IL-22 as well, depends on activation of the key regenerative and reparative transcriptional activator YAP (66). Whereas IL-6-induced STAT3 activation depends on the JAK subgroup of tyrosine kinases, YAP activation depends on Src tyrosine kinases (66). Notably, STAT3, JAK, YAP, and Src/Yes activation is not restricted to mouse models of CAC but was found to take place in 70% of human CRCs (67).

The common occurrence of STAT3 and YAP activation in sporadic CRC indicates that inflammatory processes are also activated in the major form of CRC. Indeed, large-scale epidemiological studies had shown that the incidence of CRC is substantially lower in individuals who take nonsteroidal anti-inflammatory drugs, including aspirin (68). However, it took some time to understand how inflammation is initiated in sporadic and familial CRC. As mentioned above, the key oncogenic event in sporadic and familial CRC is loss of the *APC* tumor suppressor. Using the CPC-*APC* mouse model of CRC, in which formation of colonic adenomas depends on *Apc* loss of heterozygosity (69), we found that in addition to activation of β-catenin, loss of *APC* compromises barrier integrity (17). Reduced expression of the junctional adhesion proteins JAM-A, B, and C, as well as mucin 2 (Muc2), was observed in early ACF lesions. Moreover, using an inducible biallelic loss of *Apc*, we detected JAM-A, JAM-B, and Muc2 downregulation at both the RNA and protein levels within three weeks after *APC* loss (17). Barrier disruption resulted in translocation of endotoxin and other microbial products that led to TLR2/4/9-dependent induction of IL-23 in lamina propria myeloid cells. Importantly, elevated expression of IL-23 was also observed in human CRC, where it correlates with a worse prognostic outcome (70). In CPC-*APC* mice, ablation of the *Il23p19* or the *Il23r* gene attenuated development of colonic adenomas and reduced their histopathological grade (17). IL-23 receptor (IL-23R), however, is not expressed in either normal or transformed epithelial cells, and its effect on tumor growth is mediated through expansion of IL-17-producing T cells, including Th17 and γδ T cells. Correspondingly, IL-17 receptor A (IL-17RA) ablation attenuated colonic tumor growth in CPC-*APC* mice (17). Unlike IL-23R, IL-17RA is expressed in IECs, in which it mediates NF-κB and ERK activation and stimulates cell proliferation within ACF lesions, thereby leading to formation of colonic adenomas (71). Similar findings regarding the importance of IL-17A and IL-17RA signaling were made in *Apc* mice infected with *Bacteroides fragilis* (72–74). Elevated expression of IL-17A was also observed in early human CRC, and high IL-17A expressers were found to be at a much higher risk of lethal metastatic disease than low IL-17A expressers (75). Likewise, an *IL-17A* gene polymorphism (rs2275913, G198) was linked to increased CRC risk and worse prognostic outcome (76). Moreover, T cell—specific ablation of IL-1R1 decreased tumor-elicited inflammation dependent upon IL-17A and IL-22, thereby reducing CRC progression (77). Curiously, however, in patients with advanced CRC, high IL-17A expression correlated with improved outcome (78), suggesting that at some point IL-17A may stimulate antitumor immunity. These observations, however, are at odds with the general observation that most CRCs are refractory to checkpoint

inhibitor therapy, whose success requires activation of tumor-resident T cells (79, 80). Another IL-17 family member, *IL-17C*, was also found to be upregulated in mouse CRC through microbial dysbiosis (81). Although its mechanistic basis remains obscure, barrier disruption also seems to be the inflammatory driver that accounts for development of serrated adenomas in mice with IEC-specific disruption of the atypical protein kinase C ζ (PKCζ) and PKCλ/ι (82). Just as first found in CPC-*APC* mice (17), adenoma development in *Prkci*$^{fl/fl}$ *Prkcz*$^{fl/fl}$ *Villin-Cre* mice is inhibited by antibiotics (82). As aPKC downregulation and inflammation were also detected in human serrated tumors, it appears that barrier loss is a general and key event in all forms of CRC. Barrier loss may precede microbial dysbiosis, but microbial factors can further enhance barrier loss (Figure 3).

MICROBES IN GASTROINTESTINAL CANCER

Dietary and various environmental factors modulate the composition and metabolic activity of the gut microbiota, which in turn can impact health. Furthermore, dietary factors also modulate barrier function (83–85). Particularly, high-fat diet (HFD) induces barrier dysfunction and dysbiosis and alters the gut metabolome (34, 86–90). HFD-induced dysbiosis is thought to promote obesity by increasing the capacity for energy harvest and storage (20), but it can also operate through inflammation-dependent mechanisms (91, 92). In particular, dysbiosis-induced inflammation was proposed to contribute to nonalcoholic steatohepatitis (NASH) development and thereby increase HCC risk (34, 93, 94), but as mentioned above, dysbiosis can be secondary to barrier disruption (95). Regardless of this classic chicken-or-egg question, dysbiosis can trigger intestinal inflammation and barrier impairment, but barrier impairment is also likely to precede dysbiosis (56, 89). A summary regarding the role of the most abundant bacterial phyla and their metabolites and corresponding physiological impact on health and cancer has been provided in Supplemental Table 1. Either way, microbial products can reach the liver via the portal circulation to induce hepatic inflammation and contribute to NASH and its progression to HCC (96). Although the main inducer of steatohepatitis remains to be identified, it could be none other than endotoxin (97). Although correlative studies suggest a disconnect between gram-negative bacteria, endotoxin, and NASH, these factors were also elevated in healthy obese individuals not suffering from NASH (98). The gut microbiome was also proposed to modulate gut and liver immunity through short-chain fatty acids (SCFAs), tryptophan metabolites that bind to the aryl hydrocarbon receptor (AhR), and retinoic acid (99–101). SCFAs (acetate, propionate, and butyrate) can be detected by the intracellular receptor PPARγ and the G protein—coupled receptors (GPRs) GPR41, GPR43, and GPR109a, the last of which also binds butyrate. Paradoxically, however, SCFAs enhance barrier function and immune tolerance and promote gut homeostasis through increased mucus production by goblet cells (100). SCFAs inhibit NF-κB, activate inflammasomes and induce IL-18 production, increase IgA secretion by B cells, reduce expression of T cell —activating molecules on antigen-presenting cells, and increase the number and function of colonic Tregs. Commensal *Lactobacillus* uses tryptophan to produce AhR ligands, such as indole-3-aldehyde (102). AhR activation is critical for the organogenesis of intestinal lymphoid follicles (ILFs) and AhR-expressing immune cells, including RORγt^{+} ILC3s that are involved in ILF genesis (103). In addition, AhR-induced IL-22 production by ILCs

drives secretion of the antimicrobial peptides lipocalin-2, S100A8, and S100A9, which provide protection from translocating microbes (103, 104), as well as *Candida albicans* (102). Furthermore, IL-22 is a potent regenerative cytokine that restores barrier integrity (105). Several bacterial factors that engage noncanonical PRRs have also been identified, including polysaccharide A (PSA), formyl peptides, and D-glycero-β-D-manno-heptose-1,7-biphosphate (HBP). PSA from *Bacteroides fragilis* can alter the Th1–Th2 cell balance (100, 101). Formyl peptides released by all bacteria bind formyl peptide receptors (FPRs), which are GPRs found on neutrophils and other immune cells (100–103). *Staphylococcus aureus* formyl peptides can signal through FPR1 and contribute to activation of nociceptor-driven mechanical pain and release of immunosuppressive neuropeptides (106). At high nanomolar concentrations, *S. aureus* formyl peptides, also known as phenol-soluble modulins (PSMs), stimulate massive neutrophil influx to infection sites by binding FPR2 (100). Induced neutrophil activation leads to an oxidative burst. PSMs affect the adaptive immune system by inducing a tolerogenic phenotype in DCs and inhibiting Th1 differentiation (107). These are just a few examples of how bacterial products and metabolites can regulate adaptive immune cells and therefore modulate GI cancer development (23, 100), both positively via TLRs and negatively via tolerogenic GPRs.

Another way in which the intestinal microbiota and barrier disruption can affect HCC development in mice and humans is through modulation of IgA plasmocyte development. The term gut-liver axis was first described when researchers reported production of IgA antibodies to dietary antigens in patients with liver cirrhosis, indicating interactions between the gut and liver (108). IgA can also be derived from naive B cells recruited into the liver tumor microenvironment (TME) by CAF-generated chemokines (109, 110). After binding specific antigens that could be bacterium, food, or tumor derived to B cell receptors (BCRs) and further exposure to TGF-β and other cytokines, including IL-21 from circulatory follicular T helper (Tfh) cells, lymphotoxin β (LTβ), IL-33, and IL-10, naive B cells undergo class-switch recombination (CSR) to produce IgA (34, 110, 111). While the initial inflammatory response in the liver entails induction of B cell—recruiting chemokines, such as CXCL12 and CXCL13, chronic hepatitis eventually results in production of high amounts of TGF-β, an anti-inflammatory cytokine that is typical of the healing phase of the inflammatory response (112–114). In addition, both NASH and alcoholic steatohepatitis (ASH) result in recruitment of circulating Tfh cells that produce IL-21 (34). Together, TGF-β and Tfh-expressed IL-21 initiate T cell—dependent CSR that converts IgM-expressing naive B cells to IgA^+ plasmablasts and plasma cells (collectively referred to as plasmocytes) that also express high amounts of the immunosuppressive molecules IL-10 and PD-L1 (34). Correspondingly, both human and mouse NASH-afflicted livers contain numerous IgA^+ plasmocytes that express high amounts of IL-10 and PD-L1 (34). Although these cells are most likely generated within the liver through a T cell—dependent mechanism, gut sterilization results in their disappearance and inhibition of NASH to HCC progression. IgA ablation also inhibits NASH to HCC progression, which is supported by IgA^+ plasmocytes that induce the exhaustion of HCC-directed cytotoxic T lymphocytes (CTLs). By contrast, depletion of polymeric immunoglobulin receptor gene (*Pigr*) enhances HCC development, indicating different functions of secretory IgA (sIgA) and IgA^+ plasmocytes in HCC (34). In addition to inducing CTL exhaustion, IgA^+ plasmocytes can also regulate and dampen

neuroinflammation (115). These anti-inflammatory and immunosuppressive effects are in line with the well-established homeostatic and regulatory role of IgA^+ plasmocytes in mucosal immunity (28, 116, 117). Given that the primary role of IgA is to maintain bacterial homeostasis, IgA^+ plasmocytes may suppress the growth of tumors that depend on microbial signals, like CRC. Accordingly, IL-33-deficient mice showed decreased IgA level and dysbiosis, which support IL-1α-dependent colitis and CAC (118). The gut microbiome can also affect the liver immune system through bile acid regulation of chemokine-dependent accumulation of natural killer T (NKT) cells (119).

Barrier disruption as an early event in CRC development places the gut microbiota as the key instigator of tumor-elicited inflammation in both *APC*-dependent and *APC*-independent CRC. Treatment of CPC-*APC* or a PKC-deficient mice with broad-spectrum antibiotics, which get rid of approximately 99.5% of the colonic microbiota, attenuates development of both tubular (17) and serrated adenomas (82). A similar effect has been observed after triple ablation of TLR2, 4, and 9 in bone marrow—derived cells, suggesting that most colonic bacteria act nonspecifically through pathogen-associated molecular pattern (PAMP)-mediated activation of TLR signaling. Other studies, however, have implicated specific microbes in CRC development. Toxigenic *Escherichia coli* and *B. fragilis* were reported to invade polyps and shown to encode colibactin and *B. fragilis* cancer-promoting oncotoxins, respectively (120, 121). Colibactin can alkylate DNA to cause damage that contributes to genomic instability, mutations, and cancer (121). However, it is questionable whether the number of colibactin-producing *E. coli* is sufficiently high to induce such damage. Likewise, there is little evidence that *B. fragilis* populates premalignant lesions. Only one bacterium, *Helicobacter pylori*, has been confirmed to act as a carcinogen in the stomach (6, 122). However, even in this case, only 2% of *H. pylori*—infected individuals ever develop gastric cancer. Moreover, the carcinogenic activity of *H. pylori* depends on a particular variant of its cytotoxin-associated gene A (*CagA*) locus, which codes for a scaffold protein that modulates Ras and Wnt signaling (123). Furthermore, even the oncogenic *CagA* variant does not act alone, as it only leads to induction of gastric metaplasia, whose further progression to dysplasia requires epithelial injury and inflammation brought about by secondary factors, such as foods with high salt content or high levels of nitrates (124). An etiologic relationship between gut bacteria and immune-suppressive inflammation in PDAC has also been described, showing that distinct and abundant microbes like *Bifidobacterium pseudolongum* drive suppressive monocytic cellular differentiation via selective TLR engagement that leads to T cell anergy and enhanced tumor growth (125).

THE MANY FACES OF INFLAMMATION IN HEPATOCELLULAR CARCINOMA

HCC, the main type of liver cancer and the second leading cause of cancer-related death, is the prototypical inflammation-dependent cancer (Figure 4). The main cause of HCC is viral hepatitis caused by HBV or HCV However, whereas HBV is a DNA virus that integrates into the host genome and leads to induction of oncogenic mutations by insertion mutagenesis (126), HCV is a nonintegrating RNA virus that exerts its oncogenic effect via induction of inflammation and endoplasmic reticulum (ER) stress (127, 128). HBV infection results in $CD8^+$ T cell activation, but these cells quickly assume an exhausted phenotype (129). By contrast, the immune/inflammatory response evoked by HCV is mainly

mediated by innate cells, since HCV does not sustain an effective T cell response. Like HCV, whose importance as an HCC initiator is declining due to the recent introduction of highly effective anti-HCV drugs, the two major nonviral causes of HCC, NASH and ASH, also operate through inflammation and ER stress (130). The availability of reasonably good mouse models of NASH-induced HCC (131) revealed that the two main tumor-promoting cytokines in the liver are TNF and IL-6 (132–136). Whereas TNF exerts its oncogenic effect through NF-κB (134), IL-6 mainly functions through STAT3 activation (132, 133). Nonetheless, hepatocyte-specific ablation of either IKKβ, the protein kinase responsible for NF-κB activation, or STAT3 does not always lead to inhibition of HCC development. Under certain circumstances, particularly in models that are associated with induction of hepatocyte necrosis or repetitive liver injury, IKKβ/NF-κB or STAT3 ablation can actually accelerate HCC development (137). Moreover, damaged hepatocytes coordinate myeloid cell accumulation and fibrosis within the liver and support metastasis. Interestingly, during early pancreatic tumorigenesis in mice, hepatocytes show activation of STAT3 signaling, increased production of serum amyloid A1 and A2 (SAA), and release of IL-6, which supports the establishment of a prometastatic niche in the liver (138). Gut inflammation may also contribute to the growth of metastatic CRC in the liver (139), but the mechanisms remain to be elucidated. The involvement of certain microbiota strains to support CRC metastasis has also been recently described (140) (Supplemental Table 1).

NASH-induced HCC is also supported by IL-17A produced by Th17 cells (141). IL-17A is likely to act through activation of NF-κB in epithelial cells (71). Consistent with its ability to stimulate the proliferation of HCC progenitors, expression of constitutively active IKKβ in mouse hepatocytes accelerates HCC development (142). However, in addition to stimulating hepatocyte proliferation, IKKβ/NF-κB activation results in production of organotypic cytokines that orchestrate the generation of ectopic lymphoid clusters (ELCs), composed of T cells, B cells, and stromal fibroblasts/HSCs, that provide niches that support the growth of HCC progenitors. These niches may also protect HCC progenitors from killing by activated CTLs.

Another immune related mechanism through which chronic hepatitis supports HCC development involves the generation of IgA^+ plasmocytes, which as discussed above suppress HCC-directed CTLs that otherwise prevent growth and expansion of HCC progenitors (34). While HCC-specific antigens that are recognized by HCC-targeting T cells remain to be identified, T cell receptor (TCR) sequencing indicates that the HCC-elicited immune response is oligoclonal in nature, encompassing the selection and amplification of approximately 20–30 immunodominant clones. Given the presence of exhausted but HCC-directed $CD8^+$ T cells, treatment of HCC-bearing mice with a blocking PD-L1 antibody that induces reinvigoration of the latter results in regression of 60–70% of large liver tumors (34). In accordance with the important role of the physical interaction between PD-L1-expressing B cells and PD-1-expressing Tfh cells in sustaining the CSR reaction (143), anti-PD-L1 treatment also results in a substantial reduction in the number of liver-resident IgA^+ plasmocytes, further facilitating CTL reinvigoration (34). In fact, circulating IgA was also described to be elevated in ASH and other chronic liver diseases, and its amounts show a direct correlation with the extent of liver fibrosis (34), which is not all that surprising given the profibrogenic function of TGF-β (144, 145), the main inducer

of IgA CSR. Most likely, the PD-L1- and IL-10-expressing IgA^+ plasmocytes in human liver carry out the same immunosuppressive and HCC-promoting functions ascribed to their mouse counterparts. Furthermore, the likely involvement of these cells in HCC development explains the surprisingly good response of human nonviral HCC to PD-1 blockade (146). By contrast to HCC, the majority of CRC is refractory to PD-1 blockade, with the exception of mismatch repair—deficient and microsatellite instability—high tumors (80, 147, 148), an effect that was correlated with the number of somatic mutations (149). Another key difference in the immunobiology of CRC versus that of HCC lies in their relationship with IgA^+ plasmocytes, as also mentioned above. Although ER stress in hepatocytes drives NASH development (134), in IECs ER stress orchestrates a protective IgA response (150).

CONCLUSIONS AND FUTURE PROSPECTS

While the tumor-promoting function of chronic inflammation has been recognized and amply reviewed (2, 4, 151, 152), more recent work highlighted above indicates that most tumor-promoting inflammation, at least in cancers of the GI system, originates in barrier disruption. Initially described as a source of tumor-elicited inflammation (17), barrier disruption can precede tumor development and contribute to pathological conditions that greatly increase cancer risk. Such pathologies include IBD, steatohepatitis, alcoholic hepatitis, and chronic pancreatitis. So far, the protumorigenic function of barrier disruption is mainly supported by association studies and by the ability of broad-spectrum antibiotics to inhibit CRC, HCC, and PDAC in mouse models (17, 34, 125). Pending development of the right experimental tools, we hope that future work will allow clinical investigators to determine the prevalence of barrier disruption in human GI malignancies and their associated premalignant states—IBD, hepatitis, and pancreatitis. Just as important is the development of specific experimental and pharmacological tools that can prevent barrier deterioration or enhance barrier restoration. In addition to establishing the importance of barrier disruption, such tools can be used to prevent oncogenic progression of chronic GI-related inflammatory conditions and reduce the enormous toll levied by highly aggressive malignancies such as HCC, PDAC, and liver-metastatic CRC.

Although translocating gut microbes and microbial products can trigger tumor-promoting inflammation through general means such as TLR engagement, we should not discount the possible existence of cancer-promoting bacterial toxins and metabolites. If the carcinogenic activity of such substances is validated in human disease, future research should be directed at identification and development of specific antidotes and protective interventions.

In summary, tumor-promoting inflammation is initiated as a protective response to translocating commensals. In addition to stimulating the proliferation and survival of tumor progenitors, chronic tumor-promoting inflammation also acts via immune mechanisms, such as the TGF-β—and Tfh-driven generation of immunosuppressive IgA^+ plasmocytes. Much more effort is needed to better understand the immune mechanisms through which chronic inflammation supports the growth and progression of colonic and pancreatic adenomas and adenocarcinomas. Such understanding will improve our ability to successfully use immunotherapeutics, such as checkpoint inhibitors, in cancers where they have not been proven effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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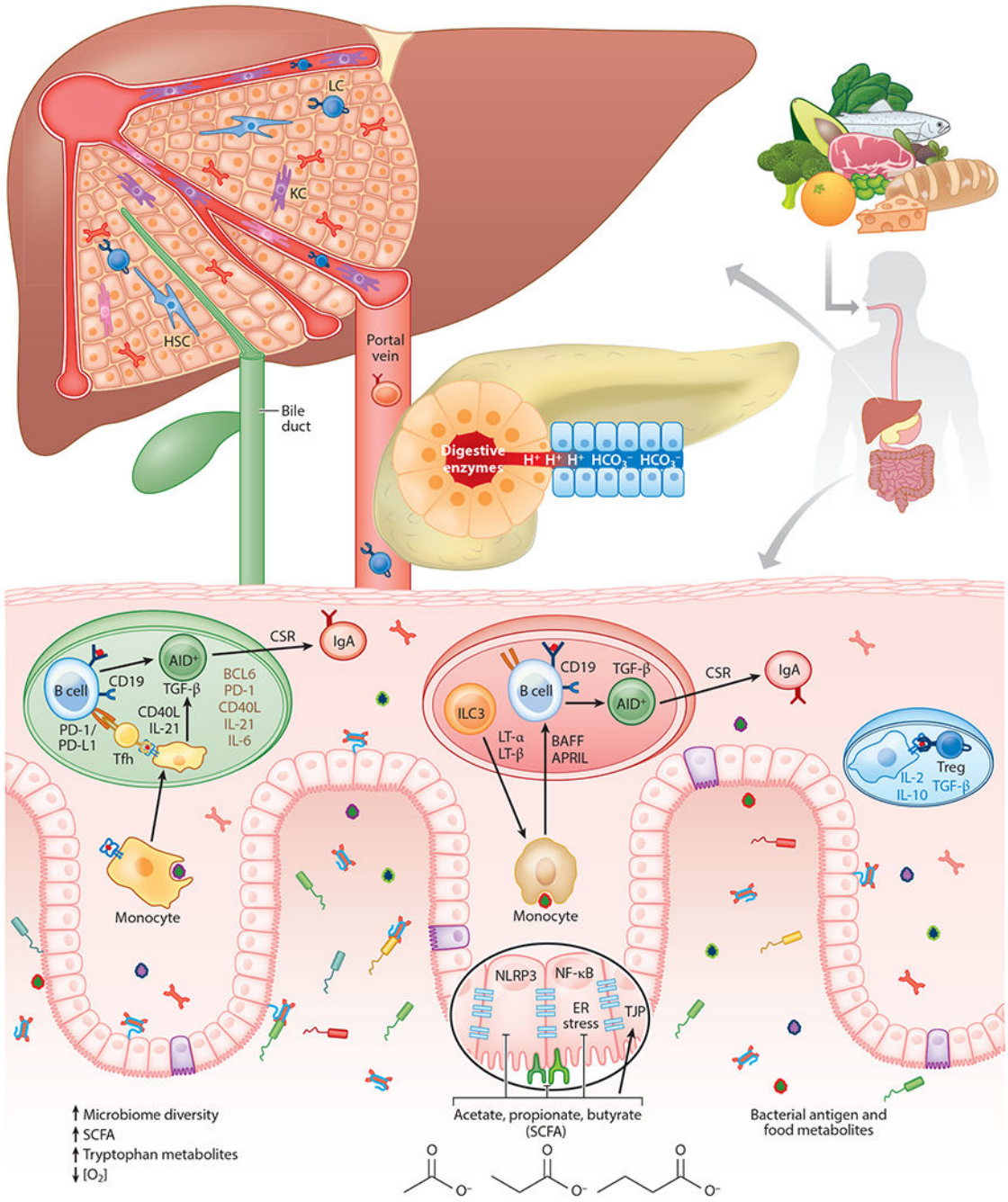

Figure 1.

A schematic describing the interaction between the GI tract, liver, and pancreas in steady state. The gut-liver axis, which is based on the anatomical and physiological connection between the liver and the gut through the biliary tract and portal vein, allows delivery of liver-produced bile acids to the GI tract, while receiving lipid-rich and endotoxin-containing blood from the GI tract to be filtered and detoxified in the liver. The liver's supply of blood has two sources: the hepatic artery and the portal vein. Some 70–75% of the liver's blood supply is derived from the portal vein, which drains blood from mesenteric veins of the

intestinal tract. In steady state, IgA^+ cells, Tregs, myeloid cells, and ILCs regulate gut and liver homeostasis. Different populations of myeloid-derived antigen-presenting cells take up antigens, traffic to MLNs, and present them to naive T cells in the presence of TGF-β and RA, which favor the generation of food/bacterium-antigen-specific Tregs. IL-10 promotes Treg proliferation and IgA CSR. TGF-β, likely produced by Tregs or Tfhs, regulates B cell antibody class switching to IgA^+ cells. Secretory IgA is transported across the epithelial barrier via pIgR into the intestinal lumen, where it regulates the entrance of luminal food- and bacterium-derived antigens and contributes to microbiome homeostasis. Tregs and IgA^+ cells eventually exit the gut and enter the blood to regulate systemic tolerance to dietary and bacterial antigens. Healthy diet supports microbiome diversity and increased amounts of SCFA and tryptophan metabolites, which in turn suppress inflammation by inhibiting NF-κB and NLRP3 and increase TJP expression and IEC homeostasis. Abbreviations: CSR, class-switch recombination; ER, endoplasmic reticulum; GI, gastrointestinal; HSC, hepatic stellate cell; IEC, intestinal epithelial cell; ILC, innate lymphoid cell; KC, Kupffer cell; LC, lymphocyte; MLN, mesenteric lymph node; pIgR, polymeric immunoglobulin receptor; RA, retinoic acid; SCFA, short chain fatty acid; Tfh, follicular T helper cell; TJP, tight junction protein; Treg, regulatory T cell.

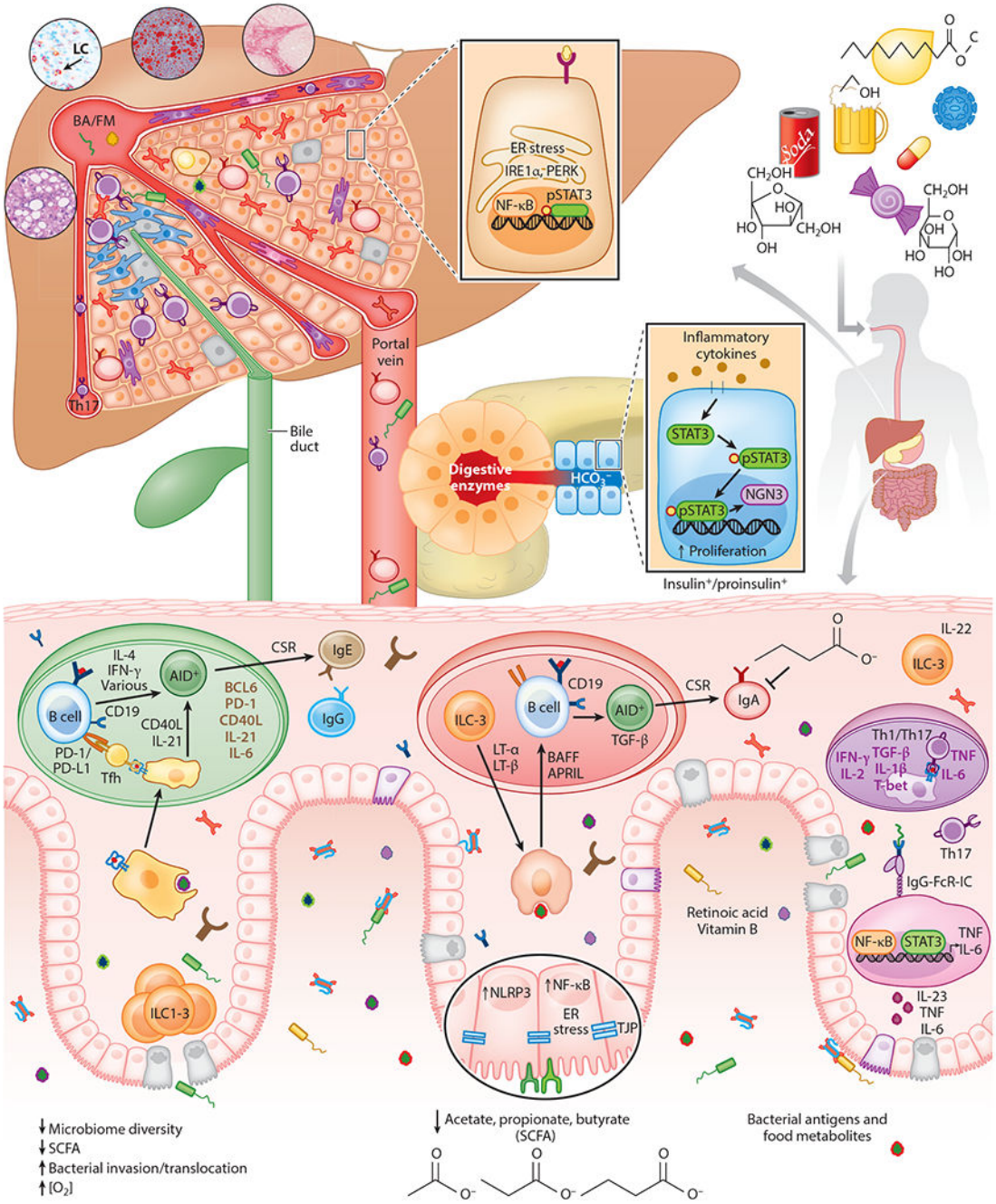

Figure 2.

A schematic describing the interaction between the GI tract, liver, and pancreas during inflammatory conditions. If the gut barrier is disrupted and its contents enter the submucosa, the liver is the first organ in the body to encounter microbial products, toxins, and microorganisms (such as bacteria and fungi) from the intestine. The liver, therefore, serves as a receptacle and sensor for compounds and substances originating from the intestine to which it must respond. Moreover, hypernutrition, alcohol abuse, and other factors that can disrupt the gut barrier induce chronic intestinal inflammation and also affect

the liver to support NASH and ASH development. Hypernutrition and alcohol decrease microbiome diversity and SCFAs and induce inflammation through activation of NF-κB and NLRP3. IL-1β and IL-23-induced IL-17 also contribute to intestinal inflammation and the likely induction of IgG and IgE. Abbreviations: ASH, alcoholic steatohepatitis; BA, bacterial antigen; CSR, class-switch recombination; ER, endoplasmic reticulum; FM, food metabolite; GI, gastrointestinal; IgG-FcR-IC, IgG Fc receptor immune complex; LC, lymphocyte; NASH, nonalcoholic steatohepatitis; SCFA, short chain fatty acid; Tfh, follicular T helper cell; Th, helper T cell; TJP, tight junction protein.

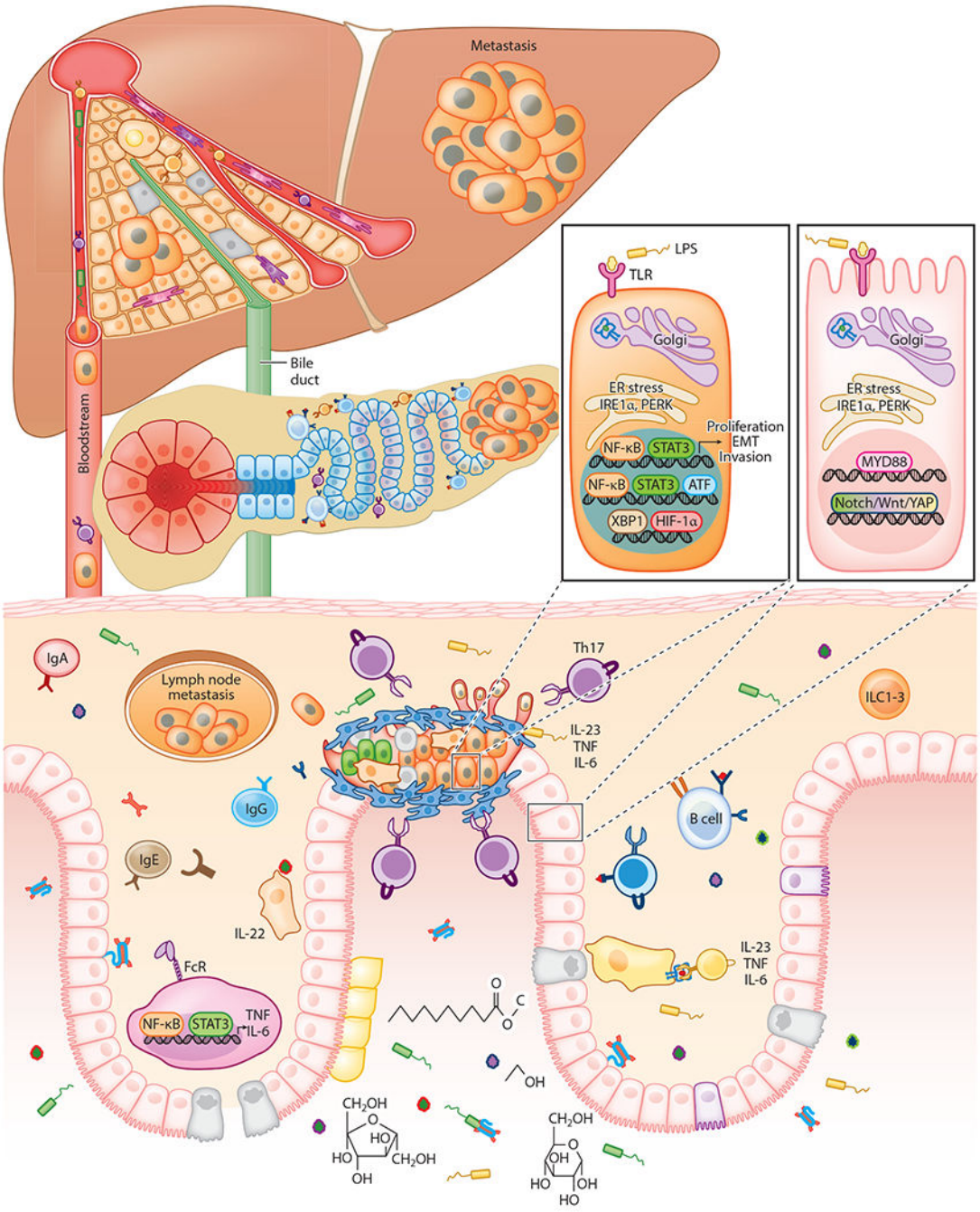

Figure 3.

Chronic inflammation and its role in colorectal and pancreatic cancer development and metastasis to the liver. Bacterial translocation due to barrier disruption induces myeloid cell expression of TNF, IL-6, and IL-23, which in turn activate and expand Th17 cells, support NF-κB and STAT3 activation in intraepithelial cells, and accelerate tumor development and metastatic spread. Abbreviations: ER, endoplasmic reticulum; FcR, fragment crystallizable receptor; LPS, lipopolysaccharide; Th17, T helper type 17; TLR, Toll-like receptor.

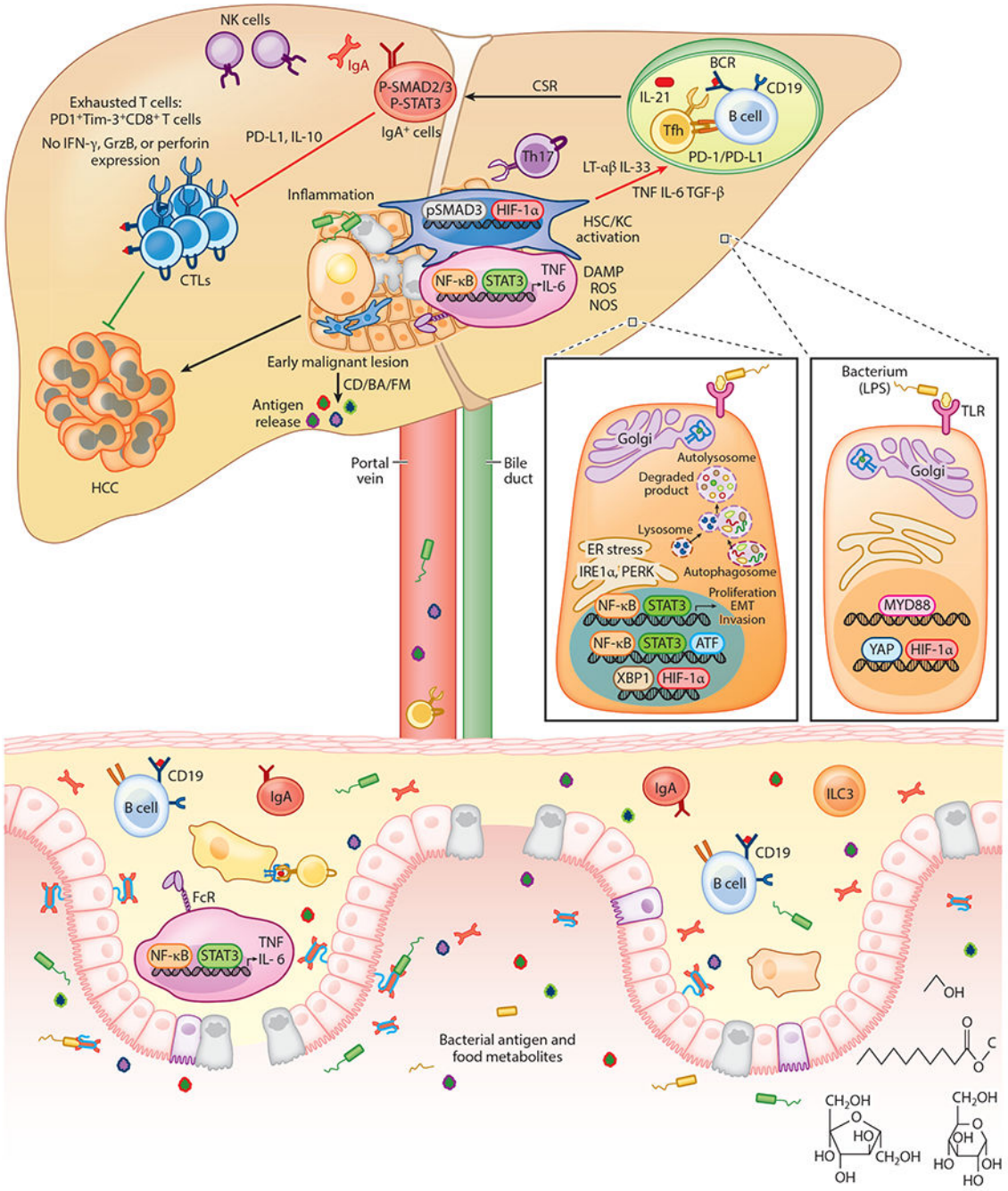

Figure 4.

Hepatocellular carcinoma and the effect of barrier disruption on its development. Chronic inflammation and sustained production of the two main tumor-promoting cytokines, TNF and IL-6, support HCC development. TNF exerts its oncogenic effect through NF-κB, whereas IL-6 mainly functions through activation of STAT3. However, release of tumor, bacterial, or food antigens, in combination with cytokines and chemokines produced by different types of monocytes and activated HSCs, can activate humoral and cellular immune cells, like tumor-promoting Th17 cells, Tregs, and IgA^+ cells that compromise

the antitumorigenic activity of different immune cells such as CTLs (cytotoxic $CD8^+$ T cells). Abbreviations: BA, bacterial antigen; BCR, B cell receptor; CD, cell death; CSR, class-switch recombination; CTL, cytotoxic T lymphocyte; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; FcR, fragment crystallizable receptor; FM, food metabolite; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; KC, Kupffer cell; LPS, lipopolysaccharide; NK, natural killer; NOS, nitric oxide synthase; ROS, reactive oxygen species; Tfh, follicular T helper cell; TLR, Toll-like receptor.

Table 1

Similarities and differences between colorectal cancer and colitis-associated cancer

Disease		Colorectal cancer	
		Sporadic/familial CRC	**CAC**
Origins		Mutational accumulation or family history (30% of CRC) (47)	Chronic inflammation (e.g., IBD) CAC accounts for 1–2% of all CRCs (40)
Presusceptibility and risk factors		History of CRC in first-degree relatives, obesity, red meat consumption, cigarette smoking, sedentary lifestyle, and low fruit and vegetable consumption (54)	IBD: UC (colon) and CD (SI & colon)
Genetic predisposition mutations	**Precancerous** [a]	Adenomatous polyps (46): Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, Tacstd1/EpCAM*—70%[b]) FAP (*APC*—90%[b]) Hamartomatous polyps (46): Peutz—Jeghers syndrome (*STK11*—50–70%[b]) Juvenile polyposis syndrome (*SMAD4, BMPR1A*—<50%[b]) Cowden syndrome (*PTEN*—65–80%[b]) *BRCA1* (45)	47 risk loci identified with UC and 71 for CD. 30% shared between both (41)[c] *GNA12*[d], *HNF4A*, *CDH1*, *ERRFI1*, *MUC19*, *ITLN1*[d], *REL*, *PTGER4*, *NKX2-3*, *STAT3*, *PLA2G2A/E*, *SLC9A4*, *SLC22A5*, *SLC22A4*[d], *AQP12A/B*, *SLC9A3*, *SLC26A3*, *NOD2*[d], *ATG16L1*[d], *XBP1*[d], *CARD9*[d], *SLC11A1*, *FCGR2A*[d]*/B*, *CCL11/CCL2/CCL7/CCL8*, *CCR6*, *IL8RA/IL8RB*, *MST1*[d], *ERAP2*[d], *LNPEP*, *DENND1B*, *IL23R*[d], *JAK2*, *TYK2*[d], *ICOSLG*, *IL21*, *TNFSF15*[d], *NDFIP1*, *TNFSF8*, *TAGAP*, *IL2*, *TNFRSF9*, *PIM3*, *IL7R*[d], *IL12B*, *PRDM1*, *IFNG*, *IL5*, *IKZF1*, *BACH2*, *IRF5*, *IL10*, *IL2*[d], *SBNO2*, *CREM*, *IL1R1/IL1R2*, etc. (41)
	Cancerous	Early *APC* (81%[e]), late *TP53* (60%[e]), KRAS (43%[e]), *SMAD4* (10%[e]), *MSI, EGFR2*, etc. (50, 51)	Late *APC* (13%[e]), early *TP53* (63%[e]), *KRAS* (20%[e]), *SMAD4* (13%[e]), *EGFR2, MLL, EP300, MSI, RNF43*, etc. (50, 51)
Signaling pathways		WNT/β-catenin, K-Ras, p53, TGF-β, NF-κB, STAT3, etc. (44)	
Percentage of cancer occurrence within individual patient		Lynch syndrome: 2–4% of CRC cases (46) FAP: 1% of new CRC cases (46) Hamartomatous polyposis syndromes: <0.5% of CRC cases (46)	1.5- to 2.4-higher risk to develop CAC (40) CAC-UC: 18% after 30 years of disease (43) CAC-CD: 8% after 30 years of disease (43)
Liver metastasis		>50% of advanced CRC patients will develop liver metastases during their lifetime (139)	
Cytokine involvement		Dysregulated production of TNF, IFN-γ, IL-17, IL-12, IL-23, etc.	
Treatments	**IBD related**	Anti-$\alpha_4\beta_7$ (e.g., vedolizumab), anti-TNF (e.g., infliximab, adalimumab), anti-IL-12/IL-23 (e.g., ustekinumab), anti-IL-6 (e.g., tocilizumab), anti-IL-2 receptor (e.g., basiliximab), anti-CD20 (e.g., rituximab), anti-IFN-γ (e.g., fontolizumab), JAK inhibitor (e.g., tofacitinib), etc. (44)	
	Cancer related	Chemotherapy: combination therapy of 5-fluourouracil, fluoropyrimidine, oxaliplatin (e.g., FOLFOX, CAPEOX, FOLFIRI); targeted therapy: EGFR inhibitors (e.g., panitumumab, cetuximab), VEGF inhibitors (e.g., bevacizumab, ramucirumab); patients with MSI: PD-(L)1 inhibitors (e.g., nivolumab, pembrolizumab) (44, 48)	

[a] Although a family history of CRC is reported in 30% of CRC patients, only 5–6% have germline mutations in familial cancer syndrome–associated genes (46).

[b] Percentage of patients with specified mutations in genes associated with familial CRC (46).

[c] Green font represents mutations specific to UC, purple font represents mutations specific to CD, and red font represents mutations related to both UC and CD.

[d] Coding mutation.

[e] Mutation frequency of commonly mutated genes in nonhypermutated sporadic CRC and CAC (51).

Abbreviations: CAC, colitis-associated cancer; CAPEOX, capecitabine; CD, Crohn disease; CRC, colorectal cancer; FAP, familial adenomatous polyposis; FOLFIRI, fluorouracil and irinotecan; FOLFOX, fluorouracil and oxaliplatin; IBD, inflammatory bowel disease; JAK, Janus kinase; MSI, microsatellite instability; SI, small intestine; UC, ulcerative colitis.