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Microbiome, bile acids, and obesity: How microbially modified metabolites shape anti-tumor immunity

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Abstract

Bile acids (BAs) are known facilitators of nutrient absorption but recent paradigm shifts now recognize BAs as signaling molecules regulating both innate and adaptive immunity. Bile acids are synthesized from cholesterol in the liver with subsequent microbial modification and fermentation adding complexity to pool composition. Bile acids act on several receptors such as Farnesoid X Receptor and the G protein-coupled BA receptor 1 (TGR5). Interestingly, BA receptors (BARs) are expressed on immune cells and activation either by BAs or BAR agonists modulates innate and adaptive immune cell populations skewing their polarization toward a more tolerogenic anti-inflammatory phenotype. Intriguingly, recent evidence also suggests that BAs promote anti-tumor immune response through activation and recruitment of tumoricidal immune cells such as natural killer T cells. These exciting findings have redefined BA signaling in health and disease wherein they may suppress inflammation on the one hand, yet promote anti-tumor immunity on the other hand. In this review, we provide our readers with the most recent understanding of the interaction of BAs with the host microbiome, their effect on innate and adaptive immunity in health and disease with a special focus on obesity, bariatric surgery-induced weight loss, and immune checkpoint blockade in cancer.

Keywords

bariatric surgery; immunometabolism; microbiome; mitochondria; obesity; tumor microenvironment

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CONFLICT OF INTEREST

No authors have conflict.

1 | INTRODUCTION

The human microbiome and diversity therein colonize niches on and throughout the human body, including the mammary gland and ducts, where it confers the host with non-mammalian genetic capacity to generate critical metabolites.[1,2] While we are at the precipice of understanding their roles in disease, we believe the microbiota regulate metabolism through fundamental host-microbial interactions.[1,2] Both the overall diversity of the microbiome and specific microbes regulate immune responses and this review will focus on the immune milieu in cancer. In this review, we discuss obesity, weight loss through bariatric surgery, and the potential impact of microbially modified bile acid (BA) composition and signaling. We pay most attention to breast cancer (BC), the most common cancer and the second cause of cancer-related deaths in US women, however touch upon other cancers. Several cancers are associated with changes in the gut microbiome including stomach, colon, liver, lung, and skin.[3–8] Microbes appear to correlate with and mediate cancer onset. While the gut has been the main focus of microbiome research in the past, a largely underexplored yet impactful realm is the contribution of the extra-intestinal or local resident microbiome. We have published that certain microbes correlate with tumor stage, tumor subtype, and race in BC patients.[9] Microbes also regulate immunological response to therapy and anti-tumor immunity with *bona fide* impacts on clinical outcomes. For example, *Akkermansia muciniphila*, which confers metabolic benefits despite colonizing the gut in low abundances, restored sensitivity to immune checkpoint blockade (ICB) therapy in murine models and correlated with ICB therapeutic response in BC patients.[10,11] This field is in its infancy but it is believed that microbes may play a central role in cancer biology in several ways: (a) microbes and bacterial-derived proteins directly regulate immune cell content and activation[12–15]; (b) microbes regulate metabolism of our diet (ie, fiber[16,17]); (c) microbes alter estrogen bioavailability[18–21]; (d) bacterial-derived quorum-sensing proteins[12–14] which are found in the mammary gland[22,23]; and (e) microbes modify local or systemic levels of their own metabolites and host metabolites, such as short-chain fatty acids or BAs.[2] With this examination of the most recent literature and trials, we implore the reader to consider how obesity, microbes, and metabolites derived from gut or extra-intestinal depots impact tumor onset, progression, anti-tumor immunity, and response to therapy.

2 | BILE ACID METABOLISM AND SIGNALING

Primary BAs, including cholic acid (cholate, CA), chenodeoxycholic acid (CDCA), and muricholic acid (MCA, in mice), are synthesized from cholesterol by hepatocytes via the classic and alternative pathways. Synthesis is regulated by negative feedback from BA through intracellular signaling pathways, including the small heterodimer partner (SHP). Primary BAs are conjugated with glycine (“G”-GCA and GCDCA) or taurine (“T” in TCA and TCDCA) in the liver before being stored in the gall bladder or immediately released into the intestine. In rodents, 95% of conjugates are T, while humans generally display a 3:1 ratio of G:T conjugation.[24] Within the gut, microbial enzymes such as bile salt hydrolases deconjugate glycine and taurine salts, rendering the bile structure susceptible to further microbial fermentation. One common reaction is the conversion of primary BA into secondary BA by the microbial enzyme 7-alpha-hydroxylase, resulting in secondary BAs

lithocholic acid (LCA) and deoxycholic acid (DCA). Deconjugated primary and newly formed secondary BA can be conjugated with taurine and glycine in the liver to provide a diverse composition of BA species present in the circulating BA pool.[25] Collectively, BA comprises 80% of secreted bile salts, providing an amphipathic detergent solution that facilitates dietary fat absorption by emulsifying lipids and forming micelles for absorption in the mid-jejunum.[24] The majority of bile salts are reabsorbed by the time they arrive in the ileum, mediated by sodium/bile salt cotransporters to shift BAs into portal blood circulation and back to the liver.[26] Some deconjugated hydrophobic BAs, such as CA and DCA, are passively reabsorbed across the colonic mucosa, where no active BA transporters exist. The liver efficiently extracts bile salts from portal blood to maintain the hepatic BA pool. Total BA pool in circulation is approximately 2.5 grams with only minimal 5% losses daily in feces.[27]

Bile acids provide hormone-like receptor signaling functions on numerous pathways, including the enteroendocrine system, that regulate energy expenditure, inflammation, and diseases such as cancer in part through activation of transmembrane or nuclear hormone BA receptors. Bile acids activate BA receptors (BAR) primarily through G protein-coupled BA receptor 1 (*GPBAR1* or TGR5) and the nuclear hormone receptor farnesoid X receptor (*NR1H4* or FXR). Other nuclear hormone receptors targeted by BAs include pregnane X receptor (PXR), vitamin D receptor (VDR), constitutive androstane receptor (CAR), and membrane bound receptors such as sphingosine-1-phosphate receptor 2 (S1PR2) and cholinergic receptor muscarinic 2 (CHRM2).[28] While most BAs have some activity against the various receptors throughout the body, the affinity of each BA species for each BA receptor varies. For instance, FXR is activated at lower EC_{50} by primary BAs whereas TGR5 is activated more potently by secondary BAs. FXR is the master regulator of BA metabolism including homeostasis through regulation of synthesis and transport.[29] Thus, the specific composition of circulating BA fundamentally provides regulation of important homeostatic systems.

Bile acids mediate enteroendocrine hormone release to shape central and peripheral homeostasis. Within the gut, BAs also directly innervate the enteric nervous system through TGR5, which regulates many local physiological aspects the gut and mucosal associated immune tissues (20236244). One enteroendocrine molecule is cholecystokinin (CCK), which is secreted by intestinal I-cells when chyme reaches the duodenum (upper small bowel), triggering gallbladder contraction and relaxation of the sphincter of Oddi to cause a slow and sustained BA release into the duodenum. In contrast, upon reaching the ileum (lower small bowel), BA stimulation of glucagon-like peptide-2 (GLP-2) release from intestinal L-cells stimulates gallbladder refilling and may influence satiety.[30,31] As such, BAs are emerging as a potential mechanism of improving metabolic homeostasis. Furthermore, recent studies reveal that BA regulated enteroendocrine hormones confer potent immunomodulatory functions. For instance, circulating GLP-2 levels are demonstrated to inhibit macrophage and microglial activation in response to bacterial lipopolysaccharide (LPS) stimulation.[32,33] In addition to receptor-mediated functions, BAs can also influence cell membranes by physically inserting into the bilayer and participating in membrane dynamics, as they are cholesterol derivatives. While 20–40 μmol/L levels of BAs are found in circulation, supraphysiological levels of BA administration are

demonstrated to lyse cell membranes and disrupt mitochondrial membrane structure.[34,35] Another receptor-independent function is allosteric activities, where BAs can inactivate or stabilize enzymes.[36]

Since gut microbes harbor enzymes that modify BAs hydroxylation configurations, the gut microbiome composition and functions shape circulating BA pools and their signaling mediated affects throughout the body. For instance, the bacteria *Clostridium cluster 14* and *Bacteroides* contain high levels of 7-alpha-hydroxylase, which convert primary BAs to secondary BAs by removing hydroxylation at the 7 alpha carbon position.[24] In addition, many common commensal bacteria harbor the bile salt hydrolase (ie, remove glycine or taurine), which is posited to confer bacterial resistance to the highly antibacterial activity of BAs.[37] On the other hand, deconjugation renders BAs more hydrophobic, decreasing their digestive activity and decreasing reabsorption which leads to increased fecal loss. Other fermentation reactions by the gut microbiome result in tertiary BAs, including ursodeoxycholic acid (UDCA), which results from the microbial epimerization of CDCA. Collectively, the array of enzymes contained within the gut microbiota fundamentally shapes the BA pool containing various conjugated primary, secondary, and tertiary BAs (Figure 1A). The microbiome and dietary factors also influence BA reabsorption, hepatic synthesis, and intestinal motility, which in part regulate the amount of BAs lost daily through feces. BA sequestrants (cholestyramine, colestipol) are negative charged compounds administered orally that bind BA within the intestinal lumen, preventing reabsorption, and leading to increased fecal BA losses. Since BAs are synthesized from cholesterol, sequestrants lower circulating cholesterol but also improve enteroendocrine signaling. The latter effect is thought to be mediated by diverting BAs along the distal bowel where they are still able to bind enteroendocrine cell surface receptors on their path out of the gut.

As BAs emerge as important immunometabolism mediators, pharmacologic agonists, antagonists, and sequestrants have been developed and used both clinically and experimentally. Pharmacological agonists are FDA approved including obeticholic acid, an FXR agonist. Given the numerous functions of FXR in various tissues, including the intestine, liver, muscle, and adipose, the effects of obeticholic acid provided mixed human clinical trial results in improving metabolic homeostasis. For instance, while improvements in glucose control have been observed in some diabetic patients,[38] another clinical trial found increased fasting insulin following obeticholic acid administration.[39] Intestinal FXR stimulates release of fibroblast growth factor (FGF) 19 in humans and FGF15 in mice, which suppresses hepatic BA synthesis through the rate-limiting enzyme *Cyp7a1*. Intestinal FXR also stimulates the release of ceramides, which stimulate lipogenesis and induce hepatic insulin resistance.[40] Interestingly, the conjugated secondary BA, TUDCA, is a natural FXR antagonist in the intestine and improves metabolic outcomes. Consistent with this, experimental work with intestinal specific FXR knockouts demonstrate protection from diet-induced obesity, insulin resistance, and liver disease. On the other hand, hepatic specific FXR knockouts display susceptibility to metabolic syndrome when challenged with cholesterol diets. These contradictory phenotypes highlight the periphery vs intestinal role of FXR signaling in mediating metabolic homeostasis.

Taken together, the microbiome provides intricate control over circulating BAs, which result in various signaling cascades as well as regulation of energy expenditure, physiological responses, and immune cell phenotype and activation.

3 | OBESITY, BARIATRIC SURGERY-INDUCED WEIGHT LOSS, AND BILE ACIDS

Obesity and metabolic syndrome are epidemics in the United States and many Westernized countries worldwide. The rise of obesity has correlated with numerous comorbidities, such as diabetes, heart disease, and cancers.[41,42] Obesity is directly responsible for as many as three million deaths globally each year. As dietary weight loss is difficult to implement clinically with low adherence and a marked rebound effect, bariatric surgery has become more prevalent for sustained weight loss and long-lasting metabolic benefits in patients. While originally reserved for morbidly obese patients with body mass index (BMI) greater than 60, accumulating data demonstrate metabolic surgery also benefits type 2 diabetes and other comorbidities in lesser BMI patients. Therefore, metabolic surgeries have recently been expanded to less morbidly obese patients who also have significant health comorbidities. Metabolic surgeries, such as Roux-En-Y gastric bypass and vertical sleeve gastrectomy (VSG), are hypothesized to modify metabolic setpoints through alteration of endocrine and neuronal regulation. Evidence of this hypothesis is the observation that the beneficial metabolic effects of bariatric surgery are conferred upon patients within hours and days following surgery, long before weight loss outcomes are achieved.[43] This implies that the fundamental mechanisms underlying metabolic surgery, including potentially the microbiome, BA homeostasis, endocrine regulation, and neuronal signals, are responsible for regulating metabolic homeostasis and providing key input into body weight set point. Metabolic surgery approaches, including VSG and Roux-En-Y gastric bypass, remain the most effective and sustainable treatments for obesity. VSG is typically the first-line approach for surgical weight loss. VSG serves as an attractive therapeutic approach to sustain weight loss because it causes little rearrangement of the intestinal tract with minimal nutrient malabsorption, yet so far has provided weight loss comparable to Roux-En-Y without the risk of surgical complications.[44,45] VSG typically removes about 80% of the stomach, leaving a sleeve-like stomach which restricts intake. Roux-En-Y approaches include creating a small pouch by removing a portion of the stomach before connecting the gastric pouch directly to the small intestine, which lead to both restrictive food intake as well as malabsorption to reduce caloric intake. Gastric banding has become less common due to physical complications of the band and gastric organ.[46] The various surgical strategies and mechanisms of action have been reviewed in detail elsewhere,[47] but generally include some degree of gastric volume restriction, alteration to endocrine signaling, vagal stimulation, and BA metabolism, with changes in the microbiome.

While the molecular basis for the metabolic improvements from bariatric surgery is multifaceted and discoveries are ongoing, increasing evidence attributes these improvements to microbially influenced BAs and BAR signaling.[44,47–49] Elevated BA pools are a mechanistic feature of improved outcomes after gastric bypass surgery that are proposed to be central to weight loss and other metabolic benefits in many, but not all, human and animal

studies. In addition, elevated BAs after bariatric surgery may be one of the mechanisms that eliminate obesity-associated microbial dysbiosis due to anti-microbial effects of BA.[25] While correlations in total circulating BA levels across metabolic phenotypes are not uniformly consistent in the literature, trends can be gleaned from large human studies. One such study examined plasma BAs from patients with normal weight (BMI 18–25), obesity (BMI ~ 48), or anorexia nervosa, and observed the greatest total circulating levels of BA in patients with obesity.[50] However, other critical work demonstrated leanness is associated with large postprandial fluctuations in circulating BA levels, despite lower faster BA levels, suggesting that the timing and concentration of BAs may be important metabolic regulators.[51] In this framework, consistently elevated BA levels in obesity may be the result of inefficient enterohepatic circulation and synonymous with the deleterious effects of consistently elevated insulin, cholesterol, and glucose in metabolic syndrome. In addition to total levels, changes in composition overall or specific BAs are observed in obese and diabetic patients. For instance, 12 alpha-hydroxylated BAs (CA, CDA and their salt conjugates) are elevated in individuals with insulin resistance by as much as twofold compared with healthy controls (Figure 1B).[52] Experimental induction of obesity with high-fat diet in animals also leads to greater total levels of BAs, as well as elevated levels of CA, TCA, DCA, and TDCA compared with controls.[44,53,54] High-fat diet feeding also reshapes the gut microbiome, and associations are found between total circulating BA levels, and the phyla *Firmicutes, Proteobacteria*, and *Actinobacteria*. Remarkably, when mice fed a low-fat diet are orally treated with the BAs elevated under a high-fat diet, the gut microbiota shifts to resemble a high-fat diet-fed mouse.[54] This observation suggests that BAs may confer larger regulatory roles on microbiota selection than was previously realized.

Since BAs are proposed to confer many beneficial metabolic effects following various bariatric surgical strategies, Pierre and colleagues employed a novel metabolic surgery that specifically elevated BAs to determine their effects on systemic glucose tolerance in obesity. This bile diversion surgery (BD) elevates systemic BAs without any gastric volume restriction or other gross anatomical rearrangement of the intestinal tract.[44,48] In BD surgery, the gallbladder is anastomosed to the ileum and the bile duct is ligated to divert BAs further down the intestinal tract, increasing BA reabsorption and shortening enterohepatic circulation time, which functionally results in elevated systemic BAs.[44,48,49] In obese animals, BD surgery improved obesity-driven components of metabolic syndrome with no adverse malabsorptive effects on fecal lipid or BA excretion but this depends on location of anastomosis to the ileal cecal valve.[44,49] Pierre et al reported that BD led to sustained weight loss, reduced adiposity to lean levels, and normalized glucose tolerance by 2 weeks after surgery.[44,48] Strikingly, BD surgery resulted in sustained weight loss despite continued high-fat diet exposure. BD-associated browning of white adipose induced thermogenesis which was associated with weight loss, improved insulin sensitivity, and reduced insulin and leptin levels compared to lean or weight-matched controls. Notably, BD tripled systemic BA concentrations through increasing BA enterohepatic circulation.[44,45] Critically, circulating BA changes were uniquely associated with BD—weight-matched sham controls who became as lean as BD-mice did not display elevated BAs. Therefore, these changes are not just the result of weight loss. After BD, primary BA levels increased including CA, TCA, TβMCA, and TCDCA, whereas BD significantly decreased the relative composition of

secondary BAs DCA and LCA compared to sham. Pierre and others further reported that FXR is critical for BAR-mediated metabolic improvements after BD-induced weight loss using FXR deficient mice.[48,49]

Specific microbes may also mediate some beneficial effects of metabolic surgery. After *BD, Firmicutes* were decreased and *Bacteroidetes* were increased.[44] Specifically, the mucin colonizer *Akkermansia muciniphila* was enriched in the gut microbiome in BD animals,[44] which correlated with marked increases in both total circulating primary BAs and GLP-1 levels. This finding was consistent with Yan et al[55] who observed that Roux-En-Y gastric bypass elevated *A muciniphila* and GLP-1 levels in diabetic rats. A significant and lasting increase in *A muciniphila* has also been observed in human patients following Roux-En-Y, but not in VSG, suggesting diversion of BAs conferred by BD or Roux-En-Y surgery may be necessary for alteration in the distal gut microbiome.[56] Dietary interventions also modulate the gut microbiome.[57] Consistent with observations in bariatric surgery and obesity, high-fat diet-induced obesity suppresses *A muciniphila* abundance in animal models.[58] Numerous other human and animal studies also correlate *A muciniphila* levels with improvements in diabetes and obesity,[59,60] and recent observations suggest extracellular vesicles released by *A muciniphila* may mediate these beneficial effects.[61] Therefore, alteration of BA pools, specifically through modification of enterohepatic circulation, serves as an attractive method to modify *Firmicutes, Bacteroidetes,* and *A muciniphila* in the gut without the use of probiotics, which have heretofore proven variable and ineffective in large human trials.

In sum, weight loss through surgical-specific alterations in the microbiome and/or microbially derived metabolites, such as BAs as focused on in this review, may explain mechanistically driven improvements after weight loss and help pinpoint the critical inputs in set point theory of global energy homeostasis. These pathways should be the focus of future experimental models and human studies to definitively show surgery-specific mechanisms, since emerging evidence now supports the notion that BA pools may also influence obesity-associated comorbidities, such as cancer progression, through reprogramming of the immune microenvironment (as discussed further below).

4 | BREAST CANCER, OBESITY, AND WEIGH LOSS

Obesity is currently associated with 13 cancers.[62] Obesity leads to a higher risk of invasion, metastases, and recurrence, as well as impaired therapeutic response through various mechanisms, which together increases mortality.[41,63–95] Triple-negative BC (TNBC) is an aggressive BC subtype that is more prevalent in young women. TNBCs also disproportionately affect African American and Hispanic women, paralleling the trends in obesity rates in minorities, which together create an urgent need to address these health disparities.[77,84–85,96–104] TNBCs, primarily basal-like and claudin-low intrinsic subtypes, comprise ~15% of BC cases.[11,105–108] Despite the lower prevalence of TNBC compared to other BC subtypes such as luminal A or B, poor TNBC survival rates emphasize a great unmet need for patients. TNBC is a subtype that is negative for estrogen receptor (ER), progesterone receptor (PR), and amplification of the human epidermal growth factor receptor 2 (HER2).[18–110] As such, no targeted therapies exist for TNBC, resulting in

elevated recurrence, metastasis rates, and poor overall survival relative to other BC subtypes.[77,111] Thus, TNBC has generally eluded personalized medicine approaches, leaving only chemotherapy with few recent advances.

Makowski laboratory has taken advantage of a genetically engineered mouse model (GEMM) of TNBC which recapitulates human TNBC, called the C3(1)-T antigen (C3(1)-Tag) model, to address some of the questions regarding how obesity drives TNBC and to determine whether the effects of obesity can be reversed. They showed that obese mice display the greatest TNBC aggression compared to tumors in lean mice with early onset (reduced latency) or increased progression and activation of certain kinases and oncogenic signaling cascades in an obesity-specific manner.[112–116] Formerly, obese mice that lost weight through diet alteration display reversal of that obesity-driven progression to lean levels in this spontaneous GEMM of basal-like TNBC,[113,116] as well as ongoing studies using orthotopically transplanted syngenetic models (data not shown).

In patients, intentional weight loss and healthy lifestyle changes during cancer treatment are difficult to prioritize and implement. However, through retrospective studies of successful bariatric surgery weight loss studies, some conclusions can be drawn about risk and potential mechanisms to be targeted therapeutically. From a recent meta-analysis, bariatric surgery—and associated physiologic and metabolic changes—significantly reduced all-cause mortality from cancer (~33%−60%).[117–131] Retrospective studies found bariatric surgery significantly reduced risk for pre- and postmenopausal BC as well as skin cancer (including melanoma).[123,132] Of note for subtype-specific BC, bariatric surgery led to a 64% reduced risk in premenopausal ER tumors like TNBC.[133] Importantly, it is not yet clear from this and other clinical studies if this benefit from surgery arises from weight loss per se or is a surgery-associated benefit.

As the role of obesity in TNBC is established in some epidemiologic studies and experimental findings from our lab and others,[79,99,101,112–116,134–144] the field continues to search for and identify novel underlying mechanisms. Systemic or local hormones and adipokines associated with obesity influence cancer growth, including insulin, IGF-1, hepatocyte growth factor (HGF), and leptin.[145] Obesity also extensively mediates normal and tumor microenvironment dysfunction through components including immune cells and growth factors, which influence tumor onset and progression.[79,146–150] Breast tumors frequently contain dense infiltrates of immune cells, especially TNBC subtypes.[151] Work by our group and others demonstrated that obesity is associated with low-grade adipose inflammation and oxidative stress in the normal human breast, non-human primate, and murine mammary gland[79,152–164] which could influence risk, tumor outcomes, and therapeutic efficacy in BC. These concepts have been reviewed in great detail elsewhere.[165,166]

Bariatric surgery may influence cancer outcomes though altering microbial and BA pools that are proposed to be central to weight loss and other metabolic benefits. Indeed, novel mediators of poor outcomes in obesity-associated TNBC are microbes and/or microbially derived metabolites, which are currently gaining great interest. In summary, bariatric surgery may inform researchers about biomarkers of immunosurveillance or novel approaches to

improve treatment. If mechanisms associated with weight loss were better understood, then they could be leveraged therapeutically—independent of surgery or weight loss—to improve anti-tumor immunity potentially through targeting microbes or microbially mediated pathways.

5 | MICROBES IN EXTRA-INTESTINAL TISSUE AND CANCER

The gut microbiome, mycobiome, and virome are associated with numerous cancers including stomach, colon, liver, lung, head and neck, cervical, salivary glands, pancreas, lymphoma, and skin.[3–8] To date, only *Helicobacter pylori* has been accepted as a causative agent in stomach cancer. Aside from the gut, microbes are also found in extra-intestinal tissue. Bacteria are found in the breast with a Shannon diversity index similar to the gut.[18] The microbiota of the breast may arise from translocation from the gut (the "enteromammary" route), through the nipple, or other routes.[167,168] Alcohol, high-fat diet, corticosterone-induced stress, or obesity can induce barrier disruption (ie, a leaky gut), which exacerbates translocation of gut bacteria peripherally.[146] *Lactobacillus* is commonly used in probiotic formulations. When consumed orally, it can lead to increased mammary gland or milk *Lactobacillus* content which was associated with decreased mastitis, suggesting a direct enteral to extra-hepatic tissue axis.[169–171] In the obese breast, most studies show an increase in the *Firmicutes/Bacteroidetes* ratio compared to lean breast tissue, a broad biomarker of dysbiosis.[167]

Examination of the local microbiome in BC compared to normal tumor-adjacent or normal mammary gland has revealed interesting alterations.[11,14,168,172–176] The Western diet is associated with obesity and poor tumor outcomes.[177] Cook et al showed for the first time that Mediterranean vs Western diet could alter mammary gland microbes, specifically increasing *Lactobacillus* by 10-fold and reducing *Ruminococcus* in the mammary gland of non-human primates.[164] The reduction of *Ruminococcus* and increase in *Lactobacillus* in monkey mammary gland is important because both genera are associated with BC. Elevations of *Ruminococcus* were found in the gut of BC patients,[11] while tumors had lower *Lactobacillus* content compared to benign tissue.[172] Of note, mice given oral consumption of *Lactobacillus* decreased 4T1 tumor growth through increased T-helper cell (Th1) activation, with open and intriguing underlying mechanisms.[178,179] Together these findings suggest that an extra-intestinal microbiome exists and is modifiable by dietary and lifestyle factors which potentially may impact the immune milieu.

We identified a unique TNBC microbial signature, with high *Streptococcaceae* and *Ruminococcus* abundance in breast tumors and tumor-adjacent breast tissue, compared to normal mammary tissue from healthy subjects.[9] We reported that microbes vary by tumor stage and subtype. Critically, we showed for the first time that abundance of microbes and microbial ratios vary by race, with African Americans displaying greater microbial dysbiosis compared to tumors from European American patients.[9] Interestingly, race is one of the strongest associations for microbes, pathways, and clinical metadata according to the Human Microbiome Project Consortium study from 2012 but notably, breast was not studied.[1] The largest study to examine microbes and BC was from The Cancer Genome Atlas (TCGA) wherein *Proteobacteria, Actinobacteria,* and *Firmicutes* were shown as the most abundant

phyla in breast tumors, which is consistent with our work and others, and reminiscent of the gut.[1,11,14,18,21,168,172–176,180,181] We detected dysbiosis in breast tumors and tumor-adjacent breast tissue compared to normal tissue from healthy subjects. Recall that *Ruminococcus* is high in the gut of BC patients[11] and reduced by Mediterranean diet in the mammary glands of monkeys.[164] These findings are important because health disparities associated with both obesity and BC exist, and are linked to poor cancer outcomes.

Finally, while functional effects are likely due to groups of microbes, evidence supports certain microbes that correlate with both obesity and therapeutic efficacy. For example, *Akkermansia muciniphila*, which as discussed above is decreased by obesity and elevated after bariatric surgery, restored sensitivity to ICB therapy in murine models and correlated with ICB therapeutic response in patients.[8] These findings, conserved across species in both preclinical and clinical setting, are encouraging. Some of these microbial-cancer associations have only recently been described, and it is likely that other, as yet unappreciated associations remain to be discovered.

6 | BILE ACIDS IN EXTRA-INTESTINAL TISSUE AND CANCER

Primary and microbially modified secondary BAs have been shown to regulate cancer progression or metastasis in certain cancers. Selective targeting of gram-positive vs gram-negative bacteria induced changes in BA profiles and tumor progression using narrow-spectrum antibiotics. This approach was used successfully by Ma et al[182] to stably modify the microbiome to test role of primary vs secondary BAs in hepatocellular carcinoma. Ma from the Greten group took advantage of the fact that Vancomycin (Vanco) depletes gram-positive bacteria (primarily *Clostridium* cluster XIV[183]), which express 7-alpha-hydroxylase, the most important enzyme in the gut-mediated production of secondary BAs from primary BAs. Overall, Vanco depleted *Clostridium,* increased primary BAs, and reduced secondary BAs.[182] Likewise, secondary (ω-MCA) vs primary CDCA BA feeding reduced or increased natural killer T cell (NKT) content in hepatocellular carcinoma.[182] The proposed mechanism of action was through a BA responsive ligand-positive NKT population. Primary BAs drive expression of the CXCR6 ligand, CXCL16, whereas secondary BAs reduce CXCL16. Vanco increased anti-tumor CXCR6+ NKT cells in Ma's hepatocellular carcinoma model as the driving mechanism of tumor reduction.[182] In summary, the "BA→BAR→CXCR6+ NKT" pathway is protective in hepatocellular carcinoma.

Can BAs also influence BC? The presence of BAs in breast tissue was identified decades ago in humans—with evidence that oral BA administration preferentially accumulated in the breast.[184,185] Cook et al reported that Mediterranean diet-consuming monkeys had significantly higher mammary gland levels of the primary BAs CA and CDCA, as well as bile salts GCA and TCA, compared with monkeys fed a Western diet.[164] Strikingly, no difference in circulating BAs, except CA, was detected between dietary groups, emphasizing the potential for unique generation or accumulation of BAs in the local microenvironment of the mammary gland.[164] Therefore, microbes associate with tumor subtype and stage, race, and diet, and microbes are altered by diet and BAs in the mammary gland.

BC patients had lower circulating primary BAs (CA, CDCA, GCA, TCA) which may imply a decreased activation of FXR.[186] FXR is detected in benign and malignant breast tissue and associated with increased apoptosis in BC.[187] Activation of FXR by BA endogenous ligand CDCA or synthetic FXR agonist GW4046 induced apoptosis in normal and malignant BC cells of various BC subtypes and reduced MCF-7 xenograft growth.[188,189] High FXR associated with smaller tumor size, high proliferation rate, relapse-free survival, distant metastasis-free survival, and overall survival in BC patients.[190,191] Indeed, FXR is an independent prognostic factor for overall and disease-free patients' survival.[191] Potential mechanisms of action include FXR-mediated inhibition of leptin-induced oncogenic cancer-associated fibroblasts (CAFs) in multiple BC cell lines by increasing suppressor of the cytokine signaling 3 (SOCS3) expression downstream of FXR-implicating an obesity-specific susceptibility.[188] SOCS3 is downregulated in BC.[192] FXR may also mediate tumor effects through destabilization of hypoxia-inducible factor-1 alpha (HIF1-α), a master regulator that reprograms cancer cell metabolism and increases growth factors.[193–195] In addition, secondary BAs such as LCA also appear to be cytostatic through TGR5-dependent effects on cancer cell metabolism, lipogenesis, epithelial mesenchymal transition (EMT), pro- and anti-apoptotic signaling, and anti-tumor immunity in vitro and in vivo.[186,196,197] Furthermore, FXR and TGR5 also inhibit COX2 and NFκB, which are both important to cancer biology.[198,199] Finally, tumoricidal CXCR6+ NKT cell content is differentially regulated by primary and secondary BAs, discussed below.

7 | ANTI-TUMOR IMMUNITY

Immune checkpoint blockade has transformed the treatment of many cancers, showing unprecedented durable anti-tumor responses. However, a limitation of ICB is that responders are a minority; most patients do not respond due in part to immunosuppression, a major problem in the clinic. The immune checkpoints programmed cell death protein-1 (PD-1), PD-ligand 1 (PD-L1, CD274), and cytotoxic CD8+ T-lymphocyte antigen 4 (CTLA-4) are immune-inhibitory (ie, immunosuppressive). Immune checkpoint signaling depends on crosstalk between the cancer cell, T cells, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer T cells (NKT), among others.[20–205] PD-L1 is expressed on tumor epithelial cells, T cells, TAMs, DCs, MDSCs, other immune cells and stromal cells such as adipocytes, which implies a complex biology.[22–207] For example, PD-L1 concentration correlates with FoxP3+ regulatory T cells (Tregs) which create an immunosuppressive tumor microenvironment, especially in basal-like TNBC and even in early lesions including basal-like ductal carcinoma in situ (DCIS).[28,209] Higher PD-L1 expression is detected in TNBC vs non-TNBC samples and associates with poor prognosis.[20,209–216] Immunotherapy non-responders also have high levels of circulating MDSCs.[217–221] TNBC patients harbor higher levels of MDSC populations than non-TNBC patients. Consequently, TNBC patients who have high levels of circulating MDSCs respond poorly to ICB.[222]

The FDA recently approved ICB combination therapy for TNBC using anti-PD-L1 atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane) for the treatment of unresectable, locally advanced, or metastatic PD-L1+ tumors in March of 2019. However, this combination therapy is effective only in a subset of patients that highly expressed PD-L1.[223]

Due to these therapeutic limitations, patients with TNBC typically experience elevated recurrence and metastasis and poorer overall survival compared to patients with other BC subtypes. Anti-programmed death 1 (PD-1) monoclonal antibody pembrolizumab (Keytruda, Merck Sharp & Dohme) is effective with low-grade side effects when used as first-line treatment in patients with metastatic TNBC.[211,224,225] Treatment with pembrolizumab plus neoadjuvant chemotherapy, with or without carboplatin, had shown efficacy with few major toxic side effects in patients with locally advanced TNBC in the phase 1b portion of the KEYNOTE-173 trial.[226] Results from I-SPY2 phase 2 trial demonstrated that human epidermal growth factor receptor 2 (HER2)-negative BC patients had a higher pathological complete response compared to those who received neoadjuvant chemotherapy alone.[227] Results from the KEYNOTE-522 phase 3 trial examining neoadjuvant pembrolizumab with chemotherapy or chemotherapy alone, followed by adjuvant pembrolizumab or placebo in TNBC patients with early disease were recently published in *New England Journal of Medicine*.[228] Schmid et al report significantly greater pathological complete response in the neoadjuvant pembrolizumab + chemotherapy group compared to controls receiving just placebo and chemotherapy. While another trial reported efficacy of a PD-L1 inhibitor only in patients with PD-L1-positive metastatic TNBC in the IMpassion130,[223] Schmid's study using neoadjuvant plus adjuvant pembrolizumab was effective regardless of PD-L1 expression levels.[228] Targeting solid tumors with ICB is difficult but the field continues to push forward to find novel ways to improve anti-tumor immunity.

8 | OBESITY, THE MICROBIOME, AND THE OBESITY PARADOX IN IMMUNE CHECKPOINT INHIBITION

Obesity dramatically changes the immune milieu.[165] Obesity's effects on immunotherapy responses are a critical area of intense research.[229,230] Interestingly, PD-1 and PD-L1 expression on ligand-positive immune cells are increased by obesity, such as on DCs in obese patients.[24,231,232] Accumulation of PD-1+ T-cells is detected in visceral adipose of obese mice and human omental adipose of obese tumor-free patients.[232] PD-1 and PD-L1 are increased in prostate tumors of obese mice.[231] Furthermore, inflammatory cytokines present in the obese microenvironment stabilize cancer cell PD-L1 protein expression through de-ubiquitination.[233] Thus, inflammation associated with the obese tumor microenvironment may synergistically increase PD-L1 or PD-1, enabling a more efficient immune checkpoint-mediated immunosuppression. Elevated immune checkpoint protein expression may be fortuitous for patients who generally anticipate less favorable outcomes.[234] Indeed, clinical reports show that obese or overweight patients have improved immunotherapy efficacy in metastatic melanoma, non-small cell lung cancer (NSCLC), and other cancers leading to increased overall survival and/or progression-free survival with higher PD-L1 associated with better hazard ratios.[235–240] Proposed mechanisms of action include inflammatory cytokines and mediators such as C-reactive protein or leptin signaling to modulate the T cell repertoire.[238,241–245] Specifically, patients treated with ICB had reduced risk of death by 3.6% with every point increase in BMI.[237,246] While those studies find an obesity-ICB efficacy link regardless of sex for most survival measures, one study found the obesity-associated boost in ICB efficacy for males only.[236] Of special consideration is cytokine release syndrome or "cytokine storm" and immunotherapy-induced

immune-related adverse events (irAEs) that may be potentially exacerbated in obesity, reported in one mouse obesity study in tumor-free mice.[229,247] In our hands, however, immunotherapy does not induce cytokine release syndrome in obese mice with tumors (unpublished observations). Emerging data are exciting and clearly indicate that further study on the mechanisms underlying ICB and obesity is paramount.

To complicate matters, obesity also changes gut microbes, as discussed above. Emerging studies reported that the gut microbiome influences response to ICB,[10,248–253] which obesity could modulate. Fecal microbial transplant, antibiotics, or feeding certain organisms to mice have been reported to alter ICB efficacy in cancers such as sarcoma and melanoma.[10,251,254,255] Tumors may reflect a portion of gut microbes as in pancreatic cancer after transfaunation[256] but this is not clear yet for all cancers. In sum, bacteria's role in anti-tumor immunity is unclear. Clarifying mechanisms underlying clinical efficacy of ICB, the microbiome, locally relevant microbes and associated metabolites such as BAs, and potential modification by obesity are critical. Clinically, obesity as measured by BMI or waist to hip ratio (WHR) should be used to stratify patients in trials and in predicting risk or outcomes.

9 | BILE ACID SIGNALING IN KEY IMMUNE CELLS

As the role of obesity in TNBC is established in epidemiologic studies[11,140–144] and experimental findings are formed from our laboratory and others,[79,99,112–116,134–139] it is essential to identify novel underlying mechanisms associated with obesity, weight gain, or weight loss that impact TNBC outcomes. Inflammation associated with obesity is one well-studied consequence that influences risk, tumor outcomes, and therapeutic efficacy.[165,166] Breast and other tumors frequently contain dense infiltrates of immune cells.[151] The novel link between obesity, BAs, and cancer outlined above coalesces in the interaction between systemic or local BAs and BAR in adaptive and innate immune cells and is summarized below (Figure 2).

9.1 | Tumor-associated macrophages

Macrophages are a heterogeneous population of cells within the innate immune system that play critical roles in a myriad of processes including development, tissue homeostasis, host defense, and disease pathogenesis such as atherosclerosis, diabetes, and cancer.[257–259] Macrophages exhibit a diverse spectrum of phenotypes from pro- to anti-inflammatory, phagocytic, to extracellular matrix remodeling, among others which are often overlapping and overall flexible depending on the unique characteristics of the microenvironment. Along with these phenotypes are typical metabolic characteristics of certain macrophage types.[260–268] In vitro studies have informed early findings that classically activated ("M1"-like) macrophages utilize primarily glycolysis, which is linked to the pro-inflammatory phenotype characterized by the production of high levels of pro-inflammatory cytokines, reactive oxygen and nitrogen metabolites, microbicidal and phagocytic properties, and the generation of critical intermediates for anabolic pathways.[269–271] On the other hand, alternatively activated ("M2"-like) macrophages predominantly rely on mitochondrial oxidative metabolism[146,162,271–276] with a lesser dependence on glycolysis[277–280] and are associated with tissue homeostasis and resolution of the inflammatory response. Yet in vivo and recent

in vitro studies underscore that classical and alternative phenotypes are not dichotomous but rather present overlapping phenotypes and flexible metabolism.[162,281–284]

Work completed by our group and others demonstrated that obesity is associated with low-grade adipose inflammation and crown-like structures (CLS) in fat depots throughout the body including subcutaneous and visceral adipose[162,165,283] as well as the lesser studied fat depot of the normal human breast in humans, non-human primates, and mammary gland in mice.[79,152–164] In visceral fat, macrophages can comprise up to 50% of the cellularity of an adipose depot. Obesity-increased CLS are detected in obese patient breast adipose tissue compared to non-obese breast.[160] Dannenberg et al reported that breast CLS (CLS-B) associate with poor patient survival, even when lean.[285–287] In patients, TAMs impact every aspect of tumorigenesis, growth, and negatively influence response to anticancer therapies through establishing an immunosuppressive microenvironment, thus disallowing anti-tumor immune cells such as tumoricidal macrophages, cytotoxic (CD8+) T cell, and NKT cell activity.[79,155,163,288–303] Elevated TAMs in breast tumors are independent prognostic indicators of reduced relapse-free survival and decreased overall survival.[288,300,302,304–314] Therefore, microbially derived metabolites such as BAs may have a great impact on macrophages, such highly prevalent and dynamic cells.

In monocytes and macrophages, the BARs TGR5 and FXR are highly expressed. Activation of signaling via these receptors is mostly immunosuppressive or anti-inflammatory.[315,316] BAs suppress LPS-induced cytokine expression (TNFα, IL-6) and phagocytosis in primary human macrophages, murine macrophages, and Kupffer cells through either the TGR5-cAMP-PKA pathway or impaired activation of NFκB.[317–322] In monocytes, while BAs and TGR5 activation inhibited the secretion of the pro-inflammatory cytokines TNF-α and IL-12, it did not change the secretion of anti-inflammatory IL-10.[315,318] These findings suggest a “mixed” phenotype macrophage in response to BAs, wherein the immunosuppressive M2-like phenotype predominates, as evidenced by an increase in the IL-10:IL-12 synthesis ratio.[315,317–318,323,324] Similarly, FXR activation in macrophages by CDCA reduced NFκB-responsive cytokines after LPS-activation.[325] While FXR activation in macrophages causes a robust downregulation of the expression of several IFNγ-regulated genes, FXR itself is reciprocally downregulated by IFNy-STAT1 signaling suggesting that strength and timing of stimuli are necessary to consider in FXR and inflammatory signaling.[326]

The anti-inflammatory effects of BAs may be mediated through the inflammasome. Inflammasome activation plays a key role in host defense against pathogens and inflammation and its over-activation is integral to several inflammatory disorders including obesity.[327] Guo et al[328] showed that BA signaling through TGR5 inhibits NLRP3 inflammasome caspase-1 activation and IL-1β secretion in several disease states including type 2 diabetes. High levels of circulating bile salts (in this case due to cholestasis or sepsis) activate the NLRP3 inflammasome in macrophages to cleave caspase-1 which induces maturation of pro-IL-1β.[328–331] Thus, BARs may act as regulators of inflammation by preventing the activation of the inflammasome pathway or other signaling cascades. Taken together, these studies propose BAR agonism as a suitable therapeutic approach to prevent pro-inflammatory activation. How BAs effect macrophages in the obese adipose tissue

including the mammary gland or breast fat pad are unknown. Likewise, the impact on TAMs is currently undefined.

9.2 | Dendritic cells

Dendritic cells are a subset of innate immune cells which present antigens on major histocompatibility complex (MHC) molecules to T cells.[332,333] DCs are a heterogenous population that comprises three major subsets: (a) conventional DCs which are further divided into two distinct subtypes: cDC1 and cDC2; (b) plasmacytoid DCs which are major producers of type 1 interferons; and (c) monocyte-derived DCs which play a substantial role in inflammation.[334] BARs such as FXR and GPBAR1 are expressed by DCs in addition to their presence in other myeloid immune cells (macrophages and monocytes).[321,335] Interestingly, two studies have reported that pharmacological activation of FXR by BAR agonist obeticholic acid reduced differentiation and activation of intestinal DCs, with downregulated pro-inflammatory factors such as TNFα in mouse models of colitis.[335,336] Agonizing TGR5 induces differentiation of human CD14+ monocytes into IL-12 hypo-producing DCs via the TGR5-cAMP pathway.[335] However, the role of BARs in DC subset differentiation and activation in pathological conditions such as cancer and inflammation remains unknown and requires further studies.

9.3 | Myeloid-derived suppressor cells

Myeloid-derived suppressor cells are a poorly understood innate immature immunosuppressive cell population that emerges from the bone marrow and drastically expands in pathological conditions such as cancer and chronic inflammation.[337] MDSCs are heterogenous and comprise two distinct subtypes: polymorphonuclear (PMN-MDSCs) which resemble neutrophils and monocytic (M-MDSC) which are monocyte-like.[338] Both MDSC subtypes suppress innate and adaptive immunity in the tumor microenvironment. The main function of MDSCs limits T cell-mediated immune responses through production of immunosuppressive factors such as arginase 1 which depletes L-arginine, an amino acid which is essential for T cell proliferation and activation.[339] In a study published by Zhang et al[340], FXR activation in MDSCs enhanced their suppressor function which attenuated immune-mediated liver injury. Mechanistically, FXR-mediated activation of MDSCs was dependent on FXR binding to the paired Ig-like receptor B (PIR-B) promoter which resulted in upregulation of S100 calcium-binding protein A8 (S100A8). This is the only study reporting the role of BARs in MDSCs and more studies are needed in order to understand how BARs affect MDSCs in both autoimmune diseases and cancer.

T cells including regulatory T cells (Treg), Th17, mucosal-associated invariant T (MAIT), natural killer T cells (NKT), and B cells.

Although most work has focused on BA regulation of innate immune cells, exciting investigation of the adaptive immune cell compartment in various diseases has been forthcoming. In congruence with the immunosuppressive effects of BA, LCA impedes Th1 activation in human and mouse CD4+ T cells through decreasing production of Th1 cytokines IFNγ and TNFα.[341] Additionally, FXR agonists obeticholic acid and CDCA treatment ameliorated experimental autoimmune encephalomyelitis (EAE) in mice by

suppressing lymphocyte activation and pro-inflammatory cytokine production. Interestingly, obeticholic acid treatment of EAE mouse model reduced CD4+ T cells and CD19 B cells, as well as their expression of PD-1 and PD-L1. However, obeticholic acid treatment increased CD8+ T cells and their expression of PD-1. Taken together, these findings highlight a positive role of BAs and FXR signaling in regulating neuroinflammation and propose FXR agonism through obeticholic acid as a potential therapeutic approach for multiple sclerosis (MS).[342]

In a recent study, Hang et al[343] screened BA metabolites and found two LCA metabolites (namely 3-oxo-LCA and isoallo-LCA) that regulated T cell differentiation. 3-Oxo-LCA blunted differentiation of Th17 cells through retinoid-related orphan receptor-γt (RORγt). Interestingly, isoallo-LCA functioned through a different mechanism to increase Treg (Foxp3+) differentiation in a mitochondrial reactive oxygen species (mitoROS)-dependent manner. Combined treatment of mice with these LCA metabolites therefore skewed T cells in the intestinal lamina propria from Th17 toward Treg.[343] Further analysis has shown genetic ablation of BA metabolic pathways in individual gut symbionts significantly decreased Treg populations.[344] These data suggest that BA and microbes regulate Tregs and Th17 cells in the gut and possibly other tissues which could have potent impacts on anti-tumor immunity.

As introduced above, Ma and colleagues showed a direct link between the microbiome, BA, and hepatocellular carcinoma through the recruitment of natural killer T-cells (NKT). Primary BAs increased NKT cell accumulation via liver sinusoidal endothelial cell (LSEC) CXCL16 expression which effectively reduced liver tumor growth. When microbiota was present and conversion of primary BAs into secondary BAs occurred, NKT cells failed to be recruited and the tumor growth was elevated.[182] In sum, Greten's group demonstrated a direct link between microbiota, BAs, and the immune tumor microenvironment through the "BA→BAR→CXCR6+ NKT" pathway.

Lastly, crosstalk between macrophages and T cells may be through the FXR downstream mediator SHP which is found in macrophages and blunts NFκB activation.[345] The orphan nuclear receptor SHP acts as a negative regulator in inflammatory signaling triggered by Toll-like receptors. High SHP in macrophages led to reduced activation and proliferation of T cell expansion with reduction especially in Tregs through reduced IL-2 and TGFβ, while SHP knockdown led to Treg expansion. SHP enrichment was found in the promoters of IL-2, CD86, MHCII, and NOS2. Under normal conditions, SHP likely limits indiscriminate inflammation (ie, macrophage cytokine driven pro-inflammatory activation) but promotes a targeted T cell response (ie, skews T cells toward Teffector vs Tregs).[346]

Mucosal-associated invariant T (MAIT) cells are a relatively new subset of innate-like T cells which are highly abundant in the human liver. MAITs comprise from 10% to 50% of total liver T cells.[347] MAITs are also localized to the gut mucosa.[347,348] Importantly, the development of MAITs is absent in germ-free mice, indicating that microbiota are essential for the differentiation of MAIT cells.[347] In children from the Lifestyle Immune System Allergy (LISA) cohort, Mendler and colleagues showed that BAs positively associated with pro-inflammatory markers such as C-reactive protein, IL-8, and MIP-1α. In contrast, a

negative association between conjugated-BA concentrations and the number of activated MAIT cells was found.[349] Furthermore, BA-mediated inhibition of MAIT cell activation in vitro was shown. Interestingly, overweight children in the LISA study had reduced MAIT activation[349] in agreement with obesity-associated alterations in MAIT cell function and distribution in children and adults.[350] Recent studies indicate that MAIT cells display tumor promoting functions by suppressing T cells and NK cells in a murine model of melanoma lung metastasis.[351] The role of BA and MAITs in cancer is completely unexplored.

In summary, most publications to date on BA and BAR in immune cells focus on gut-associated disease, autoimmune disease, or acute phenomena such as sepsis, with little work on the tumor microenvironment, demonstrating a large gap in our knowledge which we intend to fill with this review. It is apparent that the role of BARs in innate and adaptive immunity implies that BAs or agonism of BARs leads to a general downregulation of inflammation in some cell types but an activation of other cells such as NKT. This will continue to be an area of active investigation.

10 | CONCLUSIONS AND FUTURE DIRECTIONS

Compelling evidence suggests a protective role of BAs and BAR agonists involved in metabolic and immune -linked pathologies which with further study could be exploited in the treatment of cancer and other autoimmune diseases. To attempt to address the lack of evidence for BARs in cancer, using online expression data from tumors, we examined BAR TGR5 expression in correlation with immune cell infiltrate and overall survival. Correlation of TGR5 expression with immune infiltration level in BC overall and skin cutaneous melanoma showed positive and significant associations for all cell types examined. TGR5 expression has significantly positive correlations with infiltrating levels of CD8+ T cells and DCs as determined by gene expression signatures for immune cells using the Tumor IMmune Estimation Resource (TIMER) database[352] (Figure 3A). Cumulative survival was also examined for high and low expressers of TGR5 in tumors from BC and melanoma patients and specific immune signatures. CD8+ T cells and DCs predicted significantly improved overall survival in patient tumor’s that highly expressed TGR5 compared to patient tumors with low expression (Figure 3B). In melanoma, B cells and neutrophil population levels also associated with better survival in TGR5 high expressing tumors compared to low expressing tumors (data not shown). Our novel findings support BARs as a promising target for additional preclinical and clinical studies.

Our lack of understanding of how the gut and/or extra-intestinal microbiome affect the molecular mechanisms and signaling pathways mediating effective anti-tumor outcomes poses a substantial obstacle to advancement in cancer therapy, as well as a potential therapeutic opportunity. It is possible that immune perturbations resulting from microbiome composition and microbially modified metabolites can be targeted for therapeutic benefit. To date, several current clinical trials are testing probiotics or examining gut microbiome in BC, with some analyzing the mammary microbiome. Probiotics, which have heretofore proven variable and somewhat ineffective in large human trials, may not be effective in restoring tissue dysbiosis. Only one clinical trial to date is examining the role of bariatric surgery intervention on biomarkers of BC in high-risk patients (NCT02681120). The National

Cancer Institute (NCI) and National Institute on Dental and Craniofacial Research (NIDCR) are participating in a recent program announcement entitled “Microbial-based Cancer Therapy-Bugs as Drugs” and another with NCI participating entitled “Modulating Intestinal Microbiota to Enhance Protective Immune Responses against Cancer.” Thus, these recent NIH program announcements show increased evidence of commitment toward understanding the contribution of microbes in regulation of the immune response and anti-tumor therapy.

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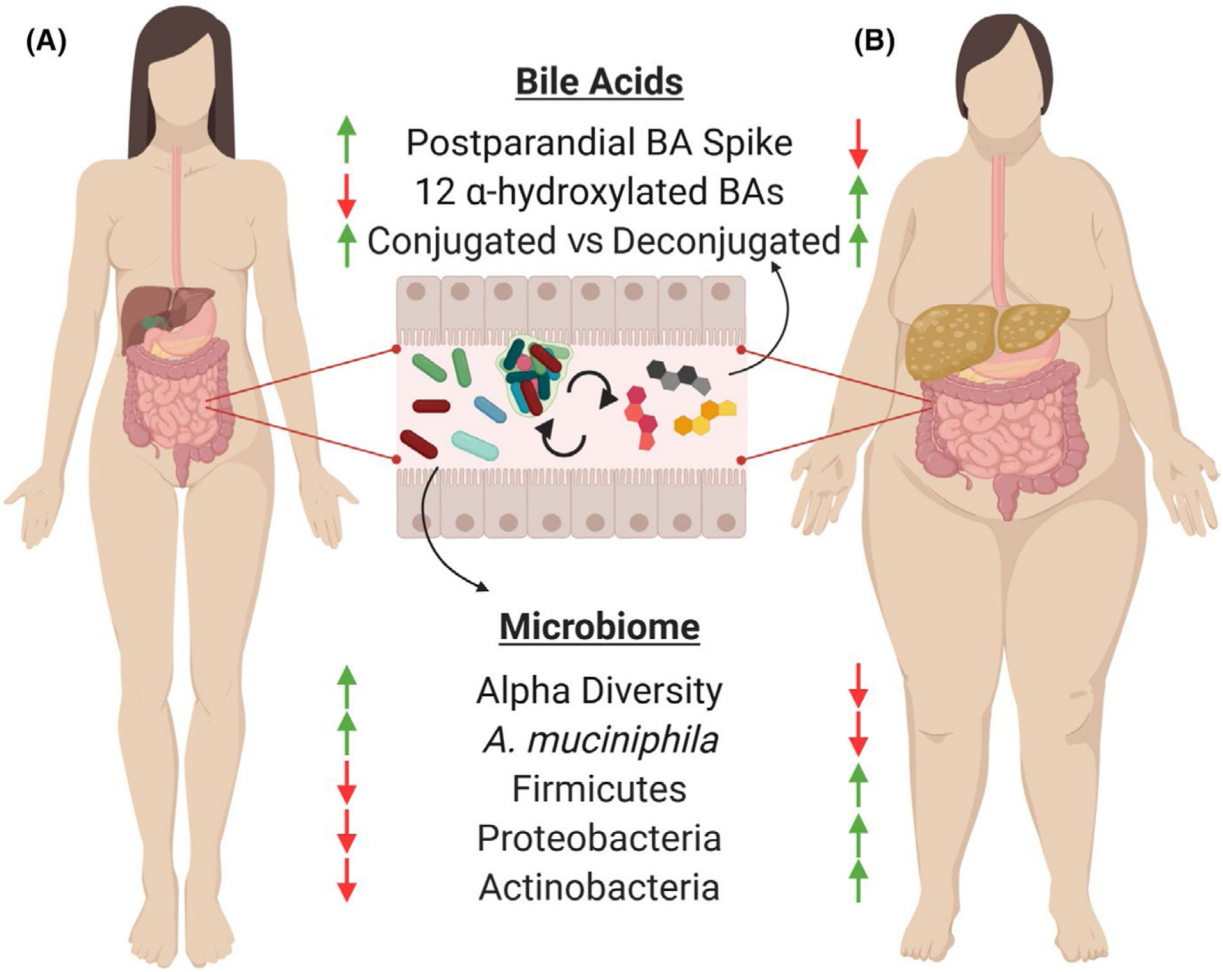

FIGURE 1.

The gut microbiome, enterohepatic circulation, and obesity. The liver generates primary bile acids (BAs), usually conjugated with taurine and glycine, in part to aid with lipid and nutrient absorption immediately following meals. Within the gut, the microbiota deconjugate and ferment BAs into secondary BAs that are subsequently reabsorbed and may be further modified by the liver, a cycle known as “enterohepatic circulation.” This iterative process leads to diverse composition in the BA pools within the gut lumen, in circulation, and within various tissues. In addition to nutrient absorption, BAs serve as potent hormone-like signaling molecules through numerous receptors that confer a variety of metabolic and immunological effects throughout the body. Obesity disturbs this process, leading to blunted postprandial BA release, increased levels of the 12 alpha-hydroxylated BA forms, decreased intestinal microbiome diversity, and changes in taxonomic composition. Obesity is associated with a loss of the mucosal colonizing microbe, *Akkermansia muciniphila,* which has been shown to confer beneficial metabolic and immunotherapeutic anti-tumor benefits when administered to mouse and man

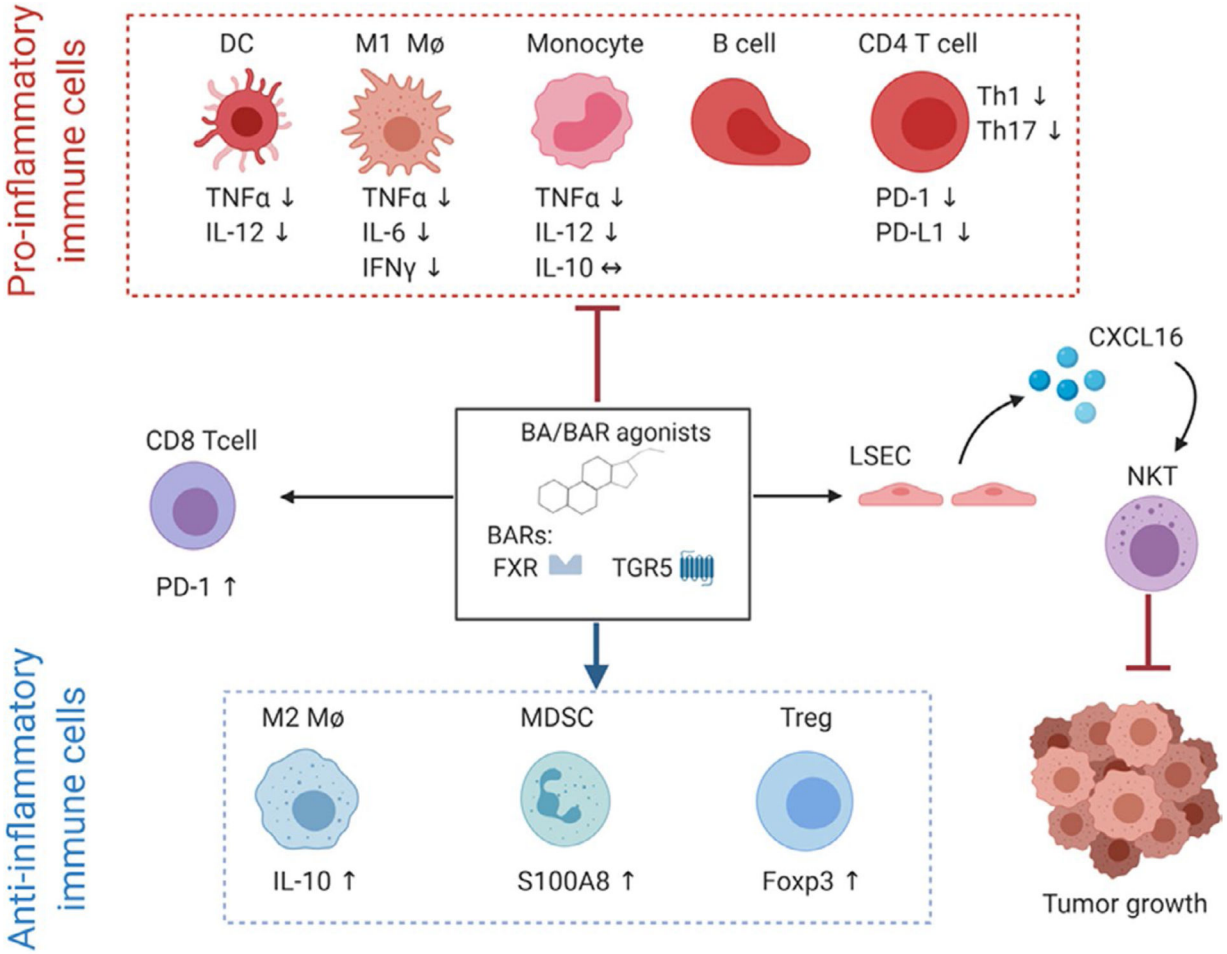

FIGURE 2.

Bile acids or small molecule effects of bile acid receptors (BARs) Farnesoid X Receptor (FXR) and G Protein-coupled bile acid receptor (TGR5) agonism on immune cell populations. BAR agonism impairs pro-inflammatory functions of immune cells by downregulating tumor necrosis factor alpha (TNFα) and interleukin 12 (IL-12) on dendritic cells (DCs) and monocytes. BAR agonism also impairs M1-like pro-inflammatory polarization of macrophages (Mϕ) by downregulating TNFα, IL-6, and interferon gamma (IFNγ). Additionally, BAR agonism decreases the abundance of B cells and CD4 T cells, downregulates protein death receptor 1 (PD-1) and its ligand PD-L1 on CD4 T cells and impairs Th1 and Th17 polarization. On the other hand, BAR agonism favors anti-inflammatory cells such as myeloid-derived suppressor cells (MDSC) via upregulation of the calcium-binding protein S100A8, T regulatory cells (Treg), and immunoregulatory M2-like polarization of macrophages via upregulation of IL-10. BAR agonism also induces the expansion of CD8 T cells and their upregulation of PD-1; however, BA-induced expansion of CD8 T cells remains unknown. Finally, primary BAs induce liver sinusoidal endothelial cells (LSEC) to release the chemokine CXCL16 which will attract Natural Killer T cells (NKT) into the tumor site and inhibit cancer growth

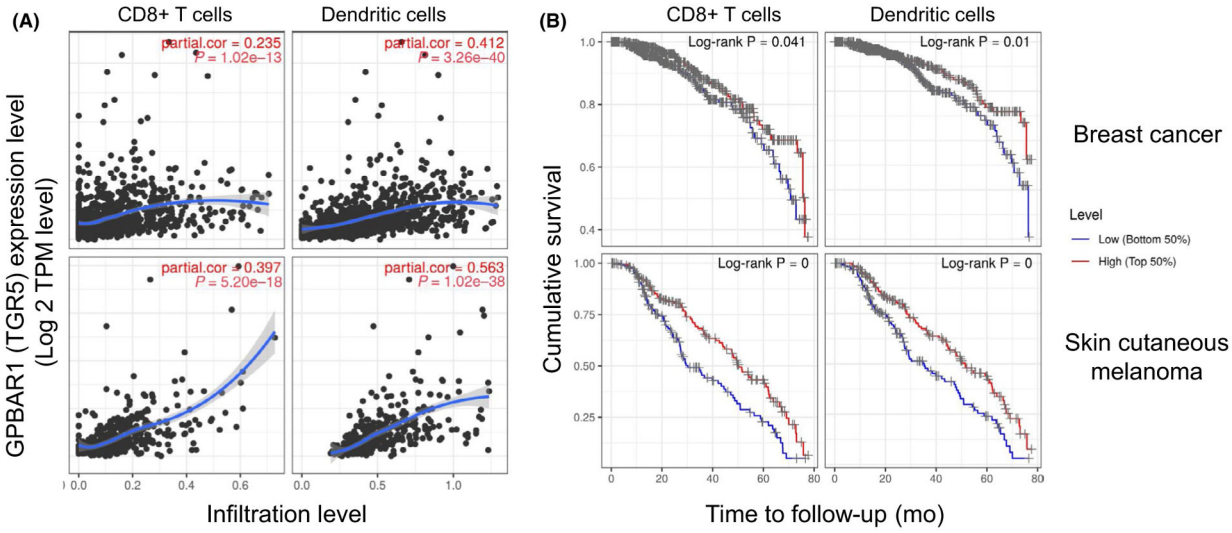

FIGURE 3.

Correlation of GPBAR1 (TGR5) expression with immune cell infiltration levels in breast cancer and skin cutaneous melanoma. Breast cancer is depicted in top graphs and skin cutaneous melanoma in bottom graphs. A, GPBAR1 expression has significant positive correlations with infiltrating levels of CD8+ T cells and dendritic cells determined by using TIMER database.[352] B, High expression of GPBAR1 has a significant favorable overall survival when correlated with high infiltration of CD8+ T cells and dendritic cells as compared to low expression of GPBAR1 in both breast cancer and skin cutaneous melanoma (TIMER database). Cumulative survival is shown for 80 mo