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Review

Role of microbiota-derived short-chain fatty acids in cancer development and prevention

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ABSTRACT

Following cancer, cells in a particular tissue can no longer respond to the factors involved in controlling cell survival, differentiation, proliferation, and death. In recent years, it has been indicated that alterations in the gut microbiota components, intestinal epithelium, and host immune system are associated with cancer incidence. Also, it has been demonstrated that the short-chain fatty acids (SCFAs) generated by gut microbiota are vitally crucial in cell homeostasis as they contribute to the modulation of histone deacetylases (HDACs), resulting effected cell attachment, immune cell immigration, cytokine production, chemotaxis, and the programmed cell death. Therefore, the manipulation of SCFA levels in the intestinal tract by alterations in the microbiota structure can be potentially taken into consideration for cancer treatment/prevention. In the current study, we will explain the most recent findings on the detrimental or protective roles of SFCA (particularly butyrate, propionate, and acetate) in several cancers, including bladder, colon, breast, stomach, liver, lung, pancreas, and prostate cancers.

1. Introduction

Cancer is commonly known to be caused by an interaction between environmental factors and the genetics of the host [1]. In addition to genetic determinants, many studies have indicated the pivotal role of microorganisms in cancer biology [1]. Several carcinogenic pathogens including, hepatitis C (HCV) and B (HBV) viruses, *Helicobacter pylori*, and human papillomaviruses (HPV), have been observed in about 20% of all cancers [2]. Accordingly, additional oncogenic microorganisms may be present with a synergic function to start or develop tumorigenesis. This microbial population, known as the microbiota, has been recently identified as essential factors in cancer biology [1]. In recent years, state-of-the-art technologies have been developed to analyze the human microbiota to quantify the microbiome community members and determine their role in cancer development [3].

Despite various investigations on the association between gut microbiota and cancer, the exact mechanisms of this interplay are not thoroughly investigated. However, it has been demonstrated that this interaction may be subsequent to bacterial metabolites [4]. Gut microbiota generates numerous short-chain fatty acids (SCFAs) from non-digestible and fermentable carbohydrates, including dietary fiber [5]. Main SCFAs with total intestinal concentration exceeding 100 mM include propionate, acetate, and butyrate [6]. Recently, it has been indicated that SCFAs can affect the progress of various diseases, such as inflammatory bowel disease (IBD), diabetes, atherosclerosis, and colorectal cancer (CRC) [7–9]. Researchers have predominantly focused on the effect of SCFAs on CRC [10,11]. Investigations have shown that the fecal SCFA levels declined in CRC patients compared to the control

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following the decreased number of SCFAs-producing bacteria [12,13].

It has been found that several bacteria could generate tumor-boosting metabolites such as secondary bile acids, whereas some bacteria could secrete tumor-suppressing metabolites like SCFAs [14,15]. Based on the significance of SCFAs, substantial epidemiological data established that an enhanced rate of inflammatory disorders and cancer was mediated to subjects with diets poor in SCFAs or diminished amount of fecal SCFAs, particularly for breast as gastric cancers [16]. SCFAs in the host gut and other parts could extensively diminish carcinogenesis and prevent and treat gastrointestinal and lung cancers by inhibiting cell growth and migration, suppressing histone deacetylases (HDAC), and inducing apoptosis [17]. Additionally, epidemiological investigations have found that high-fiber diets are mediated to a low incidence of cancer compared to red meat consumptions, which have been noted to enhance cancer risk [18–20]. Currently, it has also been found that the key for high fiber diets to exert anti-cancer influences is the formation of SCFAs like butyrate via the action of the microbiota [15]. Here, we will discuss the current evidence from the most recent studies on the association between SCFAs generated from gut microbial population and selected cancers.

2. The production and metabolism of microbiota-derived SCFAs

2.1. Microbiota in the gastrointestinal tract

Our lifestyle, including exercise, diet, microbial exposure during childhood, and antibiotic treatment, can markedly affect our microbiota [21]. Two bacterial phyla that prevail in the human gut are *Bacteroidetes* and *Firmicutes* [21]. Over the recent decades, different technologies for bacterial classification to specific genus and species have resulted in various reclassifications [21]. Bacterial species can be further classified into subspecies according to trivial but relevant alterations within a species [21]. Based on different immune antigens on the bacterial surface, further classifications into strains or serovars are specified outside nomenclature rules [21]. This level of complexity explains the aim of determining microbial metabolites within the gut community, thereby preventing the complications of bacterial species while focusing on their metabolism [21]. Epidemiological studies have demonstrated an association between bacterial colonization and cancer progression [21]. However, determining the function of bacterial cells in cancer development is difficult owing to the impact of host determinants in cancer susceptibility, the ubiquitous nature of bacteria, and the prolonged period of overt cancer development following the introduction of bacterial cells [22]. This can be complicated by environmental factors with more significant roles in determining one's microbiota structure than genetic factors [23]. While data on bacterial interaction with human cells is rapidly increasing, there is a great potential for further innovation when considering other microbes (viruses and fungi) that reside in the gastrointestinal tract [24].

2.2. Microbiota and short-chain fatty acids formation

Members of the gut microbiota produce several SCFAs from dietary fiber [4]. Propionate, acetate, and butyrate belong to SCFAs, and their total intestinal concentration may exceed 100 mM [6]. Most SCFAs are the final product of bacterial fermentation, and endogenous host synthesis is usually trivial (Fig. 4) [25]. SCFAs are produced by two major bacterial groups: propionate and acetate are formed by *Bacteroidetes*, while butyrate is produced by *Firmicutes* [26]. SCFAs are important players in the interaction between the host and gut microbiota [4]. SCFAs can affect the colon and other organs via blood flow: the uptake of SCFAs following fasting can contribute to elevated serum acetate levels [4]. Recent studies have indicated that SCFAs could affect the progression of different diseases, like IBD, diabetes, atherosclerosis, and CRC [4, 7–9]. Many studies have particularly focused on CRC [11]. Based on clinical case studies, fecal SCFAs levels declined in CRC patients compared to the control groups, which can be attributed to the reduced number of SCFAs-producing organisms, including *Lachnospiraceae*, *Roseburia* spp., *Bifidobacterium* spp. [12,13].

3. The interaction between intestinal barrier function, inflammation, and carcinogenesis

3.1. Inflammation, microbiota, and carcinogenesis

Following disturbance of normal microbiota and immune cells, including interleukins (ILs), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and tumor necrosis factor (TNF) are released [27]. While pattern recognition receptors (PRRs) are involved in reinforcing cellular junctions to support the epithelial barrier, the proinflammatory cytokines increase mucosal permeability of the paracellular routes for microbe entry [27]. Both growth factors and cytokines induce inflammation, which negatively impacts differentiation by maintaining the survival and growth of dysplastic cells [27]. Tumor and bacterial cells may produce large amounts of cytokines in a self-maintaining manner [28]. In case inflammation persists, the continued propagated inflammatory signals, hindered apoptosis, and elevated levels of growth factors all contribute to cancer development [29].

In many diseases that microbiota involve in progression, it has been found that disruption of the epithelial layers results in microorganisms and their metabolites reaching compartments that are not usually in close contact with microorganisms [30]. This situation could induce local chronic inflammatory reactions because of prolonged injured tissue and, hence, a constant stream of infiltrating microorganisms and their metabolites. For instance, in CRC and IBD, the underlying mucosal layers are interrupted, exposing the deep sections and resident immune components to further rates of microorganisms and their metabolites [30,31]. This situation accelerates tumor progression via pro-tumorigenic factors such as chemokines and cytokines that could act as growth factors that some activates like the stimulation of migration and enhance the angiogenesis. It has currently been found that commensal bacteria stimulate the Interleukin 6 (IL-6), Interleukin 17 (IL-17), Interleukin 22 (IL-22), and Interleukin 23(IL-23) signaling in colon adenoma models because of defects in integrity of colon barrier, and antibacterial drug therapy, as well as genetic ablation of IL-23, abrogates tumorigenesis [32].

Along with microbiota dysbiosis, pathogenic bacteria have a crucial activity in some diseases such as CRC [30]. In this regard, various bacteria were noted to trigger CRC, such as certain strains of *Helicobacter pylori, Escherichia coli*, *Bacteroides fragilis, Streptococcus gallolyticus*, *Enterococcus* spp, and some member of Enterobacteriaceae [30,33,34]. These bacteria can bind to the target tissue's epithelial layers and directly stimulate the growth and proliferation of epithelial cells, resulting in hyperplasia. Besides, these bacteria could generate toxins that cause epithelial barrier integrity disruption, as well as inflammation.

Different cytokines may be used as biomarkers in therapy [27]. A classification system (Immunoscore®) may be used for improving the prognosis of CRC [27]. According to several studies, the Immunoscore was more efficient in determining microsatellite instability for survival prognosis [35–37]. Following the interruption of eubiosis, IL-6, TGF-β, and TNF generated by T cells and macrophages leading to the differentiation of naive CD4 T cells into pro-inflammatory T helper 17 (Th17) cells which play a significant role in the adaptive immune response against pathogens [27,38,39]. Following persistent inflammation of the mucosa, the continued presence of Th17 is associated with CRC progression. Th17 infiltration to CRC tissue and increased concentrations of IL-22 and IL-17 are linked with declined survival rate [40,41]. Interestingly, several microbiota members, particularly *Clostridia* species, and dysplasia promote the production of Th17 and IL-17 in epithelial cells. Th17 has also been indicated as an essential factor in CRC in

murine models exposed to Enterotoxigenic *Bacteroides fragilis* (ETBF) [27]. Reduced microadenoma has been noted by the restriction of Th17 following T-regs depletion [42,43].

Furthermore, tumors with increased infiltration of CD3+ (and probably CD8+) are linked with improved survival [44]. IL-6 is a potent proinflammatory cytokine that seems to be associated with angiogenesis and CRC progression [27]. IL-6 formed by T cells, macrophages, and fibroblasts of the tumor-supporting stroma can trigger signal transducer and activator of transcription 3 (STAT3), contributing to tumor progression. In CRC patients, increased serum IL-6 levels could be considered as a prognostic biomarker for tumor mass, metastases, and low survival [45,46]. TGF-β generated by macrophages and inflammatory cells, is essential in cell differentiation, growth, and programmed cell death. In normal conditions, cell growth is prevented following the activation of TGF-β in epithelial cells, while mutations in TGF-β signaling and receptors have been significantly found in CRC [47,48]. TGF-β formed by tumor stromal fibroblasts has a contradictory impact and induces the growth and propagation of CRC cells [27]. Elevated TGF-β production increases the risks of tumor recurrence following treatment due to increasing the survival rate of metastatic cells [49]. TNF produced by macrophages also contributes to the recruitment of inflammatory cells, increased mitogenic signaling, and vascular permeability [27]. TNF induces oncogenic signaling pathways such as the Wnt and Nuclear factor-kappa B (NF-κB) in epithelial cells, thereby controlling cell survival and growth [27]. When epithelial cells are exposed to TNF, CIS and mutation frequencies increase, implying the direct contribution of TNF to cancer progression [50–53]. Serum levels of TNF have been linked with disease advancement and low survival rates in CRC patients [54,55]. Serum levels of TNF have been linked with disease advancement and low survival rates in CRC patients [54,55]. Also, potential pathophysiological routes of inflammation are comprised of the oxidative stress stimulated by an imbalance between the generation of reactive oxygen species (ROS) and antioxidant protection after DNA disruption and dysplasia, which support tumor progression [27]. Oxidative stress increases tumor-promoting or pro-inflammatory cytokines and anti-apoptotic signaling by NF-κB, thereby linking chronic inflammation to cancer [27]. NF-κB can direct several genes (including Bcl-x and surviving), thereby enhancing tumor cell proliferation and hindering apoptosis [28,56]. Of note, obesity induces the expression of NF-κB in most tissues and increases the risk of type-2 diabetes [27]. NF-κB could link type 2 diabetes, obesity, IBD, and cardiovascular disease with cancer [57,58].

Interestingly, several microbiota members, particularly *Clostridia* species, promote Th17 and IL-17 in epithelial cells. Th17 has also been indicated as an important factor in CRC in murine models exposed to Enterotoxigenic *B. fragilis* (ETBF) [27]. Reduced microadenoma has been noted by the restriction of Th17 following T-regs depletion [42, 43].

4. The mechanism of short-chain fatty acids in cells

SCFAs show both extracellular and intracellular outcomes by being

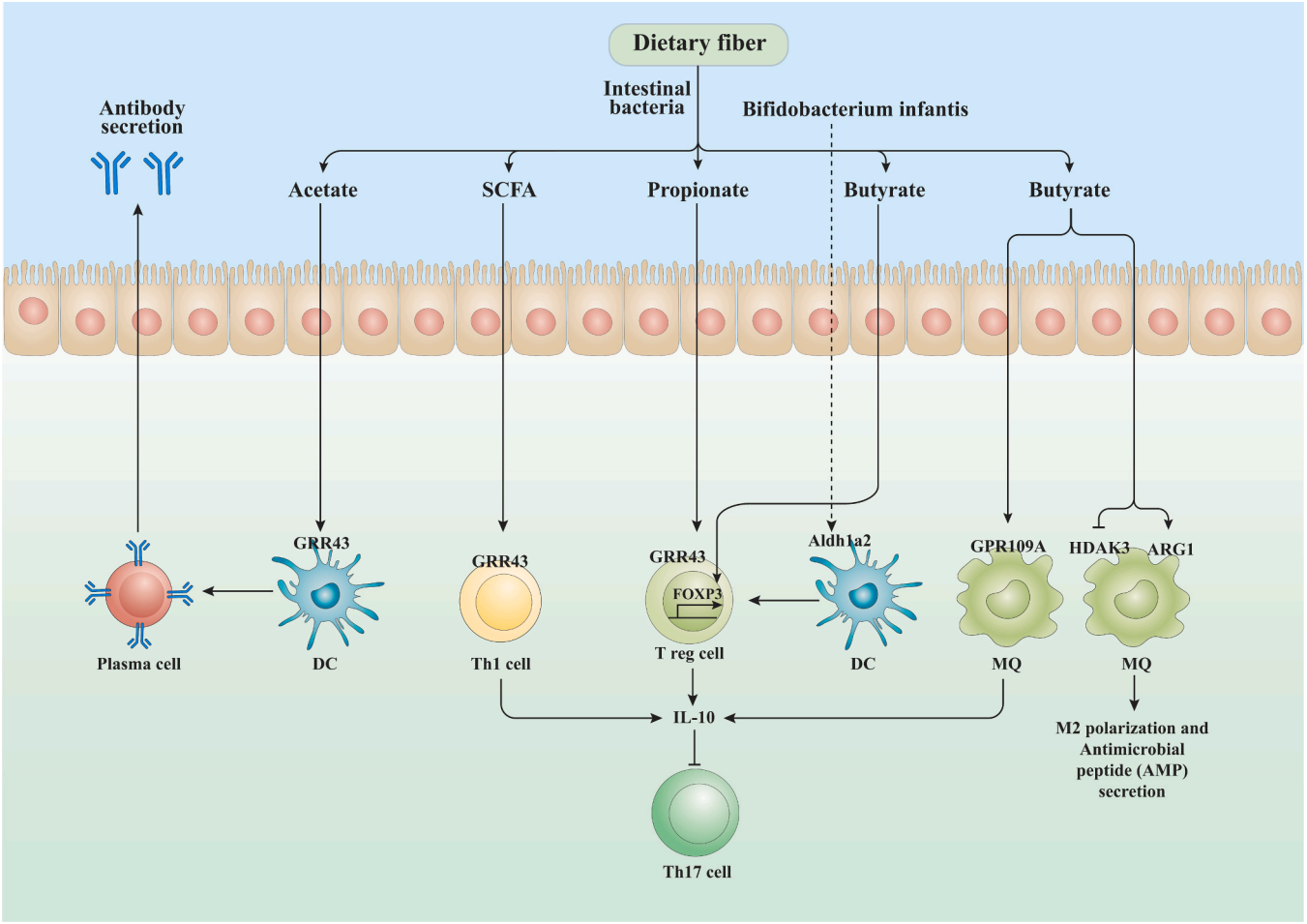

Fig. 1. Mechanisms of signaling from short-chain fatty acid derived from bacteria in gut immune cells. Short-chain fatty acids (propionate, butyrate, and acetate) involve in a complexed host-microbiome interaction to intestinal immune reactions (for example development of Regulatory T cells (Tregs), the activity of Dendritic cell (DC) and macrophage, and the anti-inflammatory cytokines production, proliferation of plasma B cell, as well as production of antibody) by inhibition of histone deacetylase (HDAC) and activation of GPR109A and GPR43, finally exerting anti-inflammatory impacts and conferring tolerance toward microbial pathogens.

ligands to their receptors and functioning as epigenetic regulators, respectively (Fig. 1) [59]. Receptors of SCFAs are present throughout the human body [59]. These receptors belong to G-protein coupled receptors (GPCRs), suggesting their role in several cellular pathways [59]. GPR109A is a surface receptor of adipocytes, colonocytes, and macrophages [60]. This receptor in adipocytes is commonly involved in releasing fat stores in deprivation conditions [61]. The reduced expression of GPR109A can also lead to CRC progression [60]. Reportedly, GPR109A contributes to the differentiation of T reg cells and the formation of both anti-inflammatory (IL-10) and proinflammatory (IL-18) cytokines [60]. These responses have been associated with carcinogenic outcomes, as shown in Niacr1-/- mice [62]. Moreover, cell cycle regulation and apoptosis can be affected by SCFAs [4]. GPR41/43 activation promotes the intracellular levels of Ca^{2+} and promotes the stimulation of mitogen-activated protein kinases (MAPK) p38 in MCF-7 cells [4]. These results are widely linked with cellular stress responses and even carcinogenesis [63,64]. Also, GPR43 is not present in metastatic cells and colon tumors, suggesting its role in carcinogenesis. G0/G1 cell cycle arrest and apoptosis have been occurring following the restored expression of GPR43 in adenocarcinoma cell lines [65].

A possible association between SCFAs and cancer may be owing to the stimulation of GPCRs [4], which can trigger the cascades of responses that either leads to malignancy or hinder it (Fig. 2) [4]. SCFAs may act as ligands to membrane receptors, thereby affecting cell metabolism [4]. Butyrate may employ sodium-coupled monocarboxylate transporter (SMCT1) for cell entry. This transporter was first characterized as a potential tumor suppressor [4,66]. Butyrate can also use other transporters to circulate inside the body [4]. One of the main carriers is the MCT4 (monocarboxylate transporter 4), which fluxes butyrate to the blood flow [67], allowing butyrate to demonstrate a systemic impact on the host organism within the bloodstream [4]. Butyrate can enter back to the intestinal lumen with BCRP (breast cancer resistance protein) [4]. The reduced mRNA expression of BCRP is possibly linked with colorectal adenoma progression, which might be associated with butyrate accumulation within cells [68].

Following cell entry, butyrate can affect histone deacetylases (HDACs) [4]. These enzymes are primarily involved in cell cycle regulation, proliferation, and programmed cell death [69]. Butyrate and its binding to HDACs have been associated with CRC development [70,71]. Following the binding of butyrate to HDACs, its enzymatic activity is hindered, leading to histone hyperacetylation and altered gene expression [4]. Finally, butyrate can suppress the growth of tumor cells by

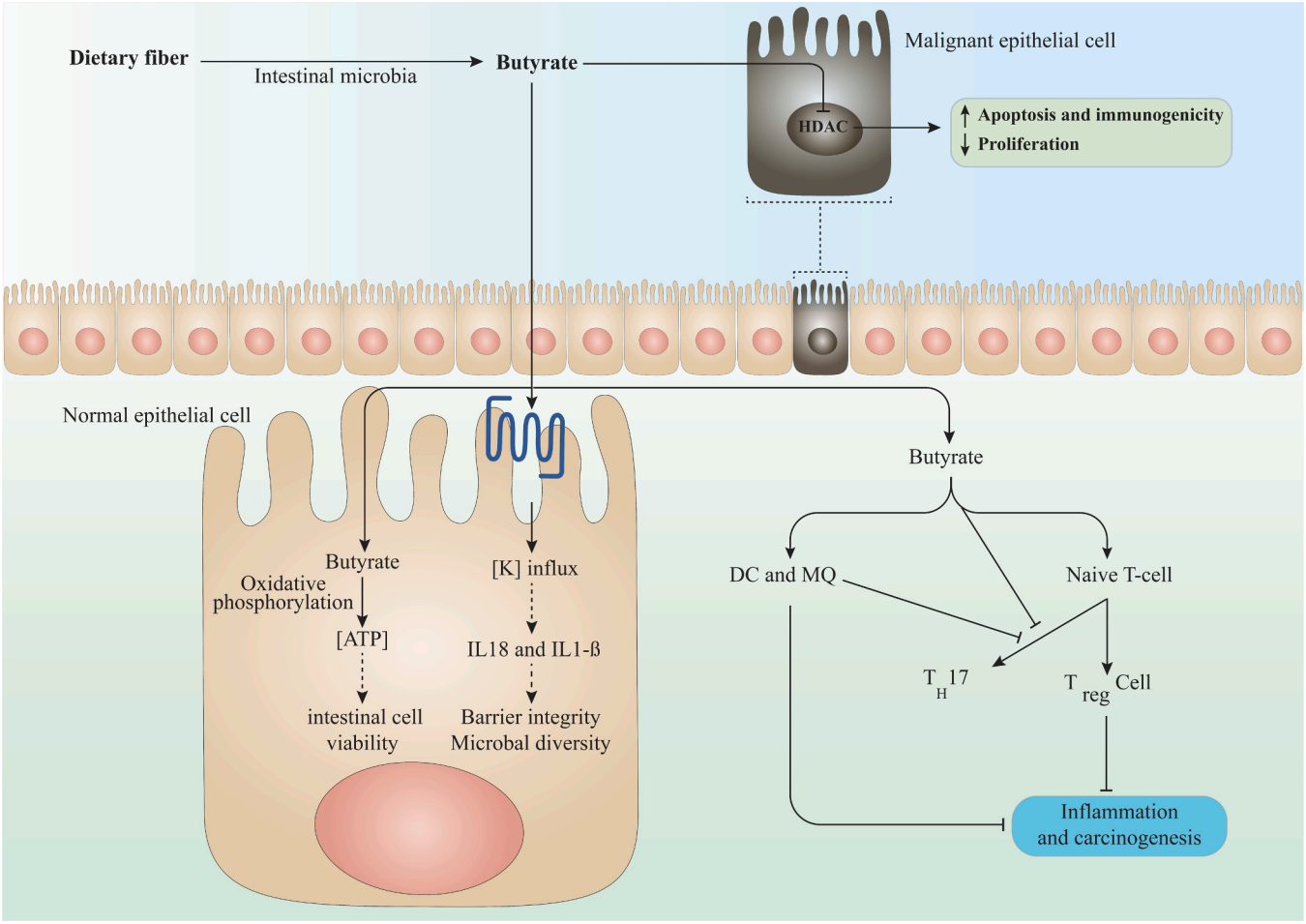

Fig. 2. Impacts of the short-chain fatty acids (SCFAs) on the function of immune cells. A) The enhanced rate of butyrate suppresses the activity of histone deacetylase (HDAC) and stimulates apoptosis, reduces growth, and prompts immunogenicity of the cancer cell. B) In the human normal epithelial cell, butyrate is metabolized via OXPHOS (oxidative phosphorylation) and applied by the cell for the source of energy. C) Additionally, butyrate activates NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasomes via binding to G-protein-coupled receptors (GPRs), cause the expression of Interleukin 1 beta (IL-1β) and Interleukin-18 (IL-18). On the other hand, IL-18 promotes the diversity of intestinal bacteria and strengthens the intestinal barrier integrity. The impacts of butyrate on human immune cells in the lamina propria could be defined as promoting the role of anti-inflammatory factors, like Regulatory T cells (Tregs) while inhibiting function immune cells involving in inflammation, for example, butyrate inhibits the Dendritic cell (DC) maturation, limit its potential to prime Cytotoxic T lymphocyte (CTL) and diminishes the pro-inflammatory cytokine formation of in macrophages and DC that, overall, diminishes inflammation and the development of T-helper cell 17 (Th17) that involve in carcinogenesis in intestinal cells.

activation of cell cycle arrest and apoptosis [4]. Butyrate could affect other processes involved in epigenetic regulation, including histone phosphorylation and methylation, DNA methylation, and hyper-acetylation of nonhistone proteins [4,72,73].

5. The effects of short-chain fatty acids in cancer

5.1. Colorectal cancer

CRC is the third most prevalent fatal cancer in the world [74,75]. Diet is one of the most critical determinants involved in CRC progression [76,77]. Among SCFAs, butyrate is a significant metabolite that mediates CRC suppression through dietary fiber [76]. Unlike other SCFAs, butyrate is mainly metabolized by colonocytes cells and is involved in epigenetic modifications, where it elevates the rate of histone acetylation by blocking histone deacetylases [76,78]. At proper concentrations, butyrate increases differentiation reduces proliferation, and induces programmed cell death in CRC cells [70,76]. Of note, the effect of butyrate on cell apoptosis and proliferation is attributed to its colonocyte metabolism [79,80]. Many studies have indicated that colonocytes are involved in the beta-oxidation of butyrate, which can be affected by exogenous agents [81,82]. Moreover, the proliferation of cancerous colonocytes reduces following exposure to butyrate, while that of non-cancerous colonocytes increases [76]. Therefore, butyrate has various effects on both cancerous and non-cancerous colonocytes with different metabolic traits.

Interestingly, Ohara et al. [83] noted that enhanced CRC risk linked tightly to the changed gut microbiota, the diminished concentration of SCFAs, and further inflammation situation. Besides, in a systematic and meta-analysis study by McLoughlin et al. [84], they examined the evidence for the effect of SCFAs, prebiotics, and synbiotics on systemic inflammation in healthy populations, diabetes, overweight, and obesity, kidney disease, cancer, liver disease, and bowel diseases. They found half of the included studies noted a significant diminish in ≥ 1 systemic inflammatory biomarker, and meta-analyses showed that prebiotic and synbiotic supplementation are mediated to diminished systemic inflammations such as TNF-α, C-reactive protein (CRP), and IL-6, although the association was stronger with certain supplement types (particularly oligosaccharides) [84]. Additionally, Nomura et al. [85] evaluated fecal and plasma SCFAs in patients with solid cancers treated with programmed cell death-1 inhibitors (PD-1i). They found that fecal SCFA rates can be related to PD-1i efficacy; hence, SCFAs can link the gut microbiota and PD-1i efficacy. Because fecal examinations are noninvasive, they can be applied for routine monitoring of patients, thus, enhancing SCFAs formation through regulation of gut microbiota should have a bright future in anti-cancer therapy. Besides, in a systematic review and dose-response meta-analysis of prospective studies, Aune et al. [86] surveyed dietary fiber, whole grains, and risk of colorectal cancer. Additionally, many epidemiologic studies support the role of dietary fiber in the protection against colorectal cancer and, in this regard, various mechanisms have been noted for fiber's cancer-preventive properties including a reduction in transit time of the feces in the gut that diminishes exposure of the mucosa to luminal carcinogens, absorption of biogenic amines, bile acids, bacterial toxins, as well as the formation of SCFAs like butyrate [87–107].

Over the past few decades, it has been demonstrated that the gut microbiome, which could be influenced by diet, is essential in CRC initiation [108]. After digestion and absorption, different foods leave residues in the digestive tract [108]. As food moves throughout the colon, gut microbiota ferments the residues of dietary fiber to generate SCFAs, affecting intestinal epithelial cells and gut microbiota [97,109]. Research has indicated butyrate as the primary energy source of the intestinal epithelial cells, rather than glucose, establishing the basis for the notion of mutualism between intestinal epithelial cells and gut microbiota [110]. Butyrate could impede CRC progression and improve intestinal health by several mechanisms [108].

Butyrate has anti-tumor and anti-inflammatory traits and can be an energy source for intestinal epithelial cells [108]. A recent mechanism proposed for the impact of butyrate molecule on CRC development is the reduced expression of butyrate transporter protein in cancerous tissue and the subsequent reduced intestinal butyrate transport and metabolism (Fig. 3) [111]. The impairment of butyrate metabolism has been linked with different colonic disorders [112]. Currently, it has been well established that the pathogenesis of CRC is associated with the disruption of the intestinal epithelial barrier, which leads to the stimulation of tumor-related macrophages, generation of inflammatory cytokines, and tumor development [113]. Butyrate could enhance the assembly of the tight junction by stimulating the AMPK (Amp-activated protein kinase) [113]. It can maintain the intestinal epithelial barrier's function by triggering the expression of MUC2 in LS174T (the human colon cancer cell line) [114–116]. It can also reduce the movement of the gastrointestinal tract, thereby reducing the rate of intestinal transport and affecting the incidence of CRC [108]. According to different studies, butyrate can affect the internal nervous system and modulate the excitability of neurons, leading to the reinforced extracorporeal contraction action [117,118].

Hence, butyrate is pivotal for maintaining the balance of intestinal microbiota balance and colon health. Also, different works have demonstrated that butyrate could hinder the occurrence and progression of CRC by different mechanisms [108]. Conversion of butyrate to acetyl-CoA occurs through beta-oxidation, which is then totally oxidized the Krebs cycle [108]. This conversion is crucial for inducing the enzymatic role of histone acetyltransferase [108]. Owing to the Warburg effect, butyrate is not usually metabolized in cancer cells. Yet, it could be accumulated as an HDAC inhibitor (HDACi) in the nucleus and subsequently modulates downstream target gene expression [108]. HDAC enzymes are crucial for gene expression, and their expression in tumor cells varies in different tumor types [79]. For instance, HDAC1 is present mainly in gastric cancer, prostate cancer, breast cancer, lung cancer, and esophageal cancer, while HDAC2 is present primarily in cervical cancer, colorectal cancer, and gastric cancer [108] (Fig. 4).

Furthermore, HDAC3 is present mainly in colorectal cancer and breast cancer, whereas HDAC6 is present mainly in neuroblastomas [119,120]. In most tumors, acetylation will lead to the altered expression of several genes that mediate various signaling pathways, including extracellular-signal-regulated kinase (ERK) and Wnt, and further influences the protease system and the functions of several enzymes such as protein kinase C [121]. HDACi can lead to cell death through various processes such as alterations in histone modifications, gene expression, and epigenetic alterations [122]. Following the blockade of histone acetylation, chromatin lysis occurs, leading to better exposure of DNA [108]. The reduced activity of HDAC has been linked with the hindrance of tumor cell progression [123]. Butyrate has different functions in histone acetylation and can affect the progression of tumor cells by the activation of the cell cycle arrest and programmed cell death.

5.2. Bladder cancer

Bladder cancer is the ninth most common malignancy, with more than 160,000 deaths annually worldwide [124]. The risk of developing this disorder increases with age, and it occurs three times more often in male populations [124]. As most cases are $>$ 65 years old and owing to the rise in life expectancy, it is estimated that the prevalence of patients with this disorder will increase shortly [125]. In addition to environmental and genetic factors, studies have shown that microbiota is vitally important in maintaining health and preventing the occurrence of various diseases [124]. Using DNA-based techniques, studies have indicated that disturbance in microbiota is linked with different disorders [124].

SCFAs might be involved in hindering pathological conditions like cancer and IBD for their anti-inflammatory, immune-modulatory, and anti-neoplastic traits. Besides, butyric acid exerts a direct inhibitory

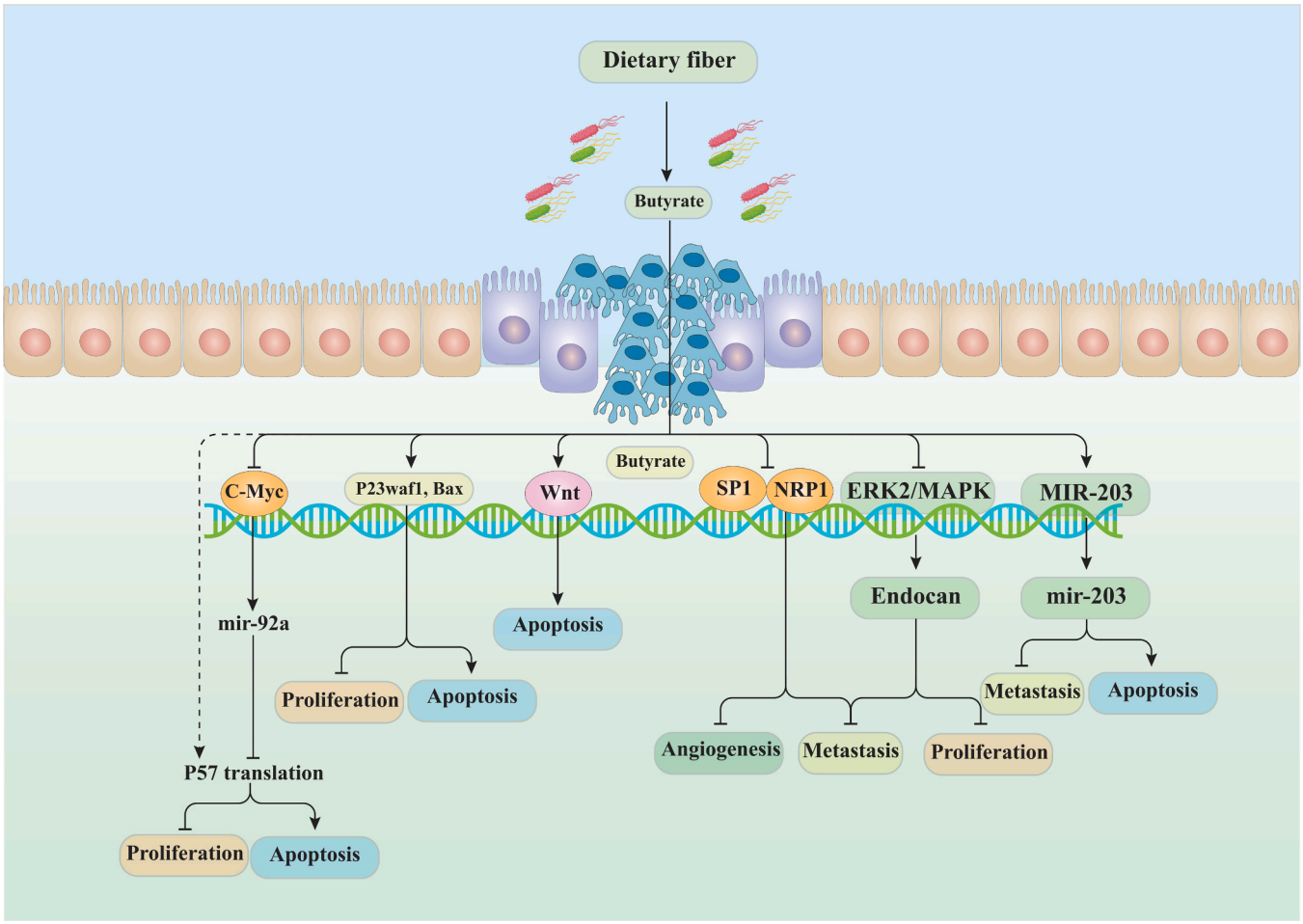

Fig. 3. The routes that butyrate inhibits the development of colorectal cancer. Butyrate could diminish the expression of Neuropilin 1 (NRP1) by suppressing the transactivation of Sp1 to inhibit the angiogenesis, metastasis, and survival of colorectal cancer cells, and butyrate could trigger the colorectal cancer cells apoptosis by activating the signaling of Wnt. Furthermore, butyrate could restrict the proliferation of cells, cell invasion, colony formation as well as activation of cell apoptosis in colorectal cancer cells via upregulating the miR-203, bax P21waf1 expression, and activation of the expression of endocan. Interestingly, SCFA butyrate could enhance Wnt expression, which attach to its receptor Fzd to induce Wnt signaling pathway. Hence, Fzd stimulates LRP5/LRP6/Dvl complex, which phosphates GSK-3beta that diminishes the beta-catenin degradation, resulting in accumulation of beta-catenin. When beta-catenin attaches to p300 protein, it causes apoptosis. Also, butyrate could enhance p57 levels by suppressing the c-Myc formation, which diminishes the miR-17-92a. Overall, the interplays between butyrate, NRP-1, endocan, Wnt, bax, P21waf1, miR-92a as well as miR-203 relate to the pro-apoptosis and anti-proliferation activity of butyrate in colorectal cancer cells.

impact on bladder cancer cells by preventing cell growth and activating programmed cell death in vitro [126]. Although various studies indicate that the intake of fruits and vegetables is negatively correlated with bladder cancer, the underlying mechanisms of persistence of cancer are still unclear.

The treatment of bladder cancer is highly costly, and there is an immediate need for developing novel potential therapeutic targets and pathways [127]. Earlier studies have demonstrated that the abnormal composition of fecal microbiota and disrupted gut epithelial barriers induce bladder cancer [127]. He et al. [127] have investigated the gut microbiome of patients with bladder cancer to find a potential therapeutic option. In their study, the Prevotella and Clostridium cluster XI rates were remarkably lower in patients with bladder cancer than the healthy individuals [127]. Up to 90% of SCFAs are absorbed from the colonic lumen and partly used by colonic epithelial cells that can be transferred to circulation and/or excreted in feces [128]. Hence, protective influences by SCFAs are seen in intestinal mucosa and extended to other parts of the body in the host. *Clostridium* cluster XI is known to produce SCFAs [129]. *Prevotella* is positively correlated with the consumption of dietary fiber and fermentation of complex polysaccharides [130].

Meanwhile, SCFAs (especially butyric acid) were reduced in cancer patients [131]. Butyrate can also sensitize bladder cancer cells to anti-cancer drugs in vitro [132]. The reduced concentrations of butyrate in bladder cancer patients might reduce the proliferation and growth of IECs and reduce their negative effect on bladder cancer [127]. Nevertheless, the current study is of a relatively small number of cases in all stages, reflecting the low incidence of bladder cancer, so that larger sample sizes will be needed to further prove these findings. According to the studies, fruit intake is positively correlated with the numbers of *Prevotella* and the amount of butyrate [127]. Therefore, insufficient fruit intake might slightly lead to alterations in gut microbiota and SCFAs in patients with bladder cancer.

5.3. Breast cancer

Breast cancer is the most common malignant disorder among female populations, affecting 2.4 million cases with more than 500,000 deaths worldwide [133]. In 2015, 3.4 million breast cancer cases survived in the United States, and this frequency seems to be increasing [134–136]. The survival rate of breast cancer patients at least five years of diagnosis is about 90% [134], and this disorder is currently considered a chronic disease [137,138], which enables the improved endurance of survivors [134]. Nevertheless, a high-fat and high-sugar diet low in fiber and

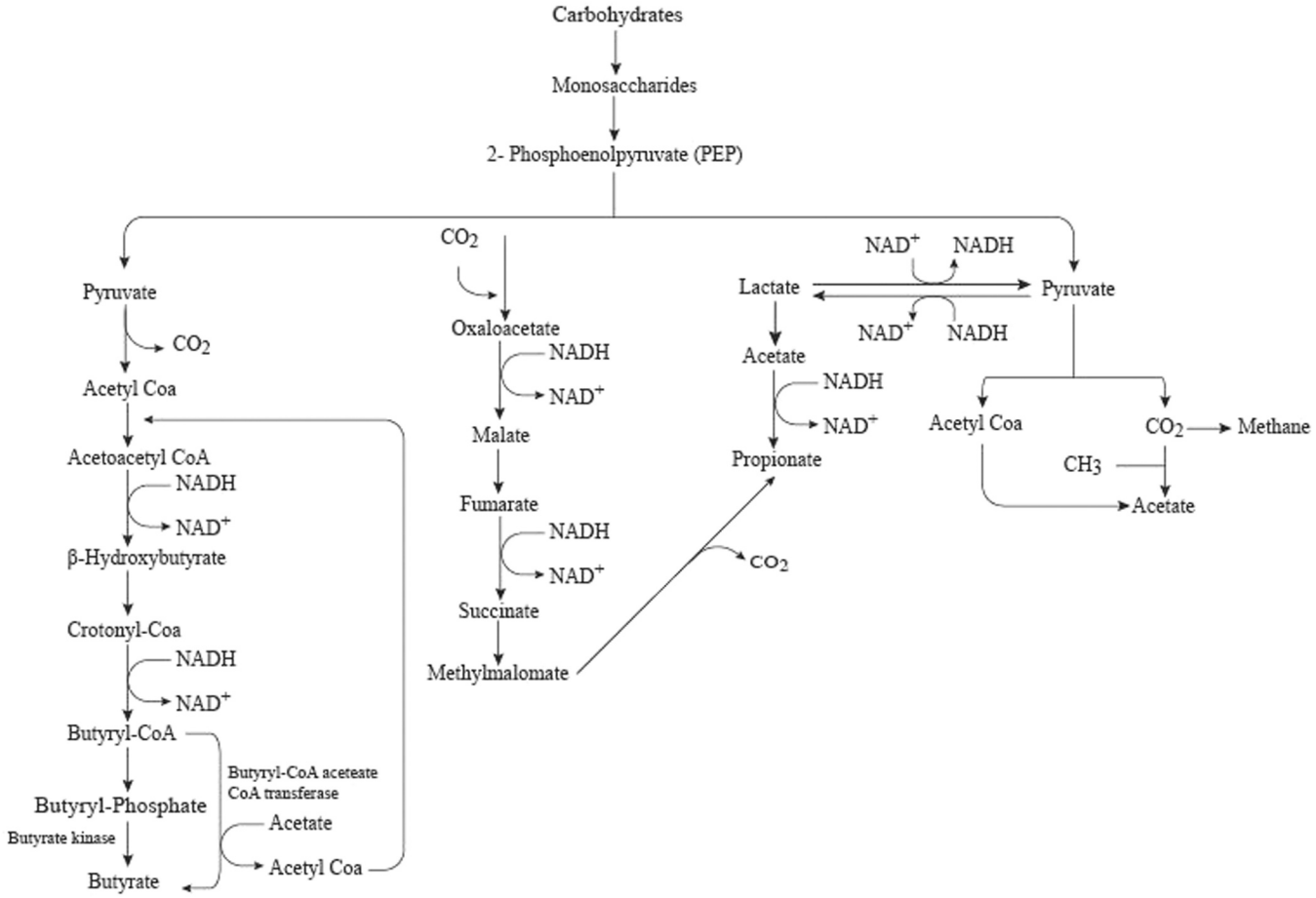

Fig. 4. The schematic representation of acetate, propionate and butyrate production.

minimum activity increases the risk of breast cancer [134]. Diet is crucially important in the interplay between the gut microbiome and estrogen metabolism, thereby affecting breast cancer metastasis and recurrence [134]. The typical American diet increases the growth of unhealthy bacteria with high levels of β-glucuronidase [134]. This enzyme conjugates estrogen and returns it to the bloodstream, thereby increasing its accessibility to drive estrogen-responsive cancers [134]. This diet reduces the generation of SCFAs, including propionate, butyrate, and acetate, which can inhibit "leaky gut syndrome" [134]. This syndrome increases the flow of harmful inflammatory outputs into the bloodstream, leading to breast cancer recurrence and progress [134]. Inflammatory proteins increase insulin resistance and leptin levels, which are involved in the modulation of carcinogenesis [139]. Binding of insulin molecules to steroid hormone-binding globulin (SHBG), increases estrogen concentrations and accessibility, thereby contributing to breast carcinogenesis [140,141]. Reduced adiponectin levels contribute to insulin resistance and enhanced levels of insulin-like growth factor 1 (IGF-1), which can provoke cell proliferation [140].

On the contrary, a high-fiber diet leads to enhancing "healthy" microbiota [134]. Reduced β-glucuronidase activity reduces estrogen levels and elevates SGBH besides the fecal excretion of estrogen [134]. Following an increase in SCFAs, the colonic mucosa is preserved from inflammation, leaky gut syndrome, and cancer development [140,142,143]. Estrogen molecules are conjugated in the liver and secreted into the digestive system; they are then deconjugated by microbial β-glucuronidase and reabsorbed as free estrogen in the circulatory system [134]. Several bacterial species contribute to this process; nevertheless, those with the ability to generate high levels of β-glucuronidase remain controversial [134]. *Bacteroidetes* and *Firmicutes* are predominant bacteria that contribute to the metabolism of polyphenols and fiber [134]. Researchers have reported different results on the effect of these phyla on obesity (a remarkable risk factor for breast cancer) [144–147].

Leaky gut syndrome and the subsequent inflammation may decrease by the intake of a high-fiber diet, leading to intestinal alkaline phosphatase and SCFAs production [148]. Intestinal alkaline phosphatase is essential for maintaining the integrity of intestinal endothelia [149–151]. In addition to SCFAs, gut alkaline phosphatase reinforces the colonic mucosa's tight junction, thereby reducing the leakage of pathogenic bacteria and their carcinogenic effect [149–151]. The gut microbiota may enhance chronic inflammation by affecting self-proliferation and programmed cell death [152,153].

A subset of bacteria in gut microbiota control the genetic capability of estrogen metabolism: the estrobolome [134]. These bacteria use fiber as their main energy source [134]. Following the consumption of a diet high in fiber, the estrobolome promotes estrogen metabolism and subsequently its removal from the body [134]. As about 70% of breast cancer cases are fueled by estrogen, a high-fiber diet eliminates estrogen, reducing breast cancer cells' availability [134]. The "commonsense" recommendation for breast cancer patients to consume dietary fiber leads to reduced inflammation [134]. The prolonged intake of fiber and polyphenols enhances the breast cancer survival rate [138,154].

Deregulation of epigenetic mechanisms, including post-translational histone modifications, has been indicated in women's breast carcinogenesis owing to the silencing of essential genes involved in tumor suppression [155]. Contrary to genetic alterations, epigenetic alterations are thought to be reversed and have been evaluated for their potential in cancer treatment [156]. Bioactive dietary ingredients with anticancer effects can modulate DNA methylation and histone acetylation [157,158]. Reactivation of epigenetically silenced genes by food ingredients could be employed for cancer control [159]. As a dietary

HDACi, Butyrate is of great significance because of its anticancer effect and has been employed in phase I clinical trials for cancer treatment [160–162]. This SFCA is formed through the fermentation of dietary fiber by gut microbiota [163]. Butyrate is considered a promising approach for the management of breast cancer [164,165]. Various studies have indicated that butyrate limits the proliferation of breast cancer cell lines by functioning as an HDACi and stimulating the formation of cyclin-dependent kinase inhibitor p21 [165–167].

The combination of retinoid and HDACi could potentially control cancer; however, few studies have indicated its efficiency in breast cancer [168]. Prior research showed that retinoic acid (RA) therapy increased the inhibitory properties of trichostatin (a synthetic HDACi) on human breast cancer cells [169]. More importantly, reactivation of RA receptor beta (RAR-β) by the synthetic HDACi enhanced the susceptibility of breast cancer cells to the inhibitory function of RA [169]. Despite the anticancer potential of HDACi combined with retinoid, few investigations have focused on the efficacy of such treatment, particularly for breast cancer control [168]. Interestingly, although vitamin A does not block the proliferation of MCF-7 cells, it potentiates the hindrance of cell growth by butyrate [169,170]. This combinatorial effect may be attributed to the arrest of MCF-7 cells in the G2/M phase [169, 170]. This enhances the efficacy of dietary HDACi butyrate along with retinoid in breast cancer control [171]. Nonetheless, the association between butyrate and vitamin A does not exert any combinatorial effect on hindering the proliferation of estrogen receptor-negative MDA-MB-231 breast cancer cells [171]. This implies that the breast cancer type should be taken into consideration when considering the co-administration of butyrate and retinoids for cancer treatment.

5.4. Gastric cancer

Gastric adenocarcinoma is the third common cause of cancer-mediated mortality worldwide [172]. Previous studies have indicated that genetic and environmental factors and bacterial infections can lead to cancer [173,174]. *H. pylori* is the most critical risk factor associated with human gastric cancer [175]. Chronic inflammation triggered by *H. pylori* can disrupt the function and structure of the gastric epithelium [176]. Nevertheless, successfully eliminating *H. pylori* bacterium does not entirely hinder gastric carcinoma development, and only up to 1% of the infected patients face gastric cancer development [177–179]. These findings imply that other determinants can be involved in the carcinogenesis of human gastric cancer, and further investigations are required to determine these factors.

Similar to the findings on the contribution of SCFAs in maintaining the integrity of the intestinal barrier and microbiota balance, as well as the hindrance of cancer and inflammation, Hu et al. [172] indicated that pathways contributing to SCFAs formation in gastric cancer are depleted, suggesting the presence of a more inflammatory condition and dysbiotic bacterial communities in gastric cancer. In contrast to these results, two investigations using 16 s rRNA to determine the microbiota of gastric mucosa demonstrated the pathways related to the generation of SCFAs in gastric cancer patients [180,181]. Nevertheless, it should be noted that the current study is limited by relatively small sample size and, hence, further longitudinal studies with more significant numbers of subjects are required. This discrepancy can be explained by the differences in sample type, study population, and methodology. Further metagenomic, metaproteomic, and metatranscriptomic investigations are needed to confirm these results.

Sodium acetate is an SCFA commonly used in the food industry to flavor food agents control pH [182]. The cytotoxicity of sodium acetate has also been widely evaluated [182]. Reportedly, sodium acetate promotes differentiation and apoptosis and impedes the growth of CRC cell lines [182]. The anti-cancer properties of acetate originate from its capability to trigger apoptosis or necrosis in CRC cells by mitochondria [183]. Prior investigations have also demonstrated that sodium acetate at 12.5 mM concentration induces gastric adenocarcinoma cell growth and viability in a dose-dependent manner [182].

Nevertheless, sodium acetate at concentrations > 12.5 mM impedes cell proliferation in a dose-dependent manner [182]. Besides, cells treated with sodium acetate for 24 h demonstrated increased expression of IL-8, IL-1b, and TNF-α, the effect of which has been confirmed in mice [182]. The cytotoxic influences of sodium acetate on colonic epithelial cells have been investigated extensively. Nevertheless, once introduced to the human body through oral administration, organs such as the stomach can be exposed to sodium acetate; hence, the biological toxicity of sodium acetate cannot be limited to the colon and can extend to other parts. In this regard, Xia et al. [182] indicated the cytotoxicity of food with high doses of sodium acetate. Acetic acid has also been demonstrated to inhibit the activity of NF-κB in Colo320DM cells [161]. In inflammatory conditions, acetate suppresses the migration of human neutrophils towards formyl- methionyl-leucyl-phenylalanine (f MLP) or C5a depending on GPR43 [184].

The Fas receptor (FasR)/Fas ligand (FasL) complex is a primary apoptotic route essential for the maintenance of cell colony, removal of malignant cells, and modulation of apoptosis [182]. Most human cancer cells harbor this complex [182]. The interplay between FasR and FasL on the surface of tumor cells leads to the initiation of apoptotic signaling, resulting in the stimulation of caspases, which in turn interacts with cytoplasmic signaling proteins that activate apoptosis [185]. Xia et al. [182] demonstrated the increased mRNA expression of FasL and FasR after the addition of 12.5–50 mM sodium acetate in a concentration-dependent manner. Subsets of caspases are triggered following Fas-initiated apoptosis [182]. Caspase-8 is the initial phase in the Fas-induced cascade of apoptosis [182]. Caspase-8 is activated following cleavage and activates other downstream caspases, thereby inducing apoptosis [186].

5.5. Liver cancer

The occurrence of hepatocellular carcinoma (HCC) is clinically increasing [187], and both genetic and environmental determinants have been suggested in its initiation [187]. While susceptibility genes, ranging from traditional tumor suppressor genes to immune cell markers, have been identified, the potential environmental factors are not fully investigated [188]. Clearly, specific hepatotoxins such as aflatoxin, organochlorine compounds, and organochlorine compounds are markedly involved in the development of HCC similar to preneoplastic injuries linked with hepatitis C virus infection [189–191]. The involvement of gut microbes in the initiation and progression of HCC is yet to be identified [187]. Gut microbes are involved in the conversion of intestinal nitrates to nitirites and nitrosoamines which have been associated with CRC [192]. Besides, recent investigations have indicated the ability of *Helicobacter hepaticus* in inducing aflatoxin-promoted HCC in mice, which involves the formation of inflammatory and pro-proliferative cytokines [193]. These studies are consistent with the results of studies on humans where *Helicobacter* spp. could be isolated both from the intestine and liver [194,195]. Therefore, microbial metabolism of ingested food and byproducts and immune reactions to the bacteria contribute to liver cancer initiation and progression.

Obesity and a high-fat diet are considered as primary risk factors for HCC progress; however, the exact molecular mechanisms remain unclear [196]. Alterations of intestinal microbiota may contribute to this pathogenetic pathway [196]. Yoshimoto et al. [197] investigated hepatocarcinogenesis in obese mice. They demonstrated that antibacterial drugs could reduce the risk of HCC development in treated mice by modulating dysbiosis and the subsequent secretion of pro-carcinogenetic and proinflammatory factors. Notably, fermentable non-digestible carbohydrates might also contribute to the control of tumor growth outside the digestive system [198]. Reportedly, oral administration of inulin-type fructans (ITF), as non-digestible carbohydrates, reduces the tumor size in breast or liver cancer animal models [199,200]. Saccharolytic bacteria can ferment inulin-type fructans,

thereby increasing SCFA production in the murine caecum [201]. As a prebiotic nutrient, ITF alters the activity and composition of the gut microbiome and controls the host immunity and metabolism [202–204].

Bindels et al. [198] showed the reduced proliferation of cancerous hepatocytes and reduced inflammation linked with cancer development following ITF administration to the leukemia mouse model. They also indicated the cyclic adenosine monophosphate (cAMP) level-dependent impact of propionate and the altered proliferation of cancer cells due to free fatty acid receptor 2 (FFA2) [198]. These results confirm the role of gut microbiota in controlling cancer progression. The human gut microbiota could affect the progression of BaF3 cells by inducing metabolomics alterations [198]. Bindels et al. [198] hypothesized that the increased concentration of metabolites derived from gut microbiota following ITF administration could pose a protective effect. Propionate has all of these requirements as it is generated in the portal vein of rats fed with ITF and is majorly taken up by the liver [192,205]. Bindels et al. [198] showed the increased levels of propionate in the portal blood of the BaF3-ITF mice. Notably, butyrate and propionate levels reduced following cancer [198]. This could be due to the alterations in the structure and composition of gut microbiota or the reduced food consumption at the end of the therapy, which might have reduced the substrate supply.

Dietary fiber-derived SCFAs may also affect extraintestinal cancer cell growth; they elevate the portal propionate concentrations to hinder the proliferation of cancerous hepatic cells [198]. Interestingly, a validated in vivo study indicated that pectin alleviates NAFLD (non-alcoholic fatty liver disease) by SCFAs [206]. In contrast, diets supplemented with soluble fiber led to icteric HCC in dysbiotic mice [207]. The suppression of gut fermentation and inhibition of dietary fiber hindered HCC [207]. Pharmacologic hindrance of fermentation or excluding fermenting bacteria significantly decreases the rate of intestinal SCFAs and inhibits HCC [207].

Gut microbiota has been linked with hepatocarcinogenesis due to hepatic inflammation via activating toll-like receptor 4 (TLR4) or forming cytotoxic secondary bile acids [208,209]. Singh et al. [210] indicated that disruption of microbiota hemostasis, dysmetabolism of SCFAs and bile acid, and hepatic inflammation could lead to HCC development. Several works have presented the anti-tumorigenic properties of SCFAs and inulin [210]. Nevertheless, they hypothesized that the formation of high butyrate levels following cholemia, dysbiosis, and inflammation might instead form a tumor-inducing condition that could prevail over its beneficial properties [210]. This hypothesis agrees with the "butyrate paradox,'' which asserts that the capability of butyrate to provoke or prevent cell proliferation depends on time, cell-type, and concentration [211]. The concentrations of SCFA that exceed the threshold and can be tolerated by the host have been indicated to promote colonic inflammation and tumorigenesis, induce urethritis and hydronephrosis, and promote obesity by aggravating hyperphagia and hepatic lipogenesis [210]. Janssen et al. [212] demonstrated that the consumption of dietary guar gum (a soluble fiber containing galactose [1,6-linked] and mannose [b1,4-linked]) for over 4 months protected mice from diet-induced obesity; however, it promoted the inflammation of the liver due to elevated plasma levels of total bile acid (TBA) and impaired circulation within the liver. Although Janssen et al. [212] did not observe HCC, their findings confirm that the consumption of soluble fiber might not be useful to the host liver in case functional gut bacteria are absent.

5.6. Lung cancer

Human lung cancer is one of the most fatal disorders with the fastest-growing rate of mortality and morbidity in the world [213]. The association between lung cancer and gut microbiota has been studied [213], and increased numbers of *Enterococcus* spp. and reduced numbers of *Actinobacteria* and *Bifidobacterium* have been linked with lung cancer [213]. Besides, disruption of the normal activity of gut microbiota affects lung cancer progression [214]. In another study, reduced numbers of *Enterobacter*, *Dialister*, *Fecalibacterium*, *Kluyvera*, *Escherichia–Shigella*, and higher Fusobacterium numbers *Bacteroides,* and *Veillonella* were found in lung cancer patients compared to the control [215]. The association between relative frequency of the bacteria as mentioned above and systemic inflammation-related markers, such as neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index, platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), were investigated [216]. The findings demonstrated that *Enterobacter* and *Escherichia–Shigella*, were positively correlated with serum levels of NLR, while *Dialister* was negatively correlated with serum levels of NLR and PLR [216]. Furthermore, *Dialister* was also associated with serum contents of IL-12 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) [215]. Alterations in gut microbiota have been correlated with the development of immune-mediated diarrhea in patients with lung cancer following treatment with antibodies against anti-PD-1 (anti-programed cell death protein-1) [213]. In patients without diarrhea, *Bacteroides*, *Phascolarctobacterium*, and *Parabacteroides* were more abundant, while *Veillonella* was less abundant [217].

It is well defined that gut microbiota affects human gastrointestinal cancer [218]. It has also been proposed that gut microbiota mediate extraintestinal cancers [219]. Several investigations have found an association between gut microbiota and lung cancer [220]. Zhang et al. [221] demonstrated that in lung cancer patients *Fusobacteria*, *Bacteroidetes*, *Spirochaetes*, *Cyanobacteria*, and *Lentisphaerae* were more abundant, while *Verrucomicrobia* and *Firmicutes* were less abundant compared to the healthy group. According to their study, eight predominant bacterial genera were markedly diverse between the two groups [221]. Investigations have implied that patients with lung cancer have diverse gut microbiota and, more importantly, these microbiota influence the therapeutic prognosis of human lung cancer [220]. According to a study, early resistance to immune checkpoint inhibitors could be due to gut microbiota's abnormal structure and composition [222]. Since *Akkermansia muciniphila* levels are often reduced in patients with lung cancer, supplementation with this bacterium could enhance the immune checkpoint inhibitor responses [222]. Another investigation on the lung cancer mouse model reported that the commensal bacteria are involved in the anti-lung cancer reaction, and simultaneous treatment with probiotics promotes the pro-apoptotic and anti-growth properties of cisplatin [220].

In a recent study, sodium butyrate treatment upregulated miR-3935, which in turn inhibited the growth and migration of a549 cells [223]. Microbiota-derived SCFAs influence colon cancer progression by dysregulating Bax, p21, Bcl-2, and regulating histone hyperacetylation [224,225]. Furthermore, sodium butyrate could also inhibit lung and prostate cancer growth by modulating p21 expression [226]. Most investigations on SCFAs have focused on butyrate, while the function of propionate in lung cancer is not well established [226]; however, one study focused on the association between lung cancer and propionate and provided information concerning the function of propionate in lung cancer treatment [225,227]. According to their study, although propionate inhibited cell growth and induced apoptosis in CRC cell lines, it could also show anticancer properties for lung cancer by activating cell apoptosis and cell cycle arrest by reducing the Survivin expression and increasing p21 expression [226]. Therefore, despite facing several problems associated with SCFAs application for lung cancer, treatment, dietary and microbiome-derived SCFAs may be beneficial; nevertheless, in vivo works are required to confirm the efficacy of sodium propionate.

5.7. Other cancers

Pancreatic ductal adenocarcinoma (PDAC) is a fatal disorder with a mortality rate of 94% has been reported within five years of diagnosis [228]. PDAC is the fourth most common human cancer. Globally, in 2018 alone, 458, 918 PDAC cases were reported, among which 432,242

cases died [229]. The rate of PDAC cases has increased and is estimated to grow even more sharply in the future [230,231]. The association between microbiota and PDAC was first suggested by identifying *H. pylori* in patients with pancreatitis [232]. This was followed by findings regarding the relationship between the fecal, pancreas, gut, oral microbiota, the mycobiome, and pancreatic cancer [232–235].

Several works have suggested alterations in the proportions, diversity, and dominant constituents of the microbiota (*Neisseria Porphyromonas, Streptococcus, Actinomycetes, Bacteroides Fusobacterium* and *Bifidobacteria*) might be linked with PDAC initiation and progression [236–239]. Acetate can alleviate pancreatitis, thereby protecting against a risk factor of PDAC [240]. Acetic acid triggers the epigenetic reprogramming of mesenchymal stem cells to cancer-related fibroblasts that improve the invasiveness of PDAC cells [241]. At a concentration of 2 mM, butyric acid can diminish the growth of cultured PDAC cells (HPAF and Panc-1 cells) and activate differentiation towards a secretory phenotype specified by ultrastructural alterations [242]. Besides, a hyaluronic acid conjugate of butyrate was cytostatic in a cultured PDAC cell line [243]. A branched-chain SCFA (valproic acid) was also cytostatic in PDAC cells when administered in combination with 5-fluorouracil, implying similar traits for bacterial SCFAs [244]. In the PDAC-related oncobiome, butyrate-forming microbes reduced, implying that the abovementioned beneficial impacts of SCFAs are inhibited in this cancer type [237].

Prostate cancer is the second leading cause of human death in the United States, approximately 20% in men [245]. The lifetime risk for human prostate cancer is approximately 16%, with 276,000 new cases in 2018 [246]. Common therapy for human prostate cancer is mainly based on androgens; nevertheless, this does not cover other risk factors for human prostate cancer, including environmental factors, inflammatory markers, and microbial infections [247]. One of the first investigations on the link between commensal bacteria and the prostate was carried out by Cavarretta and his colleagues [248]. Banerjee et al. [249] addressed the relationship between microbiota and prostate cancer more comprehensively. The employed microarray metagenomic analysis of formalin-fixed tissue to identify bacterial, viral, and fungal signature of 50 prostate cancer patients and 15 patients with benign prostatic hyperplasia [249]. Most isolated bacteria were Gram-negative, including *Firmicutes, Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* [249]. A hierarchical evaluation indicated that particular clusters of bacterial signatures are correlated with the grade of human prostate cancer [249]. Additionally, *Propionibacterium acnes* has been demonstrated to be involved in human prostate cancer progression [250,251]. Recently, the pro-carcinogenic properties of bacterial products have been implicated. For instance, in breast cancer, bacterial peptides have been attributed to tumor cell angiogenesis and invasion [252]. This could be a new field of investigation, and the bacterial metabolites in the prostate should be thoroughly studied (Tables 1 and 2).

Table 1
Short-chain fatty acids and their bacterial producers.

Metabolite	Bacterial producer	Ref.
Butyrate	*Coprococcus catus, Coprococcus comes, Anaerostipes spp., Coprococcus eutactus, Eubacterium hallii, Eubacterium rectal, Roseburia* spp., *Faecalibacterium prausnitzii, Clostridium butyricum, Ruminococcus, Anaerostipes* spp., *Coprococcus catus,*	[274,275, 276,277]
Propionate	*Dialister* spp., *Megasphaera elsdenii, Bacteroides* spp. *Phascolarctobacterium succinatutens, Coprococcus catus, Veillonella, Roseburia inulinivorans, Ruminococcus obeum, Salmonella* spp.	[274,275]
Acetate	*Akkermansia muciniphila, Bacteroides* spp., *Prevotella* spp. *Bifidobacterium* spp., *Clostridium* spp., *Ruminococcus* spp., *Streptococcus* spp., *Blautia hydrogenotrophica, Coprococcus* spp.	[274,275, 278]

Table 2
Short-chain fatty acids in various cancers.

Cancer	Short chain fatty acid	Function	Ref.
Colorectal cancer	Butyrate	Butyrate mediates the suppression of NF-κB, inhibits HDAC, induces WNT/beta-catenin activity and apoptosis, activates MAPK signaling pathway by the upregulation of GADD153 or activation or phosphorylation of JNK.	[279]
	Acetate	Acetate triggers apoptosis in colorectal cancer cells activates cathepsin D release and induces lysosomal membrane permeabilization. In return, cathepsin D protects colorectal cancer cells from apoptosis by disruption of damaged mitochondria	[280, 281]
	Propionate	Propionate reduces the expression of PRMT1, induces apoptosis in colon cancer by hindering p70 S6 kinase phosphorylation.	[282]
Bladder cancer	Butyrate	Sodium butyrate triggers AMPK/mTOR pathway-activated autophagy and reactive oxygen species overproduction through the miR-139–5p/Bmi-1 route. Butyrate inhibits cell growth and triggers apoptosis in bladder cancer cell lines.	[283]
	Acetate	Acetate shows inhibitory impacts on the invasion and migration of T24 and RT4 in human bladder cancer cells.	[284]
Breast cancer	Acetate	Ethyl acetate shows an anti-proliferation impact on breast cancer cells in a ROS-dependent manner.	[285]
	Butyrate	Sodium butyrate induces apoptosis following increased ROS levels, increases caspase activity, and decreases mitochondrial membrane potential in both normal breast and breast cancer cells.	[286]
Gastric cancer	Butyrate, propionate	Butyrate and propionate regulate the cell cycle, apoptosis, glucose-6-phosphate dehydrogenase activity, and glutathione availability in the Kato III human gastric cell lines. Both butyrate and propionate reduced the numbers of cancer cells in G0/G1 phase and elevated the numbers of cells in the G2-M phase of the cell cycle.	[287]
	Butyrate	Butyrate induces the increased numbers of cells in the S phase of the cell cycle.	[287]
	Acetate	Acetic acid induces lipid peroxidation following oxidative stress resulting in gastric epithelial cell apoptosis.	[288]
Liver cancer	Butyrate	Butyrate hinders cell proliferation and triggers apoptosis in both Hep3B and HepG2 cells. Long-term exposure to butyrate increases hepatocyte growth and fibrosis in the liver. Butyrate influences the proliferation of liver cells.	[210]
	Acetate	Protein kinase C (PKC) α promotes the activation of MEK/ERK for 12-O tetradecanoylphorbol-13-acetate -induced inhibition of HepG2.	[289]
Lung cancer	Butyrate	Sodium butyrate increases the expression levels of P-gp and STAT3. It also increases STAT3 phosphorylation and improves mRNA stability of ABCB1 in human lung cancer cells.	[290]
	Propionate	Propionate acts as an anticancer component for lung cancer therapy, by triggering cell apoptosis and cell cycle arrest by up-and down-regulation of	[291]

(*continued on next page*)

Table 2 (*continued*)

Cancer	Short chain fatty acid	Function	Ref.
		p21 and Survivin expression, respectively.	
Pancreatic cancer	Butyrate	Sodium butyrate hinders the expression of b4 Integrin, reduces the cell surface expression of b4, and hinders the invasion of pancreatic cancer.	[292]
	Acetate	Medroxyprogesterone acetate blocks the proliferation of pancreatic carcinoma cell lines (Capan-2, AsPC-1, and MiaPaCa-2) and leads to cell detachment and reduces cell density.	[293]
Prostate cancer	Butyrate	Sodium butyrate reduces the expression of androgen receptor (AR) in LNCaP and LAPC4 prostate cancer cells, with a significant role in the initiation and progression of prostate cancer.	[294]
	Acetate	Acetate increases the need for these lipids in cancers with elevated cell turnover.	[295]
	Propionate	Employment of propionates (e.g., naproxen and ibuprofen) reduces the risk of human prostate cancer progression.	[296]

6. Clinical studies

Investigations of different types of cancer [222,253,254] have proposed that the gut microbiome profile is a potential agent correlated with the efficiency of immune checkpoint inhibitors. Various preclinical and clinical investigations have established a relationship between the gut microbiome and the efficiency of immune checkpoint inhibitors, but how this relationship roles in the tumor microenvironment continues unclear. The SCFAs have been validated to modulate immune system response (Table 3) [85]. Recently, in a study, Yu et al. [255] investigated the relationship between fecal butyrate, acetate, and propionate concentration and NRP1 (Neuropilin 1) expression in human colonic mucosa. In the current study, adenomas showed extensive, weaker staining for NRP-1, which contrastingly correlated positively with butyrate level. Besides, in a study by Lewis et al. [256], they found that bowel transit rate is a determinant of stool SCFA concentration, including butyrate and distal colonic pH. In summary, this may explain the inter-relations between colonic cancer, dietary fiber intake, stool output, and stool pH.

Nomura et al. [85] found that high concentrations of fecal or plasma SCFAs were mediated to respond to PD-1i treatment and longer progression-free survival. SCFAs exhibit immunomodulatory activities in the host, affecting CD4+ T lymphocytes as well as antigen-presenting cells. Butyrate has been shown to induce FOXP3+ CD4+ Treg differentiation [257,258]. Nevertheless, a recent report found that butyrate and other SCFAs increase IFNγ and granzyme B expression in CD8+ cytotoxic T cells and IL-17–secreting CD8+ T cells [259]. Another function of SCFAs is inhibition of HDACs; in this regard, it has been found that HDAC inhibition was found to upregulate PD-1 ligands in melanoma cells, increase the immunotherapy reactions, suppress apoptosis of CD4+ T lymphocytes within tumor parts, upregulate the antitumor immune response, and inhibition of tumor cell proliferation [85,259].

Interestingly, Harig et al. [260] were the first to treat diversion colitis successfully with SCFA irrigation (acetate 60 mM, propionate 30 mM, n-butyrate 40 mM). In distal ulcerative colitis, impaired mucosal oxidation of SCFAs has been described despite their luminal abundance [260]. Pilot studies using either the SCFA mixture or butyrate monotherapy have yielded promising results [260]. Nevertheless, extended confirmatory studies with a larger sample size have not yet been performed. Preliminary data are also available for the administration of SCFA in pouchitis and radiation proctitis [260]. In summary, SCFA topical therapy seems to be a promising option in distinct forms of IBD; nevertheless, the usual administration of SCFAs cannot be recommended until their efficacy has been confirmed in larger trials.

A Pilot Randomized study evaluated butyrate irrigation before ileostomy closure on the colonic mucosa in rectal cancer patients (BUTYCLO) has started [261]. The influences of butyrate irrigations before ileostomy closure on colonic mucosa will be studied in 45 rectal cancer patients. In their study, short-term outcomes, colonic microbiota composition, and functional outcomes will be evaluated after ileostomy reversal [261]. All in all, it seems that the fecal SCFA concentrations are associated with the efficacy of immune checkpoint inhibitor therapy. SCFAs fecal analyses are entirely noninvasive; they may be suitable for regular monitoring of cases with cancer. Clarification of the mechanisms in which SCFA modulation immune response could enable discovering innovative targets to promote immune checkpoint inhibitor efficacy in cancer cases. Further studies as validation investigations are required to confirm the recent findings.

Table 3
The impact of levels of different short-chain fatty acids on the treatment of cancer.

Type of cancer	Type of SCFAs	Levels of SCFAs	Source of concentration	Result	Ref.
Colorectal cancer	Butyrate	Decreased	Fecal	Butyrate concentration was inversely associated with the NRP-1 and tumor growth.	[297]
Colorectal cancer	Acetate	Decreased	Fecal	–	[297]
Colorectal cancer	Propionate	Decreased	Fecal	–	[297]
Solid cancer tumors	Butyrate	Decreased in non-responder than responder to anti-PD1 therapy	Fecal and plasma	The results of this cohort study suggest that fecal SCFA concentrations are associated with the efficacy of PD-1i treatment.	[85]
Solid cancer tumors	Acetate	Decreased in non-responder than responder to anti-PD1 therapy	Fecal and plasma	–	[85]
Solid cancer tumors	Propionate	Decreased in non-responder than responder to anti-PD1 therapy	Fecal and plasma	–	[85]
Melanoma	Butyrate	–	In vitro and in vivo	This investigation revealed that systemic microbial SCFA modulates anti-CTLA-4-provoke immune responses and its antitumor potency.	[273]
Breast cancer	Butyrate	–	Cell line	The finding of the investigation for the first time demonstrated that butyrate is a BCRP substrate. It is crucial in the setting of the high concentration of BCRP production in the colon and the anticarcinogenic, anti-inflammatory capacity of butyrate at that level.	[298]

7. Roles of microbiota-derived short-chain fatty acids in response to cancer immunotherapy

Using advanced high-throughput techniques, it has been indicated that microbiota affects oncogenesis and immunotherapy [262]. The commensal bacteria can negatively or positively affect tumor occurrence and progression [263]. Particular bacteria generate toxins or tumorigenic components that lead to immunosuppressive or inflammatory responses that favor oncogenesis [262]. On the contrary, gut microbiota may tackle cancer by boosting anti-tumor immunity [263]. Furthermore, the commensal bacteria impair the efficacy of anti-cancer treatment and toxicity by altering the local and systemic immune responses [264]. Analysis of microbial metabolites, including SCFAs, and impairment of gut microbiota balance regarding their effects on immune responses will improve the knowledge of several common etiology diseases [265]. SCFAs, mainly acetate, butyrate, and propionate, are present in certain concentrations, and their proportions can alter depending on age, diet, and disease [265]. SCFA concentrations are mainly modulated by the proportion of gut microbiota, and dysbiosis can imbalance the generated SCFAs [265]. It has also been established that SCFAs impede the activity of HDAC, which is mainly involved in the process of deacetylation and histone crotonylation [265]. These properties of SCFAs potentiate their immunomodulatory effects and support the anti/pro-inflammatory hemostasis [265]. SCFAs have local functions in the intestines colonized by gut bacteria, have an impact on gut immune cells, and regulate the immune system by multi-protein inflammasome complexes [265]. SCFAs are essential for immune modulation [266]. Butyrate has systemic anti-inflammatory functions by altering adhesion, migration, and cytokine expression of immune cells and affecting cellular processes such as propagation, activation, and apoptosis [267].

Notably, among SCFAs, butyrate is frequently associated with immune-modulation, mainly through the induction of T-reg cells [268]. Studies recommend that the structure of human intestinal microbiota is related to anti-tumor effectiveness in patients with metastatic melanoma treated with anti- PD-1 and anti-CTLA-4 monoclonal antibodies [253, 269,270]. Also, the gut microbiome composition seems to be correlated with the risk of increasing anti-CTLA-4-stimulated colitis in patients with metastatic melanoma [270,271]. These recent studies indicate the connection between the presence of certain bacteria and clinical response and/or toxicities. Importantly, gut microbiota with high numbers of *Faecalibacterium* and other *Firmicutes* was linked with a good clinical reaction to anti-PD-1, ipilimumab, and ipilimumab/anti-PD-1 treatment in human melanoma patients [270,272]. Based on these studies, it seems that *Faecalibacterium* is majorly mediated to clinical reactions in metastatic melanoma patients treated with immune checkpoints [273].

Nevertheless, few studies have indicated the way that gut microbiome composition could affect a tumor. Regarding the previous findings on the relationship between gut microbiota structure and clinical response and the impact of SCFAs on the immune responses, Coutzac et al. [273] investigated the induction of anti-cancer (metastatic melanoma) response due to systemic bacterial SCFA and anti-CTLA-4 blockade. This study demonstrated that systemic bacterial SCFAs regulate anti-CTLA-4-stimulated immune responses and their anti-tumor effectiveness [273]. Overall, they indicated that the systemic butyrate (and propionate) constrain the anti-tumor properties of anti-CTLA-4 [273]. These results suggest an association between the structure of human gut bacteria and the clinical reactions to ipilimumab through microbiota-derived metabolites. Overall, as these microbial SCFAs have various roles in the immune system in different situations, these metabolites may be involved in immunotherapy against cancers of the intestinal and extraintestinal tract. Further works are needed to define the exact roles and mechanisms of bacterial spp. (In particular metabolite products) to improve cancer treatment approaches.

8. Conclusion

It has been indicated that microbiota can alter the host immune responses, inflammation, and metabolic pathways, thereby playing a central role in cancer occurrence and progression. Similarly, the SCFAs generated by gut microbiota have crucial roles in cancer occurrence and progression. The alternations in gut structure change SCFA levels, thereby affecting HDAC, cell adhesion, cytokine production, chemotaxis, immune cell recruitment, and apoptosis. Therefore, studies in this field can help us combat cancer. Although many studies have been conducted on SCFAs and their association with cancer, most studies have focused on CRC.

Functional foods like prebiotics and probiotics have beneficial influences in controlling and preventing cancer in preclinical and animal models. As a result, these agents have attracted attention for playing a role in preventing cancer development. In this regard, it has been found the immunomodulatory influences of SCFAs generated by probiotics, but the processes of their activities still need much investigation. The administration of probiotic bacteria to treat and prevent intestinal dysbiosis that can cause SCFAs formation seems to be crucial for further study. Microbiota-derived SCFAs seem to act synergistically on anti-tumor approaches, such as drugs to control immune reactions to cancer cells by dampening stimulation of inflammatory cytokines and activation of Tregs that have a crucial activity in controlling the tumor cells. In summary, further studies should focus on the mediation of SCFAs in other GI cancers to determine their exact role in cancer development and treatment. Finally, pinpointing a particular pathway involved in SCFA-mediated immune-modulatory effects is an attractive area of research that could enable the detection of targets to improve cancer therapy.

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Declaration of conflicting interests

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