Journal of Cancer Research and Clinical Oncology (2019) 145:2169–2197
https://doi.org/10.1007/s00432-019-02997-x

REVIEW – CANCER RESEARCH

Protective effect of the "food-microorganism-SCFAs" axis on colorectal cancer: from basic research to practical application

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Received: 6 June 2019 / Accepted: 5 August 2019 / Published online: 10 August 2019

Abstracts

Background Recent studies have shown that the short-chain fatty acids (SCFAs) produced by the gut microbiota play a positive role in the development of colorectal cancer (CRC).

Aims This study aims to elucidate the "food-microorganism-SCFAs" axis and to provide guidance for prevention and intervention in CRC.

Methods The PubMed, Embase and Cochrane databases were searched from their inceptions to August 2018, and 75 articles and 25 conference abstracts were included and analysed after identification and screening.

Results The concentrations of SCFAs in CRC patients and individuals with a high risk of CRC were higher than those in healthy individuals. The protective mechanism of SCFAs against CRC has been described in three aspects: epigenetics, immunology and molecular signalling pathways. Many food and plant extracts that were fermented by microorganisms produced SCFAs that play positive roles with preventive and therapeutic effects on CRC. The "food-microorganism-SCFAs" axis was constructed by summarizing the pertinent literature.

Conclusions This study provides insight into the basic research and practical application of SCFAs by assessing the protective effect of SCFAs on CRC.

Keywords Diet · Microorganism · Short-chain fatty acids · Butyrate · Histone deacetylase · Colorectal cancer

Abbreviations

AC	Aberrant crypt
AhR	Aryl hydrocarbon receptor
Aldh1A2	Aldehyde dehydrogenase 1A2
ANT	Mitochondrial adenine nucleotide translocator
AP-1	Activator protein-1
AWGL	Auto-digested reishi G. lingzhi
AX	Arabinoxylans
BRE	Butyrate-responsive elements
BSG	Brewer's spent grain
CALB2	Calbindin 2
CRC	Colorectal cancer
DCs	Dendritic cells
DMH	Dimethylhydrazine
ERK	Extracellular signal-regulated kinase
ERK1/2	Extracellular-regulated kinase 1/2
ETBF	Bacteroides fragilis enterotoxin

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-02997-x) contains supplementary material, which is available to authorized users.

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FFAR2	Free fatty acid receptor 2
FFAR3	Free fatty acid receptor 3
FOS	Fructo-oligosaccharides
HAMS	High-amylose maize starch
HCAR2	Gαi-protein-coupled niacin receptor
HDAC	Histone deacetylase
HFD	High-fat diet
HPD	High-protein diet
IDH1	Isocitrate dehydrogenase 1
IDO1	Indoleamine 2,3-dioxygenase 1
IL	Interleukin
INF	Interferon
LGG	Lactobacillus rhamnosus GG
LGT	Lateral gene transfer
MAPK	Mitogen-Activated Protein Kinase
MLH1	MutL homolog 1
MSH2	MutS protein homolog 2
PDH	Pyruvate dehydrogenase
PKC	Protein Kinase C
SCFAs	Short-chain fatty acids
SLC5A8	Solute Carrier Family 5 Member 8
TET	Ten-eleven translocation
Treg cells	T regulatory cells
α1-AcT	α1-Antichymotrypsin
α-KG	α-Ketoglutarate

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumours worldwide. The incidence of CRC has significantly increased in recent years, and it is a serious threat to human health (Jalaeikhoo et al. 2018; Shuwen et al. 2018). The intestinal microecosystem consists of abiotic components, such as undigested food, and biological components, such as native bacteria, foreign bacteria, and epithelial cells, as well as the microorganism metabolites and secretions from the stomach, intestines, pancreas and liver, such as hormones, enzymes, mucus, and bile salts (Han et al. 2018; Li et al. 2017). Intestinal mucosal cells have direct contact with the microecosystem for a long time, and the interaction between them has an important impact on the physiological functions of the intestinal mucosal epithelial cells (Sun et al. 2017; Sinha et al. 2016). In the event of microecological imbalance, intestinal microorganisms and their metabolites act on the genetically predisposed host to produce immune responses and genetic changes, and all three play a "trigger" role in the formation and development of CRC (Wang et al. 2017a; Rezasoltani et al. 2017).

Recent epidemiological investigations have shown that high-fat diets, high-protein diets and low-fibre diets are the causes of CRC (Han et al. 2019; Saetang and Sangkhathat 2017; Tak et al. 2017) Many correlative studies have shown that the microbiome is closely related to the occurrence and development of CRC. For instance, intestinal protective probiotics include *Lactobacillus acidophilus*, *Bifidobacterium*, *Lactobacillus rhamnosus* and *Streptococcus thermophilus* (Dodoo et al. 2017; Quagliariello et al. 2016; Yoon et al. 2014). Some pathogenic microorganisms that cause CRC include *Enterococcus faecalis*, *Enterotoxigenic bacteroides fragilis*, *Streptococcus bovis*, *Salmonella*, *Clostridia* and *Fusobacterium nucleatum* (Adesida et al. 2017; Fukugaiti et al. 2015; Paritsky et al. 2015). In recent years, studies have shown that microbial primary metabolites, including amino acids, nucleotides, polysaccharides, lipids and vitamins(Singh et al. 2017), and microbial secondary metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, alkaloids, phenols, antibiotics, and pigments, are involved in the occurrence and development of colorectal cancer (Han et al. 2018; Shi et al. 2017; Narsing et al. 2017; Wang et al. 2017b). Building a complete model of CRC from inducement to occurrence will better explore the pathogenesis, guide diets to prevent CRC and optimize treatment options for CRC. Thus, we propose the "food-microorganism-metabolite" axis. In the intestinal microecosystem associated with colorectal cancer, food and food residues are the initiators of CRC induction. Intestinal microorganisms that breakdown the food are the drivers of CRC. Changes in the metabolites produced by the intestinal microorganisms, which drive the immune responses and genetic changes in the intestinal mucosa, eventually lead to colonic carcinogenesis.

Recently, the development and progress of microbiology and metabolomics have provided technical support for the elucidation of intestinal microecosystems (Wang et al. 2018; Cani 2018). Great progress has been made in the study of the microbiology and metabolites related to CRC (Sinha et al. 2016). However, there is still a long way to go to clarify the "food-microorganism-metabolite" axis and provide guidance for the prevention and treatment of CRC. The main problems include the following three aspects: (1) the complexity from the enormous number of microorganisms and metabolites, the variability in the different diets and times and the individuality of each intestinal microecosystem results in poor reproducibility and decreased accuracy in the results. (2) There is a lack of research on the entire "food-microorganisms-metabolites" axis and a lack of translation between basic research and applied research. (3) The complete networks that can clarify the relationships between food and microorganisms and the relationships between microorganisms and metabolites have not yet been constructed.

There is now an abundance of evidence showing that SCFAs that are produced by intestinal microorganisms during the fermentation of partially digestible and nondigestible food are involved in CRC. SCFAs, mainly including acetate, propionate, butyrate and valerate (Kilner et al. 2016),

are produced from dietary fibre, resistant starch, oligosaccharides and other sugars that cannot be directly digested by intestinal digestive enzymes during the fermentation action of some intestinal microorganisms, such as *Clostridium, Bacteroides, Lactobacillus,* and *Bifidobacterium* (Hester et al. 2015; Yu et al. 2018; Nowak et al. 2015). High-fibre diets, low-fat diets and low-protein diets can effectively increase the SCFAs concentration in the intestinal tract (Bishehsari et al. 2018; Wu et al. 2018; Chen and Vitetta 2018; Zeng et al. 2018; Mu et al. 2016). SCFAs promote apoptosis and inhibit the proliferation of CRC cells by inducing epigenetic changes, such as methylation and deacetylation (Pan et al. 2018), inducing T cell-mediated immune responses (Zhang et al. 2016) and activating intracellular signalling pathways (Lim et al. 2009). Thus, the "food-microorganisms-SCFAs" axis may provide a case of meaningful reference for building the complete network of the "food-microorganisms-metabolites" axis.

In the present study, we strive to construct a relatively complete "food-microorganisms-SCFAs" axis via reviewing and reanalysing the pertinent literature. This work provides a methodological and theoretical basis for the further construction of a complete "food-microorganisms-metabolites" axis, clarifies the intestinal microecosystem and provides guidance for further research, prevention and intervention in CRC.

Methods

Search strategy

The PubMed, Embase and Cochrane databases were searched for pertinent literature published from their inception on August 11, 2018. To achieve maximum sensitivity with the search strategy and identify all relevant studies, the following terms were combined: CRC [("colorectal" or "colon" or "rectal" or "large intestine" or "large bowel" or "intestinum crassum") and ("neoplasms" or "tumor" or "carcinoma" or "cancer")] and microorganisms ("microflora" or "flora" or "microorganism" or "microbiome" or "microbiota" or "microbe" or "microbiology" or "germ" or "bacteria" or "bacterium" or "fungus") and SCFAs ("short-chain fatty acids" or "acetic acid" or "propionic acid" or "methylacetic" or "propanoic acid" or "monoprop, isobutyric acid" or "butyrate, butyric acid" or "propane carboxylic acid" or "ethacetic acid" or "common valeric acid" or "delphinic acid" or "isopentoic acid" or "isopentanoic acid" or "pentanoic acid" or "pentoic acid). All relevant abstracts were retrieved independently by two authors, and the articles with available information for the present systematic review were fully reviewed. A total of 75 articles and 25 conference abstracts were included and analysed after identification and screening. The detailed search strategy is presented in Fig. 1.

Study selection

Studies with the following criterium were considered for inclusion: studies that involved intestinal microorganisms and SCFAs in CRC. The exclusion criteria were as follows: (1) letters, case reports, reviews and author's views; (2) studies not written in English; (3) studies not predominantly focused on intestinal microorganisms and SCFAs in CRC; (4) studies that did not involve CRC; and (5) study results not supported by clear research data. Information from repeated reports is based on the latest report.

Results

Correlation study assessing the SCFAs produced by microorganisms in CRC

We conducted an inductive analysis of the studies that did not involve molecular experiments to clarify the correlation between SCFAs and CRC. Pertinent literature is listed in Table 1 in chronological order. CRC patients, individuals with a high risk of CRC and experimental mice were the main research subjects. Most studies showed that the SCFA levels in CRC patients and individuals with a high risk of CRC were higher than those in healthy individuals.

However, there are also totally different results for the levels of SCFAs in non-Hispanic African Americans. Panel No. 1.1 in Table 1 shows that non-Hispanic African Americans had higher total levels of SCFAs in stool samples than Americans of other races and ethnicities; the exact opposite is shown in Panels No. 1.5, No. 1.13 and No. 1.14. In addition, African Americans had lower total levels of SCFAs in stool samples than native Africans (as shown in Panel No. 1.10). Moreover, several pertinent studies (Panels No. 1.3, 1.4, 1.5, 1.6, 1.12 and 1.15) that showed the correlation between SCFAs and microorganisms in CRC are also listed in Table 1. The interaction between the microorganisms and SCFAs is shown in Fig. 3.

Mechanism study assessing the SCFAs in CRC

In recent years, many studies have been conducted on the molecular mechanisms of SCFA-induced CRC. A total of 31 articles assessing the molecular mechanisms of SCFA-induced colorectal cancer were included and analysed after identification and screening. As shown in Table 2, most studies were on butyrate, and the CRC cell model was used as the research subject. The experimental results for the SCFAs assessments in different studies are summarized

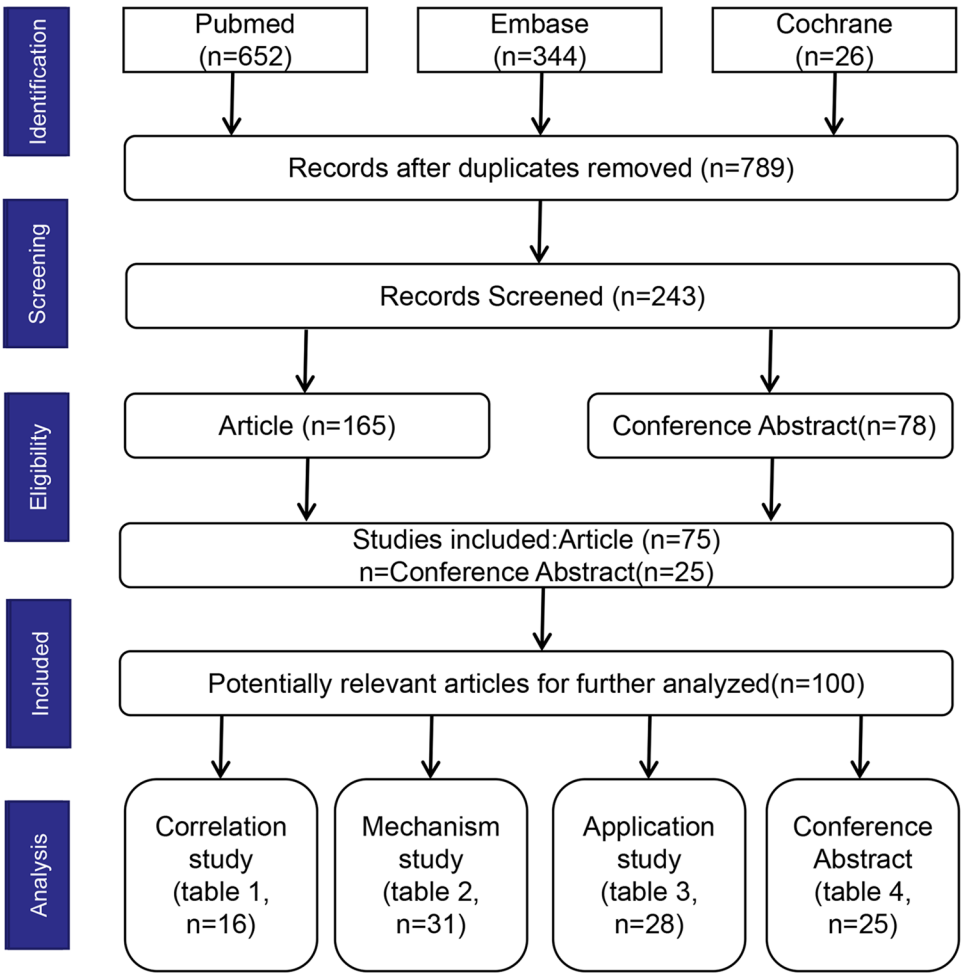

Fig. 1 Literature search strategy. The PubMed, Embase and Cochrane databases were searched for pertinent literature published on August 11, 2018. All relevant abstracts were retrieved independently by two authors, and the articles with available information for the present systematic review were fully reviewed. A total of 78 articles and 25 conference abstracts were included and analysed after identification and screening

in the results column. As shown in Fig. 2, pertinent literature was divided into the three aspects including categories epigenetics, immunology and molecular signalling pathways through summary and analysis. The specific research results are shown in Fig. 2 using the form of a route diagram.

Figure 2a shows the mechanism study assessing the role of butyrate in CRC from the perspective of epigenetics. Butyrate, as a histone deacetylase (HDAC) inhibitor, can suppress HDAC expression and enhance the acetylation of regulatory proteins to suppress proliferation and induce apoptosis in CRC cells. Moreover, DNA demethylation in the promoters of regulatory genes is also involved in the epigenetic mechanism of butyrate in CRC. Figure 2b shows the mechanism from the perspective of immunology. SCFAs and their receptors, including GPR109A, GPR43 and FFAR2, play a protective role against CRC by regulating immune cells, including regulatory T cells, dendritic cells, natural killer cells and macrophages, and immune factors, such as interleukins (ILs) and interferon-gamma (INF-γ), through various molecular mechanisms. Figure 2c shows the mechanism from the perspective of molecular signalling pathways. The PI3 k/Akt signalling pathway, STAT signalling pathway, cytosolic Ca^{2+} signalling pathways, AP-1 signalling pathway, heregulin/ErbB signalling pathway and several microRNA regulatory signalling pathways are involved in the molecular regulation of butyrate in CRC. Butyrate-responsive elements, such as the TATA box and proximal CCAAT box, participate in the regulation at the gene transcription level. Related molecular mechanisms, such as protein phosphorylation regulation, noncoding gene regulation and gene damage repair mechanisms, were also involved.

Preventive and therapeutic effects of SCFAs on CRC

SCFAs are produced by microorganisms during the fermentation of food. Microorganisms can produce SCFAs from many food and plant extracts during fermentation. These SCFAs play positive roles in the preventive and therapeutic effects on CRC. As shown in Table 3, pertinent literature describing medicine and food studies involving SCFAs produced by microorganisms in CRC have been summarized. Mouse models are the main research approach. A low-fat diet (panel No. 3.1), a low-protein diet (panel No. 3.14), high-fibre diets (panels No. 3.4, No. 3.19 and No. 3.22) and some foods, including yogurt

Table 1 Correlation study assessing the SCFAs produced by microorganisms in CRC

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
1.1	Bridges et al.	2018	Non-Hispanic African-Americans ($n=17$), Non-Hispanic White ($n=24$); Hispanic ($n=7$)	–	Acetate, Butyrate, Propionate and Valerate	African Americans had higher total levels of SCFAs in their stool samples than non-Hispanic White and Hispanic Americans	Jalaeikhoo et al. (2018)
1.2	Wang et al.	2017	CRC patients (nine males and six females) and 12 healthy control individuals	*Bacteroides, Dialister, Pseudobutyrivibrio, Fusobacterium* and *Ruminococcus*	Acetic acid, valeric acid, isobutyric acid and isovaleric acid	The SCFA levels in CRC patients are higher than those in healthy individuals	Shuwen et al. (2018)
1.3	Braten et al.	2017	A/J Min/+ mice	*Ruminococcaceae* and *Ruminococcu*	Butyrate	Ruminococcaceae and Ruminococcus were negatively correlated with butyrate levels, but there were no significant correlations between butyrate levels and tumour loads in CRC-bearing mice	Han et al. (2018)
1.4	Jeraldo et al.	2016	Two CRC patients and two subjects with a negativ ecolonoscopy	*Butyricicoccus pullicaecorum*	Acetate and butyrate	*Butyricicoccus pullicaecorum* produces SCFAs, including acetate and butyrate	Li et al. (2017)
1.5	Hester et al.	2015	Hispanics ($n=5$) and non-Hispanic African Americans ($n=5$), American Indians ($n=5$), and Whites ($n=5$)	*Clostridium* and *Bacteroides*	Acetate, propionate, butyrate and valerate	African Americans had significantly lower levels of acetate, butyrate, and total SCFAs than Americans of all other races and ethnicities. Clostridium levels were found to be significantly and inversely related to total SCFA levels. Bacteroides levels were found to be positively associated and Clostridium levels were found to be negatively associated with the levels of butyrate	Sun et al. (2017)
1.6	Amiot et al.	2015	247 patients with an average risk of CRC (personal or familial history of colorectal polyp or cancer or any digestive symptom that required colonoscopy)	*Faecalibacterium prausnitzii* and *Clostridium leptum species*	Valerate, acetate, propionate, and butyrate	Faecal concentrations of four short-chain fatty acids (valerate, acetate, propionate, and butyrate) increased in patients with advanced CRC and were associated with *Faecalibacterium prausnitzii* and *Clostridium leptum* species	Sinha et al. (2016)

Table 1 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
1.7	Baxter et al.	2014	Germ-free mice	*Bacteroides, Parabacteroides, Alistipes, Akkermansia*and *Clostridium XIVa*	Butyrate	Gram-negative bacteria, including Bacteroides, Parabacteroides, Alistipes, and Akkermansia, were positively correlated with CRC, and Gram-positive bacteria, including multiple members of Clostridium Group XIVa, were negatively correlated with CRC. Butyrate production was negatively correlated with CRC	Wang et al. (2017a)
1.8	Wu et al.	2013	CRC patients ($n=19$) and healthy control subjects ($n=20$)	*Faecalibacterium* and *Roseburia*	Butyrate	The butyrate-producing genera Faecalibacterium and Roseburia were decreased in CRC patients	Rezasoltani et al. (2017)
1.9	Weir et al.	2013	Healthy adults ($n=10$) and CRC patients ($n=11$)	–	Butyrate and acetate	The relative concentrations of butyrate and relative abundance of butyrate-producing bacterial genera were lower, while the relative concentrations of acetate were higher in stools from CRC patients	Han et al. (2019)
1.10	Ou et al.	2013	African Americans ($n=12$) and age- and sex-matched native Africans	*Clostridium IV* and *Clostridium XIVa*	Acetate, propionate and butyrate	Butyrate-producing bacteria and SCFAs were more abundant in faecal samples from native Africans with a low risk of colon cancer	Saetang and Sangkhathat (2017)
1.11	Ohigashi et al.	2013	CRC patients ($n=93$) and healthy individuals (22 with adenoma and 27 without adenoma)	–	Acetate, propionate and butyrate and valeric acid	Faecal SCFAs, including acetate, propionate and butyrate and valeric acid, were decreased in CRC	Tak et al. (2017)
1.12	Wang et al.	2012	CRC patients ($n=46$) and healthy volunteers ($n=56$)	*Roseburia* and *Lachnospiraceae A2-166*	Butyrate	4 OTUs belonging to the butyrate-producing genus Roseburia and 1 OTU that was closely related to the A2-166 and butyryl-CoA CoA transferase genes from the butyrate-producing bacterium Lachnospiraceae were lower in CRC patients	Dodoo et al. (2017)

Table 1 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
1.13	Ou et al.	2012	African Americans ($n=12$) and Caucasian Americans ($n=10$) native Africans ($n=13$)	–	SCFAs	The levels of SCFAs were lower in African Americans with a high risk of CRC and Caucasian Americans who consumed a high-fat diet compared to native Africans who subsisted on a low-fat diet	Quagliariello et al. (2016)
1.14	O'Keefe et al.	2009	African Americans ($n=17$) and Caucasian Americans ($n=17$) native Africans ($n=17$)	–	SCFAs	Total SCFAs and butyrate levels were higher in native Africans with a low risk of CRC who consumed a staple diet of maize meal that was rich in resistant starch and low in animal products	Yoon et al. (2014)
1.15	Balamurugan et al.	2008	CRC patients ($n=20$) and healthy volunteers ($n=17$)	–	Butyrate	Levels of butyrate-producing bacteria, including *Eubacterium rectale* and *Faecalibacterium prausnitzii*, were decreased approximately fourfold in colorectal cancer patients	Adesida et al. (2017)
1.16	Weaver et al.	1988	Polyp-colon cancer ($n=54$) and normal subjects ($n=35$)	–	Acetate and butyrate	The level of acetate was higher and the level of butyrate was lower in enema samples from polyp-colon cancer patients	Fukugaiti et al. (2015)

Table 2 Mechanism study assessing the SCFAs produced by microorganisms in CRC

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.1	Sun et al.	2018	HT-29 and Caco-2 cells	–	Butyrate	Butyrate suppressed proliferation, potentiated differentiation, and induced apoptosis in CRC cells through alpha-ketoglutarate (alpha-KG) mediating the histone acetylation of H3 and H4 and the DNA demethylation of the promoter of the DNA mismatch repair (MMR) gene	Jalaeikhoo et al. (2018)
2.2	Pan et al.	2018	Apc(Min/+) and the azoxymethane (AOM)-treated mice	–	Butyrate	Free fatty acid receptor 2 (FFAR2) was activated by butyrate, inhibited colon carcinogenesis by attenuating the downstream cAMP-PKA-CREB pathway and suppressed histone deacetylase (HDAC) expression and the hypermethylation of inflammation suppressors	Shuwen et al. (2018)
2.3	Kim et al.	2018	APC(Min/+)mice, Gpr43$^{-/-}$ mice	*Firmicutes (lachnospiraceae), Firmicutes (lactobacillus), Firmicutes (sfb), Bacteroidetes (porphyromonadaceae), Bacteroidetes (b. fragilis),* and *Proteobacteria (enterobacteriale)*	SCFAs	The SCFA/GPR43 (SCFAs and their receptors) axis suppressed bacterial invasion and the associated Th17-driven chronic inflammation as well as colon carcinogenesis	Han et al. (2018)
2.4	Ang et al.	2018	HEK293 cells	–	SCFAs	Free fatty acid receptor 2 (FFAR2) and Free fatty acid receptor 3 (FFAR3) interacted to form a receptor heterodimer. The FFAR2-FFAR3 heterodimer enhanced cytosolic Ca(2+) signalling and beta-arrestin-2 recruitment	Li et al. (2017)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.5	Zeng et al.	2017	HCT116 Cells and NCM460 Colon Cells	–	Butyrate	Butyrate inhibited cell proliferation and induced cell apoptosis and genomic DNA fragmentation through increasing H3 histone deacetylation and p21 tumour suppressor expression and decreasing phosphorylation of extracellular-regulated kinase 1/2(p-ERK1/2) in HCT116 cells	Sun et al. (2017)
2.6	Li et al.	2017	HCT116, HT29, HCT8, LOVO cells	–	Butyrate	Butyrate suppressed the motility of CRC cells via inhibiting HDAC3 to deactivate Akt/ERK signalling	Sinha et al. (2016)
2.7	Jin et al.	2017	YAMC mouse colonocytes and Caco-2 cells	–	Butyrate, propionate and acetate	SCFAs (butyrate, propionate and acetate) enhanced histone acetylation and the recruitment of the AhR to the Cyp1a1/CYP1A1 promoters in CRC cells	Wang et al. (2017a)
2.8	Daniel et al.	2017	Homozygous Smad3 mice	*Lachnospiraceae bacterium A4*	Butyrate	Lachnospiraceae bacterium A4, which modulates inflammation and promotes tumour formation by decreasing the RNA transcripts of butyrate kinase, decreased butyrate production	Rezasoltani et al. (2017)
2.9	Cresci et al.	2017	Caco-2 cells	–	Butyrate	Butyrate protected CRC cells against the adhesion of *Campylobacter jejuni* by influencing the presence of HCAR2 (butyrate receptor) and SLC5A8 (butyrate transporter) on the cell surface	Han et al. (2019)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.10	Bachmann et al.	2017	Caco-2 cells	–	Butyrate	Butyrate enhanced IL-22R1 expression, thereby enforcing the expression of the prototypic STAT3-downstream target genes α1-antichymotrypsin (α1-AcT) and suppressor of cytokine signaling (SOCS)-3	Saetang and Sangkhathat (2017)
2.11	Kilner et al.	2016	–	–	Propionate and valerate	SCFAs (propionate and valerate) exhibited antimitotic capabilities in CRC cells, disrupting microtubule (MT) structural integrity via dysregulation of beta-tubulin isotypes	Tak et al. (2017)
2.12	Kang et al.	2016	HCT116 cells	–	Butyrate	Butyrate-resistant CRC cells were more tolerant of apoptosis induced by chemotherapy drugs	Dodoo et al. (2017)
3.13	Gurav et al.	2015	Wild-type C57BL/6 mice, OT-II transgenic mice, Germ-free and age-matched conventional mice	–	Acetate, propionate and butyrate	Slc5a8, a Na^+-coupled high affinity transporter for the bacterial fermentation product butyrate, protected CRC cells under conditions of low-fibre. Butyrate promoted the expression of the immunosuppressive enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and Aldh1A2 (aldehyde dehydrogenase 1A2) in dendritic cells (DCs), promoted the conversion of naive T cells into FoxP3+ (immunosuppressive forkhead box P3+) Tregs (regulatory T cells) and suppressed the conversion of naive T cells into proinflammatory interferon (IFN)-γ-producing cells	Quagliariello et al. (2016)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.14	Hu et al.	2015	Human tissue samples at the University of Chicago Medical Center,HCT116 (male, CCL-247) and HT29 (female, HTB-38)	–	Butyrate	Butyrate inhibited miR-92a transcription by reducing c-Myc expression to stimulate CRC cell apoptosis	Yoon et al. (2014)
2.15	Hague et al.	2015	CRC cells(AA/CI, RG/C2 and BH/CI) and carcinoma cell line (S/KS/FI)	–	Butyrate	Butyrate induced apoptosis of CRC cells via elevated levels of bak or reduced levels of bcl-2	Adesida et al. (2017)
2.16	Bardhan et al.	2015	IFNγ KO mice (129S7(B6)-Ifngtm1Ts/J) and age-matched WT control mice (BALB/cJ), SW480, SW620, SW116 and T84, and mouse colon carcinoma cell line CT26	–	SCFAs	IFNγ-activated pSTAT1, which then directly bound to the promoter of p300. p300 then bound to the GPR109A (the receptor for SCFAs) promoter to induce H3K18 hyperacetylation, resulting in chromatin remodelling in the methylated GPR109A promoter, which induced GPR109A silencing to suppress CRC	Fukugaiti et al. (2015)
2.17	Singh et al.	2014	WT and Niacr$^{1-/-}$ mice	–	Butyrate	GPR109A (encoded by Niacr1), a receptor for butyrate and niacin, suppressed colonic inflammation and carcinogenesis via enabling colonic macrophages and dendritic cells to induce the differentiation of Treg cells and IL-10-producing T cells	Paritsky et al. (2015)
2.18	Meehan et al.	2014	Gene sequence data reanalysis	–	Butyrate	Butyric acid production-related genes were identified inhuman gut-associated Lachnospiraceae, which possess genes for endospore formation	Singh et al. (2017)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.19	Nepelska et al.	2012	HT-29 and Caco-2	–	Propionate and butyrate	Propionate and butyrate produced by commensal bacteria activated the AP-1 signalling pathway to prevent CRC. Butyrate and PMA displayed synergistic activation of the AP-1 pathway	Shi et al. (2017)
2.20	Hu et al.	2011	HCT-116 cells	–	Butyrate	Microbe-derived butyrate regulated host p21 gene expression through the modulation of miR-106b expression to prevent CRC	Narsing et al. (2017)
2.21	Ooi et al.	2010	HT-29 cells	–	Butyrate	Butyrate and four butyrate analogues (propionate, 4-benzoylbutyrate, 4-(4-aminophenyl)butyrate and benzyloxyacetate) induced dose-dependent increases in apoptosis and decreases in cell proliferation in HT-29 cells by decreasing histone deacetylase activity	Wang et al. (2017b)
2.22	Häner et al.	2010	CaCo-2, HT-29, Co-115/3 cells	–	Butyrate	Calretinin suppresses CRC cells via bipartite putative butyrate-responsive elements flanking the TATA box	Wang et al. (2018)
2.23	Hague et al.	2010	PC/JW/FI and S/KS/FI cells	–	Butyrate	Sodium butyrate induced apoptosis of CRC cells	Cani (2018)
2.24	Lim et al.	2009	CaCo-2 and SNU-C4 cells	–	Butyrate	Butyrate inhibited the proliferation of CRC cells by suppressing the heregulin/ErbB signalling pathway	Kilner et al. (2016)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.25	Fung et al.	2009	HT29 cells	–	Butyrate	Cellular pathways, including those involved in the remodelling of the actin cytoskeleton, inhibition of protein biosynthesis and dysregulation of the cell stress response, were involved in butyrate insensitivity in CRC cells	Hester et al. (2015)
2.26	Lecona et al.	2008	BCS-TC2 cells	–	Butyrate	Annexin A1 promoter activity was controlled by functional cooperation between p53 and factors binding to the proximal CCAAT box. Butyrate activity involved both the p38 MAPK-dependent p53 activation and p38 MAPK-independent release of NF-γ from its promoter	Yu et al. (2018)
2.27	Hatayama et al.	2007	LS174T cells	–	Butyrate	Butyrate was an HDAC inhibitor that inhibited the proliferation of CRC cells by stimulating MUC2 production	Nowak et al. (2015)
2.28	Ohkawara et al.	2005	Jcl:ICR mice	*Butyrivibrio fibrisolvens MDT-1*	Butyrate	*Butyrivibrio fibrisolvens* MDT-1 produced butyrate to suppress CRC cells, which was associated with the decrease in beta-glucuronidase activity and the increase in the numbers of NK and NKT cells	Bishehsari et al. (2018)
2.29	Jan et al.	2002	HT29 cells and Caco2 cells	*Propionibacterium*	Propionate and acetate	Propionibacterium induced apoptosis of CRC cells via SCFAs (propionate and acetate) acting on the CRC mitochondria	Wu et al. (2018)

Table 2 (continued)

No.	Authors	Year	Object	Microorganism	SCFAs	Results	References
2.30	Domon-Dell et al.	2002	HT29 cells and Caco2 cells	–	Butyrate	Butyrate inhibited the cell growth and stimulated the cell differentiation and apoptosis of CRC cells by stimulating Cdx2 mRNA and protein expression as well as the transcriptional activity of its promoter	Chen and Vitetta (2018)
2.31	Mahyar-Roemer et al.	2001	HCT116 cell	–	Butyrate	N-butyrate stimulated p21 expression and induced apoptosis independent of p53 to protect against CRC cells	Zeng et al. (2018)

(panel No. 3.3), reishi mushroom (panel No. 3.8), nuts (panel No. 3.13), high-amylose maize starch (panels No. 3.16, No. 3.17, No. 3.25, and No. 3.27), arabinoxylans (panel No. 3.21), wheat aleurone (panel No. 3.26) and fructans (panel No. 3.28) can each play a positive role in preventing CRC by increasing the levels of SCFAs. Some reagents, including sericin (panel No. 3.23), and plant extracts, including EPS1-1 extracted from *Rhizopus nigricans* (panel No. 3.5) and polymethoxyflavones extracts (panel No. 3.6), play a positive role in inhibiting the proliferation of CRC cells by influencing the levels of SCFAs. *Lactobacillus* (panel No. 3.9, No. 3.10, No. 3.15, No. 3.18, and No. 3.23) and aloe vera gel endophytic microbiota can change the intestinal microecosystem and increase the levels of SCFAs that play a protective role against CRC. Moreover, the butyrate produced from dietary fibre during microbial fermentation can improve the clinical effect of CPT-11 (irinotecan) (panel No. 3.7) and reduce CPT-11 toxicity (panel No. 3.20).

Conference abstracts assessing the SCFAs produced by microorganisms in CRC

Many conference abstracts assessing the SCFAs produced by microorganisms in CRC have been published. As shown in Table 4, the relevant conference abstracts were included after identification and screening according to the inclusion and exclusion criteria. Most of the conference abstracts have been reported in the previous literature. Moreover, the following information needs to be added. Several conference abstracts (panels No. 4.1, No. 4.11, No. 4.15, and No. 4.16) showed that energy metabolism is involved in the protective effect of butyric acid on CRC through interference with the Warburg effect.

Food-microorganisms-SCFAs axis

Pertinent literature have been further analysed to elucidate the food-microorganisms-SCFAs axis. As shown in Fig. 3, microorganisms that changed the levels of SCFAs, including acetate, propionate and butyrate, are shown in a circular pattern after further refining with the related content in the literature. A more concise explanation on how SCFAs are produced from food and plant extracts through microbial fermentation in CRC is shown in Fig. 4; the framework of the food-microorganisms-SCFAs axis in CRC has been preliminarily established.

Discussion

Despite the contradictions among the difference studies on the levels of SCFAs in non-Hispanic African Americans compared with Americans of other races and ethnicities, the general view is that SCFAs are inversely associated with

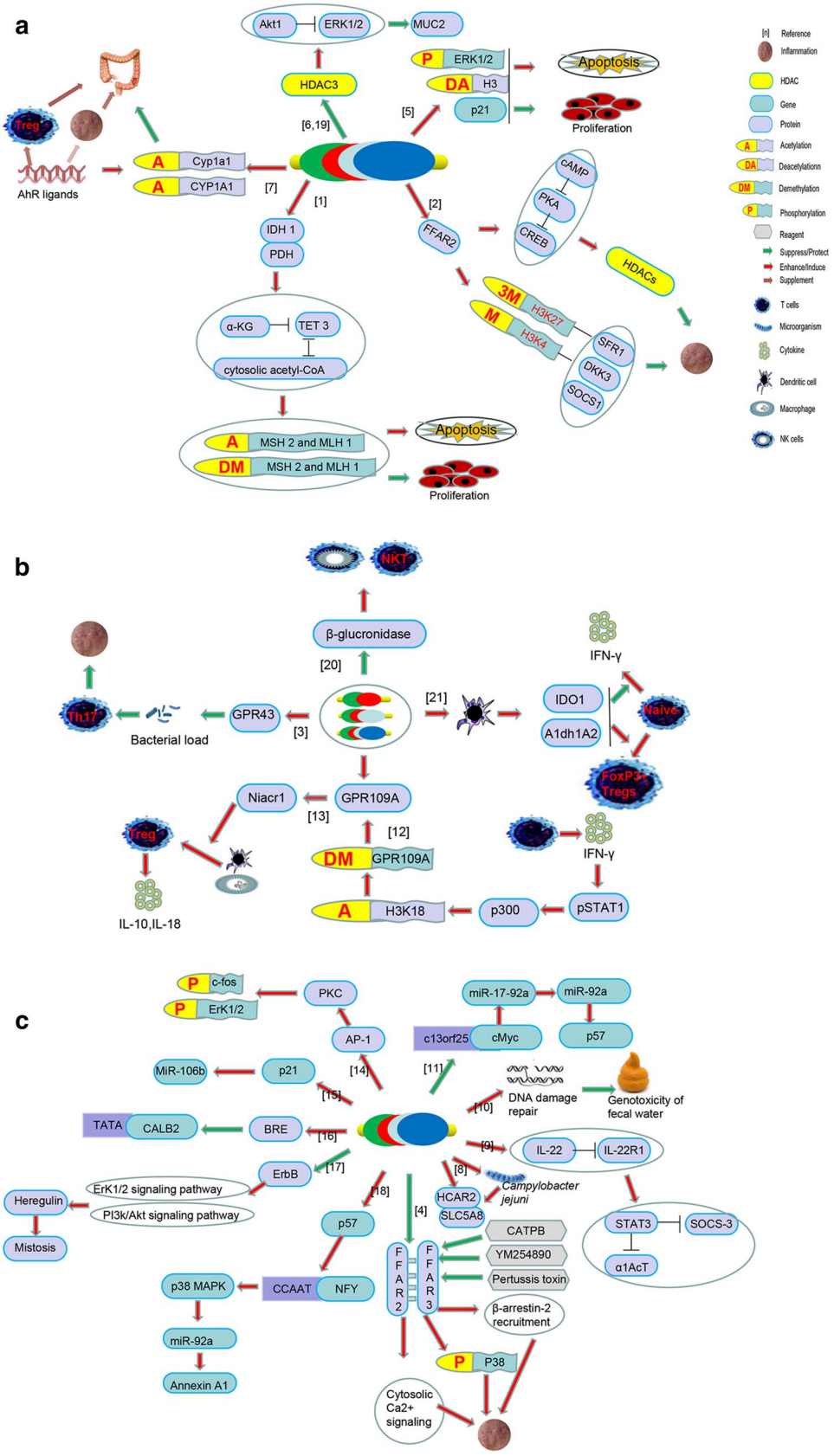

Fig. 2 Mechanism study assessing the SCFAs in CRC. A mechanistic study of the SCFAs in CRC was divided into three categories, epigenetics, immunology and molecular signalling pathways, through summary and analysis. **a–c** Are shown from the perspectives of epigenetics, immunology and molecular signalling pathways, respectively. The specific research results and research ideas were shown using the form of a route diagram. Due to differences in the understanding of the original articles and the need for visualization with a figure, some route diagrams may be not completely consistent with the original intention of the author. The original articles listed in the figure are taken as the standard. Relevant references are included in Supplement 1

Table 3 Pertinent literature assessing the food and plant extracts involved in the production of SCFAs by microorganisms in CRC

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.1	Zeng et al.	2018	C57BL/6 mice	High-fat diet	*Barnesiella*	Acetate	A high-fat diet (HFD) promoted colonic aberrant crypt (AC) formation. The abundance of *Bacteroides, Barnesiella* and *Lachnoclostridium*, which can all produce SCFAs, and acetate content were lower in mice fed with a high-fat diet	Jalaeikhoo et al. (2018)
3.2	Yin et al.	2018	HCT-116 cells	Inulin	*Lactobacillus, Enterococcus faecalis, Enterococcus faecium* and *Streptococcus thermophilus*	Acetate, propionate and butyrate	Inulin was fermented and promoted the conversion of lactate to acetate, propionate and butyrate by the faecal microbiota. Butyrate in the fermentation products could cause apoptosis via inducing DNA fragmentation in HCT-116 cells	Shuwen et al. (2018)
3.3	Ohara et al.	2018	27 healthy persons; DLD-1 cells and WirDr cells	Yogurt	*Bifidobacterium longum* (BB536-γ)	Acetate, isobutyric acid and Butyrate	The intake of yogurt containing BB536-γ and fructo-oligosaccharides(FOS) enhanced the production of SCFAs to suppress CRC-related bacteria (putrefactive bacteria) and *Bacteroides fragilis* enterotoxin (ETBF)	Han et al. (2018)
3.4	Bishehsari et al.	2018	Double heterozygous mice with deletion of the adenomatous polyposis coli gene (APCD468)	High-fiber diet	(Bifidobacterium: total SCFA and acetate); (*Lachnospiraceae*: total SCFA, acetate, and butyrate); (S24-7: propionate)	SCFA butyrate	Dietary fibre promoted SCFA production by SCFA-producing bacteria to prevent CRC	Li et al. (2017)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.5	Yu et al.	2018	BALBB/c mice	Extracellular polysaccharide (EPS1-1) extracted from Rhizopus nigricans	*Lactobacillus, Bacteroides* and *Prevotella.*	Acetate and propionate	EPS1-1 extracted from the fermentation broth of *Rhizopus nigricans* increased the concentration of SCFAs produced by microorganisms in the faeces of CRC-bearing mice	Sun et al. (2017)
3.6	Wu et al.	2018	ICR mice with CRC induced by benzo[a] pyrene/dextran sulfate sodium (BaP/DSS)	Polymethoxyflavones	*Ruminococcaceae* and *Blautia* spp.	Butyrate	Polymethoxyflavones extracts increased the amounts of butyrate-producing probiotics (Ruminococcaceae and Blautia spp.) and decreased the amounts of CRC-related bacteria (Erysipelortrichales and Lactobacillales)	Sinha et al. (2016)
3.7	Encarnação et al.	2018	WiDr,C2BBe1 and LS1034 cells	Dietary fiber	–	Butyrate	Butyrate and irinotecan acted synergistically in the CRC cells	Wang et al. (2017a)
3.8	Yang et al.	2017	Sprague–Dawley rats	Reishi mushroom	–	Propionate	The reishi mushroom and the auto-digested reishi *G. lingzhi* (AWGL) could increase the content of caecal propionate in rats	Rezasoltani et al. (2017)
3.9	Ni et al.	2017	ApcMin/+ mice	*Lactobacillus rhamnosus GG*	*Roseburia* and *Coprococcus*	SCFAs	*Lactobacillus rhamnosus* GG (LGG) enriched the microbes involved in (e.g., Roseburia and Coprococcus) or microbial activities related to short-chain fatty acid production	Han et al. (2019)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.10	Hibberd et al.	2017	Fifteen patients with stage I–III colon cancer	*Bifidobacterium lactis Bl-04* and *Lactobacillus acidophilus NCFM*	*Faecalibacterium* and *Clostridiales* spp.	Butyrate	CRC patients who received probiotics (*Bifidobacterium lactis* Bl-04 and *Lactobacillus acidophilus* NCFM) had an increased abundance of butyrate-producing bacteria, especially Faecalibacterium and Clostridiales spp., in the tumour, non-tumour mucosa and faecal microbiota	Saetang and Sangkhathat (2017)
3.11	Constante et al.	2017	Azoxymethane/DSS CRC mice	Heme	–	Butyrate	Dietary haeme reduced butyrate levels in faecal material from CRC-bearing mice	Tak et al. (2017)
3.12	Al-Madboly et al.	2017	Human peripheral blood mononuclear cells (PBMCs) and Human dermal fibroblast cells (FB)	Aloe vera gel	*Bacillus cereus, Bacillus licheniformis, Lactobacillus paralimentarium, Yeast: Clavispora lusitaniae*	Butyrate	Butyrate fermented by aloe vera gel endophytic microbiota regulated the inflammatory responses via the reduction of reactive oxygen species and both COX 1 and 2 enzymes to prevent CRC	Dodoo et al. (2017)
3.13	Schlormann et al.	2016	–	Nuts	–	Butyrate	Butyrate fermented by nuts might prevent CRC	Quagliariello et al. (2016)
3.14	Mu et al.	2016	Wistar rats	High-protein diet	*Ruminococcus bromii* and *Faecalibacterium prausnitzii*	Acetate, propionate, and butyrate	A high-protein diet (HPD) reduced the butyrate-producing bacteria content, including *Ruminococcus bromii* and *Faecalibacterium prausnitzii*, in faeces and induced intestinal disease via downregulation of the genes involved in mitochondrial OXPHOS	Yoon et al. (2014)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.15	Nowak et al.	2015	Caco-2 cells	Inulin and dextrin	*Lactobacillus rhamnosus* 0900, *L. rhamnosus* 0908, and *Lactobacillus casei* 0919. *Lactobacillus delbrueckii* ssp. *bulgaricus* 0987 isolates from the feces of 7-month-old girl and *Lactobacillus mucosae* 0988 isolates from the feces of 18-month-old boy, rhamnosus GG, *L. casei* DN 114-001, *L. mucosae* 0988, *B. animalis* ssp. *lactis* Bb-12	Acetate, propionate and butyrate	SCFAs produced by *Lactobacillus mucosae* 0988 and *Bifidobacterium animalis* ssp. lactis Bb-12 decreased the DNA damage induced by faecal water, and fermented inulin and fermentation-resistant dextrin could improve DNA repair	Adesida et al. (2017)
3.16	Le Leu et al.	2015	23 individuals	Butyrylated high-amylose maize starch	*Clostridium coccoides Ruminococcus bromii. Parabacteroides distasonis* and *Faecalibacterium prausnitzii*	Acetate, propionate and butyrate	Butyrylated high-amylose maize starch consumption prevented red meat-induced adduct formation to decrease CRC risk, and might be associated with increased stool SCFA levels	Fukugaiti et al. (2015)
3.17	Hu et al.	2015	Sprague–Dawley (SD) rats	Dietary resistant starch (RS) and green tea extract (GTE)	*Turicibacter* and *Aerococcus*	Acetate, propionate and butyrate	Dietary resistant starch increased SCFA levels, which were linked to *Turicibacter* and *Aerococcus,* and the expression of SCFA receptor GPR43 mRNA to protect against CRC	Paritsky et al. (2015)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.18	Zhu et al.	2014	50 male F344 rats	Lactobacillus salivarius Ren	*Prevotella* and *Bacillus*	Acetate, propionate and butyrate	The amounts of Prevotella-related strains were increased, and Bacillus-related strains were decreased in 1,2-dimethylhydrazine (DMH) mice treated with *Lactobacillus salivarius* Ren. These changes were accompanied by increased short-chain fatty acid levels	Singh et al. (2017)
3.19	Donohoe et al.	2014	BALB/c mice	Dietary fiber	*Butyrivibrio fibrisolvens*	Butyrate	Dietary fibre diets elevated the butyrate level produced by fermentation by *Butyrivibrio fibrisolvens* and functioned as an HDAC inhibitor to protect against CRC	Shi et al. (2017)
3.20	Lin et al.	2014	Female Fisher 344 rats	Dietary fiber	–	Butyrate	Dietary fibre diets reduced CPT-11 toxicity by increasing butyrate production, which was positively correlative with the expression of MCT1 (monocarboxylate transporter 1) and the bacterial butyryl-CoA gene	Narsing et al. (2017)
3.21	Reis et al.	2014	Faecal samples were obtained from three healthy human volunteers	Arabinoxylans(AX) from brewer's spent grain (BSG)	–	Acetate, propionate and butyrate	Arabinoxylans (AX) from brewer's spent grain (BSG) increased the production of SCFAs by fermentation in modulated gut microbiota to prevent CRC	Wang et al. (2017b)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.22	Chen et al.	2013	CRC patients ($n=47$) and healthy individuals ($n=47$)	High-fiber diet	*Clostridium, Roseburia,* and *Eubacterium*	Butyrate	Lower dietary fibre consumption patterns and consistently lower faecal SCFAs (acetate, propionate and butyrate) and butyrate-producing bacteria content (Clostridium, Roseburia, and Eubacterium) were seen in advanced CRC patients	Wang et al. (2018)
3.23	Thirabunyanon et al.	2013	Healthy infant feces samples at 1–14 days after birth ($n=17$)	healthy infants faeces	*Lactobacillus salivarius FP35*	Butyrate and propionate	*Lactobacillus salivarius* FP35 obtained from healthy infants inhibited the proliferation of CRC cells through triggering the bioproduction of short-chain fatty acids, mainly butyrate and propionate	Cani (2018)
3.24	Okazaki et al.	2011	Sprague–Dawley mice	Sericin(a cocoon proteins synthesized by silkworm Bombyx mori)	–	Acetate and *n*-butyrate	Sericin elevated caecal acetate and n-butyrate to prevent CRC in rats fed a high-fat diet	Kilner et al. (2016)

Table 3 (continued)

No.	Authors	Year	Object	Nutrition	Microorganism	SCFAs	Results	References
3.25	Abell et al.	2011	Sprague–Dawley mice	Resistant starch	*Ruminococcus, Lactobacillus gasseri* and *Parabacteroides distasonis*	Propionate and butyrate	Consuming 10% high-amylose maize starch (HAMS, high resistant starch) increased the propionate concentration in the distal colonic digesta and was associated with the presence of faecal bacteria, including *Ruminococcus bromii*-like bacteria. Cooked 10% butyrylated HAMS increased the propionate and butyrate concentrations in the distal colonic digesta and was associated with the presence of the two non-butyrate-producing bacteria, *Lactobacillus gasseri* and *Parabacteroides distasonis*	Hester et al. (2015)
3.26	Borowicki et al.	2010	HT29 cells	Wheat aleurone	–	Acetate, propionate and butyrate	Wheat aleurone increased the levels of SCFAs and induced growth, apoptosis and cell cycle arrest in CRC cells	Yu et al. (2018)
3.27	Le Leu et al.	2007	Sprague–Dawley mice	Resistant starch	–	Butyrate	Dietary resistant starch suppressed CRC by increasing the production of butyrate	Nowak et al. (2015)
3.28	Pool-Zobel et al.	2002	APCMIN mice	Fructans	–	Butyrate	Prebiotic fructans reduced the risk of colon cancer associated with the increase in butyrate concentrations	Bishehsari et al. (2018)

Table 4 Conference abstracts assessing the SCFAs produced by microorganisms in CRC

No.	Authors	Year	Microorganism	SCFAs	Results	Titles
4.1	Simon et al.	2018	–	Butyrate	The knockdown of PDK2 could increase butyrate oxidation and the levels of acetyl-CoA and decrease PDH phosphorylation and lactate production in CRC cells	Inactivation of the pyruvate dehydrogenase complex results in a decrease in butyrate oxidation and enhancement of cellular proliferation
4.2	Zeng et al.	2017	Barnesiella	Acetic acid	The abundance of certain SCFA-producing bacteria (e.g., Barnesiella) and the amount of faecal SCFA (e.g., acetic acid) were lower in C57BL/6 mice with azoxymethane (AOM)-induced colonic ACF (aberrant crypt foci, preneoplastic lesions) who were fed a high-fat diet (HF, 45% of energy content from fat)	Aberrant crypt formation accompanies an increase of opportunistic pathogens/bacteria in the inflammatory gut of C57BL/6 mice fed a high-fat diet
4.3	Zapletal et al.	2017	–	Butyrate	Butyrate altered the metabolism/toxicity of BaP (benzopyrene) through reducing the binding of HDAC1 (histone deacetylase) to the enhancer region of the CYP1A1 (cytochrome P450 family 1) gene, and this effect was linked with the upregulation of CYP1A1 expression/activity in human HCT116 cells	Butyrate as a modulator of xenobiotic-metabolizing enzymes in colon epithelial cells
4.4	Yusuf et al.	2017	Bifidobacterium	Acetate, propionate and butyrate acids	Bifidobacterium disappeared and the concentrations of SCFAs (acetate, propionate and butyrate acids) were lower in stool samples from CRC patients	Altered profile of gut microbiome and the level short chain fatty acids in colorectal cancer patients
4.5	Yang et al.	2017	Ruminococcus	Butyrate	Butyrate producers (Ruminococcus) reduced the increased risk of CRC in Korean population	Fecal microbiota differences according to the risk of advanced colorectal neoplasms
4.6	Han et al.	2017	–	Butyrate	Butyrate regulated SCAD (short chain acyl-CoA dehydrogenase) by inhibiting histone deacetylases (HDACs) in CRC cells	"Butyrate regulates its own metabolic fate as an HDAC inhibitor in colorectal cancer cells
4.7	Zeng et al.	2016	–	Butyrate	Butyrate led to apoptosis, histone deacetylation, genomic DNA fragmentation and p21 tumour suppressor expression in CRC cells, while butyrate increased the phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) in non-cancerous colon cells	Butyrate plays differential roles in cellular signaling in cancerous HCT116 and noncancerous NCM460 colon cells

Table 4 (continued)

No.	Authors	Year	Microorganism	SCFAs	Results	Titles
4.8	Seidel et al.	2016	–	Acetate, isobutyrate, isovalerate and valerate	Dried plums decreased the faecal SCFAs (acetate, isobutyrate, isovalerate and valerate) concentrations and inhibited inducible nitric oxide synthase (iNOS) expression to regress early colon cancer lesions	Dried plums modify fecal short chain fatty acid concentrations and gene expression in a rat model of colon carcinogenesis
4.9	Manini et al.	2016	–	Butyrate	Fermented bran increased the production of butyrate	Wheat bran sourdough-like fermented: A potential source of prebiotics and probiotics
4.10	Golovko et al.	2016	Blautia, Ruminococcus, Roseburia, Faecalibacterium and Bifidobacterium spp Collinsella spp.	Acetate, propionate, butyrate	The levels of SCFA-producing microbiota at the tumour site were decreased compared to those of the adjacent normal tissue	Changes in the microbiota at the crc tumor site contributes to metabolic diversity which favors inflammation
4.11	Fedorak et al.	2016	Lachnospiraceae	Butyrate	A high-sugar diet increased the risk of CRC through enhancing inflammation, which was associated with decreased levels of butyrate producers within *Lachnospiraceae*	High sugar diets promote an inflammatory microbiota and reduce gene expression related to intestinal barrier function
4.12	Zeng et al.	2015	–	Butyrate	Butyrate increased p21 (tumour suppressor gene) expression in the cell cycle and apoptosis pathways	Butyrate and deoxycholic acid play common and distinct roles in HCT116 human colon cell proliferation
4.13	Woods et al.	2015	–	Acetate, propionate and butyrate	High intensity running increased the levels of potentially beneficial acetate, propionate, and butyrate	Exercise alters the gut microbiome and microbial metabolites: Implications for colorectal cancer and inflammatory bowel disease
4.14	Vipperla et al.	2014	–	Butyrate	A low-meat and -fat and high-fibre 'traditional African' diet increased the expression of functional microbial genes encoding butyrate in association with a reduction in the CRC risk	A 14-day in-house dietary modification of a 'Western' diet to an 'African' diet changes the microbiota, its metabolome, and biomarkers of colon cancer risk
4.15	Goncalves et al.	2014	–	Butyrate	Butyrates reduced the 18F-FDG uptake, increased glycolysis to interfere with the Warburg effect and suppressed CRC cells	Is 18F-FDG uptake in three different colon cancer cell lines affected by incubation with sodium butyrate?
4.16	Goncalves et al.	2014	–	Butyrate	Butyrate interfered with the Warburg effect and suppressed CRC cells	May butyrate interfere with Warburg effect in colon cancer cells?
4.17	Ahmed et al.	2014	–	Butyrate	*Clostridium cluster* XIVa, which can produce butyrate close to the epithelium, increased in response to radiation injury	Clostridium cluster XIVa species an early biomarker in radiation injury

Table 4 (continued)

No.	Authors	Year	Microorganism	SCFAs	Results	Titles
4.18	Hu et al.	2014	–	Butyrate	Butyrate modulated the transcription of microRNAs 92A and 222, p57 expression and the cell cycle to prevent CRC	Butyrate modulates microrna 92A and 222 transcription, p57 expression and the cell cycle in human colon cancer cells
4.19	Weir et al.	2013	–	Butyrate	Faecal butyrate concentrations and butyrate-producing species numbers were lower in CRC samples	Fecal metabolome and microflora differences between colorectal cancer patients and healthy adults
4.20	Ou et al.	2012	–	SCFAs	Major SCFA stool concentrations were significantly ($p < 0.05$) higher in rural South Africans (BMIs > 30 kg/m^2)	Obesity and colon cancer risk: Is it the fat?
4.21	O'Keefe et al.	2012	–	Butyrate	Compared with those of native Africans, faecal butyrate concentrations were lower in African Americans who have the highest risk of developing and dying from CRC	Can dietary modulation of the microbiota lower colon cancer risk in African Americans?
4.22	Carbonero et al.	2012	–	Butyrate	Increased butyrate levels in Zulu Africans play anti-inflammatory roles and reduce mucosal proliferation to reduce susceptibility to CRC	Traditional african and western diets select distinct phylogenetic and functional colonic microbiota among different populations
4.23	Ohara et al.	2012	–	SCFAs	The intake of the probiotics *Bifidobacterium longum* (BB536) and fructo-oligosaccharide increased the total amount of SCFAs and suppressed the production of putrefactive bacteria and *Bacteroides flagilis* enterotoxin to prevent CRC	Intake of BB536 and fructo-oligosaccharide may prevent colorectal carcinogenesis
4.24	Ohara et al.	2010	–	Isobutyric acid	The intake of *Lactobacillus gasseri* OLL2716: LG21 suppressed the production of faecal putrefactive bacteria and increased the production of isobutyric acid and the activity of NK cells	Probiotics may prevent the onset of colorectal cancer
4.25	Clarke et al.	2009	–	Butyrate	Butyrate reduced the risk of CRC by protecting from carcinogen-induced genetic damage and increasing the rate of apoptotic clearance of damaged cells	Butyrate provides dose-related reduction in colorectal cancer risk in genotoxin-treated rats

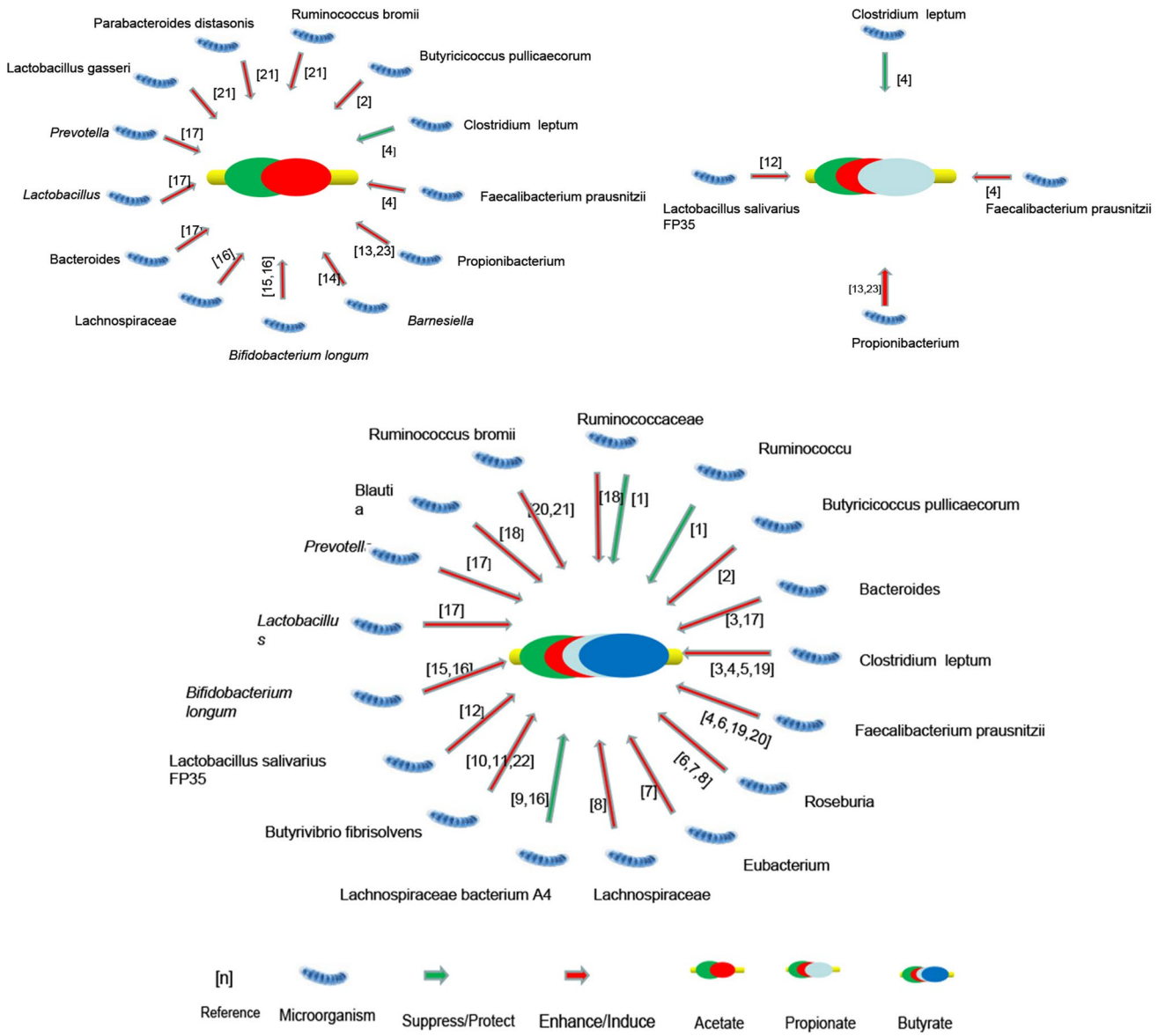

Fig. 3 Interaction between microorganisms and SCFAs in CRC. Microorganisms that changed the levels of SCFAs, including acetate, propionate and butyrate, are shown in a circular pattern with further refining by the related content in the literature. Relevant references are included in Supplement 2

the risk of CRC. An increase in the sample size and application of a meta-analysis will contribute to clarify the truth.

We proposed three aspects including epigenetics, immunology and molecular signalling pathways for the mechanistic study of SCFA-induced CRC through the screening, summary and analysis of the previous literature. Epigenetics, immunology and molecular signalling pathways were interrelated with each other. There are studies finding that *Lachnospiraceae*, a family of digestive tract-associated bacteria, can produce butyrate and possess genes for endospore formation. Butyrate production-related genes were detected in CRC (Meehan and Beiko 2014). Such evidence suggests that lateral gene transfer (LGT) may provide a bridge for the intraluminal butyrate and mucosal mutation. In future research, we should start from these three aspects and conduct in-depth studies. The entire molecular network should be assessed by linking the three directions based on previous research.

Irinotecan is a first-line treatment for advanced colorectal cancer that induces adverse effects with serious life-threatening toxicities in CRC. The toxic and side effects of chemotherapy drugs are always a thorny clinical problem in the treatment of CRC. Increasing the levels of SCFAs used to reduce chemotherapy drug side effects may open another

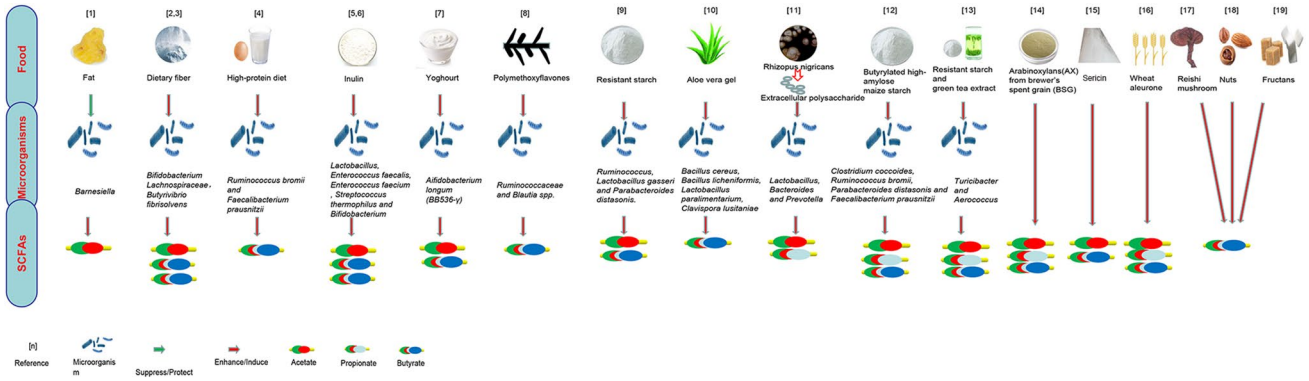

Fig. 4 Food-microorganisms-SCFAs axis in CRC. Pertinent literature have been further analysed to elucidate the food-microorganisms-SCFAs axis. The framework of the food-microorganisms-SCFAs axis in CRC has been preliminarily established. Relevant references are included in Supplement 3

window for providing solutions to this clinical problem. If the clinical application of dietary management is used to increase the efficacy and reduce the side effects of chemotherapy, then it will bring many benefits, including reducing medical expenses, increasing treatment compliance and improving the quality of life of CRC patients.

As a probiotic, *Lactobacillus* cannot produce SCFAs by itself, but it can change the community structure and diversity of the intestinal microbiome to increase the levels of SCFAs (Ni et al. 2017; Hibberd et al. 2017). Infant faecal transplantation, which transfers material rich in *Lactobacillus*, will provide novel ideas for the prevention and treatment of CRC. This approach is more beneficial than mere supplementation with *Lactobacillus* (Thirabunyanon and Hongwittayakorn 2013). The study of microbiology and the elucidation of microbial interactions will contribute to increasing the efficacy and controlling the risks of stool transplantation.

The unusual observation that butyrate can stimulate the proliferation of normal host cells but inhibit the proliferation and induce apoptosis in CRC cells has emerged in the literature; it is called the "butyrate paradox" (Vakhitov et al. 2016). The energy metabolism of cancer cells is different from that of normal tissue cells. The Warburg effect is defined as cancer cells that can consume many glucose molecules but cannot produce energy efficiently. Many studies have shown that butyrate can interfere with the Warburg effect and suppress CRC cells (Sebastian and Mostoslavsky 2014). The Warburg effect may provide theoretical support for the explanation of this phenomenon. However, there is not enough evidence to support this conclusion at this point.

There are some limitations in the present study. Most studies have focused on butyrate, and there are relatively few studies on acetate and propionate. Due to the differences in the understanding of the original articles and the need for visualization with a figure, some research route diagrams may not be completely consistent with the original intention of the authors. Some literature may still be missed despite keywords plus free words being used to search multiple databases as comprehensively as possible.

Conclusion

Changing dietary habits to prevent CRC is a long-term process. Clarifying the "food-microorganisms-metabolites" axis is of great significance since it could change the diet of the population and prevent the occurrence of CRC. The "food-microorganisms-SCFAs" axis, as a constituent part of the "food-microorganisms-metabolites" axis, plays a positive role in the prevention and treatment of CRC. This study provides insight into the basic research and practical application of SCFAs by assessing the protective effect of SCFAs on CRC.

Acknowledgements This work was supported by the Science Technology Projects of Zhejiang Province (No. 2017C33207), Zhejiang Medical and Health Technology Projects (2019RC283) and Huzhou Public Welfare Technology Application Research Program (2018GY21). The studies that did not involve molecular experiments were analysed to clarify the correlation between SCFAs and CRC and are presented in this table. Most studies showed that the concentrations of SCFAs in CRC patients and individuals with a high risk of CRC were higher than those in healthy individuals. Seven pertinent studies (Panel Nos. 1.3, 1.4, 1.5, 1.8, 1.13, 1.14 and 1.15) that showed a correlation between SCFAs and microorganisms in CRC are also listed in this table. Many studies have been conducted on the molecular mechanisms of SCFA-induced colorectal cancer. A total of 31 articles assessing the molecular mechanisms of SCFA-induced colorectal cancer were included and analysed after identification and screening. As shown in this table, most studies were on butyrate, and the CRC cell model was used as the research subject. The experimental results of SCFAs in different studies are summarized in the results column. Many food and plant extracts fermented by microorganisms can produce SCFAs that play positive roles in the preventive and therapeutic effects on CRC. Pertinent literature assessing the medicines and foods digested by microorganisms to produce SCFAs in CRC have been summarized. Many

conference abstracts assessing the SCFAs produced by microorganisms in CRC have been published. A total of 25 abstracts were included in the table after identification and screening according to the inclusion and exclusion criteria.

Author contributions All authors participated in the conception and design of the study. HS and WW conceived of the study. HS and YX wrote the manuscript. DM and YX designed and drawn the network. HS, QQ, ZZ and ZJ reviewed and sorted out the literature. All authors read and approved the paper.

Funding This work was supported by the Science Technology Projects of Zhejiang Province (No. 2017C33207), Zhejiang Medical and Health Technology Projects (2019RC283) and Huzhou Public Welfare Technology Application Research Program (2018GY21).

Compliance with ethical standards

Conflict of interest No potential conflict of interest relevant to this article was reported.

Human and animal rights statement This article does not contain any studies with human participants performed by any of the authors.

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