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Research progress on cancer-promoting mechanisms of high-fat diet

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ABSTRACT: Cancer is the leading cause of death in China and many other countries. In addition to individual lifestyle choices, environmental factors and pathogenic infection, unhealthy dietary pattern, particularly high-fat diet (HFD), has been implicated in the pathogenesis of cancer. Recent studies have demonstrated that HFD can initiate carcinogenesis by promoting intestinal microbial dysbiosis, inducing chronic inflammation, reprogramming metabolic pathways, and impairing anti-cancer immunity. These HFD-induced alterations contribute to angiogenesis, cancer cell growth, proliferation, metastasis, and invasion. This study summarizes the current knowledge on how HFD promotes the initiation and progression of cancer. This review provides new ideas for the prevention and/or alleviation of cancer, and the development of functional foods.

Keywords: high-fat diet; cancer; intestinal microbial dysbiosis; inflammation; anti-cancer immunity

1. Introduction

With the changes of people's lifestyle and cooking methods, an increasing number of individuals like unhealthy dietary patterns, particularly high-fat diet (HFD). However, long-term intake of HFD is associated with the increased incidence of various cancers [1-3]. Accumulating evidence has showed that gut microbial dysbiosis is a key factor to induce obesity-associated carcinogenesis [4-6]. Meanwhile, other studies have reported that HFD-induced intestinal carcinogenesis is caused by gut microbial dysbiosis independently of obesity [7]. These findings confirm that intestinal microbial dysbiosis are involved in HFD-induced diseases. In addition to intestinal microbial dysbiosis, many studies have revealed that HFD-induced inflammation, defective anti-cancer immunity and metabolic reprogramming contribute to tumor formation by promoting angiogenesis, cancer cell growth, proliferation, metastasis, and invasion [8-14]. Therefore, it is essential to explore the mechanisms by which HFD facilitates tumorigenesis. This article summarizes the tumor-promoting mechanisms of HFD from the perspectives of gut microbial dysbiosis, inflammation, defective anti-tumor immunity and metabolic reprogramming (Fig. 1).

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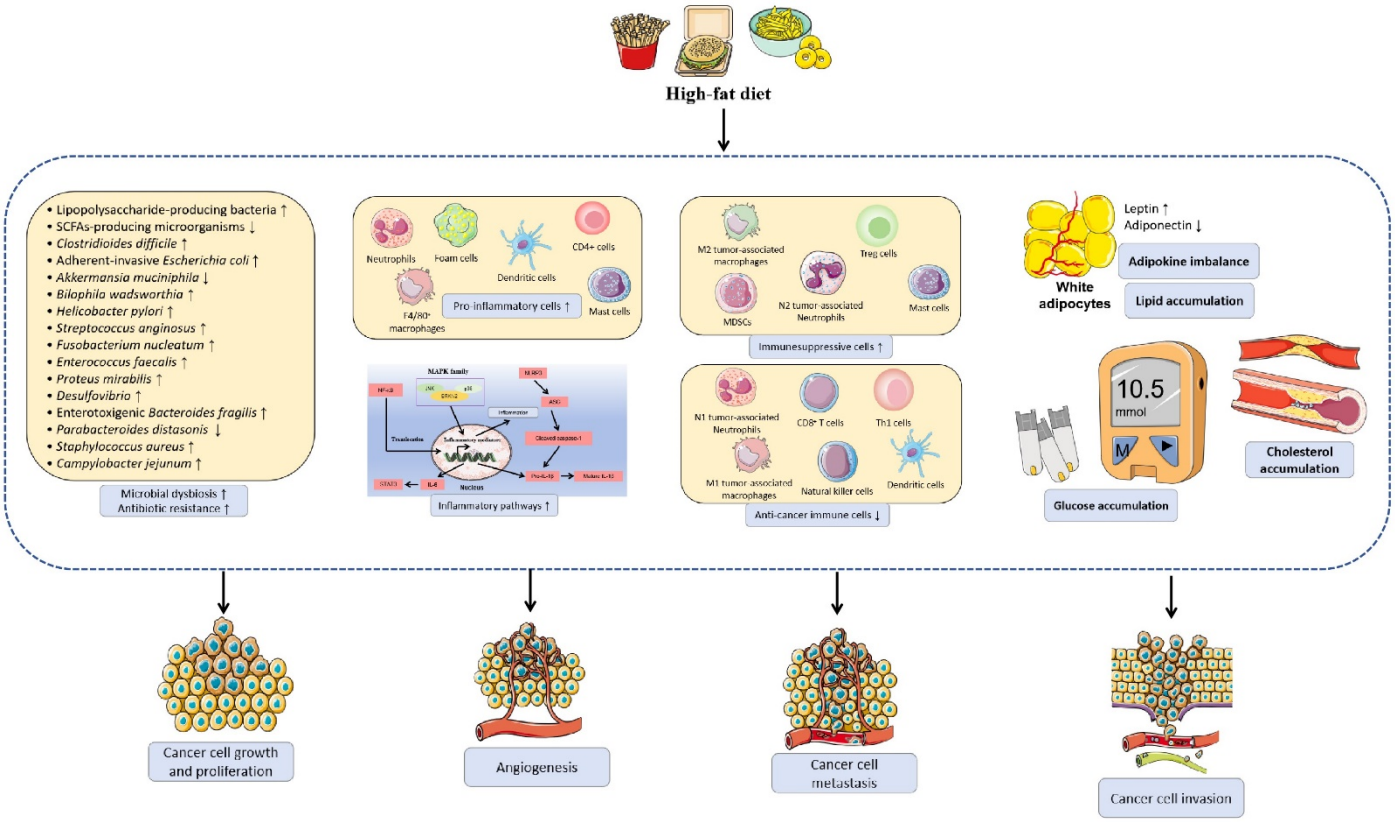

Fig. 1 The tumor-promoting mechanisms of high-fat diet (HFD). HFD promotes angiogenesis, cancer cell growth, proliferation, metastasis and invasion by inducing microbial dysbiosis and inflammation, suppressing anti-cancer immunity and reprograming metabolism.

2. Relationships between HFD and carcinogenesis

In nature, lipids can be classified into three types: unsaturated fats, trans fats and saturated fats [15]. Usually, unsaturated fat is beneficial to human health. However, long-term excessive intake of trans fats and saturated fats easily triggers the pathogenesis of metabolic diseases [16]. HFD (mainly refers to high-saturated fat diet) also contributes to intestinal microbial dysbiosis, inflammation, defective anti-tumor immunity, oxidative stress, endoplasmic reticulum stress and metabolic reprograming [7, 9, 14, 15, 17, 18], all of which are involved in the initiation and progression of cancer. Many findings have revealed that HFD or HFD-induced metabolic diseases increases the incidence of carcinogenesis, including liver cancer [19], lung cancer [20-21], pancreatic cancer [22-23], breast cancer [24], gastric cancer [25], prostate cancer [26-28] and intestinal cancer [7, 11, 12, 29-30]. Furthermore, HFD-induced progression of pancreatic cancer and breast cancer can be alleviated by dietary caloric restriction diet or low-fat diet [31-32], indicating that HFD is a contributing factor to induce the development of tumor formation.

HFD promotes the proliferation and migration of prostate cancer cells, and also stimulates angiogenesis, a process that provides sufficient nutrients and oxygen for cancer cells [33]. Accumulating evidence has suggested that HFD exacerbates the development of cancer by activating nuclear factor-κB (NF-κB) [34], phosphoinositide 3-kinase (PI3K)/Akt [35], mitogen-activated protein kinase (MAPK) [35], Janus kinase/signaling transducer and activator of transcription (JAK/STAT) [36], transforming growth factor-β (TGF-β) [37], Wnt/β-catenin [24] and Leptin/Notch signaling pathways [38]. Both *in vitro* and *in vivo* experiments

have revealed that HFD blocks ferroptotic and apoptotic signaling pathways to protect cancer cells against abnormal cell death [22, 39]. The carcinogenesis-promoting signaling pathways activated by HFD are shown in Fig. 2.

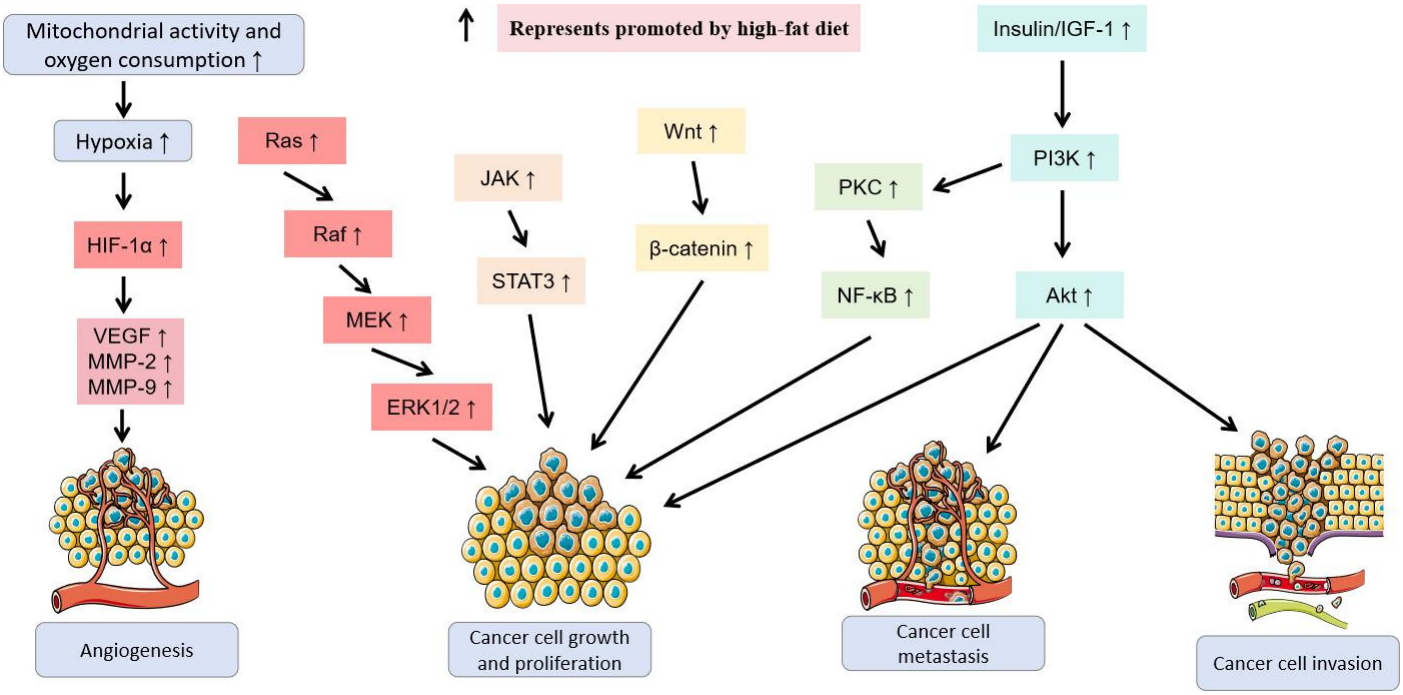

Fig. 2 The potential HFD-mediated pro-carcinogenic pathways. At the molecular level, HFD promotes the initiation and development of cancer by upregulating the expression of VEGF, MMP-2 and MMP-9, and activating Ras/Raf/MEK/ERK, JAK/STAT3, Wnt/β-catenin, PI3K/Akt and PI3K/PKC/NF-κB signaling pathways.

3. HFD induces carcinogenesis by modulating gut microbiota and their metabolites

Many studies have indicated that diet obviously regulates gut microbiota composition and microbial metabolites, and further affects host health [40]. A 6-month randomized and controlled-feeding trial discovers that HFD changes intestinal microbial composition, increases the production of metabolites *p*-cresol and indole, and also enriches biosynthetic pathways involved in arachidonic acid and lipopolysaccharide, which subsequently creates a chronic inflammatory environment [41]. Meanwhile, another report has revealed that HFD-induced gut microbial dysbiosis promotes intestinal tumor formation in the *K-ras*-mutated mice independently of obesity [7]. This investigation also discovers that the fecal microbiota from HFD-fed mice with intestinal cancer is enough to induce intestinal carcinogenesis in the healthy *K-ras*-mutated mice fed with low-fat diet, while the use of antibiotics completely suppresses HFD-induced tumor formation [7]. Although antibiotics have the abilities to kill several pathogens in the gastrointestinal tract, HFD promotes the amplification and transfer of antibiotic resistance genes among microbes [42-43], and subsequently increases the antibiotic tolerance of intestinal pathogens [44]. More seriously, HFD and antibiotics cooperatively impair intestinal barrier and cause gut inflammation by inducing serious oxidative stress, endoplasmic reticulum stress, abnormal apoptosis and mitochondrial dysfunction [45-46]. These results highlight the notion that HFD promotes the proliferation of pathogens and reduces the relative abundance of symbiotic microorganisms in the gut, resulting in intestinal microbial dysbiosis and alterations in microbial metabolites and metabolic pathways (Table 1).

Table 1 Effects of HFD on the gut microbiota and their metabolites

Table 1 Effects of HFD on the gut microbiota and their metabolites			
Experimental models	**Duration of intervention**	**Key findings**	**References**
HFD-fed healthy young adult people	6 months	Increased the relative abundance of *Alistipes*, *Bacteroides* and bile salt hydrolases-expressing bacteria in the gut. Decreased *Faecalibacterium* level in the gut. Decreased the concentration of total short-chain fatty acids (SCFAs) and butyrate. Increased the concentration of secondary bile acids, including deoxycholic acid and taurodeoxycholic acid. Promoted microbial lipopolysaccharide biosynthesis and arachidonic acid metabolism.	[41]
HFD-fed mice	8 weeks	Increased the relative abundance of *Lactococcus*, *Ruminococcus*, *Escherichia*, *Helicobacter* and *Streptococcus* in the gut. Decreased the concentration of methylpentanoic acid, imidazoleacetic acid, 3-ureldopropionic acid and γ-aminobutyric acid.	[43]
HFD-fed *K-ras*^{G12Dint} mice	24 weeks	Increased the relative abundance of *Helicobacteraceae*, *Lactobacillaceae*, *Enterobacteriaceae*, *Clostridiaceae* and *Peptostreptococcaceae* in the small intestine. Decreased the relative abundance of *Bifidobacteriaceae*, *Porphyromonadaceae* and *Alcaligenaceae* in the small intestine. Increased the relative abundance of *Enterobacteriaceae*, *Desulfovibrionaceae*, *Porphyromonadaceae*, *Rikenellaceae*, *Ruminococcaceae*, *Lachnospiraceae*, *Coriobacteriaceae* and *Deferribacteraceae* in the colon. Decreased the relative abundance of *Bifidobacteriaceae*, *Peptostreptococcaceae*, *Roseburia* and *Butyricicoccus* in the colon.	[4]
High-fat high-cholesterol diet-fed mice	14 months	Increased the relative abundance of *Mucispirillum*, *Desulfovibrio*, *Anaerotruncus* and *Desulfovibrionaceae* in the intestine. Decreased the relative abundance of *Bifidobacterium* and *Bacteroides* in the intestine. Increased the production of gut bacterial metabolite taurocholic acid. Decreased the production of gut bacterial metabolite 3-indolepropionic acid.	[19]
HFD-fed rats	4 weeks	Increased the activities of tumorigenic bacterial *β*-glucuronidase and mucinase in the gut. Increased the concentration of total bile acids. Decreased the concentration of total short-chain fatty acids.	[47]
HFD-fed APC$^{min/+}$ mice	10 weeks	Changed the composition of primary and secondary bile acids. Increased the concentration of tauro-β-muricholic acid and deoxycholic acid.	[17]
HFD-fed rats	8 weeks	Increased the relative abundance of *Helicobacter*, *Ruminococcus*, *Desulfibrionales*, *Oscillibacter* and *Olsenella* in the colon.	[59]
HFD-fed azoxymethane-treated *Apc*$^{min/+}$ mice	22 weeks	Increased the relative abundance of pathogenic bacteria *Alistipes sp. Marseille-P5997* and *Alistipes sp. 5CPEGH6* in the colon. Decreased the relative abundance of probiotic *Parabacteroides distasonis* in the colon. Decreased the concentration of anti-cancer molecule nordihydroguaiaretic acid. Increased the concentration of pro-tumorigenic metabolites	[30]

		lysophosphatidic acid and lysophosphatidylcholine.	
HFD-fed mice	8 weeks	Increased the ratio of *Firmicutes* to *Bacteroidetes*. Decreased the relative abundance of SCFAs-producing bacteria. Decreased the concentration of SCFAs.	[180]
HFD-fed mice	7 weeks	Increased the relative abundance of *Incertae sedis*, *Allobaculum*, *Helicobacter*, *Dorea*, *Intestinimonas*, *Bilophila*, *Anaerotruncus*, *Roseburia*, *Oscillibacter*, and *Desulfovibrio*. Decreased the relative abundance of *Bacteroides*, *Blautia*, *Odoribacter*, *Parabacteroides* and *Coprococcus*.	[181]
HFD-fed mice	8 weeks	Increased the relative abundance of *Proteobacteria*. Decreased the relative abundance of *Actinobacteria*.	[182]
HFD-fed rats	6 weeks	Decreased the concentration of SCFAs. Increased the concentration of succinic acid.	[183]
HFD-fed mice	Nm	Enhanced *Escherichia coli* choline catabolism.	[184]
HFD-fed mice	14 weeks	Increased gut microbial diversity. Increased the relative abundance of *Desulfovibrionaceae*, *Rikenellaceae* RC9 gut group and *Mucispirillum*. Decreased the relative abundance of *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Faecalibaculum* and *Blautia*.	[185]
HFD-fed rats	16 weeks	Decreased the relative abundance of *Lactobacillus intestinalis* in the gut. Increased the relative abundance of *Blautia producta*, *Phascolarctobacterium*, *Bacteroides vulgatus*, *Bacteroides fragilis*, *Parabacteroides distasonis*, *Morganella morganii* and *Bilophila wadsworthia* in the gut.	[186]
HFD-fed mice	10 weeks	Increased the *Firmicutes* and *Bacteroidetes* ratio in the gut. Increased the relative abundance of *Lachnoclostridium*, *Coriobacteriaceae*, *Desulfovibrionaceae*, and *Helicobacter* in the gut.	[187]
HFD-fed rats	4 weeks	Increased the relative abundance of *Clostridiaceae*, *Enterobacteriaceae*, and *Helicobacteriacea* in the intestine.	[188]

3.1 HFD-induced intestinal microbial dysbiosis is involved in cancer initiation

The high-throughput sequencing technologies, metabolomics and bacterial culture also reveal that several specific bacterial strains and microbial metabolites are involved in the initiation and/or progression of tumorigenesis (Table 2). In the colon, HFD promotes gut microorganisms to produce β-glucuronidase and mucinase rather than carbohydrate-degrading enzymes [47]. As reported, β-glucuronidase enzymatically converts pro-carcinogen into carcinogen, while mucinase hydrolyzes mucus layer and further exposes intestinal cells to carcinogens. As known, *Helicobacter pylori* can induce the pathogenesis of gastric cancer. *H. pylori*-derived outer membrane proteins and toxin proteins CagA and VacA promote tumor formation by causing inflammation and DNA damage [48-49]. Moreover, *H. pylori* also promotes the proliferation of *Proteobacteria*, *Spirochetes* and *Acidobacteria*, forming a pro-tumorigenic micro-environment [50]. Recently, Fu et al. (2024) has identified pro-carcinogenic *Streptococcus anginosus*, a pathogenic strain that is abundant in the gastric mucosa of patients with gastric cancer. The interaction of *S. anginosus* surface protein (TMPC) with Annexin A2 (ANXA2) receptor on the gastric epithelial cells is essential for *S. anginosus* to induce gastric inflammation and cell proliferation and block apoptosis, which further contributes to gastric carcinogenesis [51]. On the atrophic gastric mucosa, lactic acid bacteria promote the proliferation of other pro-tumorigenic microorganisms, such as *Veillonella*, *Fusobacterium* and *Leptotrichia* [54]. Metagenomic

analysis shows that the relative abundance of *Fusobacterium nucleatum*, *Peptostreptococcus stomatis*, *Parvimonas micra* and *Solobacterium moorei* is positively associated with the incidence of colorectal cancer [55]. Similarly, collagenase-producing bacteria *Enterococcus faecalis* and *Proteus mirabilis*, enriched by HFD, also increase the occurrence of colorectal cancer [56]. The *Fusobacterium* adhesin A produced by *F. nucleatum* upregulates Annexin A1 expression and activates β-catenin pathway, thereby enhancing colorectal cancer cell proliferation [60]. Moreover, *F. nucleatum* mediates the metastasis of colorectal cancer cells [61]. As reported, colibactin-producing *Escherichia coli*, toxin-producing enterotoxigenic *Bacteroides fragilis* and cytolethal distending toxin-producing *Campylobacter jejuni* promote DNA mutation and further contribute to colorectal tumor formation [62-64]. HFD-fed mice also have higher relative abundance of pathogenic microbes *Alistipes sp. Marseill-P5997* and *Alistipes sp. 5CPEGH6*, and lower proportion of probiotic bacterium *Parabacteroides distasonis* in the gut. The use of antibiotics and fecal microbiota transplantation reveals that this HFD-induced alteration in intestinal microbiota composition is essential to cause intestinal carcinogenesis [30]. Both human investigation and animal experiments elucidate that the relative abundance of *Alistipes* is positively associated with the occurrence rate of colorectal cancer [65-66]. On the contrary, *P. distasonis* suppresses colonic cancer cell proliferation by deactivating Toll-like receptor (TLR)-4 and Akt signaling pathways [67]. The HFD-induced shift in intestinal microorganisms also changes microbial metabolites, including nordihydroguaiaretic acid, nervonic acid and lysophosphatidic acid [30]. The pro-oncogenic lysophosphatidic acid can enhance the cell growth and proliferation of colorectal cancer cells and pancreatic cancer cells [30, 68]. By contrast, nordihydroguaiaretic acid and nervonic acid block cancer cell proliferation and colony formation, thereby exerting their anti-cancer effects [30].

Table 2 Regulatory effects of gut microbiota and their metabolites on the initiation and progression of carcinogenesis

Intestinal microbiota or metabolites	Key findings	References
Fusobacterium nucleatum	Contributed to aggressive tumor behavior in the esophageal tissues.	[189] [190]
	Reduced the cytotoxicity of NK cells and T cells against tumor cells.	[61]
	Activated TLR-4/NF-κB signaling pathway in the colorectal cancer cells.	
	Increased the expression of anoctamin-1 in the colorectal cells and blocked apoptosis.	
	Promoted the metastasis of colorectal cells by activating autophagy.	
Lactic acid bacteria	Promoted the colonization of other carcinogenic microorganisms on the atrophic gastric mucosa, including *Veillonella*, *Prevotella*, *Fusobacterium* and *Leptotrichia*.	[54]
Enterococcus faecalis* and *Escherichia coli	Decreased the proportion of $CD206^+$ M2-like tumor-associated macrophages, $CD4^+$ T cell and $CD8^+$ T cells.	[132]
	Promoted the growth of pancreatic cancer cells and caused innate and adaptive immunosuppression.	
Colibactin-producing *E. coli*	Induced DNA damage.	[62]
	Damaged DNA repair system.	[191]
	Promoted the occurrence and development of colorectal cancer *via* MAPK signaling pathway.	[192]
	Increased the expression of proliferative nuclear antigen in the epithelial cells.	

Campylobacter jejuni	Increased the occurrence of colorectal cancer by activating cytolethal distending toxin B gene.	[64]
Bilophila wadsworthia	Aggravated HFD-induced inflammation, intestinal barrier dysfunction and bile acid dysmetabolism, forming a pro-tumorigenic micro-environment.	[69]
Malassezia spp.	Activated complement pathway and C5a recruited myeloid-derived suppressor cells (MDSCs) into tumors.	[193]
Parabacteroides distasonis	Suppressed colorectal cancer by blocking TLR-4 and Akt signaling pathways.	[67]
Desulfovibrio spp.	The relative abundance of *Desulfovibrio spp*. was positively associated with colorectal cancer. Formed a pro-tumorigenic micro-environment by inducing intestinal barrier dysfunction and inflammation.	[59]
Alistipes sp. Marseille-P5997 **and** ***Alistipes sp. 5CPEGH6***	The relative abundance of *Alistipes sp. Marseille-P5997* and *Alistipes sp. 5CPEGH6* was positively associated with colorectal cancer.	[65] [30]
Alistipes finegoldii	Induced colorectal tumor formation *via* IL-6/STAT3 pathway.	[194]
Streptococcus anginosus	Disrupted gastric barrier function. Promoted cell proliferation. Inhibited apoptosis. Induced progressive chronic gastritis, parietal cell atrophy, mucinous metaplasia, and dysplasia.	[51]
Enterotoxigenic ***Bacteroides fragilis***	Degraded colonic mucus. Promoted the adhesion of *E. coli* and colibactin-induced DNA damage to colonic epithelial cells.	[195]
β-glucuronidase	Hydrolyzed pro-carcinogen into carcinogen.	[47]
Mucinase	Hydrolyzed the protective mucin coat in the intestinal wall and exposed the underlying colonocytes to the luminal carcinogens.	[196]
Helicobacter pylori **toxin protein CagA**	Activated NF-κB signaling pathway and caused DNA damage.	[48] [49]
Lactic acid	Provided energy for cancer cells. Promoted inflammation, angiogenesis, metastasis and epithelial-mesenchymal transition. Enhanced intestinal stem cell stemness and proliferation.	[52] [197]
Lipopolysaccharide	Blocked p53 pathway and enhanced DNA-damaged cell survival *via* IL-6-activated JAK-STAT3 pathway and IL-1β-activated PI3K pathway. Promoted the proliferation and migration of gastric cancer cells through the TLR4/MD-2 signaling pathway.	[198] [115] [199]
N**-nitroso compounds**	Promoted mutation and angiogenesis. Upregulated proto-oncogene expression. Inhibited apoptosis.	[53]
Fusobacterium **adhesin A**	Promoted colorectal cancer cell proliferation by activating β-catenin pathway.	[60]
Bacteroides fragilis **toxin**	Combined with extracellular IL-17 to activate NF-κB signaling pathway and recruit immunosuppressive myeloid-derived suppressor cells.	[63] [132]
Flagellin	Increased the production of IL-6 and other chemokines by colorectal cancer cells.	[200]
Hydrogen sulfide	Promoted the proliferation, anti-apoptosis, angiogenesis and migration of esophageal cancer cells. Promoted gastric cancer cell metastasis by upregulated CD36 expression and reprogramming lipid metabolism.	[58] [201]
Fibroblast activation protein 2 of ***F. nucleatum***	Decreased the proportion of $CD3^+$ T cells and $CD4^+$ T cells. Increased immunosuppressive M2-like tumor-associated macrophages. Enhanced immune evasion of pancreatic cancer cells.	[134]
Tryptophan-associated metabolites	Activated AhR transcription factor and repaired DNA damage and inhibited cellular proliferation by inhibiting the Wnt pathway.	[202]

Reuterin	Protected against colorectal cancer cells by increasing protein oxidation, decreasing ribosome biogenesis and decreasing protein translation.	[203]
***S. anginosus* surface protein**	Interacted with Annexin A2 receptor on the gastric epithelial cells to promote the colonization of *S. anginosus* and activate MAPK pathway.	[51]
Nordihydroguaiaretic acid	Inhibited colorectal cancer cell growth and colony formation. Inhibited lung carcinogenesis and non–small-cell lung cancer growth.	[30] [204]
Nervonic acid	Inhibited colorectal cancer cell growth and colony formation.	[30]
Lysophosphatidic acid	Interacted with autotaxin to promote pancreatic ductal adenocarcinoma cell proliferation.	[68]
Butyrate	Normalized dendritic cell recruitment in the gut-associated lymphoid tissues. Alleviated intestinal tumor progression.	[4]
Isobutyric acid and isovaleric acid	Their concentration was positively associated with the occurrence of benign prostatic hyperplasia.	[90]
Short-chain fatty acids	Induce the development of prostate tumor formation via IGF-1 pathway. Created a tumor-promoting micro-environment for hepatocellular carcinoma	[91] [92]
Deoxycholic acid	Induced mutations in anti-tumorigenic genes. Promoted intestinal cancer cell invasiveness *via* NF-κB signaling pathway. Antagonized FXR to promote the proliferation and DNA mutations of $LGR5^+$ intestinal cancer stem cells. Maintained the survival, proliferation and development of tumor cells by activating Ras/Raf/MAPK/ERK, PI3K/Akt and Wnt/β-catenin signaling pathways.	[73] [75] [17] [78] [79] [80]
Lithocholic acid	Damaged gene structures and DNA repair enzymes. Increased the invasiveness of colorectal cancer cells.	[74] [81]
Ursodeoxycholic acid	Upregulated the expression of Bax and Caspase-3, and downregulated epidermal growth factor receptor expression.	[70]
Bile acids	Upregulated the expression levels of genes encoding virulence and infection *via* type III secretion system. Increased the expression of *Campylobacter jejunum* virulence- and colonization-associated genes. Activated the spore germination of *Clostridium difficile*. Upregulated the expression of flagella and adhesion proteins on the membrane of pathogenic *E. coli*.	[84] [85] [86] [87] [88]

HFD also changes the composition of bile acids and increases the relative abundance of secondary bile acid-producing bacteria, resulting in bile acid dysmetabolism [17, 69, 70]. Accumulating evidence has suggested that HFD-induced bile acid dysmetabolism participates in tumor formation [17, 70, 71]. In the intestinal lumen, liver-synthesized primary bile acids are enzymatically hydrolyzed into secondary bile acids *via* gut microbiota-mediated 7α-dehydroxylation [72]. The common secondary bile acids mainly include deoxycholic acid, ursodeoxycholic acid and lithocholic acid. Higher levels of these bile acids contribute to the initiation, progression and metastasis of colorectal cancer cells [70]. Firstly, deoxycholic acid-mediated oxidative stress causes DNA damage and gene mutations. For example, deoxycholic acid induces mutations in anti-tumorigenic genes, including *p53* and *APC*, leading to the onset of tumorigenesis [73]. Similarly, higher level of lithocholic acid damages gene structures and DNA repair enzymes [74]. Deoxycholic acid promotes intestinal cancer cell invasiveness *via* NF-κB signaling pathway [75]. As an endogenic ligand of farnesoid X receptor (FXR) [76], antagonized FXR by tauro-β-muricholic acid and deoxycholic acid also promotes the

proliferation and DNA mutations of leucine-rich repeat containing G protein-coupled receptor 5 $(LGR5)^+$ intestinal cancer stem cells [17], one type of intestinal stem cells that are the cell origin of colorectal cancer cells [77]. Deoxycholic acid also maintains the survival and proliferation of tumor cells by activating Ras/Raf/MAPK/ERK, PI3K/Akt and Wnt/β-catenin signaling pathways [78-80]. On the contrary, ursodeoxycholic acid exerts anti-cancer effects by upregulating the expression of Bax and Caspase-3, and downregulating epidermal growth factor receptor (EGFR) expression [70].

In addition, several bacteria, like *Lactobacillus spp*., can hydrolyze tryptophan into indole-3-aldehyde [72, 82]. As a ligand of aryl hydrocarbon receptor (AhR), microbiota-derived indole-3-aldehyde activates AhR on the intestinal cell membrane, and subsequently inhibits the cell proliferation and self-renewal of intestinal stem cells by inactivating Wnt signaling pathway [83]. In the presence of chemical carcinogens, activated AhR suppresses abnormal cell proliferation by downregulating *c-Myc* expression, degrading β-catenin complex and promoting cell cycle arrest [84-86]. A previous study fully elucidated that AhR inhibited colonic tumor lesion formation under HFD feeding [87]. These findings highlight that targeting AhR is effective to suppress tumor formation.

3.2 HFD-induced intestinal microbial dysbiosis is involved in cancer progression

As reported, several pathogenic metabolites are involved in the progression (including angiogenesis, metastasis and invasion) of cancer. Surprisingly, lactic acid bacteria participate in the development of gastric cancer. Firstly, lactic acid provides energy for cancer cells and also mediates angiogenesis, metastasis and epithelial-mesenchymal transition [52]. Similar to lactic acid, lactic acid bacteria-produced *N*-nitroso compounds can promote DNA mutation and angiogenesis, activate proto-oncogene and suppress apoptosis [53]. HFD increases the proportion of hydrogen sulfide-producing bacteria, including *Desulfovibrio* and *Clostridium lavalense* [57]. Pro-carcinogenic hydrogen sulfide stimulates the proliferation, angiogenesis and migration of esophageal tumor cells [58]. Similar investigation also reveals that HFD-fed rats and patients with colorectal cancer have higher proportion of *Desulfovibrio*, and *Desulfovibrio* creates a pro-tumorigenic micro-environment [59]. Moreover, hydrogen sulfide reprograms lipid metabolism and stimulates gastric cancer cell metastasis [176]. Similarly, lithocholic acid increases the invasiveness of colorectal cancer cells [81].

Thus, HFD-induced microbial dysbiosis is a necessary prerequisite for carcinogenesis [7].

4. HFD induces carcinogenesis by disrupting immune homeostasis

HFD-induced immune homeostasis disruption not only participates in the pathogenesis of metabolic diseases [76, 88], but also triggers carcinogenesis [89]. In detail, HFD-induced disruption in the immune system includes inflammation and immunological suppression, both of which are conducive to creating a pro-tumorigenic micro-environment [9].

4.1 HFD induces inflammation via multiple mechanisms

As reported, HFD induces inflammation by contributing to microbial dysbiosis, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, adipokine imbalance and defective autophagy, regulating inflammatory cell phenotype, damaging intestinal barrier and activating inflammatory cascades [1,

[88]. In the intestine, HFD induces microbial dysbiosis, characterized by the bloom of pathogens and reduction in the relative abundance of symbiotic microorganisms [6]. Subsequently, pathogens and their metabolites, including lipopolysaccharide, secondary bile acids, *H. pylori* toxin protein CagA and VacA, *B. fragilis* toxin, flagellin and hydrogen sulfide, may cause intestinal inflammation and barrier dysfunction [70, 72, 90, 91]. The fecal microbiota from HFD-fed mice also causes inflammation in the normal mice [92], confirming that HFD evokes inflammation partly *via* intestinal microbiota and their metabolites.

In addition to promoting gut microbial dysbiosis-induced inflammation, HFD also triggers sterile inflammation. Similar to lipopolysaccharide, several free fatty acids, such as oleic acid and palmitic acid, are TLR-4 ligands and initiate downstream pro-inflammatory signaling pathways, including NF-κB and MAPK pathways [93-95]. The free fatty acids-mediated sterile inflammation is closely associated with mitochondrial dysfunction, oxidative stress, defective antioxidant system, endoplasmic reticulum stress and defective autophagy [95-100]. Surprisingly, pathogenic metabolites, including hydrogen sulfide, lipopolysaccharide, indoxyl sulfide, *H. pylori*-derived toxin protein VacA, isoallolithocholic acid, 4-(trimethylammonio) pentanoate valerate, 3-methyl-4-(trimethylammonio) butanoate, trimethylamine-*N*-oxide and trimethyl-5-aminovaleric acid, induce mitochondrial dysfunction, and subsequently initiate inflammatory cascades and damage intestinal barrier [101-104]. Therefore, it is speculated that HFD induces systemic inflammation and intestinal barrier dysfunction in microbial dysbiosis-dependent and amicrobic manners.

In the context of HFD feeding, long-term exposure to high levels of bile acids results in serious oxidative stress, mitochondrial dysfunction and destruction of cell membrane, all of which initiate inflammatory signaling pathways [93]. Mechanistically, secondary bile acid deoxycholic acid specifically activates pro-inflammatory signaling pathways, including NF-κB and MAPK pathways [79, 94]. Similarly, deoxycholic acid also activates NLRP3 inflammasome and further promotes the secretion of pro-inflammatory cytokines. Moreover, oral administration with deoxycholic acid downregulates the expression of intestinal tight junction proteins, decreases the relative proportion of goblet cells and Paneth cells, and reduces the production of secretory immunoglobulin A [71], thereby inducing intestinal inflammation and disrupting intestinal physical and chemical barrier.

HFD also triggers local and systemic inflammation *via* adipokine imbalance [1]. In addition to regulating metabolism, adipose tissue-secreted adipokines exert regulatory effects on the immune system [95]. The common adipokines are leptin, adiponectin, resistin and visfatin. As reported, both resistin and visfatin promote the production of pro-inflammatory cytokines and chemokines *via* NF-κB signaling pathway [96-97]. Similar to resistin and visfatin, leptin is thought to be a pro-inflammatory adipokine. It is reported that leptin enhances the differentiation and proliferation of pro-inflammatory cells, including T helper 1 (Th1) cells, Th17 cells and mast cells, and promotes the release of Th1-type cytokines [98-100]. By contrast, leptin also reduces the number of anti-inflammatory regulatory T (Treg) cells [101]. On the contrary, adiponectin exerts anti-inflammatory effects by increasing the production of anti-inflammatory cytokine IL-10 and switching from M1 macrophages to M2 phenotypes [102-103].

4.2 HFD-induced inflammation promotes carcinogenesis

As mentioned above, HFD significantly increases the concentration of pro-inflammatory cytokines, chemokines and adipokines in the serum and adipose tissue. Experimental data have found that the serum or adipose tissue-derived media from HFD-fed mice promotes the proliferation, migration and invasion of cancer cells [33, 104, 105]. Similarly, HFD-mediated increased leukocyte population also stimulates angiogenesis, cancer cell proliferation and metastasis in the cancer tissues [20]. Tumor-promoting inflammatory cells increase the production of growth factors, pro-tumorigenic chemokines and cytokines, and pro-angiogenic/pro-invasive matrix-degrading enzymes [10]. HFD also promotes the infiltration of tumor-associated macrophages into the tumor tissues and these macrophages produces pro-carcinogenic cytokines [106-107]. The animal experiments have found that HFD activates mast cells and these activated mast cells specifically stimulate prostate cancer cell growth and proliferation *via* histamine signaling pathway [27]. Another interesting finding of this investigation is that obese patients exhibit higher proportion of mast cells in the prostate cancer tissues [27].

In the context of HFD feeding and pathogenic antigens, pro-inflammatory cells and cancer cells produce pro-inflammatory cytokines and chemokines *via* inflammatory signaling pathways. These pro-inflammatory cytokines, chemokines and pathways are involved in carcinogenesis. After activation, TLR-4 signaling stimulates intestinal neoplasia and enhances colorectal cancer cell adhesiveness in β-catenin- or PI3K/Akt-dependent manners [108-109]. Genetic ablation of TLR-4 or myeloid differentiation factor 88 (MyD88, an adaptor protein of TLR-4) obviously suppresses intestinal tumorigenesis [7, 110]. Similar investigation also has discovered that palmitic acid stimulates lung cancer cell metastasis *via* TLR-4/TIR-domain-containing adaptor inducing interferon-β (TRIF)/NF-κB signaling pathway [21]. HFD increases the production of macrophage inhibitory cytokine-1 (MIC-1) and subsequently promotes the proliferation and invasion of prostate cancer cells [111]. Inflammatory signaling pathways increase the expression of pro-inflammatory and pro-carcinogenic cytokines, including IL-6, TNF-α and IL-1β. In the liver, Kupffer cells-produced IL-6 and TNF-α activate STAT3 pathway and induce the development of hepatocellular carcinoma [112]. The MAPK and JAK/STAT3 signaling pathways activated by IL-6 promote the expression of androgen receptor-mediated gene, which is conducive to the growth of prostate cancer cells [113]. Moreover, IL-6 polarizes macrophages into tumor-promoting macrophages and stimulates the production of pro-tumorigenic chemokine CC-chemokine-ligand-20 (CCL-20) [114]. IL-1β negatively regulates p53 pathways and further promotes DNA-mutant cell proliferation [115]. The use of TNF-α knockout mice reveals that TNF-α activates Wnt signaling pathway and upregulates the expression of Wnt target oncogenic genes, such as *C-myc* and *Cyclin D1*, indicating that TNF-α is strongly implicated in colonic carcinogenesis [116]. Collectively, these findings underscore the important roles of HFD-induced inflammation in the growth, proliferation, metastasis and invasion of cancer cells as well as angiogenesis.

4.3 HFD-induced defective anti-tumor immunity promotes carcinogenesis

In the tumor tissues, tumor micro-environment is composed of cancer cells, various types of immune cells, stromal cells, blood vessels and extracellular matrix [9]. In addition to fighting against pathogens and

their antigens, the immune system also eliminates cancer cells and mutant cells to perform immune surveillance. Therefore, apart from inflammation, HFD-induced defective immune surveillance (namely immunosuppression) is also conducive to tumor formation. Many kinds of immune cells, including neutrophils, myeloid-derived suppressor cells (MDSCs), macrophages, $CD8^+$ T cells, natural killer cells, dendritic cells, Th1 cells, Th2 cells and Treg cells, are closely associated with immune surveillance [9, 13, 117, 118]. Although MDSCs, Th2 cells and Treg cells enhance immune tolerance, these immune cells are also involved in carcinogenesis. On the contrary, pro-inflammatory cells, such as $CD8^+$ T cells, natural killer cells and Th1 cells mediate anti-tumor immunity in spite of their pro-inflammatory functions. Surprisingly, neutrophils and macrophages exert both pro-tumorigenic and anti-tumorigenic effects.

Owing to its cytotoxic function, $CD8^+$ T cells are the most effective cells in the anti-tumor immunity [119]. In the context of tumorigenesis, HFD significantly increases the number of programmed death-1 $(PD\text{-}1)^+$ $CD8^+$ T cells, one type of exhausted T cells that lose their cytotoxic function and anti-cancer efficacy [118, 120]. Similar results also elucidate that HFD damages $CD8^+$ T cell function and subsequently dampens immune surveillance [14]. Moreover, $PD\text{-}1^+$ $CD8^+$ T cells produce osteopontin [118], and accumulated osteopontin promotes tumorigenesis by stimulating angiogenesis, blocking apoptosis and weakening $CD8^+$ T cell cytotoxic function [121-122]. HFD also weakens anti-cancer responses of natural killer cells as indicated by the decrease in the release of perforins and granzymes [9]. As reported, lipid accumulation disrupts the antigen-presenting ability of dendritic cells and subsequently fails to activate anti-cancer immune responses [123].

In the tumor micro-environment, MDSCs play an important role in tumorigenesis. HFD-induced expansion of MDSCs inactivates $CD8^+$ T cells and induces $CD8^+$ T cell apoptosis [124-125]. Pro-inflammatory cytokine IL-6 increases the relative proportion of MDSCs and indirectly suppresses anti-cancer immunity [117]. At the early stage of tumorigenesis, M1 tumor-associated macrophages-mediated inflammation initiates tumor formation [126]. In the late period, M2 tumor-associated macrophages are involved in the inactivation of $CD8^+$ T cells, angiogenesis, cancer cell invasion and epithelial-mesenchymal transition remodeling [127-128], while M1 tumor-associated macrophages exert anti-tumorigenic effects. Similarly, N1 tumor-associated neutrophils promote $CD8^+$ T cell expansion and cancer cell apoptosis, whereas N2 tumor-associated neutrophils mediate immunosuppressive activities and angiogenesis [129].

In addition to inducing tumor-promoting inflammation, HFD-induced microbial dysbiosis also damages anti-tumor immunity. The major histocompatibility complex class II (MHC-II) on the cell membrane of antigen-presenting cells, such as dendritic cells, macrophages and intestinal epithelial cells, is essential for pathogenic and cancer immune surveillance [130]. On the one hand, HFD reduces the expression of MHC-II on the surface of intestinal epithelial cells [18]. This may be closely associated with HFD-induced lower microbial diversity as germ-free mice or antibiotics-treated mice exhibit decreased microbial diversity and MHC-II expression [131]. Several pathogens, including *E. faecalis* and *E. coli*, translocate into the pancreatic tissues and trigger the progression of cancer by increasing the abundance of $CD206^+$ M2 tumor-associated macrophages,

and reducing the proportion of M1 tumor-associated macrophages, Th1 cells and $CD8^+$ T cells [132]. Enterotoxigenic *B. fragilis* cooperatively interacts with IL-17 to recruit and activate MDSCs [133]. In the context of HFD feeding, *Malassezia spp*. also translocates into the pancreas and activates complement pathway to produce C5a. Subsequently, C5a promotes the recruitment of MDSCs and damages immune surveillance [8]. On the contrary, symbiotic microorganism *Akkermansia muciniphila* increases the population of cytotoxic T cells and further blocks tumor formation [134].

Several pathogenic metabolites also participate in immunosuppression. In the pancreatic tissue, *F. nucleatum*-derived fibroblast activation protein 2 (Fap2) suppresses the expansion of $CD3^+$ and $CD4^+$ T cells, and decreases M2 tumor-associated macrophage population [135]. Mechanistically, Fap2 specifically binds to T cell immunoglobulin and ITIM domain (TIGIT) expressed on the NK cells and T cells, and subsequently reduces NK cell cytotoxicity and inhibits the activities of $CD3^+$, $CD4^+$ and $CD8^+$ T cells [164]. Further use of *F. nucleatum* mutants also confirms that the suppressive effects of *F. nucleatum* on these anti-cancer immune cells are dependent on the interaction of Fap2 with TIGIT [164]. Lipopolysaccharide inactivates anti-cancer immunity *via* histamine signaling pathway [27]. Recently, a study has revealed that HFD significantly increases the production of intestinal microorganisms-derived leucine, and excessive level of leucine promotes the differentiation of polymorphonuclear MDSCs *via* mTORC1 pathway [136]. Clinical investigation also shows that leucine concentration is positively associated with the relative abundance of infiltrated polymorphonuclear MDSCs [136], highlighting the tumor-promoting roles of leucine. Both secondary bile acid (deoxycholic acid) and bacteria harboring deoxycholic acid biosynthetic genes damage $CD8^+$ T cell function and suppress anti-tumor immune responses [137].

5. HFD induces carcinogenesis by reprograming cell metabolism

As known, HFD disrupts lipid metabolism, glucose metabolism, cholesterol metabolism and energy metabolism, leading to the accumulation of lipids, glucose and cholesterol in the target tissues and circulation [1, 138, 139, 140]. Mechanistically, long-term HFD may promote intestinal lipid absorption, *de novo* lipogenesis, triglyceride synthesis, intestinal glucose absorption, hepatic gluconeogenesis, insulin resistance, intestinal cholesterol reabsorption and *de novo* cholesterol synthesis [1]. Subsequently, this accumulation of lipids, glucose and cholesterol not only contributes to metabolic diseases, but also participates in the initiation and progression of tumor formation. Therefore, HFD-induced metabolic reprograming is conducive to tumor formation.

The high levels of free fatty acids promote breast cancer cell invasion and metastasis *via* plasminogen activator inhibitor-1 (PAI-1) and SMAD4 [141]. HFD also enhances the number and self-renewal potential of $LGR5^+$ intestinal stem cells in a peroxisome proliferator-activated receptor-δ (PPAR-δ)-dependent manner, thereby promoting intestinal tumorigenicity [11]. Consistent with these findings, another investigation reveals that HFD enhances intestinal stemness and tumorigenicity by activating PPAR-δ or PPAR-α/carnitine acyl transferase-1α (CPT-1α) pathways and promoting fatty acid oxidation [12]. The genetic knockout or chemical inhibition of CPT-1α notably reduces the number, proliferation and regenerative capacity of intestinal stem

cells, and consequently suppresses HFD-induced adenoma formation and progression [12, 142]. These results highlight that HFD-enhanced fatty acid oxidation is essential for intestinal carcinogenesis. In the tumor micro-environment, HFD makes cancer cells to increase nutrient-acquiring efficiency from fatty acid uptake and oxidation, thereby reducing the nutrient availability of $CD8^+$ T cells and dampening $CD8^+$ T cell function [14]. In the context of HFD, apart from cancer cells, pro-tumorigenic tumor-associated macrophages and polymorphonuclear MDSCs also enhances lipid metabolism to win a niche [9]. HFD and palmitic acid specifically activate beta2-adrenergic receptor (β2AR), and activated β2AR phosphorylates hormone-sensitive lipase (HSL) at the site of serine 522, a key lipolytic enzyme that catalyzes triglyceride into free fatty acids [143]. This HFD-mediated metabolic reprogramming may provide enough energy for colorectal cancer cells [143].

Different from normal cells, cancer cells change glucose metabolism into aerobic glycolysis (namely Warburg effect). This metabolic reprogramming significantly decreases the efficiency of energy production as compared to mitochondrial oxidative phosphorylation in the normal cells. Therefore, cancer cells need more glucose and increase the expression of glucose transporters to meet their energy demand [10]. It is speculated that HFD-induced glucose accumulation is conducive to cancer cell growth. As reported, HFD-induced lower insulin sensitivity causes more insulin production and easily contributes to hyperinsulinemia. Excessive levels of insulin and insulin-like growth factor-1 (IGF-1) abnormally activate PI3K/Akt and Ras/MAPK signaling pathways, both of which are involved in cancer cell proliferation [106]. Similar studies also reveal that insulin and IGF-1 promote intestinal stem cell proliferation and prostate adenocarcinoma *via* PI3K/Akt signaling pathway [28, 144]. In the obesity-related colonic, breast or prostate tumors, insulin enhances mitochondrial glucose oxidation of cancer cells [106]. Thus, the reversal of hyperinsulinemia is beneficial to prevent/alleviate tumor formation [145].

High cholesterol level caused by HFD aggravates liver cancer, indicating that cholesterol plays a contributing role in tumorigenesis [19]. HFD promotes cholesterol biosynthesis, and increases the content of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [72]. As reported, LDL and VLDL activate Akt signaling pathway and stimulates angiogenesis, facilitating cancer cell proliferation and metastasis [146]. Under the catalysis of acetyl-CoA acetyltransferase 1 (ACAT1), cholesterol can be esterified to cholesterol ester, and cholesterol ester promotes cancer cell proliferation *via* PI3K/Akt pathway [147]. Meanwhile, ACAT1 also blocks $CD8^+$ T cell proliferation [148].

In addition to inducing inflammation, HFD-induced adipokine imbalance (higher leptin level and lower adiponectin concentration) also disrupts cell metabolism, and promotes cancer initiation and progression. HFD-induced higher leptin concentration activates PI3K/Akt/mTOR/STAT3 signaling pathway and subsequently evokes lung tumorigenesis [149]. This is closely associated with leptin-mediated angiogenesis, and the proliferation, motility and invasiveness of cancer cells [20]. However, leptin knockout or mutant leptin receptor abrogates HFD-induced gastric cell stemness and precancerous changes, highlighting the critical

roles of leptin and leptin receptor in carcinogenesis [25]. On the contrary, adiponectin inhibits colorectal carcinogenesis by blocking mTOR signaling pathway [29].

6. Discussions

6.1 Potential relationships among HFD, gut microbial dysbiosis, inflammation, defective anti-cancer immunity and metabolic disorder

As mentioned in Section 4.2, HFD causes inflammation in intestinal microbial dysbiosis-dependent and/or mitochondrial dysfunction-induced amicrobic manners. As reported, HFD-induced inflammation disrupts lipid and glucose metabolism, leading to the accumulation of lipids and glucose [1, 138]. For instance, inflammation blocks white adipose tissue browning and beige adipose tissue thermogenesis, thereby suppressing energy expenditure [138]. Pro-inflammatory signaling pathways, including MAPK and IKK/NF-κB pathways, enhance the serine/threonine phosphorylation of insulin receptor substrate and inactivate insulin signaling, thereby reducing insulin sensitivity and promoting glucose accumulation [1]. In the context of HFD feeding, intestinal microbial dysbiosis also weakens anti-cancer immunity (as mentioned in Section 4.3). Accordingly, HFD firstly contributes to mitochondrial dysfunction or gut microbial dysbiosis, and subsequently leads to inflammation, defective anti-cancer immunity and metabolic disorder, all of which easily trigger carcinogenesis. Considering that gut microbial dysbiosis also promotes mitochondrial dysfunction [154-155], HFD-induced intestinal microbial dysbiosis is the most important factor to induce mitochondrial dysfunction, inflammation, defective anti-cancer immunity, metabolic disorder and carcinogenesis.

6.2 Current treatment strategies for HFD-induced cancer

As mentioned above, HFD-induced gut microbial dysbiosis induces mitochondrial dysfunction, oxidative stress, inflammation, defective anti-cancer immunity and metabolic disorder, all of which are involved in carcinogenesis. Therefore, targeting intestinal microbial dysbiosis is beneficial for the prevention or alleviation of HFD-induced cancer. In the fields of nutrition and food science, current effective strategies for intestinal microbial dysbiosis contain probiotics and indigestible prebiotics. Accumulating evidence has revealed that indigestible prebiotics, such as natural polysaccharides, possess the abilities to improve gut microbiota composition, scavenge free radicals, inhibit inflammation and improve lipid and glucose metabolism [156-159]. Importantly, several types of edible fungal polysaccharides have been reported to exert anti-cancer effects by inhibiting gut microbial dysbiosis and inflammation [160].

The main function of probiotics is to improve intestinal micro-environment and maintain human health. Thus, many types of probiotics have been determined to reduce the relative abundance of pathogens and expand the population of commensals [161]. These probiotics have been used in the prevention and/or alleviation of obesity, type II diabetes, inflammatory bowel disease and cancer. Many animal experiments have found that probiotics prevent and/or alleviate cancer by suppressing gut microbial dysbiosis [162], reducing pro-carcinogenic compounds [163], increasing the efficacy of anti-cancer therapies [164], inhibiting

inflammation [165], enhancing anti-cancer immunity [166] and improving lipid and glucose metabolism [167-168]. Similarly, many clinical trials also have confirmed that probiotics alleviate anti-cancer therapies-induced side effects [169], improve host metabolism [170], regulate tumor suppressor genes and oncogenes [171], inhibit inflammation [172], enhance anti-cancer immunity [173] and eradicate carcinogenesis-promoting pathogens [174-177, 170]. These findings fully highlight the potential of probiotics in cancer therapy.

6.3 Other factors to affect HFD-induced cancer

Many other factors, including host genetic background [177], sex [178], lifestyle and environmental factors [179], also affect HFD-induced cancer. Recently, a study has fully evaluated the effects of HFD on 15 genetically distinct Collaborative Cross mice [177]. The results show that the number of small intestinal polyps in the male population of Collaborative Cross lines IL-72 and IL-5012 is significantly increased under HFD feeding, indicating that genetic differences affect HFD-mediated intestinal cancer [177]. In the context of HFD feeding, male mice gain more fat accumulation and exhibit disturbances in metabolic activities [178]. This phenomenon is caused by inherent sex differences in the catabolic versus anabolic neurological signaling pathways [178]. Similarly, male mice on HFD feeding have higher numbers of intestinal polyps than females [177]. The unhealthy lifestyles, including tobacco use and excessive drinking, exacerbate the development of HFD-induced cancer [179]. Moreover, HFD also increases the cancer incidence of people who are exposed to strong ultraviolet radiation and pro-carcinogenic substances. Considering the differences in genetic background, gut microbiota composition, dietary patterns, lifestyle and environmental factors, it is very difficult to comprehensively evaluate the effects of these factors on HFD-induced cancer.

7. Conclusion

Nowadays, cancer has been the first leading cause of death in China and other countries [150-151]. Many factors, including smoking, secondhand smoke, abuse drinking, lack of exercise, unhealthy dietary patterns, environmental pollution and pathogenic infection [152]. Since dietary patterns can rapidly and reproducibly change gut microbiome, and intestinal microbiota composition is closely associated with human metabolic health and diseases [16, 153], unhealthy dietary pattern, such as HFD, may contribute to the pathogenesis of cancer. Accumulating evidence has confirmed that HFD promotes carcinogenesis *via* multiple mechanisms [11, 39 72, 144]. Firstly, HFD obviously changes intestinal microbiota composition and microbial metabolites, which subsequently causes inflammation and tumorigenesis. Apart from microbial dysbiosis, HFD triggers inflammation by evoking mitochondrial dysfunction, endoplasmic reticulum stress and adipokine imbalance, and activating inflammatory pathways. Then, these inflammatory pathways, chemokines and cytokines promote angiogenesis, cancer cell growth, proliferation, metastasis, migration and invasion. On the other hand, HFD dampens anti-cancer immunity by downregulating MHC-II expression on the cell membrane of antigen-presenting cells, reducing the antigen-presenting ability of dendritic cells, decreasing the number of $CD8^+$ T cells, natural killer cells, M1 tumor-associated macrophages and N1 tumor-associated neutrophils, and increasing the relative proportion of MDSCs, M2 tumor-associated macrophages and N2 tumor-associated neutrophils in the tumor micro-environment. Since adipokine imbalance and excessive

levels of lipids, glucose and cholesterol disrupt immune homeostasis and support cancer growth and proliferation, HFD-mediated metabolic reprograming is also involved in carcinogenesis. Collectively, HFD promotes tumorigenesis by inducing gut microbial dysbiosis, disrupting immune homeostasis and reprograming cell metabolism. Thus, targeting gut microbial dysbiosis, inflammation, defective anti-cancer immunity and metabolic disorder may be effective to prevent or attenuate HFD-induced cancer.

Declaration of Competing Interest

All authors declare that they have no known competing financial interests.

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