In recent years, chronic overnutrition, such as consumption of a high-fat diet (HFD), has been increasingly viewed as a significant modifiable risk factor for diseases such as diabetes and certain types of cancer. However, the mechanisms by which HFDs exert adverse effects on human health remains poorly understood. Here, this paper will review the recent scientific literature about HFD-induced inflammation and subsequent development of diseases and cancer, with an emphasis on mechanisms involved. Given the expanding global epidemic of excessive HFD intake, understanding the impacts of a HFD on these medical conditions, gaining great insights into possible underlying mechanisms, and developing effective therapeutic strategies are of great importance.

Keywords: high-fat diets, inflammation, disease, mechanisms, drug therapy

INTRODUCTION

At present, obesity has reached epidemic proportions. It develops from an imbalance of energy homeostasis and contributes dramatically to the global disease burden, predisposing individuals to chronic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and certain types of cancer (1, 2). Excessive consumption of high fat diets (HFDs) has undoubtedly exacerbated the obesity epidemic and the development of obesity-related metabolic disorders (3, 4). Despite substantial work demonstrating that obesity develops from an imbalance between energy intake and energy expenditure, the underlying mechanisms for the detrimental effects of HFDs seem to be more complicated than the simple concept of energy imbalance (5). In this context, a better understanding of the pathogenesis of HFD-driven metabolic disorders may help to reduce the disease burden worldwide. This review will elaborate on the precise pathology and etiology of diseases induced by a HFD, and will evaluate the possibility of therapeutic targeting of free fatty acids (FFAs) and low-grade systemic inflammation to reduce HFDs-stimulated diseases.

HFDs INDUCE A SYSTEMIC CHRONIC LOW-GRADE INFLAMMATION

Following the ingestion of HFDs, inflammation develops in the central nervous system (CNS) including the hypothalamus and in the peripheral tissues including the liver, adipose tissue,
skeletal muscle, and intestine (6). Concerning the development of chronic systemic inflammation, alterations in the gut microbiota triggered by HFDs and direct effects of FFAs on intestinal cells may be the first step (7). Evidence to support this hypothesis is that germ-free mice exhibited neither obesity nor upregulation of intestinal TNF-α level compared to conventionalized mice when fed a HFD, whereas reconstitution of the gut microbiota from obese mice in the germ-free mice produced an increase in body fat (8). Furthermore, after comparing microbiota of obese vs. lean subjects, a recent study suggested that individuals with high bacterial richness were associated with less significant adiposity and inflammation than low bacterial richness subjects (9), which is line with HFD-induced inflammation and decrease of bacterial diversity. In particular, increased levels of Firmicutes and a reduced relative abundance of Bacteroidetes were observed in both humans and animals following HFD intake. Shifts in gut microbiota populations activate Toll-like receptor (TLR) signaling pathway, leading to increased intestinal permeability to endotoxins [such as lipopolysaccharides (LPS)] and thus promoting the translocation of LPS to the circulation (10–12). In addition, increased amounts of FFAs present in HFDs may directly act on intestinal cells. Therefore, elevated release of LPS and/or increased FFAs levels led to elevated production of pro-inflammatory cytokines [i.e., interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α] in the gut (13–17). The second step may consist in increased delivery of intestinal LPS, pro-inflammatory cytokines, and FFAs into the systemic circulation and portal circulation, thus leading to a systemic low-grade inflammation (15, 18). Elevated plasma FFAs and LPS can upregulate the expression of TLRs in circulating macrophages, enabling macrophages to be activated (M1 phenotype), which in turn produce proinflammatory cytokines (11, 12).

Before the onset of obesity, these factors in the circulating system triggers inflammatory pathways in the brain. More especially, elevated FFAs and cytokines first activate hypothalamic IkB kinase β (IKKβ)/nuclear factor of kappa B (NF-κB) signaling directly or indirectly through the following two ways: (i) through activating TLR located at cellular surface; (ii) through inducing various cellular stresses including oxidative stress and endoplasmic reticulum stress (ERS) in the hypothalamus (19–21). Hence, activated IKKβ/NF-κB signaling blunts central leptin and insulin sensitivity and initiates gene expression of inflammatory response molecules in the hypothalamus (19, 22, 23). Meanwhile, activated inflammatory macrophages (M1) in plasma can reach the adipose and muscular tissues, pancreatic islets, and blood vessels, leading to peripheral inflammation (12, 24). Notably, accumulation of CD8+ T-cells in the adipose tissue contributes to M1 macrophage recruitment in the adipose tissue (25). In addition, under HFD feeding stress the adipose tissue fails to store the excess lipids, which are thereafter deposited into other tissues including the liver, pancreas, skeletal muscle, and blood vessels (24). Ectopic lipid accumulation contributes additionally to the expression of proinflammatory mediators and the recruitment of M1 macrophages, thus aggravating systemic inflammation (26, 27). Moreover, the liver is also exposed to relatively high concentrations of different mediators (i.e., LPS, proinflammatory cytokines, and FFAs) released by the gastrointestinal tract (15). These mediators lead to accumulation of Natural killer T (NKT) cells and activation of Kupffer cells in the liver, thereby contributing to hepatic and systemic inflammation (28).

Altogether, under HFD conditions, a complicated network of signals interconnecting several organs acts in synergy to elicit a low-grade systemic inflammation (Figure 1). HFD-related inflammation leads to the failure of adipocytes to effectively remove circulating FFAs, and is pivotal to disease progression and the development of complications, such as T2DM, CVD, liver disease, atherosclerosis, and certain types of cancer (Figure 2, discussed in detail below).

HFD-INDUCED DISEASES

Insulin Resistance and T2DM

Insulin resistance is the condition where the body fails to respond appropriately to circulating insulin, leading to the impaired systemic glucose clearance and uptake in several tissues including the adipose tissue, liver, and muscle (29). Exposure to a HFD often results in insulin resistance and pancreatic β cell dysfunction. For example, after only 3 days of HFD feeding, systemic insulin resistance, and glucose intolerance developed in mice (30). Other studies have also shown that mice fed a HFD for several weeks exhibited increased glucose intolerant and impaired insulin sensitive, reflecting insulin resistance and initiating β cell compensation (31, 32).

Although not fully explored, current evidence has established causative and correlative links between HFD-induced inflammation and the pathogenesis of insulin resistance (27, 33). Under HFD conditions, insulin secretion from β cells and peripheral insulin action can be impaired by hypothalamic inflammation (34). Proinflammatory cytokines produced by β cells themselves due to macrophages accumulation in islets may further block β cell function (35). In addition, HFDs can activate 12-lipoxygenase activity in β cells through cytokines, FFAs, and increased blood glucose, thus increasing the production of 12-hydroxyeicosatetraenoic acid (12-HETE). 12-HETE promotes oxidative stress and blunts Nrf2 function, eventually leading to β cell apoptosis and glucose intolerance (36). Therefore, HFDs lead to an increase in insulin release from β cells and thus hyperinsulinemia. In adipose tissue, hyperinsulinemia combined with an inflammatory response promotes lipolysis, thus enabling FFAs and glycerol to flow to the liver to promote gluconeogenesis. At the same time, elevated insulin concentrations increases muscle glycolysis and lactate production, which is released into the circulation and can be used as a substrate for gluconeogenesis in the liver (37). Subsequently, increased gluconeogenesis enhances glucose production in the liver and thereby leads to systemic insulin resistance (38). As a consequence, T2DM ensues due to systemic insulin resistance and relatively diminished insulin secretion from pancreatic β cells (29). In addition, recent studies indicated that the A2b adenosine receptor (A2bAR), an established mediator of inflammation, control pancreatic dysfunction in HFD-induced obesity (39). In particular, macrophage A2bAR has been recently identified as an important mediator of HFD-induced hallmarks
FIGURE 1 | High-fat diets (HFDs) induce metabolic inflammation throughout the organism. The levels of endotoxins (e.g., LPS), circulating free fatty acids, and inflammatory mediators are increased in response to HFDs, resulting in low-grade systemic inflammation and altered homeostasis in many organs (see text).

of T2DM (40, 41). Therefore, regulation of macrophage A2bAR, either by genetic manipulations of monocytes or pharmacologically, may be a promising therapeutic approach. Taken together, chronically overconsumption of HFDs is mechanistically associated with the development of insulin resistance and T2DM.

**Cardiovascular Disease**

Although some controversy still exists, an increasing number of studies have highlighted the crucial effects of HFDs on the development of CVD (42, 43). For instance, administration of HFDs (20 g of fat/100 g of diet) to adult male rats for 30 days led to simultaneous increase in nitric oxide (NO) production and oxidative stress, causing the augmentation of infarct size after myocardial infarction (43). Low-grade systemic inflammation related to a HFD resulted in cardiovascular complications partially through infiltration of adipose and vascular tissues by effector T cells (44). In support of this notion, a cohort of 1,172 subjects was selected and stratified in three groups (i.e., lean, overweight, and obese). Results showed that the blood of overweight and patients with obesity had elevated numbers of CXCR3 effector memory T cells (a pro-inflammatory effector memory-like phenotype) compared to lean subjects. Similar phenotype was also found in mice. Upon further investigation, the same group found that this differentiation of CXCR3 effector memory T cells was partially mediated by the PI3K p110δ-Akt signaling pathway (44). Apart from infiltration of adipose and vascular tissues by effector T cells, the vascular endothelial dysfunction may also exert a role in the onset and propagation of CVD induced by a HFD (45, 46). Evidence for this hypothesis is provided by observations that mice fed with a HFD rich in lard exhibited an inhibition of the L-arginine-NO pathway in red blood cells (RBCs) of mice (47). RBCs-produced NO can contribute to the intravascular NO pool and suppression of platelet aggregation, thus regulating vascular homeostasis (48). Hence, decreasing NO bioavailability contributes to CVD via impairing vascular endothelial function. The adverse effects of HFD on endothelial function may be mediated independently by hyperglycemia, insulin resistance, and FFAs consequent to a HFD (49). Analogous to endothelial dysfunction, RBCs dysfunction takes place early during HFD-induced obesity and may contribute to the development of CVD (50). More especially, mice fed a 60% HFD for 12 weeks displayed a marked increase in the level of chemokines, which were bound to RBC via Duffy antigen receptor for chemokines. Moreover, RBCs from HFD-fed mice showed elevated cholesterol content and membrane phosphatidylserine externalization, accompanied by increased phagocytosis of RBCs by macrophages in vitro and by the spleen in vivo, thus contributing to atherosclerosis (50). Altogether, a HFD may promote the development of CVD via infiltration of adipose and vascular tissues by effector T cells, endothelial dysfunction and RBCs dysfunction.
Intestinal Diseases

A HFD-induced intestinal inflammation contributes to not only a systemic low-grade inflammation but localized tissue dysfunction (51, 52). For example, HFD feeding can exacerbate chemically-induced dextran sodium sulfate colitis by increasing pro-inflammatory cytokines (53–55) and can increase mucosal tissue damage in mouse models of ileitis (Mdr1a−/− mice) (56, 57) and spontaneous colitis (Muc2−/−, TNFARE mice) (58). Consistently, human studies have involved HFD consumption with an increased risk of functional bowel symptoms (59), such as inflammatory bowel diseases (IBD) (60). The increased incidence of IBD such as Crohn's disease (CD) in developed countries parallels escalating consumption of fat (60, 61). A HFD promotes the development of CD partially via promoting gut inflammation and microbiome perturbations. Previous studies have shown that a HFD increased intestinal permeability, promoted intestinal mucosa dysbiosis, and altered microbiota composition with a profile characterized by the expansion of pro-inflammatory Firmicutes and Proteobacteria and the reduction of protective bacteria such as Bacteroidetes. These effects triggered by a HFD were accompanied by downregulated expression of PPARγ and GPR43. Thus, the activation of PPARγ signaling and GPR43 receptor pathway could be viewed as an effective strategy to treat CD patients (62, 63). Moreover, after intestinal inflammation, intestinal morphofunctional rearrangement of the enteric nervous system occurs in the murine model of HFD-induced obesity, contributing to the pathophysiology of digestive motor abnormalities (64, 65). Recent studies further report that excitatory tachykinergic pathways, which can be regulated by A2bAR, are involved in the pathogenesis of colonic dysmotility induced by intestinal macrophages in HFD-induced obesity (16, 17).

Osteoporosis

Osteoblasts and adipocytes are derived from the same mesenchymal stem cell (MSC) source (66), leading to interactions between osteoclastogenesis and adipogenesis that can be affected by dietary fat intake (67). Epidemiological evidence has suggested that consuming HFDs promotes obesity, which is closely associated with lower bone mineral density (BMD) and a higher risk of osteoporotic fractures (68–70). Similar observations have also been observed in animal studies. Mice given HFDs (21.1% fat) for 13 weeks had lower bone mass, which was associated with oxidative stress (71). Likewise, HFDs (45% energy as fat) for 14 weeks led to decreased trabecular bone volume and trabecular number in the proximal tibia (72). These results suggest that HFDs affect adversely bone quantity. In contrast, other human and animal studies have shown that HFDs induced higher BMD because of elevated mechanical loading (73, 74). Recently, it has been reported that short-term consumption (8 weeks) of HFDs increased bone mass via elevated mechanical loading; however, long-term consumption (16 and 24 weeks) of HFDs exerted negative effects on bone mass (75). Therefore, it raises the possibility that HFDs initially augment bone deposition because of elevated mechanical demand but eventually impairs bone formation and turnover due to metabolic dysregulation (76, 77).

Mice received HFDs (60 kcal% fat) for 6 weeks before challenge with B16F10 melanoma cells exhibited elevated bone marrow (BM) adipocytes compared with mice received with normal diets. The increased presence of adipocytes largely changes the hematopoietic stem cell niche in the BM microenvironment and sets up a niche for tumor cells, increasing their proliferation by IL-6 and Janus Kinase 2 (JAK2). Moreover, cancer cells interact with fat in the BM facilitates the accumulation of osteoclasts in the BM by expressing osteopontin.
Therefore, the IL-6-JAK2-osteopontin axis is a critical signaling pathway for building the metabolic tumor niche in the context of a HFD-induced obesity (78). In addition, HFD can also regulate bone deposition via the hormone leptin secreted by HFD-induced adiposity (79). Taken together, HFDs regulate bone metabolism and lead to osteoporosis partially through proinflammatory cytokines (IL-6) and adipokines (leptin).

**Chronic Kidney Diseases**

A strong association between intake of SFAs, hyperalbuminuria and kidney dysfunction was observed in a cross-sectional study including more than 19,000 adults > 45 years of age (80). Increasing studies using rodent models have address potential mechanisms for the development of kidney disease driven by HFDs. Rats fed HFDs (35% kcal from fat) for 10 weeks developed proteinuria, accompanied by increased inflammatory markers (TNF-α and NF-κB) and oxidative stress markers (NADPH oxidase) in the renal cortex (81). Another study using HFD-fed Sprague-Dawley rats (58% fat-derived calories, 6 weeks) has demonstrated similar molecular and metabolic effects (82). The effect of hyperlipidemia-driven inflammation on the development of kidney dysfunction was further demonstrated in Apo E−/− mice fed HFDs for 4 weeks (83). These mice displayed greatly increased levels of TNF-α and IL-6, inducing renal inflammation, mesangial cell proliferation, and the progression of proteinuria. However, these effects were strongly attenuated in mice after treatment with anti-IL-6 receptor antibody. Upon further investigation, studies found that the activity of proinflammatory cytokines and profibrotic growth factors may be enhanced by renal sterol-regulatory element binding protein (SREBP1). Mice fed HFDs (60% fat) became obese, hyperinsulinemic, and hyperglycemic, associated with increased levels of SREBP1/2 (84). More importantly, deletion of SREBP1 in the mice blocked renal inflammation and proteinuria (85). These data suggest that a SREBP1-enhanced renal inflammation may represent a mechanism for the development of HFD-induced chronic kidney diseases.

**Central Nervous System Disorders**

The neuroinflammation has been observed in brain structures such as the hypothalamus, hippocampus, amygdala, cortex, and brainstem, increasing the incidence of CNS pathologies such as cognitive impairments (86), behavioral abnormalities (such as depressive- and anxiety-like behaviors) (87), Alzheimer’s disease (AD) (88). For instance, after 14 weeks feeding of HFDs (40% energy from fat), mice exhibited altered brain insulin signaling and cognitive functions (89). Without induction of obesity, HFDs (60% fat calories, 10 weeks) via alterations in gut microbiota can decrease memory and augment anxiety and stereotypical behaviors in mice (90). Long-term (16 months) exposition to HFDs has been shown to favor the deposition of amyloid beta (Aβ) peptide in the brain of mice, which is associated with the incidence of AD (91). These data underscore the strong effects of a HFD-induced changes on brain damage.

HFD-induced cognitive deficits may be associated with oxidative stress in the brain. Total levels of reactive oxygen species, superoxide, and peroxynitrite were significantly increased in mice fed HFDs (45% kcals from fat) compared to mice fed a control diet (10% kcals from fat) (92). Other studies also found elevated oxidative stress in HFD-fed mice which show clear cognitive impairment (86, 93). These studies highlight a role for oxidative stress in HFD-induced cognitive impairment. Unlike the underlying mechanisms for the induction of cognitive impairment, HFD promotes the development of anxiety-like behavior probably via upregulated expression of IL-1β in the amygdala (86) and changes in the GABAergic neurotransmission within the dorsomedial hypothalamus (94). In addition, HFD dramatically promotes the progression of AD-like pathology via elevation of cerebral amyloid deposition and oxidative stress, as demonstrated by previous studies (95). In particular, intake of HFDs results in peripheral insulin resistance and obesity, resulting in the disruption of the blood-brain barrier. Therefore, the transport of glucose and insulin to the CNS is limited, thus decreasing insulin signaling in the CNS. Hence, HFD-triggered peripheral hyperinsulinemia to some extent can initially provokes insulin deficiency in the brain, leading to lower expression of insulin degrading enzyme and less degradation (accumulation) of Aβ (96). At the same time, HFD-induced oxidative stress further contributes to impaired insulin signaling, thus increasing GSK-3β levels and Tau hyperphosphorylation. Increased Aβ levels and Tau hyperphosphorylation give rise to neurodegeneration and diminished synaptic plasticity, respectively, thus leading to the incidence of AD (89). Taken together, a HFD-induced damage to the brain is triggered by a number of mediators including inflammation, changes to integrity of blood-brain barrier, insulin resistance, and oxidative stress. These findings have important implications for better understanding how HFD may potentially induce brain dysfunction and the development of neurodegenerative disorders such as AD.

**Liver Cancer**

The current Western lifestyle will increase the risk of fatty liver disease. Non-alcoholic steatohepatitis (NASH) can be developed from fatty liver disease (steatosis) and can proceed to fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC). Therefore, to better understand how dietary-induced metabolic changes contribute to the development of hepatic inflammation and NASH, a recent study used a HFD-induced obese murine model of NASH progression over 16 weeks (28). After 16 weeks, HFDs induced an obese and inflammatory phenotype in mice. More importantly, mice fed HFDs exhibited increased infiltration of NKT-cells and clusters of differentiation CD8+ T-cells in the liver. To further confirm a role for NKT cells and CD8+ T-cells, the same group used CD1d knockout (KO) and mAb mice experiments, respectively. Notably, CD1dKO mice have no functional NKT cells. After 16 weeks of HFDs, the researchers found that CD1dKO mice were protected against obesity and NASH progression, and CD8+ T-cell-depleted mice were also protected from NASH while continuing to result in weight gain. In addition, increased CD8+ T-cells were also observed in human liver sections from patients with NASH. Therefore, these data suggest that under HFD feeding stress, NKT cells and CD8+ T-cells synergistically contribute to the inflammation and
fibrosis related to NASH progression (28). To further explore the underlying mechanisms for the development of NASH and HCC, a recent study used a rodent mole of long-term choline-deficient HFD to recapitulate NASH and NASH-induced HCC in humans. The analysis revealed that NKT cells primarily evidenced by remarkable increases in the expression of LAMP2A (the lysosomal marker), COX IV (the mitochondrial marker), and its induced fibrotic remodeling and breast cancer progression (99). Upon further investigations, the researchers found that myofibroblast differentiation was increased by HFDs via downregulating miR-140 expression in mammary adipose tissue through a TGF-β1/SMAD3/miR-130 negative-feedback loop. In particular, HFD-increased TGF-β1 signaling leads to activation of SMAD3, which binds to and suppresses miR-140. This blocks miR-140 from targeting SMAD3 for degradation, causing upon exposure to HFDs may blunt tumor initiation and progression. Existing evidence has linked a HFD to intestinal cancer (2, 105–107). For instance, a recently published article showed that a long-term HFD (60% fat diet, 9–14 months) contributes to the early intestinal tumorigenesis (108). Similar findings were obtained in another study, showing that HFDs could promote intestinal tumor progression in genetically susceptible K-ras deficiency in mice in the absence of obesity but based on marked alterations in gut bacterial communities (109). Exposure to HFDs led to many intestinal adaptations: (i) intestinal villi became shorter, while intestinal crypt depth was increased (108, 110); (ii) the numbers of intestinal stem cells (ISCs) increased while those of Paneth niche cells decreased; (iii) ISCs could expand in the absence of signals from Paneth cells; (iv) progenitors became more stem-cell like, acquiring the capacity to form intestinal organoids. These adaptations may partially contribute to the development of early intestinal tumorigenesis and subsequently cancer (108). There are two well-defined mechanisms for increased cancer risk induced by HFDs. One is via enhancing stemness and tumorigenicity of intestinal progenitors through activation of PPARδ/β-catenin signaling cascade (108). Consistently, other studies also show that HFDs and sustained PPARδ activation are associated with colorectal cancer initiation and progression (107, 111, 112). However, inhibition of PPARδ signaling may exert modest anti-cancer effects (113). The other is through inactivation of nuclear bile acid (BA) receptor farnesoid X receptor (FXR), which resulted in BA deregulation and promoted colon cell proliferation (110). These data indicate that inhibition of PPARδ and activation of FXR after exposure to HFDs may blunt tumor initiation and progression. Future investigations are needed to address how HFDs induce activation of PPARδ signaling and inhibition of FXR signaling.

**Gastric Cancer**

Epidemiological evidence has demonstrated that dietary fat is a critical risk factor for gastric cancer, which is a malignant tumor that originated from gastric mucosal epithelial cells (101–103). However, little is known about how dietary fat influences the function of gastric mucosal cells and contributes to precancerous lesions and hence gastric cancer. One recent study showed that in the precancerous gastric mucosa, fat deposition was obtained in the gastric pits in mice exposed to a HFD (60% fat calories) at 12 weeks. Ectopic fat accumulation then led to the disruption of organelle homeostasis in the gastric mucosa, as evidenced by remarkable increases in the expression of LAMP2A (the lysosomal marker), COX IV (the mitochondrial marker), Calnexin (the ER marker), and GM130 (the Golgi marker) in the gastric mucosa at 20 weeks (104). Therefore, HFD feeding first leads to excess lipid incorporation in the stomach, and then causes the disruption of organelle homeostasis in the precancerous gastric mucosa. In addition, HFD promoted stem-cell divisions and the development of gastric malignancies in the gastric mucosa, accompanied by activation of β-catenin pathway. However, β-catenin activation and stem cell marker-positive cells were not observed in mice with no leptin signaling. Meanwhile, the PI3K pathway, the downstream of leptin receptor, was also decreased (104). These data suggest that leptin signaling regulates β-catenin signaling. Taken together, HFD-driven lipid accumulation and organelle biosynthesis dysregulation confer cancer stem-cell-like properties to the gastric mucosa via leptin, PI3K, and β-catenin signaling pathways (104).

**Intestinal Cancer**

Existing evidence has linked a HFD to intestinal cancer (2, 105–107). For instance, a recently published article showed that a long-term HFD (60% fat diet, 9–14 months) contributes to the early intestinal tumorigenesis (108). Similar findings were obtained in another study, showing that HFDs could promote intestinal tumor progression in genetically susceptible K-ras deficiency in mice in the absence of obesity but based on marked alterations in gut bacterial communities (109). Exposure to HFDs led to many intestinal adaptations: (i) intestinal villi became shorter, while intestinal crypt depth was increased (108, 110); (ii) the numbers of intestinal stem cells (ISCs) increased while those of Paneth niche cells decreased; (iii) ISCs could expand in the absence of signals from Paneth cells; (iv) progenitors became more stem-cell like, acquiring the capacity to form intestinal organoids. These adaptations may partially contribute to the development of early intestinal tumorigenesis and subsequently cancer (108). There are two well-defined mechanisms for increased cancer risk induced by HFDs. One is via enhancing stemness and tumorigenicity of intestinal progenitors through activation of PPARδ/β-catenin signaling cascade (108). Consistently, other studies also show that HFDs and sustained PPARδ activation are associated with colorectal cancer initiation and progression (107, 111, 112). However, inhibition of PPARδ signaling may exert modest anti-cancer effects (113). The other is through inactivation of nuclear bile acid (BA) receptor farnesoid X receptor (FXR), which resulted in BA deregulation and promoted colon cell proliferation (110). These data indicate that inhibition of PPARδ and activation of FXR after exposure to HFDs may blunt tumor initiation and progression. Future investigations are needed to address how HFDs induce activation of PPARδ signaling and inhibition of FXR signaling.

**POTENTIAL TREATMENT OPTIONS**

The demonstration of a link between HFDs and metabolic disorders and certain types of cancer has prompted research into strategies to reduce HFD-driven diseases and cancer. Undoubtedly, lifestyle changes, such as improving dietary regiments and enhancing physical activity, are the most successful interventions. In this regard, dietary interventions aimed at decreasing circulating FFAs and limiting inflammation originated from alterations in gut microbial communities are attracting increasing clinical interest. Although still in its infancy, promising findings have been reported by several...
studies. Circulating FFAs levels are strongly decreased without causing ectopic lipid accumulation in HFD-fed mice with dietary supplementation of Atglistatin, a selective inhibitor of adipose TG lipase, accompanied by decreased weight gain, insulin resistance, and liver diseases (114). Preclinical studies have also reported a metabolic benefit associated with the anti-inflammatory impacts of targeting PPARy (115), ERS (116), IKKβ/ NF-κB (117), and shifts in gut microbial communities (118). For instance, HFD-fed mice treated with Lactobacillus plantarum KY1032 and Lactobacillus curvatus HY7601 exhibited decreased body weight, fat mass, and levels of circulating leptin, insulin, total cholesterol and liver toxicity biomarkers, accompanied by alterations in gut bacterial composition and diversity (118). In addition, markers of inflammation are reduced with dietary supplementation with amino acid (especially leucine) and plant components (such as luteolin and flavonoids), alone or in combination, as were performed in HFD-fed mice (46, 119–123). Although there are additional undefined approaches, the above-mentioned findings give the field a critical boost and may be translated into human studies, thus improving interventional strategies to stem the negative effects of HFDs.

**CONCLUSIONS AND PERSPECTIVES FOR FUTURE STUDIES**

The literature reviewed here suggests that FFAs and LPS have been established as independent factors aggravating inflammation during HFD-induced chronic diseases and certain type of cancer. Targeting these factors may provide effective approaches for therapies against associated metabolic perturbations. Although great strides have been made in animal models to understand the signaling pathways implicated in HFDs-induced chronic diseases and certain type of cancer, more efforts should be made to confirm whether these signaling pathways are physiologically valid in humans, and additional transcription factors and target genes need to be identified to reduce the overwhelming burden of chronic diseases and cancer.

**AUTHOR CONTRIBUTIONS**

YD and LZ wrote the manuscript, KX designed the manuscript, CZ, BS, FL, and XK revised the manuscript. All authors read and approved the final version of the manuscript.

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**REFERENCES**

1. Stevens GA, Singh GM, Lu Y, Danai G, Lin JK, Finucane MM., et al. National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr.* (2012) 10:22. doi: 10.1186/1478-7954-10-22
2. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* (2004) 4:379–91. doi: 10.1038/nrc1408
3. Kennedy A, Martinez K, Chuang CC, LaPoint K, McIntosh M. Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. *J Nutr.* (2009) 139:1–4. doi: 10.3945/jn.108.089269
4. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev.* (2013) 93:359–404. doi: 10.1152/physrev.00033.2011
5. Murphy EA, Velasquez KT, Herbert KM. Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk. *Curr Opin Clin Nutr.* (2015) 18:515–20. doi: 10.1097/MCO.0000000000000209
6. Guillenot-Legris O, Masquelier I, Everard A, Cani PD, Alhousayek M, Muccioli GG. High-fat diet feeding differentially affects the development of inflammation in the central nervous system. *J Neuroinflamm.* (2016) 13:206. doi: 10.1186/s12974-016-0666-8
7. Sammiguel C, Gupta A, Mayer EA. Gut microbiome and obesity: a plausible explanation for obesity. *Curr Obes Rep.* (2015) 4:250–61. doi: 10.1007/s13679-015-0152-0
8. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE., et al. A core gut microbiome in obese and lean twins. *Nature* (2009) 457:480–4. doi: 10.1038/nature07540
9. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G., et al. Richness of human gut microbiome correlates with metabolic markers. *Nature* (2013) 500:554–6. doi: 10.1038/nature12506
10. Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock N, Magness S., et al. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLOS ONE* (2010) 5:e12191. doi: 10.1371/journal.pone.0012191
11. Kim KA, Gu W, Lee IA, Joh EH, Kim DH. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLOS ONE* (2012) 7:e47713. doi: 10.1371/journal.pone.0047713
12. Bleau C, Karelis AD, St-Pierre DH, Lamontagne L. Crosstalk between intestinal microbiota, adipose tissue and skeletal muscle as an early event in systemic low-grade inflammation and the development of obesity and diabetes. *Diabetes Metab Res Rev.* (2015) 31:545–61. doi: 10.1002/dmr.r2617
13. Fujiyama Y, Hokari R, Miura S, Watanabe C, Komoto S, Oyama T., et al. Butter feeding enhances TNF-alpha production from macrophages and lymphocyte adherence in murine small intestinal microvessels. *J Gastroen Hepatol.* (2007) 22:1838–45. doi: 10.1111/j.1440-1746.2007.04905.x
14. Yoshida H, Miura S, Kishikawa H, Hirokawa M, Nakamizo H, Nakatsumi RC., et al. Fatty acids enhance GRO/CINC-1 and interleukin-6 production in rat intestinal epithelial cells. *J Nutr.* (2001) 131:2943–50. doi: 10.1093/jn/131.11.2943
15. Konrad D, Wuest S. The gut-adipose-liver axis in the metabolic syndrome. *Physiology* (2014) 29:304–13. doi: 10.1152/physiol.00014.2014
16. Antonioli L, Caputi V, Formai M, Pellergrini C, Gentile D, Giron MC, et al. Interplay between colonic inflammation and tachykininergic pathways in the onset of colonic dysmotility in a mouse model of diet-induced obesity. Int J Obes. (2018). doi: 10.1038/s41366-018-0166-2. [Epub ahead of print].

17. Antonioli L, Pellergrini C, Formai M, Tirotta E, Gentile D, Benvenuti L, et al. Colonic motor dysfunctions in a mouse model of high-fat diet-induced obesity: an involvement of A2B adenosine receptors. PRRsureric Signal. (2017) 13:97–510. doi: 10.1101/s13102-017-9577-0

18. Tsukumo DM, Carvalho BM, Carvalho Filho MA, Saad MJ. Translational research into gut microbiota: new horizons on obesity treatment: updated 2014. Arch Endocrinol Metab. (2015) 59:154–60. doi: 10.1590/2359-3997201500029

19. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappa B and ER stress link overnutrition to energy imbalance and obesity. Cell (2008) 135:61–73. doi: 10.1016/j.cell.2008.07.043

20. De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollo RL, Boscheri AC, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology (2005) 146:4192–9. doi: 10.1210/en.2004-1520

21. Cai D, Liu T. Hypothalamic inflammation: a double-edged sword to nutritional diseases. An NY Acad Sci. (2011) 1243:E1–39. doi: 10.1111/j.1749-6632.2011.06388.x

22. Wang J, Obici S, Morgan K, Barzilai N, Feng Z, Rossetti L. Overfeeding rapidly induces leptin and insulin resistance. Diabetes (2001) 50:2786–91. doi: 10.2337/diabetes.50.12.2786

23. Woods SC, D’Alessio DA, Tao P, Rushing PA, Clegg DJ, Reinitz SC, et al. Consumption of a high-fat diet alters the homeostatic regulation of energy balance. Physiol Behav. (2004) 83:573–8. doi: 10.1016/j.physbeh.2004.07.026

24. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic diseases. J Clin Invest. (2011) 121:2111–7. doi: 10.1172/JCI57132

25. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. Adipose tissue inflammation in obesity. J Clin Invest. (2009) 119:914–20. doi: 10.1038/jni.2009.164

26. Cairo S, Tregarollos V, Kovatcheva-Datchary P, Cani PD, Backhed F. Crostall talk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab. (2015) 22:658–68. doi: 10.1016/j.cmet.2015.07.026

27. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. BBA Mol Basis Dis. (2014) 1842:446–62. doi: 10.1016/j.bbadis.2013.05.017

28. Bhattacharjee J, Kirby M, Softic S, Miles L, Salazar-Gonzalez RM, Shivakumar P, et al. Hepatic natural killer T-cell and CD68+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. (2009) 15:914–20. doi: 10.1038/nm.1964

29. Yao K, Duan Y, Li F, Tan B, Hou Y, Wu G., et al. Leucine in the diet alleviates the impact of chronic inflammation on CSF tau and amyloid-beta levels in obstructive sleep apnea syndrome. PLoS ONE (2014) 9:e97875. doi: 10.1371/journal.pone.0097875

30. Martins F, Campos DH, Pagan LU, Martinez PF, Okoshi K, Okoshi MP, et al. High-fat diet promotes cardiac remodeling in an experimental model of obesity. Arq Bras Cardiol. (2015) 105:479–86. doi: 10.5935/abc.20150099

31. Calegari VC, Torsoni AS, Vanzela EC, Araújo EP, Morari J, Zoppi CC, et al. Hepatic natural killer T-cell and CD8+ T-cell signatures affect cardiac function after myocardial infarction? J Cell Mol Anesth. (2017) 2:23–8. doi: 10.22037/jcm2/a714288

32. Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, Maor-Cahn R, et al. The A2b adenosine receptor modulates glucose homeostasis and obesity. PLoS ONE (2012) 7:e40584. doi: 10.1371/journal.pone.0040584

33. Johnston-Cox H, Eisenstein AS, Koupovena M, Carroll S, Ravid K., et al. The macrophage A2b adenosine receptor regulates tissue insulin sensitivity. PLoS ONE (2014) 9:e98775. doi: 10.1371/journal.pone.0098775

34. Aghajani M, Imani A, Faghihi M, Mahdavi MRV, Mahboubi S, et al. Does increased nitric oxide production and oxidative stress due to high fat diet affect cardiac function after myocardial infarction? J Cell Mol Anesth. (2017) 2:23–8. doi: 10.22037/jcm2/a714288

35. McArthur C, Smith J, Cucchi D, Cole D, Fu H, Bonacca F., et al. Obesity-induced metabolic stress leads to biased effector memory CD4+ T-cell differentiation via PI3K p110delta-Akt-mediated signals. Cell Metab. (2017) 25:593–609. doi: 10.1016/j.cmet.2017.01.008

36. Dunn SM, Hilgers RHP, Das KC. Endothelial dysfunction and outward remodeling in coronary and mesenteric arteries in response to high fat diet in mice. FASEB J. (2016) 30:1282– 6. doi: 10.1096/fj.201501282.6

37. Gentile D, Formai M, Pellergrini C, Colucci R, Benvenuti L, Durante E., et al. Lutein prevents cardiometabolic alterations and vascular dysfunction in mice with HFD-induced obesity. Front Pharmacol. (2018) 9:1094. doi:10.3389/fphar.2018.01094

38. Martins MA, Catta-Preta M, Mandarim-de-Lacerda CA, Aguila MB, Brunini TC, Mendes-Ribeiro AC. High fat diets modulate nitric oxide biosynthesis and antioxidant defence in red blood cells from C57BL/6 mice. Arch Biochem Biophys. (2010) 499:56–61. doi: 10.1016/j.abb.2010.04.025

39. Owizyaman B, Grau M, Kelm M, Merx MW, Kleinbongard P. RBC NOS: regulatory mechanisms and therapeutic aspects. Trends Mol Med. (2008) 14:21 –24. doi:10.1016/j.molmed.2008.05.002

40. Zhang H, Dellsperger KC, Zhang C. The link between metabolic abnormalities and endothelial dysfunction in type 2 diabetes: an update. Basic Res Cardiol. (2012) 107:237. doi: 10.1007/s00395-011-0257-1

41. Unrath D, Srinivasan R, Benson T, Haigh S, Coyle D, Batra N., et al. Red blood cell dysfunction induced by high-fat diet: potential implications for obesity-related atherosclerosis. Circulation (2015) 132:1898–908. doi: 10.1161/CIRCULATIONAHA.115.017313

42. Guilhane M, Murray L, Lourie R, Tong H, Sheng YH, Wang R., et al. High fat diets induce colonic epithelial cell stress and inflammation that is reversed by IL-22. Sci Rep. (2016) 6:28990. doi:10.1038/srep28990

43. Ho W, Spiegel BM. The relationship between obesity and functional gastrointestinal disorders: causation, association, or neither? Gastroenterol Hepatol. (2008) 24:57–82.

44. Kim IW, Myung SJ, Do MY, Ryu YM, Kim MJ, Do EJ., et al. Western-style diets induce macrophage infiltration and contribute to colitis-associated carcinogenesis. J Gastroen Hepatol. (2010) 25:1785–94. doi: 10.1111/j.1440-1746.2010.06332.x

45. Laroui H, Ingersoll SA, Liu HC, Baker MT, Ayyadurai S, Charania MA., et al. Dextran sodium sulfate (DSS) induces colitis in mice by forming nano- lipocomplexes with medium-chain-length fatty acids in the colon. PLoS ONE (2012) 7:e23084. doi: 10.1371/journal.pone.0032084

46. Okada Y, Tsuzuki Y, Sato H, Narimatsu K, Hokari R, Kurihara C., et al. Trans fatty acids exacerbate dextran sodium sulphate-induced colitis by promoting the up-regulation of macrophage-derived proinflammatory
cytokines involved in T helper 17 cell polarization. Clin Exp Immunol. (2013) 174:459–71. doi: 10.1111/cei.12200

56. Lu P, Bar-Yousef F, Levi L, Lifshitz Y, Witte-Bouma J, de Brujin AC, et al. High beta-palmitate fat controls the intestinal inflammatory response and limits intestinal damage in mucin muc2 deficient mice. PLoS ONE (2013) 8:e68578. doi:10.1371/journal.pone.0068578

57. Paik J, Fierce Y, Treuting PM, Brabb T, Maggio-Price L. High-fat diet-induced obesity exacerbates inflammatory bowel disease in genetically susceptible Mdr1a(-/-) male mice. J Nutr. (2013) 143:1240–7. doi:10.3945/jn.113.176175

58. Gruber L, Kisling S, Lichti P, Martin FP, May S, Klingenspor M, et al. High fat diet accelerates pathogenesis of murine crohn's disease-like ileitis independently of obesity. PLoS ONE (2013) 8:e71661. doi:10.1371/journal.pone.0071661

59. Fyskeidis M, Bouchouicha M, Bihan H, Reach G, Benamouzig R, Catheline JM. Prevalence and co-occurrence of upper and lower functional gastrointestinal symptoms in patients eligible for bariatric surgery. Obes Surg. (2011) 22:403–10. doi:10.1007/s11695-011-0396-x

60. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol. (2011) 106:563–73. doi:10.1038/ajg.2011.44

61. Chapman-Kiddell CA, Davies PS, Gillen L, Radford-Smith GL. Role of diet in the development of inflammatory bowel disease. Inflamm Bowel Dis. (2010) 16:137–51. doi:10.1002/ibd.20968

62. Tomas J, Mulet C, Saffarian A, Cavin JB, Ducroc R, Regnault B, et al. High-fat diet modifies the PPAR-γ pathway leading to disruption of microbial and physiological ecosystem in murine small intestine. Proc Natl Acad Sci USA. (2016) 113:E5934–43. doi:10.1073/pnas.1612559113

63. Agus A, Denizot J, Thévenot J, Martinez-Medina M, Massier S, Sauvanet P, et al. Western diet induces a shift in a microbiota composition enhancing susceptibility to Adherent-Invasive E. coli infection and intestinal inflammation. Sci Rep. (2016) 6:19032. doi:10.1038/ srep19032

64. Bertrand RL, Senadheera S, Markus I, Liu L, Howitt L, Chen H, et al. A western diet increases serotonin availability in rat small intestine. Endocrinology (2011) 152:36–47. doi: 10.1210/en.2010-0377

65. Nezami BG, Mwangi SM, Lee JE, Jeppsson S, Anitha M, Yarandi SS, et al. Extreme obesity reduces bone mineral density: complementary evidence from mice and women. Obesity (2007) 15:1980–7. doi:10.1038/oby.2007.236

66. Chen GL, Luo Y, Eriksson D, Meng X, Qian C, Bauerle T, et al. High fat diet increases melanoma cell growth in the bone marrow by inducing osteopontin and interleukin 6. Oncotarget (2016) 7:26653–69. doi:10.18632/oncotarget.8474

67. Styner M, Thompson WR, Galior K, Uzer G, Wu X, Kadari S, et al. Bone mineral density and micro-architecture changes in trabecular bone of NHANES III. J Nutr. (2006) 136:159–65. doi:10.1093/jn/136.1.159

68. Corwin RL, Hartman TJ, Maczuga SA, Graubard BI. Dietary saturated fat decreases cancellous bone mass enhancing susceptibility to Adherent-Invasive E. coli infection in young rats. Biochim Biophys. Res. Commun. (2014) 455:133–8. doi:10.1016/j.bbrc.2014.10.131

69. Zhao LJ, Liu YJ, Liu PY, Hamilton J, Ingram DK., et al. Cognitive impairment following high fat diet consumption is exert different effects on changes in trabecular bone micro-structure. J Nutr Health Aging (2018) 22:361–70. doi:10.1007/s11603-017-0933-0

70. Malvi P, Piprode V, Chauve B, Pote ST, Mittal M, Chattopadhyay N, et al. High fat diet promotes achievement of peak bone mass in young rats. Biochim. Biophys. Res. Commun. (2014) 455:133–8. doi:10.1016/j.bbrc.2014.10.131

71. Núñez NP, Carpenter CL, Perkins SN, Berrigan D, Jaque SV, Ingles SA, et al. Extreme obesity reduces bone mineral density: complementary evidence from mice and women. Obesity (2007) 15:1980–7. doi:10.1038/oby.2007.236

72. Xiao Y, Cui J, Li YX, Shi YH, Wang B, Le GW, et al. Dyslipidemic physiology ecosystem in murine small intestine. Physiol Behav. (2012) 32:287–309. doi:10.1016/j.physbeh.2011.06.027

73. Reid IR. Fat and bone. Arch Biochem Biophys. (2005) 434:276–89. doi:10.1016/j.abb.2004.07.002

74. Lecka-Czernik B, Stechschulte LA, Czernik PJ, Dowling AR. High bone mass in adult mice with diet-induced obesity results from a combination of initial increase in bone mass followed by attenuation in bone formation; implications for high bone mass and decreased bone quality in obesity. Mol Cell Endocrinol. (2015) 410:35–41. doi:10.1016/j.mce.2015.01.001

75. Tian L, Wang C, Xie Y, Wan S, Zhang K, Yu X. High fructose and high fat exert different effects on changes in trabecular bone micro-structure. J Nutr Health Aging (2018) 22:361–70. doi:10.1007/s11603-017-0933-0
associated with brain inflammation. *J Neuroinmunol.* (2010) 219:25–32. doi: 10.1016/j.jneuroim.2009.11.010
94. de Noronha SR, Campos GV, Abreu AR, de Souza AA, Chianca DA, de Menezes RC. High fat diet induced-obesity facilitates anxiety-like behaviors due to GABAergic impairment within the dorsomedial hypothalamus in rats. *Behav Brain Res.* (2017) 316:38–46. doi: 10.1016/j.bbr.2016.08.042
95. Lin B, Hasegawa Y, Takane K, Kobuchi N, Cao C, Kim-Mitsuyama S. High-fat-diet intake enhances cerebral amyloid angiopathy and cognitive impairment in a mouse model of Alzheimer's disease, independently of metabolic disorders. *J Am Heart Assoc.* (2016) 5:e003154. doi: 10.1161/JAHA.115.003154
96. Petrov D, Pedrós I, Artiach G, Pedrós I, Artiach G, Sureda FX, Barroso E, Pallàs M., et al. Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. *Sci Transl Med.* (2015) 7:330ra130. doi: 10.1126/scitranslmed.3010467
97. Wolf MJ, Adili A, Piotrottiz M, Abdulaziz B., et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* (2014) 514:508–12. doi: 10.1038/nature13398
98. Duan et al. High Fat Diets and Diseases
99. Seo BR, Bhardwaj P., Choi S, Gonzalez J, Andresen Eguiluz RC, Wang MT., et al. High-fat-diet intake enhances stemness and tumorigenicity of intestinal progenitors. *Cancer Prev Res.* (2014) 7:662–3. doi: 10.1158/1940-6261.CAPR-09-0017
100. Arita S, Kinoshita Y, Ushida K, Enomoto A, Inagaki-Ohara K. High-fat diet promotes mammary gland myofibroblast differentiation through microRNA 140 downregulation. *Mol Cell Biol.* (2017) 37:e00461-00416. doi: 10.1128/MCB.00461-16
101. Abraham S, Haughey B, Marshall J, Brasure J, Zielenez M, Freemanheim J, et al. Diet in the etiology of gastric-cancer. *Nutr Cancer* (1990) 13:19–34. doi: 10.1080/01635589009514042
102. Wolfson B, Zhang Y, Gernapudi R, Duru N, Yao L, Lo PK., et al. A High-fat diet promotes mammary gland myofibroblast differentiation through microRNA 140 downregulation. *Mol Cell Biol.* (2017) 37:e00461-00416. doi: 10.1128/MCB.00461-16
103. Neels JG, Grimaldi PA. Physiological functions of peroxisome proliferator-activated receptor beta. *Physiol Rev.* (2014) 94:795–858. doi: 10.1152/physrev.00027.2013
104. Schaefer M, Ronauch M, Schreiber R, Grabner GF, Hütter S, Kotzbeck P., et al. Pharmacological inhibition of adipose triglyceride lipase corrects high-fat-diet-induced insulin resistance and hepatosteatosis in mice. *Nat Commun.* (2017) 8:14859. doi: 10.1038/ncomms14859
105. Mihaylova MM, Sabatini DM, Yilmaz ÖH. Dietary and metabolic control of stem cell function in physiology and cancer. *Cancer Cell* (2014) 26:549–64. doi: 10.1016/j.ccell.2014.09.003
106. Evers BM, Adili A, Piotrottiz M, Abdulaziz B. High-fat-diet-induced dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* (2014) 514:508–12. doi: 10.1038/nature13398
107. Baltgalvis KA, Berger FG, Peña MM, Davis JM, Carson JA. The interaction of high-fat-diet feeding promotes stemness and precancerous changes in murine fat diet promotes mammary gland myofibroblast differentiation through microRNA 140 downregulation. *Mol Cell Biol.* (2017) 37:e00461-00416. doi: 10.1128/MCB.00461-16
108. Seo BR, Bhardwaj P., Choi S, Gonzalez J, Andresen Eguiluz RC, Wang MT., et al. High-fat-diet intake enhances stemness and tumorigenicity of intestinal progenitors. *Cancer Prev Res.* (2014) 7:662–3. doi: 10.1158/1940-6261.CAPR-09-0017
109. Hofbauer LC, Haughey B, Marshall J, Brasure J, Zielenez M, Freemanheim J, et al. Diet in the etiology of gastric-cancer. *Nutr Cancer* (1990) 13:19–34. doi: 10.1080/01635589009514042
110. Wolfson B, Zhang Y, Gernapudi R, Duru N, Yao L, Lo PK., et al. A High-fat diet promotes mammary gland myofibroblast differentiation through microRNA 140 downregulation. *Mol Cell Biol.* (2017) 37:e00461-00416. doi: 10.1128/MCB.00461-16
111. Neels JG, Grimaldi PA. Physiological functions of peroxisome proliferator-activated receptor beta. *Physiol Rev.* (2014) 94:795–858. doi: 10.1152/physrev.00027.2013
112. Schaefer M, Ronauch M, Schreiber R, Grabner GF, Hütter S, Kotzbeck P., et al. Pharmacological inhibition of adipose triglyceride lipase corrects high-fat-diet-induced insulin resistance and hepatosteatosis in mice. *Nat Commun.* (2017) 8:14859. doi: 10.1038/ncomms14859
113. Neels JG, Grimaldi PA. Physiological functions of peroxisome proliferator-activated receptor beta. *Physiol Rev.* (2014) 94:795–858. doi: 10.1152/physrev.00027.2013
114. Mihaylova MM, Sabatini DM, Yilmaz ÖH. Dietary and metabolic control of stem cell function in physiology and cancer. *Cell Stem Cell* (2014) 14:292–305. doi: 10.1016/j.stem.2014.02.008
115. Sinicane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ., et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* (2011) 377:557–67. doi: 10.1016/S0140-6736(10)62037-5
116. Mihaylova MM, Sabatini DM, Yilmaz OH. Dietary and metabolic control of stem cell function in physiology and cancer. *Cell Stem Cell* (2014) 14:292–305. doi: 10.1016/j.stem.2014.02.008
117. Gentile D, Fornai M, Pellegrini C, Colucci R, Blandizzi C, Antonioli L., et al. Synergistic effects of leucine and resveratrol on insulin sensitivity and fat metabolism in adipocytes and mice. *Nutr Metab* (2012) 9:77. doi: 10.1186/1743-7075-9-77
118. Park DY, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R., et al. Supplementation of Lactobacillus curvatus H7601 and Lactobacillus plantarum KY1132 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PloS ONE* (2013) 8:e59470. doi: 10.1371/journal.pone.0059470
119. Smith SA, Weisberg SN, Raunov N, Xiang RY, smartphone, Xue Y, Li S., et al. Synergistic effects of leucine and resveratrol on insulin sensitivity and fat metabolism in adipocytes and mice. *Nutr Metab* (2012) 9:77. doi: 10.1186/1743-7075-9-77
120. Gentile D, Fornai M, Pellegrini C, Colucci R, Blandizzi C, Antonioli L. Dietary flavonoids as a potential intervention to improve redox balance in obesity and related co-morbidities: a review. *Nutr Res Rev.* (2018) 31:239–47. doi: 10.1016/j.nutrresrev.2018.05.008
121. Gentile D, Fornai M, Colucci R, Pellegrini C, Tirotta E, Benvenuti L., et al. The flavonoid compound apigenin prevents colonic inflammation and motor dysfunctions associated with high fat-diet-induced obesity. *PloS ONE* (2018) 13:e0195502. doi: 10.1371/journal.pone.0195502

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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