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Review

High fructose diet: A risk factor for immune system dysregulation

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ABSTRACT

Excessive intake of sweets is a predisposing factor for metabolic disorders, and fructose, as one of the major dietary sugars in the diet, has been shown to be a major cause of obesity, diabetes, and metabolic syndrome. These disorders are usually associated with immune dysfunction. Therefore, exploring the effects of a high fructose diet on the immune system may provide insight into the underlying mechanisms of these diseases. We synthesized the available evidence to suggest that excessive fructose intake disrupts the body's immune homeostasis by promoting immune cell metabolic rearrangements, alterations in gut microbial community structure, and intestinal barrier permeability. Indeed, not only does fructose itself affect immune system homeostasis, but its metabolites also have a profound influence. The metabolites from fructolysis are mainly produced in the small intestine and liver and subsequently enter the systemic circulation. Elevated levels of fructose metabolites, such as uric acid, FFAs, and lactate, are closely associated with oxidative stress and local tissue and organ inflammatory responses. In this review, we will focus on the link between fructose and inflammatory responses. In the meanwhile, we will also briefly summarize the studies of cancer development and immune escape mediated by fructose, as it might be beneficial for cancer immunotherapy.

Contents

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1. Introduction

Over the past few decades, the incidence of chronic diseases such as obesity, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes has increased dramatically. The development of these diseases is closely related to the dietary habits that people have developed in better living conditions[1–3]. Recent studies point to high fructose intake as a possible culprit for these diseases[4–7]. Fructose is an isomer of glucose that is found in honey, fruits, and vegetables. Driven by the pleasurable experience of sweetness, fructose, with a unique sweetness, is added to numerous beverages and manufactured food products, leading to a 1000% increase in world fructose consumption[8].

The liver was initially thought to be the primary site of fructose metabolism due to the high expression of enzymes associated with fructose metabolism in the liver [9]. However, recent evidence suggests that low doses and slower rates of fructose appearance are primarily cleared by the small intestine, while higher doses and faster rates saturate the metabolic capacity of the intestine and reach the liver and circulation [10,11]. Distinct from glycolysis, the classical pathway of glucose metabolism, the metabolism of fructose begins with its phosphorylation to fructose 1-phosphate (F1P) by the enzyme ketohexokinase (KHK) and without any negative feedback regulation [12]. Phosphofructokinase (PFK) is the most heavily rate-limiting enzyme in glycolysis and is closely regulated by the cellular metabolic status and energy status [13]. However, F1P can be cleaved directly into dihydroxyacetone phosphate (DHAP) and glyceraldehyde (GA) by the enzyme aldolase B, thereby bypassing this restriction [14]. Thus, fructose is catabolized at a much higher rate than glucose and can provide more potent substrates not only for energy production through glycolysis and the tricarboxylic acid cycle, but also for the synthesis of nucleotides and a range of amino acids [15].

The metabolism of fructose, compared to glucose, may be important for the organisms to integrate nutrients and energy, but it can also have detrimental consequences [13]. Many clinical and animal studies have shown that excessive fructose intake leads to hepatic lipid accumulation and decreased insulin sensitivity, accompanied by a large increase in inflammatory factors [16–18]. Obesity and metabolic syndrome caused by high fructose intake are proven to be risk factors for the development of many types of cancer [19]. Indeed, there is a direct link between immune function and metabolism, with the immune system monitoring and responding to specific metabolic signals to maintain the homeostasis of the microenvironment within the system [20]. The levels of several cytokines, hormones, and transcription factors in the body are often altered during fructose metabolism [21–24]. In turn, these signals influence numerous physiological functions, including immune homeostasis [1,7]. Many studies have revealed the interaction between inflammatory factors and immune cells with fructose [25,26]. Understanding the effects of fructose intake on the immune system may provide fundamental insights for understanding pathogenic mechanisms.

2. Elevated fructose exposure directly affects innate immune cells

Innate immune cells, including macrophages, dendritic cells (DCs), natural killer (NK) cells, mast cells, and granulocytes, represent the first line of defense against pathogens and disturbances in tissue homeostasis with several roles, such as secretion of cytokines and chemokines, antigen presentation, and phagocytosis [27]. In most cases, innate immune cells are relatively quiescent during steady state, but can respond rapidly when exposed to infection, inflammation, and other perturbations. Activation of immune cells typically involves the specific expression of a large number of genes and leads to alterations in cell morphology and the acquisition of new functions, while metabolic pathways in the cell play a key role in this process [28].

A recent study showed that LPS-stimulated monocytes treated with fructose directed pyruvate to the mitochondrial tricarboxylic acid (TCA) cycle for OXPHOS, without conversion to lactate [25]. This seems to indicate an unusual coupling of glycolysis and OXPHOS of the tricarboxylic acid TCA cycle in fructose-treated monocytes. They further found that fructose-treated monocytes rely on incorporated elevated amounts of glutamine-derived carbon to the TCA cycle to maintain sustained oxidative phenotype [25]. The distinct metabolic characteristics of monocytes support an enhanced inflammatory phenotype at the expense of metabolic flexibility. Glutaminolysis has previously been shown to activate the mTOR complex 1 (mTORC1) [29]. Under certain conditions, circulating monocytes in vivo migrate toward sites of inflammation and differentiate into macrophages of anti-inflammatory (alternatively activated) or pro-inflammatory (classically activated) phenotypes based on cues present in the microenvironment [30]. Increased mTORC1 activity promotes the formation of macrophages with a pro-inflammatory phenotype, leading to increased secretion of inflammatory cytokines including TNF, IL-1β, and IL-6 [31]. Also, the activation of mTORC1 can drive glycolysis by inducing the central transcription factor HIF-1α to further promote the metabolic rearrangement of monocytes induced by fructose [32,33].

In another study, acute exposure (24 h) of human DCs to high fructose environment promotesd the formation and accumulation of advanced glycation end products (AGEs) and enhances the expression of its receptor RAGE [34]. Intermediate products of glycolytic metabolism are the main source of AGEs. Fructose promotes glycolysis and the production of trisaccharides, which indirectly promote AGEs generated by glycosylation reactions. Rai et al. showed that oxidative stress and inflammation in rat skeletal muscle cells under fructose exposure may be associated with metabolic disorders caused by the accumulation of AGEs [35]. The binding of AGEs to RAGE activates multiple signaling pathways, including MAPks, STAT3, and Akt [36]. These cellular signals in turn induce activation of downstream effectors such as NF-κB and EGR-1 [37,38]. Jaiswal et al. also demonstrated that the high levels of IL-1β secreted by DCs acutely exposed to fructose are driven by activation of the NF-kB signaling pathway [34]. However, increased secretion of TNF-α and IL-6 in DCs chronically exposed (72 h) to high fructose is mainly due to a shift towards glycolysis [34]. In addition, long-term dietary fructose increases ROS production in rat peripheral blood mononuclear cells, leading to oxidative stress and apoptosis [39]. All of these findings show that high fructose treatment enhances cellular inflammatory response by inducing metabolic rearrangement.

3. Gut microbiota mediates inflammation induced by high fructose diet

The gut microbiota encompasses a diverse bacterial community that influences host nutrient metabolism and immune system regulation [40]. If the gut microbiota balance is disturbed, a series of inflammatory responses can be triggered, leading to dysregulation in the immune system or even chronic diseases in the host [24]. Several lines of evidence suggest that high levels of fructose in the diet increase the accumulation of lipids and pro-inflammatory cytokines by modulating the gut microbiota and its metabolites [24,41]. Zhao et al. proposed a dual mechanism that might explain hepatic fat accumulation, whereby fructolysis within hepatocytes promotes the expression of adipogenic genes

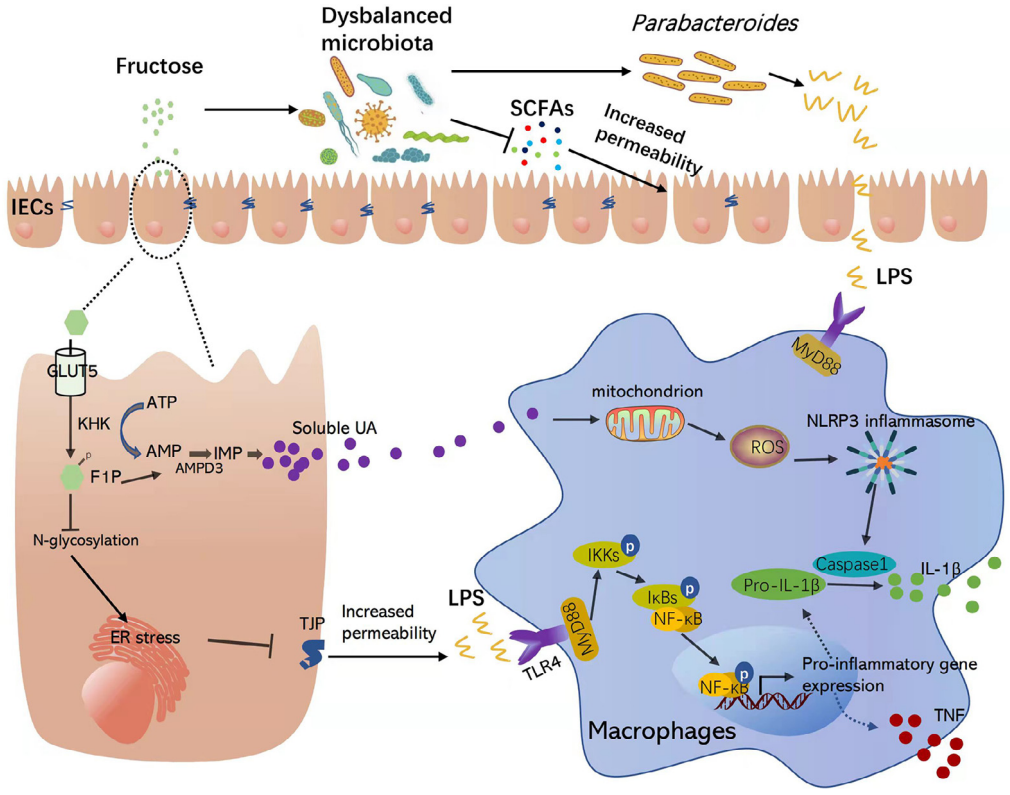

Fig. 1. Macrophage pro-inflammatory responses mediated by fructose in vivo. High fructose concentrations lead to a disruption of the intestinal microbial community, with a significant increase in the number of *Parabacteroides,* which are the key source of lipopolysaccharide (LPS). Disturbed microbes also reduce the production of short-chain fatty acids (SCFAs), which are essential for maintaining the function of the intestinal barrier. Small intestinal epithelial cells (IECs) uptake fructose via GLUT5 and metabolize it via ketohexokinase (KHK), causing endoplasmic reticulum stress (ER stress) and the production of uric acid (UA). ER stress downregulates tight junction protein (TJP) gene expression, which further deteriorates the integrity of the intestinal barrier and leads to bacterial invasion and increased LPS levels. LPS is associated with TLR-4 binding, triggering the macrophage NF-κB pathway, leads to elevated expression of pro-inflammatory factors. On the other hand, UA promotes IL-1β production through activation of NLRP3 inflammasome.

including *ChREBP-β*, *Acaca*, *Fasn,* and *Aldob*, and microbial fructose metabolism provides acetate lipogenic pools of acetyl-CoA [42]. The Bacteroidetes/Firmicutes ratio was significantly reduced in the gut of fructose-fed mice, whereas the relative abundance of *Bacteroides* showed opposing patterns [41]. The massive expansion of Bacteroidetes may contribute to the proliferation of intraepithelial lymphocytes (IELs) in the colon and ultimately to elevated IL-6 level [43]. Moreover, there was a significant increase in the abundance of *Parabacteroides*, a major source of lipopolysaccharide (LPS) production, including *Escherichia coli* and *Desulfovibrio vulgaris*, which was an important cause of elevated serum endotoxin levels [44,45]. Wang et al. also observed a significant increase in the relative abundance of pro-inflammatory bacterium *Marvinbryantia* associated with bowel dysfunction and intestinal inflammation [26].

Almost 10% of human daily energy sources are short-chain fatty acids, which are the most abundant metabolic products of intestinal microorganisms [24]. Short-chain fatty acids (SCFAs), consisting mainly of acetate, propionate and butyrate, act as signaling factors on host metabolism and immunity, regulating the proliferation, differentiation, and gene expression of virtually all immune cells in the gut [46,47]. They are able to prevent the influx of toxins by maintaining the integrity of the intestinal barrier [48] (Fig. 1). SCFAs also have been shown to control intestinal inflammation through inhibition of the inflammatory response of macrophages, stimulating Treg proliferation and promoting B-cell IGA production [49–51]. However, significantly lower concentrations of total SCFAs were observed in fructose-fed mice than in controls [52]. Importantly, SCFAs were able to activate STAT3 and mTOR pathways in Th1 cells and consequently upregulated transcription factor B lymphocyteinduced maturation protein 1 (Blimp-1), which mediated the production of the immunosuppressive cytokine IL-10 [53]. Therefore, this reduced concentration of SCFAs may partially explain the reduced IL-10 levels in the serum of fructose-fed mice. Oral administration of SCFAs or broad-spectrum antibiotics inhibited hippocampal neuroinflammatory responses in fructose-fed mice and reduced IL-1β, TNF-α, and IL-6 mRNA levels in hippocampal tissue [52]. In addition, fecal bacterial transplantation in inflamed mice caused intestinal inflammation and constipation in normal mice [41]. These findings indicate that the occurrence of intestinal inflammation induced by a high fructose diet is mediated primarily by fructose-induced alterations of the microbiota and its metabolites, rather than by fructose itself.

4. Fructose induces intestinal barrier dysfunction

Chronic intake of fructose is also associated with deterioration of the intestinal barrier and subsequent endotoxemia [54]. The intestinal barrier represents a selective semipermeable barrier involving various elements, both intra- and extracellular. The dysfunction of the intestinal epithelial barrier exhibited by excessive fructose consumption is mainly due to the decreased expression of tight junction proteins (TJPs) and adherent junction proteins (AJPs), such as, occluding, zonula occludens 1, claudin-1, adhesion molecule A, β-catenin and E-cadherin [55,56]. Altered microbial structure in fructose-fed mice resulted in the production of a large number of pro-inflammatory metabolites, including indole sulfate, arachidonic acid, and stearic acid [41]. These metabolites continue to send signals to the intestines, causing changes in TJPs, which ultimately lead to an increase in the permeability of the intestinal

barrier [24,57]. Cho and colleagues reported that fructose-fed mice increased the intestinal cytochrome P450-2E1 levels with elevated oxidative and nitrative stress, which can decrease TJP/AJP with increased apoptosis marker proteins such as phosphorylated-JNK, Bax, and cleaved-caspase 3, as well as apoptosis of enterocytes [58]. In addition, Todoric et al. recently showed that the main culprit in intestinal mucosal damage and reduced TJP protein synthesis seems to be the fructose metabolite F1P [18]. F1P is a toxic metabolite in humans that can affect protein transport and assembly by interfering with N-glycosylation, thereby triggering endoplasmic reticulum (ER) stress [18,59] (Fig. 1). ER stress not only inhibits total cellular protein synthesis but also induces apoptosis of Paneth cells, which produce antimicrobial peptides in the intestine, and loss of self-renewal capacity of epithelial stem cells [60]. Also, the abundance of Akkermansia, Bacteroides, and Ruminococcus was significantly increased in fructose-fed mice, and these bacteria can use their specific enzymatic activity to degrade mucins to release monosaccharides [41,61].

The consequences of these changes are severe, disrupting the intestinal barrier integrity increasing the exposure of various metabolites to the immune system, which allows endotoxin translocation to the portal vein, and subsequently an inflammatory response in the liver [62]. Specifically, LPS binds to Toll-like receptor (TLR)-4 on liver-recruited macrophages and activates the NF-κB signaling pathway through the adaptor protein myeloid differentiation factor 88 (Myd88) to induce the expression and secretion of TNF-α [18] (Fig. 1). Additionally, ER stress abrogates the immunosuppressive effect of IL-10 on LPS-stimulated macrophages by inhibiting the activation of STAT3, leading to an increased production of Pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-23 [63].

5. High levels of fructose enhance TLRs activation

Toll-like receptors (TLRs) are known as one of the earliest determinants of immune activation, bridging innate immunity and subsequent adaptive immunity in the host defense program. As previously mentioned, the elevated levels of endotoxin and oxidative stress induced by high fructose intake promoted the activation of TLR-4. Indeed, not only the expression of the bacterial endotoxin receptor TLR-4 was elevated, but Wagnerberger et al. also observed significantly elevated expression levels of TLR -1, 2, 3, 6, 7 and 8 in fructose-fed mice [64]. TLRs, a type I integral membrane receptor, can be activated directly by proteins, nucleic acids, and lipopolysaccharides from pathogens, and even from proteins released during host injury [65]. All TLR signaling pathways rely on Myd88 to initiate intracellular signal transduction pathways to regulate inflammation, except for TLR-3 and limited TLR-4 [66]. The N-terminal death domain of MyD88 is capable of recruiting IRAKs, which drive auto-phosphorylation and subsequent recruitment of the E3 ubiquitin ligase TRAF6 [67]. TRAF6 further activates the downstream kinase TAK1, which stimulates the IkB kinase (IKK)-mediated NF-kB signaling pathway and the mitogen-activated protein kinase (MAPK)-mediated AP-1 signaling pathway [68].

Heterodimers formed by TLR-2 and TLR-6 have previously been shown to recognize diacylated lipopeptides (cell wall components of Gram-positive bacteria, yeast, and mycoplasma) and are potentially important drivers of Th1 and 17-mediated inflammatory responses in IBD patients [69]. Fructose treatment enhances α-SMA and collagen expression through TLR-6-regulated ROS and NF-κB signaling pathways, which produces oxidative stress and an inflammatory response in cardiomyocytes, and consequently to myocardial fibrosis in mice [70]. TLR-6 knockout mice have a protective effect on myocardial fibrosis induced by high fructose diet, due to the lower phosphorylation levels of IKKα and NF-κB and the production of ROS compared with the wild type [70]. The elevated serum levels of LPS in fructose-fed mice may be an important cause of hepatitis. Chronic intake of 30% fructose solution resulted in a significant increase in blood endotoxin levels (approximately 27-fold) in both TLR-4 mutant and wild-type mice, while hepatic steatosis levels in TLR4-deficient mice were significantly reduced compared to the wild-type mice [71]. Thus, the signaling pathway regulated by TLR-4, which is the receptor for LPS, is closely associated with the persistence of the inflammatory response and the development of infection. Zhou et al. found that feeding juglanin can block the phosphorylation of key enzymes in the activation of MAPK and NF-kB, which inhibits the TLR-4 signaling pathway, thereby reducing fructose-induced inflammation and cell apoptosis in rats [72]. Furthermore, Tan et al. showed that conjugated linoleic acid ameliorated fructose-induced renal inflammation in rats, in which the molecular mechanism may be related to the inhibition of NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome and TLR-4 signaling pathway [73]. On the other hand, one recent study showed that TLR-4 signaling deficient mice (C3H/HeJ) were more susceptible to fructose-induced disease than wild-type mice (C57BL/6J) [74], suggesting the regulation mechanism of fructose is a more complex regulatory process and needs to be further determined. The reason for this difference may be related to the way of fructose feeding, the duration of fructose exposure, and the mouse strain. More likely, TLR-4 signaling may not be the only crucial factor of fructose-induced metabolic complications.

6. Pro-inflammatory metabolites under high fructose consumption

The accumulation of different metabolites may directly affect the normal function of the immune system [75]. Fructose differs significantly from glucose in terms of metabolic pathways, metabolites, and regulatory mechanisms. Fructose is initially absorbed mainly by the glucose transporter 5 of the intestinal cells and subsequently metabolized to produce lactate, Free Fatty Acids (FFAs), very low-density lipoprotein (VLDG), ceramide, Uric Acid (UA) and methylglyoxal (MG) [76]. Peripheral plasma fructose concentration can increase acutely by 10-fold after fructose consumption, but returns to fasting levels within 2 h [13]. This rapid clearance can lead to a massive and rapid expansion of fructose-derived metabolites. Below, we describe some of the metabolites that accumulate under a high fructose diet and the association between these metabolites and immune dysregulation and chronic inflammation.

6.1. Uric acid (UA)

The uncontrolled phosphorylation of fructose to F1P leads to a sustained depletion of intracellular adenosine triphosphate (ATP) levels and activation of adenosine monophosphate (AMP) deaminase, which cleaves AMP to produce inosine monophosphate (IMP) and promotes uric acid (UA) production [77,78]. Although UA acts as an antioxidant in the extracellular environment by preventing oxidative stress caused by cancer and aging, once UA enters some cells, it produces a series of adverse effects, including inhibition of NO production and induction of elevated expression of pro-inflammatory and pro-thrombotic factors [79]. Long-term fructose consumption inhibits renal uric acid excretion and promotes elevated serum uric acid levels, and even a single administration of fructose in rats has been shown to diminish the function of ileal UA excretion [80]. The elevated circulating UA levels caused by excessive fructose intake in adult males con-

tributes to the increased risk of hypertension and accompanying symptoms of metabolic syndrome [81]. Elevated serum UA concentrations have been shown to be strongly associated with signs of inflammation, such as increased white blood cell counts, increased levels of oxidative stress, and increased numbers of cytokines involved in the innate immune response, including monocyte chemotactic protein (MCP)-1, IL-6, IL-1β, and TNFα [82,83]. UA promotes the activation of nicotinamide adenine dinucleotide (NADPH) oxidase, which is thought to be one of the most important causes of ROS production in cells and can be transferred to mitochondria to participate in mitochondrial oxidative stress [84,85]. This increase in ROS activates the NLRP3 inflammasome in fructose-fed rats by inducing p38 MAPK phosphorylation and thioredoxin-interacting protein (TXNIP) expression [86]. Activation of the NLRP3 inflammasome and subsequent recruitment of caspase 1 protein is a well-known pathway for IL-1β production by macrophages [87] (Fig. 1). In addition, elevated uric acid levels can activate NF-κB signaling pathways in mouse kidney, pancreas, and hypothalamus cells by inducing the phosphorylation of IKK and IκBα, triggering inflammation and dysfunction in these organs [86]. Notably, UA generated in fructose metabolism can stimulate endogenous fructose production by activating aldose reductase in polyols, a positive feedback regulatory mechanism that further amplifies UA levels [88]. These findings link fructose intake, UA production, and the development of metabolic syndromes and highlight the pathological role of uric acid in the progression of these diseases.

6.2. Free fatty acids (FFAs)

Fructose feeding promotes de novo lipogenesis (DNL) in mouse liver by upregulating the expression of genes related to carbohydrate metabolism and adipogenesis, including *Srebf1*, *Mlxipl*, *Acaca*, *Fasn*, and *Acly* [18]. Varma et al. also found that fructose can alter glucose metabolism in adipocytes to meet its own metabolic endpoints via an oxidative pathway, a process in which fructose stimulates adipocytes to de novo FFAs synthesis [89]. Fructose-induced inflammation, on the other hand, up-regulates the activity of 11-B hydroxysteroid dehydrogenase type 1 in adipose tissue and liver, which enhances the glucocorticoid response and promotes elevated intracellular cortisol levels [90]. Increased cortisol levels in adipocytes are often accompanied by an increased flux of fatty acids [91]. These FFAs enter the liver directly through the portal circulation and affect hepatic metabolism. FFAs are oxidized or esterified to triglycerides (TGs) in the liver and secreted as very low density lipoproteins (VLDL) -TG [92]. Thus, when the rate of oxidation and esterification of FFA is higher than the rate of VLDL production, accumulation of TGs and FFAs occurs in the liver and extrahepatic tissues, which triggers activation of protein kinase C (PKC) and consequently insulin resistance [90]. In turn, insulin resistance increases the release of FFAs through lipolysis, promoting elevated levels of serum FFAs [93]. Activation of PKC induced by FFAs can promote ROS production in patients with insulin resistance status through activation of NAD(P)H oxidase [94]. In addition, FFAs can directly activate the NF-κB signaling pathway in macrophages and adipocytes via TLR-4, inducing the expression of pro-inflammatory factors and thus promoting obesity-dependent insulin resistance [95]. Interestingly, FFAs had no direct effect on the pro-inflammatory response of DCs, but rather exacerbated TH1/ TH17-mediated inflammation by sensitizing DCs [96]. Heart, adipose tissue, pancreatic islets, and skeletal muscle are more susceptible to metabolic disorders and pro-inflammatory responses because of their high expression of FFA transporter proteins (FATPs) and CD36, which are able to uptake high fructose-induced FFAs [97]. High fructose diets increase levels of CD36 in the heart, liver and blood, and CD36 has been shown to be a key regulator of fatty acid uptake [98]. In particular, CD36 signaling in macrophages regulates their migration through NADPH oxidation-dependent ROS production to trap them in the arterial intima, and makes macrophages turn into lipid-laden foam cells by increasing the accumulation of fatty acids, leading to the aggravation of atherosclerosis [99–101].

6.3. Lactate

There are differences in the metabolic kinetics and fate of fructose and glucose in hepatocytes. Liu et al. have shown that hepatocytes convert fructose to lactate twice as fast as glucose [15]. High fructose intake can induce a sustained increase in plasma lactate concentration, leading to hyperlactatemia [102]. It is possible that the reduced uptake and consumption of glucose in skeletal muscle observed in mice on a high fructose diet is mediated by lactate production from the metabolism of fructose. As an important factor for maintaining insulin resistance, lactic acid can reduce the level of Glut-4 and inhibit the activity of HK and PFK, resulting in a decrease of skeletal muscle glycolytic flux [76,103]. Lactate can function through the plasma membrane Gi-protein-coupled receptor 81 (GPR81) to activate the expression of genes related to lactic acid metabolism in tumor cells, and maintain the proliferation of tumor cells in the absence of glucose and the presence of lactate [104]. Of note, GPR81 knockdown strongly enhances *pro-Il1b* and *Nlrp3* expression in Kupffer cells (hepatic macrophage), promoting hepatocyte apoptosis and liver inflammation [105]. Transient engagement of lactate in the physiological concentration range (3–4 mmol/L) to GPR81 inhibits TLR4- and TLR9-mediated pro-inflammatory responses in Kupffer cells by preventing activation of the NF-kB pathway [105]. However, long-term exposure to super-physiological concentrations of lactic acid can cause intracellular acidosis, which stimulates MD-2, a co-receptor of TLR-4, and enhances the expression of inflammatory genes [106]. Lactate levels increase with the degree of inflammation, which triggers a series of intracellular signals that drive certain chronic inflammatory processes. In synovial joints of rheumatoid arthritis patients, lactate interacts with the $CD4^+$ surface lactate transporter protein SLC5A12 to interfere with glycolysis and activate a stop migration signal, while sodium lactate can inhibit $CD8^+$ migration via the sodium lactate transporter protein SLC5A12 [107]. In addition, sodium lactate induces differentiation of naïve $CD4^+$ T cells to the Th17 subset and IL-17 production [108]. Lactate inhibits the proliferation and cytokine production of cytotoxic CD8+ T cells, resulting in impaired CD8+ T cell-mediated killing function [109]. Overall, lactate detrimentally increases chronic inflammation by inhibiting T-cell migration and regulating T-cell function, such as promoting inflammatory factor release and decreasing cytolytic capacity.

7. Fructose promotes resistance to cancer immunotherapy

Fructose was shown to stimulate DNL and steatosis through inflammatory signals such as NF-κB pathway and TNF secretion [18]. DNL can dramatically changes the membrane lipid saturation of cancer cells to protect them from free radicals and chemotherapeutic agents [110]. Cancer cells utilize fructose as fuel by GLUT5, a specific fructose transporter that has been found to be expressed on the surface of a variety of cancer cells including acute myeloid leukemia (AML), rectal, breast, pancreatic, glioblastoma, liver, and lung cancers [14,19]. Weng et al. suggested that upregulation of GLUT5 expression in non-small cell lung cancer contributes to the metabolism of fructose by cancer cells under glucose-restricted conditions and promotes cancer proliferation, migration, and invasion [111]. Likewise, high expression of GLUT5 was found in myeloid cells of AML patients and tumor cells of glioma patients,

which was closely associated with the malignancy and poor clinical prognosis of tumor patients [112,113]. In addition, the role of aldolase B and KHK-A in mediating fructose-induced cancer metastasis seems distinct. Goncalves et al. studied primary colon carcinoma and liver metastasis samples and found that the upregulation of aldolase B expression in liver metastases enhanced fructose metabolism compared with primary tumors, while GLUT5 levels were not significantly different [114]. The *KHK* gene expresses two isoforms, KHK-A and KHK-C. KHK-C is primarily expressed in the liver and is thought to be the major enzyme in fructose metabolism. In contrast, KHK-A is expressed at low levels in most tissues and has a much lower affinity for fructose than KHK-C [115]. However, most cancer cell lines predominantly express KHK-A rather than KHK-C, and KHK-A acts as a protein kinase to promote fructose-induced breast cancer migration [116]. Under fructose stimulation, KHK-A is transported to the nucleus and phosphorylates the Ser25 site of YWHAH, which inhibits the expression of E-cadherin, thereby leading to breast cancer cell migration [116].

Compared to glucose, fructose has a more pronounced advantage in driving the cancer process. Even moderate doses of fructose in the diet can lead to KHK-dependent tumor growth associated with PFK activation and enhanced glycolysis [117]. Most solid tumors are hypoxic to some degree due to inadequate oxygen supply caused by abnormal vascular structure, while the presence of fructose promotes tumor survival in a hypoxic microenvironment. In hypoxic colorectal cancer cells, the fructose metabolite F1P inhibits the M2 isoform of pyruvate kinase (PKM2), then amplifies the activity of HIF-1α to promote cancer cells survival [118].

The successful application of immune checkpoint blockers anti-CTLA-4 and anti-PD-1/PD-L1 has initiated a new era of cancer immunotherapy, but these therapies have failed to generate sustained benefit in some patients. One study reported that dietary fructose induces the expression of the protective protein heme oxygenase-1 (HO-1) in melanoma tumor cells, allowing tumors to resist the immune-mediated killing elicited during checkpoint-blocking immunotherapy [119]. Notably, the receptor involved in fructose uptake by tumor cells in this process does not appear to be GLUT5. HO-1 enhances the antioxidant, antiapoptotic, and anti-inflammatory properties of cells through its metabolites biliverdin/bilirubin and CO, and participates in the protective defense mechanisms of tumor cells [120]. The use of HO-1 inhibitors significantly improved the immunotherapeutic outcomes of melanoma in fructose-fed mice [119]. A growing body of studies indicates that extracellular acidosis suppresses T lymphocyte-mediated immunity and that there is a strong correlation between the protumor effect of lactate and immune evasion by tumors [107,121]. Feng et al. recently found that lactate concentrations in a range induced PD-L1 expression levels in human lung adenocarcinoma in a dose-dependent manner [122]. PD-L1 is a ligand for PD1, interaction of them generates specific conformation changes that protects tumors from immune recognition and inhibits tumor cell destruction by cytotoxic T cells. Lactate activates the transcriptional cofactor TAZ through its receptor GPR81, which promotes the upregulation of PD-L1 in lung cancer cells at the transcriptional level [122]. In co-culture experiments, this upregulation reduced interferon-γ production in T cells and induced apoptosis [122]. Another study showed that high levels of lactate blocked the expression of IFN-g and granzyme B in mouse NK cells, which directly inhibited the NK cell-mediated response [123]. Collectively, elevated lactate levels on a high fructose diet may be associated with being an alternative mechanism by which fructose promotes tumor immune evasion. Therefore, targeting fructose metabolism may be beneficial in tumor immunotherapy.

8. Conclusion

Chronic low-grade inflammation contributes to the development of multiple diseases, including cardiovascular disease, obesity-related metabolic syndrome, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and many types of cancer, which are important risk factors facing society today. Fructose appears to be one of the triggers of signaling pathways for chronic low-grade inflammation. High fructose intake disrupts gut microbial community homeostasis and decreases intestinal barrier permeability, which in turn induces inflammation in the organism. In addition, fructose promotes cellular metabolic rearrangement, inflammatory cytokine production, and tumor immune escape due to its unique metabolic pattern. Interventions in the metabolic process can slow down the fructose-induced inflammatory response and pro-tumor effects, such as inhibition of KHK, GLUT8, GLUT5, etc. [14,112,124]. It is important to note that in some cells, fructose is not dependent on KHK, but HK for catabolism [125,126].

Although there is enough evidence to support the idea that fructose mediates inflammation, many important questions still need to be addressed. For example, fructose promotes cellular glycolysis and metabolic rearrangement, but most of the current research has focused on the effects of fructose on innate immunity, and knowledge of adaptive immunity remains limited. Furthermore, studies in rats indicate that females are more susceptible to fructose diet than males [124], but the complete physiological function of these sex differences remains obscure. Because of complexity, legitimacy, and potential ethical issues, most studies on high fructose diets have relied on animal models, which can't provide a full feature of the effects of fructose on humans. Overall, further research is needed on the underlying mechanisms by which fructose causes disease and immune system disorders so that we can implement effective programs to change our current dietary habits.

CRediT authorship contribution statement

Hao Cheng: Writing – original draft, Writing – review & editing. **Jingyang Zhou:** Writing – review & editing. **Yutong Sun:** Writing – original draft. **Qipeng Zhan:** Writing – review & editing. **Dunfang Zhang:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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