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Blocking Fructose could be a Novel Approach against Cancer

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Abstract

Despite of the appreciation for the recent advance of anti-cancer therapy, the effect remains unsatisfactory. Since obesity and metabolic syndrome are strongly associated with cancers, there might be a common pathway underlying these disorders. Recently, sugar, particularly fructose, has emerged as a potential driving force to develop obesity and metabolic syndrome, and also associated with several types of cancers, suggesting that fructose might be a link between these disorders as fructose, as opposed to glucose, drives several pathways for cancer growth. A unique property of fructose is to produce uric acid which causes an imbalance favoring glycolysis over mitochondrial respiration, resembling the Warburg effect in cancer cells. Fructose also activates the pentose phosphate pathway, resulting in the synthesis of nucleotide and amino acid. Lactate production is also accelerated as an alternative energy while *de novo* lipogenesis links to energy supply and membrane formation for proliferating cells. Here, we discuss the role of fructose in several types of cancers and propose that blocking fructose metabolism could be an additional therapy to alleviate the cancer growth.

Keywords: Uric acid; Lactate; Glycolysis; Mitochondria; The warburg effect; Pentose phosphate pathway; Lipogenesis

Introduction

Metabolic syndrome is associated with cancer. Cohort studies showed that the presence of metabolic syndrome was associated with liver, colorectal, and bladder cancer in men, and with endometrial, pancreatic, breast postmenopausal, rectal, and colorectal cancers [1]. There might be a common mechanism driving these disorders. While several mechanisms are now proposed, unhealthy diet could contribute to an increase in cancer risk [2,3].

Glucose has been thought to be a major energy source for cancer growth [4-7]. In 1924 Otto Warburg initially mentioned that cancer cells, as opposed to normal cells, exhibit a unique property to ferment glucose into lactate even in the presence of sufficient oxygen [8,9]. Importantly, the Warburg effect is characterized by a low respiration rate in mitochondria despite of relatively the high rate of glucose uptake [10]. However, the fact is that some types of cancers fail to utilize glucose as an energy source [11], suggesting that there might be another source of energy for cancer growth.

Fructose is a simple sugar in fruits that has a role in storing fat and glycogen, developing insulin resistance, and increasing sodium reabsorption, all of which are likely survival processes for wild animals, great apes, and humans during time of food shortage [12]. However, we are currently consuming a large amount of fructose in the form of sugar because sugar makes foods tasty. As a result, fructose has emerged as culprits for the current epidemic of obesity, diabetes and metabolic syndrome in the modern society [13]. The rise in fructose consumption over the last century has paralleled the rising prevalence of obesity and metabolic syndrome as well as some types of cancers, leading to the hypothesis that the excessive amount of fructose could be a link between these disorders.

Pathways of fructose-driven cancer growth

Several factors are required for cancer growth, including energy source, nucleotide, lipid, and redox balance. The Warburg effect is also important. Fructose is metabolized through four pathways and contributes to meet the demand for cancer (**Figure 1**).

Glycolysis for energy production

The first enzyme for fructose metabolism is fructokinase (known as ketohexokinase; KHK), which phosphorylates fructose to produce Fructose 1-phosphate (Fru1P). Fructokinase is predominantly expressed in the liver, the kidney and other organs, but the liver is the primary site for dietary fructose metabolism [14,15]. Interestingly, recent studies have shown that microbiota in the gastrointestinal tract plays a substantial role in fructose metabolism [16,17]. Furthermore, recent experiments using mice with the selective knockout of fructokinase in the liver or intestine document that, while the

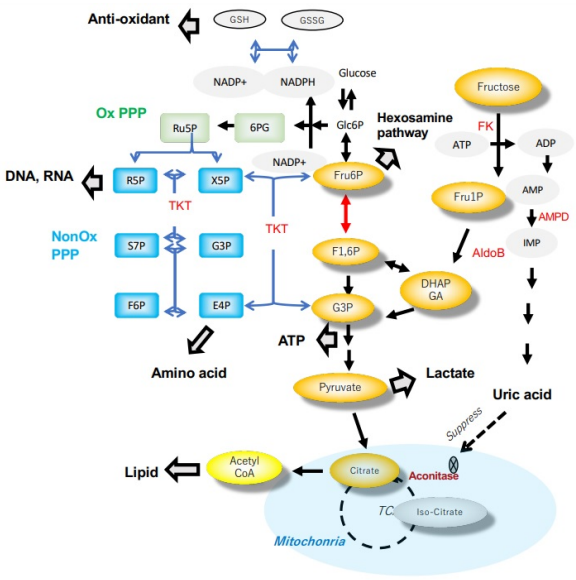

Figure 1: Fructose metabolism for cancer growth. In fructose metabolism glycolysis results in the production of ATP and lactate. Uric acid blocks aconitase, resulting in the disconnection of fructose metabolism from mitochondrial respiration. As a result, citrate is converted to acetyl-CoA, which is metabolized by subsequent reaction to form fatty acid. Glucose 6-phosphate (Glc6P) is metabolized in the oxidative pentose phosphate pathway (Ox PPP), to produce Ribulose 5-phosphate (Ru5P) and NADPH. NADPH is utilized to turn glutathione disulfide (GSSG) to glutathione (GSH). In turn, Ru5P links with the non-oxidative PPP (NonOx PPP), which is activated through Fructose 6-phosphate (F6P) and Glyceraldehyde 3-phosphate (G3P) with transketolase (TKT) activation. In the non-oxidative PPP, erhthrose 4-phosphate (E4P) is utilized for amino acid formation. AR: aldose reductase; FK: fructokinase; AldoB: aldolase B; AMPD: AMP deaminase.

intestine has an important role in clearance and intake, the liver metabolism of fructose is responsible for most of the features of metabolic syndrome [18]. Fru1P is subsequently metabolized by aldolase B and triokinase to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate to enter the glycolytic pathway distal to phosphofructokinase. Recently, a key role of aldolase B in cancer growth was shown that aldolase B mediates colon cancer liver metastasis and that reducing dietary fructose diminishes liver metastatic growth in mice [19].

Subsequently, glyceraldehyde-3-phosphate is metabolized into pyruvate in glycolytic pathway to produce ATP and NADH (**Figure 2**). Pyruvate is further converted into lactate using lactate dehydrogenase. This reaction is usually stimulated by low oxygen, but is accelerated by fructose even under aerobic condition [20]. The lactate seems to be an energy for cancer growth as blocking lactate production by blocking LDH-A with a chemical inhibitor or gene deletion ameliorated angiogenesis and inhibited cancer cell proliferation [21,22].

In addition, fructose may facilitate glucose utilization by activating glucokinase. Glucokinase (hexokinase (HK) IV) is negatively regulated by glucokinase regulator protein (GKRP) binding with Fru6P and is sequestered in the nucleus, but in the presence of fructose Fru6P is replaced by Fru1P to release glucokinase from GKRP into cytosol for stimulating glucose uptake and glycolysis [23-25]. However, glucokinase is usually expressed only in hepatocyte and pancreatic β cells, but is less expressed in cancer cells [26] so that the role of glucokinase needs to be clarified in the cancer. A recently discovered enzyme, ADP-dependent glucokinase (ADPGK) could be involved in the cancer growth [27] as this enzyme is highly expressed in human tumors and tumor cell lines [28]. ADPGK may function under stress conditions where the supply of ATP is limited [29]. In turn, it has been well documented that HK II is overexpressed in cancer cells to facilitate glycolysis, suppress the death of cancer cells, and promote metastasis [26].

Pentose phosphate pathway for nucleotide, amino acid, and redox balance

The pentose phosphate pathway (PPP) is activated by fructose, and is composed of two sections, oxidative pathway and non-oxidative pathway (**Figure 2**). Glucose 6-phosphate, a fructose metabolite, is metabolized by three sequential reactions to produce NADPH for reducing oxidative stress with GSH production in the oxidative pathway. In turn, two forms of fructose carbon backbones, fructose 6-phosphate and glyceraldehyde-3-phosphate, are catalyzed by transketolase to enter the non-oxidative pathway. The activation of the transketolase drives nucleotide formation through ribose 5-phosphate while erythrose 4-phosphate are metabolized into amino acid. Liu et al. found that using pancreatic cancer cells, fructose and glucose exhibited the same effect on cell proliferation, but their intracellular metabolism was different [30]. The productions of lactate, CO^2, and fatty acid were significantly higher in cells with glucose compared to those with fructose. However, fructose was more potent to activate the non-oxidative pentose phosphate pathway in association with intracellular transketolase activation, and accelerate ribose synthesis and uric acid production [30]. Alternatively, activated hexokinase could convert fructose into fructose 6-phosphate, which might be at link between glycolysis and the non-oxidative PPP in cancer cells.

Lipogenesis

Lipids are likely required as an energy source and for membrane formation, and as signaling molecules in cancer (**Figure 2**). Therefore, cancer cells actively uptake lipid and promote *de novo* lipogenesis [31,32]. Fructose is metabolized in glycolytic pathway to provide the carbon backbone as acetyl-CoA for *de novo* lipogenesis, and also promotes fatty acid synthesis to form palmitate. In turn, glyceraldehyde-3-phosphate carrying fructose carbon backbone is also utilized to form triglyceride. Importantly, triglyceride levels were elevated in several types of cancer and associated with an increased risk of cancer [33-35]. Fructose acts as a carbon source and stimulates some intracellular signaling, including Carbohydrate-responsive element-binding protein (ChREBP) [36,37] and glucokinase regulatory protein (GKRP) [23,24]. In turn, a recent study using a mouse model demonstrated that fructose-mediated fatty liver disease is likely mediated by impairment of fatty acid oxidation due to deacetylation of Acyl-CoA dehydrogenase, long chain (ACADL) and carnitine palmitoyl-transferase 1α (CPT1α) [38].

Uric Acid for Warbug effect

Fructokinase activation rapidly sequesters a phosphate, consequently activating AMP deaminase to cleave AMP to IMP [39]. However, the phosphate levels subsequently increase due to the slower aldolase reaction with Fru1P. This reaction is further accentuated by the increased IMP, which is an aldolase B inhibitor [40]. Sequential enzymatic activation metabolizes IMP and eventually produce uric acid [13,37,41]. Recently, our research group has attempted to clarify the role of uric acid in fructose metabolism [13,41]. We found that uric acid could prevent fructose metabolites from channeling into mitochondrial oxidation in the human hepatocellular carcinoma cell line HepG2 [42]. A potential mechanism was the ability of uric acid to suppress aconitase activity in the mitochondria, and to disconnect fructose metabolites from mitochondrial oxidation. Since aconitase lies at the junction of acetyl-CoA oxidation, blocking aconitase leads to acetyl-CoA shuttling out of the mitochondria, resulting in the accumulation of citrate in the cytosol, where citrate was utilized for lipid synthesis by sequential ATP-citrate lyase and fatty-acid synthase [42]. A key point is that uric acid does not totally block aconitase activity so that mitochondria respiration remains operated (**Figure 2**).

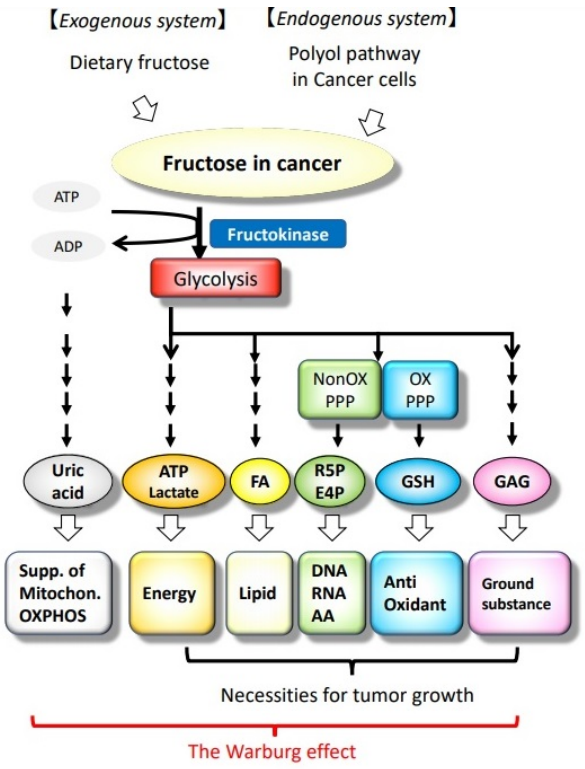

Figure 2: A schema of fructose linking four pathways meeting the need for cancer. Fructose metabolism drives several pathways, including energy production, lipogenesis, the pentose phosphate pathway, the hexosamine pathway and the suppression of mitochondrial oxidative phosphorylation (OXPHOS) by uric acid. The Warburg effect is produced by the combination with these pathways. AA: Amino acid; OX: Oxidative; GAG: Glycosaminoglycan.

In terms of the Warburg effect, several investigators have re-evaluated the role of mitochondria, and showed that mitochondria were commonly required for tumor growth. A key point is that the glycolytic rate may far exceed the maximal rate of mitochondrial pyruvate oxidation, thus making lactate excretion unavoidable in the presence of abundant glucose [10]. In fact, Weinberg et al indicated that tumor cells would require mitochondria-derived reactive oxygen species (ROS), but not OXPHOS, for cell proliferation [43].

Role of fructose in Cancer

The Nurses' Health Study showed that fructose intake was the strongest risk factor for pancreatic cancer in subjects who were overweight or sedentary [44]. Subsequently, the combined analysis with Nurses' Health Study and the Health Professionals Follow-up Study showed that sugar-sweetened beverage consumption was associated with an increase in risk for pancreatic cancer among women, but not men [45]. Alternatively, a food-frequency questionnaire with 77,797 women and men in Sweden also found that high consumption of sugar and high-sugar foods resulted in a greater risk of pancreatic cancer [46]. In addition, serum concentration of fructose was also higher in patients with pancreatic cancer than healthy patients [47].

Several clinical studies found a positive association between sugar/fructose intake and the risk of several types of cancers, including colorectal cancer [48] and breast cancer [49]. For breast cancer cells, fructose caused greater adhesion of cancer cells to endothelium and enhanced aggressive migration compared to glucose [50]. Jiang et al. also found that a fructose diet stimulated tumor growth of breast cancer with the expression of 12-lipoxygenase and the production of the arachidonate metabolite 12-hydroxy-5Z,8Z,10E,14Z-eicosate-traenoic acid production, and the spread of metastatic tumors in the lung, compared to either a glucose or control starch diet [51].

Other types of cancers would be also promoted by fructose. Weng et al. showed that compared to glucose, fructose was more potent to produce ATP and fatty acids for lung cancers [52]. The causal role of fructose could be also supported for by the fact an increase in GLUT5 expression was associated with poor prognosis in patients with lung adenocarcinoma [52]. Likewise, AML patients were found to exhibited an increase in GLUT5 gene expression in myeloid cells, while increased fructose utilization was associated with poor clinical outcomes [53]. In brain, it was also found that fructokinase and GLUT5 were highly expressed in glioma and were also correlated with malignancy and poor survival of glioma patients [54,55] (**Table 1**).

Blocking fructose metabolism in cancer

Goncalves et al. investigated the effects of dietary fructose (~3% of total daily caloric intake) in adenomatous polyposis coli mutant mice, which are predisposed to develop intestinal tumors [56]. The fructose-treated mice showed a substantial increase in tumor size and tumor grade in the absence of obesity and metabolic syndrome. They confirmed that fructose was

converted to fructose-1-phosphate, leading to activation of glycolysis and increased synthesis of fatty acids that support tumor growth in tumor, and that knocking down fructose metabolism by deleting fructokinase (ketohexokinase) gene suppressed cancer growth in response to HFCS [56].

Alternatively, an inhibiting aldolase B could also block fructose metabolism, but the anti-cancerous effect remains controversial. Several studies showed that fructose-mediated aldolase B drives either colon cancer [57,58] or its liver metastasis [19]. In turn, a recent study has shown that systemic or liver-specific aldolase B knockout promotes tumorigenesis in mice through enhancing G6PD activity and pentose phosphate pathway metabolism [59-61].

Type of cancer	References
Pancreatic cancer	[44] [45] [46] [47] [60] [30]
Colorectal cancer	[48] [56]
Breast cancer	[49] [50] [51]
Lung cancer	[52]
Acute myelogenous leukemia	[53]
Glioma	[54,55]
Hepatocellular carcinoma	[61]

Table 1: Types of cancers in which fructose contributes to tumor growth.

Conclusion

An increased fructose intake is associated with a risk for several types of cancer, suggesting that fructose might be an alternative fuel for cancer growth. A mechanism could be accounted for by the ability of fructose to drive four pathways for cancer growth. Necessities for cancer growth including energy, nucleic acid, amino acid, redox balance and the Warburg effects could be provided by fructose metabolism. Blocking fructose metabolism cannot eliminate cancer, but may slow the progression of cancer growth.

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