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**Review Article**

# Fructose, Another Sweet for Cancer: A Context Acting Nutrient Hypothesis

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## Abstract

Rapidly proliferating cancer cells exhibit a high energy demand. However, their utilization of the glycolytic pathway is inefficient, leading to a compensatory effect wherein cancer cells consume ten to twenty times more glucose than normal cells. In cases where glucose availability is limited due to a poorly perfused hypoxic microenvironment, cancer cells resort to alternative energy sources, including fructose. Certain tumors have been found to rely heavily on fructose, and fructose utilization contributes to pro-tumoral signaling and increased cancer risk. Over the past 70 years, dietary fructose intake has steadily increased, resulting in a rise in obesity and metabolic syndrome, both of which elevate cancer risk. In this paper, we present compelling evidence that highlights the role of fructose and the glucose transporter GLUT5 in promoting specific types of tumors. We summarize the existing evidence and pathways through which fructose contributes to cancer metabolism, particularly in cases where glucose availability is restricted. Furthermore, we propose a hypothesis that elucidates the regulation of the lipogenic phenotype by dietary fructose intake and cellular energy status. It is important to note that the effects of fructose are context-dependent, with its tumor-promoting effects varying based on the energy status of the cell. We comprehensively analyze why targeting fructose uptake and fructolysis should be important for the management of some tumors and cancer prevention.

## Introduction

Glucose is classically considered the primary source of energy for cancer cells.[1–5] Glucose uptake by malignant cells is more than ten times higher than in normal cells.[6–9] The increased tumor glucose uptake has led to the development of a very useful diagnostic method to visualize them: the $^{18}$F-2-fluoro-2-deoxyglucose positron emission tomography (PET).[10]

Paradoxically, despite the much higher glucose uptake in malignant cells, tumor glucose concentrations are much lower than in their normal counterparts.[11,12] However, this apparent paradox has an explanation. There is no paradox: all the glucose taken up in tumors is swiftly used by the elevated metabolism of tumor cells, and thus very little remains in the tumor microenvironment. PET, mentioned above, uses the derivative of glucose, $^{18}$F-2-fluoro-2-deoxyglucose, to detect tumor cells. The reason why PET shows high $^{18}$F-2-fluoro-2-deoxyglucose concentrations in tumors is that this derivative of 2-deoxyglucose blocks glycolysis, and there is no further degradation,[13] allowing accumulation of an $^{18}$F-2-fluoro-2-deoxyglucose for visualization.[14]

The increased glucose uptake of tumors, and the fact that the arrival of nutrients to a very hypoxic, poorly perfused tumor is limited, should prompt a question: how can cancer cells get all the necessary energy needed from glucose in a depleted environment that is difficult to replenish? Beyond glutamine as a proxy, this question has not yet been fully answered. One possibility is that fructose is an important energy source in at least some types of cancer, and there is evidence to support this concept.[15–18] However, evidence suggests that fructose uptake is significantly reduced in certain tumors, such as hepatocarcinoma, compared to normal liver tissue.[19] So perhaps, there is a situation whereby in most tumors, fructose is an important contributor to tumor growth and metabolism, but this is not the case in hepatomas.

Interestingly, the situation may vary in different types of tumors. In prostate cancer, glucose is not the primary energy source, at least in the early stages.[20] This explains why PET studies based on glucose uptake in prostate cancer have a low diagnostic value.[21–23] Fructose is transported passively across cell membranes

**Keywords:** Cancer; Fructose; Glucose; GLUT5; Tumors.

**Abbreviations:** ACC, Acetyl CoA Carboxylase; ADP, adenosine diphosphate; AMPK, adenosine monophosphate kinase; ATP, adenosine triphosphate; ChREBP, Carbohydrate Responsive Element Binding Protein; HIF-1α, hypoxia-inducible factor 1-alpha; IMP, inositol monophosphate; KHK, Ketohexokinase; PET, positron emission tomography; PFK, phosphofructokinase; RR, relative risk; SREBP1, Sterol regulatory element binding protein-1.

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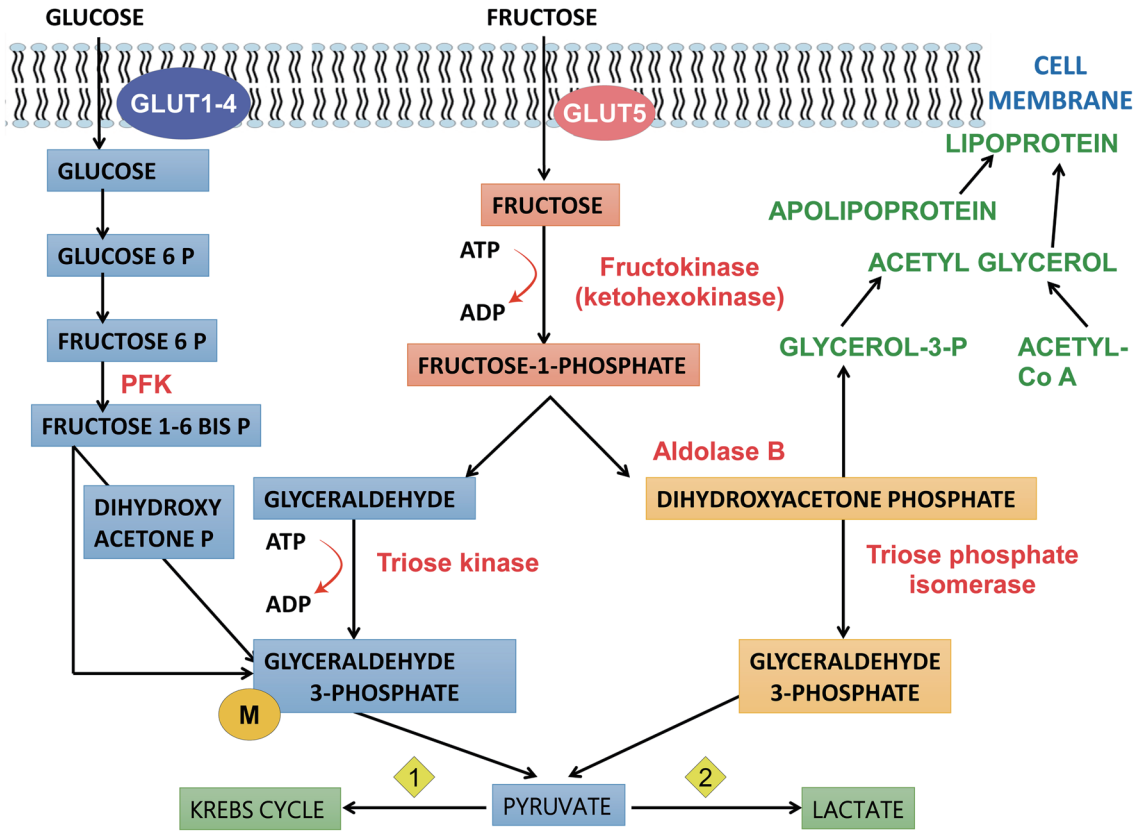


**Fig. 1. Fructose metabolism.** Fructose is transported into the cell by GLUT5 and is phosphorylated by Fructokinase, also known as ketohexokinase. Aldolase B splits the molecule into two trioses: dihydroxyacetone phosphate and glyceraldehyde. Glyceraldehyde is phosphorylated by a triokinase-producing glyceraldehyde 3-phosphate. Dihydroxyacetone phosphate is changed to glyceraldehyde 3-phosphate by an isomerase. "1" represents oxidative metabolism, and "2" the glycolytic pathway. After the glyceraldehyde 3-phosphate stage is reached, glucose and fructose metabolism merge. However, fructose achieves this stage without passing through the phosphofructokinase enzymatic action as glucose metabolism does. Phosphofructokinase (PFK) is a metabolic checkpoint under insulin control. ATP, adenosine triphosphate; ADP adenosine diphosphate; PFK, phosphofructokinase.

by the glucose transporter GLUT5,[24] whereas GLUT1 is selective for glucose.[25] It has been shown that prostate high-grade intraepithelial neoplasias show increased expression of GLUT5 and an absence of GLUT1, suggesting that early prostate malignancies use fructose rather than glucose as an energy source.[26,27] It seems that the importance and uptake of fructose may vary from one type of malignancy to another.

## Fructose metabolism

To understand the role of fructose in tumor malignancy, it is crucial to understand its metabolism compared to glucose. Fructose and glucose are metabolized differently. Both require transporters to cross the cell membrane, but glucose is taken up by glucose transporters 1 to 4 (GLUT 1–4), while fructose requires the specific transporter GLUT5.[28,29] The tissue uptake is also different for the two sugars. Almost all fructose is normally metabolized in the liver (80%), while glucose can be metabolized in any tissue.[30] Another difference is in the first step of metabolism. Although the fructose molecule is very similar to glucose, it is not readily phosphorylated by hexokinases that phosphorylate glucose.

Cells that can metabolize fructose, therefore, use a ketohexokinase called fructokinase. This is followed by a step with aldolase B (Fig. 1).[31–34] The two steps in fructolysis begin with fructose phosphorylation by the enzyme fructokinase. ATP is used to donate the phosphate group producing fructose-1-phosphate. In the second step, another enzyme, aldolase B splits the molecule into two trioses: dihydroxyacetone phosphate and glyceraldehyde. The other parts of the pathway are like glucose metabolism. Glyceraldehyde needs to be phosphorylated to continue its metabolism, and this is done by a triokinase-producing glyceraldehyde 3-phosphate. For glycolysis or oxidative metabolism pathways, dihydroxyacetone phosphate is changed to glyceraldehyde 3-phosphate by an isomerase, and now the two glyceraldehyde 3-phosphate trioses can follow the same steps (Fig. 1).

Figure 1 also shows the pathway leading to lipid synthesis from fructose. The pathway that leads to glycogen formation in the liver is not shown. The fact that fructose is mainly metabolized in the liver and normally only to a minor extent in other tissues means that when tumors use fructose as an energy source, these malignant tissues develop normal hepatic abilities.

There are notable differences in regulation between glycolytic enzymes and fructolytic ones. Firstly, the hexokinase enzymes (except for the hexokinase IV, or glucokinase, expressed in the liver and kidney tubular cells, enterocytes, and pancreatic alpha- and beta-cells) are inhibited by increased concentrations of their product, glucose-6-phosphate. Second, phosphofructokinase (PFK) is tightly regulated in glucose metabolism, and fructose, arrives

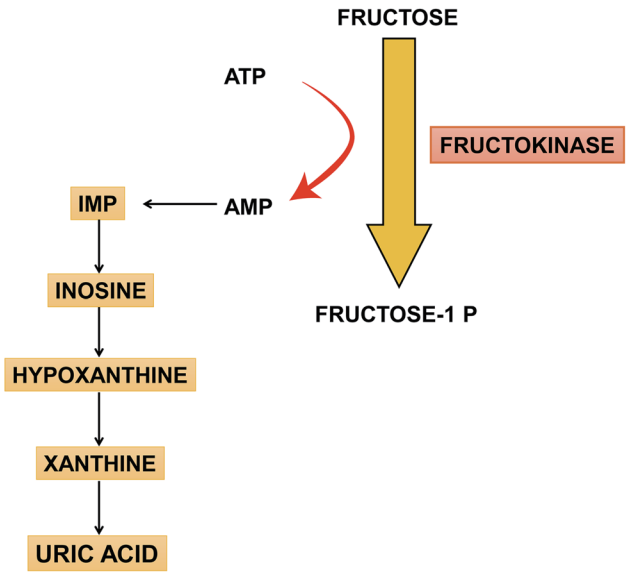


**Fig. 2. Increased uric acid production due to increased fructose catabolism.** AMP, adenosine monophosphate; ATP, adenosine triphosphate; IMP, inositol monophosphate.

at the triose pool bypassing PFK without these restrictions.[31,35] Therefore, trioses produced from fructolysis can swiftly and unrestrictedly generate a substrate for the pathways shown in Figure 1, including lipogenesis.

Another metabolic problem with fructolysis is caused by the rapid phosphorylation of fructose to fructose-1- phosphate. If it is not matched by downstream ATP production from fructose-1-phosphate catabolism, this can lead to a drop in hepatic ATP stores and a rise in hepatic inorganic phosphorus concentration. This can cause acute hepatic dysfunctions due to hepatocytes' energy deprivation, resulting in hypoglycemia and increased uric acid production. Additionally, fructose-1-phosphate can indirectly stimulate glucokinase by activation of a glucokinase-regulating protein. This effect may contribute to hypoglycemia development by decreasing hepatic glucose production (Fig 2).[35,36]

There are two possible pathways for fructose (Fig. 1) which leads us to a question: what makes uncontrolled fructolysis go one way or the other? A possible answer is that fructolysis goes toward energy production when energy requirements are not met. Otherwise, it goes toward lipogenesis. This needs experimental confirmation and is further discussed in section "I" below.

Fructose-1-phosphate is an allosteric activator of pyruvate kinase, representing glycolysis' last step.[37] It also activates transcription factors such as Sterol regulatory element binding protein-1 (SREBP1) and Carbohydrate Responsive Element Binding Protein(ChREBP). SREBP-1 is a transcription factor for genes that participate in glucose metabolism and lipogenesis.[38] It is involved in the growth and progression of prostate cancer,[39] promotes migration and invasion of breast cancer,[40] regulates fatty acid synthase,[41] which is also pro-carcinogenic, promotes invasion and metastasis in hepatocarcinoma,[42] among other pro-tumoral effects. Activation of SREBP-1 by fructose-1-phosphate may promote tumors as it has been shown that down-regulation/inhibition of SREBP-1 has antitumoral effects in glioblastoma[43] and other tumors.[44] The other transcription factor activated by fructose-1-phosphate, ChREBP, stimulates many glycolytic and lipogenic enzymes that are potentially important in cancer progression.[45] It contributes to cell proliferation[46] and aerobic glycolysis.[47,48] It also regulates the androgen receptor transcription in prostate cancer.[49]

Fructose is obtained from the diet, and how dietary input is handled is quite interesting. Short-term elevations in the human diet of fructose increase hepatic glucose production. They also increase basal and postprandial blood triglyceride concentrations and intrahepatic fat content. These metabolic alterations may be early markers of metabolic dysfunction or adaptations to the specific two-step fructose metabolism.[35] Dietary fructose is efficiently absorbed in the lower duodenum and jejunum and is processed in the liver. GLUT5 serves as the primary transporter responsible for fructose absorption. In mice, the deletion of GLUT5 leads to a significant reduction of 75% in fructose absorption in the jejunum, as well as a substantial decrease of 90% in serum fructose levels.[50] Absorbed fructose circulates in the serum and is delivered to the liver and to other tissues. Some tumors over-expressGLUT5[51–53] and this is an indirect sign that these tumors have developed the ability to absorb fructose from the serum and are obtaining part of their energy from fructose.

### *Evidence of fructose as an important source of energy in cancer cells*

There is abundant evidence that fructose can be an essential energy source for cancer cells. We divide this evidence into six general types. Firstly, many studies have demonstrated that the fructose transporter GLUT5 is upregulated in cancer cells. This was shown in breast cancer cells,[18,54] where it was also demonstrated that GLUT5 is almost absent in normal cells.[54] Other cancers in which GLUT5 was upregulated include clear cell renal carcinoma,[53] ovarian cancer tissues,[52] acute myeloid leukemia cells,[51] microglia of human gliomas,[55] lung tumor tissue of patients with adenocarcinoma,[56] human colorectal cancer specimens,[57] Philadelphia positive acute lymphoblastic cells,[58] endothelial cells from hepatocellular carcinoma,[59] glioma cells[60] and colorectal cancer cells.[61] The exact mechanism by which GLUT5 expression is increased is not completely clear. There are some reports of factors that may be involved. Medina Villaamilet et al.[62] found a correlation between HIF-1α (hypoxia-inducible factor 1-alpha, a transcription factor that regulates angiogenesis and tumor growth and metastasis) and GLUT5 expression. Another study showed that the inflammatory IL-6/STAT3 axis activates GLUT5 regulating the fructose metabolism in oral squamous cell carcinoma cells and prostate cancer cells. STAT3 transcription factor binds the GLUT5 gene's promoter region, enhancing its transcription.[63] However, it is unclear if these are the only factors involved, and details of GLUT5 induction pathways remain to be elucidated. However, several studies have demonstrated that increased GLUT5 expression results in increased fructose uptake. This was shown in acute myeloid leukemia cells,[51] clear renal cell carcinomas[53] and glioma cells.[60] In several cases the increase in fructose uptake was correlated with factors such as malignant progression and differentiation.[53] To summarize, many studies in different cancer types have shown that GLUT5 expression is elevated, and several other studies have confirmed these results in increased fructose uptake.

The second type of evidence supporting a fructose role in tumors are several studies showing that knockdown or inhibition of GLUT5 has inhibitory effects on tumors' cell growth, viability, migration, and proliferation. These studies were demonstrated in various cancer types and different circumstances. An example of a competitive inhibitor of fructose transport by GLUT5 is 2,5-anhydro-D-mannitol, and administration of this compound could markedly suppress clear cell renal cell carcinoma growth.[64] Similarly, in

acute myeloid leukemic cells, pharmacological blockade of fructose uptake with the same compound weakened the malignant phenotype and increased cell sensitivity to chemotherapeutic drugs,[51] while in colon cancer cells, a different GLUT5 inhibitor N-.4-(methylsulfonyl)-2-nitrophenyl-1,3-benzodioxol-5-amine, significantly decreased viability of these cancer cells but had little effect on the viability of normal colon epithelium cells.[57] Knockdown of GLUT5 may be a more specific method of reducing GLUT5 activity, and several studies have shown that this has beneficial effects on preventing tumor cell growth and malignancy traits. For example, Jin et al.[64] deleted the GLUT5 gene from clear cell renal cell carcinomas cells. Cell malignancy was attenuated, and apoptosis was activated. Similar results were shown with the knockdown of GLUT5 in glioma cells,[60] ovarian cancer cells,[52] and two types of human breast cancer cells, MCF-7 and MDA-MB-231 cells.[65] Very recently, Groenendyk et al.[66] also demonstrated that CRISPR/Cas9 mediated inactivation of the SLC2A5 (GLUT5) gene inhibited cancer cell proliferation and migration in vitro, as well as metastases in vivo in several different animal models. Moreover, SLC2A5 attenuated cells significantly altered mitochondrial architecture and localization, indicating an important role in directing mitochondrial function for cancer cell motility and migration. The study used MIA PaCa-2 cells, a highly metastatic pancreatic ductal adenocarcinoma cell line and HT-1080 human cells derived from connective tissue of a patient with fibrosarcoma. Overall, these types of studies demonstrate that inhibition or knockdown of GLUT5 affects several different types of cancer cells, having beneficial effects such as inhibiting tumor growth and survival. These studies confirm that induction of expression of the GLUT5 gene in these cancers, has real and significant effects with regards to tumor progression.

A third line of evidence that supports the vital role of fructose as an energy source for tumors are the effects of high fructose in the "diet"of cells, animals, or humans. Several results show that in animal models, elevated dietary fructose enhances carcinogenesis. For example, a dietary treatment with fructose increased hepatocarcinogenesis in a rat model treated with N-nitrosomorpholine.[67] The same group used a similar model to show that high dietary fructose enhanced nodules of atypical acinar nodule cells, which are precursors of pancreatic lesions.[68] Elevated levels of fructose in the "diet" of cells could support breast cancer cell proliferation when glucose levels were reduced.[18] In a separate breast cancer model, substituting the energy source in MDA-MB-468 breast cancer cells with fructose induced a more aggressive phenotype characterized by enhanced migration and invasion capabilities.[16] Effects of high fructose in the medium of cells were shown in several other studies, including glioma cells, where it promoted tumor progression and GLUT5 expression.[60] Another paper[69] examined many different cell types and showed that cells chronically cultured in fructose develop high fructose lysis ability. The SLC2A5 (GLUT5 transporter) gene was specifically upregulated, as was fructose usage. Fructose elevated GLUT5 expression and stimulated cell proliferation.

Elevated levels of fructose in animal diets have also been shown to enhance tumorigenesis in several animal models. This occurred in lung metastasis and mammary gland tumorigenesis[70] and a mouse model of hepatocarcinoma.[71] Kuehm et al.[72] also demonstrated that in melanoma tumors in the C57BL/6 mouse model of diet-induced obesity, dietary fructose promoted cytoprotection and resistance to immunotherapy. Mice with a high fructose diet had increased expression of the cytoprotective enzyme heme oxygenase-1, which shielded tumor cells from immune-mediated killing. The increase of this protein was recapitulated in human A375 melanoma cells exposed to fructose in culture. Another recent publication also showed that dietary fructose improves the survival of intestinal cells and increases villus length in several mouse models.[73]

The elevation of fructose in the diet of humans has been analyzed, mainly by examining the incidence of various tumors in populations or groups with high fructose input. For example, a study of over 80,000 women[74] found an association between higher fructose intake in obese, sedentary women with increased pancreatic cancer risk. Another association was published by Larsson *et al*.,[75] who found increased pancreatic cancer risk in obese women with high consumption of sweetened soft drinks (sweetened soft drinks contain a high level of fructose). Moreover, a different sizeable multiethnic cohort study showed an increased relative risk for pancreatic cancer in people with high fructose intake.[76] Finally, a retrospective analysis of a large population, including ten cohorts, did not show an association between pancreatic cancer risk and intake of diets high in glycemic index, glycemic load, total carbohydrates, or sucrose. However, there was enhanced pancreatic cancer risk with high fructose diets.[77] These studies support the concept that aside from all the animal studies and studies in culture described above, humans are also susceptible to elevated levels of fructose in their diet.

Here we also suggest that the levels of fructose updated in the "diet" can compensate for decreased or blocked glucose usage and stimulate glucose usage. Cancer cells have significantly elevated levels of glycolysis and high metabolic activity with subsequent high energy usage.[78] As glucose is the often-used substrate of cancer cells, one would believe that blockage of glycolysis should be a useful anti-cancer strategy. 2-deoxyglucose blocks glucose metabolism; however, it has failed in tests as an anti-cancer drug.[79] We suggest that the failure of anti-glycolytic approaches may be due to using fructose as an alternative energy source. Fructose metabolism bypasses the glycolytic obstruction induced by 2-deoxyglucose. One example was a study demonstrating that fructose was an important fuel for lung adenocarcinoma when glucose levels were low.[80] However, it is also interesting that fructose metabolism can stimulate the glycolytic pathway, which can stimulate cancer growth and metastasis.[15] Thus, fructose can substitute for glucose where needed and stimulate glucose use if available, thus promoting tumor progression.

A fourth line of evidence that supports the critical role of fructose in human cancer development is the clinical correlation that suggests that fructose metabolism is important in human tumor progression. For example, GLUT5 expression is elevated in human glioma tissues, and GLUT5 is correlated with glioma progression and poor survival in glioma patients.[60] A similar correlation of GLUT5 levels with ovarian cancer tumor malignancy and progression-free survival has also been reported,[52] GLUT5 was also upregulated in lung adenocarcinoma patients and correlated with poor prognosis.[56] There is an almost 2.5-fold ($p < 0.001$) increase in GLUT5 mRNA expression level in colorectal cancer specimens compared with the healthy intestinal mucosa.[57] GLUT5 was also overexpressed in a survey of 215 different human tumor samples.[81] Immunolocalization studies revealed that GLUT5 is highly expressed in vivo in human breast cancer but is absent in normal human breast tissue.[54] Similar to the effect with GLUT5, ketohexokinase, a key enzyme of fructose catabolism, is over-expressed in gliomas. This overexpression correlated with tumor progression and poor survival of glioma patients.[82] Thus, in several different types of cancers, GLUT5 and another key enzyme of fructose me-

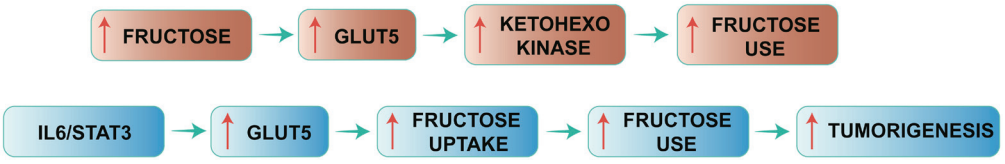


**Fig. 3. Relationship among fructose metabolism, glut5, hexokinase and tumorigenesis.**

tabolism, ketohexokinase, are upregulated and this elevation correlates with detrimental effects on human health. This indicates that fructose metabolism is linked to cancer progression in humans. On its own, clinical correlates of expression with cancer progression are only indirect evidence at best, but when one considers the other data above such as knockdown and inhibitor studies in animals and cells described above, this provides good evidence for an important role of fructose metabolism in tumor progression.

A fifth line of evidence supporting fructose's role in cancer progression are the metabolic alterations or reprogramming that occur in many tumors that allow them to use fructose more efficiently. For example, colon cancer cells overexpress aldolase B when metastasizing in the liver. Aldolase B enhances fructose metabolism. Restricting dietary fructose or targeting aldolase B decreased the growth of liver metastases without affecting the primary tumor.[83] Another enzyme that is altered is transketolase. Fructose can induce transketolase flux which promotes pancreatic cancer.[84] Through increased fructose in dietary sugar, the lipoxygenase pathway in mice was increased, raising the risk of breast cancer development and metastases.[70] In another study, it was shown that fructose, but not glucose, reprogrammed malignant human prostate cancer cells. It significantly altered mRNA expression of Hexokinase 2, type-C fructokinase, pyruvate kinase M2 and type-A lactate dehydrogenase. Various metabolic alterations improving fructose utilization also occurred in pancreatic stem cells,[85] and prostate cancer cells using fructose as a main energy source when GLUT5 was overexpressed.[86] In tumor endothelial cells from hepatocellular carcinoma, fructose treatment promoted proliferation, migration and angiogenesis. Fructose metabolism was elevated and both GLUT 5 and ketohexokinase were upregulated. Knockdown or inhibition of these proteins abolished fructose-induced tumor angiogenesis and suppressed tumor growth.[59] Demonstration of elevation of ketohexokinase in response to elevated dietary fructose has been shown several times. This also occurred in fructose fed mice[87] and in colon cancer cells, where GLUT5 expression inhibited ketohexokinase degradation.[61] In hepatocellular carcinoma, fructose promoted aggressiveness, and mice with a fructose enriched diet had appropriate metabolic reprogramming that increased energy, NADPH, and nucleotide production, allowing for increased tumor cell aggressiveness.[88]

A sixth line of evidence shows the relationship between fructose metabolism and tumor immunology. Kuehm et al.[72] found that mice melanoma tumors in animals with a high-fructose diet were resistant to immunotherapy. They also found increased expression of heme oxygenase-1, a cytoprotective enzyme to which they attributed possible participation in the process. Interestingly, when exposed to fructose, A375 melanoma cells in culture showed high heme oxygenase-1 expression. This expression was causally linked to resistance to immune checkpoint inhibitors.

Based on the above-mentioned reports, there is evidence of a fructose-dependent pathway and a GLUT5-dependent pathway in cancer that stimulate tumorigenesis,as shown in Figure 3.

The above information makes it clear that fructose uptake and GLUT5, the fructose transporter, are important in at least some types of cancer and facilitate the growth and proliferation of cancer cells.

### *Fructose levels in the bloodstream*

Notably, the peripheral plasma fructose concentration is relatively low (approximately 0.04 mM). After fructose ingestion, GLUT5 expression is increased in the intestine.[89,90] Fructose levels can increase 10-fold and return to normal after 2 hours fasting.[91,92] Fructose levels in the bloodstream have also been shown experimentally to increase in response to fructose ingestion. This was shown in humans with acute fructose administration[93] and with the administration of high-fructose corn syrup-sweetened soft drinks, where dramatic increases in fructose concentrations were shown with ingestion.[94] It is also important to note that the fasting serum concentration of fructose is significantly higher in pancreatic cancer patients than in healthy individuals.[95]

### *Further details on the relationship of GLUT5 with cancer*

#### Localization

GLUT5 is a fructose transporter that facilitates the diffusion of fructose in a concentration-dependent manner.[96] It is highly expressed on the apical border of intestinal mucosa cells. It has modest expression levels in other tissues such as adipocytes, kidneys, and skeletal muscles,[97,98] while other tissues have no or minimal expression of GLUT5. As noted above, some tumors express GLUT5, while their corresponding healthy tissues do not express GLUT5. GLUT5 is the vehicle for the rapid absorption of fructose into cells, and the liver metabolizes approximately 70–80% of the absorbed fructose. Very little is known about GLUT5 regulation in tumors. It is unclear if the regulatory proteins that work on GLUT5 in some tissues (Fig. 4) are operative in tumors. As always, suspicion is cast on several putative tumor drivers, but experimental evidence is lacking (Fig. 4).[24,89–105]

#### Regulation of expression

Tumors are highly hypoxic, and this may be the cause of GLUT5 over-expression. Hypoxia in adipocytes was demonstrated to increase GLUT5 levels.[104] Additionally, hypoxia elevated levels of GLUT5 mRNA and protein in breast cancer cells. However, this depended on the type of breast cancer cell.[105] Breast cancer samples from patients showed increased expression of all GLUTs and HIF-1α compared to control tissue. Triple-negative breast cancer tends to be more severe than other types. In triple-negative breast cancer, the samples showed greater GLUT1, GLUT5, and HIF-1α expression levels than ER-positive cases.[105]

Godoy et al.[81] studied GLUT isoform expression in different benign and malignant tumors. GLUT1 was the main isoform detected in tumor tissues. However, GLUT5 was extensively expressed in malignant tumors suggesting that fructose transport for use as an energy substrate was widespread. GLUT5 was detected in colon adenocarcinoma, ependymomas, plexus choroids papilloma, lung mesothelioma, liver carcinoma, lymphomas (only GLUT5), tes-

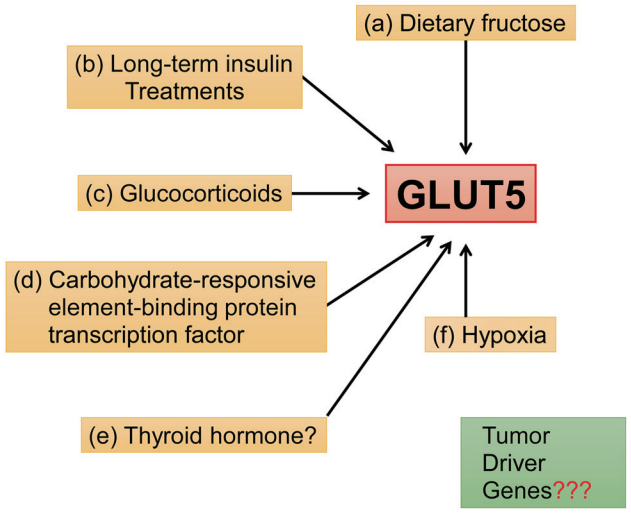


**Fig. 4. Regulatory mechanisms of GLUT5.** These seem to work in the intestine and other tissues. a, dietary fructose elevates GLUT5 expression;[89,99,100] b, insulin treatment can increase GLUT5 expression including elevated transcription and protein levels;[101] c, Developmental reprogramming and induction of rat GLUT5 requires glucocorticoid receptor translocation to the nucleus;[24] d, carbohydrate responsive element-binding protein is a transcription factor that regulates GLUT5 expression in response to carbohydrates;[102] e, fully differentiated Caco-2/TC7 (human colon adenocarcinoma) cells, thyroid hormone, and glucose increase GLUT5 mRNA abundance in dose-dependent manners;[103] f, In human adipocytes hypoxia increases GLUT5 expression markedly.[104] Some of these mechanisms may work in tumors such as hypoxia,[105] but further studies are required to better characterize this in tumors.

tis seminoma, and uterus leiomyoma. GLUT5 was also detected in breast tumor cells and was more intense than normal cells, especially in invasive ductal carcinoma samples. GLUT2, a lower affinity fructose transporter, was similarly expressed in elevated amounts in tumor tissues when GLUT5 expression was elevated.

### Downstream effects of GLUT5 expression

GLUT5 also plays an important role in lung cancer cell growth where the tumor seems to be fructose dependent. Chen et al.[106] found that by up-regulating GLUT5, these cells could use fructose as an alternative to glucose in vivo. Importantly, this fructose was mainly used for lipid synthesis. Deletion of the GLUT5 gene (SLC2A5) impaired proliferation, which could be restored by administering fatty acids. They also showed that GLUT5-mediated fructose import was necessary to inhibit AMPK, thus allowing mTORC1 to promote lung cancer growth.

### GLUT5 expression and chemoresistance

Several studies have shown that elevated expression of GLUT5 induces resistance to chemotherapy or correlates with beneficial effects (from the tumor's point of view). For example, Ramzy et al.[107] demonstrated that GLUT5 was significantly upregulated in colorectal cancer cells and this induced drug resistance to chemotherapy treatments. A similar effect on chemotherapy resistance was also found by Shen et al. in colorectal cancer cells.[61] A different study on colorectal cancer cells[108] suggested that regulation by AKT was responsible for elevated GLUT5 expression and resistance to chemotherapy. Silencing either AKT or GLUT5 expression attenuated migration, invasive behavior, and inhibition of GLUT5 activity with 2,5-anhydro-d-mannitol re-sensitized these cells to chemotherapeutic treatments. These results were more than a correlation of behavior and, more specifically, confirmed the role of GLUT5. It is worth mentioning that another study[109] also showed a connection between AKT, GLUT5, and cancer cell migration. In that study in lung cancer cells, overexpression of GLUT5 promoted cell migration and AKT activation. Again, the use of GLUT5 inhibitors blocked cell migration and AKT activation. There is clearly a link between GLUT5 and AKT and cancer cell behavior, including migration and chemoresistance.

## Ketohexokinase (hepatic fructokinase)

As noted above, ketohexokinase is elevated in several types of cancer, and reduction or inhibition of the protein can inhibit the malignant phenotype. Here we describe some further details about this enzyme. Ketohexokinase (KHK) is the enzyme that converts fructose to fructose-1-phosphate[110,111] using one molecule of ATP or GTP as a cofactor (Fig. 1). This occurs in the presence of $K^+$ and $Mg^{++}$ with no rate variations in enzyme activity within the pH range of 6 to 9. The reverse reaction occurs only at an acidic pH between 5 and 6, which is usually impossible in the cell. There are two KHK isoforms, KHK-A and KHK-C. They are generated through mutually exclusive alternative splicing of KHK pre-RNAs. KHK-C displays greater affinity for fructose compared with KHK-A, and KHK-C is produced primarily in the liver. This restricts fructose metabolism almost exclusively to this organ.[112,113] Mirtschink et al.[113] found that hypoxia can induce changes in splicing, switching KHK-A to KHK-C isoform in the myocardium and thus enforcing fructose metabolism. This has not been investigated in tumors, but we may speculate that something similar may happen. In addition to KHK canonical enzymatic function, it also has non-canonical activities as a protein kinase.[114]

Ketohexokinase acts as a nuclear kinase that has pro-tumoral effects such as:

1. Promoting tumor progression of glioma;[82]
2. Promoting progression of non-small lung cancer;[115,116]
3. Promoting pancreatic cancer growth by activating MAP Kinases pathway;[117]
4. Driving hepatocellular carcinoma formation by a cMyc-induced splicing switch to isoform KHK-A;[118]
5. Promoting fructose-induced metastasis of breast cancer.[87]

In summary, ketohexokinase consists of two isoforms, and the relative amount of each varies. Aside from phosphorylating fructose and beginning the fructolytic pathway, the kinase has other pro-tumoral effects contributing to cancer growth and metastasis.

## Interventions to inhibit fructose as a source of energy in cancer

Given that fructose can be an important source of energy for cancer and that fructose utilization can stimulate glycolysis and may have other pro-tumoral effects, it is important to discuss how to prevent these dangerous consequences of fructose metabolism. There are several possible approaches to prevent the use of fructose as an energy source in cancer. These include:

1. Dietary restriction of fructose.
2. Drugs such as 2,5-anhydro-D-mannitol (2,5-AM), a fructose analog with a high affinity for GLUT 5 that acts as a competitive inhibitor.[119]

Dietary modifications for enhanced cancer therapy have been considered.[120] Mostly, these have been concerned with treatments such as fasting and glucose restriction. Fasting has long been con-

sidered in mice, where combining fasting cycles with chemotherapy improves responsiveness. However, this is quite a harsh therapy. Glucose has many tumorigenic roles, as discussed above, and glucose restriction has been tested and has value. However, cells seem to be able to rewire their metabolic programs in response, as noted above.[120] Fructose restriction has not been as well studied, but some evidence has suggested that, at least in mouse models, it can have beneficial effects.[120,121]

As noted above, compounds such as 2,5-anhydro-D-mannitol can theoretically have beneficial effects, such as re-sensitizing cells to chemotherapeutic treatments.[108] The idea of targeting fructose metabolism in tumors that over-express GLUT5 is not overly complicated because fructose-restricted diets are well tolerated, and the uptake inhibitor 2-5-anhydro-D-mannitol is a non-toxic compound. However, further study is needed.

Other compounds that have been reported to have GLUT5 inhibitory abilities are:

- MSNBA (N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3-benzodioxol-5-amine);[122]
- Conjugates of 2,5-anhydro-mannitol also inhibit GLUT5.
- 6-O-allyl-d-fructofuranose;[123]
- 1,3-oxazolidin-2-thiones and 1,3-oxazolidin-2-ones;[123]
- Green tea and chamomile tea;[124]
- allylamine derivative of 2,5-anhydro-d-mannitol;[119]
- Flavonoids: epigallocatechingallate and apigenin but not quercetin;[125]
- Astragalin-6-glucoside;[126]

None have been clinically tested.

## When to treat

Patients with tumors expressing high levels of GLUT5 might benefit from both the above-mentioned treatment strategies. There is clear evidence of this in acute myeloid leukemia.[51] In other tumors like breast, colon, and pancreatic carcinomas expressing GLUT5, treatments modulating fructose intake or uptake would probably delay growth and metastases, but this needs verification.

## General Discussion

Glucose is the main energy source of cancer cells. However, tumors are often poorly perfused and the concentration of nutrients such as glucose is often lower in tumors than in normal tissues. Thus, glucose depletion affects tumors' ability to proliferate. Different cancer cell lines show different sensitivities to glucose depletion.[127] With the effects of glucose depletion, in certain tumors, fructose becomes a very important energy source and can even replace glucose as the main nutrient. Fructose consumption is associated with a more malignant phenotype with increased proliferation, invasion, and metastasis.[128] However, in 2009, an epidemiological study could not confirm that high dietary fructose intake increased cancer risk.[129] Nevertheless, other studies have shown some associations between elevated fructose and cancer frequency, but this is not always true.[130,131] Though these results are conflicting (see also below), they do not mean that fructose has no role in cancer development. At the clinical level, fructose indirectly participates in cancer through obesity and metabolic syndrome. At the molecular level, fructose has an important role in the development of a more aggressive cancer phenotype in some tumors.[18,27]

The importance of fructose in cancer seems to stem from three different roles:

1. As a source of energy;
2. Reprogramming of cellular metabolism;
3. Stimulating synthesis of fatty acids necessary for the lipogenic phenotype.

Here we review some of the more critical aspects of these three capabilities of fructose.

### *Fructose as a source of energy*

High intake of dietary fructose is increasingly being considered a causal factor of obesity,[132] metabolic syndrome,[133–135] and indirectly, insulin resistance.[136] While studying metabolic syndrome, interesting clues were discovered on the role of fructose beyond its energetic function. Metabolic syndrome and insulin resistance increased the expression of interleukin-6,[137] Akt, NF-kB,[138] and TNFα via hepatic production. All these compounds have protumoral activity. Thus fructose, while promoting metabolic syndrome, obesity, and insulin, simultaneously increases the production of compounds that promote tumorigenesis. These findings have not been mechanistically well characterized. Fructose supplementation in the diet has been shown to impair signaling in insulin-sensitive tissues (Fig. 4).[139]

Whatever the cause, metabolic syndrome and obesity can increase cancer risk. One study of 38,940 cases of cancer[140] found that metabolic syndrome had an increased relative risk(RR) for hepatic (RR = 1.43), colorectal (RR = 1.25), and bladder (RR = 1.10) cancers in men, and endometrial (RR = 1.64), pancreatic (RR = 1.58), postmenopausal breast (RR = 1.56), and rectal (RR = 1.52) cancers in women. Another prospective study of 90,000 people beginning without cancer showed that in obese people, the risk of death from cancer was 52% (RR = 1.52) higher in men and 62% (RR = 1.62) higher in women, compared with the non-obese population.[141]

It should be noted that dietary fructose intake has increased dramatically in the United States, and many authors consider that this is partly responsible for the obesity epidemic.[102,142–148] However, other authors do not accept this as the cause of energy over-consumption, independent of fructose.[149,150]

### *Fructose reprogramming cellular metabolism*

Fructose can increase aerobic glycolysis (bypassing glycolytic restrictions and activating pyruvate kinase) and lipogenesis. In prostate cancer, a lipogenic phenotype was found in many tumors.[151] De novo lipogenesis is a consequence of androgenic stimulation of SREBP.[152] De novo lipogenesis is also one of the effects of fructose (Fig. 4). Prostate cancer patients treated with androgen deprivation can retain their lipogenic phenotype thanks to the activity of fructose metabolites as suggested by Carreño et al.[153] Support for this concept came in one study that showed that adding fructose to the medium of cultured adipocytes increased lipogenesis.[154] Fructose can also induce insulin resistance by activating the peroxisome proliferator-activated receptor γ coactivator-1 β (PGC-1β), which is a co-activator of SREBP-1. Knockdown of PGC-1β improved insulin resistance.[155]

### *Fructose and the lipogenic phenotype*

Fructose is implicated in the lipogenic phenotype, insulin resistance, and metabolic syndrome.[156] Increased fructose intake seems to be directly responsible for enhanced obesity and de novo lipogenesis.[157] However, a panel of experts convened by The Center for Food, Nutrition, and Agriculture Policy was asked to examine the scientific literature on the relationship between high fructose intake and obesity. They concluded that high dietary fructose intake "does not appear to contribute to obesity any differently than

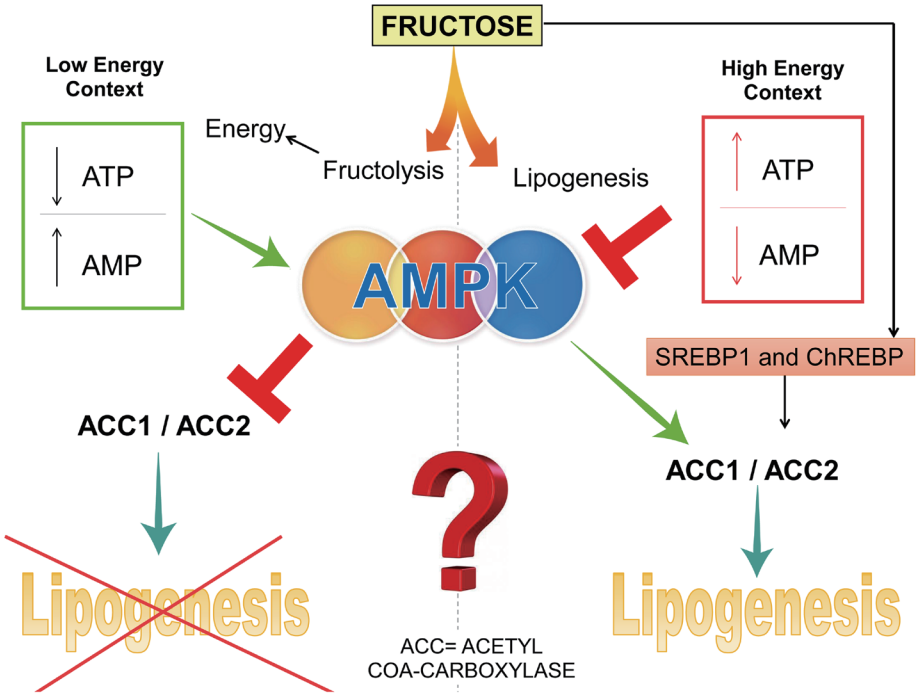


**Fig. 5. Possible relationships between high fructose intake, insulin resistance, obesity, metabolic syndrome, lipogenic phenotype, and cancer.** Fructose is a key figure that integrates these concepts. High fructose intake can lead to metabolic syndrome, obesity, a lipogenic phenotype, and insulin resistance, with downstream effects that may promote cancer. This mechanism is more evident if previous energy requirements are fulfilled. AMP, adenosine monophosphate; ATP, adenosine triphosphate.

do other energy sources".[158] This makes us speculate that the lipogenic phenotype induced by fructose appears only if energy requirements are fulfilled first.

Based on the above evidence, Figure 5 was constructed assuming that the energy requirements were adequately fulfilled. If this were not the case, fructose would only be used to produce energy. The cause of the switch from energy production to lipoprotein production is the energy balance. This is probably gauged by AMPK (AMP kinase). Activation of AMPK through a low ATP/AMP ratio (through the liver kinase B, LKB) inhibits ACC1 and ACC2 (Acetyl CoA Carboxylase) activity, inhibiting lipogenesis.[159–161] The results of Woods et al.[161] support this hypothesis. They demonstrated that chronic activation of AMPK through experimental mutation impedes lipogenesis in the liver of mice with a high fructose diet. The chronic activation of AMPK produces a surplus of ATP (Fig. 5).

What we propose here, based on the published literature, is that fructose can be metabolized in two different cellular contexts:

1. Poor intracellular energy (low ATP, high AMP)
2. High intracellular energy (high ATP, low AMP).

In the first situation, fructose would mainly follow the fructolytic pathway, merging the glycolytic pathway at the level of glyceraldehydes-3-phosphate and producing energy. In the second situation, with full ATP coffers, fructose would mainly be used in the lipogenic pathway, as proposed in Figure 5.

Figure 5 hypothesizes, for the first time, a contextual-dependent metabolism for fructose. A consequence of this proposed mechanism of action would be that administration of fructose under hypocaloric conditions would not induce the lipogenic pathway. Stansbie et al.[162] showed that under fasting conditions, an overload of fructose generated double the amount of lactic acid compared to a non-fasted state. This suggests that fructose is mainly metabolized under hypocaloric conditions in the fructolytic pathway.

Koo et al.[163] have shown that high fructose intake induced the over-expression of certain genes, such as fructokinase and aldolase B. This is logical regarding the need for these enzymes for fructolysis. However, other enzymes related to glycolysis were also over-expressed, like phosphofructokinase. Finally, there was a substantial over-expression of ChREBP. It is interesting to note that ChREBP mRNA and protein are significantly elevated in colon cancer cells compared to the normal colon, and their expression is positively associated with advanced stages of cancer.[45]

### *Other effects of fructose*

Two other effects of fructose also can stimulate carcinogenesis. The first is its production of reactive oxygen species. Fructose utilization generates 100-fold more reactive oxygen species than glucose, thus, creating oxidative stress that can lead to necroinflammation,[164] and oxidative stress can lead to carcinogenesis.[165] The second effect is a temporary reduction in ATP levels. An overload of dietary fructose can produce a temporary ATP reduction due to the swift action of fructokinase-1 and the slow activity of aldolase B (Fig. 1).[166–168] This can create an energy shortage that may temporarily restrain the lipogenic pathway. Lipogenesis is also another path that can lead to ATP depletion.[169]

### *Fructose in diagnostics*

Recently, a PET scanner has been developed to image GLUT5 in breast cancer using 6-deoxy-6-[18F] fluoro-D-fructose as a radiotracer.[170] This simplifies the diagnosis of fructose-dependent tumors. Another tracer that detects GLUT5 is [99mTc] glucarate, which was proposed for detecting fructose-consuming tumors in breast cancer.[171]

## Conclusions

Glucose is the main energy source of cancer cells. Different cancer cell lines respond with considerable variations to glucose depletion.[127] In certain tumors fructose becomes a very important energy source and can even replace glucose as the main nutrient. Fructose consumption is associated with a more malignant phenotype with increased proliferation, invasion, and metastasis. Some epidemiological studies with large populations could not fully confirm that high dietary fructose intake increases cancer risk.[129] However, this does not mean fructose has no role in cancer development. At the clinical level, fructose indirectly participates in cancer through obesity and metabolic syndrome. At the molecular level, fructose is essential in developing an aggressive cancer phenotype in some tumors.

### *Clinical implications*

There are several instances whereby targeting GLUT5 may be a valuable approach for clinical treatments. One of these may be in the treatment of gliomas. Gliomas have a very poor prognosis, and no effective treatment has yet been developed. Therefore, finding a new way to address this disease would be a precious tool for fighting this disease. Evidence shows that, at least in the laboratory, targeting fructose metabolism could represent an interesting add-on to conventional treatments of gliomas.[60,82] Clear cell renal carcinoma over-expresses GLUT5, which represents another case in which GLUT5 targeting may improve results.[64]

One of the objections to the importance of fructose as an alternative energy source for cancer is the low levels of fructose in blood. This objection is invalid in colorectal cancer because fructose concentration is much higher in intestinal circulation. Moreover, as noted above, fructose concentrations can increase several folds in the bloodstream after ingestion and are increased in some types of cancer.[91,92,95] Another point is that fructose can be produced endogenously from glucose through the polyol pathway, as found in diabetic patients. This pathway can convert up to 50% of glucose into fructose.[172–174] The polyol pathway plays a role in cancer. The gene aldo-keto-reductase-1-member-B1, which codes for one of the two enzymes that participate in the polyol pathway, correlates with epithelial-mesenchymal transition in lung cancer patients and a colon cancer mouse model.[175,176]

### *Dietary effects*

The effects of fructose in the diet deserve some more consideration. As noted above, the concept of restriction of dietary fructose to reduce cancer risk is controversial. Some researchers have suggested excessive intake of dietary fructose is an increased risk factor for cancer or related syndromes that promote cancer,[17,75–77,102,128,142–148,177,178] while others could not confirm increased cancer risk in other population studies, even examining the incidence of disease in the same types of tissue.[77,129–131,149,150,179] Despite this controversy, it is clear that fructose is associated with factors that indirectly have strong influences on carcinogenesis, such as obesity[154,180] metabolic stress,[174] diabetes[155,181] and pro-inflammatory effects.[182] Section "C" above proves that fructose and its metabolism and transport can promote cancer cell growth and metastasis. Therefore, decreasing dietary fructose intake should be considered as part of a cancer prevention scheme. It is unclear why population-based studies have such different and controversial results. This could be due to study group size, other parameters not controlled for, and sometimes due to differences in the types of cancer surveyed. As noted above (Fig. 5), context-dependent use of fructose may occur, and the use of fructose for metabolic activities that promote cancer may only occur in cases where high energy content is already present in cells. This could undoubtedly confuse the statistical analysis of human populations. Certain subfractions of the population may "respond" to fructose consumption more than others for this and possibly other reasons. A possibility is that GLUT5 expression levels may respond more to fructose in some parts of the population than others, possibly due to context-dependent effects. It may be that determining GLUT5 expression in individual patients could indicate a greater role of fructose in those individuals, allowing more personalized medical treatment, including fructose restriction. However, despite all the evidence on the importance of fructose metabolism in cancer, determining GLUT5 expression in cancer cells has not yet entered standard oncology practice. Targeting fructose metabolism is not part of mainstream treatments.

Related treatments, such as energy restriction, have been examined experimentally. Although successful in the laboratory, the energy restriction treatment as a stand-alone therapy with 2-deoxyglucose could not be introduced at the bedside.[183] The reasons are high dose requirement, toxicity,[184] and poor patient compliance. We also think that one possible explanation for this failure is the replacement of glucose with fructose as an energy source. As noted above, 2-deoxyglucose blocks glucose metabolism; however, it failed in tests as an anti-cancer drug.[79] Fructose may be an alternative energy source when glucose levels are low.[80] While elevated fructose metabolism by some cancer cells is not only an energetic matter, it is worth noting that 2-deoxyglucose can also decrease fructolysis.[185,186] However, it is unclear whether this effect can be exploited in humans and if 2-deoxyglucose can inhibit the utilization of both fructose and glucose in tumors.

We suggest it is a mistake to consider fructose as a lonely player in cancer. The entire team of fructose, GLUT5, and KHK must be viewed as a group of pro-cancer drivers. However, GLUT5 and KHK overexpression are the product of increased fructose presence. Furthermore, each of them can independently participate in tumor progression.

### *Benefits of fructose restriction*

We think there are beneficial effects of restriction of fructose in the diet. Western diets and sweetened beverages contain very high levels of fructose. Additionally, high fructose consumption parallels obesity incidence.[187] High fructose in the diet also correlates with the progression of hepatocellular carcinoma.[188] In mice predisposed to develop intestinal tumors, modest levels of high fructose corn syrup substantially increase tumor size and grade even in the absence of obesity.[121] Overall, these results suggest that fructose could have an important effect on cancer patient's diets. However, further studies are needed to demonstrate the beneficial effect of fructose restriction in humans in specific cancer types.[187]

Fructose consumption has experienced a significant surge since the 1960s, primarily attributed to its prevalence in high-fructose corn syrup found in soft drinks and processed foods. The relationship between high fructose intake and certain diseases remains incompletely understood. However, it is established that:

1. Increased fructose consumption can lead to weight gain and obesity through elevated lipogenesis and a surplus of calories;
2. This predisposes individuals to metabolic syndrome;
3. It also contributes to insulin resistance and diabetes;
4. Additionally, it can induce hepatic inflammation accompanied by heightened production of reactive oxygen species;
5. Ultimately, these factors collectively increase the risk of cancer.

From a molecular perspective, fructose serves as an energy source and a signaling molecule with pro-tumoral properties.

In light of this, we propose that the effects of fructose are con-

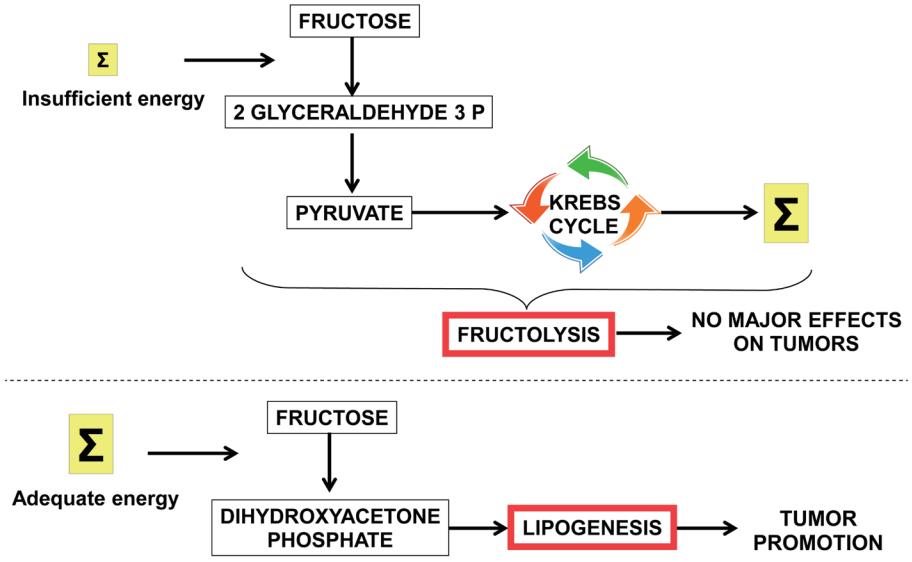


**Fig. 6. Context-dependent metabolism of fructose.**

tingent upon cellular energy availability, as illustrated in Figure 5 and Figure 6. In this hypothesis, fructolysis under conditions of low energy availability would have minimal or no impact on tumors. Conversely, fructose metabolism favors lipogenesis under sufficient energy availability, thereby promoting tumor growth.

This hypothesis could elucidate the discrepancies observed in population studies and the heightened cancer risk associated with obesity and metabolic syndrome.

Furthermore, certain tumors become highly dependent on fructose, displaying a more malignant phenotype. Consequently, this finding has practical implications: patients with overexpression of the glucose transporter GLUT5 may benefit from interventions targeting fructose metabolism. Therefore, further research, including well-designed clinical trials utilizing personalized medicine, should be pursued to ascertain whether GLUT5 is overexpressed in patients' tumors.

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## Conflict of interest

The authors declare no conflict of interests.

## Author contributions

Review conception (TK); investigation, resources, writing-review, and editing (TK and LF).

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