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Review Article

Fructose Metabolism and Acute Myeloid Leukemia

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Abstract

The dietary consumption of fructose has increased in the last five decades, paralleled by an increase in obesity. Excess fructose intake is linked to obesity, metabolic syndrome, non-alcoholic fatty liver disease, diabetes, hypertension, cardiac disease, and several aggressive types of cancer. The incidence of acute myeloid leukemia (AML), a lethal hematologic malignancy, has also increased in parallel. Despite significant advances in our understanding of AML, including molecular genetics and more effective targeted therapies, relapse is frequent and outcomes remain poor. Moreover, except for several known causes for a small proportion of AML cases, virtually nothing is known about the initial causative leukemogenic event. In this study, the author asked and intended to answer the question, "can excess fructose intake lead to the initial cellular event that causes AML?" The author reviewed published literature to answer the above question and, subsequently, to identify novel AML therapies based on fructose metabolism. In this article, fructose metabolism and its relationship with metabolic pathways essential for AML, including regulation by hypoxia inducible factor, are described. Evidence for the potential etiologic role of fructose in AML is summarized for the first time. To conclude, excess fructose can lead to the initial AML-causative cellular event. Based on this study, future studies are warranted to determine if restricting fructose intake can prevent AML. Therapeutically, the development of hypoxia inducible factor and glucose transporter 5 inhibitors should be pursued for the treatment of AML.

Introduction

In normal human body cells, glucose is converted to pyruvate that enters the tricarboxylic acid (TCA) cycle aerobically. The electron transport chain, also known as the respiratory chain, is found in the mitochondria of cells and is the final common pathway by which electrons are transferred to oxygen. The energy released in the process phosphorylates adenosine diphosphate (ADP) stored as adenosine triphosphate (ATP). This process, known as oxidative phosphorylation, generates large amounts of energy.[1,2]

In addition to that energy, cancer cells require energy for rapid cell division. Therefore, tumor cells reprogram their cellular metabolism, and published literature to date indicates that this reprogramming involves virtually all facets of metabolism, including that of carbohydrates, proteins, and fats. This effect in cancer was observed almost 100 years ago by Otto Warburg, a Professor of Biochemistry in Germany, who studied tumors *in vitro* and showed that tumors preferentially ferment glucose to lactic acid.[3] In a series of experiments, Warburg showed that from 100 cc blood, tumors consume 70 mg of glucose, split 66% of that glucose into lactate, and oxidize the remainder (34%) to carbon dioxide and water. Warburg showed that both fermentation and respiration need to be blocked to kill the tumor cells and that blocking only one of these processes is not sufficient for that purpose.[3]

Based on decades of research and after describing the chemical reaction in which ADP is phosphorylated to ATP, in 1956, Warburg described a clear difference between normal cells that respire aerobically using oxygen and cancer cells that use fermentation as the preferential energy-producing process even in the presence of oxygen.[4] In that highly cited paper, Warburg described two steps in the origin of cancer cells, initiated by the irreversible damage of respiration followed by fermentation, with the latter occurring

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Abbreviations: 2ME2, 2-methoxyestradiol; AML, acute myeloid leukemia; ADP, adenosine diphosphate; ATP, adenosine triphosphate; APL, acute promyelocytic leukemia; BMI, body mass index; BM, bone marrow; BcCML, blast crisis of chronic myeloid leukemia; ChREBP, carbohydrate response element binding protein; CoA, coenzyme A; FAO, fatty acid oxidation; GLUT, glucose transporter; HIF-1, hypoxia inducible factor 1; HIF-1α, hypoxia inducible factor 1 alpha; HSC, hematopoietic stem cells; LSC, leukemic stem cells; MDS, myelodysplastic syndromes; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; PPAR, peroxisome proliferator-activated receptor; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid; UCP, uncoupling protein.

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after a latent period that leads to cancer, and which does not occur in healthy regenerating liver.[4] However, it should be noted that, in a subsequent publication in 1962, Warburg revised his earlier conclusion of impaired respiration to insufficient respiration in cancer, as reviewed by Koppenol *et al*.[5]

Numerous published articles have discussed the Warburg effect[5–8] and the significant role of oxidative phosphorylation and mitochondria in cancer.[9] Normal cells generate up to 32 molecules of ATP by complete oxidation of one glucose molecule via oxidative phosphorylation.[1] Notably, in the same time taken by a normal cell to complete one cycle of oxidative phosphorylation, cancer cells generate a much greater number of ATP molecules using only the glycolytic pathway when enough glucose is present.[5,8] Importantly, the intermediate products of glycolysis lead to biosynthetic pathways that are crucial for the development and proliferation of cancer cells.[6]

Much has been learned in the last two to three decades about the regulation of glycolysis after the discovery of hypoxia inducible factor 1 (HIF1), which regulates glycolysis in hypoxic states and in cancer[10–12] and is overexpressed in many types of cancer.[13] The metabolic phenotype of tumor cells depends on both intrinsic and extrinsic variables. These include molecular genetic abnormalities in tumor suppressor genes or oncogenes, which may alter the cell metabolic pathways, and the state of the microenvironment in which the tumor cells live. The latter variables include hypoxia, pH, and glucose levels.[7,14] Ultimately, metabolic reprogramming in cancer meets three essential needs: the increased cellular energy demands, the need to synthesize additional cellular constituents, and the need to maintain the redox balance.[14]

The consumption and expenditure of energy are intricately related to excess body weight, including overweight and obesity, defined as a body mass index (BMI) ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively. Since 1975, excess body weight has increased globally, primarily due to increased consumption of energy sources (food and drink) and increased physical inactivity. Notably, these increases parallel a global increase in cancer burden.[15] As reported by an extensive global analysis that included 1,698 population-based data sources, with > 19.2 million adults (9.9 million men, 9.3 million women) in 186 countries, the age-standardized prevalence of obesity increased from 3.2% (2.4–4.1) in 1975 to 10.8% (9.7–12.0) in 2014 in men, and from 6.4% (5.1–7·8) to 14.9% (13.6–16.1) in women.[16] Alarmingly, obesity is estimated to affect 1 in 2 adults in the USA by 2030.[17]

The dietary consumption of fructose has also increased, particularly after the introduction of high fructose corn syrup in the 1970s.[18–20] Substantial accumulated published evidence indicates that excess consumption of fructose is associated with increased occurrence of obesity, cardiovascular disease, diabetes, hypertension, hyperuricemia, metabolic syndrome, and non-alcoholic fatty liver disease (limited references cited due to space).[18–25] Fructose is also produced endogenously from glucose in hyperglycemic states.[26] Further, excess intake of fructose-sweetened beverages was shown to be associated with an increased cancer risk in a prospective 2009–2017 French study with a median follow-up of 5.1 years.[27] Another study reported significantly higher risks of breast and prostate cancer and trends for higher colorectal and pancreatic cancer risk in a 2003–2020 meta-analysis.[28] Excess fructose intake in African American women has been correlated with a significantly increased risk of ovarian cancer.[29] Notably, fructose metabolism is associated with aggressive cancer in the brain,[30,31] pancreas,[32] colon,[33–35] liver,[36,37] ovary,[38] breast,[39] prostate,[40] kidney,[41,42] and lung[43] in pre-clinical and clinical studies[30–43] and an aggressive breast cancer cell line from an African American woman.[44]

Acute myeloid leukemia (AML) is a lethal hematologic malignancy with an increasing incidence and prevalence. The underlying molecular genetics in AML have been studied intensively in the last two decades,[45,46] with specific targeted drugs available since 2017.[47] AML is characterized by a clonal proliferation of immature myeloid cells, which arise from leukemic stem cells (LSC) in the bone marrow (BM). Obesity is associated with AML, as reviewed herein, but specific studies of excess fructose (due to dietary intake or endogenous production) in AML have not yet been performed.

Here, the physiologically inter-linked metabolism of glucose and fructose are described, including aspects unique for fructose metabolism that are pathogenetic, followed by our current understanding of fructose metabolism and AML. The purpose of this study was to determine, for the first time, if excess fructose intake can lead to the initial cellular event that causes AML and, subsequently, to provide insight into novel therapies for AML.

Dietary fructose intake, absorption, and metabolism

Glucose is the preferred energy source for human cells and is available through various carbohydrate dietary sources, including monosaccharides, disaccharides, and polysaccharides. If dietary intake is insufficient, the body's glycogen stores supply glucose, and when glycogen is depleted, glucose is synthesized (gluconeogenesis) from proteins. The main dietary sugars include glucose, fructose, sucrose, lactose, and maltose.[19] Lactose is composed of glucose and galactose, which are absorbed as glucose after galactose is converted to glucose. Maltose is composed of two molecules of glucose and is absorbed similarly to glucose.[1,2,19] Therefore, sugar metabolism to be considered for both healthy and diseased cells is primarily that of glucose and fructose.

Dietary fructose intake

Fructose is present in several types of foods, including sugars, honey, fruits, and some vegetables (food content in cited reference).[18] In most foods, fructose occurs naturally in conjunction with glucose and the disaccharide, sucrose, which is composed of equimolar glucose and fructose.[18] Man-made high fructose corn syrup, introduced in the USA in 1970s, most commonly includes 55% or 42% fructose.[19] In a span of three decades, 1970 to 2000, there was a 25% increase in the availability of sweeteners in the USA, which are comprised of approximately 50% fructose.[19] During 1975–1990, the consumption of fructose increased by ten-fold.[18] In a survey-based study during 1994–1996, the average individual intake of added sugars was 79 gm/day (or 316 kcal/day), with half of that comprised of fructose.[19,20] Importantly, the intake of added sugars was 137 gm/day (548 kcal) for the top one-third and 178 gm/day (712 kcal/day) for the uppermost 10% of sugar-consumers.[19] Carbonated beverages provide approximately 50% of calories from fructose,[18] and consumption of soft drinks increased from approximately 2/week in 1947 to 2/day in 2000 in the USA.[20]

In 2008, fructose consumption accounted for about 330–380 kcal/day, corresponding to 17–20% of the energy intake in the average American diet,[48] higher than the 2015 World Health Organization recommended upper level of 10% of daily energy intake of total added sugars.[49] Interestingly, the sugar consumption habits of some populations might explain why African Americans have higher rates of obesity, hypertension, diabetes, renal, and cardiac diseases.[21]

Dietary sugar absorption

Monosaccharides are transported across human cell membranes by the glucose transporter (GLUT) family of integral membrane transporter proteins. These include 14 proteins with different tissue localization and substrate specificities (reviewed in the cited references).[50,51] The solute carrier family 2 (*SLC2*) genes encode for the respective GLUT proteins. One or more of these proteins is present in all cells in the human body, with glucose transported by 11 of 14 proteins under experimental conditions, likely due to the critical need for glucose by human cells.[51] GLUT1-5 appears to be the most studied and involved in glucose and fructose transport across cell membranes.[50] The *SLC2A1* gene encodes for GLUT1, a primary glucose transporter expressed in many cell types, including erythrocytes and brain. Messenger RNA homologous to GLUT1 mRNA was detected in cell lines for AML (K562) and human colonic adenocarcinoma (HT-29) and in kidney disease in 1985.[52]

The GLUT5 protein, encoded by *SLC2A5* located on the short arm of chromosome 1p36.2, is the primary transporter for fructose and is expressed in the small intestine, testes, kidneys, adipose tissue, skeletal muscle, and brain.[50,51] GLUT2, encoded by *SLC2A2*, has a low affinity for glucose, galactose, mannose, and fructose and is expressed in the liver, absorptive intestine, kidney, pancreas, and brain.[51] Fructose is absorbed in the jejunum through GLUT5 on the luminal cell surface, then into the blood via GLUT2, and metabolized primarily in the intestine, liver, kidneys, and adipose tissue.[48,53]

Fructose metabolism

It is critical to remember that although glucose and fructose are both 6-carbon sugars with the same chemical composition, their metabolism differs.[1,2,18,19,21,22] In contrast with glycolysis, fructose metabolism is not regulated by insulin and consumes ATP, leading to *de novo* lipogenesis. Fructose is unique among all sugars in that it generates uric acid leading to hyperuricemia,[21,22] which further increases fructolysis. Our current understanding of fructose metabolism and the inter-linked glucose metabolism in normal cells, based primarily on studies in non-proliferating cells (including the steps for lipogenesis from fructose) is depicted in Figure 1.

Figure 2, also in normal cells, shows the pentose phosphate pathway (PPP) and the serine synthesis pathway, which require intermediate glycolysis metabolites as substrates for cellular biosynthesis. Interestingly, fructose directs the intermediate products of glycolysis, as shown by tracer studies, to enter the one-carbon serine pathway instead of the TCA cycle, which then facilitates fructose-induced lipogenesis.[54]

Many proteins regulate the pathways of glycolysis, with HIF1 alpha (HIF1-α) as a master regulator.[10–13] HIF1 is a heterodimeric protein regulated by cellular oxygen tension and is composed of an oxygen-dependent subunit, HIF1-α, and a constitutively present subunit, HIF1 beta. When O_2 levels are sufficient, HIF1-α is rapidly degraded due to hydroxylation of the conserved proline residues in the HIF1-α subunit and binding of HIF1-α to the von Hippel-Lindau tumor suppressor protein, followed by polyubiquitination and proteasomal degradation of HIF1-α. The hydroxylation of HIF1-α requires molecular oxygen. Therefore, in hypoxic states, HIF1-α is stabilized, accumulates, and translocates to the nucleus for subsequent events that lead to the transcription of genes that promote adaptation to hypoxia. HIF1-α promotes glycolysis and suppresses oxidative phosphorylation in hypoxic states and regulates several glycolytic pathway enzymes, as previously reviewed.[10,12]

The carbohydrate response element binding protein (ChREBP) is a transcription factor present in the intestine and liver that regulates glycolysis, fructolysis, the PPP, and *de novo* hepatic lipogenesis. Significantly, *Chrebp*-deficient mice cannot metabolize fructose.[55] Recently, *in vivo* isotope tracing demonstrated that dietary fructose led to acetyl coenzyme A (CoA) production directly from acetate produced by gut microbiota; ChREBP also converts microbiota-derived acetate to acetyl CoA for lipogenesis.[56] While it is known that ChREBP regulates *de novo* lipid metabolism from fructose via these pathways, the effect of suppressing ChREBP on lipogenesis is currently unknown.[57]

Obesity is associated with AML

The absence of body fat is currently understood to prevent cancer involving the gastric cardia, esophagus (adenocarcinoma), colorectum, liver (hepatocellular), pancreas, uterine endometrium, ovary, breast (post-menopausal), kidney, meninges (meningioma), and multiple myeloma.[58] Indeed, a multi-institutional, randomized clinical trial in diabetic, obese individuals showed that intensive lifestyle intervention with weight loss reduced the incidence of obesity-related cancers by 16%.[59] However, the absence of obesity as a preventive AML-causative factor is currently unknown. The known causative agents for AML include tobacco smoking, exposure to various chemicals, radiation, and cytotoxic therapies.

Epidemiology of AML

In the USA, the incidence of AML increased from 3.43 per 100,000 per year in 1973 to at least 4.2 per 100,000 per year in 2016.[60] In 195 countries, the global burden of AML increased significantly from 1990 to 2017.[61] Four main risk factors were described for AML-related mortality, including smoking and increased BMI as the first and second most significant factors, respectively. AML incidence rose in resource-rich countries and south Asia, with the highest incidences of AML in India, China, and the USA in 1990 and 2017.[61] In parallel, there was a significant increase in the prevalence of overweight men and women in China and India from 1975 to 2014.[16] However, India and China also had the highest and second highest prevalence of underweight men and women in 1975 and 2014.[16] Whether AML prevalence increased only in the obese or also in underweight individuals would require further study.

Obesity in AML

Active smoking and increased BMI were positively associated with AML in a large Canadian population-based study with 1,068 incident adult leukemia cases, including 358 AML and 5,034 healthy controls, with cases identified by provincial cancer registries in a 1994–1997 database. In that study, there was no leukemia risk with fruit and vegetable intake (by dietary servings/week in a self-reported questionnaire).[62]

In 2007, Larsson *et al*. analyzed nine cohort studies between 1966–2007 that had prospectively evaluated the relative risk of developing leukemia among overweight and obese individuals.[63] Four of those nine cohorts from Norway, Sweden, and the USA included a total of 4,804 specified AML patients, among whom there was an overall increased [1.52; 95% confidence interval (CI)

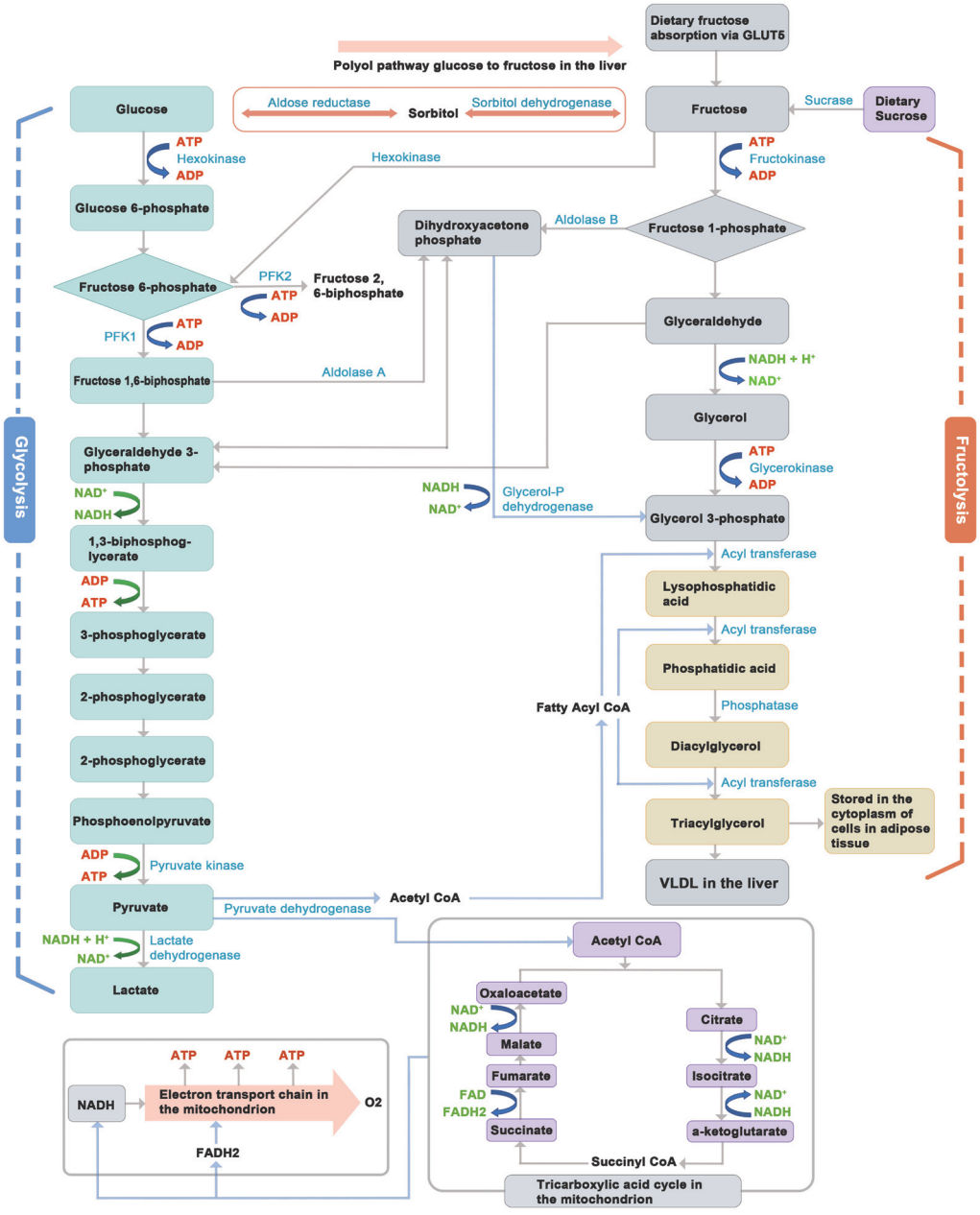

Fig. 1. Fructose metabolism in normal, non-proliferating cells showing the inter-connected glycolytic pathway with the tricarboxylic acid cycle and the hepatic lipogenesis pathway. Conceptually, this figure shows the pathways that underlie the ability of fructose to provide abundant energy for malignant cells. The figure shows (a) fructose metabolism after dietary absorption of fructose in the small intestine, including hepatic lipogenesis, (b) the pathways that link the metabolism of fructose with the glycolysis pathway, and (c) the mitochondrial TCA cycle with the electron transport chain. The TCA cycle requires oxidized nicotinamide adenine dinucleotide (NAD+) from the electron transport chain (not illustrated). The electron transport chain requires oxygen as the final oxygen acceptor, and therefore, indirectly, the TCA cycle requires oxygen. In contrast, the glycolysis pathway does not require oxygen. The three regulatory steps for glycolysis are catalyzed by hexokinase, phosphofructokinase 1, and pyruvate kinase. Fructose can also be generated endogenously from glucose in hyperglycemic conditions through the polyol pathway in the liver, wherein sorbitol dehydrogenase catalyzes the conversion of sorbitol to fructose. Like glucose, fructose must first undergo phosphorylation to enter the cellular metabolic pathways. In the liver, fructose is metabolized to fructose 1-phosphate, which is cleaved by aldolase B to glyceraldehyde and dihydroxyacetone phosphate that enter the glycolysis pathway. Significantly, accumulated ATP inhibits glycolysis with phosphofructokinase 1 enzyme activity as the most important rate-limiting step for glycolysis, which is bypassed by fructokinase, leading to rapid fructose metabolism. If fructose is in excess, *de novo* lipogenesis occurs in the liver, with the steps shown in the figure. The glycerokinase enzyme, which phosphorylates glycerol to glycerol 3-phosphate in the fructolysis pathway, is present in the liver and absent in adipose tissue. Glycerol 3-phosphate leads to the synthesis of triacylglycerol and phospholipids (latter not shown). The conversion of glycerol 3-phosphate to triacylglycerol requires fatty acyl coenzyme A synthetase (also known as thiokinase) to convert acetyl coenzyme A to fatty acyl coenzyme A, followed by the addition of three acyl groups by acyltransferase and removal of the phosphate group by phosphatase. Triacylglycerols comprise the primary constituent of very low-density lipoproteins in the liver and are stored in adipose tissue. Enzymes are shown in blue text. PFK1, phosphofructokinase 1; PFK2, phosphofructokinase 2; CoA, coenzyme A; TCA, tricarboxylic acid; VLDL, very low-density lipoproteins.

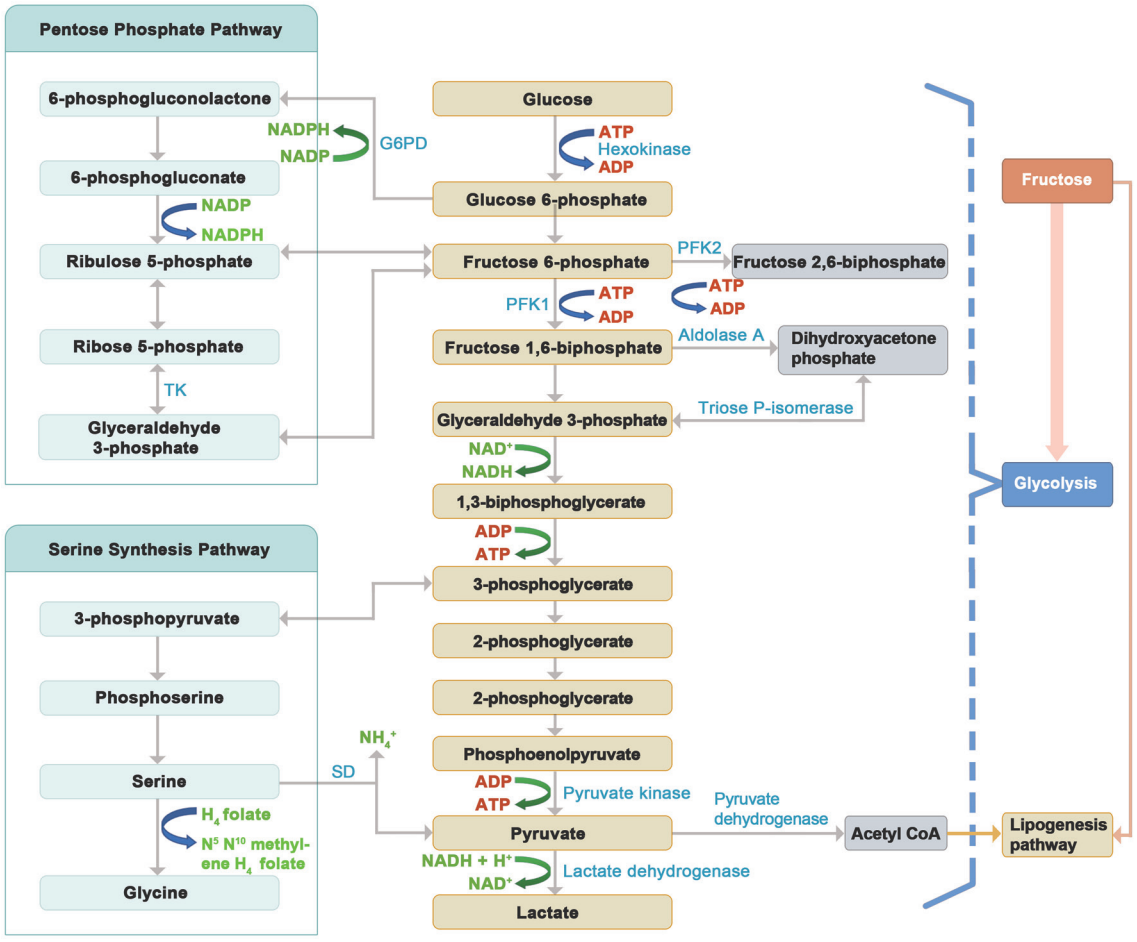

Fig. 2. Fructose metabolism connected to glycolysis, the pentose phosphate pathway, and the serine synthesis pathway can provide the cellular constituents essential for malignant cells. Conceptually, this figure shows the pathways in normal cells through which fructose can direct energy towards building the structures of the malignant cells. The figure shows the pentose phosphate pathway and the serine synthesis pathway, starting from intermediate products in glycolysis depicted by arrows. The pentose phosphate pathway generates 5-carbon sugars, including ribose 5-phosphate, which serves as a precursor for the synthesis of nucleotides, coenzymes, and nucleic acids. In the oxidative part of the pentose phosphate pathway, nicotinamide adenine dinucleotide phosphate hydrogen is generated, which reduces glutathione and supports biosynthesis. The serine synthesis pathway generates serine and glycine and may also lead to lipogenesis, with that path depicted by arrows. Enzymes are shown in blue text. CoA, coenzyme A; G6PD, glucose 6-phosphate dehydrogenase; PFK1, phosphofructokinase 1; PFK2, phosphofructokinase 2; SD, serine dehydratase; TK, transketolase.

1.19–1.95] relative risk of developing AML with obesity.[63] Notably, one of those four cohorts represented USA male veterans hospitalized with a diagnosis of obesity from 1969–1996, including 3,668,486 White and 832,214 Black individuals. In this large study with a 27-year follow-up (average 12 years per individual) by Samanic *et al*., the highest relative risk [2.64 (CI 1.80–3.85)] was observed in Black men with AML (n = 287), in contrast with a relative risk of 1.59 (CI 1.33–1.90) in White men with AML (n = 1,607);[63,64] neither racial nor ethnic origin was described.[64]

Interestingly, there was no difference in obesity prevalence among adult men from different ethnic groups (Mexican American, non-Hispanic White, and non-Hispanic Black) in the civilian USA population during 1999–2004.[65] Since the Black population includes African Americans, the similar obesity prevalence regardless of racial/ethnic origin in conjunction with a high risk of AML in Black obese men suggests that African Americans could have an increased risk of developing AML. Further, studies addressing disparities in racial/ethnic origin in AML have primarily examined prognostic factors, treatment, and outcomes (citations in reference).[66] Whether the African American population has a higher risk of AML remains to be determined.

State-based studies in the USA showed an increased risk or association of obesity with AML. In the prospective Iowa women's study of 40,000 primarily White women, aged 55–69 years during 1986–2001, 74 women developed AML. The risk of AML, with a median follow-up of 14.3 years, was higher with overweight or obesity and increased with increasing BMI.[67] Similarly, a Texas case-control study with 638 adult *de novo* AML patients, including 46% women and 636 controls, showed a significantly increased AML risk in women due to obesity [univariate 1.87 (CI 1.25–2.78); multivariate 1.62 (1.06–2.47)]; obese men also had an increased AML risk.[68]

In a 2016 study of 420 AML, 265 myelodysplastic syndromes (MDS), and 1,388 control individuals (98% non-Hispanic White) in Minnesota, obesity, but not overweight, was increased in adult (age 20–79 years) men and women with AML, and obesity was increased in women with MDS.[69] The strongest associations were in individuals with class II/III obesity (BMI ≥ 35 kg/m^2),[69] similar

to the Iowa women's study.[67]

In contrast, overweight and obesity were both associated with an increased incidence of AML [relative risk 1.23; (CI, 1.12–1.35)] in a 2017 meta-analysis of 26 studies that included 12,971 AML patients, including 866 patients with acute promyelocytic leukemia (APL), a specific genetic subtype of AML.[70] Additionally, high BMI predicted worse outcomes in APL but not in non-APL AML.[70] A UK population-based study, including 26 APL and 1,012 non-APL AML among 5.24 million adults, also showed increased APL risk with obesity [hazard ratio 1.44; (CI, 1.00–2.08), per 5 kg/m^2 increase in BMI], with similar findings in APL cohorts from Spain, Italy, and the USA.[71]

While obesity is clearly associated with an increased risk of AML, as evident from the studies summarized above, the underlying mechanisms are unclear for AML. A mechanism involving inflammatory mediators for cancer in obesity might be relevant for obesity and excess fructose in AML.

Effects of fructose metabolism on AML

A critical difference between glucose and fructose metabolism is that only fructose leads to *de novo* lipogenesis, which implicates excess fructose in the pathogenesis of cardio-metabolic diseases.[18–25] However, cancer cells, including leukemic cells in AML, require sugars, amino acids, and fatty acids to form their cellular structures and proliferate. As depicted in Figures 1 and 2, excess fructose could provide the required energy and cellular biosynthesis sources to the microenvironment from which cancer cells originate and grow (if there are no underlying enzymatic deficiencies in the individual). In this context, prior and recent studies of AML are reviewed in this section.

GLUT5 in cancer and normal tissues

Table 1 summarizes the results from studies that examined GLUT5 expression in patients with malignant and benign neoplasms from various sites compared with normal tissues and cancer cells versus normal counterparts in cell lines.[30,35,38–41,43,72–76] Notably, several tumor types were GLUT5 and GLUT2 positive,[72] indicating fructose uptake by benign neoplastic and cancer cells. Moreover, GLUT5 expression in cancer significantly correlated with aggressiveness of the malignancy and poor patient prognosis in gliomas and carcinomas in the kidney, ovary, lung, prostate, breast, and acute leukemias (lymphoid and myeloid), as shown in Table 1.

Interestingly, recent evidence from 13 different cell lines from five different originating tissues showed that the ability to metabolize fructose is not tissue site-dependent, since cells that chronically live in an environment containing fructose upregulate GLUT5 and develop the ability to metabolize fructose using hexokinase instead of fructokinase.[77] In contrast with these *in vitro* studies, genetically deleting fructokinase in mice actually prevented the development of metabolic syndrome.[78]

GLUT5 in AML

A comprehensive metabolomics study of 400 newly diagnosed AML patients and 446 age- and gender-matched healthy controls from seven hematology centers in China revealed an etiologic role of fructose in the origin of AML. Among 47 altered metabolic pathways, the results showed a distinct glucose metabolic profile for AML with significantly altered metabolites of glycolysis and the TCA cycle in conjunction with a decrease in fatty acids required for leukemic cell synthesis.[79] Further, increased glycolysis decreased the sensitivity to anti-leukemic therapy *in vitro*, while inhibiting glycolysis suppressed AML cell proliferation and increased cytotoxicity.

Subsequently, in 2016, Chen *et al*. showed that fructose utilization was increased in four AML cell lines (U937 with *CALM/AF10,* OCI-AML3 with mutated *NPM1* and *DNMT3A*, HL-60 with amplified *MYC*, and K562 with *BCR-ABL*) in the absence of or low levels of glucose, with increased *SLC2A5* and GLUT5 expression. AML cell proliferation increased in the presence of fructose, in contrast with normal monocytes that showed little or no increased proliferation with fructose and did not express GLUT5.[76] Notably, AML blast cells showed significantly increased *SLC2A5* expression compared to normal hematopoietic cells, as evidenced by gene expression profiling data for sugar transporter genes in previous AML datasets (referenced in their publication).[76]

GLUT5 inhibitors in AML

Several inhibitors of GLUT1 are in development. Most GLUT1 inhibitors cause cancer cell apoptosis only in synergy with another chemotherapeutic agent; a specific GLUT1 inhibitor is being studied for breast cancer (see references in cited review).[80] Notably, a specific GLUT5 inhibitor, N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3-benzodioxol-5-amine (MSNBA), did not affect glucose transport by GLUT1-4 or fructose transport by GLUT2 in humans[81] and decreased the viability of colon cancer cells.[35] GLUT5 inhibitors have not yet been studied in AML.

Serine synthesis in AML

Serine is a major source of one-carbon units and is essential for the synthesis of proteins, including nucleotides.[1] Jeong *et al*. showed that two AML cell lines (MOLM13 for *FLT3*-ITD AML and K562) used fructose at a slower rate than glucose, while two other cell lines (THP1 for *MLL-AF9* AML and KASUMI for *AML1-ETO* AML) used fructose and glucose similarly.[82] The MOLM13 and K562 cell lines used hexokinase and not fructokinase in the presence of fructose, and isotope tracing showed a higher signal for glycine and serine, indicating that fructose activated the serine synthesis pathway that has glycine as the end-product.[82]

In the same context, Bjelosevic *et al*. showed that serine is essential for the viability of *FLT3*-ITD positive AML cells in a genetically engineered mouse model with doxycycline-inducible *FLT3*-ITD and *MLL*-rearranged AML.[83] In their transcriptomic analysis, *FLT3*-ITD upregulated the uptake and *de novo* synthesis of serine. The loss of *FLT3*-ITD led to a significant reduction in one-carbon metabolism and serine and nucleotide biosynthesis. Inhibiting *FLT3*-ITD also markedly reduced glucose incorporation into serine and glycine in AML cells.[83]

Fatty acid metabolism in AML

Fatty acids are absorbed into cells by specific proteins, including CD36, activated to acyl-CoA esters and transported by carnitine palmitoyltransferase 1 (CPT-1), the carnitine shuttle, into mitochondria.[1,84] Mitochondrial β-oxidation is the primary pathway for fatty acid oxidation (FAO). In humans, three acyl-CoA dehydrogenases, very long-chain, medium-chain and short-chain, catalyze long-, medium- and short-chain acyl-CoA oxidation, respectively.

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Table 1. GLUT5 expression in cancer and normal cell lines and in patient neoplastic and normal tissues

Publication, tissues studied	GLUT5 in cancer and normal cell lines and in patient neoplastic and normal tissues		Additional results and correlation, if available
	Results in cancer and normal cell lines	Results in neoplastic and normal tissues	
Godoy *et al.*,[72] human tissues	Fructose uptake by cancer cell lines at least 4x > human myeloid HL-60 cells; HL-60: 20 ± 1 pmol/10^6 cells; human choroid plexus papilloma HCPPC-1: 80 ± 15 pmol/10^6 cells; human breast cancer ZR-75-1: 110 ± 20 pmol/10^6 cells; human hepatoma HepG2: 260 ± 40 pmol/10^6 cells; MCF7, MDA468 and ZR-75 breast cancer cell lines express GLUT1, GLUT2, and GLUT5	Normal tissues: GLUT5 IHC$^+$ membranous: RBCs, kidney proximal tubules, colon epithelial cells, testes spermatids, adrenal gland zona fasciculata; GLUT5 IHC$^+$ cytoplasmic: breast myoepithelial cells, prostate glandular cells, smooth muscle cells, hepatocytes; stomach IHC$^+$ pattern not specified	
		IHC$^+$ n^+/n^{total} Invasive breast ca 28/33; colon cancer 12/12; pancreatic cancer 0/3; gastric cancer 0/6; hepatocellular ca 2/4; ovarian ca 0/6; pleural mesothelioma 4/4; testicular seminoma 2/8; uterine leiomyoma 2/4; ependymoma 3/27; choroid plexus papilloma 2/5; *non-Hodgkin lymphoma 4/6	Low affinity GLUT2 IHC$^+$ breast ca, colon ca, pancreatic ca (2/3), gastric ca 2/6; hepatocellular ca, ovarian ca 1/6; pleural mesothelioma, testicular seminoma, uterine leiomyoma, ependymoma, choroid plexus papilloma
Villaamil *et al.*,[41] renal cell cancer	Cell lines not examined	GLUT5 IHC$^+$ high intensity in 46/80 RCC patient tissues, in tumor cell membranes and cytoplasm; expression higher in clear cell RCC, correlated with moderately differentiated RCC	GLUT5 expression correlated with patients with pelvic invasion, capsular invasion
Su *et al.*,[30] brain gliomas	Glioma cell lines LN229 and U87: mRNA expressed; Normal glial cell lines HEB, N9: mRNA not expressed	GLUT5 IHC$^+$ cytoplasmic in glioma tissues (n=85 studied); IHC Negative in normal glial tissues ($p < 0.01$); mRNA higher expression in gliomas vs normal glial tissues	GLUT5$^+$ correlated with malignancy and poor patient survival; in mice, excess fructose increased tumor volume
Jin *et al.*,[38] ovarian cancer	Ovarian cancer cell lines OVCAR83, SKOV3 utilize fructose, highly express GLUT5, and knockdown of GLUT5 stops proliferation; normal ovarian cell line IOSE80 did not use fructose	GLUT5 IHC$^+$ membranous and cytoplasmic in ovarian cancer cells (n=137 patient cases), positivity much less in normal ovarian tissue as described; GLUT5 mRNA levels higher in cancer than in normal ovarian tissue	GLUT5$^+$ no correlation with histologic type; correlated with late stage, higher grade, metastasis; high IHC+ correlated with worse patient overall and 3-year survival
Bono *et al.*,[73] thecoma	Cell lines not examined	GLUT5 IHC$^+$ in ovarian thecoma (n=5 patient cases)	Initial misdiagnosis as cancer due to uptake
Fan *et al.*,[39] breast cancer	Breast cancer MCF-7 and MAD-MB-231 (human), 4T1 (mouse), and other cancer cells T47D, A549, HeLa, HepG2 had higher GLUT5 protein levels than non-tumor 3T3 (mouse), 293T, HBL100 & MCF-10A (human) cells; non-tumor cell lines did not use fructose; MCF-7 and MAD-MB-231 utilized fructose**	GLUT5 protein highly expressed in breast cancer tissues but not in normal breast tissues (n=10 patient tissues)	Fructose promoted metastasis of breast cancer in mice
Nahrjou *et al.*,[74] breast cancer cells	GLUT5-negative normal breast 184B5 cells; GLUT5$^+$ breast ca MCF7 cell line, GLUT5$^+$ human breast invasive ductal carcinoma MDA-MB-231 cell line		Explored GLUT5-mediated drug delivery in cancer
Carreño *et al.*,[40] prostate cancer	GLUT5 and GLUT9 overexpressed in prostate cancer LNCaP and PC3 (human) cell lines when compared with benign prostate RWPE-1 cell line	GLUT5 and GLUT9 IHC highly expressed in tumor cells in 25 matched tumor and non-tumor prostate cancer tissues	Fructose stimulated proliferation and invasiveness in cancer cells and patient-derived xenografts

(continued)

Table 1. *(continued)*

Publication, tissues studied	GLUT5 in cancer and normal cell lines and in patient neoplastic and normal tissues		Additional results and correlation, if available
	Results in cancer and normal cell lines	Results in neoplastic and normal tissues	
Weng *et al.*,[43] lung cancer	Lung adenocarcinoma A549 and H1299 cell lines utilized fructose	*SLC2A5* expressed in lung adenoca and squamous cell ca, but not in normal lung tissue; IHC GLUT5 expressed in cancer tissues, much weaker expression in normal tissues	Invasive ability increased if *SLC2A5* expressed; *SLC2A5* high expression correlated with poor patient prognosis
Wlodarczyk *et al.*,[35] colon cancer	GLUT5 expressed in colon cancer HT-29, higher than normal colonic epithelial CCD 841 CoN cells	GLUT5 mRNA expressed in 98% of 30 colorectal cancer tissues and 50% of 30 normal intestinal tissues	A specific GLUT5 inhibitor significantly reduced viability of cancer cells *in vitro*
Zhao *et al.*,[75] childhood Ph^+ ALL	TKIs (imatinib, dasatinib) repressed *SLC2A5* expression and fructose uptake by SUP-B15 cells (human Ph+ALL cell line)	*SLC2A5* significantly high expression in Ph^+ALL patients compared with Ph^- ALL (total 69 childhood ALL patients)	$SLC2A5^{high}$ correlated with recurrence in 3 y, early relapse, short complete remission, MRD+ after treatment
Chen *et al.*,[76] AML; see text for AML	Four AML cell lines, U937, OCI-AML3, HL-60, K562: expressed $SLC2A5^{high}$, increased GLUT5, and increased fructose uptake compared with normal monocytes	*SLC2A5* gene expression significantly increased in blast cells in AML patients compared with normal hematopoietic cells	$SLC2A5^{high}$ expression and enhanced fructose utilization were associated with poor outcomes in AML patients

IHC, immunohistochemistry; IHC^+, positive by IHC; RBCs, red blood cells; ca, cancer; adenoca, adenocarcinoma; RCC, renal cell carcinoma; Ph^+, Philadelphia chromosome-positive; ALL, acute lymphoblastic leukemia; TKIs, Tyrosine kinase inhibitors; MRD, minimal residual disease; AML, acute myeloid leukemia. *Non-Hodgkin lymphomas stated as GLUT5 positive in the publication text, with discrepancy in the glucose transporter in the tabular data (this discrepancy was in the published article by Godoy *et al.*[72] itself). **Cancer cell lines Panc-1, HPAF, Capan, HCT114, HepG2 use fructose (reference cited in Fan *et al.*[39]). GLUT5, glucose transporter 5.

Physiologically, ATP production by FAO is crucial for the heart, skeletal muscle, and kidneys.[84]

Previously, co-cultured AML cells on a mesenchymal stromal cell layer were shown to accumulate lactate with decreased pyruvate metabolism, consistent with the Warburg effect, which was mediated by mitochondrial uncoupling.[85] The latter is a process wherein ATP generation uncouples from the electron transport chain, which occurs physiologically in mammals for cold acclimatization and is mediated by uncoupling proteins. In that study, the co-cultured AML cells expressed mitochondrial uncoupling protein 2 (UCP2),[85] and the uncoupling occurred in FAO so that ATP was generated by glycolysis and not by FAO.[86]

AML cells rely on fatty acids along with other essential energy sources for their metabolic needs. FAO was recently shown to be essential for leukemic cells in AML,[87] for which, notably, fructose metabolism, as depicted in Figure 1, would be directly supportive.

Reactive oxygen species, fructose, and AML

Reactive oxygen species (ROS) include superoxide and hydroxyl free radicals and non-radical oxygen and hydrogen peroxide molecules. These molecules are constantly generated by multiple normal enzymatic and non-enzymatic reactions in the mitochondria, peroxisomes, endoplasmic reticulum, and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family of enzymes in the cell membrane, including during fatty acid metabolism.[88,89] ROS, which may be induced by hypoxia, endoplasmic reticulum stress, metabolic defects, and oncogenes, can react with many cellular constituents and cause oxidative damage, including to DNA and proteins. The production of ROS is balanced in the normal state by ROS scavengers, which include glutathione, NADPH, transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), and the effects of tumor suppressor genes and dietary anti-oxidants, with NRF2 considered to be a master regulator of the intra-cellular anti-oxidant response.[89]

Like UCP2 in AML cells,[85] following an injury to the central nervous system, UCP2 decreases ROS production, which would otherwise mediate oxidative damage; thereby UCP2 prevents neuronal cell death.[85,90] Free fatty acids are increased in ischemic or traumatic brain injury and stimulate mitochondrial UCP2 to decrease ROS production.

Interestingly, the metabolic state in neuronal injury appears to have similarities with AML, with significant alterations in FAO and glycolysis reported in conjunction with increased ROS in AML.[91,92] Moreover, mutated isocitrate dehydrogenase genes (*IDH1/IDH2),* which cause gliomas and AML,[9,93] may lead to the inability of the mutated cells to neutralize ROS due to depleted NADPH in the production of the oncometabolite, (R)-2-hydroxyglutarate, by the mutated IDH1/IDH2 enzymes, as previously reviewed.[93]

Fructose and the redox balance in cancer, including AML

Excess dietary fructose has several undesirable metabolic effects that include increased ROS production as an underlying effect of fructose metabolism.[94] In a mouse model it was shown that fructose caused fibroblasts to transform to mature adipocytes, with increased lipid metabolism in adipocytes and generation of free fatty acids.[95]

Glycolysis and the PPP (as illustrated in Figure 2) have essential roles in maintaining the anti-oxidant response.[88] NADPH, which is

required to maintain glutathione in the reduced state, is generated by the oxidative part of the PPP and the one-carbon serine pathway.[1,2,88,96] A disrupted redox balance between ROS generation and anti-oxidants is implicated in the pathogenesis of aging, neurodegenerative and cardiac diseases, and cancer.[88] Significantly, ROS can cause either proliferation or cell death in cancer, depending upon the cancer stage, with a pro-oncogenic effect in the earlier stages of cancer.[97] In addition, multi-faceted effects of the various types of ROS serve as specific messengers in different subcellular locations, which are only beginning to be understood.[96] Increased ROS have been observed in both lymphoid and myeloid leukemias, including AML.[98] In AML, the NADPH oxidases family of enzymes are considered the primary source of increased ROS levels.[92] As described above, the undesirable effects of fructose include the generation of ROS via the various metabolic pathways derived from fructose metabolism, including FAO,[96] which are vital for leukemic cells in AML.

ROS may be present intracellularly and extracellularly, including in the microenvironment of tumor cells.[88] Leukemic cells in AML reside in the BM, and the microenvironment of the leukemic cells includes the marrow adipose tissue cells. Therefore, ROS in an imbalanced state or excess could affect any elements in the tumor cellular microenvironment, including adipose cells in the BM. Normally, with increasing age, there is an increase in the BM adipose tissue with decreased BM hematopoietic cellularity, and AML occurs most commonly in older individuals. It is therefore possible that increased ROS might interact with adipose tissue cells in the BM by yet undescribed mechanisms and contribute to the development of AML.

Normal adult hematopoietic stem cells and leukemia stem cells in AML

In 1994, Dr. John Dick's group transplanted leukemic cells from patients with all French-American-British subtypes of AML into severe combined immunodeficient mice and identified leukemia-initiating stem cells (LSC) as the originating cell from which AML cells arise.[99] The LSC were heterogeneously derived from hematopoietic stem cells (HSC) and are considered the source of relapse in AML.[100] Therefore, targeting LSC in AML is of significant therapeutic interest.

Normal adult HSC in the BM

Normal adult HSC are rare, multipotent cells that are understood to reside in a perivascular niche with other cellular and stromal elements in the BM microenvironment.[101] HSC have the unique capabilities of self-renewal to form additional self-renewing HSC and differentiation to progenitor cells that further differentiate to mature hematopoietic cells. HSC can be long-term or short-term, with the former required for complete hematopoiesis after BM transplantation. Quiescent HSC have few mitochondria and use glycolysis, while progenitor cells have many mitochondria and use oxidative phosphorylation for their energy needs.[102]

Long-term HSC reside in a hypoxic niche and express HIF1-α mRNA and protein, which likely stimulates the use of glycolysis instead of oxidative phosphorylation for the long-term HSC to remain quiescent. This process is necessary for maintaining HSC capacity for self-renewal. A low ROS environment is required to maintain HSC quiescence, self-renewal, and long-term survival.[92] It has been shown, however, that both quiescent and cycling HSC can be hypoxic and express high levels of HIF1-α protein.[103]

Importantly, HIF1-α finely regulates HSC proliferation and differentiation, with lower levels being beneficial for maintaining quiescent HSC and higher levels detrimental to HSC,[102] similar to the regulation by HIF in other cells.[10] However, since the oxygen thresholds at which the HIF system activates are cell-type-specific,[10] the optimal level of HIF1-α for maintaining HSC and the oxygen threshold at which HIF1-α activates are likely to be different for HSC than other types of cells. Further, in addition to HIF1-α, the maintenance of stem cells crucially depends upon other factors, including forkhead box O (FOXO), liver kinase 1 (LKB1), and LIN28 (as reviewed previously),[104] and the NADPH oxidases.[92]

The balance between quiescence and proliferation in HSC depends critically on nutrient-sensitive pathways, including FAO, glutaminolysis, and the phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway that relies on growth factors, glucose, and amino acids for its activation.[104] Of interest, in this regard, FAO has a critical role in the maintenance of HSC.[105] Notably, other stem cells, including adult neural stem/progenitor and intestinal stem cells, also require FAO for maintenance (as previously reviewed).[106] The metabolism of long chain fatty acids, comprised of 14–20 carbons, is regulated by a nuclear peroxisome proliferator-activated receptor (PPAR) delta (PPARδ), which represents one of three human isoforms, α, β/δ (referred to as δ), and γ, of PPAR. In mice, *ppard*-deletion in HSC was shown to profoundly impact long-term post-transplantation repopulating capability, and conversely, activating PPARδ improved HSC function.[105]

PPARγ is primarily expressed in adipose tissue with essential roles in the regulation of adipocyte differentiation, adipogenesis, and lipid metabolism. PPAR agonists have been investigated as therapeutic agents in metabolic syndrome and non-alcoholic fatty liver disease. However, the function of PPARγ is unclear in the context of BM adipose tissue and hematopoiesis. Nonetheless, BM adipocytes differ from adipocytes at other adipose tissue sites and secrete stem cell factor, which is important for HSC maintenance. Recent studies indicate that stem cells and different types of progenitor cells may reside in spatially different niches. Single cell sequencing studies of mesenchymal stromal cells in the BM have identified distinct gene expression profiles for perisinusoidal and periarteriolar stromal cells, suggesting that each type of cell was poised for adipogenesis or osteogenesis, respectively (reviewed in reference).[107]

The effects of various stressors on the interactions between HSC and their stem cell niche in the BM are being studied (reviewed in cited references).[107,108] Restricted caloric intake has been shown to have a beneficial effect in maintaining HSC quiescence; however, the mechanisms underlying this effect are not yet understood.[107]

LSC in AML

In contrast with normal HSC that use glycolysis, established LSC require mitochondrial oxidative phosphorylation. LSC isolated from primary human AML specimens based on their functional properties showed low ROS levels and were characterized as quiescent with low energy production compared to higher ROS levels in the bulk AML cells.[109] Those low-ROS LSC overexpressed BCL2, an anti-apoptotic member in the BCL2 family of proteins, which, when inhibited, eradicated the LSC, indicating the importance of mitochondrial metabolism in LSC in primary AML.[109] Subsequently, Pollyea *et al*. analyzed LSC in pre- and post-treatment samples from 33 single institution, newly diagnosed, elderly AML patients effectively treated with venetoclax, a selective inhibitor

of BCL2, combined with a hypomethylator, azacytidine.[110] LSC, identified by low-ROS and mass cytometry phenotype ($CD34^+$, $CD38^-$, Lin^-, $CD123^+$), were rapidly eliminated after therapy. The post-treatment LSC showed a disrupted TCA cycle and reduced oxidative phosphorylation.[110] Notably, venetoclax alone did not suppress oxidative phosphorylation,[110] in contrast with the findings from their earlier pre-clinical study.[109]

Interestingly, in a murine model of blast crisis of chronic myeloid leukemia (BcCML), LSC located within gonadal adipose tissue showed an inflammatory gene expression profile.[111] The investigators isolated and analyzed cells from the murine gonadal and inguinal adipose tissue, spleen, BM, and peripheral blood. Only gonadal adipose tissue showed the presence of leukemic cells and LSC, with the latter characterized by the Sca-1+/Lin− phenotype and a pro-inflammatory profile. Moreover, severe fat atrophy was observed due to lipolysis in the leukemic gonadal adipose tissue, with increased levels of free fatty acids; inguinal fat atrophy was also noted, despite a low level of leukemia cells in that site. Further, in this murine BcCML model, surface CD36 was not detected on normal HSC, but two metabolic types of LSC were identified based on surface CD36 expression. Both $CD36^+$ and $CD36^-$ LSC were functionally similar in the ability to generate leukemic cells, but $CD36^+$ LSC had a high FAO rate, low ATP, and depended more on glycolysis, similar to quiescent HSC. In the same study, the leukemic cells from 4 of 8 human BcCML and 4 of 8 human AML specimens also showed $CD36^+CD34^+$ cells among the $CD34^+$ cells, with increased FAO in the $CD36^+$ cells. However, LSC had a higher FAO rate than the leukemic cells or the HSC among the studied cells, and the presence of CD36 on LSC in the gonadal adipose tissue protected the LSC from chemotherapy.[111]

In the same murine model, LSC in the liver, a common extramedullary site for leukemic infiltration, showed increased pathways for lipid metabolism in the absence of an inflammatory profile.[112] The metabolome of cells isolated from the liver and BM showed abundant polyunsaturated fatty acids in the hepatic lin^- leukemic cells. Significantly, culturing LSC with polyunsaturated fatty acids increased the number of LSC, with linoleic acid being the most mitogenic fatty acid. In mice with hypercholesterolemia, reduced high-density lipoproteins (HDL), and slightly increased low-density lipoprotein (LDL)/very low-density lipoprotein (VLDL) levels, the hepatic LSC transcriptomic profile related to metabolism was distinct from that of BM LSC. In those mice, there was increased hepatic LSC expression of *LIPG*, which encodes for a lipase that metabolizes the phospholipids in HDL to lysophosphatidylcholine and fatty acids, thereby decreasing the HDL level. Overexpression of *LIPG* (approximately twice normal) *in vitro* led to increased linoleic acid and increased leukemic cell proliferation, which was further stimulated by adding HDL. The LSC with overexpressed *LIPG* showed a higher ROS level. Moreover, *LIPG* was overexpressed in post-chemotherapy BM LSC. These findings showed that hepatic LSC used HDL to proliferate, and *LIPG* protected the BM LSC from chemotherapy.[112]

HIF1-α and LSC in AML

In a mouse model derived from human AML samples, $CD34^+CD38^-$ LSC showed increased expression of HIF1-α and GLUT1 mRNA and increased accumulated HIF1-α protein. Echinomycin, a HIF1-α inhibitor, effectively eliminated the LSC that also lost their capability to form AML colonies.[113] AML human samples and cell lines also overexpress HIF1-α, with elimination of that expression by the HIF1 inhibitor, 2-methoxyestradiol (2ME2), which causes apoptosis of leukemic cells by the mitochondrial apoptosis pathway without affecting normal hematopoietic cells.[114] Interestingly, in AML cell lines exposed to 2ME2, the expression of the anti-apoptotic BCL2 and HIF1-α decreased simultaneously with increased expression of the pro-apoptotic BCL2 family members. Since HIF1-α reduces ROS generation, ROS levels also increased and mediated the 2ME2-induced apoptosis of leukemic cells.[114]

In a study of 60 AML patients compared with 20 normal control individuals, HIF1-α mRNA was significantly overexpressed in leukemic cells, with higher levels in extra-medullary (hepatosplenic and lymph node) leukemic infiltration. Particularly, AML patients with higher HIF1-α levels did not achieve complete remission, and higher HIF1-α levels correlated ($p < 0.001$) with shorter disease-free survival.[115]

Further, analyses of 183 previously characterized, French-American-British-classified patients with low- and high-risk MDS, a pre-leukemic disease that frequently progresses to AML, revealed HIF1 activation as the underlying pathogenetic mechanism in MDS. Echinomycin improved the dysplastic features of MDS and prolonged survival in mice.[116] HIF1 is also a potential therapeutic target in *JAK2*V617F-positive chronic myeloproliferative neoplasms,[117] which may also progress to AML. Moreover, HIF1-α is crucial for glioblastoma multiforme, a lethal brain tumor, and echinomycin effectively inhibited tumor growth and improved survival in a glioblastoma mouse model.[118] These studies indicate that HIF1 inhibitors should be pursued for treating patients with AML, including myeloid neoplasms that may progress to secondary AML, and non-hematologic cancer.

Future directions

This review suggests that the metabolism of normal adult HSC is likely to be very finely regulated. A focus on normal HSC in the BM microenvironment and the effect of any suspected etiologic agents, including excess dietary fructose intake, on the normal homeostatic milieu will likely answer questions surrounding the origin of AML. Figure 3 depicts the potential role of excess fructose at the origin of AML and after overt AML has developed. Future collaborative, multidisciplinary studies are needed to answer the following questions: (1) What are the interactions and role of the adipose tissue in the BM microenvironment in the initial development of AML compared with the normal BM with adipose tissue; (2) What are the targets and interactions of the specific types of ROS within the BM microenvironment where HSC and LSC reside, including with the adipocytes in the normal and leukemic BM (keeping in mind that these are likely to be different at the time of the initial leukemogenic events and at relapse after AML has already developed); (3) Can excess fructose, with or without excess body weight and other measures of adiposity, lead to AML in the BM (under any condition); (4) Based on reviews for dietary consumption of fructose in African Americans[21] and increased risk of AML in Blacks,[64] does ethnicity have a role in fructose intake and metabolism and AML occurrence, and is there a higher risk of AML in the African American population; (5) Can excess fructose, with or without obesity, lead to AML in the presence of germline mutations that may be familial and predispose to AML (reviewed in the reference);[119] (6) Can an intervention in dietary and lifestyle factors, including restriction of excess fructose intake, in individuals with or without excess body weight and other measures of localized adiposity, prevent the occurrence of AML; (7) Therapeutically, can HIF1 inhibitors improve patient survival in AML; and (8) Do GLUT1 or GLUT5 inhibitors impact outcome in AML patients?

Continued development in technological advancements and

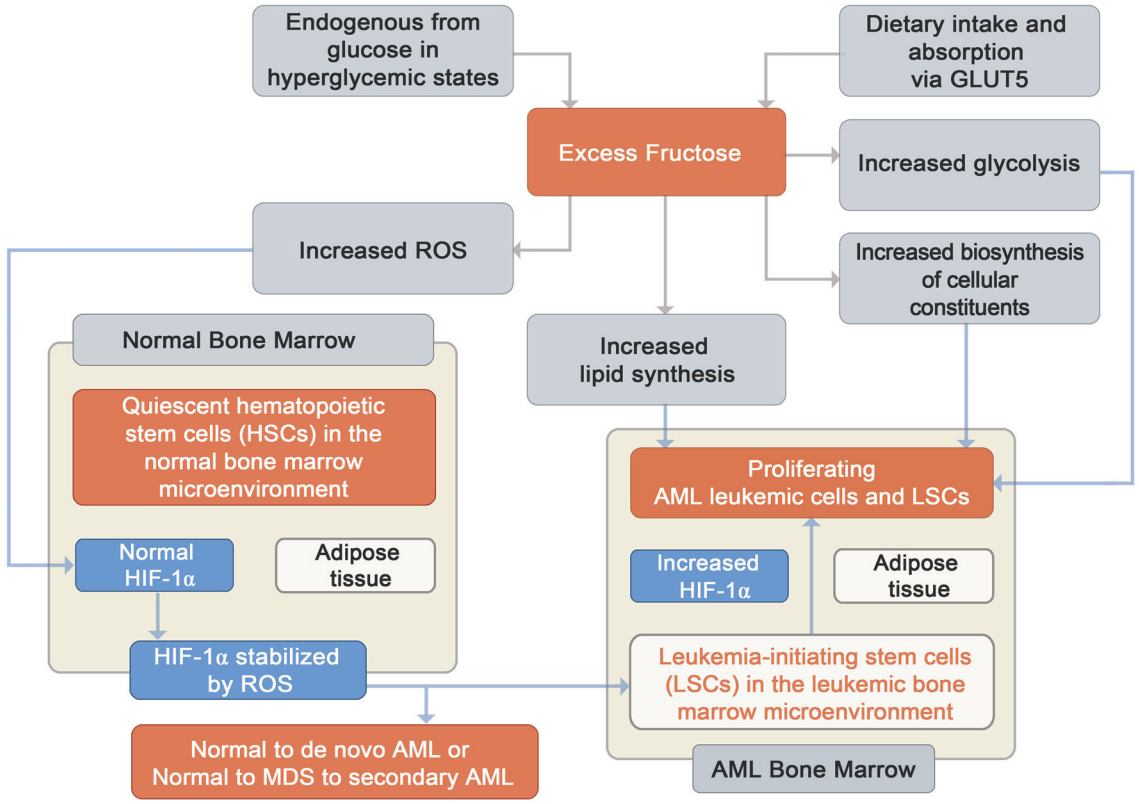

Fig. 3. Prospective etiologic role of excess fructose in acute myeloid leukemia. This figure depicts the potential etiologic role of fructose in two separate bone marrow environments: (1) benign with normal adult HSC in their normal microenvironment with marrow adipose tissue, and (2) overt AML leukemic bone marrow with LSC in their microenvironment, also with adipose tissue. Questions for future research are presented in the text. AML, acute myeloid leukemia; HSC, hematopoietic stem cells; HIF-1α, hypoxia inducible factor 1 alpha; LSC, Leukemia stem cells; MDS, myelodysplastic syndromes; ROS, reactive oxygen species.

new and safe therapeutic agents will hopefully pave the way for the necessary breakthroughs to elucidate the origin of AML to enable the prevention of malignancy and cure AML and related diseases in the future.

Conclusions

This article describes how excess fructose provides abundant energy sources and potentially provides the substrates for the biosynthesis of the cellular constituents essential for malignant cells to originate and proliferate. The evidence reviewed in this article for the etiologic role of fructose metabolism in AML collectively warrants further investigation. If ascertained that excess fructose can cause AML, then, importantly, there would be a simple way to prevent this deadly disease. Crucially, studies along this line of investigation could elucidate the etiologic mechanisms that may lead to urgently needed therapies to improve long-term patient survival in AML. The evidence to date indicates that HIF1 and GLUT5 inhibitors could be pursued in clinical studies to evaluate their therapeutic impact on AML patients.

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Conflict of interest

The author is a consultant for and has received consultation fees from Astellas; however, this study is solely the author's work without any connection with Astellas.

Author contributions

R.K. conceived of the subject content for this manuscript, researched and analyzed the literature, originally designed and created the figures, and wrote the entire manuscript.

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