Relationship between Fructose Metabolism Pathway and Hepatocellular Carcinoma and Colorectal Cancer

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Abstract. Colorectal cancer and liver cancer have become the second and the third primary causes of cancer death around the world. In recent years, the important role and mechanism of fructose in cancer and other diseases have also attracted widespread interests, but the interaction between fructose metabolism and the development of colorectal cancer and liver cancer remains unclear. This review discusses the research progress in recent years on the mechanism of fructose metabolism in promoting hepatocellular carcinoma and colorectal cancer, including i) Promoting cancer cell growth through indirect effects such as promoting O-GlcNAcylation via microbial-derived acetate and inhibiting M1-like tumor-associated macrophage polarization. ii) Directly affecting cancer cell metabolic reprogramming by regulating metabolic-related enzymes (aldolase B, KHK-A) and upregulating reactive oxygen species (ROS). This review summarizes the different promotion of fructose metabolism in the Growth-Colorectal cancer liver metastasis-Colonization process of colorectal cancer.The future research directions and priorities around fructose metabolism are discussed and proposed at the end of this review, indicating the importance and potential value of fructose metabolism in cancer development research.

Keywords: Tumor Microenvironment; Fructose metabolism; Hepatocellular carcinoma; Colorectal cancer; Metabolic reprogramming.

1. Introduction

Fructose, the second most common sugar in the human diet after glucose, is widely present in natural foods like honey, fruit juices, and grains, making it an essential part of daily nutrition. Since the 1960s, fructose has been predominantly consumed in the form of high-fructose corn syrup (HFCS), leading to a significant rise in its consumption. HFCS, which contains roughly 45% glucose and 55% fructose, is sweeter than traditional sucrose, making it highly favored in the food industry. However, recent epidemiological studies have revealed a concerning trend: excessive fructose consumption is strongly linked to various health problems, including obesity, diabetes, hypertension, hyperuricemia, Metabolic-Associated Fatty Liver Disease (MAFLD), and some types of cancer [1]. These findings have sparked considerable attention and concern within the global scientific community and public health sectors. Among them, the influence of fructose which serve as an important energy substance in the human body on the cancer development through metabolism is gradually gaining people's attention. In recent years, many articles have revealed various mechanism of action between fructose metabolism and cancer development. For instance, an article has shown that fructose cannot provide energy for cancer cells directly. However fructose can be converted into lysophosphatidylcholines (LPCs) through some specific cells like liver cell. The cancer cells then absorb the LPCs which serve as the membrane synthesis material from plasma [2]. In addition, in the study by Yan et al, fructose can enhance the interaction between hexokinase2 (HK2) and inositol-1, 4, 5-triphosphate receptors that located on endoplasmic reticulum membrane in BMDMs, thereby anticipating that fructose can inhibit M1-like tumor-associated macrophage polarization to promote development of colorectal cancer (CRC) cells [3]. Although research on the promoting effect that fructose mechanism acts on cancer cell is gradually deepening, details in this filed are still unclear. In particular, most researches

have focused on the impact in the growth stage of cancer cells, while its role in the occurrence, metastasis and colonization stages has been less involved.

Thus, this review select hepatocellular carcinoma (HCC) and CRC as the subjects, trying to explore the relevant research progress in HCC and CRC from the four important stages of cancer cell occurrence, growth, metastasis and colonization. The future research directions are included at the end of the review.

2. Review of Fructose Absorption and Metabolism in the Small Intestine and Liver

2.1. Fructose Absorption (GLUT2/5)

Fructose is predominantly absorbed in the mucosal cells of the small intestine through the specific transporter GLUT5, which facilitates the passive diffusion of fructose into the cells [4]. This transporter ensures efficient uptake of fructose, which then travels to the liver via the portal circulation. Within the liver, fructose transport is mediated by GLUT2, a transporter that allows the free exchange of fructose across hepatocyte membranes [5]. This mechanism enables the liver to regulate fructose concentrations and release it into the bloodstream based on physiological requirements. Consequently, only a minimal amount of dietary fructose enters systemic circulation, even when consumed in high quantities.

In the liver, fructose metabolism leads to the production of LPC, a blood-soluble lipid molecule that can be taken up by cancer cells [2]. LPC provides essential molecules for cell membrane synthesis, thereby supporting the rapid proliferation of cancer cells. This process allows cancer cells to indirectly utilize fructose, as fructose itself does not directly promote proliferation. Instead, fructose acts as a non-cell autonomous factor, indirectly promoting tumor growth through metabolite transfer [2, 6]. his indirect effect is further supported by the overexpression of fructose transporters GLUT2 and GLUT5 in certain malignant tumor tissues, which suggests that dietary fructose may contribute to tumor growth [7].

2.2. Metabolism (KHK + Aldolase B Pathway, HK - PFK1 - GAP3 Pathway)

In the liver, fructose metabolism is primarily facilitated through two distinct pathways: the KHK + Aldolase B pathway and the HK - PFK1 - GAP3 pathway.

For the KHK + Aldolase B pathway, fructose is rapidly phosphorylated to fructose-1-phosphate by KHK upon entering hepatocytes. Notably, the activity of KHK is not regulated by insulin [5]. Subsequently, fructose-1-phosphate is cleaved into dihydroxyacetone phosphate and glyceraldehyde by Aldolase B. Dihydroxyacetone phosphate is then converted to glyceraldehyde-3-phosphate, which directly enters the glycolytic pathway. This metabolic route bypasses key regulatory steps in glucose metabolism, thereby accelerating glycolysis through the direct production of glyceraldehyde-3-phosphate [5].

The HK - PFK1 - GAP3 Pathway mirrors the metabolic cascade of glucose. Here, fructose is initially phosphorylated to fructose-6-phosphate by the enzyme HK. It is then transformed into fructose-1,6-bisphosphate via PFK1. The subsequent breakdown of fructose-1,6-bisphosphate generates glyceraldehyde-3-phosphate and 3-phosphoglycerate, catalyzed by glyceraldehyde-3-phosphate dehydrogenase. Unlike glucose metabolism, this pathway is characterized by a more rapid metabolic rate and operates independently of insulin regulation [4].

3. Abnormal Metabolism of Fructose in Cancer Cells

3.1. Overexpression of GLUT5 in Various Cancer Cells and Its Role

In various cancer cells, GLUT5 is highly overexpressed, allowing these cells to absorb more fructose to satisfy their metabolic needs. For example, Wang et al. (2024) demonstrated that elevated

GLUT5 expression is strongly linked to increased fructose metabolism, which subsequently stimulates fatty acid synthesis [8]. This process provides the essential material foundation for the rapid proliferation of cancer cells. Moreover, Zhao et al. (2024) highlighted that fructose uptake facilitated by GLUT5 can activate the AMPK/mTORC1 signaling pathway, thus enhancing fatty acid synthesis and cell proliferation [9]. The intensified fructose metabolism serves a dual purpose: it provides cancer cells with additional energy and simultaneously activates the mTORC1 signaling pathway, thereby promoting cell growth and survival [9]. These observations indicate that the overexpression of GLUT5 in cancer cells is a key driver of enhanced fructose metabolism and has a significant impact on the malignant characteristics of cancer cells.

3.2. The Role of the Polyol Pathway in Cancer Cell Metabolism

The polyol pathway is a metabolic route that converts glucose to fructose, and it is notably activated under conditions of high glucose or high fructose. In cancer cells, this pathway provides an extra source of fructose to fuel their metabolic demands. Kang et al. (2024) demonstrated that under hyperglycemic conditions, gastric cancer cells can convert glucose to fructose through the polyol pathway. This conversion subsequently activates the KHK-A (ketohexokinase A) signaling pathway, which promotes epithelial-mesenchymal transition (EMT) and enhances cell migration [10]. Additionally, Zhao et al. (2024) revealed that AKR1B1 (aldose reductase 1B1), a key enzyme in the polyol pathway, is overexpressed in cancer cells [9]. This overexpression significantly boosts fructose metabolism, thereby driving cell proliferation and migration. These findings indicate that the polyol pathway not only supplies cancer cells with additional metabolic substrates but also enhances their malignant phenotype by activating downstream signaling pathways such as KHK-A and mTORC1. Furthermore, Frezza (2024) emphasized that fructose metabolism is crucial in various cancers, and its upregulation in a high-glucose environment can accelerate tumor progression and metastasis [11].

4. The Mechanism of Fructose Metabolism in the Development of HCC

Fructose metabolism is implicated in the development and progression of HCC through a variety of mechanisms. These mechanisms can be broadly divided into two main categories: metabolic reprogramming and inflammation coupled with oxidative stress. Metabolic reprogramming involves the direct impact of fructose metabolism on hepatic metabolism, including bypassing rate-limiting steps in glycolysis, promoting lipogenesis and insulin resistance, and enhancing O-GlcNAc glycosylation via microbial metabolites such as acetate. Inflammation and oxidative stress, on the other hand, refer to the inflammatory responses and oxidative stress triggered by fructose metabolism, which further exacerbate liver damage and tumor development.

4.1. Metabolic Reprogramming

4.1.1 Fructose Metabolism and Liver Metabolism

Fructose metabolism profoundly influences hepatic metabolism by bypassing glycolysis' rate-limiting steps and directly integrating into downstream pathways. This diversion accelerates lipogenesis and insulin resistance [12]. Such metabolic alterations not only boost lipogenesis but also facilitate the rapid proliferation of tumor cells by augmenting NADPH and nucleotide production. Additionally, fructose metabolism increases uric acid levels via the pentose phosphate pathway (PPP), which in turn exacerbates metabolic syndrome features, including hypertriglyceridemia and insulin resistance [12].

4.1.2 Microbial-Derived Acetate and O-GlcNAc Glycosylation

Consumption of a high-fructose diet markedly exacerbates the progression of HCC by influencing microbial metabolites like acetate. Research by Zhou et al. (2023) elucidated that acetate, which is produced in response to a high-fructose diet, can increase the levels of UDP-GlcNAc (uridine diphosphate-N-acetylglucosamine). This increase subsequently enhances O-GlcNAc glycosylation, a

process that is vital for several intracellular functions, including cell proliferation, migration, and metabolic reprogramming. Within HCC cells, this enhanced glycosylation activates downstream signaling pathways, thereby stimulating the proliferation and migration of tumor cells [13].

4.1.3 Fructokinase (KHK) and Tumor Metabolism

In HCC, fructose metabolism undergoes a splicing shift from fructokinase C (KHK-C) to KHK-A. As shown by the study of [14], KHK-A has protein kinase activity and can phosphorylate phosphoribosylpyrophosphate synthetase 1 (PRPS1). This phosphorylation promotes nucleotide synthesis, thereby supporting the development of HCC. This metabolic reprogramming is crucial for tumor growth and survival, as it satisfies the high nucleotide requirements of rapidly proliferating cancer cells.

4.2. Inflammation and Oxidative Stress

4.2.1 Fructose-Induced Inflammation and Oxidative Stress

Fructose metabolism further aggravates liver injury and tumor development by increasing the generation of reactive oxygen species (ROS) and inflammatory responses. The study by Muriel et al. (2021) pointed out that fructose metabolism promotes oxidative stress, inflammation, and fibrosis in the liver, which ultimately lead to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), both of which are significant risk factors for HCC [15]. Additionally, fructose metabolism further intensifies liver injury and tumor development by increasing uric acid levels and oxidative stress [15].

4.2.2 Aldolase B (ALDOB) and Tumor Suppression

In HCC, the downregulation of aldolase B (ALDOB) expression is significantly correlated with tumor invasiveness. The study by demonstrated that the loss of ALDOB expression in HCC cells significantly enhances tumor invasiveness. The stable expression of ALDOB can inhibit the migratory ability of HCC cells by upregulating the expression of TET1 (Ten-Eleven Translocation 1) protein. As a DNA demethylase, TET1 suppresses the invasion and metastasis of tumor cells by regulating the gene expression profile [16].

5. The Mechanism of Fructose Metabolism in the Development of colorectal cancer (CRC)

5.1. Cell-Autonomous Metabolic Reprogramming

Under conditions of glucose deprivation in the tumor microenvironment, colorectal cancer (CRC) cells activate compensatory fructose metabolism to sustain survival and progression. Central to this adaptation is the upregulation of the fructose-specific transporter GLUT5 (encoded by SLC2A5), which facilitates efficient fructose uptake in CRC tissues [17]. Notably, metastatic CRC cells exhibit aberrant overexpression of the ketohexokinase isoform KHK-A, contrasting with the liver-specific KHK-C isoform [18]. Mechanistically, KHK-A phosphorylates the Ser37 residue of pyruvate kinase M2 (PKM2), inhibiting its tetramerization and enzymatic activity. This post-translational modification triggers PKM2 nuclear translocation, where it acts as a transcriptional coactivator to amplify c-Myc expression. c-Myc, in turn, drives the transcription of glycolytic genes (e.g., GLUT1, LDHA) and epithelial-mesenchymal transition (EMT) markers, fostering aerobic glycolysis (Warburg effect) and anoikis resistance—critical features of metastatic dissemination [18]. Intriguingly, c-Myc reciprocally enhances KHK-A alternative splicing, establishing a self-reinforcing loop that perpetuates fructose-driven metastasis.

5.2. Fructose-Mediated Regulation of Macrophage Polarization and Metabolic Adaptation

Beyond intrinsic tumor cell reprogramming, fructose exerts profound immunomodulatory effects by reshaping the tumor-associated macrophage (TAM) landscape. Recent studies demonstrate that

fructose within the tumor microenvironment binds hexokinase 2 (HK2) in macrophages, triggering a cascade of immunosuppressive events. Specifically, fructose strengthens the interaction between HK2 and inositol 1,4,5-trisphosphate receptor type 3 (ITPR3), disrupting calcium ion flux at mitochondria-associated endoplasmic reticulum membranes (MAMs) [3]. This calcium dysregulation attenuates p38 MAPK, STAT1, and NLRP3 inflammasome signaling pathways, effectively suppressing M1-like TAM polarization. Consequently, the tumor milieu becomes enriched with immunosuppressive M2-like TAMs that secrete IL-10 and TGF-β, further impairing cytotoxic T-cell responses. Such fructose-mediated immunometabolic crosstalk synergizes with tumor-intrinsic pathways to accelerate CRC progression and therapeutic resistance.

6. Comprehensive Review on the Broad-Spectrum Role of Fructose Metabolism in Cancer Development

6.1. Metabolic Reprogramming: Dual Roles of Direct Utilization and Indirect Metabolic Effects

Fructose serves as a critical alternative energy substrate in glucose-deprived tumors, imported via GLUT5 (SLC2A5)-mediated transport. In pancreatic ductal adenocarcinoma (PDAC), for instance, GLUT5-driven fructose metabolism sustains ATP production and carbon flux while enhancing metabolic flexibility under nutrient stress [19]. Beyond direct utilization, emerging evidence highlights systemic pro-tumorigenic effects of fructose metabolites. Zhang et al. (2024) revealed that hepatic fructose metabolism generates lysophosphatidylcholines (LPCs), which circulate to fuel melanoma and breast cancer growth via a "liver-tumor axis." This discovery challenges the conventional paradigm of fructose as a locally acting metabolite.

Tissue-specific heterogeneity further complicates fructose's oncogenic roles. In hepatocellular carcinoma (HCC), where the fructose-phosphorylating enzyme KHK-C is deficient, gut microbiota-derived acetate substitutes fructose to drive tumor progression through O-GlcNAcylation modifications [9]. Such diversity underscores the context-dependent mechanisms by which fructose metabolism fuels malignancy.

6.2. Immune Microenvironment Modulation: Suppression of Antitumor Immunity

Fructose's immunosuppressive effects extend across cancer types. In CRC, fructose-activated HK2-ITPR3 interaction reduces mitochondrial calcium levels in macrophages, impairing M1-like polarization and NLRP3 inflammasome activation [3]. This non-canonical signaling mechanism operates independently of downstream metabolites, revealing a novel immunoregulatory role of fructose. Similarly, in breast cancer models, fructose-enriched diets suppress dendritic cell maturation and CD8+T-cell infiltration, fostering an immune-tolerant niche (unpublished data). These findings collectively position fructose metabolism as a master regulator of both metabolic and immune landscapes in cancer.

7. Conclusion

Through the investigation and discussion of recent research, we found that for colorectal cancer and hepatocellular carcinoma, the research on the effect of fructose on the development stage of both has less been involved, while the research on fructose metabolism on the growth stage is got more clear. Include excessive dietary fructose causing colorectal cancer cells to produce ROS due to metabolize fructose, which cause cancer cells to produce VEGF thereby promoting angiogenesis to support the growth of cancer cells; inhibiting M1-like tumor-associated macrophage polarization so that reducing the inflammatory response around colorectal cancer; downregulating AldolaseB to enhance the invasiveness of hepatocellular carcinoma and enhancing the progression of hepatocellular carcinoma by causing the protein eEF1A1 to be highly O-GlcNAcylated at T279 by microorganisms. The mechanism of action on fructose metabolism in the metastasis stage of cancer

cells focuses on the study of enzymes related to fructose metabolism. Study has shown that compared with primary tumors, KHK-A is upregulated during colorectal cancer and interacts with PKM2, promoting the migration and anti-apoptosis capability of cancer cells in fructose-dependent colorectal cancer liver metastasis progression, and the fructose absorbed by primary colorectal cancer can promote this process; for hepatocellular carcinoma, the downregulation of AldolaseB in it will inhibit the migration ability. During the post-metastasis growth stage, fructose can upregulate the levels of Aldolase B and GLUT5 in colorectal cancer cells, enhance the level of fructose metabolism in CRC. It has also been shown that fructose can serve as carbon source for CRC growth at this stage. However, the effect of fructose metabolism in hepatocellular carcinoma post-metastasis growth stage has been less mentioned. We suspect that since the occurrence of cancer involves complex changes in gene expression, the formation of the tumor microenvironment, and a series of changes in intracellular and extracellular regulatory mechanisms. This complex system has caused great interference in the research of the role of fructose metabolism in cancer occurrence. It is also possible that fructose metabolism promotes cancer occurrence by participating in or affecting other metabolic pathways (such as glucose metabolism, lipid metabolism etc.) and then through the complex interaction of its metabolites with intracellular genes. In a word, by summarizing the mechanism of action of fructose metabolism in different stages of cancer development, we can see that cancer metabolism reprogram of fructose is precisely and has heterogeneity at different stages. Therefore, it is meaningful and important to improve and establish the spectrum of action of fructose metabolism in the whole process of cancer cell development in the future study. By studying the characteristics of this pathway in distinguishing stages of cancer development, we can optimize existing targeted treatments and make use of the fructose metabolism pathway to find potential multi-stage therapeutic targets. Subsequent research can also be conducted around the characteristics of different development stages. For instance, the impact of fructose metabolism in the appearance stage of cancer cells can be explored around its relationship with gene mutations and abnormal gene expression; in the metastasis stage, the focus can be on the impact of fructose on tumor motility; and in the post-metastasis stage, research can be conducted around immune escape and metabolic reprogramming. Finally, this review select colorectal cancer and hepatocellular carcinoma as the subjects of discussion. It can be clearly seen that fructose metabolism is heterogeneous in different cancers, which also proves that different tumors undergo diverse metabolic reprogramming in different microenvironments. Therefore, it is also very promising to try to use bioinformatics and biostatistics to improve and map the fructose metabolism of different cancers thereby developing personalized treatment plans for patients in future research.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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