Role of Fat Metabolism in Gastric Cancer

A.Shafia Sultana[1] B. Dr. M. Vijaya Bhargavi[2] C. Prof. M. Sumakanth[3]
[1]*Student, RBVRR Women's College of Pharmacy*
[2]*Faculty, RBVRR Women's College of Pharmacy*
[3]*Principal, RBVRR Women's College of Pharmacy*

Abstract*: Gastric cancer is a heterogeneous dangerous illness related to ecological and hereditary inclining factors. While gastric malignant growth frequency and mortality fell enormously globally over the course of the last many years, it remains the fourth reason for disease-related death around the world. Hence, counteraction of gastric disease is a major strategy for the development of gastric malignant growth visualization. Chemotherapy has been found as a primary treatment for a metastatic gastric malignant tumor, though drug obstruction restricts the viability of chemotherapy and prompts treatment failure. Chemotherapy obstruction in malignant gastric tumors has a multifactorial mechanism, among which lipid metabolism assumes a crucial part. Raised synthesis of new lipids or take-up of exogenous lipids can lead to the quick development of malignant growth cells and cancer formation. Lipids structure the underlying premise of biofilms while serving as signal molecules and energy sources. Lipid metabolism must be fit for prompting drug obstruction in gastric malignant tumor cells by reshaping the cancer miniature climate. In this review, the new mechanism of lipid metabolism in gastric malignant tumors and the metabolic pathways associated with chemotherapy obstruction are audited. Specifically, we talk about the impacts of lipid metabolism on autophagy, biomarkers therapy, and medication obstruction in gastric malignant according to the point of view of lipid metabolism. In short, new experiences can be acquired in the advancement of promising treatments through a top to bottom examination of the mechanism of lipid metabolism reconstructing and resensitization to chemotherapy in gastric malignant tumor cells, and scientific treatment can be given by applying lipid-key enzyme inhibitors as disease substance sensitizers in clinical settings.

1. INTRODUCTION

FAs are vital for cancer cells and human cells since they keep up with membrane biosynthesis during fast multiplication and give a basic energy source in metabolically stressed settings. FAs and fatty acid metabolites have been trapped in malignant growth development and progression, and the relation between fatty acid metabolism and cancer is turning out to be more complicated as research progresses.

2. KEY MOLECULES IN FATTY ACID METABOLISM

2.1. Key Molecules for Exogenous Uptake of FAs

2.1.1. CD36: CD36 is a scavenger receptor that controls lipid uptake, immunological recognition, molecular adhesion inflammation, and death in a variety of cells [1]. CD36 stimulates cancer development and metastasis by permitting cells to take up lipids from the extracellular microenvironment and advancing the oxidation of FAs to form ATP [2-4]. CD36 can also work as a direct target molecule for hydrogen sulfide (H2S), activating long-chain FAs in the cytoplasm and causing lipid metabolic reprogramming [5]. It has also been shown that high fatty acid uptake advances CD36 transcription and works by prompting O-GlcNAcylation glycosylation and enacting the NF-B pathway, bringing about GC metastasis, and forming a vicious cycle [6]. The discoveries suggest that CD36 plays a significant role in GC metastasis, and that focusing on CD36 may help to reduce GC metastasis.

2.2.2. FABPs: Most FAs require complexes with specific proteins, like albumins, lipoproteins, and FABPs, which are characterized into nine different types [7]. FABPs bind long-chain FAs and improve fatty acid solubility, as per the recent investigations into their structure and function. They play a role in lipid metabolism by working FAs movement to the cell or mitochondrial membrane [8-11]. Fatty Acid Binding Protein 1 (FABP1) expression is increased and intense in metaplasia and a negligible part of gastric adenocarcinomas, even though it has no relation to the carcinoma's development, prognosis, or fatty acid synthase status. The results of Satoh et al. infer that a FABP1 mRNA level is a valuable tool for distinguishing people with peritoneal metastasis or at high risk of peritoneal recurrence who could benefit from more powerful adjuvant chemotherapy [12-13]. The co-expression of FABP1 and FASN might act as a biomarker for the detection of early

GC, as per the quantitative proteomic study of GC tissues [14]. Fatty Acid Binding Protein 3 (FABP3)-negative patients had a more prominent survival rate than FABP3-positive patients in GC cases [15]. The combination of UPK1B, FABP3, CASP5, and CYP4X1 could predict the consequence of GC CapeOX treatment, as per the comprehensive analysis [16]. Fatty Acid Binding Protein4 (FABP4) regulation by a small-molecule FABP4 inhibitor or siFABP4 restores primary cilia, inhibiting the cell expansion and migration of GCs, and consequently has the anticancer potential [17]. As per the GEPIA and UALCAN databases, FABP4 expression was fundamentally diminished in stomach adenocarcinoma (STAD) tissues, but Western blot results uncovered significantly high expression of FABP4 and Fatty Acid Binding Protein 5 (FABP5) in both GC cell and GC tissue. High FABP4 and FABP5 expressions are related to unfavourable pathological characteristics and a poor prognosis in GC [18]. STAT5A-managed fatty acid metabolism builds the tumorigenic capacity of GC cells in vivo by stimulating the expression of FABP5 [20], according to a recent study. The FABP5 gene was silenced, which decrease GC cell invasiveness, stopped cell expansion, and stopped the cell cycle in the G0/G1 stage, resulting in a large increase in apoptosis [19-22]. SBFI-26, a FABP5 inhibitor, may also be a GC-treating drug [95]. FABPs have been connected to apoptosis in GC, and the discoveries show that FABPs might influence apoptosis by controlling cell lipid uptake.

2.2. Key Molecules in the Endogenous Synthesis of FAs

2.2.1. Sterol Regulatory Element-Binding Protein 1 (SREBP1): SREBP1 can bind to the promoters of ATP Citrate Lyase (ACLY) and Acyl-CoA Synthetase Short Chain Family Member 2 (ACSS2) to manage lipid metabolism at the transcriptional level, and SREBP1 also influence the outflow of Acetyl-CoA Carboxylase (ACC), Fatty Acid Synthase (FASN), and Stearoyl-CoA Desaturase 1 (SCD1) [23-25]. SREBP1C expression is high in GC tissues, and the stimulation of hypoxia-inducible factor 1_ (HIF-1_) enlarge the expression of SREBP1C and FASN genes. The high-level GC VEGFR2-focusing on the drug apatinib manages glutathione peroxidase 4 (GPX4) transcription in GC cells by mediating the binding of SREBP1A to the GPX4 promoter region, which might represent the effectiveness of apatinib in multi-drug-resistant GC cells [26]. SREBP1 manage the expression of different lipid metabolism genes, and the improvement of medication focusing on SREBP1 might be another heading for GC treatment.

2.2.2. ACLY: Citrate produced by the krebs cycle (TCA) in mitochondria is moved to the cytoplasm, where it is cleaved into acetyl-CoA and oxaloacetate by ACLY, which is found on the endoplasmic reticulum, connecting glucose and fatty acid metabolism [27-28]. ACLY expression was shown to be significantly higher in GC tissues than in surrounding normal tissues, and it was connected to advanced GC, lymph node metastases, and a limited survival time [29]. The action of ACLY is restrained by high doses of sodium citrate, and intraperitoneal injections of sodium citrate suppressed the development of GC in mice [30-31].

2.2.3. ACC: ACC is an AMPK target molecule, and AMPK phosphorylation can manage ACC activity [33]. In GC, the outflow of the ACC inactivated form (phosphorylated ACC, pACC) was decreased. The level of pACC was comparatively much lower in hypofractionated GC than in highly differentiated GC, suggesting that hypofractionated GC has improved ACC activity [34]. Furthermore, GC patients with an increased level of pACC expression had a longer median survival time. Metformin (an AMPK activator)-prompted pACC overexpression inhibited GC cell development and colony formation significantly [32]. As per the discoveries, pACC downregulation is a significant step in gastric carcinogenesis and can predict patient prognosis from the beginningACLY overexpression is connected to poor GC outcomes and focusing on ACLY for GC treatment could be a viable option.

2.2.4. FASN: FASN catalyzes the production of endogenous FAs by utilizing acetyl-CoA as a primer, NADPH as a reducing equivalent, and malonyl coenzyme A as a two-carbon donor, synthesize long-chain FAs [35-36]. By targeting the mTOR/Gli1 signalling pathway, FASN inhibition also decreased GC development and metastasis [37]. FASN might be a promising prescient biomarker for GC patients, and FASN might be a possible target for GC treatment, according to the research.

2.2.5. SCD1: SCD1 is also a rate-limiting enzyme in the transformation of monounsaturated fatty acids (MUFAs) from saturated fatty acids (palmitic acid,

PA) [38-39]. Many lipids, including phospholipids, cholesterol esters, and triglycerides, are produced using SCD1's unsaturated FAs as significant substrates [40]. SCD1 expression is increased in GC, and high SCD1 expression in GC patients might indicate poor prognosis [41]. SCD1 increases the proliferative and migratory abilities of GC cells, as well as having an anti-iron death effect and accelerating the development of cancer in mice [42].In cooperation with vehicle-treated mice, the mean tumor volume in the A939572-treated group (an inhibitor of SCD1) was reduced by about 50%.

2.3. A Key Molecule in Fatty Acid Catabolism

Carnitine palmitoyltransferase 1 (CPT1): The CPT1 family, which includes CPT1A, CPT1B, and CPT1C, is found on the outer mitochondrial membrane and serves as the guardian enzyme for long-chain FAs entrance and subsequent oxidation [43]. Long-chain fatty acids should be transformed into acylcarnitine prior entering to the mitochondrial matrix for oxidation [44]. since CPT1 is blocked by malonyl coenzyme A, a part of ACC, fatty acid oxidation is boosted when ACC is suppressed. CPT1A overexpression advanced the proliferation, invasion, and epithelial-mesenchymal transition (EMT) of GC cells by activating fatty acid oxidation in GC cells by expanding the NADP/NADPH ratio [45-46]. CPT1A succinylated LDHA on K222, which upgrade GC invasion and multiplication by decreasing binding and inhibiting LDHA degradation [47]. After fenofibrate treatment, the expression levels of the fatty acid metabolism-related proteins FASN and ACC2 dropped, while the expression levels of p-ACC2 and CPT1A proteins expand altogether [48]. CPT1B was upregulated in oxaliplatin-treated GC cells (HGC27 and MGC803), and the CPT1 inhibitor perhexiline and oxaliplatin inhibited tumor xenograft movement in a subcutaneous xenograft BALB/c nude mouse model of HGC27 cells, recommending that CPT1-mediated fatty acid movement and further fatty acid oxidation might be related with oxaliplatin CPT1C expression were viewed as significantly linked to poor DFS and OS in GC patients. Hypoxia-induced CPT1C expression has been linked to a poor prognosis and has been displayed to enhance GC cell proliferation [49-50]. These discoveries suggest that CPT1 is a basic enzyme in controlling FAs oxidative catabolism and that decreasing GC development and metastasis by lowering CPT1 expression might increase the efficacy of chemotherapeutic drugs.

3. CONCLUDING REMARKS

Fatty acid metabolism makes up most of the lipid metabolism. Fatty acid production and medication catabolism are also required for normal cells, and they play a role in tumorigenesis and improvement. In this study, the relationship between fatty acid metabolism and stomach cancer is analyzed. In fatty acid anabolism, SREBP1, ACLY, ACC, FASN, and SCD1 upgrade the occurrence, metastasis, and progression, of gastric cancer, and are supposed to be potential prognostic markers. CD36, FABPs, and CPT1, which are fatty acid absorption-related molecules, additionally add to the multiplication of gastric cancer cells. Moreover, prospective drugs that target fatty acid molecules have the potential to restrict gastric cancer cell proliferation, decrease ATP generation, and promote apoptosis. In conclusion, fatty acid metabolism related compounds might play a new diagnostic or therapeutic function in gastric cancer.

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ABBREVIATIONS: GC: gastric cancer; DNL, de novo lipogenesis; FAs, fatty acids; acetyl-CoA, acetyl-coenzyme A; SFAs, saturated fatty acids; OA, oleic acid; MUFA, monounsaturated fatty acid; AA, arachidonic; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SREBP1, sterol regulatory element-binding protein 1; HIF-1α, stimulation of hypoxia-inducible factor 1α; GPX4, glutathione peroxidase 4; HMGCR, 3-hydroxy-3-methylglutarylCoA reductase; ACLY, ATP citrate lyase; TCA, tricarboxylic acid cycle; ACSs, acetyl-CoA synthases; FA-CoA, fatty acyl-CoA; DFS, disease-free survival; OS, overall survival; ACC, acetyl-CoA carboxylase; pACC, phosphorylated acetyl-CoA carboxylase; ICA, immune cytolytic activity; FASN, fatty acid synthase; mHER2, membranous HER2; SCD1, stearoyl-CoA desaturase 1; PA, palmitic acid; MUFAs, monounsaturated fatty acids; H2S, hydrogen sulfide; FABPs, fatty acid-binding proteins; STAD, stomach adenocarcinoma; TRM, tissue-resident memory T cells; CPT1, carnitine palmitoyltransferase 1; FAO, fatty acid oxidation;

EMT, epithelial–mesenchymal transition; CIC, citrate/isocitrate carrier.

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