

A Review on Cancer Cell Metabolism of Fats: Insights into Altered Lipid Homeostasis

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Abstract: The dysregulation of fat metabolism is a key characteristic of cancer cells, contributing to their survival, growth, and metastatic potential. Mutations in genes involved in fat metabolism pathways have been identified within cancer cells, impacting lipogenesis, lipid uptake, transport, lipolysis, and lipid droplet dynamics. These mutations result in altered lipid homeostasis, providing cancer cells with a continuous supply of energy substrates, signalling molecules, and building blocks for cellular processes. Targeting these mutated fat metabolism genes and pathways holds promise as a therapeutic strategy, with inhibitors of key enzymes like fatty acid synthase (FASN) showing encouraging results in early clinical trials. Challenges remain in translating these findings into personalized therapies, considering the heterogeneity of mutations across cancer types and the complex interplay between mutated fat metabolism genes and other oncogenic signalling pathways. Future research efforts aim to uncover novel therapeutic approaches that exploit the altered fat metabolism in cancer cells to improve treatment outcomes and patient prognosis.

Keywords: Cancer cell metabolism of fats; Lipid homeostasis; Fatty acid synthase; Lipid signalling; Lipid droplets.

Introduction

Cancer cell metabolism has emerged, as a captivating field of research, shedding light on the distinct metabolic adaptations that occur in cancer cells. Among the various metabolic alterations, the dysregulation of lipid metabolism has gained considerable attention^[1]. This review aims to explore the metabolism of fats in cancer cells, focusing on the alterations in lipid homeostasis that contribute to cancer progression and provide potential therapeutic targets.

In cancer cells, lipid storage and metabolism are highly coordinated processes involving multiple organelles. The endoplasmic reticulum (ER) is crucial for synthesizing lipids, such as phospholipids and cholesterol, which are essential components of cell membranes. Additionally, the ER-associated synthesis of triglycerides aids in lipid droplet formation. Mitochondria contribute by oxidizing fatty acids through β -oxidation, which generates ATP to meet the increased energy demands of cancer cells. Lipid droplets, often enlarged in cancer cells, serve as storage depots for neutral lipids, providing a reservoir for energy and membrane synthesis under metabolic stress. Peroxisomes are involved

in breaking down very long-chain fatty acids through β -oxidation, further supporting the energy needs of cancer cells. Dysregulation of lipid metabolism at the organelle level has been linked to cancer progression and chemoresistance. Targeting these organelles and their lipid-handling pathways may offer novel therapeutic approaches, such as mitochondrial inhibitors to impair fatty acid oxidation (FAO) or ER stress-inducing agents to disrupt lipid synthesis.

Lipid Acquisition and Uptake

Cancer cells exhibit an increased demand for lipids, essential components of cellular membranes and signalling molecules^[2,3]. To fulfil this demand, cancer cells utilize multiple strategies for lipid acquisition^[3]. These include upregulation of lipid uptake receptors, such as CD36 and LDL receptors, to enhance the uptake of exogenous lipids from the extracellular environment^[4]. Furthermore, cancer cells can increase de novo lipid synthesis through upregulated fatty acid synthase (FASN) and other enzymes involved in lipogenesis^[5]. The excess fatty acids are subsequently utilized for energy production, membrane biogenesis, and the synthesis of lipid-derived signalling molecules. CD36, a membrane-bound fatty acid transporter, is overexpressed in several cancers, such as breast cancer, where it enhances lipid uptake and contributes to metastasis^[6]. In particular, CD36-mediated fatty acid uptake has been shown to drive the epithelial-to-mesenchymal transition (EMT), a critical step in cancer invasion^[6]. Low-density lipoprotein (LDL) receptors, which mediate cholesterol uptake, are upregulated in cancers like glioblastoma and prostate cancer, facilitating cholesterol accumula-

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Received 18 June 2024; Revised 1 August 2024; Accepted 6 November 2024; Available Online 20 November 2024

DOI: 10.54457/DR.202402010

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tion that fuels membrane synthesis and cell proliferation^[7]. Fatty acid synthase (FASN) is similarly overexpressed in a range of cancers, including breast and ovarian cancer, where it catalyses *de novo* lipogenesis, supplying cancer cells with fatty acids necessary for membrane biogenesis and lipid signalling^[8]. Dysregulated FASN activity has been linked to poor patient prognosis and increased resistance to chemotherapy. Therapeutically, blocking CD36, LDL receptors, or FASN can disrupt the lipid supply chain to tumours, reducing their growth and metastatic potential^[6-8]. Emerging inhibitors of these proteins are showing promise in pre-clinical models, suggesting the potential for combination therapies targeting lipid metabolism alongside traditional treatments.

Altered Lipid Storage and Metabolism

Cancer cells exhibit dysregulated lipid storage and metabolism, leading to the accumulation of lipid droplets. These lipid droplets serve as reservoirs for energy and provide building blocks for cellular processes^[9,10]. The excessive lipid accumulation is mediated by various factors, including the upregulation of enzymes involved in triglyceride synthesis, such as diacylglycerol acyltransferase (DGAT)^[9]. Lipid droplets in cancer cells are also influenced by altered lipolysis, where lipases like adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) play critical roles in releasing fatty acids for energy production and signalling purposes^[9]. In cancer cells, lipid storage within lipid droplets (LDs) is significantly enhanced, providing a reservoir for energy and signalling molecules. This dysregulated storage is evident in aggressive cancers like ovarian and prostate cancer, where lipid droplets [Fig. 1](#) serve as essential energy stores during periods of metabolic stress, such as hypoxia or nutrient deprivation^[10]. In addition to storage, lipid signalling plays a key role in cancer progression. For instance, phosphatidylinositol (PI) and its derivatives, such as phosphatidylinositol-3,4,5-trisphosphate (PIP3), are involved in activating key oncogenic pathways like PI3K/Akt, promoting cell survival, proliferation, and migration^[11]. Lipid rafts, which are cholesterol and sphingolipid-rich microdomains in cell membranes, facilitate the clustering of receptors like EGFR and HER2, thereby enhancing pro-tumorigenic signalling^[12]. Disruption of lipid rafts has been shown to impair receptor signalling in breast cancer and non-small cell lung cancer. Scientifically, strategies targeting lipid droplet formation or cholesterol-enriched lipid rafts, such as statins or sphingolipid metabolism inhibitors, hold promise for impairing tumour progression by destabilizing these key lipid-dependent pathways.

Fatty Acid Oxidation (FAO) and Lipid Signalling

Cancer cells display enhanced fatty acid oxidation (FAO) as an adaptive response to nutrient availability and metabolic stress. FAO allows cancer cells to utilize fatty acids as a fuel source, thereby promoting cell survival and proliferation^[13]. The upregulation of enzymes involved in FAO, such as carnitine palmitoyl transferase 1 (CPT1)^[14] and Acyl-CoA dehydrogenases, facilitates the breakdown of fatty acids into Acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle for ATP generation^[15]. Additionally, certain lipid species and lipid-derived signalling molecules, such as phospholipids and eicosanoids, contribute to the regulation of cancer cell proliferation, invasion, and angiogenesis^[10].

Lipid Rafts and Membrane Dynamics

Lipid rafts are specialized membrane microdomains enriched in cholesterol and sphingolipids that play crucial roles in cell signalling and membrane dynamics^[12]. Alterations in lipid rafts have been observed in cancer cells, affecting various signalling pathways involved in cell survival and proliferation^[13]. Changes in lipid composition, particularly an increase in cholesterol levels and altered sphingolipid metabolism, influence the organization and function of lipid rafts in cancer cells^[14]. These changes can impact the localization and activity of receptors, kinases, and other signalling molecules, contributing to cancer cell behaviour and response to therapy^[15].

Targeting Lipid Metabolism for Cancer Therapy

The dysregulated lipid metabolism in cancer cells offers promising avenues for therapeutic intervention^[16]. Several strategies have been explored to target lipid metabolism in cancer, including inhibiting lipogenic enzymes, modulating lipid uptake receptors, and interfering with FAO^[16]. Furthermore, understanding the role of lipid signalling molecules and lipid rafts in cancer progression may provide opportunities for developing targeted therapies. Targeting lipid metabolism in cancer therapy has gained considerable interest, with multiple approaches being investigated. One strategy involves the inhibition of key lipogenic enzymes such as FASN and ACC (acetyl-CoA carboxylase)^[11]. FASN inhibitors, such as TVB-2640, have demonstrated efficacy in reducing tumour growth in preclinical studies of breast, colorectal, and lung cancers. Similarly, ACC inhibitors reduce the production of malonyl-CoA, a precursor for fatty acid synthesis, thereby limiting lipid availability for rapidly proliferating cancer cells^[17]. Another therapeutic approach involves targeting fatty acid oxidation (FAO) by using inhibitors like Etomoxir, which blocks carnitine palmitoyl transferase 1 (CPT1), an essential enzyme for mitochondrial FAO. Inhibiting FAO can deplete energy production in cancer cells that rely on fatty acids as their primary fuel source, such as in glioblastoma and pancreatic cancer. Additionally, lipid signalling pathways involving sphingolipids or phosphatidylinositol can be targeted using drugs like FTY720 (fingolimod), which modulates sphingosine-1-phosphate signalling, impairing tumour growth^[18]. Integrating lipid metabolism inhibitors with existing chemotherapies or immunotherapies may provide a synergistic effect, enhancing treatment outcomes by targeting multiple aspects of tumour biology.

Saturated Fatty Acids: Cancer cells often exhibit higher levels of saturated fatty acids compared to normal cells^[17]. These include fatty acids like palmitic acid and stearic acid, which can be synthesized by cancer cells or obtained from the diet^[19].

Monounsaturated Fatty Acids: Cancer cells may also show increased levels of monounsaturated fatty acids, such as oleic acid^[19]. These fats play a role in membrane composition and signalling pathways within cancer cells^[20].

Polyunsaturated Fatty Acids: Some studies have suggested that certain types of polyunsaturated fatty acids (PUFAs), like arachidonic acid and eicosapentaenoic acid (EPA), may be elevated in cancer cells. PUFAs are essential fatty acids that can be obtained from the diet or produced through metabolic processes^[21].

Phospholipids: Phospholipids, including phosphatidylcholine

and phosphatidylserine, are key components of cell membranes. Alterations in their metabolism and turnover can contribute to the excessive production of certain phospholipids in cancer cells^[22].

It's important to note that the lipid profile of cancer cells can vary depending on the type and stage of cancer, as well as other

factors^[23]. These alterations in lipid metabolism are often associated with the specific needs of cancer cells for energy, growth, and survival^[23]. However, the precise mechanisms and implications of these lipid changes in cancer development and progression are still areas of active research.

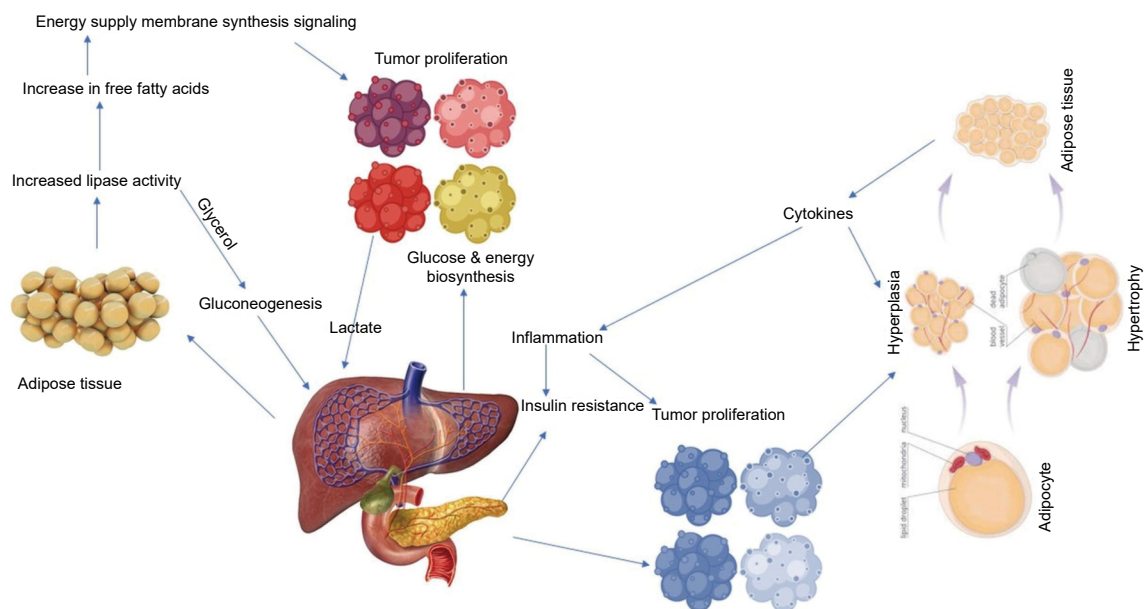
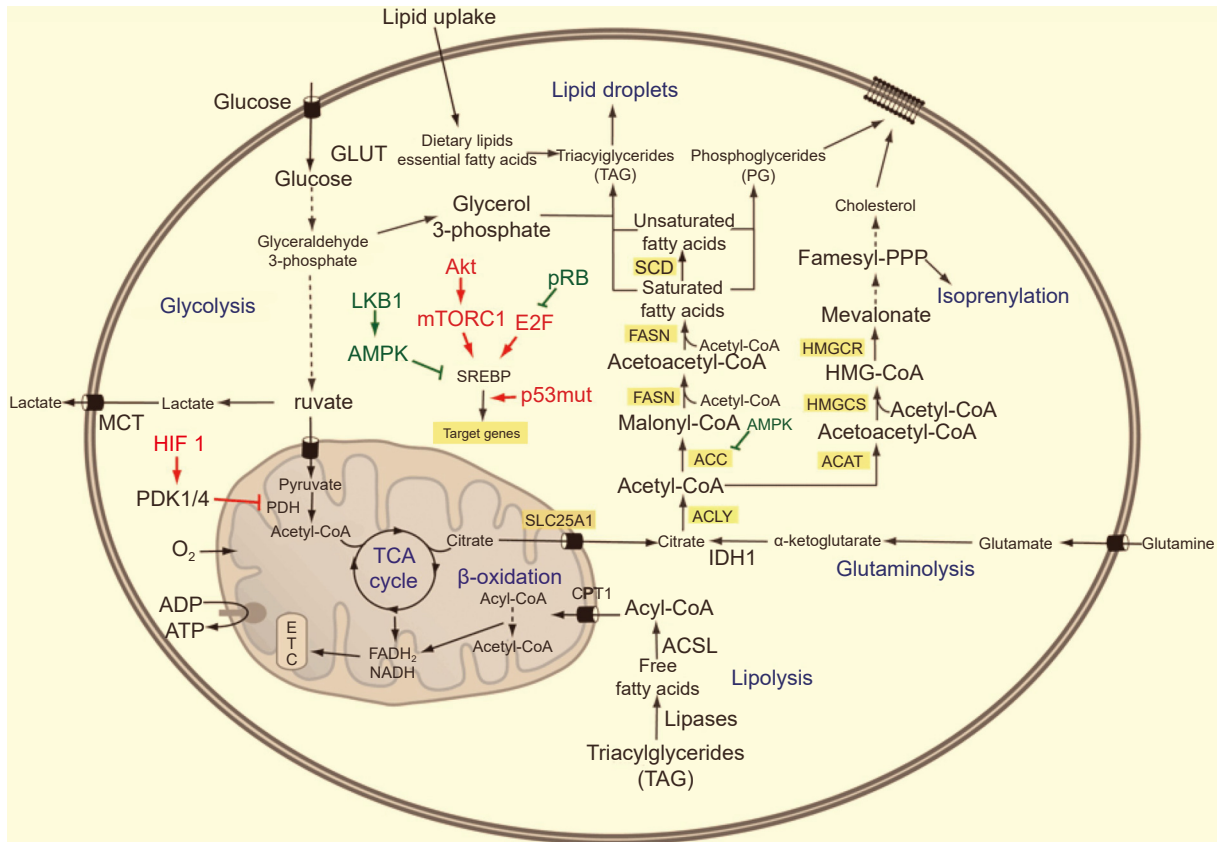


Fig. 1. Regulation of lipid metabolism by oncogenic signalling pathways.

Lipid metabolism in different types of cancer from a disease progression perspective

Breast Cancer

In breast cancer, significant alterations in lipid metabolism have been observed, particularly the overexpression of fatty acid synthase (FASN). FASN is responsible for de novo fatty acid synthesis, which provides cancer cells with the necessary building blocks for membrane formation, energy production, and signalling molecule synthesis. High levels of FASN have been linked to aggressive tumour behaviour and poor prognosis^[24]. Mechanistically, FASN-derived fatty acids are used to synthesize phospholipids and sphingolipids, which are incorporated into the cell membrane and lipid rafts, enhancing signal transduction pathways such as PI3K/Akt and ERK/MAPK^[24]. These pathways promote cell proliferation, survival, and migration. Additionally, breast cancer cells exhibit increased lipid uptake through receptors like CD36 and LDLR (low-density lipoprotein receptor), contributing to the accumulation of cholesterol and triglycerides, which further drive tumour growth^[24,25]. Targeting FASN, CD36, or LDLR may disrupt these processes, offering therapeutic potential for halting breast cancer progression and metastasis.

Prostate Cancer

Prostate cancer cells display dysregulated lipid metabolism, characterized by enhanced lipogenesis and increased fatty acid uptake. FASN and stearoyl-CoA desaturase-1 (SCD1) are highly upregulated, promoting the synthesis of saturated and monounsaturated fatty acids, which are critical for maintaining membrane integrity, supporting cell growth, and modulating lipid signalling^[26]. The overexpression of FASN has been associated with increased androgen receptor (AR) signalling, which plays a central role in prostate cancer progression^[26,27]. FASN activity enhances the availability of lipids for AR-mediated transcription, facilitating tumour cell proliferation and survival. Additionally, prostate cancer cells exhibit upregulation of fatty acid transport proteins, such as FABP5 (fatty acid-binding protein 5), which facilitates the uptake of extracellular fatty acids, fuelling lipogenesis and β -oxidation^[26-28]. Targeting lipid metabolism in prostate cancer, either by inhibiting FASN or FABP5, has shown potential in preclinical models to reduce tumour growth and enhance sensitivity to anti-androgen therapies.

Colorectal Cancer

In colorectal cancer, dysregulation of lipid metabolism has been closely linked to tumour growth, metastasis, and resistance to therapy^[29]. Colorectal cancer cells exhibit increased expression of enzymes involved in de novo lipogenesis, such as acetyl-CoA carboxylase (ACC) and FASN, which provide fatty acids for membrane synthesis and signalling pathways^[30]. Aberrant lipid metabolism in colorectal cancer also involves increased production of sphingolipids, particularly ceramide, which has been associated with apoptosis resistance and enhanced tumour cell survival. Lipidomic studies have shown that colorectal cancer cells shift toward a lipogenic phenotype, characterized by elevated levels of phospholipids and cholesterol, which support rapid cell proliferation^[30]. Additionally, altered lipid metabolism facilitates the activation of the Wnt/ β -catenin and PI3K/Akt pathways, which are

key drivers of colorectal cancer progression^[31]. Therapeutically, targeting lipid metabolism through FASN or ACC inhibition may reduce tumour growth, while simultaneously sensitizing cells to chemotherapeutic agents.

Lung Cancer

Lung cancer cells exhibit profound alterations in lipid metabolism, with increased fatty acid uptake and enhanced lipogenesis to meet the high energy demands of rapidly dividing cells^[32]. Lung cancer cells rely on elevated levels of FASN and ATP citrate lyase (ACLY) to drive de novo lipogenesis, supplying fatty acids that are incorporated into membranes and lipid rafts^[32,33]. These alterations in lipid metabolism promote the activation of oncogenic signalling pathways, such as EGFR and KRAS, which are frequently mutated in lung cancer^[34]. Additionally, lung cancer cells upregulate CPT1 (carnitine palmitoyl transferase 1), an enzyme responsible for transporting long-chain fatty acids into mitochondria for β -oxidation, further supporting their energetic requirements^[35]. Dysregulated lipid metabolism also enhances resistance to treatment, with increased fatty acid synthesis supporting cell survival under conditions of chemotherapy or radiotherapy. Targeting FASN, ACLY, or CPT1 may impair lipid metabolism and reduce lung cancer cell viability, offering potential avenues for therapeutic intervention.

Pancreatic Cancer

Pancreatic cancer is characterized by aggressive tumour behaviour and poor prognosis, largely due to the dysregulation of lipid metabolism. Pancreatic cancer cells exhibit elevated levels of lipid droplet accumulation, which provides an energy reserve that can be rapidly mobilized through lipolysis^[36]. Additionally, pancreatic cancer cells show increased fatty acid uptake through CD36, facilitating lipid droplet formation and supporting metastatic potential^[36]. Increased expression of lipogenic enzymes, such as FASN and DGAT1^[37] (diacylglycerol O-acyltransferase 1), contributes to the formation of these lipid droplets. Mechanistically, lipid droplets act as reservoirs for signalling lipids like eicosanoids, which promote inflammation and tumour growth^[38]. The high reliance on fatty acid oxidation (FAO) in pancreatic cancer cells is also notable, with enzymes like CPT1A being upregulated to maintain energy production^[39]. Inhibiting lipid droplet formation or FAO represents a promising therapeutic strategy, potentially starving pancreatic cancer cells of their critical lipid-derived energy supply^[40,41].

Liver Cancer (Hepatocellular Carcinoma)

Hepatocellular carcinoma (HCC) is associated with profound alterations in lipid metabolism, driven by increased fatty acid uptake, de novo lipogenesis, and lipid droplet accumulation^[42]. HCC cells upregulate the expression of enzymes involved in fatty acid synthesis, such as FASN and SCD1, promoting the production of fatty acids that are incorporated into triglycerides stored in lipid droplets^[43]. These lipid stores provide a readily available energy source, supporting rapid cell growth and proliferation. Additionally, HCC cells exhibit increased cholesterol biosynthesis, with the upregulation of HMG-CoA reductase (HMGCR), enhancing cholesterol availability for membrane formation and oncogenic

signalling^[44]. The dysregulated lipid metabolism in HCC also involves enhanced β -oxidation, which supports cell survival under nutrient-deprived conditions^[45]. Therapeutically, targeting lipid metabolism through inhibitors of FASN, SCD1, or HMGCR may disrupt lipid homeostasis in HCC, reducing tumour growth and overcoming therapeutic resistance.

Ovarian Cancer

Ovarian cancer cells demonstrate dysregulation in lipid metabolism, with enhanced fatty acid synthesis and lipid droplet accumulation playing key roles in tumour progression. FASN and SCD1 are highly expressed in ovarian cancer, contributing to the synthesis of fatty acids and maintaining membrane fluidity, which is crucial for cell survival and proliferation. Lipid droplets serve as energy reserves, and their mobilization through lipolysis supports ovarian cancer cell survival during metabolic stress^[46]. Additionally, ovarian cancer cells upregulate the expression of fatty acid transport proteins, such as CD36 and FABP4, facilitating the uptake of exogenous fatty acids from the tumour microenvironment^[47]. These fatty acids are used for energy production through β -oxidation, which is critical for supporting the high metabolic demands of ovarian cancer cells^[48]. Targeting FASN, CD36, or lipid droplet mobilization offers potential therapeutic strategies for disrupting lipid metabolism and inhibiting ovarian cancer progression.

Melanoma

In melanoma, lipid metabolism plays a crucial role in supporting tumour cell survival, migration, and resistance to therapy. Melanoma cells exhibit increased lipogenesis, with elevated expression of FASN and SCD1, contributing to the synthesis of fatty acids that are incorporated into cell membranes and lipid signalling molecules^[49]. Altered lipid metabolism in melanoma also includes enhanced cholesterol biosynthesis, supporting the formation of lipid rafts that cluster pro-survival receptors like PD-1 and CTLA-4, facilitating immune evasion^[50]. Melanoma cells also rely on fatty acid oxidation to generate ATP and maintain redox balance, particularly under conditions of nutrient deprivation^[51]. Inhibiting FAO or targeting lipid signalling pathways, such as sphingosine-1-phosphate (S1P) signalling, may impair melanoma progression and enhance the efficacy of immunotherapy.

Gastric Cancer

Gastric cancer is characterized by significant alterations in lipid metabolism, with increased expression of lipogenic enzymes and fatty acid uptake receptors. Gastric cancer cells upregulate FASN and ACLY, driving de novo fatty acid synthesis to supply the building blocks for membrane formation and energy production^[52]. Fatty acid uptake through CD36 and LDLR is also enhanced, providing an exogenous source of lipids that supports tumour growth and invasion^[53]. Lipid metabolism dysregulation in gastric cancer has been linked to the activation of oncogenic signalling pathways such as PI3K/Akt and MAPK, which promote cell proliferation, migration, and resistance to apoptosis^[54]. Targeting FASN, ACLY, or lipid uptake receptors may offer new therapeutic opportunities to disrupt lipid metabolism and inhibit gastric cancer progression.

Brain Tumours (Gliomas)

Gliomas, including glioblastoma, exhibit profound alterations in lipid metabolism that contribute to tumour growth, invasion, and resistance to therapy. Glioma cells show increased expression of enzymes involved in de novo lipogenesis, such as FASN and ACC, which drive the synthesis of fatty acids required for membrane biogenesis and signal transduction^[55]. Additionally, gliomas rely on enhanced fatty acid uptake through CD36, which supplies lipids for energy production via β -oxidation^[56]. Lipid metabolism dysregulation in gliomas also involves the accumulation of lipid droplets, which serve as energy reserves during periods of metabolic stress. These alterations in lipid metabolism contribute to the activation of signalling pathways like PI3K/Akt and Wnt/ β -catenin^[57], promoting cell survival, invasion, and resistance to therapy. Targeting lipid metabolism in gliomas, through inhibitors of FASN or CD36, offers potential strategies to impair tumour progression and overcome treatment resistance.

Challenges and Future Perspectives

While mutated fat metabolism genes hold promise as therapeutic targets, challenges remain in translating these findings into clinical applications. The heterogeneity of mutations across different cancer types and individual patients necessitates a personalized approach. Additionally, understanding the interplay between mutated fat metabolism genes and other oncogenic signalling pathways is crucial for developing effective combination therapies.

Fatty acid synthase (FASN) and its role in cancer progression

Fatty acid synthase (FASN) is a key enzyme involved in de novo fatty acid synthesis, a process by which cells generate fatty acids from Acetyl-CoA and malonyl-CoA. While FASN plays a vital role in normal cellular lipid metabolism^[58,59], its overexpression and dysregulation have been implicated in various aspects of cancer progression. Here, we delve into the role of FASN in cancer progression and its potential as a therapeutic target.

FASN is frequently upregulated in many cancer types, including breast, prostate, ovarian, colorectal, and lung cancers. This elevated expression of FASN is associated with aggressive tumour behaviour, poor prognosis, and resistance to therapy^[60]. One of the key roles of FASN in cancer progression is its contribution to lipogenesis, providing cancer cells with the necessary fatty acids for membrane synthesis, energy production, and the generation of lipid signalling molecules.

The overexpression of FASN in cancer cells has been linked to increased cell proliferation, survival, and resistance to apoptosis. FASN-derived fatty acids serve as building blocks for the production of phospholipids, cholesterol esters, and glycolipids, which are essential for membrane formation and cell growth^[61]. By sustaining the enhanced membrane synthesis demands of rapidly proliferating cancer cells, FASN supports their uncontrolled growth and survival.

Moreover, FASN has been implicated in promoting cancer cell migration, invasion, and metastasis. Fatty acids generated by FASN contribute to the production of lipid-based signalling molecules involved in these processes^[62]. For example, FASN-de-

rived fatty acids can be incorporated into signalling molecules like lysophosphatidic acid (LPA)^[63,64] and prostaglandins, which play crucial roles in cell motility, angiogenesis, and inflammation^[65]. FASN's involvement in lipid signalling pathways thus enhances the invasive and metastatic potential of cancer cells.

Given its critical role in cancer progression, FASN has emerged as an attractive target for therapeutic intervention. Several small-molecule inhibitors of FASN have been developed and tested in preclinical and early clinical studies^[66]. These inhibitors have demonstrated promising anti-cancer effects, including inhibition of tumour growth, induction of cell death, and sensitization to chemotherapy or targeted therapies. By disrupting fatty acid synthesis, FASN inhibitors offer the potential to specifically target cancer cells while sparing normal cells that rely on exogenous fatty acids.

However, challenges remain in translating FASN inhibitors into effective clinical therapies. The complexity of lipid metabolism and the diverse functions of fatty acids in normal physiology necessitate careful consideration of potential off-target effects and systemic lipid imbalances. Additionally, patient stratification based on FASN expression levels or genetic profiles may be necessary to identify individuals who would benefit most from FASN-targeted therapies. Fatty acid synthase (FASN) is a central enzyme in the lipogenesis pathway, catalysing the synthesis of palmitate from acetyl-CoA and malonyl-CoA. Its upregulation in cancer cells, such as those in breast, prostate, and lung cancers, provides these cells with a continuous supply of fatty acids necessary for membrane synthesis, energy production, and signalling^[67,68]. FASN has also been linked to the synthesis of lipid-based signalling molecules, such as lysophosphatidic acid (LPA), which are involved in promoting cell motility, angiogenesis, and inflammation. Beyond FASN, other key enzymes, such as stearoyl-CoA desaturase 1 (SCD1), contribute to the synthesis of monounsaturated fatty acids, which are critical for maintaining membrane fluidity and the function of lipid rafts^[69]. Inhibiting FASN, SCD1, or acetyl-CoA carboxylase (ACC) could impair cancer cell growth by disrupting lipid homeostasis. Clinically, FASN inhibitors like TVB-2640 are being tested in combination with chemotherapy to enhance anti-tumour efficacy, with preliminary results showing potential for synergistic effects.

Role of GC MS TOF analysis in identifying and profiling fatty acids of cancer cells and disease progression

Gas chromatography-mass spectrometry time-of-flight (GC-MS TOF) analysis has emerged as a valuable tool for identifying and profiling fatty acids in biological samples, including cancer cells, thus contributing to our understanding of disease progression^[70]. This analytical technique combines the separation capabilities of gas chromatography with the sensitive and accurate detection of mass spectrometry, enabling the comprehensive analysis of complex lipid mixtures present in cancer cells^[71].

GC-MS TOF analysis allows for the identification and quantification of individual fatty acids within complex lipid extracts derived from cancer cells^[72]. By employing appropriate sample preparation techniques, such as lipid extraction and derivatization, fatty acids can be converted into volatile derivatives suitable for gas chromatographic separation. The separated fatty acid derivatives are subsequently detected and characterized using mass spec-

trometry, providing precise identification and structural information.

Through GC-MS TOF analysis, researchers can elucidate the fatty acid profiles of cancer cells, facilitating comparisons between healthy and malignant cells. Altered fatty acid compositions have been observed across various cancer types, reflecting the dysregulated lipid metabolism characteristic of cancer cells^[73]. These changes may include variations in the abundance of specific fatty acids, such as saturated, monounsaturated, or polyunsaturated fatty acids, as well as alterations in the ratios of different fatty acid species.

Furthermore, GC-MS TOF analysis can provide insights into the metabolic pathways involved in fatty acid synthesis and degradation in cancer cells. By tracking the incorporation of stable isotope-labelled precursors, such as stable isotope-labelled fatty acids or glucose, into newly synthesized fatty acids, researchers can assess the contributions of *de novo* lipogenesis and exogenous fatty acid uptake^[74]. This information helps to unravel the metabolic adaptations of cancer cells and their reliance on specific fatty acid sources.

Additionally, GC-MS TOF analysis can aid in the identification of biomarkers associated with cancer progression. Fatty acid profiles obtained from different stages of cancer can be compared, allowing for the discovery of potential biomarkers indicative of disease severity or therapeutic response. These biomarkers may include specific fatty acids or ratios that correlate with tumour aggressiveness, metastatic potential, or resistance to therapy. Although gas chromatography-mass spectrometry (GC-MS) is widely used for lipid analysis due to its high sensitivity and accuracy, alternative methods such as colorimetric and spectroscopic assays are also valuable tools. For example, the Nile Red assay allows^[73] for the quantification of neutral lipids, such as triglycerides and cholesterol esters, by selectively staining lipid droplets in live cells. Similarly, the Amplex Red cholesterol assay^[73,74] provides a colorimetric method for quantifying cholesterol levels in cells or tissues. Spectroscopic techniques, including Fourier-transform infrared (FTIR) spectroscopy, enable the characterization of lipid composition based on specific molecular vibrations. These methods offer a more accessible approach to lipid quantification in cancer research, especially when high-throughput screening is required. Combining these techniques with more advanced lipidomic approaches, such as liquid chromatography-mass spectrometry (LC-MS), can provide a comprehensive profile of lipid alterations in cancer cells^[75].

Moreover, GC-MS TOF analysis can be employed in lipidomic studies to investigate lipid alterations beyond fatty acids, including other lipid classes such as phospholipids, glycolipids, and sphingolipids. This comprehensive lipid profiling provides a more holistic understanding of lipid dysregulation in cancer cells and its implications for disease progression.

Research Approach: Integrating GC-MS TOF with Lipid Metabolic Pathway Mapping in Cancer

We propose a promising research approach involving, integrating GC-MS TOF analysis with advanced lipid metabolic pathway mapping to elucidate the dynamic lipid profiles in various cancer types. This method aims to provide a comprehensive understanding of lipid metabolism alterations by combining quantitative fatty acid profiling with metabolic network analysis.

Methodology

Sample Collection: Collect tumour and adjacent normal tissue samples from patients with different cancer types, ensuring proper ethical approvals and patient consent. Additionally, plasma samples may be obtained for comparative analysis.

Lipid Extraction and Derivatization: Employ optimized lipid extraction protocols to isolate lipids from tissue samples. Derivatize the extracted fatty acids to enhance volatility and stability, facilitating their analysis via GC-MS TOF.

Fatty Acid Profiling: Utilize GC-MS TOF to identify and quantify a wide range of fatty acids, including saturated, monounsaturated, and polyunsaturated fatty acids, as well as their specific ratios.

Metabolic Pathway Mapping: Integrate the fatty acid profiles obtained from GC-MS TOF with existing lipid metabolic pathways using bioinformatics tools such as MetaboAnalyst or Lipid Maps. This will allow for the identification of key enzymes and metabolic fluxes that are altered in cancer cells.

Data Correlation with Clinical Outcomes: Correlate the lipid profiles and pathway alterations with clinical data, such as tumour stage, grade, and patient response to therapies. This analysis can reveal potential biomarkers for disease progression and therapeutic response.

Functional Validation: Conduct functional studies to validate the roles of identified lipid metabolites in cancer progression. For example, manipulating specific fatty acid levels in cancer cell lines could help elucidate their impact on cell proliferation, migration, and resistance to treatment.

Current drug therapies

Current drug development efforts targeting fatty acid metabolism in cancer treatment have focused on inhibiting key enzymes and pathways involved in lipid synthesis and utilization. One of the primary targets is fatty acid synthase (FASN), an enzyme responsible for de novo fatty acid synthesis^[76]. Several small-molecule inhibitors of FASN have been developed and are being evaluated in preclinical and clinical studies. These inhibitors disrupt lipid metabolism in cancer cells, leading to reduced cell proliferation, induction of apoptosis, and increased sensitivity to existing anticancer therapies. Additionally, drugs targeting other enzymes involved in fatty acid metabolism, such as Acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase (SCD), are being explored as potential therapeutic options^[77]. ACC inhibitors inhibit fatty acid synthesis by blocking the conversion of Acetyl-CoA to malonyl-CoA, while SCD inhibitors disrupt lipid desaturation, affecting membrane fluidity and cancer cell viability^[78]. By targeting specific enzymes involved in fatty acid metabolism, these drugs aim to selectively inhibit cancer cell growth and survival while minimizing toxicity to normal cells. Although further research and clinical trials are needed to optimize drug efficacy and assess long-term safety, targeting fatty acid metabolism holds promise as a novel therapeutic approach for cancer treatment. Statins, which are commonly used to lower cholesterol levels by inhibiting HMG-CoA reductase, have shown potential as anti-cancer agents^[79]. By reducing cholesterol synthesis, statins dis-

rupt the formation of lipid rafts, which are critical for the clustering of oncogenic receptors, such as EGFR and HER2^[80]. This disruption impairs downstream signalling pathways involved in cell survival and proliferation, particularly in cancers like breast and prostate cancer. Preclinical studies have demonstrated that statins can inhibit tumour growth, induce apoptosis, and enhance the efficacy of conventional chemotherapy^[81]. However, the use of statins in cancer therapy requires further investigation to determine the optimal dosing and minimize potential side effects, such as muscle toxicity. Combining statins with other lipid metabolism inhibitors, such as FASN or SCD1 inhibitors, may offer a more robust therapeutic strategy by targeting multiple aspects of lipid metabolism in cancer cells.

While there are currently no FDA-approved drugs specifically targeting fatty acid metabolism for cancer treatment, several drugs have been investigated in preclinical and clinical studies. Here are some examples of drugs that have shown promise in targeting fatty acid metabolism.

Orlistat: Although primarily used as an anti-obesity drug, Orlistat has been investigated for its potential anti-cancer effects. It inhibits pancreatic lipase, an enzyme involved in dietary fat digestion, leading to reduced fatty acid absorption and potentially affecting cancer cell growth^[82].

TVB-2640: TVB-2640 is an inhibitor of fatty acid synthase (FASN), a key enzyme in de novo fatty acid synthesis^[83]. It has shown efficacy in preclinical studies and is being evaluated in clinical trials for various cancer types.

Cerulenin: Cerulenin is a natural product that inhibits fatty acid synthesis by targeting FASN^[84]. It has demonstrated anticancer effects in preclinical studies, but its clinical development has been limited due to potential toxicity concerns.

Etomoxir: Etomoxir is an inhibitor of carnitine palmitoyl transferase 1 (CPT1), an enzyme involved in fatty acid beta-oxidation^[85]. By blocking this enzyme, etomoxir inhibits the breakdown of fatty acids for energy production. Although primarily investigated for cardiovascular conditions, it has also shown anticancer activity in preclinical studies.

Avasimibe: Avasimibe is an ACAT (Acyl-CoA: cholesterol acyltransferase) inhibitor that interferes with cholesterol esterification, impacting lipid metabolism^[86]. It has shown potential in preclinical studies for inhibiting cancer cell growth and metastasis.

It is important to note that the clinical development and approval status of drugs can vary over time. Therefore, it is advisable to consult reliable sources and clinical trial databases for the most up-to-date information on approved drugs and ongoing research in the field of fatty acid metabolism as a drug target for cancer treatment.

Discussion

The dysregulation of fatty acid metabolism plays a significant role in cancer cells and their progression^[1-3] see Fig. 2. Cancer cells exhibit altered pathways of fatty acid metabolism to meet their increased demands for energy, membrane synthesis, and signalling molecules^[4-6,8-10]. These changes provide cancer cells with a distinct advantage, promoting their survival, growth, and metastatic potential.

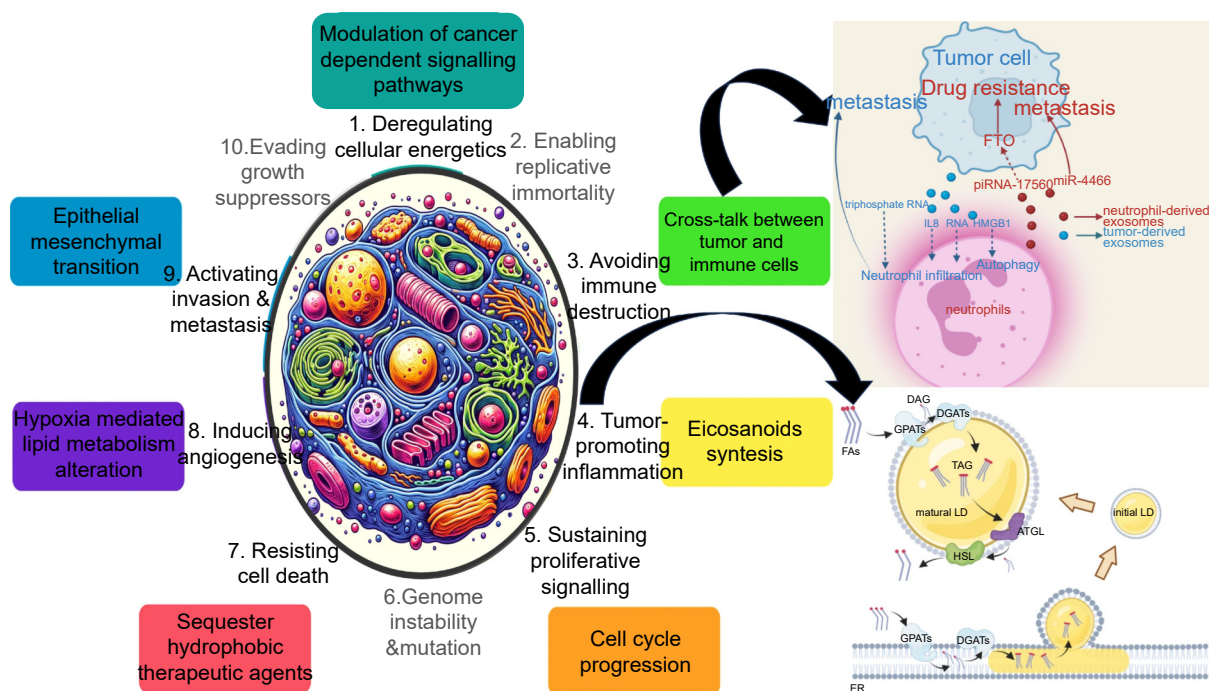


Fig. 2. Altered Lipid Homeostasis leading to modulation in cancer cell signalling pathways.

One key aspect of altered fatty acid metabolism in cancer cells is the upregulation of de novo lipogenesis, the process by which cells synthesize fatty acids. This upregulation is often driven by the overexpression and activation of enzymes such as fatty acid synthase (FASN)^[46,54,55]. The increased activity of FASN allows cancer cells to generate fatty acids, providing them with essential components for membrane biogenesis and cell growth.

In addition to increased de novo lipogenesis, cancer cells exhibit enhanced fatty acid uptake and storage. They upregulate the expression of fatty acid transport proteins and receptors, enabling them to take up exogenous fatty acids from the surrounding microenvironment. Cancer cells also display elevated lipolysis, the breakdown of stored triglycerides^[6,40,44] into free fatty acids, providing them with an additional source of energy and building blocks for various cellular processes.

The altered fatty acid metabolism in cancer cells has several implications for disease progression. Firstly, it supports the rapid proliferation of cancer cells by supplying the necessary fatty acids for membrane synthesis and cellular growth^[12,21]. Additionally, the dysregulated metabolism of fatty acids generates lipid signalling molecules that contribute to cancer cell migration, invasion, and angiogenesis^[10,45], all critical processes in tumour progression and metastasis.

Understanding the intricacies of fatty acid metabolism in cancer cells opens up potential therapeutic avenues. Targeting enzymes and pathways involved in altered fatty acid metabolism has emerged as a promising strategy for cancer treatment. Inhibitors of key enzymes like FASN have shown potential in preclinical and early clinical studies, demonstrating anti-tumour effects and sensitization to existing therapies.

The dysregulation of fatty acid metabolism is a hallmark of cancer cells and contributes to their survival, growth, and metastasis^[9,10,24,27,29]. The upregulation of de novo lipogenesis, en-

hanced fatty acid uptake, storage, and lipolysis provide cancer cells with the necessary resources for their energetic and biosynthetic demands^[4-6,8-10,45,46]. Understanding the intricacies of fatty acid metabolism in cancer cells not only deepens our knowledge of tumour biology but also offers opportunities for the development of targeted therapies aimed at disrupting the specific vulnerabilities associated with altered fatty acid metabolism in cancer cells.

Conclusion

The altered metabolism of fats in cancer cells represents a fascinating aspect of cancer biology. Dysregulation of lipid homeostasis contributes to cancer cell survival, proliferation, and signalling, providing potential targets for therapeutic intervention. Further research into the intricate interplay between lipid metabolism, signalling pathways, and membrane dynamics will enhance our understanding of cancer progression and may lead to novel therapeutic strategies aimed at disrupting lipid-dependent processes in cancer cells. Mutated fat metabolism genes play a significant role in the altered lipid homeostasis observed in cancer cells. These mutations contribute to the metabolic reprogramming of cancer cells, supporting their growth, invasion, and resistance to therapy. The identification of mutated fat metabolism genes provides opportunities for targeted therapeutic interventions, and ongoing research efforts aim to uncover novel strategies to exploit these alterations for improved cancer treatment outcomes. In conclusion, lipid metabolism alterations play a significant role in the progression and aggressiveness of various types of cancer. Dysregulation of lipogenic pathways, increased lipid accumulation, and altered lipid profiles contribute to tumour growth, metastasis, and resistance to therapy. GC-MS TOF analysis is a powerful tech-

nique for identifying and profiling fatty acids in cancer cells. This analytical approach enables the characterization of the fatty acid composition, metabolic pathways, and biomarkers associated with cancer progression. By uncovering the intricate changes in lipid metabolism, GC-MS TOF analysis contributes to our understanding of the molecular mechanisms underlying cancer development and offers potential avenues for targeted therapeutic interventions. Understanding the specific lipid metabolic changes in different cancers may provide insights into the development of targeted therapeutic approaches to combat these diseases.

Abbreviations

ACC, Acetyl-CoA Carboxylase; ACLY, ATP Citrate Lyase; AT-GL, Adipose Triglyceride Lipase; CPT1, Carnitine Palmitoyl Transferase 1; DGAT, Diacylglycerol Acyltransferase; EMT, Epithelial-to-Mesenchymal Transition; ER, Endoplasmic Reticulum; FAO, Fatty Acid Oxidation; FASN, Fatty Acid Synthase; GC-MS TOF, Gas Chromatography-Mass Spectrometry Time-of-Flight; HMGCR, HMG-CoA Reductase; HSL, Hormone-Sensitive Lipase; LD, Lipid Droplet; LDL, Low-Density Lipoprotein; PI, Phosphatidylinositol; PIP3, Phosphatidylinositol-3,4,5-Trisphosphate; PUFA, Polyunsaturated Fatty Acid; SCD1, Stearoyl-CoA Desaturase 1; TCA, Tricarboxylic Acid Cycle.

Conflicts of interest

The authors have declared that no conflicts of interest exist.

Authors' contributions

All authors contributed to this study at different levels. All authors read and approved the final version. Study concept and design: HKM, SKJ, SBP, ARP; acquisition of data: HKM, SKJ, ARP; statistical analysis and interpretation of data: HKM, SKJ, ARP, SBP; drafting of the manuscript: HKM, SKJ; critical revision of the manuscript for important intellectual content: HKM, SKJ, ARP, SBP.

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