Lipids in Health and Disease

REVIEW

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Targeting lipid metabolism: novel insights and therapeutic advances in pancreatic cancer treatment

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Abstract

Lipid metabolism in cancer is characterized by dysregulated lipid regulation and utilization, critical for promoting tumor growth, survival, and resistance to therapy. Pancreatic cancer (PC) is a highly aggressive malignancy of the gastrointestinal tract that has a dismal 5-year survival rate of less than 10%. Given the essential function of the pancreas in digestion, cancer progression severely disrupts its function. Standard treatments for PC such as surgical resection, chemotherapy, and radiotherapy. However, these therapies often face significant challenges, including biochemical recurrence and drug resistance.

Given these limitations, new therapeutic approaches are being developed to target tumor metabolism. Dysregulation of cholesterol biosynthesis and alterations in fatty acids (FAs), such as palmitate, stearate, omega-3, and omega-6, have been observed in pancreatic cancer. These lipids serve as energy sources, signaling molecules, and essential components of cell membranes. Their accumulation fosters an immunosuppressive tumor microenvironment that supports cancer cell proliferation and metastasis.

Moreover, lipid metabolism dysregulation within immune cells, particularly T cells, impairs immune surveillance and weakens the body's defenses against cancer. Abnormal lipid metabolism also contributes to drug resistance in PC. Despite these challenges, targeting lipid metabolism may offer a promising therapeutic strategy. By enhancing lipid peroxidation, the induction of ferroptosis—a form of regulated cell death—could impair the survival of PC cells and hinder disease progression.

Keywords Lipid metabolism, Tumor microenvironment, Drug resistance, Ferroptosis, Cancer therapy

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Introduction

Pancreatic cancer (PC) is a leading global cause of cancer-related death, with the American Cancer Society reporting that only about 9% of patients survive beyond 5 years [1–4]. Despite accounting for only 3% of all cancer diagnoses in the USA, pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of cancer-related death by 2030 [5, 6]. Lipids, specifically hydrophobic macromolecules, play crucial physiological roles in cellular processes. Lipid metabolism is a complex biochemical process involving the regulation of phospholipid and cholesterol levels, influenced by factors such as insulin, glucagon, diet, and various enzymes. In the context of cancer, lipids are integral to multiple processes, including cellular signaling, energy storage, inflammation, and immune responses. Dysregulated lipid metabolism has been observed in various tumors, including breast, liver, and colon. Altered lipid metabolism plays a critical role in tumor initiation, progression, and metastasis [7].

A prominent characteristic of tumor cells is their disrupted metabolism, with PC cells exhibiting significant abnormalities in glucose and lipid metabolism. Numerous studies have explored the role of lipid metabolism in carcinogenesis, highlighting its profound impact [8]. In PC, this metabolic reprogramming involves enhanced fatty acid synthesis, altered cholesterol metabolism, and the accumulation of lipid droplets, all of which play crucial roles in tumor growth and progression [9, 10]. Lipid metabolism in PC cells is often upregulated to support rapid cell division and survival under nutrient-poor conditions. Key enzymes such as fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), and ATP-citrate lyase (ACLY) are overexpressed, leading to increased lipid biosynthesis [11–13]. Furthermore, pancreatic cancer cells exhibit altered cholesterol homeostasis, which contributes to membrane integrity and signaling, while also promoting the epithelial-to-mesenchymal transition (EMT) and metastasis [14, 15]. These metabolic changes not only support carcinogenesis but also contribute to chemoresistance, as lipid-modified cellular components can sequester chemotherapeutic agents or modulate their transport. This review aims to provide a comprehensive overview of how dysregulated lipid metabolism influences PC progression. It begins with an introduction to lipid metabolism and its relevance to cancer. The focus is then shifted to how lipid metabolism becomes disrupted in PC, leading to alterations in fatty acid and cholesterol levels. The connections between abnormal lipid metabolism, cancer progression, and drug resistance are also explored. Finally, emerging therapies targeting lipid metabolism in PC are delineated.

Lipid metabolism and pancreatic cancer

Lipid dysregulation in cancer involves several key aspects: increased lipid uptake, de novo fatty acid synthesis, fatty acid oxidation (FAO), and cholesterol accumulation [16–18]. Cancer cells often enhance lipid uptake from their environment, by utilizing lipoprotein receptors such as the low-density lipoprotein receptor (LDLR) to acquire essential components for membrane formation and energy. To satisfy their high energy demands, cancer cells also engage in de novo fatty acid synthesis, driven by enzymes such as ACC and FASN, which are crucial for membrane biogenesis and signaling. Additionally, β-oxidation, the initial step in fatty acid catabolism occurring in the mitochondria, is frequently dysregulated in PC. During this process, long-chain fatty acids are broken down into two-carbon units as acetyl-CoA, which enters the citric acid cycle (TCA) to generate ATP. β-oxidation is essential for providing energy, especially during metabolic stress, and its dysregulation supports cancer cell proliferation and survival under nutrient-limited conditions [19]. Cholesterol homeostasis is similarly critical, with disruptions leading to alterations in cholesterol esters (CEs), oxysterols, and bile acids, all implicated in cancer progression [20]. Biosynthetic intermediates like squalene and isoprenoids also play a role in tumor growth. Regarding PC, lipid uptake is significantly altered to support tumor growth and metastasis [9, 10]. Also, fatty acid translocase (CD36) has been implicated in the initiation of metastasis [21] and the promotion of fatty acid β-oxidation to support proliferation [22].

Fatty acid metabolism and fatty acid synthase enzymes

Several studies indicate lipid metabolism drives cancer progression by influencing membrane synthesis, signaling molecules, and energy storage. Fatty acid metabolism is a central aspect of metabolic reprogramming in PC, where it supports the rapid growth and survival of tumor cells. Furthermore, the dysregulation of lipid metabolism in PC cells leads to the accumulation of lipid droplets, which serve as energy reservoirs and signaling platforms that contribute to the tumor ability to resist treatment and progress. FASN plays a critical role in de novo fatty acid synthesis, converting acetyl-CoA and malonyl-CoA into long-chain fatty acids [23]. FASN is crucial in catalyzing palmitate production [24, 25]. In PC, FASN expression is often upregulated and associated with poor prognosis [26]. The regulation of FASN by miR-195 affects PC progression by downregulating Wnt expression and inhibiting FASN activity, which impairs tumor cell growth and metastasis [27, 28]. In addition to FASN, ACC is another key enzyme in fatty acid metabolism that is frequently overexpressed in PC [29], driving the synthesis of malonyl-CoA, a precursor for fatty acid elongation [23]. The inhibition of FASN and ACC has shown

promising therapeutic effects in reducing PC cell growth and sensitizing tumors to chemotherapy, highlighting the potential of targeting fatty acid metabolism in the treatment of pancreatic cancer [10].

Cholesterol metabolism

Cholesterol is an energy source and a critical component of cell membranes. Cells acquire cholesterol through lipoprotein endocytosis or de novo synthesis from Acyl-CoA in the endoplasmic reticulum [30]. Additionally, cholesterol acts as a signaling molecule [31]. Dysregulated cholesterol biosynthesis plays a significant role in cancer, including PC, where abnormal cholesterol homeostasis is frequently associated with altered expression of the low-density lipoprotein receptor (LDLR) [32, 33]. In PC, changes in cholesterol levels correlate with tumor progression. For example, the frizzled class receptor 5 (Fzd5) binds cholesterol via a conserved extracellular linker region, promoting its palmitoylation, facilitating receptor maturation, and enhancing cell membrane function [34]. Cholesterol also activates critical signaling pathways, such as the Fzd5-mediated Wnt/β-catenin pathway, which drives PDAC progression [35], and the sonic hedgehog pathway, which is involved in PC tumorigenesis [36]. Furthermore, upregulation of cholesterol biosynthesis enzymes, such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), and increased LDLR expression are commonly observed in PC, facilitating tumor growth and metastasis [37, 38]. Cholesterol-rich lipid rafts, which concentrate signaling molecules, promote the activation of pathways like PI3K/Akt, enhancing cell survival, proliferation, and metastasis in PC [39]. Inhibition of cholesterol synthesis or LDLR-mediated cholesterol uptake has been shown to suppress tumor growth and sensitize pancreatic cancer cells to chemotherapy [37], suggesting that targeting cholesterol metabolism could be a promising therapeutic strategy in PC.

Cholesterol efflux

Intracellular cholesterol management involves its uptake, de novo synthesis, storage, and efflux. The rate of cholesterol efflux is influenced by factors such as cellular cholesterol load, high-density lipoprotein (HDL) composition, size, concentration, and efflux transporter expression. Cholesterol outflow occurs through four mechanisms: 1. Passive diffusion: cholesterol is transported to mature HDL particles [40]. 2. Facilitated diffusion: mediated by class B scavenger receptor type I (SR-B1). 3. Apolipoprotein A1 efflux (Pre-β1 HDL): mediated by ABCA1. 4. Efflux to mature HDL: mediated by ABCG1 [41, 42]. Cholesterol efflux may play an essential role in various cancers. HDL-C cholesterol levels are considered a potential biomarker for certain cancers, and epidemiological studies have shown that HDL-C levels are inversely associated with the risk of several malignancies [43]. Studies have shown that postmenopausal women with PC exhibit significantly lower levels of HDL-C in their blood [44]. A two-center retrospective study found that patients with PC had reduced HDL levels on admission compared with patients with other oncology [45].

In addition, SR-B1 is a multi-ligand membrane receptor that acts as a physiological HDL receptor and is frequently overexpressed in various cancers [46], including PC [47]. ABCA1 is a plasma membrane transporter that has anticancer effects by promoting cholesterol efflux and decreasing intracellular cholesterol levels [48]. Studies have shown that high expression of ABCG1 in cancer cell lines is inversely correlated with overall survival and that decreasing ABCG1 levels can lead to tumor regression [49]. In contrast, the transcriptional levels of ABCA1 and ABCG1 in PC are higher than in non-tumor tissues [50]. The relationship between ABCA1 and ABCG1 and tumor growth and survival is clear, although their role in drug resistance is unclear. ABC transporters, including ABCA1 and ABCG1, may efflux anticancer drugs from cells and have been implicated in chemotherapy resistance in PC [51]. These findings highlight the need for new diagnostic and prognostic hematological indicators, including cholesterol uptake and synthesis, which could lead to the establishment of innovative anti-tumor treatment regimens for PC.

In addition to the aforementioned relationship between lipids and the progression of tumors, there are numerous other small molecules associated with lipid metabolism disorders, including the KRAS gene and GNAS gene, as well as proteins such as BCAA, SREBP2, HSDL2, KRASG12D, PLA2G2A phospholipase, and the transcription factor SREBF1. These molecules play a significant role in the progress of cancer.

Abnormal lipid metabolism in pancreatic cancer cells fosters a favorable environment for tumor survival and progression. However, current research often focuses on individual components of lipid metabolism or changes in specific enzymes, leaving critical questions about the dynamic evolution of lipid metabolism, cross-talk between enzymes and metabolic pathways, and feedback regulation largely unexplored. A comprehensive and systematic investigation into the interplay between lipid metabolism and pancreatic cancer is essential to fully elucidate these mechanisms and identify novel therapeutic targets.

Table 1 offers a concise summary of lipid metabolism dysregulation in prostate cancer progression.

Table 1 The role of lipid metabolism dysregulation in PC

Molecular landscape	Highlight	Ref
Kirsten rat sarcoma viral oncogene (KRAS)	KRAS controls the storage and use of lipid droplets through HSL regulation that shows downregulation in PC Suppression of the KRAS/HSL axis impairs lipid metabolism and storage and suppresses invasion and metastasis	[52]
Branched-chain amino acid (BCAA)	BCAA uptake in the PC cells is mediated by solute carrier transporters The downregulation of Branched-chain amino-acid transaminase 2 (BCAT2) impairs cancer progression	[53]
Sterol regulatory element binding protein (SREBP1)	Upregulation of SREBP1 mediates poor survival and prognosis SREB1 increases ACC, FASN, Stearoyl-CoA desaturase–1 (SCD1), and lipogenesis Downregulation of SREBP1 induces apoptosis	[54]
Hydroxysteroid dehydrogenase-like protein 2 (HSDL2)	Overexpression of HSDL2 in PC mediating poor survival HSDL2 downregulation impairs lipid metabolism and proliferation	[55]
Sterol Regulatory Element-Binding Transcription Factor 1 (SREBF1)	Yarrow supercritical extract reduces SREBF1 expression to suppress lipid metabolism through the downregulation of Stearoyl-CoA desaturase (SCD) and FASN	[56]
$KRAS^{G12D}$	$KRAS^{G12D}$ increases SLC25A1 expression to enhance lipid metabolism in cancer progression	[57]
G-protein (GNAS)	GNAS mutation increases protein kinase A (PKA) -induced salt-inducible kinases (Sik1) inhibition and promotes lipid metabolism	[58]
Adipocytes	Adipocytes enhance lipid droplets in promoting cancer invasion	[59]
phospholipase A2 group IIA (PLA2G2A) phospholipase	PLA2G2A enhances FASN and energy metabolism during K-ras mutation	[60]
FASN	FASN suppression accelerates apoptosis	[61]
FAs	The FAs stimulate stromal reprogramming to enhance inflammation and fibrosis for fuelling PC	[62]
Heptadecanoic acid	Heptadecanoic acid as an FA stimulates apoptosis and promotes gemcitabine sensitivity	[63]

Functional implications of lipid dysregulation in cancer

Lipids play a pivotal role in cancer development and progression, with dysregulated lipid metabolism closely linked to key aspects of cancer biology, including initiation, growth, metastasis, and drug resistance [64]. Alterations in lipid metabolism confer survival advantages to cancer cells, such as enhanced resistance to chemotherapy and targeted therapies [65]. This metabolic reprogramming enables cancer cells to evade the cytotoxic effects of treatment, leading to increased resilience and complicating therapeutic outcomes [66]. Consequently, lipid dysregulation presents a significant challenge in cancer management, impairing the efficacy of conventional therapies.

Understanding the complex role lipids play in cancer—spanning initiation, progression, metastasis, and drug resistance—is critical for developing novel treatment approaches. Targeting lipid metabolism holds the potential to improve patient outcomes and overcome therapeutic resistance. Further research is essential to establish the intricate relationship between lipid dysregulation and cancer, leading to the establishment of new therapeutic targets and more effective interventions.

Altered membrane dynamics and oncogenic signalling drive cancer initiation

Increased lipid accumulation within the tumor microenvironment (TME) is closely associated with enhanced cancer invasion [67]. Dysregulated lipid metabolism alters the composition of cell membranes, impacting their fluidity, receptor distribution, and associated signaling pathways. These changes can promote uncontrolled cell growth, facilitating cancer initiation. Specific lipids, such as phosphoinositides and sphingolipids, are critical regulators of intracellular signaling, and their dysregulation can activate oncogenic pathways, further driving cancer initiation and progression [68].

FAs are a crucial energy source for various cellular processes, and they serve as the structural backbone of phospholipids and glycolipids in cell membranes [69]. There is a strong correlation between inflammation, metabolic syndrome, and increased consumption of saturated fatty acids (SFAs), particularly palmitate and stearate. However, polyunsaturated fatty acids (PUFAs) and other unsaturated fatty acids, such as oleate and linoleate, have been shown to mitigate or resolve inflammation [70].

Notably, palmitate, rather than glucose or insulin, has been identified as a key driver of the inflammatory and metabolic profile of adipose tissue macrophages (ATMs) in obese adipose tissue (AT) [71]. Palmitate triggers the release of inflammatory cytokines by macrophages through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a central regulator of inflammation [72]. Additionally, both stearic and palmitic acids bind to Toll-like receptors (TLRs), activating the c-Jun N-terminal kinase (JNK) and NF-κB signaling pathways [73]. This process leads to increased levels of pro-inflammatory molecules, including monocyte chemoattractant protein-1 (MCP-1), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α).

The accumulation of lipids such as diacylglycerols (DAGs) and SFAs within macrophages, as a result of macrophage scavenging activity, has been implicated in developing a pro-inflammatory M1 macrophage phenotype. This lipid buildup can exert toxic effects on the

endoplasmic reticulum, further exacerbating inflammatory responses in metabolic conditions [74, 75].

Omega-3 and omega-6 PUFAs are promising therapeutic targets for metabolic diseases and cardiovascular disease (CVD) due to their potent anti-inflammatory properties [76]. As essential fatty acids, PUFAs must be obtained through diet, and a high intake of PUFAs has been linked to a reduced risk of CVD, highlighting their regulatory role in inflammation [77]. The dysregulation of lipid metabolism in tumors supports cell proliferation and survival, as well as influences inflammatory pathways that contribute to carcinogenesis. Lipid metabolic signaling, through the crosstalk with pathways such as NF-κB and STAT3, can enhance the expression of pro-inflammatory cytokines like IL-6 and TNF-α, which in turn promote tumor progression and immune evasion [78, 79]. In PC, for example, altered lipid metabolism leads to the accumulation of lipid droplets, which can further activate inflammatory signaling pathways that create a pro-tumorigenic microenvironment [80].

Research on THP-1 macrophages has demonstrated that PUFAs, including linoleic acid, alpha-linolenic acid, and docosahexaenoic acid (DHA), can mitigate lipopolysaccharide (LPS)-induced inflammation [81]. Moreover, DHA decreases the production and secretion of pro-inflammatory cytokines IL-1β and TNF-α and enhances the secretion of the anti-inflammatory cytokine IL-10 through an autocrine mechanism. Furthermore, DHA activates key anti-inflammatory pathways involving peroxisome proliferator-activated receptor gamma ([82] PPARγ) [83] and AMP-activated protein kinase (AMPK), which in turn inhibit NF-κB, which is a major regulator of inflammation in macrophages [84].

Regarding PC, dysregulated lipid uptake through transporters such as CD36 and fatty acid-binding proteins (FABPs) facilitates the formation of lipid rafts [85, 86], which serve as platforms for the activation of oncogenic pathways such as PI3K/Akt and ERK [87, 88]. Additionally, enzymes involved in lipid metabolism, such as FASN and ACC, are often upregulated in early-stage pancreatic cancer, promoting cell survival and proliferation [89].

Metabolic reprogramming, inflammation, and immune suppression drive cancer progression

Cancer cells require abundant energy to sustain their rapid growth, and lipids serve as a critical energy source that fuels cancer cell proliferation. Dysregulated lipid metabolism profoundly influences key metabolic pathways, such as increased de novo fatty acid synthesis and cholesterol biosynthesis, essential for supporting cancer cell growth [90]. These metabolic shifts allow the modification of lipids into molecules necessary for driving vital biochemical processes within the cell [91].

Altered lipid metabolism provides energy through FAO and glycolysis, supporting tumor progression by shaping immune responses, as shown in Fig. 1 [64]. This dysregulated lipid utilization contributes to chronic inflammation and immune suppression, creating a favorable environment for cancer cells to thrive and evade immune surveillance [92]. Therefore, lipid metabolism becomes intricately linked with tumor growth and cancer cells' ability to bypass the immune system, reinforcing its critical role in cancer progression.

Lipids play a significant role in modulating the activity of myeloid-derived suppressor cells (MDSCs), critical for maintaining immune homeostasis, cell membrane integrity, and signaling. Research has shown that MDSCs isolated from cancer patients or tumor-bearing mice exhibit significantly higher lipid accumulation than controls [93], establishing a direct link between lipid buildup and immune suppression in cancer. This lipid buildup in MDSCs correlates with decreased T-cell activity, leading to immunosuppression [94–96]. It has been demonstrated that oxidized lipids serve as a key energy source supporting the immunosuppressive function of MDSCs within the tumor microenvironment. Specifically, MDSCs with excessive lipid content show a greater ability to suppress CD8 + T-cell activity compared to MDSCs with normal lipid levels [97]. A study by Cao et al. revealed that fatty acid transport protein 4 (FATP4) is overexpressed in tumor-derived MDSCs, suggesting a connection between lipid accumulation and increased fatty acid uptake [98]. This finding indicates that lipid metabolism in MDSCs is closely tied to their role in dampening immune responses, particularly in cancer settings.

Lipid accumulation is a major contributor to dendritic cell (DC) dysfunction in malignancies. Excess lipids in DCs impair their antigen-processing abilities, reduce the expression of costimulatory molecules like CD86, and increase the production of the tolerogenic cytokine IL-10, leading to immune tolerance as opposed to activation [99]. In ovarian tumors, the enzyme FASN, crucial for de novo lipogenesis, is upregulated. Consequently, these cancer cells produce more fatty acids, leading to higher fatty acid concentrations in the tumor microenvironment, which causes DCs to store excess fatty acids, thereby impairing their functionality [100].

Studies have also shown that the buildup of oxidized lipids, particularly triacylglycerol (TAG), further exacerbates DC dysfunction [101]. In ovarian cancer, lipid droplets accumulate within DCs, impairing their ability to mount effective anticancer responses. Another mechanism of DC impairment is the upregulation of carnitine palmitoyl transferase-1a (CPT1A), a key fatty acid transport protein, via the Wnt5a-β-catenin-PPARγ signaling

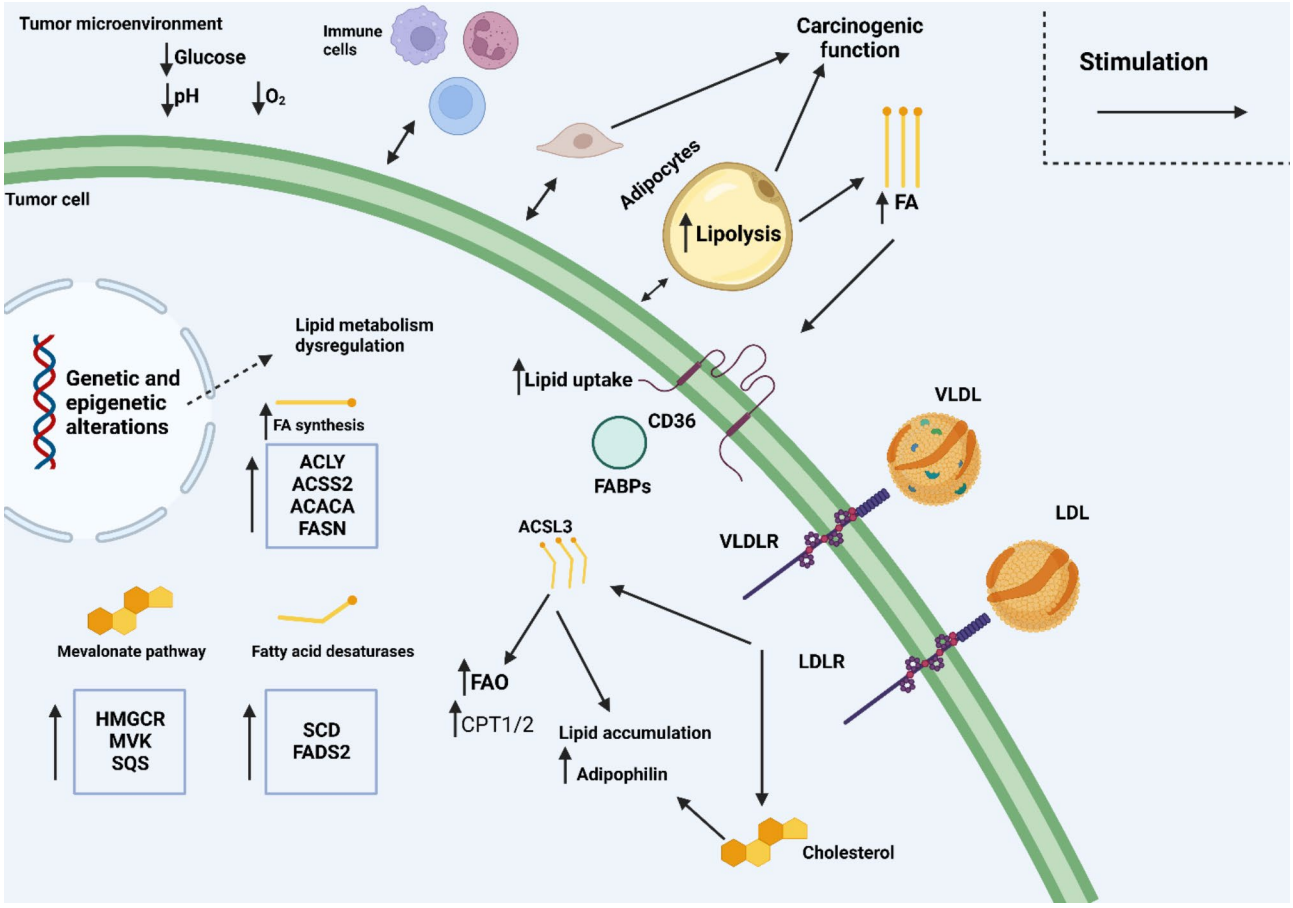

Fig. 1 Reprogramming of lipid metabolism in cancer

pathway. This enhances FAO, promoting tumor resistance, as seen in melanoma [102].

Additionally, tumor-infiltrating DCs can trigger the endoplasmic reticulum (ER) stress response through the IRE1 protein, suppressing T-cell function and contributing to tumor growth [103]. These findings highlight how dysregulated lipid metabolism in immune cells, particularly in the tumor microenvironment, interferes with their ability to regulate carcinogenesis. The altered lipid metabolism in immune cells, influenced by their interaction with tumor cells, plays a pivotal role in undermining the anticancer immune response and facilitating tumor progression.

Lipids and their metabolites exert their anti-tumor effects also by regulating macrophage polarization. Lipogenesis is crucial for lipid accumulation and phagocytosis in M1 macrophages, whereas M2 macrophages depend on fatty acid β-oxidation as their primary energy source. Markers of lipolysis and fatty acid uptake, such as CD36, also contribute to cytokine production, leading to inflammation. Therefore, to strengthen the immune system by inhibiting lipid metabolism-related factors could represent a targeted approach against tumor cells.

In PC, metabolic reprogramming is tightly linked to inflammation and immune suppression, both of which accelerate tumor progression. Altered lipid metabolism drives chronic inflammation through the activation of pathways like NF-κB and STAT3 [104]. For instance, increased LDL-cholesterol levels have been shown to enhance pancreatic cancer cell proliferation, migration, and invasion by activating STAT3 phosphorylation, which promotes tumor survival and progression by regulating critical cancer hallmarks [105]. Additionally, research has demonstrated that overexpression of FASN in vitro induces resistance to genotoxic therapies by upregulating poly (ADP-ribose) polymerase (PARP)-1 expression and DNA repair mechanisms, through the NF-κB and specificity protein 1 (SP1) pathways in PC cells [106].

Enhancement of invasive and metastatic potential of cancer cells

Lipids are essential for forming cell membranes and are crucial in enhancing cell motility and invasiveness, key factors in cancer metastasis [107]. Alterations in lipid composition can increase cancer cells' ability to adhere

to, invade surrounding tissues, and spread to distant organs. This lipid-driven enhancement of invasiveness is central to the metastatic process [108, 109]. Therefore, disruptions in lipid metabolism can destabilize these pathways, enhancing cancer cell invasion and migration, ultimately fostering cancer progression.

Two key products of lipid synthesis—FAs and cholesterol—play pivotal roles in metastatic cancers [110, 111]. For instance, chronic exposure to 27-hydroxycholesterol (27HC), an abundant cholesterol metabolite, selects for cells with increased lipid uptake and biosynthesis, enhancing their tumorigenic and metastatic capacity. This metabolic stress, driven by lipid accumulation, requires sustained GPX4 expression, a negative regulator of ferroptosis. Resistance to ferroptosis is a key feature of metastatic cells, and GPX4 knockdown reduces the tumorigenic and metastatic potential of 27HC-resistant cells [20]. In CRC, a cholesterol metabolic pathway specific to CRC liver metastasis has been identified, involving the activation of the SREBP2-dependent cholesterol biosynthesis pathway. This pathway is essential for the colonization and growth of metastatic CRC cells in the liver [112]. Anoctamin 1 (ANO1) has been identified as a key factor in driving metastasis in various metastatic cancer cell lines. ANO1 promotes cholesterol accumulation by inhibiting LXR signaling and reduces cholesterol hydroxylation by downregulating the expression of cholesterol hydroxylase CYP27A1. A novel small-molecule inhibitor of ANO1 has been shown to mitigate tumor burden at metastatic sites [113]. DHCR7 (7-dehydrocholesterol reductase), an enzyme that catalyzes the last step of cholesterol synthesis, has been reported to promote the invasion ability of cervical cancer cells and lymphangiogenesis in vitro and induced lymph node metastasis in vivo through cholesterol reprogramming-mediated activation of the KANK4/PI3K/AKT axis and VEGF-C secretion [114].

In hepatocarcinoma, the high expressed carnitine palmitoyltransferase 1 C (CPT1C) has been linked to increased cancer invasiveness and poor prognosis [115]. Reducing CPT1C levels downregulates FAO, impairing cancer cell growth, cell cycle progression, and metastatic potential [116, 117]. The role of FAO in tumorigenesis has also been highlighted in hepatocellular carcinoma, where increased FAO enhances cancer stemness. The overexpression of organic carnitine transporter 2 (OCTN2) is associated with poor prognosis in hepatocellular carcinoma. OCTN2 promotes tumor growth and invasion by enhancing FAO and mediating oxidative phosphorylation. Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) upregulates OCTN2 expression, which in turn increases the expression of Yin Yang 1 (YY1), further driving cancer progression [118]. PRP19 promoted esophageal squamous cell carcinoma growth in vitro and in vivo by enhancing fatty acid synthesis through sterol regulatory element-binding protein 1 (SREBF1), a major transcription factor of lipid synthase [117]. These studies collectively demonstrate that dysregulation of FA metabolism, particularly through mechanisms like FAO, plays a critical role in promoting cancer metastasis and immune evasion.

Increased cholesterol metabolism can significantly enhance cancer progression. Inhibiting cholesterol metabolism in T cells has been shown to boost their anti-cancer cytotoxicity, whereas suppressing cholesterol metabolism in tumor cells can hinder their metastatic potential [119]. Targets of the liver X receptor (LXR), such as ABCA1 and ABCG1, are associated with increased cancer progression. For instance, in clear cell renal cell cancer, celastrol increases LXR, leading to increased expression of ABCA1, which affects cholesterol homeostasis and contributes to cancer migration and invasion [120].

Similarly, in breast cancer, nucleobindin-2 (NUCB2)/Nesfatin-1 upregulation correlates positively with prognosis and enhances cholesterol metabolism. NUCB2/Nesfatin-1 stimulates the mechanistic target of rapamycin complex 1 (mTORC1), promoting tumor cell invasion and metastasis [121]. Additionally, cholesterol metabolism impacts immune cell activity; X-box-binding protein 1 (XBP1), an oncogenic factor, increases cholesterol production and enhances the immunosuppressive function of myeloid cells [122].

In PC, lipids can also be tumor-stroma communication mediators for cancer and stroma cells. Mice with oncogenic KRAS and p53 mutations (KPC mice) fed a high-fat diet exhibit larger primary pancreatic tumors and increased metastasis compared to those on a standard diet. Fatty acids, likely derived from adipose tissue, are taken up by pancreatic cancer cells, promoting lipid droplet (LD) formation and enhancing tumor cell migration [123]. Additionally, a recent study demonstrated that berberine, an isoquinoline alkaloid with various pharmacological properties, significantly reduces acetyl-CoA carboxylase (ACLY) expression in the cytoplasm, disrupting lipid metabolism, thereby inhibiting pancreatic cancer cell proliferation and migration [124].

Overall, the interplay between cholesterol metabolism and cancer progression highlights the potential of targeting lipid metabolism as a therapeutic approach.

Lipogenic phenotype drives altered drug transport and enhances drug resistance

Dysregulated lipid transporters significantly impact drug uptake and efflux, reducing drug efficacy. For example, the overexpression of ABC transporters is known to mitigate the effectiveness of therapeutic agents [125]. Lipids also modulate drug responses through various signaling

pathways; sphingolipids, for instance, regulate apoptosis and drug sensitivity [126]. Additionally, lipid rafts—specialized membrane microdomains—affect the localization of drug receptors [127]. The altered composition of lipid rafts can contribute to drug resistance by changing receptor distribution and function. Figure 2 shows that elevated levels of cellular FAs and cholesterol drive tumor growth and reduce the effectiveness of therapeutic drugs. In tumor-infiltrating Treg cells, increased lipid synthesis, including FAs and cholesterol, is a key metabolic change, driven by the activation of SREBPs and their target genes [128]. Treg cells also promote FA and cholesterol metabolism through the AKT-mTORC1 signaling pathway, which supports cell proliferation and the expression of immune-suppressive molecules like CTLA-4 and ICOS [129]. Therefore, targeting lipid metabolism pathways in Treg cells, such as CD36 and SREBP, could enhance cancer immunotherapy efficacy and warrants further investigation [128, 130]. Natriuretic peptide receptor A (NPRA) was upregulated in gastric cancer cells cocultured with mesenchymal stem cells (MSCs), and the knockdown of NPRA reversed MSC-induced stemness and chemoresistance. NPRA facilitated stemness and chemoresistance through FAO by protecting Mfn2 from degradation and promoting its mitochondrial localization, and inhibition of FAO with etomoxir (ETX) reduced MSC-induced chemoresistance in vivo [131]. NSD2 promotes FAO by methylating AROS (active regulator of SIRT1) at lysine 27, facilitating the physical interaction between AROS and SIRT1, ultimately affecting the effectiveness of tumor radiotherapy [132].

In healthy tissues, lipid metabolism operates within a balanced framework, but tumor cells often exhibit dysregulated lipid metabolism to develop drug resistance, marking the lipogenic phenotype as a hallmark of malignancy. This phenotype is characterized by hyperactivation of FA synthesis pathways, promoting lipid accumulation that supports cancer progression [133].

Increased lipid accumulation is observed in various cancers, including breast, colorectal, and ovarian, and

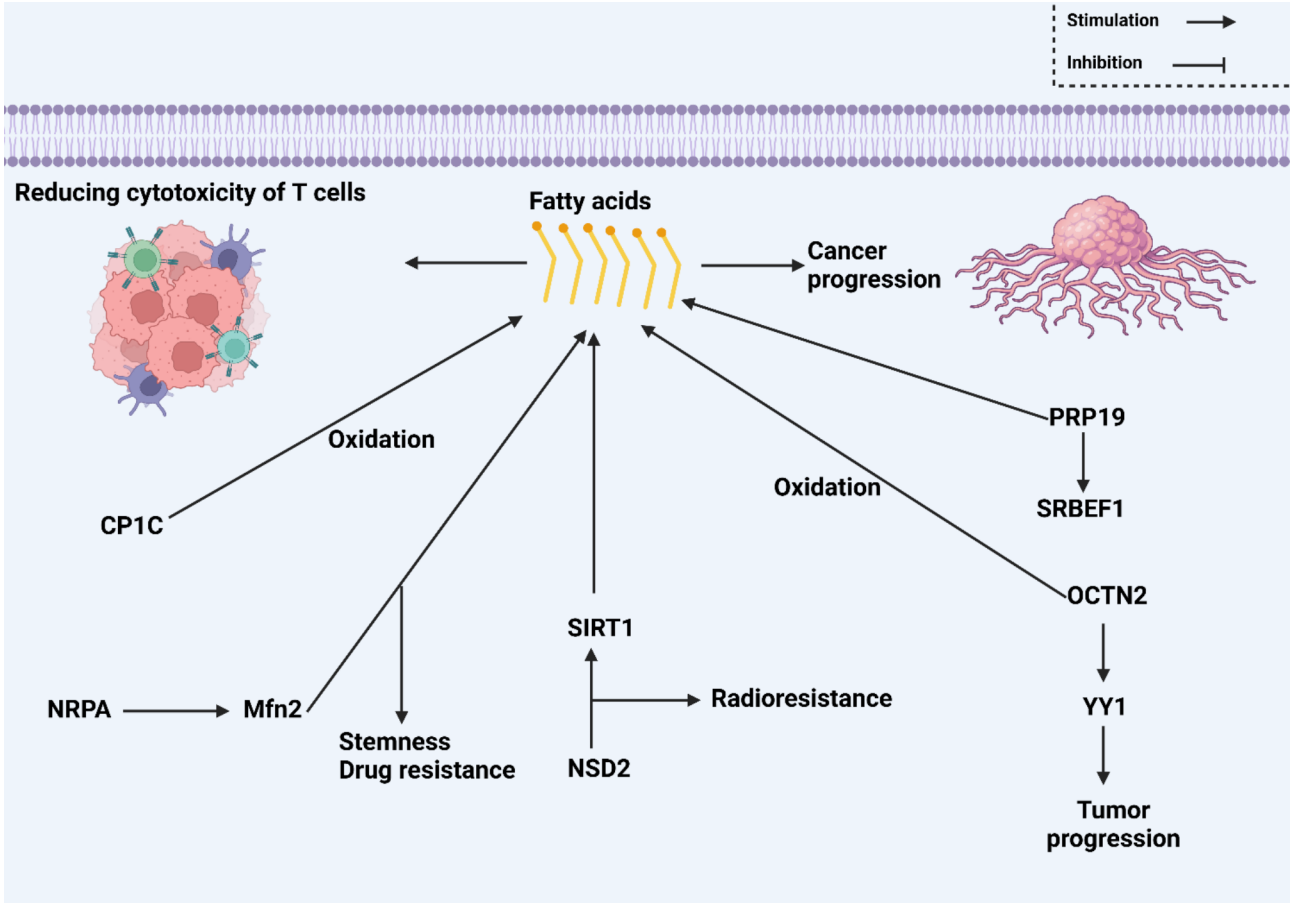

Fig. 2 Role of lipids and fatty acid metabolism in cancer development. Elevated levels of cellular FAs and cholesterol are associated with enhanced cancer progression. Increased FA and cholesterol metabolism drive tumor growth and contribute to reduced efficacy of therapeutic drugs [54]. This metabolic dysregulation also exacerbates the immunosuppressive functions of myeloid cells, potentially impairing T-cell function [143, 144]. The impact of elevated lipid metabolism on immune responses and drug efficacy underscores the critical need to target lipid metabolic pathways to combat chemoresistance. Cancer treatments aim to overcome resistance and improve therapeutic outcomes by inhibiting FA and cholesterol metabolism

correlates with poor prognosis. Elevated free FA levels in tumor cells enhance malignancy, with increased FA uptake activating the HIF1/MMP14 axis, driving invasion and metastasis [134–136]. Figure 3 illustrates lipid metabolism dysregulation in cancer.

Researchers have increasingly focused on the role of lipid metabolism in regulating PC progression, particularly regarding chemoresistance [137]. PC is characterized by rapid proliferation and metastasis, which often leads to resistance to therapy, especially in advanced stages [138]. Gemcitabine is the primary drug used to suppress PC, and understanding the molecular mechanisms behind gemcitabine resistance has been a key area of study [139]. Tadros [26] found that FASN expression increased with disease progression in a genetically engineered mouse model and was associated with poor survival and reduced gemcitabine responsiveness in human pancreatic cancer patients. FASN inhibitors, when combined with gemcitabine in both cell cultures and orthotopic models, reduced cancer stemness by inducing ER stress and apoptosis. Another study highlighted that TGFB2, stabilized post-transcriptionally by METTL14-mediated m6A modification, promotes lipid accumulation, with triglyceride buildup contributing to gemcitabine resistance as demonstrated by lipidomic profiling [140]. These findings collectively suggest that targeting lipid metabolism, particularly through inhibition of FASN and regulation of lipid accumulation, can enhance the effectiveness of gemcitabine in treating pancreatic cancer.

Lipid metabolism dysregulation has been recognized as a crucial factor in drug resistance development in PC [141]. Changes in lipid metabolism, alongside associated molecular interactions, can affect how PC cells respond to therapy. Besides, targeting lipid metabolism may also influence glucose metabolism in PC cells, potentially altering their response to chemotherapy.

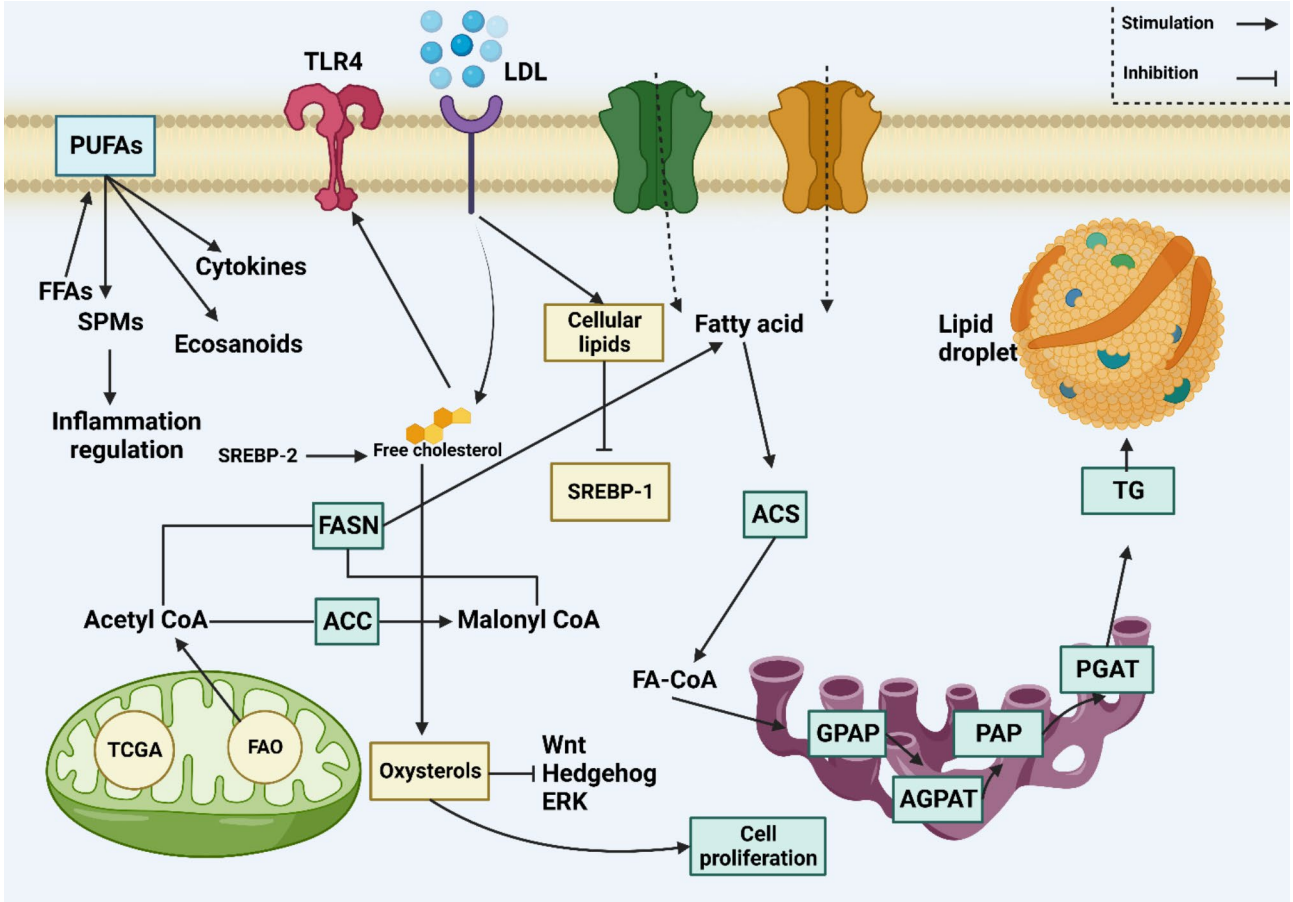

Fig. 3 Overview of lipid metabolism dysregulation in cancer. Under normal physiological conditions, acetyl-CoA is generated in the cytoplasm from citrate through the action of ATP-citrate lyase (ACLY). This acetyl-CoA is then converted into malonyl-CoA by ACC [145]. FASN is involved in FA synthesis, with ACC playing a critical role in regulating the rate of FA synthesis [146]. Subsequently, palmitic acid, a 16-carbon saturated FA, is produced. Palmitic acid can undergo elongation and desaturation to form additional saturated and unsaturated FAs [147]. Additionally, FAO increases mitochondrial acetyl-CoA levels, further supporting ongoing FA production. FAs are further processed and incorporated into lipid droplets in the endoplasmic reticulum. This overview illustrates the key enzymatic processes and pathways involved in lipid metabolism, highlighting their roles in normal and cancerous cells [148]

Dysregulated lipid metabolism plays a vital role in key processes such as cancer initiation, progression, metastasis, and drug resistance, reflecting its complex connection with cancer biology and its potential as a critical therapeutic target. However, most studies on the association between lipid metabolism and cancer are conducted in cell or animal models, leaving significant uncertainties about their applicability in clinical settings. For instance, while inhibiting specific lipid metabolic enzymes shows efficacy in in vitro studies, the complexity of the human body might alter enzyme functions and influence therapeutic outcomes. Bridging this gap between experimental findings and clinical applications remains a significant challenge.

Tumor cells frequently reprogram their lipid metabolism to enhance their survival and growth under adverse conditions. This metabolic adaptation arises from genetic and epigenetic changes and interactions with the tumor microenvironment (TME). Within the TME, tumor cells influence and are influenced by various components, resulting in alterations in multiple metabolic pathways. One significant example is the induction of lipolysis in neighboring adipocytes, which release fatty acids (FAs) that are subsequently absorbed by cancer cells. This process supports lipid accumulation and FAO in tumor cells. Tumor cells can also assimilate lipoproteins from external sources, further contributing to their lipid metabolism. Additionally, while immune cells in the TME can possess anti-tumoral properties, tumors often subvert their functions, converting them into suppressive or protumorigenic entities. Tumor cells produce lipid mediators that impact tumor progression by influencing angiogenesis and immune responses. Lipid metabolism reprogramming varies across different tumor types, reflecting the complexity and diversity of these mechanisms. Key molecules and pathways involved in this process include ACACA (acetyl-CoA carboxylase 1), ACLY (ATP-citrate lyase), ACSL3 (acyl-CoA synthetase long-chain family member 3) ACSS2 (acetyl-CoA synthetase 2), CAFs (cancer-associated fibroblasts), CPT1/2 (carnitine palmitoyltransferase 1 and 2), FABPs (fatty-acid-binding proteins), FADS2 (fatty acid desaturase 2), FASN, HMGCR (HMG-CoA reductase), LDL/LDLR (low-density lipoprotein/receptor), LPA (lysophosphatidic acid), LPL (lipoprotein lipase), MVK (mevalonate kinase), PGE2 (prostaglandin E2), SCD (stearoyl-CoA desaturase), SQS (squalene synthase), VLDL/VLDLR (very-low-density lipoprotein/receptor). This comprehensive overview emphasizes the critical role of lipid metabolism in cancer progression and highlights the diversity of metabolic adaptations employed by tumor cells [142].

Targeted therapy in pancreatic cancer through lipid metabolism reprogramming

Ongoing research indicates that dysregulated lipid metabolism plays a significant role in PC progression. These findings have led to the exploration of targeting lipid metabolism, related enzymes, and molecular pathways as a promising therapeutic strategy for PC treatment [10].

Numerous studies have highlighted FA synthesis as a potential target in PC therapy. For instance, a preclinical investigation demonstrated that the ACLY inhibitor, SB-204,990 effectively reduced mouse tumor xenograft formation [38]. Similarly, the ACC inhibitor Babay ACC002 halted tumor growth and transformed poorly differentiated histological phenotypes into epithelial phenotypes in PC xenograft models derived from cell lines and patient samples [149].

FASN is a multi-enzyme complex that is crucial for FA synthesis. It is also a key target in PC. Epigallocatechin-3-gallate (EGCG) has been shown to inhibit the β-ketoacyl-ACP synthase domain of FASN, effectively preventing pancreatic tumor formation in surgically implanted mouse models [150]. Additionally, orlistat has been found to inhibit the thioesterase domain of FASN, suppressing the growth of human PC cells. Proton pump inhibitors like lansoprazole, rabeprazole, omeprazole, and pantoprazole have also shown promise in reducing thioesterase activity, thereby promoting PC cell death [151].

Beyond FA synthesis, targeting cholesterol metabolism has also emerged as a viable strategy. Inhibiting the rate-limiting enzyme HMG-CoA reductase (HMGCR) with statins has shown anti-cancer effects, particularly in PC cells resistant to gemcitabine in in-vitro studies [152]. These findings underscore the potential of lipid metabolism reprogramming as a novel approach to overcoming chemoresistance and improving PC treatment outcomes.

Furthermore, statin treatment has been associated with improved survival rates in PC patients, as demonstrated by several meta-analyses. This finding suggests that statins, which inhibit cholesterol biosynthesis, could have a promising role in PC therapy. Additionally, emerging research points to stearoyl-CoA desaturase (SCD) as a potential target, with the inhibition of SCD showing efficacy in combating cancer progression.

Lipid metabolic reprogramming holds great promise in developing therapeutic strategies for pancreatic cancer. However, the current findings require further clinical studies for translation and validation. Additionally, a deeper understanding of dynamic lipid metabolic changes during pancreatic cancer progression and its interactions with factors such as the tumor microenvironment and cancer stem cells is needed. This knowledge could enable the development of more precise, efficient,

Table 2 The compounds targeting lipid metabolism in PC therapy

Compound	Remark	Ref
(-)-epigallocatechin-3-gallate (EGCG)	The suppression of the β-ketoacyl-ACP synthase domain of FASN to impair pancreatic cancer progression	[153]
Orlistat	FASN downregulation impairs proliferation and induces apoptosis	[89]
Proton pump inhibitors (lansoprazole, rabeprazole, omeprazole, and pantoprazole)	Inhibition of thioesterase activity to impair cancer progression	[154]
SCD inhibitor, A939572	Stearoyl-CoA Desaturase downregulation to mediate unfolded protein response in impairing cancer growth	[155]
Avasimibe encapsulated in human serum albumin	Suppressing cholesterol esterification	[156]

and safe targeted therapies or combination treatment strategies.

Table 2 summarizes various compounds that target lipid metabolism for the treatment of PC, reflecting the growing interest in this therapeutic approach. Table 3 presents an overview of the dual roles of cholesterol and FAs play in PC, either driving tumorigenesis or exerting anti-tumor effects, depending on the context of their regulation. This duality underscores the complexity of lipid metabolism in cancer and its therapeutic potential.

Conclusion and future prospects

PC cells frequently exhibit dysregulated lipid metabolism, which significantly contributes to tumor progression, drug resistance, and survival. This review highlights how targeting key molecular pathways of lipid metabolism, including lipid synthesis, degradation, and lipid droplet dynamics, presents promising therapeutic opportunities. Lipid macromolecules, such as FAs and cholesterol, play dual roles in cancer progression—promoting tumorigenesis in some contexts while exerting protective effects in others. For instance, elevated cholesterol levels and specific fatty acids might accelerate tumor growth, whereas others might suppress cancer progression.

One promising avenue of research is lipid peroxidation-induced ferroptosis, which offers a potential mechanism to restrict PC progression. However, gaps remain in linking these serum lipid changes to drug therapy responses in PC, and variations in lipid profiles across demographics and geographic locations remain poorly understood. Exploring these relationships could improve our understanding of lipid metabolism in PC and inform the design of more effective treatment strategies.

Further research is required to investigate the interactions between lipid metabolism and various cell death mechanisms, such as apoptosis, autophagy, immunogenic cell death, pyroptosis, and necroptosis. Non-coding RNAs, particularly circular RNAs, also represent an area of potential interest in understanding lipid metabolism dysregulation in PC.

Additionally, lipid metabolism reprogramming plays a critical role in enhancing drug resistance, as tumor cells adapt their metabolic pathways to evade chemotherapy, contributing to treatment failures in PC. For instance, increased FASN activity can promote chemotherapy resistance, while lowering ACSL4 levels can prevent ferroptosis, further decreasing drug efficacy. Additionally, elevated sterol regulatory element-binding protein 1 (SREBP-1) levels can disrupt lipid metabolism and interfere with therapeutic responses. Therefore, targeting key enzymes such as FASN, ACC, and SREBPs could disrupt these adaptations and improve therapeutic outcomes.

Table 3 The dual function of cholesterol and fatty acids in PC progression

Fatty acid or cholesterol	Tumorigenic or anti-tumorigenic function	Mechanism of action	References
Fatty acid	Anti-tumorigenic	The inhibition of fatty acid synthesis causes ferroptosis resistance	[157]
Fatty acid	Tumorigenic	Increase in fatty acid β-oxidation and elevation in lipid droplets in pancreatic cancer, causing metastasis	[59]
Fatty acid	Tumorigenic	An increase in fatty acid synthesis reduces apoptosis	[158]
Heptadecanoic Acid, an Odd-Chain Fatty Acid	Anti-tumorigenic	Apoptosis induction Increase in gemcitabine sensitivity	[63]
Fatty acid	Anti-tumorigenic	Fatty acid suppression results in autophagy Cytoprotective autophagy subsequently increases the survival rate of cancer cells and promotes their proliferation during hypoxia	[159–161]
Omega-3 fatty acid	Antitumorigenic	High omega-3 fatty acid causes mitigation of cancer progression	[162]
Fatty acid	Tumorigenic	Fatty acids impair the anti-cancer function of cholesterol flux suppression	[163]
Cholesterol 25-hydroxylase	Anti-tumorigenic	Upregulation of MHC-I and increase in CD8 + T cell infiltration to exert anti-cancer immune responses	[164]
LDL cholesterol	Tumorigenic	LDL cholesterol stimulates the STAT3 axis to boost tumor cell growth	[105]
HDL cholesterol	Anti-tumorigenic	HDL cholesterol promotes cholesterol elimination to suppress the growth of tumor cells	[165]

This review also discusses the interplay between lipid and glucose metabolism in PC cells. Increased FASN levels lead to elevated pyruvate kinase M2 (PKM2) expression, an enzyme involved in glycolysis, which enhances drug resistance. This metabolic shift contrasts with normal cells, which rely on oxidative phosphorylation for energy production.

To address the complexity of lipid metabolism in PC, future studies should focus on developing more specific and effective inhibitors targeting key enzymes such as FASN, ACC, and cholesterol biosynthesis pathways. Advanced technologies, such as single-cell sequencing and metabolomics, can help uncover novel therapeutic targets and refine our understanding of lipid metabolism in a clinical context. Combination strategies hold significant potential, particularly pairing lipid metabolism inhibitors with standard therapies such as gemcitabine or immune checkpoint inhibitors. Bridging the gap between preclinical findings and clinical applications will be critical, as the efficacy of lipid-targeted therapies in complex human systems remains uncertain.

Personalized treatment approaches, guided by lipidomic profiling, could help identify patients most likely to benefit from lipid-targeted therapies. Clinical trials are essential to evaluate the safety and efficacy of these combination treatments and to refine our understanding of how lipid metabolism drives tumor progression and drug resistance. Exploring the tumor microenvironment's role in lipid metabolism and immune suppression may reveal new therapeutic avenues.

As research into the role of lipid metabolism in cancer advances, lipid-targeting strategies are likely to become a key component of precision oncology, offering hope for improving survival and treatment outcomes in pancreatic cancer patients.

Acknowledgements
We thank the Biorender.com for providing drawing support.

Author contributions
YZ and ZY: Consulted the literatures , wrote the paper and prepared Tables 1, 2 and 3; YL and JP: prepared Figs. 1, 2 and 3; RL: designed and supervised; YY: provided the critical reviews and supported the funding. All authors contributed to the article and approved the submitted version.

Funding
This work was supported by the Key Science and Technology Research (Major) Project of the First Affiliated Hospital of Henan University of Science and Technology (ZLKFFJJ20230409).

Data availability
It is a review and the references are listed.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Ethical Approval is not required for this article.

Received: 11 November 2024 / Accepted: 30 December 2024
Published online: 13 January 2025

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