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Review

Review

Novel strategy for oncogenic alteration-induced lipid metabolism reprogramming in pancreatic cancer

Duancheng Guo[1,2,3,4,†], Longyun Ye[1,2,3,4,†], Weiding Wu[1,2,3,4,*], Xianjun Yu[1,2,3,4,*], and Kaizhou Jin[1,2,3,4,*]

[1]Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China, [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China, [3]Shanghai Pancreatic Cancer Institute, Shanghai 200032, China, and [4]Pancreatic Cancer Institute, Fudan University, Shanghai 200032, China

[†]These authors contributed equally to this work.

*Correspondence address. Tel: +86-21-64031446; E-mail: wuweiding@fudanpci.org (W.W.) / E-mail: yuxianjun@fudanpci.org (X.Y.) / E-mail: jinkaizhou@fudanpci.org (K.J.)

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Abstract

The pathogenesis of pancreatic cancer involves substantial metabolic reprogramming, resulting in abnormal proliferation of tumor cells. This tumorigenic reprogramming is often driven by genetic mutations, such as activating mutations of the *KRAS* oncogene and inactivating or deletions of the tumor suppressor genes *SMAD4*, *CDKN2A*, and *TP53*, which play a critical role in the initiation and development of pancreatic cancer. As a normal cell gradually develops into a cancer cell, a series of signature characteristics are acquired: activation of signaling pathways that sustain proliferation; an ability to resist growth inhibitory signals and evade apoptosis; and an ability to generate new blood vessels and invade and metastasize. In addition to these features, recent research has revealed that metabolic reprogramming and immune escape are two other novel characteristics of tumor cells. The effect of the interactions between tumor and immune cells on metabolic reprogramming is a key factor determining the antitumor immunotherapy response. Lipid metabolism reprogramming, a feature of many malignancies, not only plays a role in maintaining tumor cell proliferation but also alters the tumor microenvironment by inducing the release of metabolites that in turn affect the metabolism of normal immune cells, ultimately leading to the attenuation of the antitumor immune response and resistance to immunotherapy. Pancreatic cancer has been found to have substantial lipid metabolism reprogramming, but the mechanisms remain elusive. Therefore, this review focuses on the mechanisms regulating lipid metabolism reprogramming in pancreatic cancer cells to provide new therapeutic targets and aid the development of new therapeutic strategies for pancreatic cancer.

Key words pancreatic cancer, lipid metabolism reprogramming, tumor microenvironment, immune escape, drug resistance

Introduction

Pancreatic cancer is a malignant tumor of the digestive tract with high mortality. The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), accounting for 90% of cases [1]. Because the early symptoms of pancreatic cancer are not obvious and it has a rapid onset, the 5-year survival rate of patients with pancreatic cancer is only 11%, making it the third deadliest cancer in the United States; pancreatic cancer is predicted to become the second deadliest cancer within 5 years [2,3]. Currently, aggressive treatment, including surgical resection (usually the first choice), neoadjuvant chemotherapy, and radiotherapy, is the main treatment used in the clinic. However, only 20% of patients are eligible for surgical resection at diagnosis, and even in those who are eligible for and undergo surgery, 80% of patients eventually relapse, and relapsed PDAC is almost always fatal [4,5]. Chemotherapy is the recommended primary treatment for patients who cannot undergo surgery, but its efficacy is suboptimal due to the rapid emergence of drug resistance and severe side effects [6,7]. Hence, it is essential to explore the molecular mechanisms of pancreatic cancer evolution and develop new strategies for

pancreatic cancer diagnosis and treatment.

The most common hallmark of pancreatic cancer is mutation of an oncogene. Molecular analyses have revealed four major PDAC driver genes that are commonly mutated: *KRAS* (∼85%), *TP53* (60%–70%), *CDKN2A* (>50%), and *SMAD4* (∼50%) [8]. Genetic analysis of clinical specimens revealed that mutations in the *KRAS* oncogene are found in more than 90% of pancreatic cancers and are an early event of stage 1 pancreatic intraepithelial neoplasia (PanIN). Inactivation and deletion of the tumor suppressor genes *SMAD4*, *CDKN2A*, and *TP53* are associated with PanIN progression and invasiveness [9,10]. Somatic gene mutations increase the malignant potential of tumor cells and activate multiple signaling pathways, such as the NOTCH, Hedgehog (Hh), β-catenin, chromosomal reorganization and DNA repair pathways, promoting the proliferation of tumor cells (Figure 1). This suggests that the KRAS signaling pathway, a key driver of PDAC initiation, is a prime target for the development of inhibitors; however, it is difficult to develop therapeutic KRAS inhibitors [11,12]. Small molecule inhibitors of the KRAS G12C mutation sotorasib and adagrasib are under clinical investigation [13,14]. In addition, novel drugs need to target pathways that indirectly affect KRAS to treat pancreatic cancer.

The occurrence and development of tumors are complex biological processes with multiple mechanisms and factors. In recent years, reprogramming of energy metabolism has attracted increasing attention in cancer research. It may be an important factor for tumor cell proliferation and is beginning to be recognized as a hallmark of cancer [15,16]. Tumor metabolic reprogramming is not only limited to the Warburg effect, which is related to glycolysis and the tricarboxylic acid cycle but also involves more complex metabolic processes, such as fatty acid and glutamate metabolism [17]. Previous studies have confirmed that abnormal lipid metabolism is one of the hallmarks of malignant tumors and an important potential target for tumor therapy [18]. Energy storage, organelle and membrane maintenance, and the generation of signaling molecules in tumor cells all require fatty acid metabolism to generate energy [18]. Normal cells mainly use fatty acids derived from food, while 90% of the fatty acids used by tumor cells are derived from *de novo* synthesis, and fatty acid oxidation is enhanced to meet the needs of tumor cells in an unfavorable living environment [19]. Recent studies have shown that lipid and cholesterol accumulation increase drug resistance and promote epithelial-mesenchymal transition (EMT) in basal-type PDAC, resulting in poor outcomes of patients [20,21].

The success of pancreatic cancer immunotherapy shows the important role of the immune system in preventing the progression of tumors, and immunotherapy has become an important treatment method in addition to traditional therapy; however, an immunosuppressive tumor microenvironment is still an obstacle limiting the efficacy of tumor immunotherapy [22,23]. Reprogramming of tumor metabolism affects both immune cells and tumor growth by inducing the release of metabolites such as lactate and PGE. These effects cause metabolic competition and generate an acidic and hypoxic tumor immune microenvironment with high levels of reactive oxygen species, ultimately weakening antitumor immune responses and enabling immune escape [24–26]. Therefore, understanding how metabolic reprogramming modulates antitumor immune responses will help reveal new ideas for targeting metabolic pathways for antitumor immunotherapy.

Gene Mutations Related to Pancreatic Cancer Development and Maintenance

The occurrence and development of pancreatic cancer are generally attributed to the accumulation of genetic alterations, which leads to the activation of oncogenes and the inactivation of tumor suppressor genes. PDAC caused by malignant transformation of the ductal epithelium accounts for approximately 90% of pancreatic cancer cases. The frequency of *KRAS* mutations in PDAC is up to 85%, and *KRAS* is considered a major oncogene that regulates cell proliferation and survival pathways. The high incidence of *KRAS* mutations suggests that therapies targeting the *KRAS* signaling network may be an effective treatment for PDAC. In this section, we summarize the role of *KRAS* in pancreatic cancer, treatment options developed to target *KRAS* mutations, and related challenges. We also discuss other common genetic mutations in PDAC and their effects.

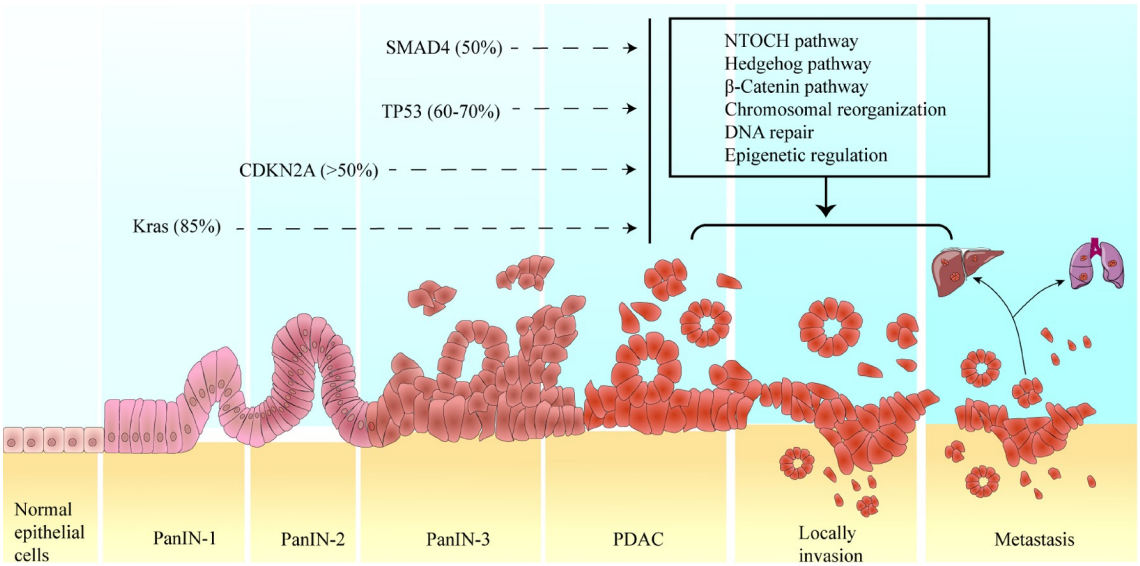

Figure 1. Oncogenic mutations and regulatory mechanisms in the development of pancreatic cancer

KRAS mutations in pancreatic cancer

KRAS is a Kirsten rat sarcoma viral oncogene homolog belonging to the mammalian *RAS* gene family. It encodes the KRAS protein, a member of the small GTPase superfamily, which is activated upon binding to GTP and is inactivated upon binding to GDP [27]. The activated GTP-bound state and inactivated GDP-bound state of KRAS are strictly regulated by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) [28,29]. The former catalyzes the formation of the active GTP-bound state, while the latter induces GTP hydrolysis to terminate signaling. In quiescent cells, KRAS is mainly present in the inactive GDP-binding state. When cellular transmembrane receptors, such as epidermal growth factor receptor (EGFR), are activated by stimulation signals, GDP is converted into GTP. Once the KRAS protein binds to GTP, the signaling switch is triggered, and KRAS can interact with numerous downstream effector proteins to activate various intracellular signaling pathways related to cell proliferation, migration, transformation, and survival. The ability of mutant *KRAS* to hydrolyse GTP is impaired, leading to an abnormal hyperactive state. In PDAC, point mutations in codon 12, in which glycine is substituted with another amino acid, are the most common *KRAS* mutations: glycine to aspartic acid mutation (G12D, 45%), glycine to valine mutation (G12V, 35%), and glycine to arginine mutation (G12R, 17%) [30–33]. Uncommon mutations, such as G13 and K117 mutations, also occur. These missense mutations cause *KRAS* to be in an abnormally active state, with consequent activation of some key downstream effector pathways, including the RAF-MEK-ERK pathway and the PI3K-AKT-mTOR pathway [34]. Many recent studies have shown that mutant *KRAS* signaling contributes to the development and maintenance of pancreatic cancer and participates in regulating the survival and metastasis of pancreatic cancer cells, tumor microenvironment remodelling, and the occurrence of metabolic disorders.

Role of *KRAS* in the development of pancreatic cancer

KRAS mutations have been identified early in PDAC development. For example, genetic analysis of clinical specimens revealed that *KRAS* mutations were already present in precancerous lesions, such as PanINs and intraductal papillary mucinous neoplasms (IPMNs), suggesting a role for those mutations in the initiation of pancreatic cancer [35]. Furthermore, additional mutations in other genes, such as inactivating mutations and deletions of the tumor suppressor genes *SMAD4*, *CDKN2A*, and *TP53*, are also required for tumor progression [36]. On one hand, *KRAS* mutations have been shown to alter many biological processes in pancreatic cancer cells, resulting in, for example, increased cell proliferation, survival, migration, and invasion and contributing to cell chemoresistance and inflammation. Furthermore, the MAPK signaling pathway was proven to be required for the formation of PanINs in mice because it promotes the dedifferentiation of acinar cells into duct-like cells, which are easily transformed [37]. In a high-fat diet-fed mouse model, oncogenic *KRAS* caused decreased expression of fibroblast growth factor 21, a metabolic regulator that prevents obesity, in acinar cells, and the mice developed extensive inflammation, pancreatic cysts, PanINs and PDAC [38]. The ERK1-MAPK pathway is associated with the resistance of pancreatic cancer cells to chemotherapeutic drugs, such as gemcitabine [39]. The nuclear factor-κB (NF-κB) pathway is related to the invasion and metastasis of pancreatic cancer cells and promotes tumor initiation, tumor cell self-renewal and erlotinib resistance [40]. On the other hand, *KRAS* mutations have been found to alter aspects of the pancreatic cancer microenvironment, such as immune cell infiltration and extracellular matrix structure. Cancer-associated fibroblasts (CAFs), various immune cells, extracellular matrix components, blood vessels and lymph-vessel networks constitute the stromal component of pancreatic tumors and play a dual role in tumor development and metastasis. In general, the mutual crosstalk between tumor cells and CAFs promotes the development of pancreatic cancer, and the Hedgehog signaling pathway is a key regulator. KRAS-mutant pancreatic cancer cells secrete Hedgehog ligands that act on Hedgehog receptor-expressing CAFs, and CAFs in turn promote the growth of pancreatic cancer cells by regulating the extracellular matrix, hyaluronic acid, collagen fibres and other factors [41,42]. Furthermore, *KRAS* mutations are also associated with immunosuppressive cell infiltration in the pancreatic cancer microenvironment. The KRAS G12D mutation induces the conversion of $CD4^+CD25^-$ T cells into regulatory T cells (Tregs) by upregulating the expressions of IL-10 and transforming growth factor-β [43,44]. This effect is achieved via the activation of the MEK/ERK pathway. Upon the induction of oxidative stress, the KRAS G12D protein in cancer cells can also be released from cancer cells into the surrounding microenvironment and then taken up by macrophages. Through STAT3-dependent fatty acid oxidation, *KRAS* G12D causes the transformation of macrophages into an M2-like protumor phenotype [45]. Pancreatic cancer cells bearing oncogenic activated KRAS release IL-4, IL-6, IL-13, MCP-1, and CSF-1, which also promotes the recruitment, aggregation, and accumulation of tumor-associated macrophages (TAMs) at tumor sites and induces their polarization into an immunosuppressive phenotype [46]. A high-fat diet combined with KRAS mutation can also induce CCL2 secretion from pancreatic epithelial cells and promote the recruitment of myeloid-derived inhibitory cells and protumor macrophages in a peroxisome proliferator-activated receptor-delta-dependent manner [47]. Through the mechanisms described above, KRAS mutations significantly increase the infiltration of protumor cells in pancreatic cancer, favoring immune escape and tumor progression. Moreover, *KRAS* mutations also contribute to metabolic disorders. It is generally believed that cancer cells take up more glucose than normal cells and prefer aerobic glycolysis to produce lactate, even in the presence of oxygen, which is called the Warburg effect [48]. The *KRAS* G12D mutation alters multiple metabolic pathways. On one hand, KRAS mutations increase glucose uptake and lactate production by increasing the expression of glucose transporters (such as Glut1/SLC2A1), key glycolytic enzymes (such as Hk1 and Hk2), and enzymes of the hexosamine pathway and nonoxidized pentose phosphate pathway via activation of the MAPK and Myc signaling pathways, thus facilitating the survival of pancreatic cancer cells in a hypoxic environment [34,49,50]. In addition to its importance for central carbon metabolism, glutamine is also a valuable and important fuel for tumors. *KRAS* mutations can stimulate glutamine metabolism by inhibiting glutamate dehydrogenase and by activating aspartate aminotransferase, which is critical for pancreatic cancer growth, development and maintenance [51]. Proliferating cells require fatty acid synthesis to produce lipids, which are used in processes such as membrane synthesis and energy generation [18]. In conclusion, the above findings demonstrate that oncogenic *KRAS* mutations promote the initiation, development and maintenance of pancrea-

tic cancer in multiple ways, and therefore, targeting KRAS signaling for the treatment of pancreatic cancer is reasonable (Figure 2).

KRAS targeting strategies and challenges

Strategies targeting KRAS as a treatment for pancreatic cancer have been widely studied, but there are substantial challenges. Current strategies mainly include directly targeting KRAS and targeting proteins upstream and/or downstream of KRAS signaling pathways. KRAS was once considered untargetable because of its high affinity for GTP, which prevented the development of competitive inhibitors of GTP binding. However, in recent years, a switch-II pocket in KRAS G12C was found to bind to a series of covalent small molecule inhibitors, causing the destruction of the switch-I and switch-II regions of KRAS, thereby locking KRAS in a GDP-bound inactive state and preventing downstream signaling [52]. Since the initial success of these selective small-molecule inhibitors targeting the *KRAS* G12C mutation, more potent covalent inhibitors, such as sotorasib [53], MRTX849 [54], JNJ-74699157 and LY3499446, have been developed. MRTX849 as a treatment for pancreatic cancer is currently being tested in clinical trials, and one patient in the phase I/Ib cohort had a partial response (NCT03785249) [55]. Epidermal growth factor (EGF) signaling stimulates KRAS activation. The binding of EGF to the EGF receptor (EGFR) on the cell membrane stimulates the phosphorylation of SHC, which complexes with the GEF son of sevenless (SOS) and growth factor receptor-bound protein 2 (GRB2) to promote the binding of GEFs to KRAS, causing KRAS to exist in the activated GTP-bound state [56]. However, first-generation EGFR inhibitors, represented by gefitinib and erlotinib, have shown very limited efficacy [57,58]. This may be due to other resistance mechanisms in pancreatic cancer that allow bypass of EGFR inhibition or resistance resulted from the non-EGFR members of the ERBB family which includes four receptor tyrosine kinases [59]. Irreversible tyrosine kinase inhibitors that can inhibit the activation of all members of the ERBB family, such as afatinib and neratinib, have also been developed and are currently being tested in clinical trials [60–62]. The RAF-MEK-ERK MAPK pathway and the PI3K-AKT-mTOR pathway are the most characteristic downstream signaling pathways of KRAS and are the focus of work to develop drugs targeting various KRAS mutations. However, currently available RAF inhibitors, such as vemurafenib and dabrafenib, have not shown therapeutic efficacy in KRAS-mutant cancers and are even thought to promote tumor development [63,64]. Clinical trials of MEK inhibitors such as selumetinib and

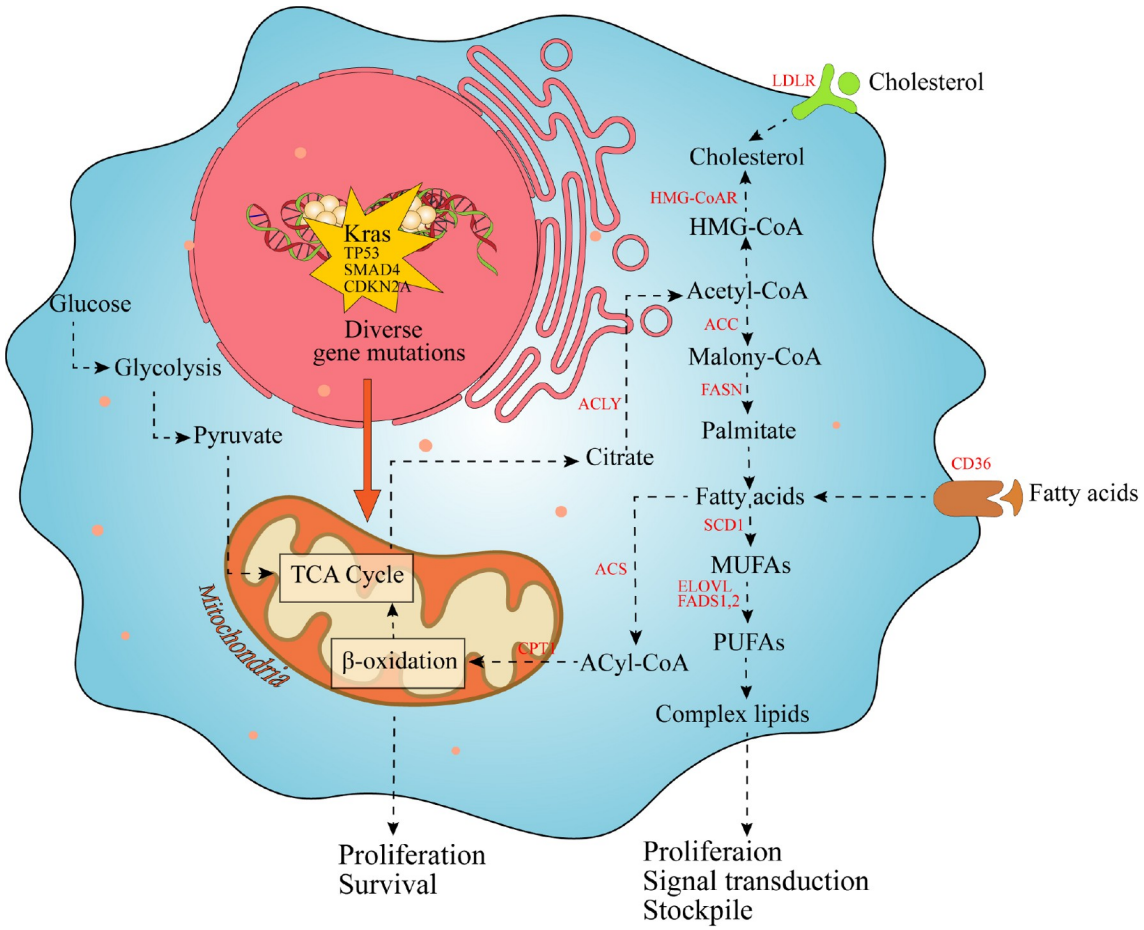

Figure 2. *KRAS* mutations in pancreatic cancer are involved in many biological processes On one hand, through the downstream RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways, *KRAS* mutations increase the proliferation and survival ability of pancreatic cancer cells, contributing to immune escape and drug resistance and leading to metabolic reprogramming. On the other hand, various substances secreted by pancreatic cancer cells caused by KRAS mutations change the tumor immune microenvironment (substances such as IL-4, IL-6, IL-10, IL-13, KrasG12D protein, TGF-β, MCP-1, CSF-1, and CCL2) and extracellular matrix structure (such as Hedgehog ligand and TGF-β) and contribute to tumor angiogenesis (such as VEGF).

trametinib in patients with advanced pancreatic cancer have also failed [65,66]. In addition, although everolimus, an mTOR inhibitor, significantly prolonged progression-free survival and decreased the severe adverse event rate in patients with progressive pancreatic neuroendocrine tumors in a phase III clinical trial [67], PI3K inhibitors are not used in the treatment of pancreatic cancer [68,69]. Despite decades of intensive efforts, no breakthroughs have been achieved in treating pancreatic cancer by targeting KRAS. This is due in part to the multiple alternative signaling pathways linked to KRAS, which may be activated when another is inhibited.

Other common gene mutations in pancreatic cancer

TP53 is a tumor suppressor gene whose encoded product (the P53 protein) plays an important role in the response to cellular stress and in the modulation of the cell cycle, cell apoptosis and cell metabolism [70]. Mutations in TP53 occur in 60%–70% of PDAC cases; these mutations lead to activation of the cell cycle, loss of cell apoptosis regulation and enhanced metabolism and reshape the tumor microenvironment to promote cancer development. *SMAD4*, also known as *DPC4*, is also a tumor suppressor gene, and *SMAD4* mutation occurs in approximately 50% of pancreatic cancers. The SMAD family plays an important role in mediating transforming growth factor (TGF)-β signal transduction [71,72]. When phosphorylated by activated TGF-β family receptors, SMAD4 migrates to the nucleus in the form of heterodimeric SMAD2/SMAD3-SMAD4 complexes and interacts with downstream proteins, leading to cell growth inhibition [73]. *SMAD4* mutations lead to the loss of activated proteins, attenuating the tumor suppressor function of the TGF-β pathway, and are associated with metastasis and related epithelial-mesenchymal transformation of tumor cells. *CDKN2A* encodes a protein that controls the G1/S checkpoint [74]. By inhibiting cyclin-CDK4 and cyclin-CDK6 complexes, which are associated with the G1/S phase transition, CDKN2A regulates cell cycle progression. Alterations in the *CDKN2A* gene have been found in >50% of pancreatic cancer cases. CDKN2A inactivation acts synergistically with *KRAS* mutations to promote malignant progression of pancreatic cancer. Generally, mutations in *KRAS* and *CDKN2A* occur during carcinogenesis and before invasion into the pancreatic parenchyma, whereas TP53 and Smad4 inactivation are relatively later events [75,76]. In addition, some low-frequency mutations have been reported in the development of pancreatic cancer, such as mutations in genes involved in the DNA damage response (*ATM* and *BRCA2*) and epigenetic regulation (*ARID1A*, *ARID1B*, *SMARCA1*, *MLL2*, *MLL3*, and *KDM6A*). The occurrence of pancreatic cancer may involve the accumulation of mutations in multiple genes [77,78].

Lipid Metabolism Reprogramming in Pancreatic Cancer and its Effect

Developing therapeutic KRAS inhibitors is a challenging process, so existing drugs and strategies that indirectly target KRAS should be explored for pancreatic cancer treatment. Metabolic reprogramming is one of the hallmarks of tumors and an important potential target for tumor therapy. During tumorigenesis and tumor progression, cancer cells need to reprogram their catabolic and anabolic processes to survive and grow; among these processes, lipid metabolism reprogramming is prominent. Research has identified that abnormal lipid metabolism contributes to pancreatic cancer, but the precise mechanism has not been explained in detail. This section reviews the research progress in understanding the role of lipid metabolism reprogramming and other regulatory mechanisms in the development of pancreatic cancer.

Lipid metabolism reprogramming in pancreatic cancer

Lipids are one of the three major nutrients and metabolites in the human body and play significant physiological roles in cells, for example, constituting the basic structure of cell membranes, storing energy, acting as signal molecules, and synthesizing hormones. There are generally two types of lipids that can be taken up by normal mammalian cells: one type is derived from food (free fatty acids or complexes formed with low-density lipoprotein, among other things), and the other type is derived from synthesis in the body (a small proportion). However, the lipids in tumor cells are mainly derived from tumor cell synthesis [79]. The process includes the following main characteristics: the *de novo* synthesis of fatty acids is increased, while the oxidation of fatty acids is decreased to meet the needs of tumor cell proliferation. The upregulation of lipid metabolism-related proteins and enzymes promotes malignant tumor progression (Figure 3) [80–82]. *De novo* fatty acid synthesis is first catalyzed by ATP citrate lyase (ACLY) to generate acetyl coenzyme A (acetyl-CoA); then, acetyl-CoA is carboxylated by acetyl-CoA carboxylase (ACC) to generate malonyl coenzyme A (malonyl-CoA). Subsequently, acetyl-CoA and malonyl-CoA are coupled to the acyl carrier protein (ACP) domain to generate fatty acid synthase (FAS). Finally, FAS catalyzes malonyl-CoA to generate palmitate in a process that involves changes in the levels of a variety of rate-limiting enzymes, mainly including increased expression of ACLY, ACC and FAS [83]. Among these enzymes, ACLY is the first enzyme in the *de novo* synthesis of fatty acids and a key enzyme linking the glycolysis and lipid metabolism pathways. ACLY is highly expressed in PDAC, and ACLY expression is negatively correlated with the prognosis of patients. *In vitro* cell experiments have shown that downregulating the expression of endogenous ACLY by siRNA can reduce the activity of pancreatic cancer cells and induce apoptosis [84]. In addition, ACLY expression in lung cancer tissue is higher than that in normal lung tissue and is associated with tumor stage, degree of differentiation and prognosis [85,86]. A previous study has also found that ACLY can regulate colon cancer invasion and metastasis through CTNNB1 and play an important role in colon cancer progression [87], which indicates that ACLY is associated with tumor progression. High expression of ACC can be detected in early-stage breast cancer, prostate cancer and hepatocellular carcinoma, and the phosphorylation level of ACC is closely related to tumor metastasis. ACC inhibitors are effective in cancer treatments [88,89]. Another study showed that inhibition of ACC can attenuate WNT and Hedgehog signaling pathways, suppress pancreatic cancer tumor growth, and induce apoptosis of the pancreatic cancer cell lines AsPC-1, BxPC-3, and PANC-1 [90,91]. Another key enzyme in *de novo* fatty acid synthesis is FAS. Upregulation of FAS expression is a very common feature of human cancer and precancerous lesions and is closely related to chemotherapy resistance, tumor metastasis and poor patient prognosis. Previous studies have shown that the upregulation of FAS expression can be used as a marker for the clinical diagnosis of pancreatic cancer [92–95]. These findings suggest that controlling rate-limiting enzymes in fatty acid synthesis can effectively inhibit tumor growth and may be a strategy for pancreatic cancer therapy. In addition to supplying phospholipids

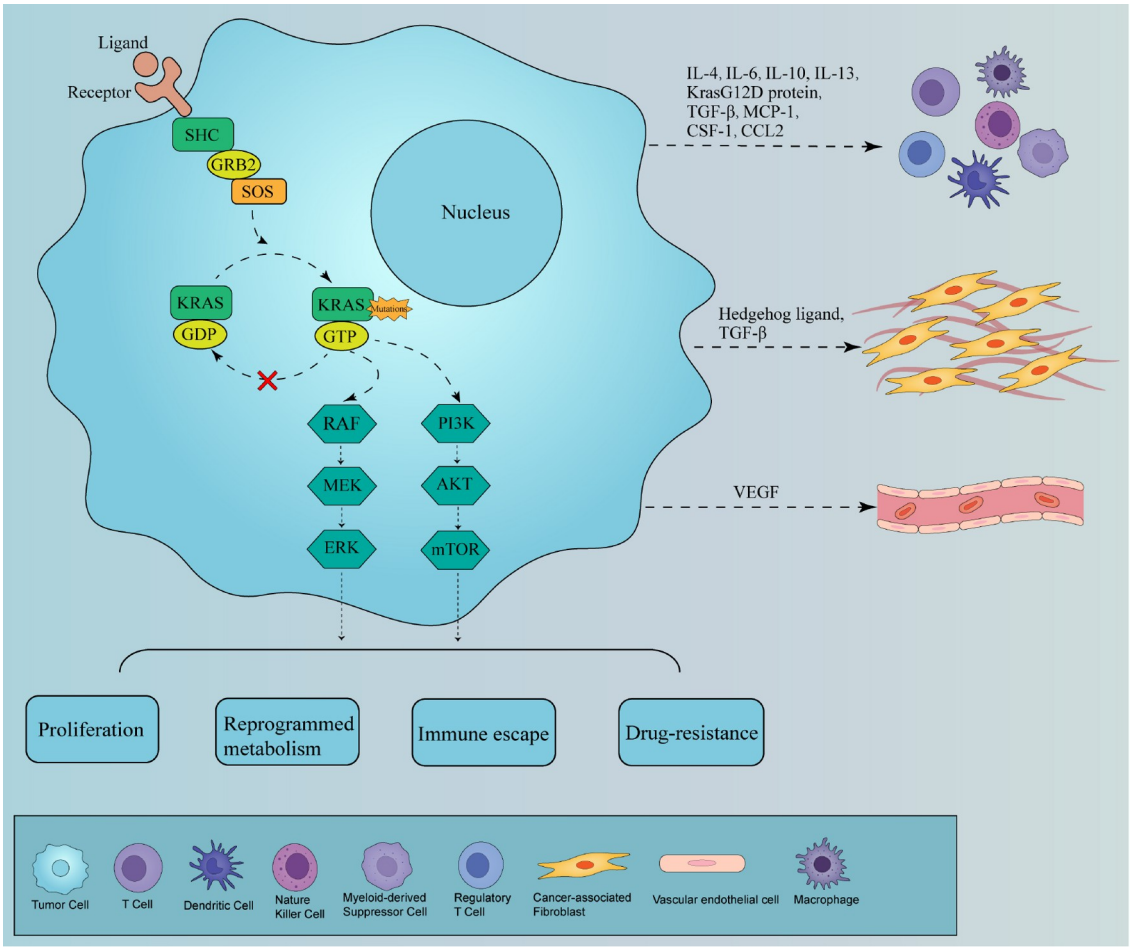

Figure 3. Gene mutations cause reprogramming of lipid metabolism in pancreatic cancer cells to meet their proliferation needs This is reflected in the increased de novo synthesis of fatty acids, enhanced activities of various rate-limiting enzymes, and upregulated expression of receptors for transporting exogenous cholesterol and lipid droplets. The synthesized lipids satisfy the proliferation and survival of pancreatic cancer and signal transduction.

and signaling molecules necessary for cell proliferation, fatty acids synthesized by tumor cells enter mitochondria to undergo β-oxidation, which is an important process that provides energy for tumor cell proliferation. Although fatty acid oxidation (FAO) is typically enhanced in other tumors, it is decreased in PDAC due to the unique tumor microenvironment of pancreatic cancer, and the reduction in fatty acid consumption is conducive to tumor cell proliferation and migration [96,97]. Carnitine palmitoyl transferase (CPT) is a rate-limiting enzyme in FAO, and there are two types: CPT1 and CPT2. CPT1 transports fatty acids into mitochondria for β-oxidation. Overexpression of CPTs in the pancreatic cancer cell lines CFPAC-1, BxPC-3, and PANC-1 inhibits tumor growth and increases sensitivity to the chemotherapeutic drug gemcitabine, whereas inhibition of CPT expression promotes pancreatic cancer progression [98]. In tumor cells, an increase in FAO occurs simultaneously with an increase in *de novo* synthesis of fatty acids. CPT1 is a key enzyme in the FAO process. Fatty acids are first activated to generate fatty acyl-CoA and then transported by CPT1 to mitochondria for FAO. After dehydrogenation, water addition, redehydrogenation and thiohydrolysis, acetyl-CoA is generated and enters the tricarboxylic acid cycle. The above process not only generates ATP to supply energy to cells but also prevents lipid toxicity caused by excessive accumulation of lipids. The generated acetyl-CoA enters the cytoplasm and participates in the metabolic reaction to produce NADPH, which generates a large amount of NADPH to support cell redox homeostasis, thus preventing oxidative damage to tumor cells [99]. FAO plays a key role in tumor cell proliferation and chemotherapy resistance. Inhibition of FAO in mitochondria affects the production of NADPH, increases the production of reactive oxygen species, promotes the consumption of ATP in tumor cells, and results in cell death [100]. Targeting CPT1, a key enzyme in the FAO pathway, can enhance the radiotherapy effect in nasopharyngeal carcinoma patients [101]. Studies have shown enhanced reprogramming of mitochondrial FAO in breast cancer, and the expression of CPT1A/CPT2 is increased in recurrent breast cancer, which is associated with poor prognosis of breast cancer patients [102]. These findings indicate that fatty acid metabolism in cancer cells can be reprogrammed according to cellular energy and nutrient needs to ensure tumor survival.

Gene mutations mediate reprogramming of lipid metabolism in pancreatic cancer

Data from a mouse model of *KRAS*-driven pancreatic cancer show that mutationally activated *KRAS* can not only drive pancreatic

carcinogenesis but also synergize with genetic alterations to reprogram lipid metabolism to promote tumor cell proliferation. The study found that *KRAS* mutation cooperates with signal transduction *GNAS* gene mutation in PDAC, and *GNAS* gene mutation can support PDAC growth by inducing salt-inducible kinases (SIKs). Proteomic studies have shown that this pathway is associated with lipid metabolism and increased content of peroxisomes, organelles required for long-chain fatty acid processing and ether lipid production [103]. Normal cell growth requires the coordinated synthesis of biological macromolecules, and a kinase complex, mammalian target of rapamycin complex 1 (mTORC1), was recently reported to sense nutrient availability and energy supply and regulate the activity of sterol regulatory element binding proteins (SREBPs) to control the synthesis of fatty acids and cholesterol [104–106]. There are three subtypes of SREBPs: SREBP1a, SREBP1c, and SREBP2 [107]. Ferroptosis is another form of cell death that depends on the accumulation of iron and reactive oxygen species in the cell, which causes lipid peroxidation [108,109]. The FBW7-NRA41-SCD1 axis synchronously regulates apoptosis and ferroptosis in pancreatic cancer cells. FBW7 functions as a tumor suppressor by targeting oncoproteins for degradation. Zeng *et al.* [7] found that FBW7-downregulated genes are widely involved in the redox reaction and lipid metabolism. FBW7 regulates lipid peroxidation and promotes cell apoptosis. Further mechanistic studies showed that FBW7 inhibits the expression of stearoyl-CoA desaturase (SCD1) by inhibiting Group 4A member 1 (NR4A1) of the nuclear receptor subfamily. Overexpression of stearoyl-CoA desaturase (SCD) in pancreatic cancer can induce resistance to apoptosis and ferroptosis triggered by hypoxia and nutrient deprivation, resulting in poor prognosis of pancreatic cancer [110,111]. Moreover, increased ferroptosis induced by lipid metabolism inhibits gemcitabine resistance in pancreatic cancer [112]. SREBP1 can affect the expression of SCD, inhibit tumor growth, and affect the occurrence and prognosis of pancreatic cancer [113,114]. The KRAS gene controls the levels of cholesterol in cancer cells, and cholesterol is the major component of synthetic hormones and biofilms. Previous studies have found that KRAS promotes the growth and metastasis of pancreatic cancer by upregulating the expressions of the transcription factors TFCP2 and SREBP2. SREBP2 can also upregulate hydroxy-methyl glutaryl coenzyme A reductase (HMGR), resulting in an increase in cholesterol synthesis and further upregulation of low-density lipoprotein receptor (LDLR) expression to increase endocytic cholesterol uptake [115,116]. The total serum cholesterol (TSC) level is an important predictor of pancreatic cancer prognosis and affects the Hedgehog and STAT3 signaling pathways to promote the proliferation of pancreatic cancer cells [117–119]. These findings suggest that inhibition of cholesterol metabolism can regulate pancreatic cancer progression. Statins can inhibit the biosynthesis of cholesterol and are not only widely used in cardiovascular disorders to treat hyperlipidemia and atherosclerosis but also show good effects in inhibiting tumor growth [120–122]. In cell experiments, statins inhibited the Akt/PKB signaling pathway through the P27X receptor, inhibited the proliferation of the pancreatic cancer cell lines PANC-1 and MIA PaCa-2, and increased the sensitivity to chemotherapy. *In vivo* experiments have shown that statins can induce the differentiation of pancreatic cancer cells of the basal phenotype in *KRAS* mutant mice by disrupting cholesterol synthesis [21,123]. KRAS can also upregulate lipid metabolism enzymes, such as acyl-coenzyme A synthetase long chain family members 3 and 4 (Acsl3 and Acsl4), to increase FAO in a mouse model. Acsl3 can promote fatty acid absorption and retention and β-oxidation and convert fatty acids into acyl-CoA [124]. KRAS can also control hormone-sensitive lipase (HSL) to regulate the accumulation and utilization of lipid droplets (LDs) and to regulate the invasive ability of pancreatic cancer [125]. Pancreatic cancer tumors have dense tissue, poor blood supply, hyperoxidation and inflammation. In such a harsh environment, tumor cells must change their metabolism to achieve rapid growth [126]. Glycerophospholipids are an important component of the cell membrane, and lysophospholipids are the metabolic intermediates of glycerophospholipids. The decrease in plasma lysophospholipid levels in patients with pancreatic cancer suggests that lysophospholipids may reduce the risk of pancreatic cancer, which may be due to the increased catabolism of lysophospholipids in pancreatic cancer cells and the abnormal liver function associated with cancer [127–131]. Bile acid is an important component of bile, and there is evidence that bile acid plays an important role in the development of gastrointestinal malignancies. The serum levels of taurocholic acid, bile acid and glycholic acid in patients with pancreatic cancer are significantly increased. Therefore, serum bile acid levels may be an important diagnostic marker in the identification of patients with pancreatic cancer [132,133]. Rozeveld *et al.* [125] reported that the oncogene KRAS controls the storage and utilization of lipid droplets in cells by regulating hormone-sensitive lipase. In pancreatic cancer cells, the destruction of the Kras-hormone-sensitive lipase axis leads to the storage of excessive lipid droplets in cells, and excess fatty acids enhance the growth and metastasis of cancer cells. In summary, gene mutations can alter lipid metabolism to sustain pancreatic cancer growth. These findings suggest that patients with pancreatic cancer who receive metabolism-modulating treatments may have significantly improved outcomes. Therefore, the study of lipid metabolism is not only beneficial for understanding the progression of pancreatic cancer but also helpful to provide new perspectives for the treatment of pancreatic cancer.

Crosstalk related to lipid metabolism reprogramming within the tumor microenvironment

The tumor microenvironment has been widely accepted to increase the metabolic reprogramming of tumor cells, providing a favorable environment for tumor growth and survival [134]. The tumor microenvironment comprises an immune microenvironment dominated by immune cells and a nonimmune microenvironment dominated by tumor cells and fibroblasts [135]. In recent years, the effect of lipid metabolism on immune cell function has been a focus of research in the field of oncology [136,137]. In normal cells, a stable network formed by factors related to the metabolism of the three major nutrients supports cell growth and function. In the tumor microenvironment, tumor cells are surrounded by layers of different types of cells, including interstitial cells and immune cells, nerve fibres and extracellular matrix. These factors influence tumor cells, generating a hypoxic or nutrient-deprived environment, which forces tumor cells to reprogram their metabolism to absorb enough nutrients from the microenvironment to resist killing by immune cells [138–140]. Lipid metabolism reprogramming in tumor cells is not only driven by the needs of the tumor cells themselves but also regulated by other cells; furthermore, it affects the function

and metabolism of surrounding cells, of which immune cells are the main affected cell population. Previous studies have found that microenvironment immunosuppression mediated by metabolic reprogramming is a key factor limiting immunotherapy efficacy. Abnormal lipid metabolism is closely related to the effector function of immune cells [141–144]. The unique lipid requirements of tumor cells increase the lipid levels in the tumor microenvironment, and a lipid-rich tumor microenvironment further affects the characteristics of immune cells, such as their proliferation, differentiation and execution of cellular functions [145,146]. In immune cells, increased expression of lipid metabolism-related enzymes, such as ACC, the fatty acid transferase CD36, CPT1A, FAS, and SCD1, affects the type of lipids and triggers the accumulation of LDs in cells, thereby affecting the status and function of immune cells [142,147]. The expression of ACC is significantly upregulated in breast and prostate cancers, and inhibition of ACC can reduce the differentiation of T cells expressing interleukin 17 (IL-17) and promote the differentiation of Tregs and tumor cell apoptosis [148]. CD36 can recognize many endogenous ligands, transport fatty acids into cells and activate FAO. Increased CD36 expression in tumors can prevent $CD8^+$ T cells from producing cytokines and support Treg survival, thereby decreasing antitumor function. Upregulation of CD36 and FAS expression in T cells is correlated with tumor progression and poor prognosis [149–151]. Increased expression of CPT1A in macrophages promotes fatty acid transport into mitochondria to promote β-oxidation, resulting in a decrease in the levels of proinflammatory cytokines secreted by macrophages. Moreover, inhibitors of CPT1A can suppress Treg differentiation and tumor cell proliferation [152,153]. In addition, while tumor cells have their own metabolic characteristics, their metabolites can also affect the activation of immune cells and induce antitumor immune responses in a variety of ways [24]. Ultimately, the microenvironment is transformed into a place that supports the proliferation and development of tumor cells.

The pancreatic cancer tumor microenvironment contains various types of immune cell subsets, including $CD4^+$ T cells, $CD8^+$ T cells, B cells, dendritic cells (DCs), macrophages, and natural killer (NK) cells [154]. Among them, DCs, $CD4^+$ and $CD8^+$ effector T cells, and NK cells are activated to inhibit tumors and prevent immune escape, while other immune cells, such as tolerogenic dendritic cells (tDCs), Tregs, and TAMs, inhibit the antitumor immune response, thereby promoting tumor cell proliferation, invasion, metastasis and angiogenesis [155–160]. Tumor tissue is infiltrated by immune cells (mainly lymphocytes), which are generally thought to attack tumor cells. However, researchers have found that tumor-infiltrating lymphocytes can promote tumor metastasis, resulting in poor prognosis of pancreatic cancer patients [161]. Tregs are an important type of tumor-infiltrating lymphocyte and are a special class of $CD4^+$ T cells that promote tumor growth and invasion by suppressing host immune responses and proinflammatory responses. Forkhead transcription factor 3 (FoxP3) belongs to the Forkhead family of transcriptional regulators. FoxP3 can inhibit the expression of target immune genes and is one of the most specific markers of Tregs in tumors [162]. $FoxP3^+$ Tregs and $CD8^+$ T cells are the two main T-cell populations in the tumor microenvironment. $FoxP3^+$ Tregs disrupt the antitumor immune response by inhibiting the function of cytotoxic T lymphocytes, thereby allowing pancreatic cancer cells to escape immune surveillance, and higher levels of $FoxP3^+$ Tregs are associated with lower overall survival and recurrence in pancreatic cancer patients [163]. Abnormal angiogenesis and activation of inhibitory checkpoint pathways in the tumor microenvironment create an immunosuppressive microenvironment, which prevents $CD8^+$ T cells from infiltrating the tumor. However, $CD8^+$ T cells may directly lead to tumor cell apoptosis by releasing perforin and granzyme, which prevents the development and progression of tumors [164–166]. B lymphocytes mediate antitumor responses by promoting antigen presentation, efficiently priming T cells, and producing antitumor antibodies. However, recent studies have found that interleukin-1β can induce the expansion of B lymphocytes and promote the proliferation of pancreatic cancer cells [167]. In general, B lymphocytes play a key role in the development of PDAC, but the mechanism of action is still controversial and needs to be further elucidated [168]. Macrophages are important immune cells that maintain tissue and immune system homeostasis. They are also one of the largest leukocyte populations in the tumor stroma and play an important role in tumor progression [169]. Macrophages can adjust their phenotype to respond to microenvironmental stimuli and transduce signals according to their functional requirements [170]. Generally, macrophages can be divided into two types, the classically activated M1 type and the alternatively activated M2 type, according to their polarization state and function [171]. Macrophages infiltrating tumor tissues, known as TAMs, can promote tumor cell growth through a variety of mechanisms, including promoting tumor angiogenesis, enhancing chemotherapy resistance, and suppressing tumor immunity. M1-type macrophages are activated by Th1 cytokines and have proinflammatory and antitumor effects; M2-type macrophages are activated by Th2 cytokines. They have anti-inflammatory effects and induce tissue remodelling and tumor cell proliferation, invasion and metastasis in early-stage tumors [172–175]. Mitchem *et al.* [176] found that inhibition of colony-stimulating factor-1 receptor (CSF1R) or C-motif chemokine ligand 2 (CCR2) on TAMs can reduce the number of tumor-initiating cells and overcome macrophage-induced $CD8^+$ cytotoxic T lymphocyte inhibition to improve the effect of chemotherapy in pancreatic cancer. Sanford *et al.* [177] found that pancreatic tumors recruit TAMs through the CCL2/CCR2 chemokine axis to generate an immunosuppressive tumor microenvironment. As such, CCR2 inhibitors may have a strong antitumor effect in PDAC patients and are worthy of further study in clinical trials. Treg infiltration is a distinctive characteristic of PDAC, and Tregs are required for pancreatic tumorigenesis. Tregs can reduce the effect of $CD8^+$ T cells and other immune cells and/or suppress T-cell function, resulting in tumor cell evasion of immune surveillance. Jang *et al.* [178] found that the development of pancreatic tumors is accompanied by the gradual accumulation of activated Treg cells, which promote PDAC progression by inhibiting the antitumor response of $CD8^+$ T cells. Therefore, a comprehensive understanding of the lipid metabolism patterns of cancer cells and immune cells will aid the development of new therapeutic strategies for pancreatic cancer. Figure 4 summarizes the effect of pancreatic cancer lipid metabolism reprogramming on the immune microenvironment.

Effects of lipid metabolism reprogramming on drug resistance

Abnormal lipid metabolism can not only alter the tumor microenvironment and cause immune escape but is also involved in the resistance to chemotherapy. For the past two decades, gemcitabine has been the cornerstone of pancreatic cancer chemotherapy and

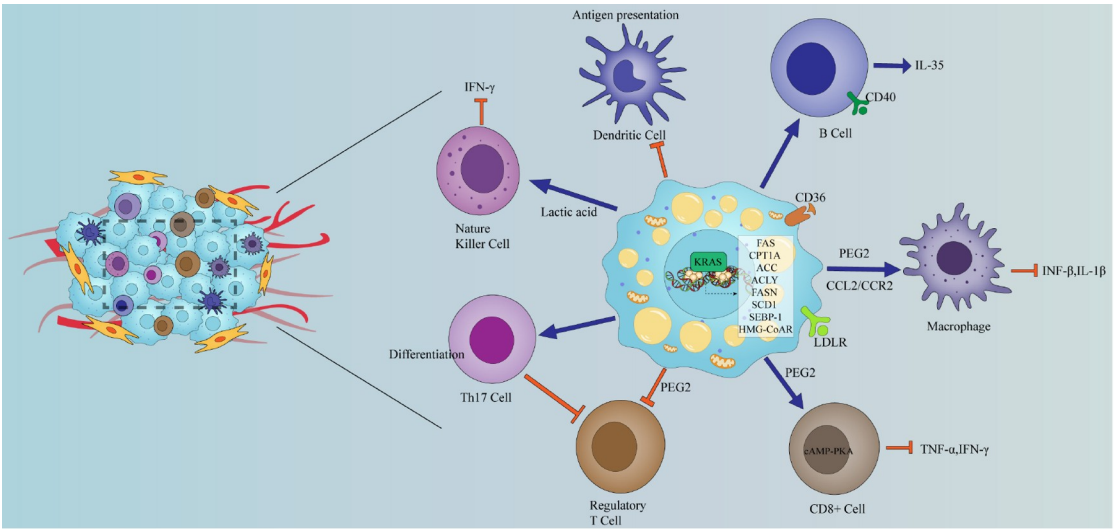

Figure 4. Excessive lipid accumulation in the tumor microenvironment of pancreatic cancer attenuates the antitumor immune response First, the upregulation of various enzymes related to lipid metabolism affects the function of immune cells, including the following aspects: overexpression of ACC and FASN can promote the differentiation of Th17 cells, inhibit the differentiation of Treg cells and promote tumor progression; CD36 and LDLR translocate excessive fatty acids and cholesterol into cells, activate fatty acid β-oxidation, inhibit the secretion of TNF-α and IFN-γ cytokines by $CD8^+$ T cells, and weaken the antitumor response; and the increased expressions of CPT1A, FAS, SCD1 and other enzymes can change the lipid type or trigger the accumulation of intracellular lipid droplets, thereby affecting the status and function of immune cells. Second, tumor cells secrete PEG2 to promote the transformation of M1-type macrophages into M2-type macrophages, and PEG2 activates the cAMP-PKA signaling pathway, leading to the growth arrest of $CD8^+$ T cells and the antitumour activity of Tregs and DCs. Tumor cells can also secrete lactic acid to cause intracellular acidification of NK cells, inhibit the secretion of IFN-γ, and promote NK cell apoptosis. Excessive lipid accumulation leads to antigen presentation dysfunction in DCs, which in turn fails to activate primary T cells and ultimately reduces the antitumour immune response. Pancreatic cancer cells activate the B-cell surface receptor CD40, and B cells secrete IL-35 to promote tumor cell proliferation. Pancreatic cancer can also recruit TAMs through the CCL2/CCR2 chemokine axis, resulting in decreased secretion of proinflammatory factors such as IFN-β and IL-1β, which in turn causes insufficient recruitment of effector T cells and NK cells and builds an immunosuppressive tumor microenvironment. Increased CPT1A expression in macrophages promotes fatty acid transport into mitochondria, promotes β-oxidation, and inhibits macrophage secretion of the proinflammatory factors IFN-β and IL-1β.

plays an important role in the treatment of borderline resectable, locally advanced or advanced metastatic pancreatic cancer. Furthermore, gemcitabine can also be used for postoperative chemotherapy, neoadjuvant chemotherapy, and palliative chemotherapy in patients with distant metastases or locally advanced unresectable disease [179,180]. Gemcitabine enters pancreatic cancer cells as a nucleotide analog and undergoes a series of complex phosphorylation steps to produce derivatives that interfere with DNA synthesis and arrest the pancreatic cancer cell cycle [181]. However, within a few weeks of starting chemotherapy, the response rate of pancreatic cancer patients to gemcitabine is less than 20%, and the remaining 80% of patients survive for less than a year. Resistance to gemcitabine is the main reason for the limited effect of chemotherapy and poor prognosis [182,183]. Fujimura *et al.* [184] used mass spectrometry to analyze the metabolomes of gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer CAPAN-1 and SUIT-2 cell lines and found differences in the amino acid, nucleotide, glucose, lipid, and energy profiles, suggesting that nutrient metabolism may be a reason for chemoresistance. In fact, pancreatic cancer cell lines with high expression of FAS have upregulated PKM2 expression and p53 signaling pathway activity, increased glycolysis to generate energy for tumor cell proliferation, and reduced endoplasmic reticulum stress, and can avoid cell death. These effects maintain the stemness of pancreatic cancer stem cells and result in drug resistance. In another *in vitro* cell experiment, the use of the FAS inhibitor orlistat increased sensitivity to gemcitabine [93,185–187]. Alzoubi *et al.* [188] also found that overexpression of tumor necrosis factor-α (TNF-α) can downregulate the protein expression of FAS/ACC, thereby inhibiting tumor growth. Preclinical studies have found that the antibiotic cerulenin inhibits the proliferation of lung cancer cells by inhibiting FAS. Although agents targeting FAS have not yet been approved for clinical use, FAS holds the promise as a potential therapeutic target [189]. In addition, activation of LDLR increases cholesterol uptake, and downregulation of LDLR induced by oridonin via the ERK/JNK signaling pathway can also increase the sensitivity of PANC-1 cells to gemcitabine and promote tumor cell apoptosis [190]. Currently, an increasing number of preclinical studies and clinical trials are focusing on the feasibility of targeting lipid metabolism-related processes in the treatment of pancreatic cancer. A phase II clinical trial that combines simvastatin with gemcitabine as treatment for patients with locally advanced and metastatic pancreatic cancer failed to achieve the expected clinical benefit (NCT00944463) [191]. Nevertheless, several clinical trials for pancreatic cancer treatment are still underway. For example, a phase I clinical trial was designed to explore whether lowering cholesterol levels with FOLFIRINOX chemotherapy as a treatment for advanced pancreatic cancer could yield beneficial outcomes (NCT04862260). Another phase III trial is testing the curative effect of the combination of simvastatin with digoxin and metformin in patients with advanced pancreatic cancer (NCT02201381).

Conclusions

Genetic alterations drive more than 95% of pancreatic cancers.

Despite decades of research, pancreatic cancer remains a highly lethal malignancy that derives minimal benefit from conventional cytotoxic therapies. Newly approved inhibitors of KRAS G12C can only benefit a subset of patients, and there are currently no drugs targeting *KRAS* G12D or *KRAS* G12V. As such, scientists should shift their focus and work to develop indirect targeting strategies. Metabolic reprogramming plays an important role in the occurrence and progression of pancreatic cancer, providing the energy and materials needed for pancreatic cancer cells to survive and further evolve in harsh environments. Immune cells also show abnormal lipid metabolism in the tumor microenvironment. These changes affect the function and status of immune cells and can result in weakened immune responses and immune escape, further promoting invasion and metastasis. Research on strategies targeting genes and enzymes related to tumor and immune cell lipid metabolism has provided powerful evidence for tumor prevention and treatment. Here, research progress in understanding the relationship between lipid metabolism reprogramming and drug resistance in pancreatic cancer was systematically reviewed to provide a theoretical basis for the development of new pancreatic cancer chemotherapy drugs and solutions to overcome the problem of drug resistance. In conclusion, since the initiation and development of pancreatic cancer are driven by various mutations and the dysregulation of signaling factors and not by disruption of a single pathway, the application of multitarget drugs is a promising direction for pancreatic cancer treatment in the future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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