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# *Targeting Lipid Metabolism in Pancreatic Cancer: Therapeutic Potential of Acetyl-CoA Carboxylase (ACC) and Fatty Acid Synthase (FASN) Inhibitors*

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***Abstract:*** Pancreatic cancer, long considered one of the most lethal malignancies, has been the focus of extensive research to develop effective treatments. Recent studies have revealed that lipid metabolism plays a crucial role in regulating the growth and proliferation of pancreatic cancer cells, offering a promising avenue for therapeutic intervention. This paper explores the intricate lipid metabolic pathways within pancreatic cancer cells, with a particular focus on key enzymes such as ATP citrate lyase (ACLY), fatty acid synthase (FASN), and acetyl-CoA carboxylase (ACC). These enzymes are integral to lipid synthesis and energy production, processes that are hijacked by pancreatic cancer cells to sustain their aggressive behavior. The findings suggest that targeting key enzymes involved in this metabolic pathway could significantly improve patient outcomes. Given pancreatic cancer cells' remarkable capacity for drug resistance and immune evasion, understanding and targeting these lipid metabolism pathways becomes particularly important for developing more effective therapeutic strategies against this aggressive disease.

***Keywords:*** lipid metabolism, FASA, ACC, Enzyme inhibitors

## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies worldwide, with a 5-year survival rate persistently below 10%, showing no significant improvement over the past decades [1]. This dire prognosis is closely linked to PDAC's aggressive biological behavior, challenges in early diagnosis, and limitations of current therapeutic strategies. Although chemotherapy regimens such as gemcitabine and FOLFIRINOX remain the primary treatment options for advanced PDAC, their clinical efficacy is substantially compromised by the widespread phenomenon of chemoresistance [2]. Furthermore, despite breakthroughs in molecular targeted therapies for other solid tumors, PDAC lacks effective therapeutic targets due to the "undruggable" nature of key driver mutations (e.g., KRAS) and pronounced tumor heterogeneity, underscoring the urgent need to explore novel therapeutic approaches.

This article focuses on the role of key enzymes in the metabolic reprogramming of pancreatic cancer and explores how enzyme inhibitors can suppress the activity of these enzymes in cancer cells. This paper aims to control and treat pancreatic cancer, hoping to pave a way for future researchers dedicated to this field.

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## 2. Reprogramming metabolism in cancer cell

### 2.1. Reprogramming metabolism and lipid metabolism

Metabolic reprogramming, a hallmark of cancer, is a key focus in PDAC research. Unlike normal cells, PDAC cells reshape metabolic pathways to meet the energy demands of rapid proliferation. The most prominent features of this reprogramming are the "Warburg effect" (aerobic glycolysis) and hyperactive lipid synthesis. Studies have demonstrated that PDAC cells preferentially convert glucose to lactate via upregulation of key enzymes such as glucose transporter GLUT1 and lactate dehydrogenase A (LDHA), sustaining ATP production in hypoxic microenvironments while providing precursors for nucleotide synthesis [3]. Concurrently, dysregulated lipid metabolism is pronounced in PDAC: elevated expression of enzymes like fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) not only promotes cell membrane biosynthesis but also activates pro-survival signaling pathways through lipid raft formation, thereby driving tumor growth and metastasis [4]. Notably, such metabolic adaptations may directly contribute to chemoresistance. For instance, glycolytic intermediates can attenuate the cytotoxicity of gemcitabine by suppressing apoptosis pathways, while lipid metabolites may enhance therapeutic resistance by regulating cancer stem cell properties [5]. Thus, deciphering the molecular interplay between metabolic reprogramming and PDAC progression not only provides novel insights into its malignant behavior but also identifies potential therapeutic targets to overcome current treatment limitations.

### 2.2. The critical enzyme of the lipid metabolism

Sterol regulatory element-binding protein 1 (SREBP1), a key transcriptional regulator of lipid synthesis, drives metabolic reprogramming in cancer cells by controlling the expression of genes like ACC, FASN, and stearoyl-CoA desaturase-1 (SCD1). Studies have demonstrated that SREBP1 is aberrantly overexpressed in PDAC, and its elevated levels correlate significantly with poor overall survival in patients [6]. Mechanistically, it binds to sterol regulatory elements (SRE) in target gene promoters, activating ACC and FASN transcription. ACC converts acetyl-CoA to malonyl-CoA, while FASN further elongates malonyl-CoA into long-chain fatty acids, synergistically promoting de novo lipogenesis to supply tumor cells with membrane components and energy storage forms (e.g., triglycerides). In PDAC cells, silencing SREBP1 markedly suppresses ACC and FASN expression, leading to reduced intracellular fatty acid and triglyceride levels, thereby inducing apoptosis and inhibiting proliferation. Notably, pharmacological inhibitors targeting lipid metabolism (e.g., TOFA for ACC and C75 for FASN) demonstrate similar tumor-suppressive effects as those observed with SREBP1 knockdown. This underscores the SREBP1-ACC/FASN axis as a critical metabolic dependency in PDAC. These findings not only elucidate the molecular basis by which SREBP1 fuels tumor progression through lipid synthesis but also provide a rationale for targeting metabolic pathways to overcome therapeutic resistance in PDAC.

## 3. Acetyl-Coa Carboxylase (ACC)

ACC, a key enzyme in lipid metabolism and downstream of SREBP1, can be targeted for cancer treatment by inhibiting it to reduce lipid resources.

### 3.1. ACC inhibition and its role in inducing apoptosis in pancreatic cancer cells

The ACC inhibitor TOFA significantly induces apoptosis in AsPC-1 and BxPC-3 cells by suppressing de novo lipogenesis (DNL), as shown in Figures 1A–C. This effect is partially reversed by exogenous palmitate supplementation (Figure 1D), suggesting that lipid depletion is the primary

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driver of apoptosis. These findings align with previous studies in hepatic fibrosis, where ACC inhibition alleviates liver injury by blocking lipotoxicity [7]. However, pancreatic cancer exhibits metabolic heterogeneity: PANC-1 cells show lower sensitivity to TOFA, likely due to reduced ACC1 expression, which is illustrated in Figure 1E, and the activation of compensatory lipid uptake pathways [8]. While ACC inhibition does not directly induce apoptosis in PANC-1 cells, it significantly suppresses proliferation (Figure 2B), suggesting that intervening in lipid metabolism may impair biosynthesis, such as membrane synthesis, rather than energy depletion. This is consistent with reports of KRAS-mutant tumors relying on DNL for membrane biogenesis [9].

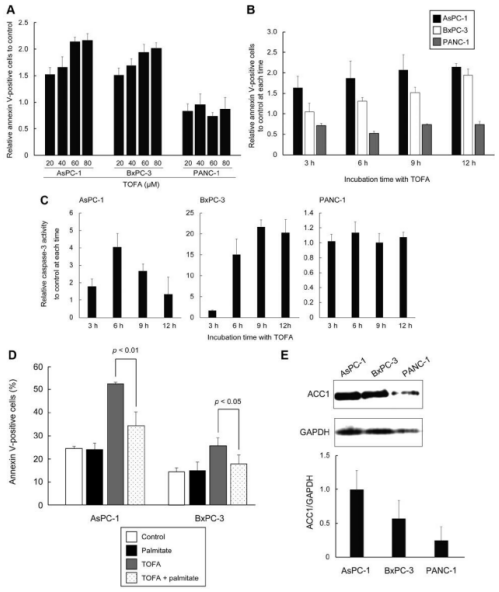



Figure 1: Effect of 5-(tetradecyloxy)-2-furoic acid (TOFA) on induction of apoptosis in pancreatic cancer cells [10]

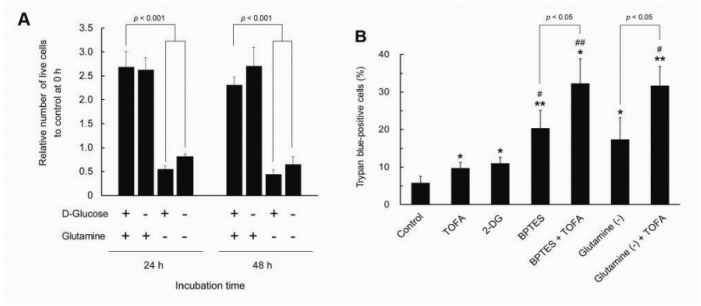



Figure 2: Effect of glutamine and 2-deoxy-D-glucose(2-DG) on proliferation of PANC-1 cells [10]

## 3.2. Dual targeting of lipid and amino acid metabolism

Further investigations reveal that PANC-1 cells proliferate under nutrient-deprived conditions in enviroment filled with EBSS and PBS, as demonstrated in Figures 3A and 3B. However, these cells exhibit a marked dependence on glutamine for survival, which is illustrated in Figure 2A [10]. The combined inhibition of ACC using TOFA and glutaminase using BPTES synergistically induces cell death in PANC-1 cells, as shown in Figure 2B. This finding highlights the potential of dual targeting lipid and amino acid metabolism to overcome tumor metabolic redundancy [10]. This synergy may arise from glutaminolysis inhibition disrupting the TCA cycle, forcing cells to rely on

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DNL for acetyl-CoA pools [11]. Additionally, ACC inhibition exacerbates this metabolic imbalance, as depicted in Figure 4, providing a novel "synthetic lethality" strategy for pancreatic cancer [10].

The antifibrotic effects of ACC inhibitors are well-established in hepatic fibrosis models [7]. This study posits that ACC inhibition may similarly target activated pancreatic stellate cells (PSCs) in the tumor stroma. PSCs share metabolic traits with hepatic stellate cells (HSCs). For instance, TGF-β-driven activation depends on glycolysis and oxidative phosphorylation [12]. Additionally, ACC-mediated DNL supplies membrane phospholipids and signaling lipids for their activation [13]. Thus, ACC inhibitors may suppress PSC metabolic reprogramming, reduce collagen deposition, and improve tumor matrix stiffness. This improvement could enhance the chemotherapeutic drug penetration, as indicated in Figure 1A [10]. This hypothesis is further supported by preclinical observations showing reduced TIMP-1 (a fibrosis marker) in hepatic models. However, validation in pancreatic cancer models is still required [7].

According to existing studies, an ACC inhibitor, ND-646, has entered clinical trials. ND-646 blocks both isoforms, ACC1 and ACC2, thereby inhibiting the progression of non-small cell lung cancer (NSCLC) [14-15]. A liver-specific variant, ND-654, was tested in mice and found to reduce hepatocellular tumors [16]. When these inhibitors were tested in combination with standard chemotherapy, they demonstrated superior efficacy in suppressing tumor growth compared to monotherapy [15-17].

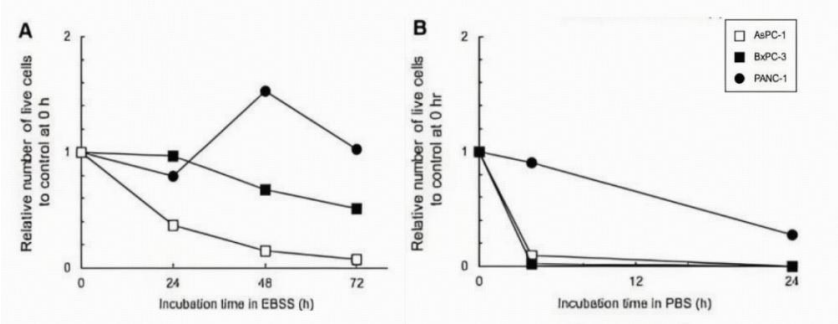



Figure 3: Effect of nutrient starvation in culture medium on proliferation of PANC-1 cells [10]

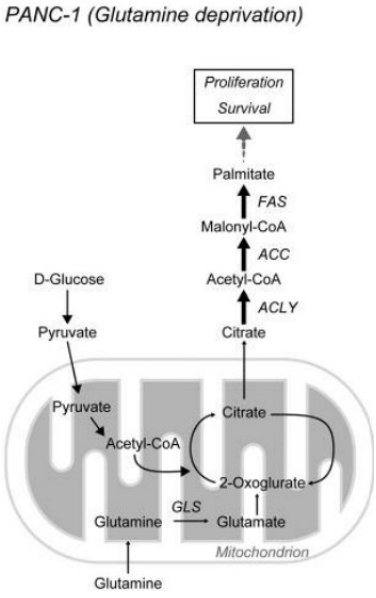



Figure 4: Proposed mechanism of survival and proliferation of pancreatic cancer cell [10]

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## 4. Fatty Acid Synthase (FASA) in a cancer cell's lipid metabolism and its inhibitor

### 4.1. The core role and mechanisms of FASN

The malignant progression of pancreatic cancer is closely related to abnormal lipid metabolism. As a core regulatory molecule, fatty acid synthase (FASN), like ACC, supports energy demand and membrane structure remodeling of cancer cells by driving de novo synthesis of fatty acids. Studies have shown that the abnormal activation of EGFR/ERK signaling pathway in pancreatic cancer can significantly increase the expression of FASN [7]. However, the excessive activation of FASN provides cancer cells with a large amount of palmitic acid, which not only promotes phospholipid synthesis, but also inhibits autophagy and enhances chemotherapy resistance by activating mTOR pathway [8]. In addition, FASN metabolites can affect cytoskeleton dynamics and metastasis ability by regulating palmitoylation modification of β-tubulin, thus further helping pancreatic cancer cells to metastasize and infect other sites [9].

### 4.2. Advances in FASN inhibitor development and their potential in combination therapies

The development of FASN inhibitors has also followed ACC inhibitors, which has become an important strategy to intervene in lipid metabolism and control the condition of pancreatic cancer. Natural inhibitors such as Orlistat inhibit palmitic acid synthesis by irreversibly binding to the thioesterase domain of FASN and exhibit multi-target properties, including inhibition of cancer promoting molecules such as Hsp90 and Annexin A2 [9]. However, Orlistat needs improvement due to its difficulty in effective absorption by the body and can also serve as an important component in synergistic therapy. Preclinical studies have confirmed that Orlistat's nano preparation can overcome its low oral bioavailability defect and synergistically induce tumor apoptosis with gemcitabine in pancreatic cancer models [10]. Although the first generation selective FASN inhibitors (such as TVB-2640) have limited monotherapy efficacy, their combination therapy strategy with EGFR inhibitors or immune checkpoint blockers has shown potential. Future research needs to analyze the heterogeneity of lipid metabolism in the tumor microenvironment and develop targeted FASN and other metabolic nodes, which may be combined with ACC inhibitors to achieve better results. What's more, RNA drugs, based on siRNA, have been developed these years. They can combine DNA fragments and prevent the enzyme from being produced, thus playing a important role as a kind of FASN inhibitor [12].

## 5. Conclusion

Emerging research has established ACC and FASN as pivotal regulators of pancreatic cancer progression through their roles in lipid metabolism. Targeted inhibition of these enzymes disrupts fatty acid synthesis, demonstrating significant anti-tumor effects in preclinical models while enhancing chemotherapy sensitivity. The development of specific inhibitors like ND-646 and TVB-2640, alongside novel RNA-based approaches, marks important progress in metabolic targeting.

However, this study has some limitations. For instance, it does not fully address the long-term effects and potential resistance mechanisms associated with the use of ACC and FASN inhibitors in clinical settings.

Due to the challenges in clinical implementation, including metabolic adaptation, stromal barriers, and tumor heterogeneity, future efforts should prioritize optimizing inhibitor specificity and delivery, developing synergistic combination strategies with immunotherapy, and identifying predictive biomarkers. These approaches may overcome current limitations and translate metabolic targeting into meaningful clinical benefits for pancreatic cancer patients.

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