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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Role of abnormal lipid metabolism in development, progression, diagnosis and therapy of pancreatic cancer

Julian Swierczynski, Areta Hebanowska, Tomasz Sledzinski

Julian Swierczynski, Areta Hebanowska, Department of Biochemistry, Medical University of Gdansk, 80-211 Gdansk, Poland
Tomasz Sledzinski, Department of Pharmaceutical Biochemistry, Medical University of Gdansk, 80-211 Gdańsk, Poland
Author contributions: Swierczynski J contributed to background research, formulation of the manuscript, revision of the manuscript, and final approval of the manuscript; Hebanowska A contributed to background research, formulation of the manuscript, and revision of the manuscript; Sledzinski T contributed to background research, formulation of the manuscript, and management of images.
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Correspondence to: Julian Swierczynski, Professor, Department of Biochemistry, Medical University of Gdansk, ul. Debinki 1, 80-211 Gdansk, Poland. juls@gumed.edu.pl
Telephone: +48-58-3491462 Fax: +48-58-3491465
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Abstract

There is growing evidence that metabolic alterations play an important role in cancer development and progression. The metabolism of cancer cells is reprogrammed in order to support their rapid proliferation. Elevated fatty acid synthesis is one of the most important aberrations of cancer cell metabolism. An enhancement of fatty acids synthesis is required both for carcinogenesis and cancer cell survival, as inhibition of key lipogenic enzymes slows down the growth of tumor cells and impairs their survival. Based on the data that serum fatty acid synthase (FASN), also known as oncoantigen 519, is elevated in patients with certain types of cancer, its serum level was proposed as a marker of neoplasia. This review aims to demonstrate the changes in lipid metabolism and other metabolic processes associated with lipid metabolism in pancreatic ductal adenocarcinoma (PDAC), the most common pancreatic neoplasm, characterized by high mortality. We also addressed the influence of some oncogenic factors and tumor suppressors on pancreatic cancer cell metabolism. Additionally the review discusses the potential role of elevated lipid synthesis in diagnosis and treatment of pancreatic cancer. In particular, FASN is a viable candidate for indicator of pathologic state, marker of neoplasia, as well as, pharmacological treatment target in pancreatic cancer. Recent research showed that, in addition to lipogenesis, certain cancer cells can use fatty acids from circulation, derived from diet (chylomicrons), synthesized in liver, or released from adipose tissue for their growth. Thus, the interactions between *de novo* lipogenesis and uptake of fatty acids from circulation by PDAC cells require further investigation.

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Key words: Pancreatic cancer; Lipid metabolism; Fatty acid synthase; Monounsaturated fatty acids; Farnesylation; Hypoxia inducible factor 1α; Cyclooxygenase-2; Oncogenes; Tumor suppressors; Lipogenic enzymes inhibitors

Core tip: Metabolic alterations associated with mutation in oncogenes and tumor suppressor genes play an important role in cancer development and progression. One of the most important aberrations of metabolism in cancer cells is an elevated synthesis of lipids, which are building blocks for cell membrane formation during cell proliferation and signalling molecules. This review aims to demonstrate the changes in lipid metabolism in pancreatic ductal adenocarcinoma, the most common pancreatic neoplasm, with very high mortality. The potential role of elevated lipid synthesis in diagnosis, prognosis and therapy of pancreatic cancer is also discussed.

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INTRODUCTION

Cancer development is generally attributed to the accumulation of genetic alterations, which leads to activation of cellular oncogenes and inactivation of tumor suppressor genes. Apart from mutations, epigenetic modulation, numerical and structural abnormalities in chromosomes, and aneuploidy are commonly observed in cancer cells, and may play a critical role in tumorigenesis[1]. In addition, carcinogenesis involves significant changes in cellular metabolism, especially in carbohydrate, lipid, nucleic acid, and amino acid metabolism (Figure 1).

The metabolism of cancer cells is reprogrammed in order to support their rapid proliferation. Nowadays, metabolic alteration, also referred to as metabolic transformation, should be added to six classic hallmarks of cancer cells proposed by Hanahan and Weinberg[2], Tennant *et al*[3] and illustrated on Figure 2. Over eight decades ago, Warburg revealed that an elevated rate of glycolysis under aerobic conditions, a phenomenon commonly known as the Warburg effect, is a distinctive feature of many human and animal tumors[4]. In the majority of cancers, glucose is converted mostly to lactate, and, therefore, only 2 moles of ATP per 1 mole of glucose are synthesized. In contrast, most non-cancer cells containing mitochondria, produce CO_2 and H_2O from glucose, and 38 moles of ATP are synthesized per 1 mole of glucose, under aerobic conditions.

Over the last two decades, several authors reported overexpression of genes encoding lipogenic enzymes in many human cancers (Table 1)[5-12]. This phenomenon is usually associated with an increased glucose carbon incorporation into lipids[13-16]. The possible pathways for the conversion of glucose into phospholipids and cholesterol, required for membrane formation in cancer cells, are illustrated on Figure 1. Pyruvate formed from glucose during active aerobic glycolysis, is either converted to lactate by lactate dehydrogenase (LDH), or can enter into mitochondria, where it is decarboxylated to acetyl-CoA by pyruvate dehydrogenase (PDH). Then, by means of reactions of citrate synthase (CS), present in mitochondria, and ATP citrate lyase (ACLY), present in cytosol, cytosolic acetyl-CoA, a key substrate for lipid biosynthesis is formed (Figure 1). Elevated activities of both enzymes (CS and ACLY) are observed in some malignancies, and the inhibition of ACLY is known to lead to cessation of tumor growth[17-21]. Interestingly, some tumors display a diminished flux of glucose carbon through PDH-catalyzed reaction, due to increased PDHK (pyruvate dehydrogenase kinase) activity, under the influence either hypoxia or oncogenic factors. This points to the possible use of carbon source other than glucose, for lipid synthesis[22-25].

Through conversion to fructose 6-phosphate, glucose also serves as a substrate for hexosamine phosphate synthesis (according to reaction: fructose 6-phosphate + glutamine → glucosamine 6 phosphate + glutamate), required for biosynthesis of glycoproteins and glycosaminoglycans. Glucose may also be converted to pentose phosphate on pentose phosphate pathway (PPP), and then to phosphoribosyl pyrophosphate (PRPP), a precursor of purine and pyrimidine nucleotides necessary for DNA synthesis (Figure 1). PPP generates NADPH, which is required for many processes, including lipid biosynthesis (Figure 1). The activity of glucose 6-phosphate dehydrogenase (G6PDH), a rate limiting enzyme of PPP, is elevated in certain cancers, including human pancreatic cancer (PC)[19,26]. Glutamine for hexosamine and nucleotide synthesis may originate from citrate produced in mitochondria. Citrate is converted by Krebs cycle to 2-oxoglutarate, a precursor of glutamate (Figure 1), and later to glutamine. However, glutamine is not synthesized on that pathway in many cancer cells, but is rather taken up from the circulation, where it is one of the most abundant amino acids[27].

Glucose and glutamine are two main sources of energy and carbon for most cancer cells[28-30]. Some data suggest that glucose accounts mainly for lipid, purine, and pyrimidine nucleotide synthesis, whereas glutamine is contributing to: (1) anaplerotic re-feeding of Krebs cycle; (2) amino acid synthesis; and (3) providing nitrogen necessary for purine and pyrimidine nucleotide synthesis[14], however, there is also evidence of glutamine participation (as carbon donor) in lipid biosynthesis[31]. High expression of glutaminase-encoding gene was revealed during the S phase of the cell cycle in some cancer cell lines (*i.e.* HeLa cells), along with the low expression in G_2/M phase[32]. Upon cellular uptake, glutamine is transported to mitochondria, and then converted to ammonia and glutamate by mitochondrial glutaminase. Then glutamate is deaminated to 2-oxoglutarate by glutamate dehydrogenase. In mitochondria, 2-oxoglutarate is further metabolized by Krebs cycle to malate (Figure 3). Part of the malate is released to cytosol, converted to pyruvate by NADP-linked malic enzyme (ME), and, finally, to lactate by LDH, similarly to pyruvate formed from glucose during glycolysis (Figure 3). The conversion of glutamine to lactate is called glutaminolysis analogically to glycolysis (Figure 3). The increased synthesis of lactic acid by cancer cells leads to the decrease in pH of tumor microenvironment, which promotes angiogenesis, invasion, and metastasis, and suppresses the anticancer immune response through diminished cytotoxic T-cell function[33] (Figure 3).

In a variety of tumors, pyruvate formed during active glutaminolysis is converted into acetyl-CoA by PDH (instead of being converted to lactate by LDH), and later to citrate, supplying carbons for lipid synthesis (Figure 3)[34,35]. Conversion of glutamine to citrate may be also the result of reductive carboxylation of 2-oxoglutarate

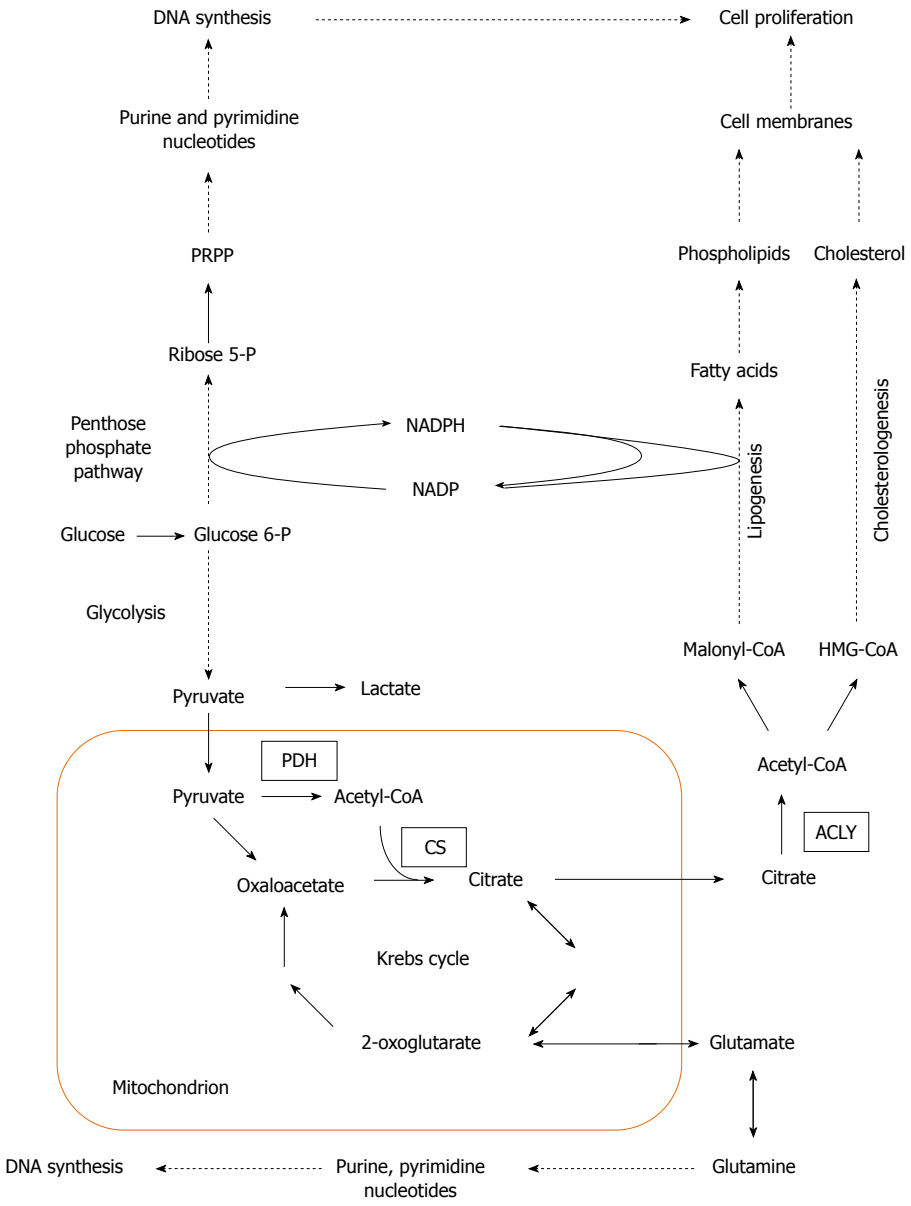

Figure 1 Cellular metabolism of cancer cells-association with cell proliferation. Solid arrows represent single reactions; dotted arrows represent processes including numerous reactions. PRPP: Phosphoribosyl pyrophosphate; Ribose 5-P: Ribose 5-phosphate; Glucose 6-P: Glucose 6-phosphate; PDH: Pyruvate dehydrogenase; CS: Citrate synthase; ACLY: ATP citrate lyase; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.

derived from glutamine, catalyzed by two isoforms of $NADP^+$-dependent isocitrate dehydrogenase - mitochondrial (IDH2), and/or cytosolic (IDH1) (Figure 1)[36-40]. In some cancer cell lines 10%-25% of fatty acids carbons are derived from glutamine under normoxia, and up to 80% under hypoxia[14,36,37]. Wise *et al*[38] suggest that IDH2 is mainly contributing to conversion of glutamine to lipids. However, other data show that in A549 (adenocarcinoma of human alveolar basal epithelial cells), and in renal carcinoma cells (RCC) cell lines IDH1 is more important[36]. In melanoma or osteosarcoma cell lines both IDH isoforms equally participate in 2-oxoglutarate reduction[37,40].

Continuous loss of citrate from mitochondria to cytosol requires replenishment of Krebs cycle intermediates. Glutamine serves as a key substrate for Krebs cycle intermediates in many cancer cells, and is critical for cell proliferation. A proliferating cell dies upon glutamine (but not glucose) withdrawal from the medium[41].

Fatty acid (FA) biosynthesis remains at a low level in most non-cancerogenic tissues, except liver and adipose tissue. The two latter lipogenic tissues convert the excess of carbohydrates to triacylglycerols[42-49]. Conversely FAs synthesized in cancer cells are esterified mainly to phospholipids required for membrane formation, which promotes cellular replication (Figure 1). Overall, coordinated enhancement of glucose, lipid, and amino acid metabolism, leading to increased synthesis of membrane lipids, nucleotides, and amino acids supports rapid proliferation of cancer cells (Figure 1).

Proliferation and metabolism of cancer cells share common regulatory pathways[50-53]. MYC, proto-oncogene and major regulator of transcription in growing cells, controls several metabolic processes such as: (1)

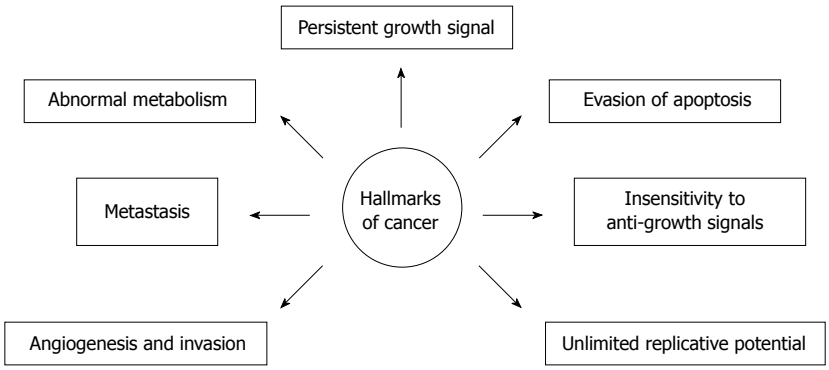

Figure 2 Hallmarks of cancer.

Table 1 Overexpression of lipogenic enzymes in human tumors

Enzyme name	Neoplasm type	Experimental model	Ref.
Fatty acid synthase	Pancreatic cancer	Human tumor tissue, cell line	[96,104,105]
(FASN)	Breast carcinoma	Human tumor tissue	[5,9,166]
	Prostate cancer	Human tumor tissue	[167]
	Melanoma	Human tumor tissue	[168]
	Nephroblastoma	Human tumor tissue	[169]
	Renal cancer	Cell line	[170]
	Endometrial carcinoma	Human tumor tissue	[12,171]
	Colon cancer	Human tumor tissue	[11,172]
	Ovarian neoplasms squamous cell	Human tumor tissue	[10,173]
	Carcinoma of the lung head and neck squamous	Human tumor tissue	[174]
	Cell carcinoma squamous cell	Human tumor tissue	[175]
	Carcinoma of the tongue	Human tumor tissue	[176]
ATP citrate lyase	Small cell lung cancer	Cell line	[251]
(ACLY)	Bladder cancer	Human tumor tissue	[7]
	Breast cancer	Cell line	[252]
	Gastric cancer	Human tumor tissue, cell line	[253]
	Colon cancer	Human tumor tissue	[254]
	Prostate cancer	Human tumor tissue	[254]
	Hepatocellular carcinoma	Human tumor tissue	[255]
Acetyl-CoA carboxylase	Prostate cancer	Human tumor tissue	[6]
(ACCA)	Hepatocellular carcinoma	Human tumor tissue	[255]
	Breast carcinoma	Human tumor tissue	[256]
Stearoyl-CoA desaturase	Pancreatic cancer	SCD1 indices in patients serum	[128]
(SCD1)	Clear cell renal cell carcinoma	Human tumor tissue	[200]
Acetyl-CoA synthetase	Colon adenocarcinoma	Human tumor tissue	[257]
(ACS)	Malignant glioma	Cell line	[258]
Citrate synthase	Pancreatic cancer	Human tumor tissue	[19]
(CS)	Renal cell carcinoma	Human tumor tissue	[20]

glycolysis and glutaminolysis; (2) nucleotide biosynthesis; and (3) lipid biosynthesis, and mitochondrial biogenesis[53]. Furthermore, MYC stimulates glutamine uptake and metabolism[54,55]. Tumor suppressor protein, p53, is involved in regulation of bioenergetic homeostasis and lipid metabolism in both normal and cancer cells[51,56-58]. p53 induces the expression mitochondrial glutaminase-encoding gene, increasing energy production from glutaminolysis[59,60]. Mutant p53 increases lipid synthesis, *via* sterol regulatory element-binding protein 1c (SREBP1c), and promotes ovarian cancer metastasis[52]. Certain oncoproteins such as: Akt, Ras, and Src, also stimulate glycolysis in transformed cells[50]. Regulation of glutamine metabolism by Rho GTPases and Ras was also proposed[61]. The oncogenes and tumor suppressor genes whose products participate in regulation of carbohydrate, lipid, nucleotide and amino acid metabolism are presented in Table 2.

Also mutations of some genes can contribute to abnormal cellular metabolism, which in turn can affect oncogenic signaling pathways. For example mutation in gene encoding IDH1/2 is associated with deregulation of cellular metabolism, especially in glioma cells[62]. In glioma IDH1/2 mutations are responsible for conversion of 2-oxoglutarate to 2-hydroxyglutarate, which, by inhibition of 2-oxoglutarate-dependent dioxygenases, affects: (1) proto-oncogene expression; (2) DNA and histone modification; and (3) alteration of extracellular matrix proteins (due to inhibition of collagen hydroxylation)[62]. This paper reviews the possible role of lipid metabolism in human cancers, particularly in PC biology, prognosis, and treatment.

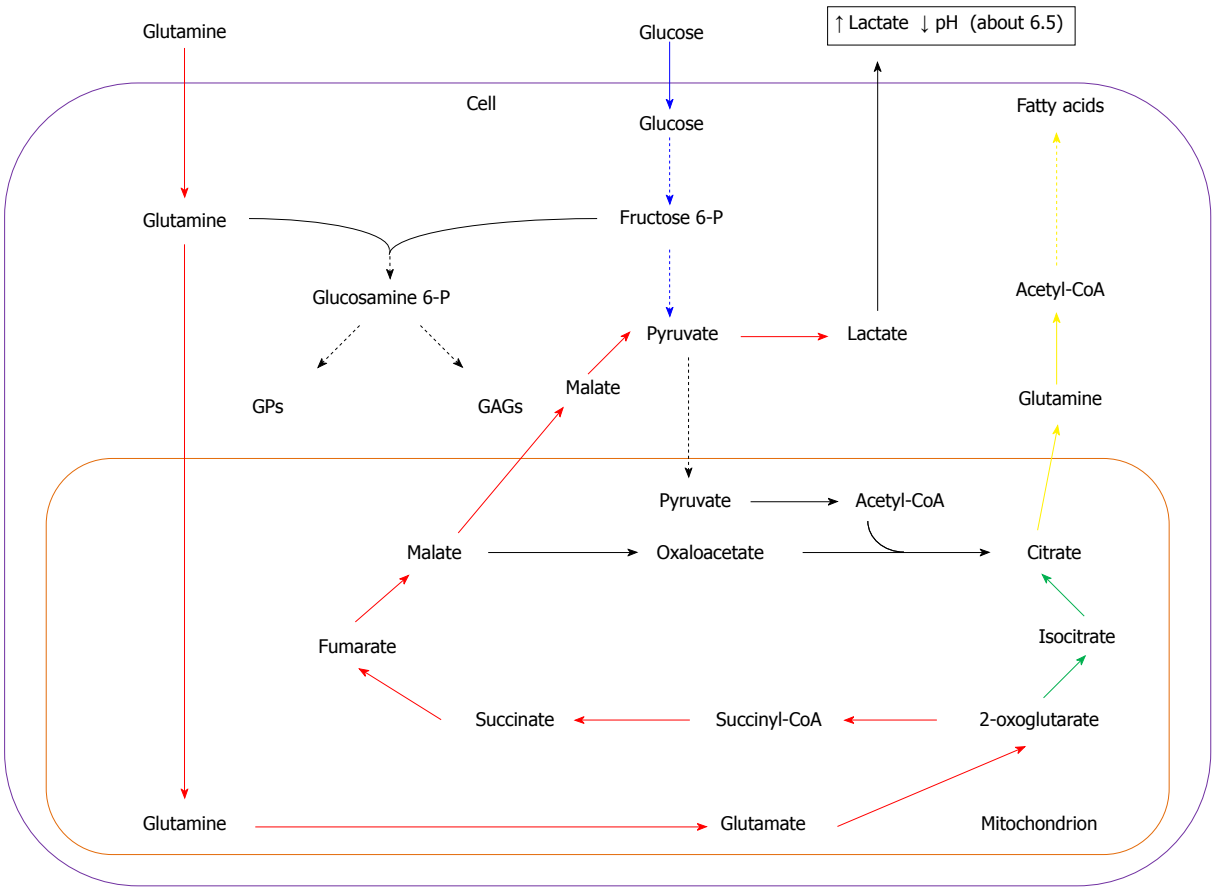

Figure 3 Glutamine metabolism of cancer cells. Red arrows represent glutaminolysis; green arrows represent "reversed Krebs cycle" reactions; blue arrows represent glycolysis; yellow arrows represent lipogenesis. Solid arrows represent single reactions; dotted arrows represent processes including numerous reactions. Fructose 6-P: Fructose 6-phosphate; GAGs: Glycosaminoglycans; GPs: Glycoproteins.

ABNORMAL LIPID METABOLISM IN PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic neoplasm, comprising approximately 90% of all pancreatic malignancies, and the eight leading cause of cancer-associated death in the world[63]. The 5-year survival rate of PDAC patients is approximately about 5%[64]. Surgery is the primary treatment modality and the only available chance for recovery, however only approximately 10% of patients are eligible for surgical treatment. Other therapies have proven ineffective thus far.

Similar to other cancers, both activation of oncogenes and inactivation of tumor suppressor genes play key role in PDAC pathogenesis. The most frequent genetic alterations documented in PCs, including PDAC, are presented in Table 3. Other pancreatic tumors show different aberrations (Table 4).

In addition to genetic and epigenetic alterations, development of PC involves significant alterations of cellular metabolism, supporting rapid proliferation of cancer cells. Reduced vascularity, leading to poor perfusion is characteristic for PC. This results in low availability of oxygen and nutrients[65,66]. The presence of hypoxia corresponds to highly aggressive character of PCs[67].

Oxygen deprivation of both non-cancer and cancer cells leads to the stabilization of hypoxia inducible factor 1α (HIF-1α), which dimerizes with HIF-1β, transfers into nucleus and binds with hypoxia-responsive elements present in DNA (Figure 4). This counteract the deleterious impact of decreased oxygen availability[68]. High level of HIF-1α is associated with increased glucose consumption due to activation of glucose transporter 1 (GLUT1), and glycolysis, especially hexokinase (1 and 2), and LDH[69-73] (Figure 4). Overexpression of HIF-1α in human PC cells makes this malignancy similar to other cancers[74]. Interestingly, the expression of HIF-1α in the hypoxic part of pancreatic tumor is at the same level as in its well-oxygenated fragments[75]. Some data indicate that phosphorylation of HIF-1α weakens the interaction of this protein with von Hippel-Lindau tumor suppressor (VHL) which normally stimulates degradation of HIF-1α during normoxia (Figure 4). The phosphorylation result from activation of MAPK or other protein kinase (putatively AKT) in cancer cells[76]. Both kinases are downstream effectors in various signaling pathways, including KRAS pathway. Continuous KRAS signaling and downstream activation of MAPK and AKT results from the mutation of KRAS (observed in 90% of PDACs), or can be stimulated by epidermal growth factor (EGF), prostaglandin E_2 (PGE_2), and some oxidants[73,77,78].

Table 2 Oncogenes and tumor suppressor genes, whose products participate in regulation of cancer cells metabolism

Oncogene/tumor suppressor	Metabolic pathway	Enzyme	Ref.
MYC	Glucose transport	GLUT1	[53-55]
	Glycolysis	Hexokinase 2	
		Phosphohexose isomerase	
		Phosphofructokinase 1	
		Aldolase A	
		3-phosphoglyceraldehyde dehydrogenase	
		Phosphoglycerate kinase	
		Phosphoglycerate mutase	
		Enolase 1	
		Pyruvate kinase 2	
		Lactate dehydrogenase A	
	Regulation of PDH	Pyruvate dehydrogenase kinase 1	
	Glutamine transport	Glutamine transporters ASCT2 and SN2	
	Glutaminolysis	Glutaminase 1	
	Serine hydroxymethyltransferase		
	Pyrimidine synthesis		
	Aminoacids metabolism	CAD	
		Ornithine decarboxylase	
	Lipogenesis	Fatty acid synthase	
p53	Glucose transport	GLUT1	[51,56-60]
	Glycolysis	Hexokinase 2	
		Fructose-2,6-bisphosphatase	
		Phosphoglycerate mutase	
	Oxidative phosphorylation	Cyrochrome c oxidase	
	Glutaminolysis	Glutaminase 2	
	Pentose Phosphate Pathway	Glucose-6-phosphate dehydrogenase	
	Regulation of PDH	Pyruvate dehydrogenase kinase 1	
	Krebs cycle	Aconitase	
KRAS	Glucose transport	GLUT1	[61,73,94]
	Glycolysis	Hexokinase 2	
		Phosphofructokinase 1	
		Lactate dehydrogenase A	
	Pentose phosphate pathway	Transketolase	
	Hexosamine synthesis	Phosphohexose aminotransferase	
	Glutaminolysis	Glutamate dehydrogenase	
		Aspartate transaminase	
Akt/PTEN	Glucose transport	GLUT1	[50,113-115]
	Lipogenesis	FASN	

PI3K/Akt signaling pathway leads to overexpression of HIF-1α, and directly participates in glucose transport and metabolism by regulating GLUT1 gene expression in PC cells, especially when the function of PTEN, tumor suppressor inhibiting PI3K/AKT pathway, is lost[79-81]. Another oncogene, MYC, interacts with KRAS and HIF-1α in PDAC metabolic switch. MYC response elements are present in most glycolytic genes, thus, allowing MYC protein to regulate glucose metabolism[73,82]. Some data suggest that activation of HIF-1α, leading to metabolic reprogramming of pancreatic cells during normoxia, is also controlled by β-adrenergic receptors through the transactivation of epidermal growth factor receptor (EGFR, requiring PKA activity), and further activation of AKT[83]. Also insulin, causing activation of PI3K/AKT and MAPK pathways, can be potential stimulator of HIF-1α activity acting independently of oxygen availability[84].

Mucin 1 (MUC1), a transmembrane protein involved in stabilization of HIF-1α is one of the newly discovered activators of HIF-1α in PC. Directly interacting with HIF-1α and DNA, MUC1 induces expression of glycolytic genes[85]. High activity of MUC1 is correlated with intensive growth and metastasis of pancreatic tumors[86,87]. HIF-1α is coexpressed with Nupr1 (also known as p8 or Com, *i.e.* candidate of metastasis) in human PDAC[88]. Nupr 1 is a chromatin protein, structurally related to the high-mobility group (HMG) protein, it interacts with several other proteins in the regulation of cell cycle, apoptosis, autophagy, and gene transcription[89]. It is responsible for increased resistance of stress-exposed PDAC cells[90] and supposedly interacts and amplify the KRAS signaling in cancer cells, in order to overcome the activity of some tumor suppressors (such as p16) action[91].

The data presented above suggest that several proteins (mainly products of proto-oncogens or tumor suppressor genes) might affect conversion of glucose to pyruvate in PDAC cells.

Most of the pyruvate formed as a result of increased glycolysis in PDAC cells, is metabolized to lactate, some pyruvate is used to citrate, and further to FAs biosynthesis[92,93]. Accordingly, the activity of CS, one of the crucial enzymes involved in pyruvate to FA conversion (Figure 1), is elevated in PC[19,20]. Thus, it is likely that citrate is synthesized from glucose in PC cells, although glutamine seems to play an important role as well.

Table 3 Oncogenes and tumor suppressor genes whose products alter the metabolism of pancreatic cancer cells

Gene	Protein	Mechanism of alteration in PDAC	Regulated processes in PDAC	Alteration in PDAC	Ref.
Oncogenes					
KRAS	KRAS	Point mutations	Cell proliferation and survival, motility, glucose transport, glycolysis, hexosamine synthesis, nonoxidative pentose phosphate pathway arm, glutaminolysis	> 95%	[73,94,259-261]
AKT	AKT	Mutations, amplification	Signal transduction, lipogenesis, glucose transport	10%-20%	[73,79-81,262-264]
c-erbB2	HER2	Overexpression amplification	Proliferation, differentiation, survival	20%-80%	[265-268]
Myc	MYC	Amplification overexpression	Glycolysis, glutaminolysis, PDH inhibition	70%	[55,73,82,94,269]
Tumor suppressor genes					
TP53	p53	Mutation and second allele deletion	Cell cycle, apoptosis, DNA repair, glucose transport, glycolysis, lipogenesis, ppp oxidative arm, glutaminolysis	50%-80%	[270-273]
Smad4/DPC4	SMAD4	Homozygous deletion, mutation and second allele deletion	Cell cycle, TGF-β signaling	55%	[274-276]
STK/LKB1	LKB1	Homozygous deletion, mutation and second allele deletion	Apoptosis, lipogenesis, energy production, protein synthesis	5%	[277-279]
CDKN2A/p16	p16	Homozygous deletion, mutation, hypermethylation	Cell cycle	95%	[280-282]
PTEN	PTEN	Hypermethylation, inhibition by miRNA	PI3K/AKT signaling pathway	30%-70%	[79,283,284]

PDAC: Pancreatic ductal adenocarcinoma.

Table 4 Most common genetic alterations observed in different types of human pancreatic cancers

Type of pancreatic cancer	Gene affected	Ref.
Pancreatic ductal adenocarcinoma (PDAC) (90% of all pancreatic cancers)	KRAS, AKT, MYC, TP53, SMAD4, CDKN2A, PTEN	[55,63,64,73,78,79,94,269,284-287]
Acinar cell carcinoma (ACCA) (< 1% of all pancreatic cancers)	APC/β-catenin (CTNNB1), BRCA2, BCL10	[288-290]
Adenosquamous carcinoma (ASC) (< 1% of all pancreatic cancers)	TP53, CDKN2A, KRAS, E-cadherin,	[291,292]
Intraductal papillary mucinous neoplasm (IPNM) (1%-3% of all pancreatic cancers)	GNAS, KRAS, RNF4, STK11/LKB1, MUC1, MUC2, hTERT, COX2, Shh	[278,293,294]
Mucinous cystic neoplasm (MCN) (< 1% of all pancreatic cancers)	KRAS, RNF4, TP53, CDKN2A	[295]
Serous cystadenoma (SCN) (< 1% of all pancreatic cancers)	VHL	[296]
Solid-pseudopapillary neoplasm (SPN) (1%-2% of all pancreatic cancers)	APC/β-catenin (CTNNB1), E-cadherin	[297,298]
Pancreatic neuroendocrine tumors (PanNET) (2%-5% of all pancreatic cancers)	DAXX, ATRX, MEN1, TSC2, PTEN, PI3KCA, CHGA, CHGB, mTOR	[299-302]

Son *et al*[94] suggested that KRAS directs glutamine carbons to Krebs cycle in PC cells, to export them to cytosol for cytosolic ME reaction. This results in the generation of NADPH, which is used for lipid biosynthesis and for redox state control. Deprivation of glutamine or inhibition of glutaminase activity are reflected by decreased production of ATP and higher levels of reactive oxygen species (ROS). Glutamine may also supply OAA, condensed with acetyl-CoA, to citrate synthesis, or be involved in citrate formation through reductive carboxylation of 2-oxoglutarate catalyzed by reverse IDH reaction. Although the involvement of glutamine was documented in some malignancies, its role in PC cells is still not completely understood[14,36-40,95]. Nevertheless, *de novo* biosynthesis of lipids (possibly from glucose and/or glutamine) is elevated in PDAC cells[96-98].

Gemcitabine, herceptin or irinotecan treatment has minimal impact on survival rates in patients with advanced PC[99,100]. In contrast treating PC patient with gemcitabine, α-lipoic acid, and hydroxycitrate yielded promising results[101]. Since hydroxycitrate is an inhibitor of ACLY, the activity of the latter lipogenic enzyme (splitting citrate to acetyl-CoA and OAA in cytosol) is likely elevated in PC cells as well, and, similar to other cancers, plays an important role in the development of this malignancy. The next stage of lipogenesis, leading to biosynthesis of malonyl-CoA (fatty acid synthase substrate), is catalyzed by acetyl-CoA carboxylase (ACCA). Phosphorylation by AMPK, leading to ACCA activity cessation, is one of the crucial stages of lipogenesis regulation in lipogenic tissues[102]. The activity of AMPK in PDAC cells is lower than in normal cells, mostly due to LKB1 tumor suppressor inhibition, leading to increased ACCA activity[103]. Fatty acid synthase (FASN) reaction constitutes the last step in palmitate synthesis. The significant role of FASN in cancer development was established approximately two

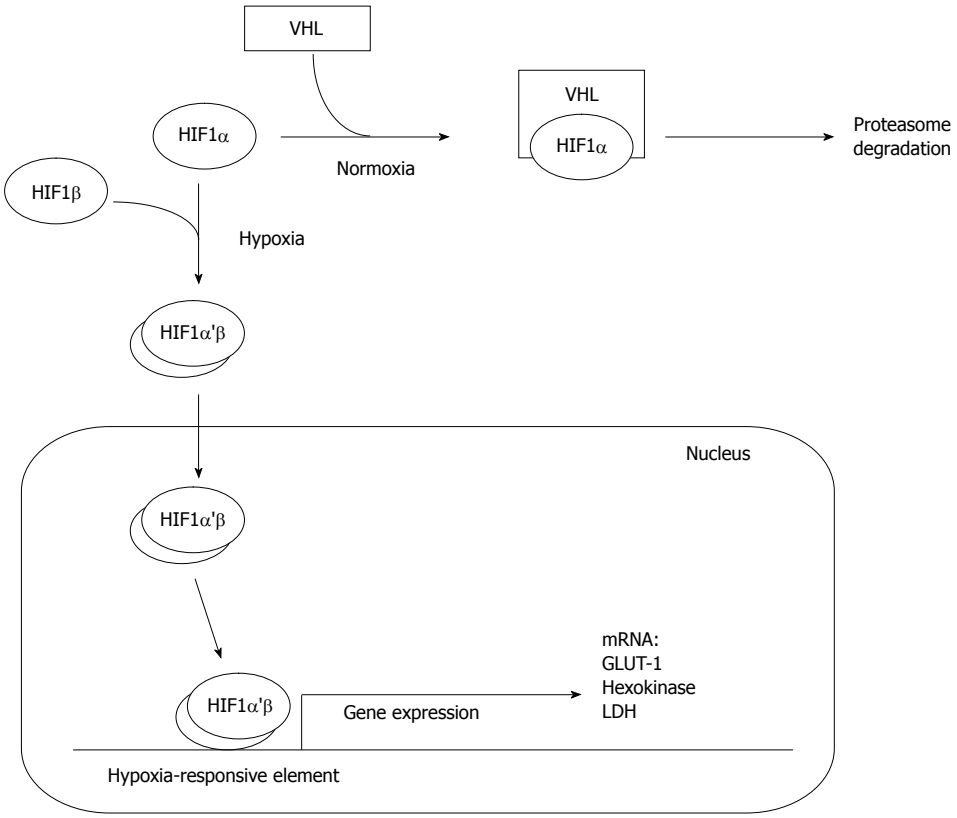

Figure 4 Role of hypoxia inducible factor 1 α'β in pancreatic cancer. HIF1α: Hypoxia inducible factor 1α; HIF1β: Hypoxia inducible factor 1β; VHL: Von Hippel-Lindau tumor suppressor; GLUT-1: Glucose transporter 1; LDH: Lactate dehydrogenase.

decades ago, when the oncogenic antigen-519 (OA-519), a molecular marker, was identified in breast cancer patients[9]. FASN utilizes acetyl-CoA (supplied by ACLY), malonyl-CoA (supplied by ACCA) and NADPH as a reducing equivalent. In the case of PC cells, NADPH is a product of PPP or reaction catalyzed by ME during oxidative decarboxylation of malate formed from glutamine (*i.e.* during glutaminolysis)[94]. FASN is the most extensively studied lipogenic enzyme in PDAC cells. Elevated expression of FASN-encoding gene was documented in human PC[96,104,105] and high level of FASN protein, both in tumor cells and in serum is associated with poor prognosis[96,98]. Furthermore inhibition of FASN activity was revealed to induce apoptosis in several tumors[106-110]. Indeed, FASN is an oncogenic protein and its overexpression in non-transformed human breast epithelial cells, can produce their cancer-like phenotype, in a HER1/2 dependent process[111]. Similar phenomenon was reported in the case of colorectal cancer cells[112]. The expression of *FASN* is strongly induced in hypoxia, by MAPK or PI3K/AKT signaling pathways. This results in activation of SREBP1c transcription factor, which directly binds to FASN promoter (and promoters of other lipogenic genes)[113,114]. Similar effect can be observed in the absence of PTEN tumor suppressor, which normally inhibits PI3K/AKT signaling[114,115]. Moreover, SREBP1c-independent regulation of *FASN*, mediated by HER2 with PI3K or mTOR involvement was observed in breast cancer cells[116]. Furthermore strong acidic environment of breast cancer may promote epigenetic modification of *FASN* promoter, leading to increased expression of this gene[117]. As all those events take place in PC cells, the mechanism of *FASN* regulation in PDAC is probably similar as in the case of other malignancies.

Inhibited activity of FASN (or other lipogenic enzymes) is reflected by decreased tumor growth and may lead to apoptosis of some cancer cells. The inhibition of FASN was revealed to diminish proliferation of osteosarcoma and colorectal cancer cells, through decrease of HER2 activity, leading to down-regulation of PI3K/Akt signaling pathway[112,118]. Induction of apoptosis is likely to result from elevated concentration of malonyl-CoA, that is reflected by decreased oxidation of FA and increased ceramide concentration. Ceramide is a well-known activator of apoptosis, and its enhanced biosynthesis (along with inhibited ceramidase activity) leads to the death of PC cells[106,119]. Furthermore the altered composition of FAs in phospholipid structure (predominance of polyunsaturated acids over saturated and monounsaturated acids) increases the oxidative stress yielding the same result[120].

Glycolytic synthesis of ATP seems the most important pathway in hypoxic cancer cells. In the cases of normoxia, glucose is rather directed to PPP for NADPH and pentose synthesis, and KRAS acts as the main controlling factor supporting tumor cell proliferation[121,122]. Both oxidative and non-oxidative phases of PPP are upregulated in PC cells. The non-oxidative phase is upregulated by KRAS[73,123], whereas G6PDH activity (main

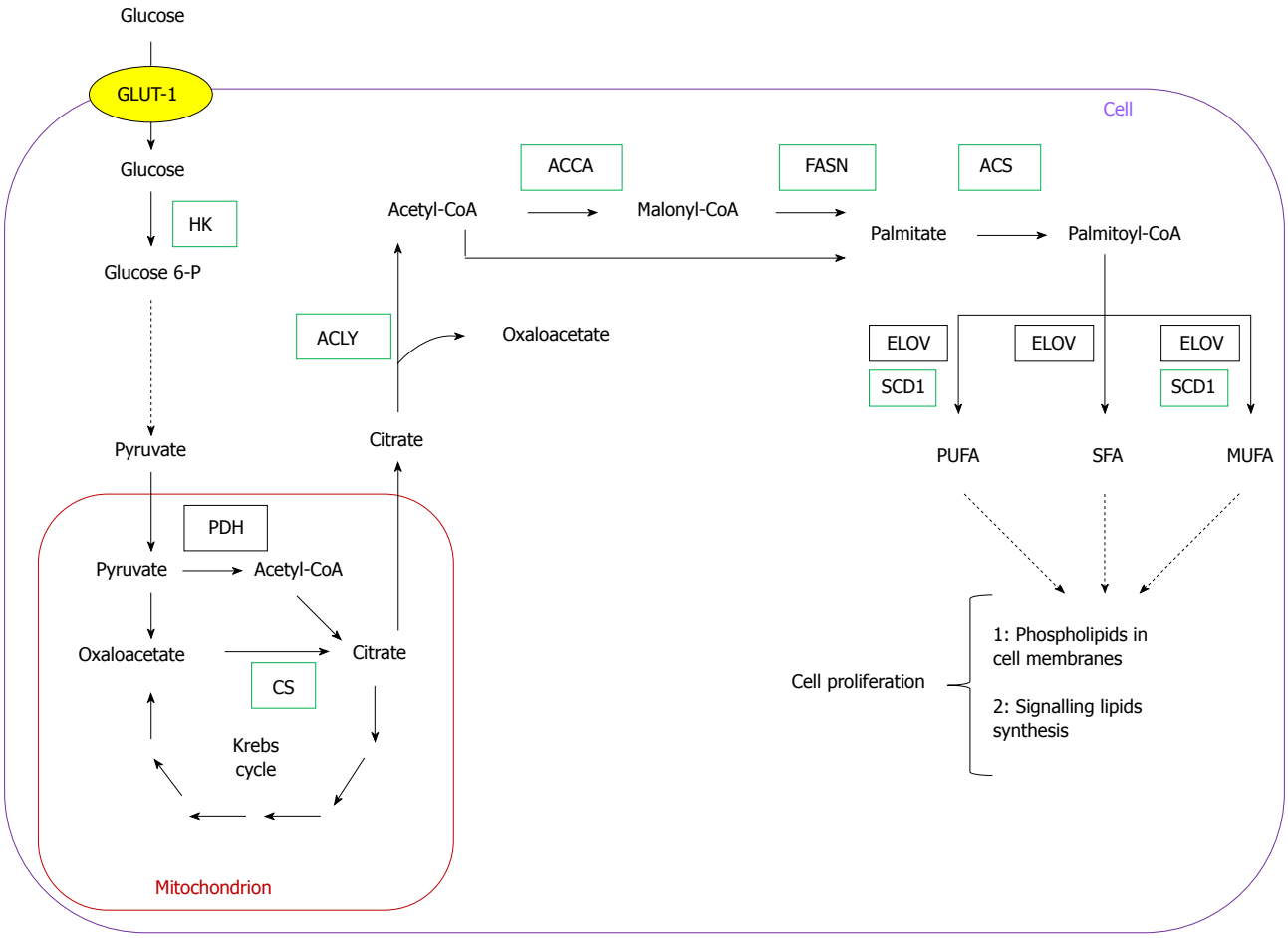

Figure 5 Fatty acid synthesis in pancreatic cancer. The up-regulated enzymes are marked in green. GLUT-1: Glucose transporter 1; HK: Hexokinase; glucose 6-P: Glucose 6-phosphate; PDH: Pyruvate dehydrogenase; CS: Citrate synthase; ACLY: ATP citrate lyase; ACCA: Acetyl-CoA carboxylase; FASN: Fatty acid synthase; ACS: Acyl-CoA synthetase, ELOV: Elongase; SCD: Stearoyl-CoA desaturase; PUFA: Polyunsaturated fatty acids; MUFA: Monounsaturated fatty acids; SFA: Saturated fatty acids.

enzyme of oxidative phase, controlling NADPH production) is increased putatively, due to p53 deficiency[19]. p53 inhibits G6PDH through direct binding, and its loss leads to the up-regulation of the oxidative PPP phase in cancer cells[73,124]. Taken together, these data suggest that similar to other malignancies, the increased glucose flux (both by glycolytic and pentose phosphate pathway) is integrated with the enhanced biosynthesis of lipids in PC cells. Pathways involved in the conversion of glucose to lipids in PC cells are presented in Figure 5.

The lipids formed in cancer cells play two important roles. Firstly, they are building blocks for cell membrane formation during cell proliferation (mainly cholesterol, phosphatidylcholine, phsphatidylserine, phosphatidylethanolamine). Secondly, they play an important role as signaling molecules (phosphatidylinositol, phosphatidic acid, diacylglycerol), or substrates for posttranslational protein modification, including palmitoylation and prenylation[125]. Mammalian cancer cells rely mostly on saturated (SFAs) or monounsaturated FAs (MUFAs). MUFAs are less susceptible to peroxidation, thus increasing the resistance of cancer cells to oxidative stress[126]. Elevated level of MUFAs is maintained mostly by stearoyl-CoA desaturase 1 (SCD1). Inhibition of SCD1 activity in some tumors (*e.g.*, in prostate cancer) leads to inhibition of cancer cell growth. Diminished SCD1 activity is reflected by lower synthesis of phosphatidylinositol, which participates in AKT activation, crucial for cancer development and growth. Additionally inhibition of SCD1 blocks oncogenic transformation of KRAS necessary for activation of this gene and further tumor growth[127]. As SCD1 is very active in PDAC cells[128], and KRAS and AKT signaling pathway are important for their development and growth, SCD1 supposedly plays an essential role in pathogenesis of that malignancy via the same mechanism as in case of other tumors.

In the context of lipid synthesis, especially FASN activity, special attention should be paid to lipid rafts. Lipid rafts are cholesterol- and sphingolipid-rich membranous lipid domains, which contain several signaling and transport proteins. According to some authors, lipid rafts play an important role in health and disease, including carcinogenesis[129]. Lipid rafts rich in proteins of the caveolin family are referred to as caveolae. Caveolin-1 encoding gene expression is altered in some cancers including colon cancer[130,131], breast cancer[132], urothelial carcinoma[133], esophageal squamous cell carcinoma[134], and prostate cancer[135]. The overexpression of caveolin -1 in

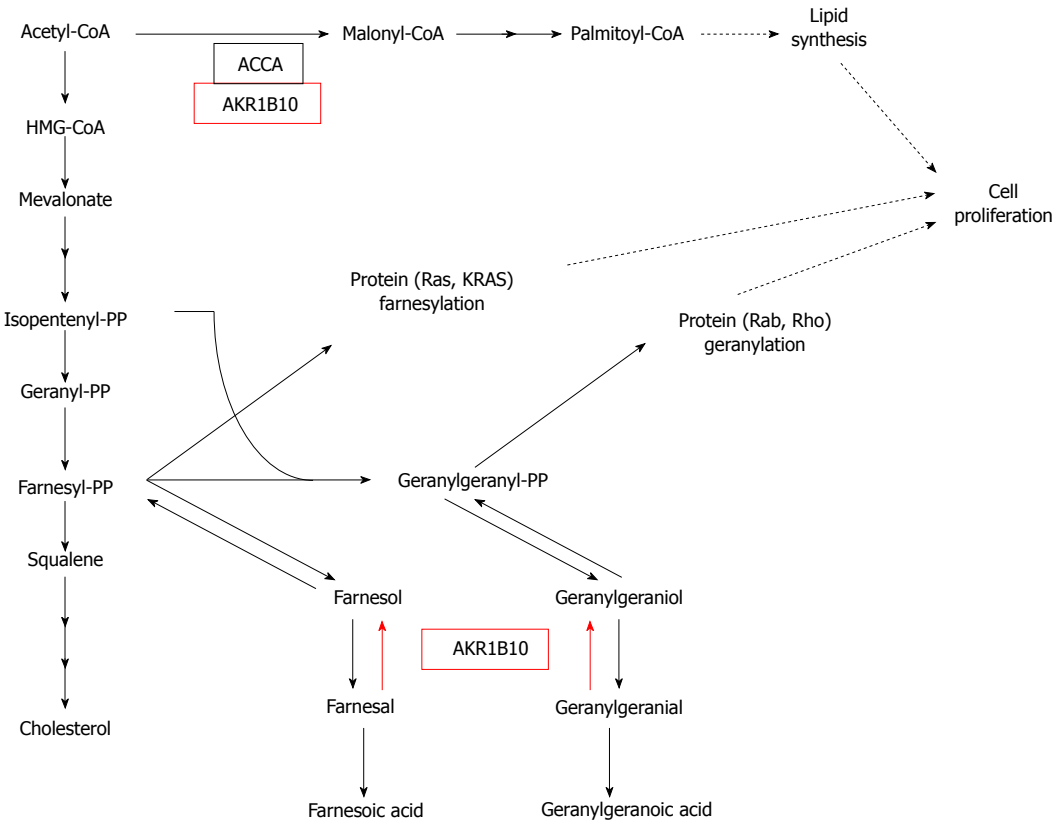

Figure 6 Possible role of aldo-keto reductase 1B10 in regulation of cell proliferation in pancreatic cancer. Binding of AKR1B10 results in stabilization of ACCA, and up-regulation of fatty acid synthesis. AKR1B10: Aldo-keto reductase family 1B10; ACCA: Acetyl-CoA carboxylase; Isopentenyl-PP: Isopentenyl diphosphate; Geranyl-PP: Geranyl diphosphate; Farnesyl-PP: Farnesyl diphosphate; Geranylgeranyl-PP: Geranylgeranyl diphosphate.

colon cancer cells is associated with elevated saturated to unsaturated FA ratio in cellular membrane[136]. Deregulation of caveolin-1 is also observed in PC cells[137]. Moreover, caveolin-1 and *FASN* are co-expressed in the cells of this malignancy. This phenomenon is consistent with histological grade and stage of the tumor (high expression of ceveolin-1 and *FASN* genes correspond with poor differentiation status)[104]. Thus, FASN and caveolin-1 were suggested as potential diagnostic and prognostic markers of PC and possible therapeutic targets[104].

Recently published data suggest that cancer cells do not rely solely on the *de novo* lipogenesis, but also utilize food-derived FAs for synthesis of phospholipids required for cell proliferation and lipid signaling[138,139]. This corroborates well with the evidence that a high dietary intake of fat constitutes potential risk factor of some malignancies[140]. Moreover, there is growing evidence that obesity, associated with elevated blood concentrations of FAs, modulates the risk and prognosis of certain cancers[141]. These findings suggest that, apart from lipogenesis, cancer cells can utilize FAs present in blood (derived from VLDL and chylomicrons or from adipose tissue) for their growth. This fact may partly explain why many promising lipogenic enzymes inhibitors tested succesfully in preclinical studies did not confirm their efficacy in further clinical trials. Furthermore, apart from inhibition of lipogenesis, also reduced dietary lipid digestion and absorption, and decreased lipoprotein lipase and FAs uptake seem necessary for the control of cancer growth[139].

Recently, overexpression and oncogenic function of aldo-keto reductase family 1B10 (AKR1B10; A-aldo, K-keto, R-reductase), tightly associated with lipid metabolism in human PC cell lines, has been reported[142]. AKR protein family consists of enzymes which catalyze the reaction: alcohol + $NADP^+$ → aldehyde (or ketone) + NADPH + H^+. These enzymes are expressed in numerous human organs/tissues. AKR1B10, the enzyme specific to such substrates as farnesal, geranylgeranial, retinal, and carbonyls[143-146], is overexpressed in certain malignancies, especially in tobacco-related cancers, including non-small cell lung carcinoma[147] and PC[142]. Oncogenic function of AKR1B10 is associated with protein farnesylation and up-regulation of FA synthesis by stabilization of ACCA[142,148]. Farnesyl diphosphate is a precursor of cholesterol biosynthesis and a substrate for protein farnesylation, which plays an important role in carcinogenesis[149]. Conversion of farnesyl diphosphate to farnesol diminishes its intracellular level, and, consequently, protein farnesylation. Farnesol can be further converted to farnesal, then oxidized to farnesoic acid. If the activity of AKR1B10 is high (as in the case of PC cells), farnesal is reduced to farnesol, following the reaction pattern: farnesal + NADPH + H^+ → farnesol + $NADP^+$. Farnesol can be re-phosphorylated to farnesyl diphosphate, increasing the ability for protein farnesylation (Figure 6). Farnesyl diphosphate, together with isopentenyl di-

phosphate, is converted to geranylgeranyl diphosphate, a substrate for protein geranylation. A geranylgeranyl diphosphate, *e.g.*, farnesyl diphosphate, can be converted to geranylgeranoic acid (*via* geranylgeraniol and geranylgeranial) (Figure 6). Similarly, high activity of AKR1B10 may cause the reversed conversion of geranylgeranial to geranylgeranyl diphospate, a substrate for protein geranylation (Figure 6). siRNA-mediated silencing of AKR1B10, knockdown of AKR1B10, or inhibition of the enzyme activity lead to decrease in protein prenylation[142]. Membrane-bound KRAS protein of PC cells, a product of point mutation in KRAS is activated by prenylation. If the expression of AKR1B10 is diminished, the activity of membrane-bound KRAS protein decreases in pancreatic cell lines[142]. Thus, the deactivation of AKR1B10 and resultant inhibition of the prenylation (fanezylation, geranylgeranylation) of protein (*e.g.*, KRAS), may constitute a promising target for PC treatment.

3-hydroxy-methylglutaryl-CoA reductase (HMG-CoA reductase) is a key enzyme of cholesterol synthesis pathway (Figure 6), which is inhibited by statins, prescribed to treat hypercholesterolemia. Since the reaction catalysed by HMG-CoA reductase provides substrate for cholesterol synthesis (that is of great importance in rapidly proliferating cancer cells), and also for isoprenoids necessary for prenylation of proteins, the application of statins as an antiproliferative drugs have been studied. Numerous *in vitro* studies, also with the use of PC cancer cells, provided promising results[150].

Cyclooxygenase-2 (COX-2) is another enzyme which plays an important role in lipid metabolism, namely in the conversion of arachidonic acid (released from membrane phospholipids by phospholipase A_2) to prostaglandins. COX-2 is overexpressed in many malignancies, including 45%-75% PCs[151-155]. This suggests, that this enzyme plays an important role in pancreatic carcinogenesis and chemoresistance of PC cells. Moreover, the overexpression of COX-2 in PC cells was postulated to be associated with greater invasiveness of this malignancy and promotion of angiogenesis. Recent data suggest that combination of COX-2 inhibitor (Celecoxib) with gemcitabine and irinotecan could be an active treatment for non-operable PC[152]. These clinical observations have been supported by the results of *in vitro* studies. Inhibition of COX-2 by non-steroidal anti-inflammatory drugs causes a dose-dependent block of pancreatic cell line proliferation[156]. According to recent reports, the anti-tumor activity of class I histone deacetylase (HDAC) inhibitors in human PC model is significantly improved by the simultaneous inhibition of COX-2[157]. Taken together, the results of clinical and *in vitro* observations suggest that COX-2 plays an important role in PC development. The up-regulation of COX-2 in PC cells and its role in carcinogenesis are probably related to inflammation. The anti-cancer action of COX-2 inhibitors is most likely associated with the reduction of inflammation that can contribute to cell proliferation. Several authors revealed that many malignancies, including PC, result from a chronic inflammatory process[158]. According to Jackson and Evers[151], several signaling pathways involving COX-2, NF-kappa B and phosphatidyl inositol 3-kinase may constitute a link between inflammation and carcinogenesis.

ABNORMAL LIPID METABOLISM AND CANCER PROGRESSION AND PROGNOSIS

Overexpression of *FASN* is associated with significantly enhanced proliferation of non-tumorigenic mammary[111] and prostate[159] epithelial cells. On the other hand, siRNA-mediated silencing of *FASN* gene expression or inhibition of FASN activity by pharmacological (synthetic or natural) agents leads to growth arrest of some cancer and normal cells[160-162]. Moreover, FASN inhibitors suppress the synthesis of DNA and induce apoptosis in cancer cell lines[163]. Previous studies confirmed the association between FASN activity and cell cycle progression[161,164]. However, activity of FASN was not reflected by cell cycle progression in some experimental models, *e.g.* MCF7 cell line[165]. Also siRNA-mediated knockdown of *FASN* gene expression did not cause a significant growth arrest in PC cell line (Panc-1)[105]. Therefore, the results published thus far do not present sufficient evidence for the role of FASN in cell cycle regulation, especially in PC cells. Nevertheless, the FASN knockdown in Panc-1 cells were revealed to show reduced resistance to gemcitabine[105].

The results of *in vitro* studies and clinical observations suggest that elevated expression of *FASN* gene in cancer cells is related to markedly worse prognosis. Overexpression of *FASN* gene was proved to be associated with cancer progression, higher risk of recurrence and shorter survival of patients with breast cancer[5,166], prostate cancer[167], melanoma[168], nephroblastoma[169], renal cell carcinoma[170], endometrial carcinoma[171], colorectal carcinoma[172], ovarian cancer[173], squamous cell carcinoma of the lung[174], head and neck squamous cell carcinoma[175], and squamous cell carcinoma of the tongue[176]. CD44 is a transmembrane glycoprotein which is involved in tumor progression and metastasis[177]. Interaction between CD44 and c-MET (tyrosine kinase), a proto-oncogene involved in several processes (including tumor growth, invasion, and metastasis)[178], is essential for activation of the latter and down-stream signaling in some malignancies[179]. Interestingly, inhibition of FASN and ACLY in human colorectal cancer cell lines (KM20, HCT116) is associated with reduced expression of CD44. This is attributed to attenuated activation of c-MET, AKT, FAK, and paxillin, factors affecting adhesion, migration and invasion of cancer cells[180]. The abovementioned phenomenon was reflected by lower metastatic potential of colorectal cancer cells. The data suggest a direct link between lipogenic enzyme activity (FASN and ACLY) and tumor progression to a metastatic phenotype. As the inhibition of FASN is related to decreased phosphorylation of c-Met in diffuse large B-cell lymphoma[181] and prostate cancer[182], one can surmise that lipogenesis is feature of

metastatic cancers, including PC. However, to date there are no evidence confirming this hypothesis.

Overexpression of *FASN* gene is associated with poor prognosis in PC patients[96,104,105]. As previously mentioned, the overexpression of *FASN* gene may be associated with gemcitabine resistance of PC cells[105], and the inhibition of FASN enhances the cytotoxicity of this agent[105]. Similar phenomenon was observed in the case of human breast cancer cells and ovarian cancer cells. According to Menendez group, the inhibition of FASN is associated with enhanced cytotoxicity of docetaxel, vinorelbine, paclitaxel, 5-fluorouracil, and herceptin in the Her-2 positive breast cancer cell lines and ovarian cancer cells[183-187].

SERUM FATTY ACID SYNTHASE LEVEL AND SERUM FATTY ACID PROFILE-POTENTIAL BIOMARKERS FOR PANCREATIC CANCER

At present there is no sufficiently specific and sensitive serum (plasma) marker of PC. Ca19-9, the most widely used marker of this malignancy (the sensitivity up to 80%), is also elevated in other conditions, including chronic pancreatitis and cholangitis, as well as in other tumors[188,189]. Moreover, Ca19-9 is not useful in detecting early stages of PC[190]. According to some authors, circulating micro-RNA (miR-21, mir-210, mir155, mir196a) could constitute novel diagnostic biomarkers of PC[191,192]. Proteomic analyses of human PCs revealed numerous differentially regulated proteins, which could be involved in the progression of this malignancy, and, consequently, could act as its biomarkers, determined in pancreatic juice and in serum[193]. Also up-regulation of numerous proteins, which can be used as biomarkers of PC, has been reported recently[194]. However, despite extensive studies, we still lack a valid approach for detection of PC, especially its early stages, and sufficiently specific and sensitive biomarkers of this malignancy.

The fact that cancer cells and the normal cells of surrounding tissues are characterized by differential expression patterns of *FASN* suggests that serum levels of FASN may constitute a good biomarker of malignancy. Indeed, up-regulation of *FASN* in cancer cells was proved to be associated with increased serum levels of this enzyme in patients with some malignancies. The serum FASN level measured by ELISA in breast, prostate, colon, and ovarian cancer patients was significantly higher than in healthy controls[195-197]. Moreover, an increase in the serum levels of FASN proved to be proportional to the clinical stage of colorectal cancer and breast cancer[196,198]. The ELISA-determined serum levels of FASN were also elevated in patients with PC and intraductal papillary mucinous neoplasm[98]. Interestingly, the serum FASN levels of most PC patients decreased after resection of this malignancy[98]. This suggests that the elevated serum level of FASN reflects its up-regulation in PC cells. However, increased levels of FASN were also found in sera of patients with chronic pancreatitis[98]. This suggests that this parameter is not a PC-specific biomarker. Nevertheless, the serum levels of FASN could potentially add to the panel of markers used in the monitoring of individuals at high risk of PC.

According to some authors, PC patients show increased proportion of total MUFA in all plasma lipid classes, a feature which is associated with increased delta 9 desaturase (SCD1) and delta 5 desaturase indices[128]. Moreover, the association between longer survival of PC patients and higher level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and with lower SCD1 index was demonstrated[128]. Recently, Yabushita *et al*[199] documented a significant decrease in serum (and pancreatic) level of palmitoleic acid in an experimental model of PDAC, and suggested that this FA could serve as a biomarker of human PC. Palmitoleic acid is a monounsaturated FA (16:1 n-9). It can be synthesized from palmitic acid, the main product of FASN, or may originate from diet. Conversion of palmitic acid to palmitoleic acid is catalyzed by SCD1, which is up-regulated in some malignancies including PC[128,200]. The reason for decrease in palmitoleic acid in patients with PC is not clear, as due to higher activity of SCD1, elevated level of this FA should be rather anticipated. Despite unknown molecular basis for the decreased serum and tissue concentration of palmitoleic acid the diagnostic value of this finding should be verified in patients with PC. Chavarro *et al*[201] showed that blood levels of some MUFAs including myristoleic acid (14:1 n-5), palmitoleic acid, and oleic acid (18:1 n-9), were associated with higher incidence of prostate cancer. This relationship was the strongest in the case of palmitoleic acid.

Recently Zhang *et al*[202] reported that PC can be diagnosed by means of ^{1}H nuclear magnetic resonance (NMR)-based metabonomic profiles. These authors showed that numerous plasma metabolites, including lipids, are either elevated (*e.g.*, VLDL) or decreased (*e.g.*, HDL, LDL and 3-hydroxybutyrate) in patients with this malignancy.

Yabushita *et al*[199] revealed that serum chenodeoxycholic acid, a major constituent of bile acids (which play a key role in lipid digestion in the alimentary tract), is elevated in the experimental model of PDAC. Also Urayama *et al*[203] claimed on elevated serum levels of some bile acids (taurocholic acid and tauroursodeoxycholic acid) in PC patients.

Overall, several PC-characteristic features of lipids metabolism have been found: (1) elevated serum level of FASN; (2) elevated serum levels of EPA, DHA and VLDL; (3) decreased serum levels of palmitoleic acid, HDL, LDL and 3-hydroxybutyrate, and (4) elevated serum levels of bile acids. All these parameters could serve as additional markers of PC.

Up-regulation of lipogenic enzymes in PC cells and resultant enhanced synthesis of lipids[19,96,104,105] seem to occur early in tumorigenesis and can be associated with

Table 5 Lipogenic enzyme inhibitors that can be used as potential antitumor drugs

Enzyme name	Inhibitor	Type of neoplasm	Ref.
Fatty acid synthase (FASN)	Cerulenin	Breast cancer, ovarian cancer	[303] [304]
	C75	Breast cancer	[216]
		Pancreatic cancer	[232]
	Epigallocatechin-3-gallate (EGG)	Prostate cancer	[228]
	C93	Lung cancer	[305]
		Ovarian cancer	[306]
	Luteolin	Breast cancer, ovarian cancer	[228]
		Pancreatic cancer	[232]
	Orlistat	Prostate cancer	[307]
ATP citrate lyase (ACLY)	SB-204990	Lung cancer	[308]
	hydroxycitrate	Brest cancer	[18]
		Pancreatic cancer	[101]
Acetyl-CoA carboxylase (ACCA)	Soraphen A	Prostate cancer	[309]
	TOFA	Lung cancer, colon cancer	[310]
Stearoyl-CoA desaturase (SCD1)	CVT-11127	Lung cancer	[222]
	TOFA	Colon cancer	[225]
Acetyl-CoA synthetase (ACS)	Triacsin c	Various cancers cell lines	[311]

the progression of the disease. Therefore, metabolic imaging with lipid precursor tracers: ^{11}C-acetate, ^{18}F-fluoroacetate (as a substrates for FA synthesis), and ^{11}C-choline, ^{18}F-fluorocholine (as a substrate for phosphatidylcholine synthesis), may constitute a novel imaging technique for diagnosis of PC, even at the very early stages of this malignancy. It is of note that ^{11}C-acetate and ^{11}C-choline have been successfully used for detecting primary prostate cancer, as well as metastases and recurrence of this malignancy[204]. However, both ^{11}C-acetate and ^{11}C-choline cannot be used in case of small metastatic foci[205]. Moreover, the sensitivity of ^{11}C-acetate in the detection of prostate cancer is decreased in patients whose PSA level is lower than 3 ng/mL[204]. Finally it should be remembered that the incorporation of ^{11}C-acetate (or its analogue ^{18}F-fluoroacetate) to lipids is determined not only by FASN activity, but also by the activity of acetyl-CoA synthetase[206].

ABNORMAL LIPID METABOLISM AS A PROMISING TARGET OF PANCREATIC CANCER TREATMENT

Chemotherapy provides only modest improvement in pancreatic cancer patients. Effective molecular therapeutic strategy requires characteristic features of the disease to be identified. As previously mentioned the values of some parameters of lipids synthesis, namely the expression of *FASN* gene and resultant activity of FASN, are significantly higher in cancer cells than in adjacent normal cells. This suggests that inhibition of FASN could constitute a selective therapeutic approach in cancer patients. Possible application of FASN as a therapeutic target is sustained by the results of many studies which showed that pharmacological blockade of this enzyme exerted cytostatic and cytotoxic effects to several tumor cells[97,109,125,207-216]. Pharmacological blockade of other enzymes involved in lipogenic pathway such as ACLY[18,209,217,218], ACCA[219-221], SCD1[222-225], and acyl-CoA synthetase[209], could also be an effective strategy for cancer treatment. Table 5 lists lipogenic enzymes inhibitor which can be potential antitumor drugs.

Similar to other malignancies, the overexpression of *FASN* observed in PC cells is associated with poor prognosis[96,104]. This suggest that FASN is involved in PC cell survival and its inhibition could constitute an effective strategy for PC treatment. Irresponsiveness to chemotherapy and radiotherapy is an important feature of PC. According to Yang *et al*[105], overexpression of *FASN* can be associated with resistance to gemcitabine and radiotherapy in PC patients. The exact molecular mechanism by which FASN induce gemcitabine resistance of PC cells is unknown. As the elevated expression of this molecule was proved to protect breast cancer cells from drug-induced apoptosis[165], also the FASN-induced resistance of PC cells to gemcitabine can result from similar mechanism. C75 (trans-4-carboxy-5-octyl-3-methylenebutyrolactone), a synthetic analog of natural cerulenin (isolated from Cephalosporum caerulens), is an inhibitor of FASN most often used in experimental models. This antitumor activity of this agent was documented in the case of human breast cancer[109], prostate cancer[226], ovary cancer[227] and mesothelioma[215] cell lines. Also many green tea polyphenols (*e.g.*, EGCG-epigallocatechin gallate or ECG-epicatechin gallate) and plant-derived flavonoids (such as luteoin) showed inhibitory effect to FASN[208]. Green tea polyphenols down-regulate *FASN* gene expression and induce apoptosis in human prostate cancer[228-230]. Luteolin (natural flavonoid) inhibits FASN *in vitro* and induces cytotoxic effects in breast, prostate cancer and hepatocellular carcinoma cells[231]. Moreover, the consumption of flavonoid rich foods was revealed to decrease the incidence of some malignancies[105]. Harris *et al*[232] studied the effect of FASN inhibitors (C75 and some phytochemicals) on the *in vitro* proliferation of PC

cells (MIA PaCa-2). They found that C75 and luteolin decreased proliferation of these cells at a similar dose. Also other tested phytochemicals, quercetin (flavonoid) and resveratrol (stilbenoid), inhibited the proliferation albeit, at significantly higher concentrations. The same authors revealed that the inhibitory effect of luteolin against PC cells results from three mechanisms: decreased synthesis of FA, and nucleic acids and decreased energy production. In contrast quercetin and resveratrol (natural inhibitors of FASN), which showed weaker inhibitory potential affect mainly glycogen metabolism. Collectively, the results published by Harris *et al*[232] suggest that the blockade of FASN by some flavonoids could lead to inhibition of pancreatic cells proliferation, similarly as in other cancer cells.

The results of clinical observations suggests that the incidence of cancer in diabetic patients, treated with metformin (an oral hypoglycemic drug, N,N'-dimethyl biguanide) is lower than in individuals with diabetes who do not receive this drug[233-236]. The anticancer properties of metformin were also confirmed by *in vitro* studies[237,238]. Recently, Nair *et al*[239] reported that metformin inhibits PC cell proliferation and tumor growth via down-regulation of Sp transcription factors and Sp regulated genes. Noticeably, *FASN* is one of the Sp regulated genes[240]. Thus, one can assume that the metformin induced blockade of PC cell proliferation and tumor growth is at least partially associated with indirect inhibition of FASN activity and lipid synthesis.

The anticancer potential of statins, inhibitors of HMG-CoA reductase also have been studied *in vitro* with various cancers cells lines. The antitumor effects of lipophilic statins (*e.g.*, lovastatin, simvastatin) resulted mainly from suppression of proliferation and promotion of apoptosis[150]. The chemopreventive effects of statins have been also reported in PC cell lines[241-243], and in mouse model of PC[244]. Available data from analyses on large human populations show, that daily intake of statins, in doses for cardiovascular event prevention, is not associated with the risk of PC[245-247]. However some recent data suggests that in subgroup of male smokers statins use may reduce the odds of PC[248], and is associated with better survival in diabetic patients[249]. The combination of statins and a FASN inhibitors used in an anticancer therapy would be of particular interest, but until now there are no data published regarding such approach.

In summary, the results presented above suggest that inhibitors of FASN (and inhibitors of other lipogenic enzymes) constitute promising anticancer agents. However, most of the known FASN inhibitors which can be potentially used as anticancer drugs displayed some side effects[250]. Nevertheless, the evidence of PC cells proliferation blockade resulting from direct or indirect inhibition of FASN, and potential involvement of FASN in gemcitabine (chemotherapeutic) resistance, substantiate further research on the role of this molecule in the biology and therapy of pancreatic malignancies. Moreover, there is an urgent need for specific/selective, side effect free inhibitors of FASN, which can be used in treatment of PC.

CONCLUSION

Similar to other malignancies, the reprogramming of lipid metabolism in PDAC, is closely connected with tumor development, growth, and progression. Hypoxia, activity of oncogenic factors, or the loss of tumor suppressors lead to significant changes in lipid biosynthesis and metabolism. KRAS, together with MYC and HIF1α, either increase the use of glucose and glutamine as substrates for FA synthesis, or regulate the lipogenesis directly. SFA and MUFA, (produced by FASN and SCD1 or taken up from blood), enhance the tumor growth by up-regulation of some oncogenic factors. FA built into phospholipids (together with caveolin-1) participate in the remodeling of cancer cell membrane structure. Other products of altered lipid metabolism, such as isoprene derivatives (farnesyl diphosphate or geranylgeranyl diphosphate), influence the activity of some proteins involved in tumorigenesis (enzymes and regulatory proteins) through their prenylation. Up-regulation of prostaglandin biosynthesis (from arachidonic acids) by COX2 links inflammation to PC development.

FASN is the most extensively studied enzyme involved in the lipid metabolism of PDAC cells. Its high activity in PC cells is associated with poor prognosis and increased resistance to chemo- or radiotherapy. Elevated serum levels of FASN, EPA, DHA or VLDL, and decreased serum levels of palmitoleic acid, HDL, LDL, or 3-hydroxybutyrate could serve as additional markers of PDAC. As the lipogenic activity of PDAC cells is higher than in normal cells, pharmacological inhibition of FASN and other lipogenic enzymes seems a promising therapeutic target. C75, some flavonoids, and metformin are good candidates for anticancer agents, but further research is required prior to their implementation to PDAC treatment.

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