Chapter 13
Targeting Metabolism

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Understanding Metabolic Reprogramming to Improve Therapeutic Strategies in Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with an unfavorable outcome and is projected to become the second deadliest cancer by 2030, and currently the overall 5-year survival rate is less than 7% [1, 2]. PDAC arises through multistage genetic and histological progression from precursors such as pancreatic intraepithelial neoplasia (PanIN). Activating mutations in the *KRAS* oncogene are observed in over 90% of PDAC patients, and using genetically engineered mouse models, it has been demonstrated that *KRAS* mutations influence tumor initiation, progression, and maintenance [3, 4]. Tumorigenesis is dependent on the reprogramming of cellular metabolism which can be a consequence of oncogenic mutations. In line with this, a profound rewiring of metabolic pathways involved in, e.g., glucose, glutamine, and lipid metabolisms, is activated downstream of oncogenic *KRAS* [5]. In general, metabolic reprogramming has now been recognized as a hallmark of cancer [6]. Cancer cells manipulate metabolisms to keep generating their own cellular components such as DNA, proteins, and lipids for maintaining rapid cell growth. Understanding and identification of metabolic reprogramming strategies of individual cancers could uncover novel potential personalized targets. This chapter provides a background of cancer metabolism focusing on glucose, glutamine, acetate, and lipid metabolism and targeting strategies for modulating enzymes/factors involved in key metabolic pathways.

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Glucose Metabolism and Pentose Phosphate Pathway in Pancreatic Cancer

Warburg Effect and Reprogramming of Glucose Metabolism: The Role of Gene Mutations

A pioneer of the study of cancer metabolic reprogramming, Otto Heinrich Warburg made a striking discovery known as Warburg effect that many cancer cells preferentially convert glucose into lactate (fermentation) rather than respiration – transporting pyruvate into mitochondria and converted it into acetyl-CoA for subsequent ATP production via the citric acid cycle and electron transport chain – even in the presence of oxygen [7–10]. Glycolysis, a metabolic pathway that converts glucose into pyruvate (and lactate) in the cytoplasm, is a sequence of ten enzyme-catalyzed reactions (Fig. 13.1). The three reactions converting glucose into glucose 6-phosphate by hexokinase (HK), fructose 6-phosphate into fructose 1,6-bisphosphate by phosphofructokinase (PFK), and phosphoenolpyruvate into pyruvate by pyruvate kinase are key steps. Oncogenic $KRAS^{G12D}$ plays a role in upregulating gene expression of the glucose transporter (GLUT) *Slc2a1* (SLC: solute carrier), *Hk1*, *Hk2*, and *Pfk1* as well as *Ldha* coding lactate dehydrogenase (LDH), an enzyme for converting pyruvate to lactate. Concomitantly oncogenic KRAS enhances glucose uptake and lactate production in a pancreatic cancer mouse model [11]. The transcription factor p53 is recognized as a key tumor suppressor and also frequently mutated in human tumors. Missense mutations such as R175H, R248Q, and R273H not only result in loss of the tumor suppressive function of p53 but also in oncogenic functions that promote invasion, metastasis, proliferation, and cell survival [12]. Mutation of p53 also enhances glucose uptake by GLUT1 translocation, glycolytic rate, and lactate production in R172H mutant-expressing p53 in murine cancer cells or fibroblasts (R172H is equivalent to human R175H) [13]. Deficiency of another tumor suppressor gene, *SMAD4*, increases GLUT1 levels and lactate production in cancer cells [14]. *KRAS*, *TP53*, *CDKN2A,* and *SMAD4* are the most prevalent genetic mutations in pancreatic cancer [1]; yet these genes are currently not druggable. However, targeting glucose metabolic reprogramming may provide a selective mechanism for eliminating cancer cells.

Targeting Enzymes and Factors Involved in Glucose Metabolism

Inhibition of GLUT, especially GLUT1 expression, can be an option to halt the proliferation of cancers. A small-molecule GLUT1 inhibitor WZB117 has been shown to block glucose uptake and tumor growth in a tumor xenograft model [15, 16]. Furthermore, WZB117 administration inhibits tumor initiation after implantation of cancer stemlike cells derived from pancreatic cancer cells without causing adverse events in host mice [17]. Overexpression of GLUT1 correlates with poor

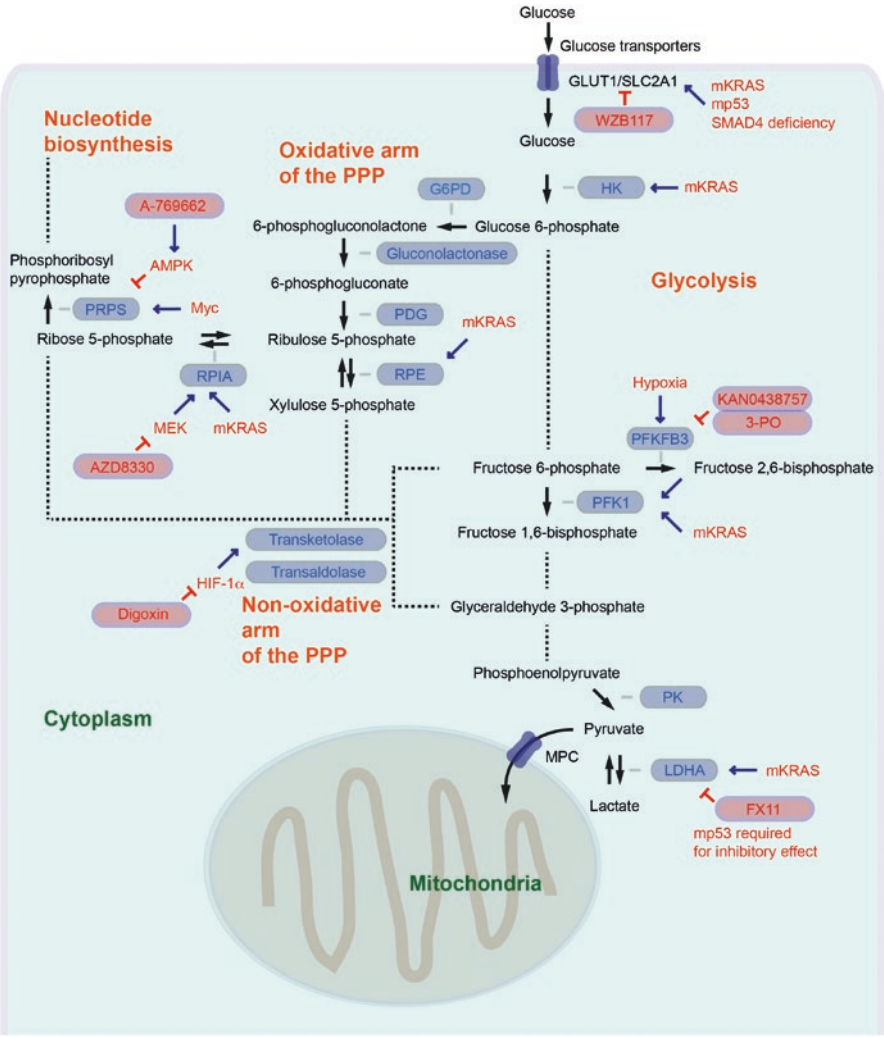

Fig. 13.1 Regulation of glycolysis, pentose phosphate pathway, and nucleotide biosynthesis. AMPK AMP-activated protein kinase, G6PD glucose 6-phosphate dehydrogenase, HIF hypoxia-inducible factor, HK hexokinase, LDH lactate dehydrogenase, mKRAS mutant KRAS, mp53 mutant p53, MPC mitochondria pyruvate carrier, PFK phosphofructokinase, PGD 6-phosphogluconate dehydrogenase PK pyruvate kinase, PPP pentose phosphate pathway, PRPS phosphoribosylpyrophosphate synthetase, RPE ribose 5-phosphate-3-epimerase, RPIA ribose 5-phosphate isomerase A, SLC solute carrier

overall survival of several solid tumors [18], and high GLUT1 expression is also suggested to predict shorter overall survival in patients with pancreatic cancer [19].

In the mammalian glycolytic pathway, PFK1 is rate-limiting and the most important control element. When PFK1 is inactive, the concentration of fructose

6-phosphate rises, and in equilibrium, the level of glucose 6-phosphate also rises. Hexokinase, another key enzyme in the glycolytic pathway, is allosterically inhibited by glucose 6-phosphate; therefore, PFK1 inhibition leads to the inhibition of hexokinase. Activity of PFK1 is stimulated by fructose 2,6-bisphosphate, which is derived from fructose 6-phosphate catalyzed by PFK2. There are four PFK2 isoforms (PFKFB1–4), and PFKFB3 is highly expressed in many types of human cancer including pancreatic cancer [20]. Expression of PFKFB3 can also be regulated by hypoxia [21]. PFKFB3 also regulates angiogenesis and vessel branching [22] and can be an emerging anticancer target. In this line, KAN0438757 has been considered as a selective PFKFB3 inhibitor, and treatment with this inhibitor radiosensitizes cancer cells [23]. Another PFKFB3 blocker 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) reduces orthotopically implanted pancreatic cancer cell development [24], suggesting that targeting PFKFB3 can be an option for pancreatic cancer treatment.

In the late step in glycolysis, pyruvate kinase plays an important role as catalyzing the last physiological irreversible reaction to produce pyruvate. In mammals, there are four pyruvate kinase isoforms encoded by two genes: isoforms PKL and PKR are derived from the PKLR gene, and PKM1 and PKM2 are derived from the PKM gene through alternative splicing. The amino acid differences in PKM2 result in a fructose 1,6-bisphosphate-binding pocket for positive allosteric regulation [25]. Activation of PFK1 (for producing fructose 1,6-bisphosphate) can therefore not only regulate hexokinase activity but also PKM2 activity. PKM2 is expressed during embryogenesis, regeneration processes, and in cancer, suggesting that PKM2 activity is important in actively proliferating cells [25]. Orthotopically implanted cancer cells expressing PKM2 support tumorigenesis, whereas cells expressing PKM1 reduce tumorigenicity, suggesting that the PKM2 splice isoform is important for cancer metabolism and tumor growth [26]. On the contrary, in some studies activation of PKM2 can inhibit cancer cell proliferation [27, 28]. Furthermore, conditional deletion of PKM2 in a pancreatic cancer mouse model (oncogenic $KRAS^{G12D}$ expression and p53 deletion) does not affect mouse survival, tumor weight, or tumor histology [29]. Therefore, targeting PKM2 might not be suitable for pancreatic cancer treatment and needs further investigation.

Pyruvate is a key metabolite in the network of metabolic pathways. Pyruvate in the cytoplasm can be converted into alanine by alanine aminotransferase (ALT) or transported into the mitochondria via mitochondria pyruvate carrier (MPC) and converted there into oxaloacetate by pyruvate carboxylase for gluconeogenesis or converted into acetyl-CoA by the pyruvate dehydrogenase (PDH) complex for the citric acid cycle. Pyruvate decarboxylase catalyzes a reaction converting pyruvate into acetaldehyde in the cytoplasm and mitochondria. Cancer cells however preferentially convert pyruvate into lactate, which is catalyzed by LDH. LDH is a tetramer of two subunits LDHA and LDHB, which assemble into five different combinations [30]. LDHA has a higher affinity for pyruvate than LDHB, and elevated levels of LDHA are a hallmark of many cancer types; hence targeting LDHA can be a promising strategy for cancer therapeutics. Consistently, FX11 (3-dihydroxy-6-methyl-7-(phenylmethyl)-4-propylnaphthalene-1-carboxylic acid), a small-molecule

inhibitor of LDHA, inhibits the progression of pancreatic cancer xenografts [31]. Interestingly, the inhibitory effect of FX11 requires mutant p53, and FX11 treatment does not inhibit tumor progression of patient-derived PDAC xenografts without p53 mutation [32], suggesting that targeting LDHA in pancreatic cancer can be an attractive stratification option since drug responsiveness in PDAC patients may depend on the genetic status.

Pentose Phosphate Pathway: Helper of Cancer's Anabolic Demands

The pentose phosphate pathway (PPP) is another pathway in the cytoplasm for glucose catabolism starting from glucose 6-phosphate. The major function of the PPP is not energy production, but generating extramitochondrial nicotinamide adenine dinucleotide phosphate (NADPH), which is required for fatty acid synthesis and for scavenging reactive oxygen species (ROS). The PPP also supports the synthesis of ribonucleotides. The PPP is divided into two parts, namely, the oxidative arm and non-oxidative arm. The oxidative arm is initiated by conversion of glucose 6-phosphate to 6-phosphogluconolactone by glucose 6-phosphate dehydrogenase (G6PD), which is converted into 6-phosphogluconate by gluconolactonase and further converted into ribulose 5-phosphate by 6-phosphogluconate dehydrogenase (PGD). In the non-oxidative phase of the PPP, ribulose 5-phosphate is either reversibly catalyzed by ribose 5-phosphate isomerase A (RPIA) for producing ribose 5-phosphate or reversibly catalyzed by ribose 5-phosphate-3-epimerase (RPE) for producing xylulose 5-phosphate [33]. Ribose 5-phosphate is converted by phosphoribosylpyrophosphate synthetase (PRPS) to phosphoribosyl pyrophosphate, which serves as the backbone for nucleotide synthesis. Oncogenic $KRAS^{G12D}$ upregulates *RPIA* and *RPE* gene expression in murine primary cells of a pancreatic cancer model with oncogenic $KRAS^{G12D}$ and p53 deficiency. Knockdown of *Rpia* or *Rpe* genes in primary cells reduces the flux of glucose into DNA/RNA synthesis and xenograft pancreatic tumor growth [11], and knockdown of *Rpia* gene inhibits human PDAC cell growth [34]. Ribose 5-phosphate and xylulose 5-phosphate in the non-oxidative branch of the PPP can also be reversibly catalyzed by transketolase and aldolase to fructose 6-phosphate or glyceraldehyde 3-phosphate, which can be utilized in the glycolysis [33]. Vice versa, fructose 6-phosphate and glyceraldehyde 3-phosphate in the glycolytic pathway can be incorporated into the PPP pathway, and many cancer cells generate ribose 5-phosphate through the non-oxidative branch of the PPP for de novo nucleotide biosynthesis [35]. Fructose induces transketolase flux and proliferation of pancreatic cancer cells [36]. High fructose intake has been suggested to be associated with increased pancreatic cancer risk [37]. A key regulator of the non-oxidative branch of the PPP is hypoxia-inducible factor (HIF)-1α which increases the carbon flux into the PPP [35], and HIF-1α directly regulates transketolase gene expression [38]. Taken together, the PPP especially the

non-oxidative arm plays an important role in de novo nucleotide biosynthesis, and directly or indirectly targeting enzymes and factors involved in the PPP is a promising therapeutic strategy against pancreatic cancer.

Targeting Enzymes and Factors Involved in the Pentose Phosphate Pathway and Nucleotide Synthesis

Oncogenic $KRAS^{G12D}$ reprograms metabolism of the PPP in PDAC through MAPK and Myc pathways [11, 34]. Myc has been further shown to control PRPS2, but not PRPS1, and functional loss of PRPS2 delays Myc-dependent tumor initiation [39]. Since KRAS and Myc are currently not druggable, targeting RPIA, RPE of the non-oxidative branch of the PPP, as well as targeting PRPS2 in the nucleotide biosynthesis pathway can be considered as therapeutic options. Inhibitors of RPIA, RPE, or PRPS remain largely undiscovered. Especially selective PRPS2 inhibitors are challenging to identify, since PRPS2 shares more than 97% amino acid identity with the PRPS1 [40]. So far, pharmacological inhibitors of effector pathways on cancer metabolism have been used. For example, treatment with the MEK inhibitor AZD8330 decreases *Rpia* gene expression in murine primary cells of a pancreatic cancer model with oncogenic $KRAS^{G12D}$ and p53 deficiency [11]. AMP-activated protein kinase (AMPK) phosphorylation leads to conversion of PRPS hexamer to monomer resulting in inhibition of nucleotide synthesis in cancer cells (AMPK activator: A-769662) [41]. Digoxin is an HIF-1α synthesis inhibitor [42], and targeting HIF-1α leads to reduction of transketolase gene expression and improved gemcitabine sensitivity in pancreatic cancer cells [38]. MEK/MAPK, AMPK, and HIF-1α regulate not only the PPP and/or nucleotide biosynthesis. However, reprogramming the reprogrammed metabolism of the PPP and nucleotide biosynthesis in cancer by modulating effectors is also a promising targeting strategy.

Lipid Metabolism in Pancreatic Cancer

Fatty Acid Synthesis as an Entrance of Lipid Metabolism and Critical for Cancer Cell Proliferation

The most prominent metabolic alteration is known as the Warburg effect. However, cancer cells manipulate many other metabolic pathways for building up their own cellular components. Especially, activating lipid synthesis is highly important for cancer cells, because lipids such as phospholipid bilayers are fundamental structural components enabling cellular proliferation. It has been shown that extracellular lipids can sufficiently stimulate pancreatic cancer cell proliferation [43]. However, in a wide variety of tumors, de novo synthesis of fatty acids (FAs) is activated

irrespective of the levels of circulating lipids. In contrast to normal cells, cancer cells may gain more than 93% of triacylglycerol FAs via de novo synthesis [44]. In the first step of FA synthesis, cytoplasmic acetyl-CoA is generated from citrate by ATP-citrate lyase (ACLY) and then converted into malonyl-CoA by acetyl-CoA carboxylase (ACC). Malonyl-CoA and acetyl-CoA are coupled to the acyl-carrier protein (ACP) domain of the multienzyme protein fatty acid synthase (FASN) (Fig. 13.2). Via repeated condensations of acetyl groups by the FASN in an

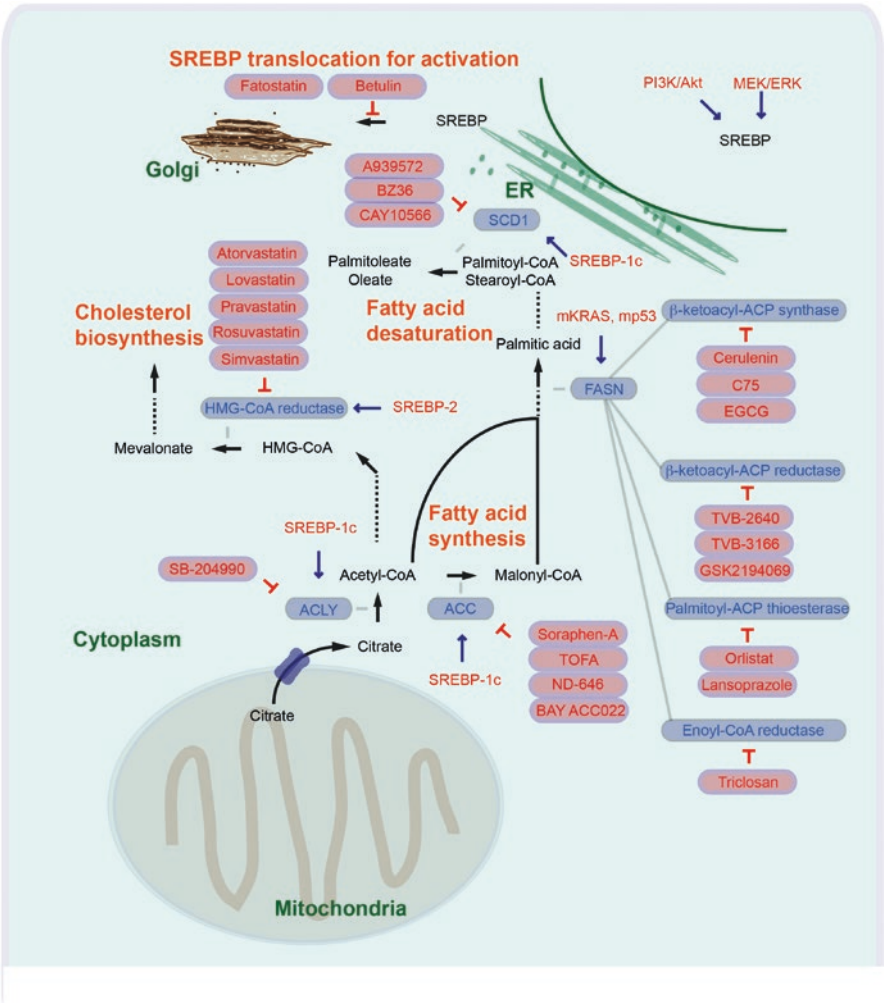

Fig. 13.2 Regulation of fatty acid synthesis, cholesterol synthesis, fatty acid desaturation, and SREBP translocation. ACC acetyl-CoA carboxylase, ACLY ATP-citrate lyase, ER endoplasmic reticulum, FASN fatty acid synthase, HMG-CoA 3-hydroxy-3-methylglutaryl-CoA or β-hydroxy-β-methylglutaryl-CoA, SCD Δ^9-stearoyl-CoA desaturase, SREBP sterol regulatory element-binding protein

NADPH-dependent manner, a basic 16-carbon saturated FA called palmitic acid is generated [45]. In cancer cells, expression of ACLY and ACC is also markedly increased [44]. Furthermore, serum FASN levels are higher in patients with PDAC, in patients with intraductal papillary mucinous neoplasm (IPMN), and in patients with chronic pancreatitis in comparison to healthy controls [46]. Pancreatic cancer patients with high FASN expression in the pancreas show a shorter overall survival than patients with low FASN expression [47]. Furthermore, FASN expression is correlated with poor response to gemcitabine therapy in pancreatic cancer cells [47, 48]. Increased *Fasn* gene expression is also observed in a pancreatic cancer mouse model with oncogenic $KRAS^{G12D}$ and p53 R172H mutation [47], suggesting that enzymes involved in fatty acid synthesis can be important targets.

Targeting Fatty Acid Synthesis in Cancer

For targeting fatty acid synthesis, several inhibitors for ACLY, ACC, and FASN blockade have been proposed. SB-204990 is an ACLY inhibitor which inhibits lipid synthesis. Intraperitoneal administration of SB-204990 leads to reduced tumor growth in mice carrying xenografts of primary mouse PDAC lines generated from oncogenic $KRAS^{G12D}$ with or without p53 R172H mutation [49]. For inhibiting ACC, soraphen A and TOFA (5-(tetradecyloxy)-2-furoic acid) have been shown to block cancer cell growth [50], and treatment with TOFA suppresses the proliferation of pancreatic cancer cells [51]. In a mouse xenograft model, it has been demonstrated that intraperitoneally administered TOFA reduces human ovarian cancer cell development [52]. Oral administration of another ACC inhibitor ND-646 suppresses FA synthesis and tumor growth in lung cancer mouse models where tumors are induced by oncogenic $KRAS^{G12D}$ with p53 deficiency or by oncogenic $KRAS^{G12D}$ with *Stk11* knockout [53]. Serine/threonine kinase 11, also known as liver kinase B1 (LKB1), activates AMPK for ACC inhibition. BAY ACC022 (another ACC inhibitor) attenuates growth of pancreatic cancer cell xenograft in mice [54]. These observations suggest that inhibiting the first step of FA synthesis is an attractive strategy for cancer therapy.

Targeting FASN can be performed by several different inhibitors, since FASN is a multienzyme protein complex with two identical polypeptides. The enzyme complex includes several catalytic domains with ACP, malonyl/acetyltransferase (MAT), β-ketoacyl-ACP synthase, β-ketoacyl-ACP reductase, 3-hydroxyacyl-ACP dehydrase, enoyl-CoA reductase, and palmitoyl-ACP thioesterase. Several inhibitors block β-ketoacyl-ACP synthase of FASN, namely, cerulenin, C75 (4-methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid, cerulenin-derived semisynthetic FASN inhibitor with improved stability), and epigallocatechin-3 gallate (EGCG) [44]. Cerulenin and C75 have been tested in several cancer xenograft models like for ovary, prostate, mesothelioma, breast, and colon cancer. Intraperitoneally administered cerulenin also suppresses liver metastasis of colon cancer cells in mice [55]. Blockage of FASN with EGCG has been considered for a broad range of cancer

types such as prostate, lung, breast, and colorectal cancer [56, 57]. EGCG inhibits pancreatic cancer cell proliferation, and antiproliferative effects are also observed with catechin gallate (CG) and epicatechin gallate (ECG) [58]. EGCG inhibits growth of pancreatic tumor cells orthotopically implanted in mice [59]. For inhibiting β-ketoacyl-ACP reductase, several compounds like TVB-2640, TVB-3166, and GSK2194069 have been proposed. TVB-2640 has entered clinical trials, e.g., for colon cancer, breast cancer, and astrocytoma. Treatment with TVB-3166 leads to inhibition of proliferation and reduction in tumor growth of multiple cancer cell lines and pancreatic cancer xenografts [57, 60]. The β-lactone orlistat blocks palmitoyl-ACP thioesterase, and enoyl-CoA reductase can be blocked by triclosan [44, 61]. Orlistat is a US food and Drug Administration (FDA)-approved anti-obesity drug, and it has been shown that orlistat reduces human pancreatic cancer cell growth [47, 62]. Inhibition of FASN with orlistat suppresses growth of EGFR tyrosine kinase inhibitor-resistant cancer cells and also tumors in EGFR mutant transgenic mice [63]. One main limitation of orlistat is its low oral bioavailability, and improved formulation of orlistat-like inhibitors may be required in the future. Alternatively, other inhibitors of palmitoyl-ACP thioesterase can be identified via in silico screening of FDA-approved drugs. Lansoprazole, rabeprazole, omeprazole, and pantoprazole are proton pump inhibitors, but also function as inhibitors of thioesterase activity, which can induce pancreatic cancer cell death [64]. In conclusion, a number of inhibitors of ACLY, ACC, and FASN have been proposed and show significant effects in cancer therapy.

Fatty Acid Desaturases: Not Just a Modifier

The main product of FA synthesis in the cytoplasm is 16-carbon saturated palmitic acid. Longer FAs are formed by reactions catalyzed by several enzymes on the cytosolic side of the endoplasmic reticulum (ER). The desaturation of fatty acids occurs also in ER membranes. These modifications support the production of a wide variety of FAs and lipids. In mammalian cells, three types of fatty acid desaturases introduce carbon double bonds at Δ^5 (Δ^5-eicosatrienoyl-CoA desaturase), Δ^6 (Δ^6-oleoyl(linolenoyl)-CoA desaturase), or Δ^9 (Δ^9-stearoyl-CoA desaturase) (SCD). SCD is the rate-limiting enzyme catalyzing the synthesis of monounsaturated 16- or 18-carbon-like palmitoleate and oleate from palmitoyl-CoA and stearoyl-CoA [65]. Enhanced FA synthesis in cancer cells also increases the requirement of enzymes for modifying FAs and lipids. SCD1 (the main isoform) has been associated with insulin resistance and diabetes. Expression of SCD1 is associated with tumor promotion, shorter survival of lung cancer patients [66], and with sorafenib resistance in liver cancer patients [67]. SCD1 expression is upregulated in human colorectal cancer tissues, and patients with high SCD1 expression levels have a shorter overall survival [68]. It has also been suggested that increased SCD1 expression is associated with shorter survival of pancreatic cancer patients [69]. SCD1 contributes to the maintenance of cancer cell stemness, and knockdown of SCD1 reduces the

expression of stemness markers like *SOX2* and *NANOG* [70]. Cancer stemness may be responsible not only for tumor initiation but also for metastasis [71]. Taken together, targeting SCD1 could be a promising option.

Targeting Fatty Acid Desaturases

However, the role of SCD1 remains controversial and requires further investigation. In a murine intestinal cancer model with a mutant allele Min (multiple intestinal neoplasia) of the Apc (adenomatous polyposis coli) locus (called $Apc^{Min/+}$ mice), conditional deletion of *Scd1* in the intestinal epithelium promotes inflammation and tumorigenesis [72]. On the other hand, the inhibitor A939572 has been applied for renal cell carcinoma treatment. Oral administration of A939572 inhibits the development of tumor xenografts in mice [73]. Intraperitoneal injection with another SCD1 inhibitor (BZ36) reduces prostate cancer xenografts in mice [74]. Furthermore, pretreatment with the SCD1 inhibitor CAY10566 suppresses ovarian tumor growth after inoculation of cancer stem cells, where inhibition of SCD1 impairs cancer cell stemness [70]. The effects these inhibitors have on pancreatic cancer cells are currently not known.

Sterol Regulatory Element-Binding Proteins: Master Regulators of Lipid Biogenesis and Cholesterol Metabolism

Expression of genes involved in FA synthesis and modification such as *ACLY*, *ACACA/B* (coding ACCs), *FASN*, and *SCD* is regulated by the transcription factor sterol regulatory element-binding protein 1c (SREBP-1c) that is itself regulated transcriptionally and/or posttranslationally by several signaling pathways and factors such as PI3K/Akt and MEK/ERK [75]. EGFR signaling is required for oncogenic $KRAS^{G12D}$-induced pancreatic tumorigenesis [76, 77], and EGFR activation also induces upregulation of FASN in pancreatic cancer cells in an ERK-dependent manner [78]. Along this line, PDAC patients with high SREBP1 expression have a shorter overall survival than patients with low SREBP1 expression, and knockdown of *SREBF1* (for SREBP1 expression) decreases pancreatic cancer cell viability and proliferation [79]. Taken together, oncogenic signaling pathways activate expression of lipogenic enzymes leading to aberrant activation of FA synthesis, which supports cancer cell development.

There are three SREBP isoforms, SREBP-1a, SREBP-1c, and SREBP-2. Both SREBP-1a and SREBP-1c are derived from a single gene but through alternative transcription start sites. Whereas SREBP-1c preferentially regulates genes of FA metabolism, SREBP-1a is a potent activator of all SREBP-responsive genes, and SREBP-2 regulates cholesterol biosynthesis [80]. Cholesterol is an essential structural component of cell membranes together with various phospholipids,

sphingomyelin, and glycolipids. Cholesterol is de novo synthesized from cytoplasmic acetyl-CoA through the mevalonate pathway. The rate-limiting step of the pathway is the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, also known as β-hydroxy-β-methylglutaryl-CoA) to mevalonate by HMG-CoA reductase [81]. In addition to the mevalonate pathway, cells can increase their cholesterol contents thought receptor-mediated endocytosis of low-density lipoproteins (LDLs) [82]. The LDL receptor (LDLR) and HMG-CoA reductase are both transcriptional targets of SREBP-2 [80]. Expression of HMG-CoA reductase and LDLR is elevated in an oncogenic $KRAS^{G12D}$ pancreatic cancer mouse model [83]. It has been suggested that cholesterol intake is associated with increased risk of pancreatic cancer [84]. Increased expression of *Ldlr* has no significant effect on overall survival of pancreatic cancer patients, but high *Ldlr* expression is associated with an increased risk of tumor recurrence. Since LDLR silencing reduces ERK signaling as well as proliferation of PDAC cells, silencing also enhances response to gemcitabine chemotherapy [83].

Targeting Cholesterol Synthesis and SREBP

The development of LDLR-inactivating agents is currently an ongoing issue. Alternatively, SREBP-1c and SREBP-2 can be potential targets for cancer therapy, since these are key regulators of FASN expression and other enzymes in fatty acid synthesis like ACLY and ACC, and it also regulates expression of SCD, LDLR, and HMG-CoA reductase. SREBPs interact with the SREBP cleavage-activating protein (SCAP), and the complex stays with the ER membrane proteins INSIG1 and INSIG2. Under physiological conditions, reduction of cellular lipid levels results in conformational change of SCAP that abrogates its interaction with INSIGs. Dissociation of the SREBP/SCAP complex from INSIGs leads to transport of the complex from the ER to the Golgi where SREBP is cleaved and activated [85]. Glucose can enhance SCAP stability and reduce its association with INSIGs allowing transport of the SREBP/SCAP complex to the Golgi [86]. Betulin and fatostatin have been proposed as SREBP inhibitors through inhibition of ER-Golgi translocation. Betulin has initially been shown to improve hyperlipidemia and insulin resistance and to reduce atherosclerotic plaques [87]. Intraperitoneal injection of betulinic acid combined with mithramycin A (DNA and RNA polymerase inhibitor) blocks the development of pancreatic cancer xenografts in mice [88]. Fatostatin injection reduces expression of FASN, ACC, SCD1, ACLY, and also *Hmgcr* (HMG-CoA reductase) and *Ldlr* transcription to a lesser extent in obese mice [85]. The inhibitor has been tested in glioblastoma and prostate cancer cell xenografts. There, intraperitoneal treatment with fatostatin reduced xenograft growth in mice [89, 90]. Inhibiting de novo cholesterol synthesis by blockage of the rate-limiting enzyme HMG-CoA reductase has also been considered for cancer therapy. Several statin derivatives such as atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin have entered clinical trials. Among the derivatives, atorvastatin and simvastatin

have been considered for pancreatic cancer treatment [57]. Taken together, there are several therapeutic options targeting SREBP and the mevalonate pathway, and a number of cancer studies are currently ongoing.

Glutamine and Acetate Metabolism in Pancreatic Cancer

Glutamine Metabolism: It Works Also Without Mitochondria

By modulating the activity of several metabolic pathways including glutamine metabolism, cancer cells aim for continuous generation of FAs necessary for cell growth. Glutamine is the most abundant and nonessential amino acid that can be synthesized from glucose. In the canonical route of mitochondrial glutamine catabolism (glutaminolysis), glutaminase (GLS) catalyzes glutamine to glutamate (Fig. 13.3). Glutamate is further converted by glutamate dehydrogenase (GLUD1)

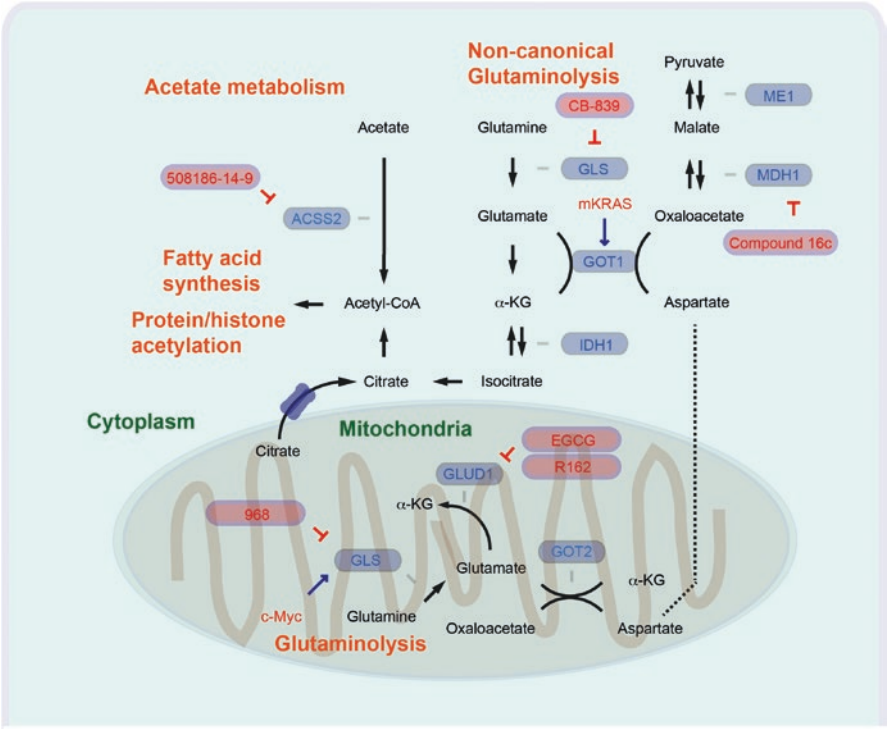

Fig. 13.3 Regulation of glutaminolysis and acetate metabolism. ACSS short-chain acyl-CoA synthetase, GLS glutaminase, GLUD glutamate dehydrogenase, GOT aspartate transaminase, IDH isocitrate dehydrogenase, MDH malate dehydrogenase, ME malate enzyme

to α-ketoglutarate (α-KG), and α-KG can then be integrated into the tricarboxylic acid cycle (TCA cycle). Glutamine is an essential nutrient for the proliferation of human cancer cells [91], and several oncogenes which activate glutaminolysis have been identified. Oncogenic c-Myc enhances expression of mitochondrial GLS supporting canonical glutaminolysis [92]. Pancreatic cancer cells rely on a cytoplasmic noncanonical glutaminolysis pathway producing pyruvate via aspartate transaminase (GOT1, catalyzes aspartate/oxaloacetate), malate dehydrogenase (MDH1, catalyzes malate/oxaloacetate), and malate enzyme (ME1, catalyzes malate/pyruvate). Oncogenic KRAS induces a shift from canonical to noncanonical glutaminolysis by inhibiting mitochondrial GLUD1 and activating cytoplasmic GOT1 [93]. By reprogramming of glutamine metabolism from the mitochondrial to the cytoplasmic system, pancreatic cancer can keep synthesis of FAs intact, because cytoplasmic isocitrate dehydrogenase (IDH1) can catalyze α-KG/isocitrate under hypoxic conditions or even with defective mitochondria [94–96].

Targeting Glutamine Metabolism

Several drugs such as 968, BPTES, and CB-839 have been developed to inhibit GLS glutamate synthesis. Treatment with 968 or with BPTES reduces pancreatic cancer cell viability [93]. Intravenous injection of BPTES nanoparticles reduces pancreatic cancer xenograft growth in mice, and combination with intraperitoneal injection of metformin enhances therapeutic effects [97]. CB-839 has already been tested in several clinical studies including a broad range of cancer types, such as clear cell renal carcinoma, breast cancer, and colorectal cancer. However, oral gavage of CB-839 has no antitumor activity in mice with oncogenic $KRAS^{G12D}$ combined with Trp53 deficiency. In addition, mice treated with CB-839 show marginally shorter survival than the group without CB-839 treatment [98]. Further investigations are therefore required to judge whether GLS inhibition is a potential therapeutic option for pancreatic cancer patients. EGCG and R162 have been considered to inhibit GLUD1 [99]. EGCG has been described as a FASN β-ketoacyl-ACP synthase inhibitor and shown to inhibit pancreatic cancer cell proliferation (see Targeting Fatty Acid Synthesis in Cancer), and it is also recognized as a GLUD1 inhibitor. Treatment with R162 inhibits proliferation of several cancer cells including primary leukemia cells. Furthermore, intraperitoneal injection of R162 inhibits the development of lung cancer xenografts in mice [100]. Oncogenic $KRAS^{G12D}$ has been suggested to inhibit GLUD1 and preferentially activate the noncanonical glutaminolysis pathway (see Glutamine Metabolism: It Works Also Without Mitochondria); thus, GLUD1 inhibition might be ineffective in pancreatic cancer. Methyl 3-(3-(4-(2,4,4-trimethylpentan-2-yl)phenoxy)-propanamido)benzoate (named compound 16c) has been synthesized to inhibit the noncanonical glutaminolysis pathway as a MDH inhibitor. This inhibitor blocks both cytoplasmic MDH1 and mitochondrial MDH2 enzymes. It has been shown that intraperitoneal administration of this inhibitor attenuates the development of colon cancer xenografts [101]. Since inhibition of

MDH1 activity leads to suppression of glutamine metabolism and reduction of pancreatic cancer cell growth [102], inhibitors for the noncanonical glutaminolysis pathway could be potential candidates for pancreatic cancer therapy.

Acetate Metabolism: Cancer Cells Are Experts in Bridging the Gap

Acetyl-CoA represents a central metabolite not only for lipid synthesis but also for regulating gene expression as a key determinant of protein/histone acetylation [103, 104]. Cancer cells preferentially convert pyruvate into lactate rather than to transport it into the mitochondria for PDH reaction and the TCA cycle. Although the IDH1-mediated non-canonical glutaminolysis pathway (see Glutamine Metabolism: It Works Also Without Mitochondria) may compensate to provide acetyl-CoA in the cytoplasm, alternative sources of acetyl-CoA could still be necessary for sufficient supporting lipid synthesis and cancer cell growth. Cells with ACLY deficiency remain viable and proliferate, where acetate supports acetyl-CoA generation and de novo lipid synthesis is supported by the enzyme called ACSS2 [105]. There have been 26 acyl-CoA synthetases (ACS) identified in the human genome. Among those, three enzymes, the short-chain ACS (ACSS) family (acetyl-CoA synthetase), are capable of catalyzing synthesis of acetyl-CoA from acetate in an ATP-dependent manner [106]. ACSS1 and ACSS3 are mitochondrial enzymes, and ACSS2 localizes to both the cytoplasmic and nuclear compartments. Silencing of ACSS2 in cancer cells reduces incorporation of acetyl units from acetate into either lipids or histones. ACSS2 is highly expressed in several human tumors, and loss of ACSS2 suppresses tumor development in certian mouse liver cancer models including c-Myc combined with PTEN knockout [107]. Under metabolic stress such as hypoxia and/or low-nutrition conditions, expression of ACSS2 is elevated, and it promotes acetate uptake for lipid synthesis and membrane phospholipids in several cancers including pancreatic cancer cells [108, 109].

Inhibitors specifically targeting ACSS2 remain largely unexplored. So far a compound 1-(2,3-di(thiophen-2-yl)quinoxalin-6-yl)-3-(2-methoxyethyl)urea (PubChem CID: 2300455; here referred to as 508186-14-9) has been proposed as a ACSS2-specific inhibitor [107]. The inhibitor has been tested and showed decreased lipid contents in bladder cancer cells, but not in non-cancer cells [110]. Targeting ACSS2 and acetate metabolism would be a highly interesting concept for treating pancreatic cancer.

Conclusion

Extensive research on cancer metabolism has revealed that a number of enzymes and metabolites are involved in reprogramming strategies of many cancer types including pancreatic cancer. Furthermore, it is evident that overexpression of

specific enzymes is not only related with metabolic reprogramming but also with cellular stemness. Several studies with inhibitors targeting specific catalyzing steps in selected metabolic pathways have shown convincing effects in inhibiting cancer development and progression. Cancers may however still find other ways to generate necessary metabolic intermediates and cellular components. Therefore, it is important to further understand not only the cross talk between oncogenic signaling pathways and metabolism but also between metabolic pathways for offering stratified and more effective therapies in the future.

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