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REVIEW

Oncometabolites in pancreatic cancer: Strategies and its implications

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Abstract

Pancreatic cancer (PanCa) is a catastrophic disease, being third lethal in both the genders around the globe. The possible reasons are extreme disease invasiveness, highly fibrotic and desmoplastic stroma, dearth of confirmatory diagnostic approaches and resistance to chemotherapeutics. This inimitable tumor microenvironment (TME) or desmoplasia with excessive extracellular matrix accumulation, create an extremely hypovascular, hypoxic and nutrient-deficient zone inside the tumor. To survive, grow and proliferate in such tough TME, pancreatic tumor and stromal cells transform their metabolism. Transformed glucose, glu-tamine, fat, nucleotide metabolism and inter-metabolite communication between tumor and TME in synergism, impart therapy resistance, and immunosuppression in PanCa. Thus, a finer knowledge of altered metabolism would uncover its metabolic susceptibilities. These unique metabolic targets may help to device novel diagnostic/prognostic markers and therapeutic strategies for better management of PanCa. In this review, we sum up reshaped metabolic pathways in PanCa to formulate detection and remedial strategies of this devastating disease.

Key Words: Metabolic reprogramming; Pancreatic cancer; Metabolic symbiosis; Therapy resistance; Anti-pancreatic cancer therapy

Core Tip: Pancreatic cancer (PanCa) is supported by reprogrammed metabolism. Cancer specific glucose, glutamine, fat, nucleotide metabolism and inter-metabolite communication between tumor and stroma, impart continual proliferation, therapy resistance, and immunosuppression. Key enzymes and intermediates of altered metabolic pathways would help to formulate disease specific markers and therapeutic approaches. This review sums up reformed metabolic pathways in PanCa to formulate detection and remedial strategies for better disease management.

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INTRODUCTION

Pancreatic cancer (PanCa) is one of the deadliest and highly aggressive malignancies worldwide, ranking third in mortality rate in both the genders in the United States. Despite recent advancements, prognosis for PanCa remains dismal, with a five-year survival rate of around 10%[1]. In 2020, globally, 495773 new cases and 466003 deaths due to PanCa with a ratio of male to female of 1.1:1, both at diagnosis and mortality are recorded[2]. GLOBOCAN 2020 points that, PanCa is 12th most common cancer accounting for 2.6%, among all cancer types and ranks 7th (4.7%) in cancer related deaths, globally[3,4]. Its lifestyle dependence is shown by the fact that countries with very high and high Human Development Index (HDI) exhibit nearly fivefold higher incidence and death rates due to PanCa as compared to low/medium HDI countries[5,6]. Insidious onset, metastatic nature, lack of specific symptoms and reliable biomarkers, ineffective screening methods, make PanCa almost undetectable at early stage[7]. Also, the repertoire of efficient therapeutic interventions remains constrained with chance of local recurrence over 80% in radical resection surgery[8].

Like other cancers, PanCa can also be detected through imaging techniques like, ultrasonography, magnetic resonance imaging, computerized tomography, and positron emission tomography (PET) scans, followed by biopsy. Elevated carbohydrate antigen 19-9 (CA19-9) in peripheral blood, specifically indicates PanCa; through false negative cases are recorded. PanCa is also associated with strong chemoresistance, possibly mediated through stromal diversity, cancer-stromal cross-talk and revised metabolism. Gemcitabine plus FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) and nab-paclitaxel are regularly used, as the first-line of treatment, though associated with towering toxicity with insignificant improvement in survival[9]. Targeted therapy using small molecules like erlotinib in singular or in combination with gemcitabine hardly showed any benefit. Despite advanced chemotherapeutic regimens, disease progression is associated with chemoresistance and unfavorable outcome[10,11]. Consequently, development of innovative treatment modalities aimed at improving prognostic trajectories is need of the hour[12].

All malignant cells undergo metabolic alterations, encompassing glucose, lipid, amino acid, nucleotide, and energy metabolism, driven by both internal and external cues[13]. Intrinsically, PanCa exhibits gain of function mutations of *KRAS* gene (approximately 90% of cases) and loss of function mutations of tumor suppressor genes, like, *TP53*, *SMAD4*, and *CDKN2A*; which maps cancer progression with metabolic reprogramming[14]. This modified metabolism is not restricted to cancer cells only, but also, to various stromal cells, comprising of fibroblasts and an array of immune-cells. All these cells communicate with each other and with tumor cells through various metabolic intermediates to deal with nutrient, oxygen and chemotoxic stress, offering maximization of nutrient utilization, and immunosuppression, forming metabolic a "symbiosis"[15], aiding in immune-escape, sustained proliferation and therapy resistance. Moreover, this metabolically diverse disease can be classified, based to its metabolic dependencies, into more aggressive and therapy resistant glycolytic and lipogenic subtypes with superior prognosis[12]. Thus, a deep understanding of cancer-specific glucose, protein, lipid and nucleotide metabolisms in PanCa is crucial. Also, as per our previous published data, it is suggested that the architecture is different when Indian-origin patient data is compared with the Western world hence target therapeutic is required[16,17]. In this review, we summarize the current knowledge in the intricate metabolic alterations and its association with treatment-resistance in PanCa. Additionally, here, we tend to discuss, preclinical and clinical trial studies with antidotes of enzymes and intermediates of metabolic pathways to deduce diagnostic and therapeutic targets, which could be effective in devising innovative treatment strategies against the deadly disease.

PANCA SPECIFIC ALTERED CELLULAR METABOLISM

Alteration of carbohydrate metabolism

PanCa cells depend on less efficient cytosolic glycolysis for ATP production rather than oxidative phosphorylation irrespective of abundance of oxygen, known as Warburg effect, unlike, typical TCA cycle and oxidative phosphorylation in normal cells. Warburg effect facilitates rapid ATP production and avails ample intermediates for further use in other auxiliary pathways: PPP, HBP, lipid synthesis, proving building blocks for uninterrupted cell proliferation[18]. Oncogenic KRAS elevates glycolytic enzymes including hexokinase 1/2, phosphofructokinase 1, enolase-2, and lactate dehydrogenases (LDHA and LDHB) in PanCa leading to increased production of lactate, accumulation of which reduces cellular and extracellular pH, promoting invasiveness through destroying immune response, and facilitating metastasis, leading to poor overall survival (OS)[19,20].

Glucose is transported into cytoplasm through cell-membrane glucose transporters (GLUT), highly expressed in PanCa cells and associated with unfavorable prognosis[21]. Activation of oncogenes (*KRAS*, *c-MYC*), inhibition/loss of mutant *P53*, *PTEN*, epigenetic alterations, overexpression of hypoxia-inducible factor-1 (HIF-1) and GLUT1 activation promotes aerobic glycolysis[22]. Repression of GLUT-1 and LDHA mediate sodium-glucose co-transporter (SGLT2) inhibition and enhanced chemotherapeutic efficacy[23]. In PanCa, HIF-1α, activated by upstream oncogenic PI3K/AKT and MAPK/ERK pathways, upregulate the expression of several key glycolytic enzymes and glucose transporters to overcome oxidative stress to preserve mitochondrial redox potential and reactive oxygen species (ROS) generation, evade immune surveillance and promote invasion[22].

In PanCa cells, accumulated lactate produced by aerobic glycolysis, is neutralized by export through membrane-monocarboxylate transporters (MCT), which are often upregulated. Mitochondrial OXPHOS and NADPH oxidases regulated by mutant *KRAS* and *P53* genes alter redox metabolism and ROS levels in PanCa[24]. Additionally, mutant *KRAS* signalling induces mitochondrial translocation of phosphoglycerate kinase 1, resulting in phosphorylated PDHK1 and restricted OXPHOS[25]. Glucose deprivation further promotes *KRAS* mutations. However, refractory tumors including PanCa shows elevated OXPHOS and overexpression of mitochondrial respiratory complex I components at both RNA and protein level. Interestingly, targeting complex I coupled with usual chemotherapy showed hopeful results in PanCa[26]. Recently a hybrid glycolytic/OXPHOS phenotype in PanCa cells is proposed[22].

PanCa exhibit increased non-oxidative PPP, controlling cencer cell growth through the supply of ribose-5-phosphate for DNA/RNA synthesis and NADPH for cellular ROS detoxification, by upregulation of ribulose 5-phosphate isomerase and ribulose-5-phosphate-3-epimerase driven by mutant *KRAS*[27]. Chronic acidosis caused due to aerobic glycolysis significantly enhances PPP, promoting cell proliferation by activating Yes1 associated transcriptional regulator (YAP)/matrix metalloproteinase-1 axis in PanCa[28].

Alternatively, glucose in PanCa through hexosamine biosynthesis pathway (HBP), produces UDP-GlcNAc, a crucial substrate for protein and lipid glycosylation. Abnormal glycosylation by hyperactive HBP aids in tumor development and drug resistance in PanCa, mediated by altered O-GlcNAcylation. Additionally, elevated glutamine-fructose-6-phosphate amidotransferase-1, key enzyme of HBP, in PanCa cells is associated with poor survival[22].

Alteration of amino acid metabolism

Taken up by micropinocytosis, amino acids act as an alternative fuel of TCA cycle in glucose deprivation, and as a potential nitrogen source required for nucleotide synthesis in PanCa. Amino acids like, glutamine (Gln) and alanine support Krebs cycle after conversion into alpha-ketoglutarate (α-KG), and pyruvate respectively[18]. Driven by mutated KRAS, Gln is converted to glutamate (Glu) by mitochondrial glutaminase, which is then further converted to α-KG by transaminase [glutamate oxaloacetate transaminase 2 (GOT2)][29]. Gln also regulates cellular ROS through upregulation of reduced glutathione (GSH), thus showing the utility of Gln in hypoxic PanCa cell survival[30]. Asparagine, another essential amino acid, helps in biosynthesis of other amino acids, NO and polyamines in pancreatic ductal adenocarcinoma (PDAC)[31]. Gln also produces NADPH through non-canonical pathway. NO is associated with invasion and proliferation in PanCa. Aspartate derived from Gln and catalyzed by GOT2, also serves as TCA cycle intermediate. It is converted into oxaloacetate by glutamate-oxaloacetate transaminase (GOT1), often upregulated in PanCa with *KRAS* mutation to generate NADPH[32]. Oxaloacetate is converted to malate by GOT1 in cytoplasm, and then to pyruvate, both of which act as TCA cycle intermediates[33].

Non-essential amino acid (NEAA), arginine in PanCa cells is produced through urea cycle from aspartate and citrulline catalysed by argininosuccinate synthetase, following argininosuccinate lyase[31]. Another NEAA, proline, often converted to Glu through proline oxidase (POX) and Δ^1-pyrroline-5-carboxylate dehydrogenase and in reverse by Δ^1-pyrroline-5-carboxylate (P5C) mediated by P5C synthase (P5CS) and subsequent P5C reductase (PYCR) in PanCa cells. POX, contributing to collagen formation is overexpressed in PanCa cells[34]. Branched-chain amino acids (BCAAs) like, valine, leucine and isoleucine donate nitrogen α-KG to form glutamate and α-keto acids, mediated by branched-chain amino acid transaminase 1 (BCAT1 & 2). BCAAs are elevated in early-stage mutant *KRAS* driven PanCa[31]. BCAA also acts as a carbon source through acetyl CoA, for fatty acid synthesis and fuel TCA cycle in PanCa cells[33]. Piling up of ROS in PanCa cells, is dealt with the help of elevated GSH, produced from glutamate, cysteine, and glycine. First γ-glutamylcysteine is formed from glutamate and cysteine and finally GSH is formed from γ-glutamylcysteine and glycine [31].

Alteration of lipid metabolism

Lipids provide cellular building blocks, signalling molecules and energy to rapidly growing cancer cells. While normal cells depend upon dietary uptake of fatty acids (FAs) and cholesterol (approximately 93%), tumor cells synthesize lipids

from mitochondrial citrate, through *de novo* Lipogenesis[35]. However, recent findings suggest the utilization of food-derived FAs for phospholipid biosynthesis required in proliferation and signalling pathways[36]. Enzymes required for lipid/cholesterol synthesis, like citrate synthase, fatty acid synthase (FASN), *etc*., and their genes are elevated in PanCa cells[37].

Oncogenic KRAS, associated with elevated lipid droplet accumulation, regulates lipid storage and metabolism, influencing disease progression in PanCa. Lipid droplets are catabolized during PanCa cell invasion[38]. KRAS also upregulates transcription factor, regulatory element-binding protein 1 (SREBP1), which promotes palmitic acid and stearic acid synthesis leading to rapid cell proliferation in PanCa cell lines and animal models[39]. SREBP1, also upregulates SCD1 to promote unsaturated fatty acid synthesis in PanCa. Furthermore, KRAS boosts fatty acid synthesis and consequent energy metabolism mediated by elevated expression of phospholipase A2 group IIA. Saturated, monounsaturated, and ω-6 polyunsaturated FAs support carcinogenesis in PanCa[40], while ω-3 polyunsaturated FAs are anti-carcinogenic[41]. Unusual arachidonic acid (AA, a ω-6 polyunsaturated FA) metabolism favors epithelial malignancies, like PanCa through modulation of lipoxygenase pathway[33].

Cholesterol or cholesteryl esters, essential constituent of plasma membrane are required in PanCa progression. Aldo-keto reductase family 1B10 (AKR1B10), boosts cell survival and modulates cholesterol metabolism through its reduced products, FPP and geranylgeranyl pyrophosphate, is overexpressed in PanCa tumors[33]. SREBP2 regulating cholesterol synthesis is also upregulated in PanCa[42]. Increased cholesterol uptake through overexpressed LDLR in PanCa demonstrates elevated risk of recurrence[33].

Alteration of nucleotide metabolism

Amplified nitrogen need is a metabolic hallmark of cancerous cells. Tomour cells undergo uncontrolled growth and proliferation, supported by altered nucleotide metabolic pathways to enhance synthesis of extra nucleic acids through *de novo* as well as salvage path[43]. Hyperactivation of mTORC1 in proliferating cells promote pyrimidine synthesis, while extracellular signal-regulated kinase hyperactivation leads to long-term stimulation of *de novo* pyrimidine and purine biosynthesis[44]. Hyperactivated Myc, also boosts purine synthesis in PanCa. Oncogenic KRAS elevates intracellular nucleotides to promote non-oxidative pentose phosphate pathway (PPP), vital for *de novo* nucleotide biosynthesis[45]. Dihydropyrimidine dehydrogenase, helping in epithelial-mesenchymal transition and cancer progression, is upregulated in PanCa. PanCa with mutant p53 alleles also facilitate inosine monophosphate dehydrgenase and guanosine monophosphate synthase expressions[46].

In *de novo* pathway, purines are synthesized directly by combining pyrophosphate at C-1 of a ribose sugar following several more steps. First, ribose-5-phosphate is converted to phosphoribosyl pyrophosphate (PRPP). Next PRPP combines glutamine to form 5-phosphoribosylamine and pyrophosphate, catalyzed by PPAT. Then inosine monophosphate (IMP) is formed. It acts as a precursor of adenosine monophosphate and guanosine monophosphate, catalysed by adenylosuccinate synthetase and inosine monophosphate dehydrogenase through several kinetic intermediates. In case of *de novo* pyrimidine synthesis, its ring structure is combined following a 6-step process, where L-glutamine and L-aspartate acts as precursors. Carbamoyl phosphate synthetase, aspartyl transcarbamoylase, and dihydroorotase catalyzes the initial 3 steps, finally forming uridine-5-phosphate, serving as a building block in pyrimidine biosynthesis. In both purine and pyrimidine nucleotide biosynthesis, the homeostasis and conversion among nucleoside triphosphate and nucleoside monophosphate are facilitated by ecto-nucleoside triphosphate diphosphohydrolase-1 (ENTPD1/CD39) and ecto-5-nucleotidase (NT5E/CD73). CD73 transforms AMP to adenosine with phosphate, and CD39 can hydrolyzes nucleoside-5-triphosphates into nucleoside-5-monophosphate and its products. CD73 and CD39 catalyzes ribose-5-monophosphate and deoxyribose-5-monophosphate to form nucleosides and deoxynucleosides. Also, purine nucleoside phosphorylase (PNP), reversibly catalyzes phosphorolysis of nucleosides to produce purine and pyrimidine base and ribose 1-phosphate. Other than nucleotide metabolism, CD39 and CD73, frequently upregulated in human cancers, play immunomodulatory roles through furnishing anti-tumor activity of various immune-cells: T cells and macrophages[46].

In salvage pathway, free bases are derived from nucleic acid turnover or dietary intake. Ubiquitous PNPs catalyze hypoxanthine-guanine phosphoribosyltransferase to monophosphates of inosine and guanosine. Ribo- and deoxyribonucleosides are converted to ribonucleotides mediated by adenosine deaminase. Uridine-cytidine kinases, rate-limiting enzymes in pyrimidine biosynthesis salvage pathway, convert uridine and cytidine to their consequent monophosphates [41].

METABOLIC SYMBIOSIS IN PANCA

Rigid, nutrient-depleted, hypoxic and desmoplastic stroma is composed of collagen meshwork enclosing pancreatic tumor. Various cells like, fibroblasts (cancer-associated fibroblasts or CAFs), endothelial and immune cells like, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and few activated cytotoxic T (Tc) cells are present in highly heterogeneous PanCa microenvironment. All these cells converse with each other and with tumor cells through soluble factors, gap junctions and exosomes, ultimately resulting in symbiosis for unlimited proliferation, invasion, metastasis, immunosuppression and chemoresistance[47] (Figure 1).

Stromal collagen fuels cancer cells, through constant supply of nutrients. Misbalanced shear stress, due to thick stoma, upregulates PI3K/AKT pathway and ROS production resulting in boosted glycolysis in PanCa cells. In PanCa cells increased glycolytic flux, is coupled with overexpression of rate-limiting glycolytic enzymes like, PFK1 and LDHA and lactate amassing[48]. Lactate surplus in hypoxic tumor-central cells is exported to periphery, through gap junction connexin-43 channels and upregulated MCT4. While lactate in normoxic PanCa cells and TME is sensed by Gi-coupled

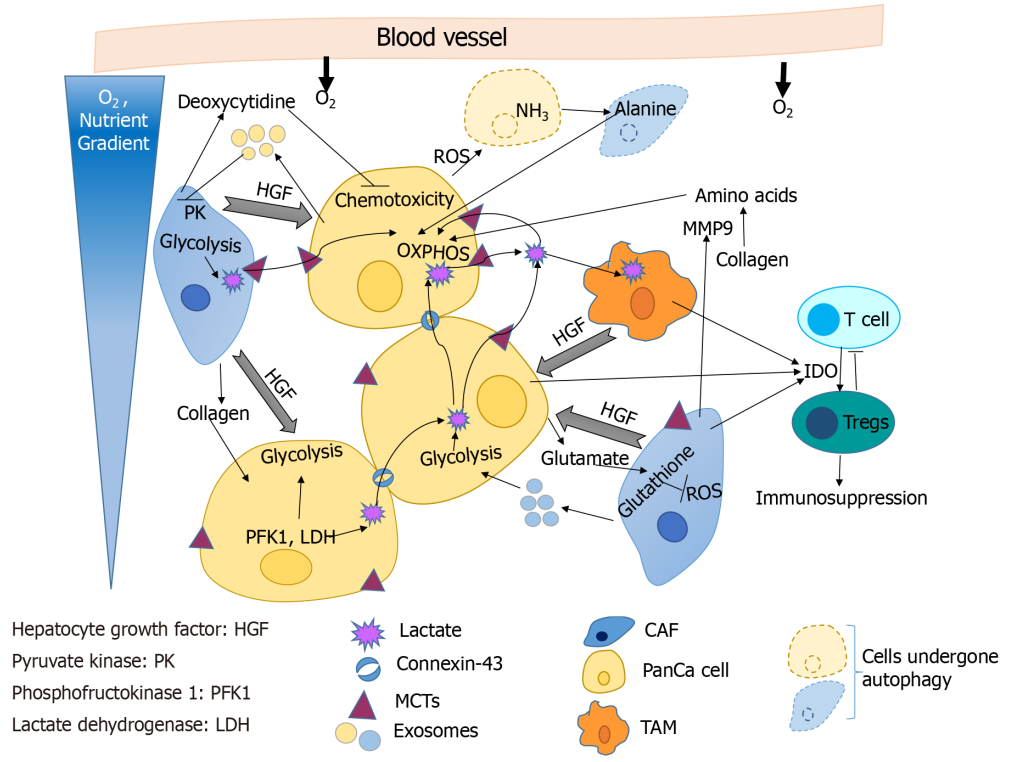

Figure 1 Metabolic crosstalk operating in pancreatic cancer and its microenvironment. HGF: Hepatocyte growth factor; ROS: Reactive oxygen species; IDO: Indoleamine 2,3-dioxygenase; CAF: Cancer-associated fibroblasts; TAM: Tumor-associated macrophage; MCTs: Monocarboxylate transporters.

receptor 81 (GPR81), overexpression of CD147, ultimately enhance MCT1 expression. Stimulated GPR81 also elevates peroxisome proliferator-activated receptor gamma coactivator-1α, which triggers mitogenesis and TCA cycle mediated respiration, using lactate as a fuel. Improved lactate absorption and utilization helps cell proliferation in glucose insufficiency and plays nonmetabolic roles like, promoting invasiveness, immunosuppression and angiogenesis in PanCa[44].

Constantly stimulated by adjacent tumor cells, CAFs show altered carbohydrate metabolism, shifting from TCA cycle/OXPHOS to aerobic glycolysis and generating various intermediate metabolites, including, pyruvate, lactate and ketone bodies. MCT-4, overexpressed in CAFs favour lactate export in TME, while MCT-1 overexpressed in normoxic tumor cells, facilitate lactate uptake from TME to fuel OXPHOS. This phenomenon of linking CAFs and neoplastic cells is known as 'reverse Warburg effect'. Stimulated CAFs also discharge exosomes, enclosing TCA cycle metabolites, lipids and amino acids, which are taken up by PanCa cells to exhibit low mitochondrial OXPHOS, while amplify glycolysis[49, 42]. Tumor cell derived exosomes on the other hand, suppress glucose uptake in stromal astrocytes and CAFs through inhibiting pyruvate kinase, thereby enhancing glucose availability for cancer cells[50]. CAFs produce a collagen-rich ECM, which acts as a reservoir of amino acids and lipids to support growth and metabolism of PDAC cells. Lipid uptake by tumor cells, support the formation of phospholipids aiding in biomembrane synthesis and lysophosphatidylcholine facilitating various regulatory pathways in PDAC[47]. Glutamate released by malignant cells encourages glutathione signalling in CAFs, restricting superoxide and ROS buildup[51]. Also, glutamine upregulate glutamine-transporters, stimulate mitogenesis while suppress mitophagy in PanCa cells[42]. CAFs expressing matrix metalloprotease 9 degrades ECM-collagens to amino acids, which are consumed by PanCa cells through macropinocytosis to fulfill their high amino acid demand[52]. Activated CAFs produce loads of type I collagen, inducing integrin-FAK signalling, leading to clonogenic amplification in PDAC cells[48]. They also secrete deoxycytidine to protect PDAC cells from chemo-toxicity [47,52]. Extreme stromal ROS results in genomic instability in tumor cells followed by their autophagy. On the other hand ammonia produced by tumor cells through glutaminolysis induces CAF-autophagy[48]. CAF-autophagy-derived alanine act as a substitute fuel of TCA cycle, generate lipids and non-essential amino acids (NEAA), in nutrient deprived PanCa cells[43]. Interestingly, PanCa cells harbouring oncogenic KRAS, activate neighboring PSCs major CAF precursors and secrete hepatocyte growth factor (HGF) which upregulate glycolytic metabolism of cancer cells[40]. TAMs, associated with tumor-immunity, favour glycolysis, in neighboring PanCa cells through HGF mediated paracrine cross-talk, promoting metastasis and angiogenesis. Consequently, microenvironmental lactate induces procancer M2-like polarization of TAMs, resulting in reduced immunity[40].

MDSCs and TAMs overexpress arginase and nitric oxide synthase, which deplete microenvironmental arginine and its metabolites (ornithine and citrulline), resulting in inhibition of T cell activation and associated immunesuppression[43]. Indoleamine2,3-dioxygenase (IDO) secreted by PanCa cells, Tregs and TAMs, also promote immunesuppression through suppression of T cell activation and NK cell activity[41]. IDO1upregulated in MDSCs promotes tryptophan breakdown, resulting in piling up of toxic guanosine, which represses immunity through enhanced conversion of T cells into Tregs [44]. Furthermore, lactic acid, accumulation in PanCa cells influence immune cells by blocking (1) The conversion of monocytes to dendritic cells; (2) Monocyte migration; (3) Cytokine release from dendritic cells and cytotoxic T (Tc) cells;

and (4) Activity of Tc cell and antigen-presenting cells, ultimately leading to immunosuppression.

PanCa cells block Gln degradation in stromal aggressive adipocytes followed by their secretion, facilitating cancer cell proliferation in murine PanCa and adipocyte cell coculture. Also, adipocytes support malignancy through their cross-talk with PSCs and tumor-associated neutrophils. Other than these, many other stromal cells influence each other in PanCa TME[26,36].

ROLE OF ALTERED METABOLISM IN THERAPY RESISTANCE OF PANCA

Altered metabolism within PanCa cells, regulated by genetic and epigenetic factors, is a significant contributor of chemoresistance, based on which, alternate therapeutic strategies to overcome chemoresistance has been developed[53,54].

Oncogenic activation of KRAS, c-MYC, and HIF-1α often promotes upregulation of glucose transporters and several key enzymes of glycolysis. Activated GLUT1 further activates NF-κB and mTOR survival pathways thereby promote chemoresistance[33]. Glycolytic enzyme, hexokinase, often upregulated in metastatic PanCa supports chemoresistance through blocking apoptosis[55]. Rate-limiting glycolytic enzyme, pyruvate kinase M2 (PKM2), elevated in PanCa causes gemcitabine resistance[56]. Enhanced LDHA in PanCa cells block ROS production and apoptosis, resulting in uninterrupted proliferation and consequent drug (gemcitabine) resistance[54,57]. Similar effects are observed with Glyceraldehyde-3-phosphate dehydrogenase[58]. HIF-1α, associated with higher invasion and migration promotes enolase-1 (ENO-1) expression in PanCa[59] ENO-1 suppresses intracellular ROS and consequent apoptosis and gemcitabine resistance PanCa cells[53]. Pyruvate dehydrogenase kinase 3 (PDK3) catalyzes the first step of OXPHOS, is another crucial enzyme for drug resistance. HIF-1α induces PDK3 expression which switches mitochondrial respiration to glycolysis for energy production[60]. In PanCa cells, enhanced nonoxPPP, causes increased level of dCTP expression which competitively inhibits GEM activity. HBP pathway active in PanCa, confers chemoresistance with higher expression of Glutamine-fructose amidotransferase 1[7]. PanCa specifically overexpress Phosphoacetylglucosamine Mutase 3 (PGM3), a key enzyme of HBP pathway. Inhibition of PGM3 in PanCa cells exhibit gemcitabine sensitivity both *in vitro* and *in vivo* models[61].

Enolase (ENO1), a glycolytic enzyme also acting as a plasminogen receptor, is over-expressed in PanCa cells. A DNA vaccine targeting ENO1, is developed in PanCa mouse model. This ENO1 targeted DNA vaccine effectively destroys tumour cells mediated by antibodies and complement-dependent cytotoxicity, upregulation of effector T cells and suppression of MDSCs and Tregs[62].

PanCa cells, characterised by overexpression of lipid metabolism and lipid uptake often contribute resistance to conventional chemotherapy. A key enzyme of lipid biosynthesis, FASN offers gemcitabine resistance, possibly mediated by PKM2 and glycolysis[63,64]. Also, HMGCR, ACAT-1, SREBP2, CRABP-II and AKR1B10, involved in cholesterol biosynthesis, are elevated in PanCa. All these regulators furnish gemcitabine resistance, while only caveolin-1 showed NAB-paclitaxel resistance[65].

Gln is essential for PanCa cell survival. All the transporters like, ASCT2, SLC1A5, enzymes, like, GLS, glutamate dehydrogenase (GDH), alanine transaminase (ALT/GPT) or aspartate transaminase (AST/GOT) and metabolic intermediates associated with Gln metabolism offers chemoresistance, possibly regulated through EGFR signalling and downstream MAPK and AKT-mTOR pathway[66]. GOT1 specifically offers NAB-paclitaxel and gemcitabine resistance [67]. Argininosuccinate synthase 1, associated with arginine catabolism enhances cisplatin resistance in PanCa[68]. Both polyamine transport and biosynthesis upregulated in PanCa provide gemcitabine resistance in mice model[69]. Endoribonuclease or dicer elevated in PanCa also contributes gemcitabine resistance[70].

Radiotherapy is suggested as a neoadjuvant treatment for resectable or borderline disease, in locally advanced and recurrent tumor, and as palliative care in advanced and terminal PanCa. Enhanced carbohydrate and nucleotide metabolism regulated by oncodrivers of PanCa facilitates radioresistance. Glucose metabolism blocker, 2-DG enhances metabolic oxidative stress and radiosensitizes PanCa cells. Carbohydrate rich diet showed radioresistance while, ketogenic diet (high fat - low carbohydrate) amplified sensitivity to radiotherapy in xenograft mouse models with PanCa. Overexpressed FASN and several enzymes in cholesterol biosynthesis pathway like, farnesyl diphosphate synthase (FDS) possibly results in radioresistance in PanCa. Radioresistance of FDS can be mitigated by zoledronic acid (ZOL). A combination of ZOL and chemoradiotherapy after surgery is assessed in an ongoing phase II trial study in PanCa (NCT03073785)[40].

ALTERED METABOLISM BASED DETECTION OF PANCA

PanCa, known for early metastasis, can be detected by the technologies associated with metabolic imaging probes, including, PET and magnetic resonance spectroscopy (MRS). PET imaging is based on the elevated glucose uptake in PanCa cells monitored by, a glucose analog, 18F fluorodeoxyglucose (FDG). FDG is metabolized in PanCa cells like glucose by hexokinase and results in its cellular accumulation, proportional to hexokinase activity. Hexokinase activity is again proportional to tumour spread and thus can predict its pathological grade, distant metastasis, and survival. However, FDG-PET is unable to differentiate between PDAC and mass-forming pancreatitis, as it also shows enhanced FDG uptake. MRS, using the conversion of 1-^{13}C-pyruvate to lactate, distinguishes between normaland cancer tissue and the disease stage. 1-^{13}C-pyruvate imaging is used in mice models of PDAC[71].

Few other studies revealing metabolic signature of PanCa are as follows: (1) PanCa specific metabolomic signature consisting of 48 differentially expressed metabolites, including, intercept, phenylalanine, tryptophan, ethanolamine and carnitine in saliva samples of affected subjects have been identified[72]; (2) Altered expression of 14 biomarkers, including, intercept, proline, creatine and palmitic acid in tissue and serum samples of PanCa patients using UHPLC-Q-TOF/MS has been shown[73]; (3) Modified expression of a panel of 16 metabolites (including, xylitol, histidine, 1,5-anhydro-d-glucitol, and inositol) using GC/MS/MS with CA19-9, is able to differentiate early PanCa from benign tumor and CA19-9 negative PanCa patients from healthy individuals with high sensitivity and specificity[74]; (4) Another panel of 6metabolites, including, 5-hydroxytryptophan, lysophosphatidylethanolamine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylcholine and sphingomyelin also exhibited high specificity and sensitivity, able to discriminate between early PanCa and benign tomours[75]; and (5) Differential lipid profiling in serum of PanCa patients, showed altered expression of sphingomyelin (41:1), sphingomyelin (42:1), sphingomyelin (39:1), ceramide (41:1), ceramide (42:1), lysoPC (18:2) and phosphocholine (O-36:3) compared to chronic pancreatitis and healthy subjects. Combination of these lipid biomarkers with CA19-9 showed better diagnostic performance compared to the metabolites or CA19-9 alone[76].

TARGETING ALTERED METABOLISM IN PANCA THERAPY

Altered metabolism, vital for carcinogenesis and therapy resistance, represents a prominent remedial target in PanCa.

Targeting glucose metabolism

Glucose metabolism suppressed by blocking GLUT1, CG-5, WZB117 and autophagy inhibitor hydroxychloroquine (HCQ) preclinically improved gemcitabine sensitivity and blocked PanCa cell proliferation (Table 1)[77]. After success in preclinical studies, HCQ was clinically assessed in a phase II monotherapy (NCT01273805) as well as in several phase I/II/II trials in combination with: (1) Gemcitabine (NCT01128296); (2) Gemcitabine + nabpaclitaxel (NCT01978184, NCT01506973); and (3) ERK inhibitor, temuterkib (NCT04386057) in advanced and metastatic PanCa. Few more phase I/II clinical evaluations of HCQ in amalgamation with: (1) Radiation + capecitabine (NCT01494155); (2) Chlorphenesin carbamate + mFOLFIRINOX (NCT05083780); (3) Kinase inhibitors (NCT03825289, NCT05518110, NCT04132505); (4) Paricalcitol + gemcitabine + nab-paclitaxel (NCT04524702); (5) Paricalcitol + losartan (NCT05365893); (6) Leflunomide or bevacizumab, (NCT06229340); (7) CPI-613 + 5-fluorouracil or Gemcitabine, (NCT05733000); and (8) paclitaxel protein bound + gemcitabine + cisplatin (NCT04669197) are in progress. Though HCQ in monotherapy furnished slight clinical effectiveness, HCQ + chemotherapy, diminished hypercoagulability, while failed to lower mortality, in advanced PanCa [77]. Interestingly, better prognosis was furnished with a pretreatment of HCQ, gemcitabine and nab-paclitaxel cocktail followed by surgery in PDAC (NCT01978184) (Table 2)[48,78].

In laboratory, glycolysis inhibited by (1) 2-Deoxy-D-glucose (2-DG)[79]; (2) Hexokinase blocker benitrobenrazide (BNBZ); (3) Phosphoglycerate mutase 1 blocker PGMI-004A and KH3[80]; and (4) Pyruvic acid analog, 3-bromopyruvate (3-BP) suppressed PanCa[81]. LDHA inhibitor, (1) N-hydroxyindole-NHI-1 singly or in combination with gemcitabine [82]; (2) Galloflavinin with anti-diabetic drug, metformin[83]; (3) Gossypol[84]; and (4) FX11 suppressed PanCa in cell-line/animal studies (Table 1). A phase I study with 2DG and/or docetaxel showed its safety and tolerance in advanced solid cancers including PanCa (NCT00096707)[85] (Table 2).

Mitochondrial enzyme, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase blocker, lipoate analog, devimistat (CPI-613/CPI), blocks energy metabolism and proliferation in PanCa cell lines and mice. CPI combined with (1) LDH blocker, galloflavin; and (2) MCT suppresser, cyano-4-hydroxycinnamic acid, showed tumor contraction in PanCa mice models[86] (Table 1). CPI + mFOLFIRINOX showed encouraging results in a phase I (NCT01835041) and in a multicenter open label, randomized phase III trial in metastatic PDAC (NCT03504423)[48,78]. A phase 1 study (NCT03435289) with a blend of CPI-613 + gemcitabine + nab-paclitaxel in advanced or metastatic PanCa is in pipeline (Table 2).

OXPHOS (complex I, NADH dehydrogenase) blocker rotenone, metformin, phenformin and IACS-010759, lowered proliferation of PanCa cell lines[26] (Table 2). To test its clinical efficacy in gemcitabine resistant metastatic PanCa, metformin was administered singly in a phase II (NCT01971034) and in combination with (1) Gemcitabine (NCT01210911, NCT02005419); (2) MFOLFOX-6 (NCT01666730); (3) Stereotactic radiosurgery (NCT02153450); and (4) Rapamycin (NCT02048384) in phase Ib/II studies (Table 2). These cocktails showed well tolerance, while, only metformin +/- rapamycin remarkably prolonged survival[77,78]. A phase II trial with neoadjuvant metformin and few phase I/II trials with a blend of metformin with (1) Gemcitabine + paclitaxel albumin-stabilized nanoparticle formulation (NCT02336087); and (2) Everolimus + octreotide LAR (NCT02294006) are in progress. IACS-010759, in a phase I study in advanced PanCa (NCT03291938), showed slim therapeutic index with growing dose-limiting toxicities (Table2)[87]. An Food and Drug Administration (FDA)-approved anti-pneumonia and anti-malaria drug, atovaquone blocking mitochondrial ETC (bc1 complex), suppressed proliferation in PanCa cell lines and animal model[74] (Table 1).

Targeting amino acid metabolism

Glutamine (Gln) addicted PanCa cells, when treated with its antagonist, 6-diazo-5-oxo-L-norleucine (DON), diminished self-renewal and metastasis *in vitro*. Sirpiglenastat, a pro-drug of DON singly or in combination with trametinib, blocked PanCa tumor growth in *in vivo* models with prolonged survival[88]. Glutaminase (GLS) suppressors in preclinical studies with PanCa, like, (1) Ss-lapachone; (2) Thiazolidine-2,4-dione derivatives; (3) Bis2- (5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide (BPTES); and (4) BPTES derivatives, compound 968 and telaglenastat (CB-839) showed optimistic results [78]. BPTES encapsulated nanoparticles in singular therapy and in combination with (1) Metforminand; and (2) ß-

Table 1 Overview of inhibitors of metabolism in pancreatic cancer

Agent	Target	Combined with	Ref.
CG-5	GLUT1	-	[1]
		Gemcitabine	
2-DG	Glycolysis	-	[2]
		Gemcitabine	
3-BP	Glycolysis	-	[3]
BNBZ	HK2	-	[4]
PGMI-004A	PGAM1	-	[4]
KH3	PGAM1	-	[4]
CPI-613	PDH	-	[5]
		Galloflavin	
		Cyano-4-hydroxycinnamic acid	
Rotenone	OXPHOS: Complex I	-	[6]
Metformin			
Phenformin			
IACS-010759			
Atovaquone	OXPHOS: Bc1 complex	-	[7]
N-hydroxyindoles	LDHA	-	[8]
N-hydroxyindole-NHI-1		Gemcitabine	[8]
Galloflavinin	LDHA	Metformin	[9]
Gossypol		-	[10]
FX11		-	[1]
Avasimibe	ACAT1	-	[11]
Luteolin	FASN	-	[12]
C75		-	[11]
Palbociclib		-	[13]
Paclitaxel nano-formulation		-	[14]
Orlistat	FASN	-	[15]
		Gemcitabine	[1]
EGCG	FASN, GLUD1 & PGAM1	-	[1,4]
Lansoprazole	FASN	-	[11]
Pantoprazole			
Rabeprazole			
Omeprazole			
DEAB	ALDH	-	[16]
		Gemcitabine	
Disulfiram	ALDH		[16]
A939572	SCD	-	[17]
CAY10566	SCD	-	[18]
		Gemcitabine	
SB-204990	ACLY	-	[11]
BAY ACC022		-	

TOFA	Fatty acid synthesis	-	[19]
Silibinin	Lipid metabolism	-	[20,21]
Atorvastatin,	HMG-CoA reductase	-	[22]
Lovastatin			
Pravastatin			
Rosuvastatin			
Simvastatin			
Etomoxir	FAO	Carnitine palmitoyl transferase I inhibitor	[11]
Artesunate	Lipid metabolism		[11]
Zalcitabine			
Avasimin	SOAT1		[11]
Opaganib	SK2		[23]
Vitamin D	Lipid metabolism		[24]
DON	Gln	-	[25]
Sirpiglenastat	Gln	-	[25]
		Trametinib	
ss-lapachone	GLS	-	[1]
Thiazolidine-2,4-dione derivatives			
BPTES	GLS	-	[26]
		ß-lapachone (ß-lap)	[27]
968	GLS	-	[26]
CB-839	GLS	-	[26]
		ß-lap	[27]
		BSO	
BPTES encapsulated nanoparticles	GLS	-	[26]
		Metformin	
GPNA	Gln transporter	-	[28]
ASNase	Asparagine	GCN2iA/B	[29]
		PD-325901	
Indoximod	IDO	-	[30]
Carbidopa		-	
Epacadostat	IDO	-	[27]
PEG-ADI	Arginine metabolism	-	[23]
		Radiotherapy	[27]
		Gemcitabine	
		Gemcitabine + docetaxel	
		Panobinostat	
SM-88	Mucin-1 synthesis	-	[23]
AG-270	MAT2A	-	[23]
		Taxane-based chemotherapy	

FASN: Fatty acid synthase; GLUT: Glucose transporter; OXPHOS: Oxidative phosphorylation; PEG-ADI: Pegylated arginine deiminase; SCD: Stearoyl-CoA desaturase; IDO: Indoleamine 2,3-dioxygenase.

Table 2 Overview of inhibitors of metabolism, evaluated through clinical trials in pancreatic cancer

Agent	Target	Combined with	NCT No.
HCQ	Glucose uptake/autophagy	-	NCT01273805
		Gemcitabine	NCT01128296
		Gemcitabine + nab paclitacel	NCT01506973 NCT01978184
		Temuterkib	NCT04386057
		Radiation + capecitabine	NCT01494155
		Chlorphenesin carbamate + mFOLFIRINOX	NCT05083780
		Kinase inhibitors	NCT03825289 NCT05518110 NCT04132505
		Paricalcitol + gemcitabine + nab-paclitaxel	NCT04524702
		Paricalcitol + losartan	NCT05365893
		Leflunomide/bevacizumab	NCT06229340
		CPI-613 + 5-fluorouracil or gemcitabine	NCT05733000
		Paclitaxel protein bound gemcitabine + cisplatin	NCT04669197
2-DG	Glycolysis	Docetaxel	NCT00096707
CPI-613	PDH	mFOLFIRINOX	NCT01835041 NCT03504423
		Gemcitabine + nab-paclitaxel	NCT03435289
Metformin	OXPHOS: Complex I	-	NCT01971034
		Gemcitabine	NCT01210911 NCT02005419
		mFOLFOX-6	NCT01666730
		Stereotactic radiosurgery	NCT02153450
		Rapamycin	NCT02048384
		Gemcitabine + paclitaxel albumin-stabilized nanoparticle formulation	NCT02336087
		Everolimus + octreotide LAR	NCT02294006
IACS-010759	OXPHOS: Complex I	-	NCT03291938
Omeprazole	FASN	-	NCT04930991
Disulfiram	ALDH	Gemcitabine	NCT02671890
Simvastatin	HMG-CoA reductase	Gemcitabine	NCT00944463
		Valproic acid + gemcitabine/nab-paclitaxel-based regimens	NCT05821556
		Metformin + Digoxin	NCT03889795
		Digoxin + Gemcitabine	NCT06030622
		Standard chemotherapy	NCT06241352
Atorvastatin	HMG-CoA reductase	Evolocumab + Ezetimibe	NCT04862260
Opaganib	SK2	-	NCT01488513
Paricalcitol	Lipid metabolism	Liposomal irinotecan + 5-FU/LV	NCT03883919
		Pembrolizumab	NCT03331562
		Gemcitabine + nab-paclitaxel	NCT03520790
ERY-ASP	Asparagine	-	NCT01523808
		Gemcitabine/FOLFOX	NCT02195180 NCT03665441
Indoximod	IDO	Chemotherapy	NCT02077881
Epacadostat		Immunotherapy, chemotherapy + GVAX	NCT03006302NCT03085914

PEG-ADI	Arginine metabolism	Gemcitabine + nab-paclitaxel	NCT02101580
SM-88	Mucin-1 synthesis	-	NCT04229004
		MPS	NCT03512756

ALDH: Aldehyde dehydrogenase; FASN: Fatty acid synthase; OXPHOS: Oxidative phosphorylation; IDO: Indoleamine 2,3-dioxygenase; PEG-ADI: Pegylated arginine deiminase.

lapachone (ß-lap) suppressed tumor growth in PanCa, with enhanced effect in cocktail[31]. A cocktail of (1) CB-839 + ß-lap; and (2) CB-839 + γ-glutamylcysteine blocker, L-Buthionine-(S,R)-sulfoximine suppressed tumor growth and increased survival in PDAC mice model[31]. Gln transporter blocker, GPNA also suppressed cell growth in PanCa[88]. Asparagine blocker L-asparaginase (ASNase), in combination with, GCN2iA/B or MEK inhibitor, PD-325901, repressed PanCa in preclinical studies (Table 1). RBC encapsulated ASNase (ERY-ASP) is tolerated well by metastatic PDAC subjects (Phase I, NCT01523808)[40]. ERY-ASP+gemcitabine/FOLFOX furnished enhanced OS and progression-free survival (PFS) in PanCa (phase IIb, NCT02195180 and phase III, NCT03665441) (Table 2). Suppression of metabolism of essential amino-acids like, tryptophan, tyrosine and methionine inhibit PanCa. IDO, associated with tryptophan metabolism, when blocked with indoximod, carbidopa and epacadostat suppress PanCa in animal/cell-line studies[89] (Table 1). Indoximod + chemotherapy is assessed clinically in a phase I/II study (NCT02077881), while, epacadostat, immunotherapy and chemotherapy + GVAX pancreas vaccine in PanCa is under evaluation (NCT03006302 and NCT03085914) (Table 2)[31]. Tyrosine mimetic, racemetyrosine (SM-88) blocks mucin-1 synthesis, resulting in enhanced oxidative stress, and cell-death in PanCa[90] (Table 1). SM-88 + MPS (methoxsalen, phenytoin, sirolimus) was evaluated in a randomized phase II/III multi-center study (NCT03512756) while SM-88 monotherapy in another phase III study (NCT04229004) in metastatic PanCa is underway. Preclinically, methionine adenosyltransferase 2α (MAT2A) blocker, AG-270 in monotherapy and in amalgamation with taxane-based chemotherapy, synergistically suppressed PanCa[90] (Table 2).

In laboratory, pegylated arginine deiminase (PEG-ADI) induced arginine deficiency. PEG-ADI singly or in combination with (1) Radiotherapy; (2) Gemcitabine; (3) Gemcitabine + docetaxel; and (4) Histone deacetylase inhibitor, panobinostat showed synergistic lethality in ASS1-defficient PanCa cells (Table 1). PEG-ADI coupled with gemcitabine + nab-paclitaxel was endured well by advanced PanCa subjects in a phase I/Ib study (NCT02101580)[31] (Table 2).

Targeting lipid metabolism

Various small molecules like silibinin and ferroptosis inducer: artesunate and zalcitabine hamper lipid metabolism[91-93], and TOFA blocks fatty acid synthesis, ultimately suppressing PanCa cells proliferation and tumor shrinkage[94]. In preclinical studies in PanCa, several rate limiting enzymes of lipid metabolism are targeted: (1) Acetyl-CoA acyl transferase by avasimibe[93]; (2) Fatty acid synthase (FASN) by luteolin[95], palbociclib and, paclitaxel nano-formulation [96,97] FDA approved orlistat[98], and proton-pump blockers: Lansoprazole, pantoprazole omeprazole, and rabeprazole [93]; (3) Stearoyl-CoA desaturase by A939572 and CAY10566[99,100]; (4) ATP citrate lyase by SB-204990 and BAY ACC022 (oral)[93]; (5) Sterol-O-acyl transferase 1 (SOAT1) by avasimin[93]; (6) Sphingosine kinase-2 (SK2) by opaganib (ABC294640)[90]; (7) HMG-CoA reductase by atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin[101]; and (8) aldehyde dehydrogenase (ALDH) by N, N′-diethylaminobenzaldehyde (DEAB), and FDA-approved disulfiram with encouraging outcomes (Table 1). Some of these agents were clinically evaluated in PanCa, like: (1) FASN blocker, omeprazole in a phase I study (NCT04930991); (2) SK2 blocker, opaganib in an open-label, phase I study (NCT01488513) [90]; (3) Aldehyde dehydrogenase inhibitor disulfiram coupled with gemcitabine in a phase 1 trial (NCT02671890) and HMG-CoA reductase suppressor, simvastatin cocktailed with gemcitabine in a randomized double-blinded, phase II trial (NCT00944463)[93]. Few other phase I/Ib/II studies with simvastatin and (1) Valproic acid + gemcitabine/nab-paclitaxel-based regimens (NCT05821556); (2) Metformin + digoxin (NCT03889795); (3) Digoxin + simvastatin + gemcitabine (NCT06030622); and (4) Standard chemotherapy (NCT06241352) in metastatic PDAC are in progress. Another phase I study with atorvastatin + evolocumab + ezetimibe in advanced or metastatic PDAC (NCT04862260) is underway (Table 2).

Interestingly natural compounds like, green tea polyphenol, epigallocatechin-3 gallate (EGCG) targeting FASN, GLUD1 and PGAM1, inhibits tumor growth in PanCa mice model[80] (Table 1). Vitamin D, modifying lipid metabolism shows anti-carcinogenicity in PanCa. Few clinical trials with vitamin D analog paricalcitol, in combination with (1) Liposomal irinotecan + 5-FU/LV (NCT03883919, phase I); and (2) PD1 inhibitor, pembrolizumab (NCT03331562, phase II) are completed. Additionally, a phase I/II study with paricalcitol + gemcitabine + nab-paclitaxel concoction in metastatic PanCa (NCT03520790) is in progress[102] (Table 2).

Targeting nucleotide metabolism

Uracil analogue, fluorouracil mimicks uracil and gets incorporated into nucleic acids. 5-FU has been approved by the FDA for the treatment of various solid tumors including PanCa. Antineoplastic and antimetabolite floxuridine, a pyrimidine analogue, is metabolized to 5-FU. Floxuridine is incorporated in DNA with high specificity, resulting in inhibition of cell proliferation. Pyrimidine antimetabolite, gemcitabine, a deoxycytidine analogue, after conversion into phosphate metabolites, disrupts DNA synthesis. Gemcitabine primarily kill dividing cells undergoing DNA synthesis (S-phase) and blocks cell cycle progression in G1/S-phase. Gemcitabine is approved by the FDA for PanCa treatment in clinics[103]. Floxuridine, a fluorodeoxyuridine analoge showed promising survival and improved prognosis in a phase II

single agent clinical trials in PanCa[9].

CONCLUSION

Oncogenic metabolic adjustments support quick and uninterrupted growth, proliferation, differentiation, invasion, metastasis, angiogenesis, immune-escape and therapy resistance in PanCa. Tumor cells, CAFs and different immune cells converse with each other mediated through various metabolic cues in extremely despomplastic TME of PanCa. This metabolic symbiosis is associated with therapy resistance Key enzymes of altered metabolic pathways and the intermediates render novel approaches for anti-malignant therapy. These drugs not only suppress malignancy, but also improve chemo- and radiosensitivity in combination therapy. FDA-approved drugs, metformin, statins, omeprazole and aspirin, with multifaceted metabolic roles, are being clinically evaluated for their therapeutic efficacy in PanCa. Glucose metabolism is targeted by 2-DG, CPI-693 in clinical trials. A blend of CPI-613 and mFOLFIRINOX displayed encouraging response (phase I, NCT01835041), though associated with slight enhancement of cytotoxicity and side effects, compared to only mFOLFIRINOX. Asparagine metabolism, targeted with ERY-ASP showed good tolerance and promising results in combination chemotherapy (NCT03665441). Targeting lipid metabolism with disulphirum and paricalcitol has also assessed with encouraging results in PanCa. FDA approved gemcitabine is used as a first line of treatment of PanCa. Regardless of the accomplishments on targeting PanCa metabolism, in some cases, applications are associated with serious side effects, as these drugs target basic metabolic processes, operative in all cell types. Thus, auxiliary components of metabolic pathways should also be targeted. Moreover, small molecules raised against these enzymes often fail to differentiate between various specific subtypes expressed in malignant and nonmalignant cells. Furthermore, specific inhibitors also show limited effectiveness due to extremely heterogeneity and flexibility in PanCa metabolism. Thus to crush PanCa, simultaneous targeting of two metabolic pathways could be a better strategy[50]. Another way-out could be the detection of metabolic checkpoints between healthy and cancerous cells with different genetic aberrations[40] Also, deeper understanding to detect metabolic-hub in PanCa would be of worth. Finer knowledge not only on altered cancer metabolism but also on metabolic cross-talk with various cells in the microenvironment leading to metabolic-symbiosis would provide novel approaches in precise anti-cancer therapy.

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