Role of different immune cells and metabolic pathways in modulating the immune response in pancreatic cancer (Review)

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Received May 21, 2020; Accepted September 16, 2020

DOI: 10.3892/mmr.2020.11622

Abstract. Pancreatic cancer is an aggressive cancer, making it a leading cause of cancer-related deaths. It is characteristically resistant to treatment, which results in low survival rates. In pancreatic cancer, immune cells undergo transitions that can inhibit or promote their functions, enabling treatment resistance and tumor progression. These transitions can be fostered by metabolic pathways that are dysregulated during tumorigenesis. The present review aimed to summarize the different immune cells and their roles in pancreatic cancer. The review also highlighted the individual metabolic pathways in pancreatic cancer and how they enable transitions in immune cells. Finally, the potential of targeting metabolic pathways for effective therapeutic strategies was considered.

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Abbreviations: COX2, cyclooxygenase 2; DCs, dendritic cells; FAO, fatty acid oxidation; FAS, fatty acid synthesis; FASN, fatty acid synthetase; IDO, indoleamine-2.3-dioxygenase; LAT-1, L-type amino acid transporter; MDSCs, myeloid-derived suppressor cells; NK, natural killer; NKG_2D, natural killer group 2 member; PDAC, pancreatic ductal adenocarcinoma; SHK, sedoheptulose kinase; T-eff, effector T cells; T-regs, regulatory T cells; TAMs, tumor-associated macrophages

Key words: pancreatic ductal adenocarcinoma, metabolic pathways, immune cells, metabolites, immune response

1. Introduction

Pancreatic cancer is the 7th most common cause of cancer-related deaths in developed countries and the 3rd most common in the USA, with >250,000 deaths worldwide annually (1). Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic neoplasm and accounts for >85% of pancreatic cancer cases globally (2). It originates in the head region of the pancreas and exhibits a glandular pattern, structurally similar to that of the ductal epithelial cells (3). Despite the high mortality rate in pancreatic cancer, the disease shows no early warning signs; therefore, pancreatic tumorigenesis and progression may remain undetected in a process that takes up to 20 years (4). The lack of early diagnostic markers has led to the delayed detection and late presentation of pancreatic cancer, which is usually at a locally advanced or metastatic stage at the time of diagnosis, thus making the disease fatal (5).

The immune system, which comprises the innate and the adaptive immune system, protects the host from foreign pathogens, including cancer cells (6). The innate immune system includes antigen-presenting cells, which phagocytose invading pathogens and present antigenic determinants with the major histocompatibility complex proteins (MHC)-II to $CD4^+$ T cells. Granulocytes, mast cells, dendritic cells (DCs), macrophages and natural killers (NK) cells are also innate immune cells (7). The adaptive immune system is regulated and comprised mainly of B and T cells, which are usually activated when the innate immune system cannot eliminate the pathogens to provide long-lasting immunity (8).

The function and differentiation of immune cells are influenced by metabolism (Fig. 1) (9). Metabolism involves a series of chemical reactions that sustain life by converting food to energy and building blocks for larger compounds, such as proteins, lipids and nucleic acids (10). The chemical reactions involved in metabolism are structured into pathways.

Metabolites are end-products of metabolism, which are generated by living organisms during their life cycles and could reflect the function of the organism (10).

2. Role of immune cells in pancreatic cancer

The dysfunctional immune system in pancreatic cancer has been discovered to promote tumor growth. The pancreatic cancer microenvironment was identified to serve a vital role in tumor growth and the therapeutic response (8). Pancreatic cancer cells are rich in stroma, which comprises both cellular and acellular components, including the extracellular matrix, fibroblasts, myofibroblasts, growth factors, cytokines, pancreatic stellate cells and immune cells (11). DCs, NK cells, $CD8^+$ and $CD4^+$ T cells are some of the immune cells discovered to be activated to inhibit tumor growth and progression in PDAC (12,13). Regulatory T cells (T-regs), tumor associated macrophages (TAM), myeloid-derived suppressor cells (MDSCs) and tumor-associated neutrophils have also been reported to promote tumor growth and progression, and also to suppress antitumoral responses (8,11).

MDSCs suppress immunity by inhibiting T cell activation via the sequestration of cysteine, thereby reducing the availability of the amino acids tryptophan and arginine, which are required for protein translation by T cells and reactive oxygen species (ROS) production (14). A previous study illustrated that the growth factor granulocyte-macrophage colony-stimulating factor, secreted by pancreatic tumors, promoted the early recruitment of MDSCs (15). MDSCs inhibit the immune functions of effector T (T-eff) cells and NK cells, while the function of T-regs is promoted (16,17). Elevated MDSCs levels in pancreatic cancer were discovered to be a poor prognostic factor associated with elevated T-regs and Th2 cytokines levels (18). Using peripheral blood mononuclear cells harvested from blood samples collected from 131 patients with cancer, flow cytometric analysis revealed that both MDSC and T-reg levels were significantly elevated in patients with pancreatic cancer (18).

Macrophages switch their differentiation from M1 (proinflammatory) to M2 (anti-inflammatory) phenotypes in the presence of stimuli, such as the cytokines IL-10, IL-4, and TGF-β, which are secreted from the PDAC microenvironment (19,20). TAMs are macrophages initially recruited to the site of tumor formation in response to the chemotactic factors released by pancreatic cancer cells, and they promote tumor progression by suppressing antitumor immune responses and stimulating the vascularization and metastasis of cancer cells (21). This has been demonstrated using immunohistochemistry to identify inflammatory cells by evaluating the expression of proangiogenic and prolymphangiogenic molecules, VEGFA and VEGFC, produced by macrophages in pancreatic cancer (22). Furthermore, TAMs were discovered to regulate pancreatic intraepithelial neoplasia progression by being the main source of IL-6 in $Kras^{G12D}$-mutations, thereby promoting cancer development (23). Elevated levels of TAMs and M2 polarized TAMs were also identified to be associated with a worse prognosis in pancreatic cancer by promoting lymphatic metastasis by lymphangiogenesis (20).

$CD8^+$ T cells are affected in PDAC progression (24,25). It has been shown that increased levels of $CD8^+$ T cells led to favorable clinical outcomes and the improved survival of patients with PDAC (25). The effect of $CD4^+$ T cells depends on their differentiation into their subtypes, T helper cell type (Th)1, Th2 and Th17, and T-regs (26). $CD8^+$ T cells are compromised in human pancreatic cancer due to the degradation of MHC-1 molecules by enhanced autophagy, which leads to immune evasion and the inhibition of antitumor activity (24,27). Both cytotoxic and helper T cells were found to be impaired by the influence of immunosuppressive cytokines, which promoted Th2 responses and led to tumor growth (28,29). Immunohistochemical studies have demonstrated that the upregulation of $CD8^+$ and $CD4^+$ T cells predicted an improved prognosis in PDAC (12,30). A decrease in the levels of T-eff cells was suggested to be associated with the progression from a premalignant to malignant stage in PDAC, because it was associated with reduced tumor growth (24,31). In addition, elevated levels of Th1 cells contributed to a good clinical outcome because they produce IFN-γ and TNF-α, which promote anticancer activities by activating cytotoxic T cell responses, as well as antigen-presenting cells (32,33).

The role of Th17 cells in pancreatic cancer is not completely understood because it depends on the cancer type, tumor stage and location (34). Previous studies have revealed that an increased level of Th17 cells in murine pancreatic cancer inhibited tumorigenesis, leading to improved survival (35), while in another study, elevated levels of Th17 cells in human pancreatic cancer promoted cancer progression and were associated with a poor survival (36,37). Th2 cells exhibit a tumor-promoting function in pancreatic cancer, and this was suggested to be the result of the upregulated levels of Th2 cytokines, such as IL-13, IL-10 and IL-6, found in the plasma of patients with pancreatic cancer (38,39). T-regs depend on oxidative phosphorylation and fatty acid oxidation (FAO) for ATP upon activation (40); this permits T-regs to survive under tumor conditions in contrast to T-eff cells, which are impaired due to insufficient glucose production (41). T-reg suppress immune responses via the secretion of IL-10 and TGF-β to produce an immunosuppressive environment (42) and, in pancreatic cancer, they were discovered to be involved in the early infiltration of preinvasive lesions, promoting tumor growth and progression (31).

Cytotoxic lymphocyte-associated antigen-4 is a receptor found on T-regs that produces inhibitory signals upon interaction with its ligands, CD80 and CD86, on antigen-presenting cells, thereby inhibiting the formation of the immune synapse between $CD4^+$ T cells and the antigen-presenting cells, which normally promotes the release of cytokines for cancer cell destruction (43). In patients with pancreatic cancer, a large number of T-regs in the circulation was associated with the advancement of the disease (44). The chances of successful surgical resection and survival rate post-resection were also discovered to be associated with the decreased levels of T-regs in patients with pancreatic cancer (44). Additionally, increased numbers of mast cells were identified to be associated with metastasis and reduced survival in human pancreatic cancer (45).

DCs control immune responses by regulating the polarization of T cells into Th1, Th2 or Th3 subtypes depending on the stimulation by certain cytokines (46). The pancreatic cancer microenvironment releases tumor-derived factors,

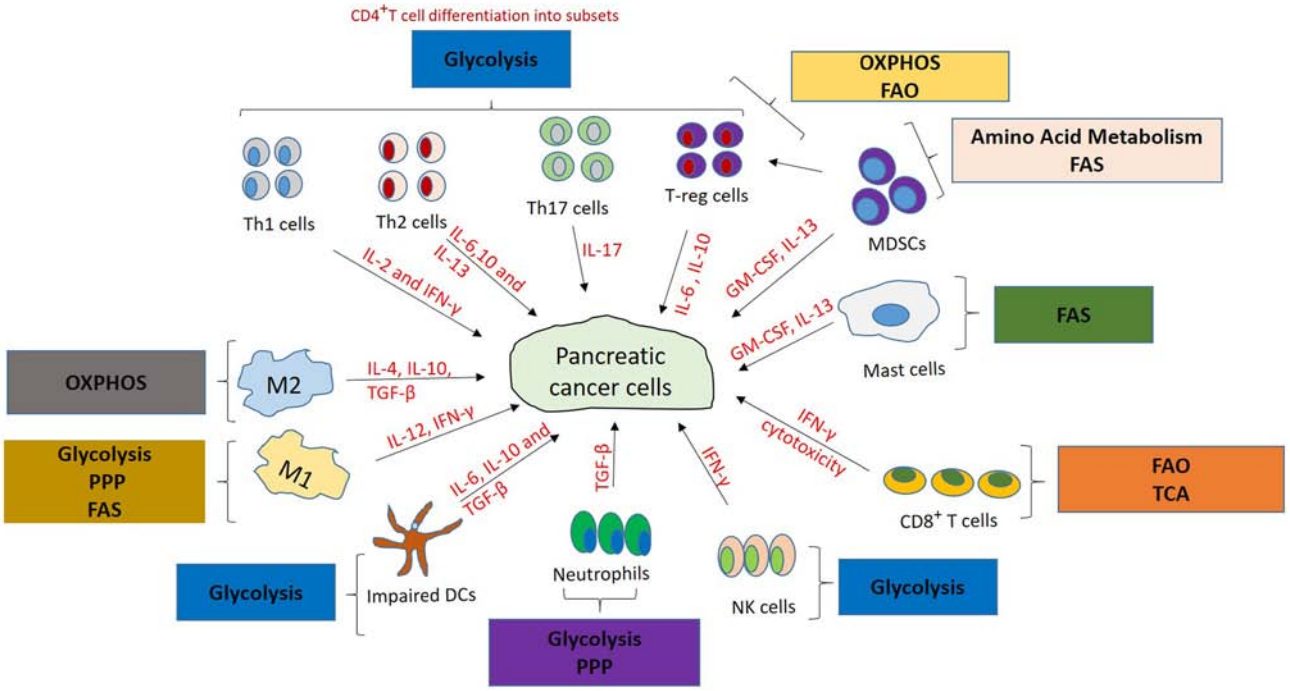

Figure 1. Interaction between the metabolic pathways and the immune cell network in pancreatic cancer. The immune network comprises the complex interactions between the innate immune cells, adaptive immune cells and the pancreatic cancer cells. Immunity in pancreatic cancer is greatly influenced by the chemokines and cytokines released by the tumor cells, such as IL-6 and IL-10, as well as those released by the immune cells, such as IL-4, IL-13 and IFN-γ. Metabolic pathways also serve an important role in the reprogramming of these immune cells, either by activating, inhibiting or polarizing these immune cells. For instance, the switch from M1 to M2 macrophages is greatly influenced by FAO and the TCA cycle. Enhanced glycolysis is necessary for T cell differentiation into their subsets, Th1, Th2, Th17 and T-regs. Th1/2/17, T helper cell type 1/2/17; T-regs, regulatory T cells; MDSC, myeloid-derived suppressor cells; DCs, dendritic cells; FAO, fatty acid oxidation; GM-CSF, granulocyte-macrophage colony-stimulating factor; PDAC, pancreatic ductal adenocarcinoma; TCA, tricarboxylic acid; PPP, pentose phosphate pathway; NK, natural killer; FAS, fatty acid synthesis.

such as IL-6 and VEGF, which promote DC impairment by reprogramming the immune cell response from a Th1 type to a Th2 type, thereby promoting cancer development (28,29). One previous study reported that the elevated levels of DCs and NK cells in PDAC were associated with a prolonged or improved survival rate (44).

The immune system uses NK cells to target cancer cells, which inhibits their growth, and a decreased level of NK cells was suggested to be associated with the advancement of pancreatic cancer. These findings were observed by determining the serum levels of soluble MHC class 1 chain-related molecule A (sMICA) and NK group 2-member D (NKG_2D) in the NK cells of patients with pancreatic cancer using immunohistochemistry. Elevated levels of sMICA were found in patients with advanced pancreatic cancer and were correlated with the downregulation of NKG_2D expression, implying decreased levels of NK cells (47). Mast cells are commonly known for their role in allergies; however, in PDAC, elevated levels of mast cells were also discovered to be associated with tumor progression (48,49).

3. Metabolic pathways and their influence on the immune response

The excessive growth of the extracellular matrix in pancreatic cancer as a result of the dense stroma was discovered to lead to the formation of barriers against the immune system, drug delivery, oxygen and nutrients (50). Hence, the cells develop mechanisms that alter the typical metabolic pathways to supply nutrients to survive (51). Immunotherapy promotes antitumor activities by reprogramming and enhancing the immune response (34,52), and the function and differentiation of immune cells are greatly influenced by metabolism, hence a combination of both could be a more effective treatment option (53). Metabolic pathways can either promote or inhibit immune cell functions, which could be essential in further understanding the immune response and in identifying novel therapeutic options to treat immune-dysfunction in numerous types of disease, including cancer (Figs. 1 and 2).

Glycolysis. Glucose uptake and glycolysis are activated in pancreatic cancer cells, and their intermediates are fed into other biosynthetic pathways, such as the pentose phosphate pathway (PPP) (54). Glycolysis involves a series of enzymatic steps, whereby glucose is metabolized to pyruvate and then finally to lactate to yield ATP and other substrates for other metabolic pathways (55,56). Glycolytic enzymes, such as hexokinase, enolase and phosphoglycerate kinase, among others, were found to be overexpressed in pancreatic cancer, promoting tumor growth and metastasis (57,58). The expression of hypoxia-inducible genes in pancreatic cancer cell lines (MiaPaca-2 and Pcl-43) under different conditions was investigated, and hexokinase was identified to be upregulated (59). Glycolysis in pancreatic cancer was revealed to promote lactate production, tumor growth and protein glycosylation (53,55,60). Although glycolysis is less energy efficient compared with the

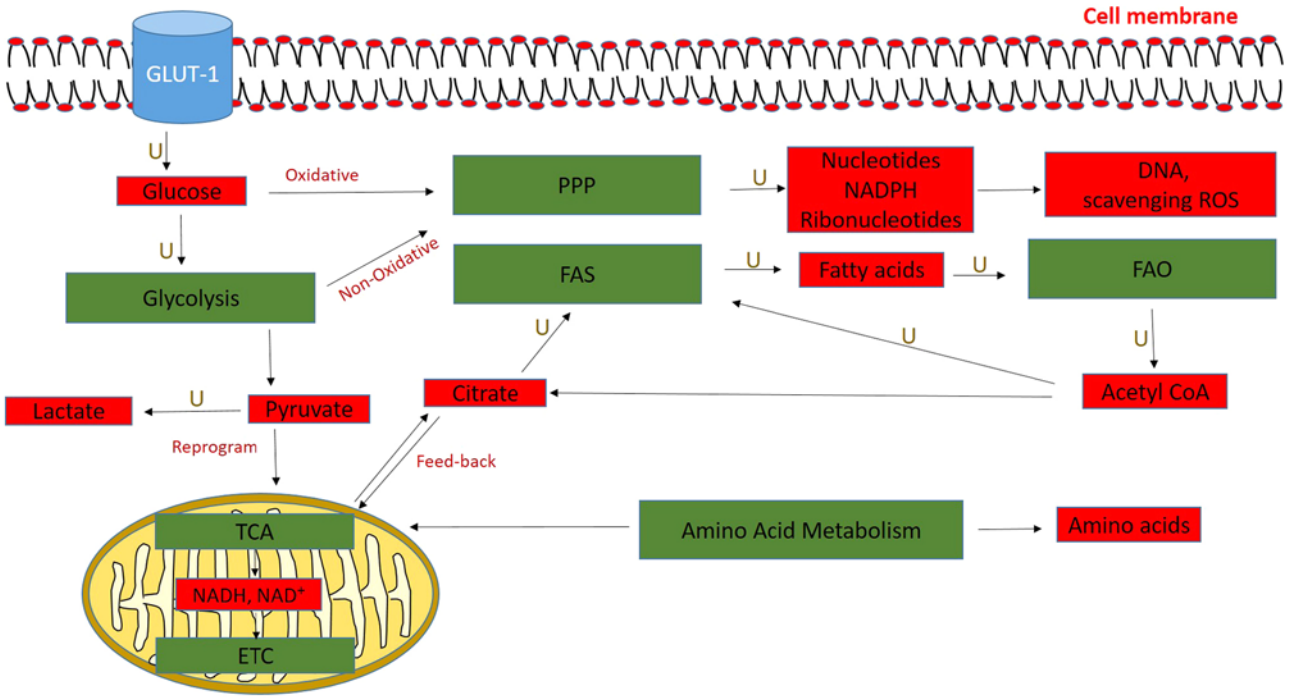

Figure 2. Metabolic pathways dysregulated in pancreatic cancer. The GLUT-1 transporter is upregulated in PDAC, which increases glucose uptake and glycolysis and promotes the flux of their intermediates into other metabolic pathways, such as the PPP. Glucose is metabolized into pyruvate, which feeds into the TCA cycle. Metabolic reprogramming of tumor cells restructures the TCA cycle and produces a high amount of lactate. The dysregulated FAS pathway contributes to the generation of building blocks for membrane synthesis. The fatty acids produced are oxidized via FAO to Acetyl CoA, which feeds back into the TCA cycle to generate NADH and NAD^+ and stimulates the electron transport chain to produce more ATP for the PDAC cells. In PDAC cells, both oxidative and non-oxidative phases of the PPP are upregulated to generate NADPH for scavenging ROS and nucleotides for DNA synthesis. Amino acid metabolism feeds into the TCA cycle to meet the high metabolic demands of the tumor cells. Red represents upregulated metabolites and green represents dysregulated metabolic pathways. PDAC, pancreatic ductal adenocarcinoma; GLUT-1, glucose transporter 1; PPP, pentose phosphate pathway; TCA, tricarboxylic acid; FAS, fatty acid synthesis; FAO, fatty acid oxidation; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; U, upregulated.

tricarboxylic acid (TCA) cycle, it is preferred by cancer cells as it produces ATP faster, occurs independently of mitochondrial function and conserves nutrients for lipids, amino acids and nucleic acid biosynthesis (55). This phenomenon is known as the Warburg effect (61,62) and, in PDAC, leads to increased lactate production, which alters the tumor stroma interface, thereby increasing invasiveness (63). Elevated lactic acid levels were identified to lead to a decreased pH in the tumor microenvironment, which inhibited cytotoxic T cell function and promoted tumor growth and progression (64).

M1 macrophages are characterized by enhanced glycolysis, while M2 macrophages exhibit decreased levels of glycolysis (65). M1-polarized macrophages are highly glycolytic due to the increased stimulation of the fructose-2,6-biphosphatase enzyme (66), which produces nitric oxide and TNF-α (67), and exhibit IL-12 and IL-23 phenotypes, while M2-polarised macrophages exhibit an IL-10 phenotype (19).

T cells require large amounts of glucose and glutamine catabolism for nucleotide and lipid synthesis, which are essential for cell growth. However, in their resting state (naïve state), they require small amounts of glucose, amino acids and fatty acids for the sustenance and maintenance of energy (68). Glycolysis is necessary for differentiating $CD4^+$ T cells into its effector subsets, as well as maintaining a proper balance between protective and suppressive immunity (69). Glycolysis is essential for T-eff cell activation and function, because T-eff cells require high metabolic flux (70). T-eff cells are activated by the mTOR signaling pathway and hypoxia-inducible factor-α transcription factors, which promote glycolysis and amino acid metabolism, but uses FAO for ATP production (71). The mTOR signaling pathway is highly involved in metabolism, altering the expression of key pathways such as glycolysis (72,73).

T-eff subsets, such as Th17, Th1 and Th2, require elevated levels of glycolysis following activation (69). Macintyre *et al* (40) demonstrated that glucose transporter (GLUT)-1 was essential for $CD4^+$ T cell activation and effector function by examining the GLUT transporter family to determine their roles in glucose uptake and metabolism in T cells. The study also revealed that the levels of T-eff cells were elevated in GLUT-1 transgenic mice, which depend solely on glucose metabolism (69). Increased levels of glycolysis were also found to be required in order for activated B cells to contribute to the immune response (74). In addition, activated neutrophils were identified to depend on glucose for ATP production via glycolysis (75).

DCs are usually found in tissues that are in contact with external environment systems (76). They process and present antigens on the cell surfaces for T cells to respond to (77). In addition, DCs regulate the immune response by regulating the polarization of T cells to Th1, Th2 or Th3 subtypes following the stimulation by cytokines (46). Enhanced glycolysis occurs in DCs, which enables them to generate sufficient ATP and intermediates to perform the immune system functions. Krawczyk *et al* (78) demonstrated that DCs undergo

maturation by Toll-like receptor signaling, and this occurred by the metabolic conversion from oxidative phosphorylation to aerobic glycolysis following the upregulation of fatty acid synthesis (FAS). The rapid induction of glycolysis was also discovered to be essential for the activation and function of DCs (79).

TCA cycle. The TCA cycle is a series of reactions that occur in the matrix of the mitochondria and involves the oxidation of Acetyl CoA to generate NADH and $FADH_2$, which is then converted to ATP via the electron transport chain (Fig. 2) (80). The TCA cycle was discovered to be dysregulated in PDAC, in which increased levels of pyruvate from glycolysis were reduced to lactate and fed the TCA cycle to generate citrate for FAS (81). Metabolites such as fumarate, succinate and D2-hydroxyglutarate were reportedly upregulated in cancer cells as a result of the dysfunction of the enzymes, fumarate dehydrogenase, succinate dehydrogenase and isocitrate dehydrogenase (82). Elevated levels of these metabolites have been shown to increase ROS levels which, in turn, activated signaling pathways, such as P13K/AKT/mTOR, which promote carcinogenesis (83,84). Macrophages are proinflammatory when there is a shift towards glycolysis and FAS, promoting the production of IL-β and TGF-β. Conversely, macrophages are polarized towards the anti-inflammatory state when there is a shift towards the Krebs cycle and FAO (66). Increased citrate synthase activity was observed in PDAC upon measuring the activity in the tissues of patients with pancreatic cancer (85); citrate synthase catalyzes the reaction between Acetyl CoA and oxaloacetate to produce citrate, which is a substrate for membrane lipid synthesis (86). Although pancreatic cancer has been associated with elevated citrate synthase levels, increased citrate production inhibits phosphofructokinase (PFK)2 (87). PFK2 is a promoter of PFK1, an enzyme that catalyzes the conversion of fructose-6-phosphate to fructose-1,6-biphosphate in the presence of ATP, thereby controlling glycolysis in cancer cells. M2 macrophages, which are observed in PDAC, utilize oxidative phosphorylation to support their metabolic demands and have an uninterrupted Krebs cycle (55,88).

PPP. The PPP consists of two phases, oxidative and non-oxidative, both of which were revealed to be upregulated in pancreatic cancer (86). The major products of the oxidative phase of PPP are nucleotides and NADPH, while the non-oxidative phase generates ribonucleotides for DNA synthesis, which is mediated by transketolase and transaldolase enzymes (89). The mRNA expression levels of transketolase were reported to be upregulated in the pancreatic cancer cell lines, Panc-1, MiaPaca-2 and CaPan-1 (90). In addition, a previous study revealed that the activation of the non-oxidative phase of the PPP in pancreatic cancer promoted resistance to gemcitabine treatment (91).

Macrophages are polarized towards an M2 phenotype when the PPP is inhibited, thus indicating the importance of the PPP in the pro- and anti-inflammatory response of macrophages, as shown in Fig. 1. Screening of 199 human kinases for their potential roles in immunoregulation revealed that the sedoheptulose kinase (SHK) enzyme, which limits the PPP, served an important role in macrophage polarization (92). In addition, the results proved that SHK enzyme downregulation was essential for the M1 reprogramming in macrophages. The PPP was found to be highly activated in lipopolysaccharide-activated macrophages due to the induction of the pyruvate kinase isoenzyme M2, which is an enzyme that diverts glycolytic intermediates to other biosynthetic pathways (93).

Amino acid metabolism. L-type amino acid transporter (LAT-1) transports large amino acids, such as tryptophan, valine, phenylalanine, tyrosine and histidine, among others (94). LAT-1 was discovered to be overexpressed in PDAC and was linked to angiogenesis and tumor cell proliferation (95). The breakdown of tissue proteins to branched-chained amino acids was revealed to be one of the early consequences of pancreatic cancer, thus, it may be used as a potential biomarker (96). For example, leucine, isoleucine and valine are branched-chain essential amino acids (97), which were reported to be elevated in pancreatic cancer because they are an alternative source of organic molecules that can fuel the TCA cycle. Exosomes derived from the tumor microenvironment were also identified to enhance the proliferation of pancreatic cancer cells by supplying metabolites, such as proteins, nucleic acids and amino acids (54,98). Due to poor vascularization, pancreatic tumors do not have a sufficient supply of glutamine; instead, they use micropinocytosis to engulf extracellular proteins, which are subsequently degraded in lysosomes to release glutamine and other amino acids (99). PDAC is characterized by a low expression of glutamate dehydrogenase and the overexpression of glutamic oxaloacetic transaminase for the conversion of glutamine-derived aspartate to oxaloacetate in the cytoplasm, which is then further converted to malate and finally into pyruvate (100). Glutamine regulates the balance between T-eff cells and T-regs; however, in the PDAC microenvironment, the transporter protein, alanine-serine-cysteine transporter 2, was found to be deficient, leading to the diminished generation and function of Th17 and Th1 cells (101), hence promoting T-reg formation.

Upon activation, T cells consume a large amount of arginine and tryptophan to generate memory T cells by switching from glycolysis to oxidative phosphorylation, which activates antitumor activities (102). Amino acids produce derivatives that support cancer growth and progression; for example, in the PDAC microenvironment, the overexpression of indoleamine-2,3-dioxygenase (IDO) and arginase depleted tryptophan and arginine, thereby suppressing T cell proliferation and activating T-reg differentiation (103). Glutamate conversion into α-ketoglutarate by glutamate dehydrogenase was discovered to promote cancer growth, because it served as an anaplerotic intermediate for the TCA cycle and provided nitrogen for non-essential amino acid biosynthesis (104).

Lipid metabolism (FAO and FAS)

FAO. FAO is an alternative source of Acetyl CoA that enters the TCA cycle for ATP production and energy (Fig. 2) (55). Pancreatic tumors and cell lines have been shown to overexpress the cyclooxygenase (COX)2 enzyme, which was identified to be associated with the invasiveness and metastasis of the disease (105). COX catalyzes the rate-limiting step in arachidonate metabolism to produce prostaglandin (106). The PDAC microenvironment was discovered to release endothelial growth factors, tumor promoters and cytokines, which

Table I. Immune cells and their role in pancreatic cancer, as well as the pathways through which they perform their functions.

A, Macrophages

Cell type	Role of immune cells in pancreatic cancer	Pathways affected by immune cells in pancreatic cancer	Immune cell function in pancreatic cancer	(Refs.)
Macrophages	Switch from M1 to M2 macrophages due to cytokines such as IL-10 and TGF-β.	OXPHOS	Immunosuppression.	(19)
Tumor-associated macrophages	Release growth factors, such as VEGF, and expresses programmed death-ligand 1 (binds to programmed cell death protein 1 on the surface of activated T cells).	Glycolysis and OXPHOS	Angiogenesis inhibition, tumor cell metastasis, inhibits T cell activation.	(22)

B, T cells

Cell type	Role of immune cells in pancreatic cancer	Pathway affected by immune cells in pancreatic cancer	Immune cell function in pancreatic cancer	(Refs.)
$CD8^+$ T cells	Suggest an improved prognosis and favorable clinical outcomes in PDAC.	FAO and TCA cycle.	Phagocytosis and inhibition of tumor growth.	(12, 110)
$CD4^+$ T cells	Th1 cells promote anticancer functions.	Glycolysis.	Inhibition of tumorigenesis.	(33,55)
	Th2 cells secrete cytokines, such as IL-13 and IL-10.	Glycolysis.	Promotes tumor growth and tumorigenesis.	(38)
	Th17 could be pro- or anti-tumorigenic.	Glycolysis.	Immunosuppression,inhibition of tumor growth.	(30,32)
T-regs	Secretion of IL-10 and TGF-β.	Oxidative phosphorylation and FAO.	Immunosuppression and tumor growth.	(42)
	Cytotoxic T-lymphocyte-associated protein is a receptor on T-regs which produces inhibitory signals.	Oxidative phosphorylation and FAO.	Inhibition of immunology synapse and destruction of infected cells. Impairs T cell activation and finally leads to T cell death.	(40)

C, Other immune cell types

Cell type	Role of immune cells in pancreatic cancer	Pathways affected by immune cells in pancreatic cancer	Immune cell function in pancreatic cancer	(Refs.)
DCs	Decreased levels are associated with a poor survival rate in PDAC.	Glycolysis and pentose phosphate pathway.	Antigen presentation.	(44,77)
Mast cells	Promote tumor progression. Elevated levels are associated with metastasis in PDAC.	FAS.	Angiogenesis and metastasis.	(48,49)
NK cells	Decreased levels are associated with a worse prognosis in PDAC.	Glycolysis.	Produces cytokines for cancer cell destruction.	(47)
MDSCs	Elevated MDSCs levels in PDAC are associated with increased levels of IL-13 and T-regs.	Amino acid metabolism, FAS.	Immunosuppression and inhibition of T cell. activation	(18)

PDAC, pancreatic ductal adenocarcinoma; TCA, tricarboxylic acid; FAO, fatty acid oxidation; T-regs, regulatory T cells; FAS, fatty acid synthesis; MDSC, myeloid-derived suppressor cells; Th1/2/17, T helper cell type 1/2/17; OXPHOS, oxidative phosphorylation; NK, natural killer.

Table II. Metabolic pathways with potential roles as effective immunotherapeutic strategies.

Metabolic pathway	Prospective immunotherapy strategies	(Refs.)
Glucose metabolism	Targeting the inhibition of tumor cell-derived lactate in human T cells, as this would enhance T cell proliferation and the cytotoxic activities of NK and $CD8^+$ T cells.	(125)
	Use of programmed cell death protein 1 blocking antibodies may promote antitumor activities by enhancing T cell proliferation via glycolysis inhibition and FAO promotion.	(135)
	Inhibition of key glycolytic enzymes, such as lactate dehydrogenase A and pyruvate kinase isoenzyme 2 is associated with the reduction of MDSCs infiltration and promote $CD8^+$ T cells, NK and T-eff cells.	(133,134)
Lipid metabolism	Targeting the inhibition of cyclooxygenase 2 and the suppression of its metabolite prostaglandin E2 using Paeonol to exert anticancer effects by inhibiting the reprogramming from M1 to M2 macrophages.	(129,132)
	FAO inhibition in MDSCs to enhance T cell function and decrease cytokine production.	(124,128)
Amino acid metabolism	Inhibition of indoleamine-2,3-dioxygenase to promote T cell proliferation and response to antigen presenting cells by secreting cytokines, which promote immunity.	(136)
	Inhibition of glutamine metabolism using aminooxyacetate to mediate cytotoxicity in tumor cells.	(130)
	Targeting LAT-1 and amino acid pathways using SM-88 or anti-LAT-1 antibodies to promote tumor growth inhibition via disruption of protein synthesis and activation of DCs and T cells.	(95)
	Blockade of adenosine production by the inhibition of CD39 and CD73 to promote the anticancer activity by activating DC maturation and T cells and NK cell activation.	(123,126,131)

NK, natural killer; FAO, fatty acid oxidation; DC, dendritic cells; MDSCs, myeloid-derived suppressor cells; LAT-1, L-type amino acid transporter.

induced COX2 expression (107). Dubois *et al* (108) showed that transforming growth factor-α and tumor promoter tetradecanoyl phorbol acetate stimulate the production of eicosanoids, such as COX2, in rat intestinal epithelial cell culture. Increased expression of COX2 plays a major role in the overproduction of prostaglandins E_2, which inhibits immune response in malignant tissues (109). FAO was also indicated to serve an important role in regulating the balance between T-eff cells and suppressive T-regs, as it was observed to promote the generation of T-regs, while inhibiting T-eff cell polarization (69). FAO also enhanced the activation and maintenance of memory $CD8^+$ T cells (110).

FAS. Products derived from other cell metabolic pathways, such as glycolysis, the TCA cycle and PPP are used by cells to generate lipids for cellular growth in the FAS pathway (55). In pancreatic cancer, FAS involves the upregulation of ATP citrate lyase, Acetyl CoA carboxylase, fatty acid synthase (FASN), Acetyl CoA synthetase, stearoyl CoA desaturase, polyunsaturated fatty acids, monounsaturated fatty acids (MUFA) and saturated fatty acids (86). Some plasma lipids, such as very-low-density lipoproteins, were also discovered to be elevated, while low-density lipoprotein, high-density lipoprotein and 3-hydroxybutyrate were decreased in patients with PDAC (111). ATP-citrate lyase, an enzyme that converts citrate to Acetyl CoA which is a precursor for FAS, was also revealed to be upregulated in PDAC (112).

Deregulated FAS in PDAC, such as the biogenesis of fatty acids due to the overexpression of FASN, reportedly promoted cancer progression via resistance to chemotherapy (113). Following resection, FASN levels are decreased in the majority of patients with PDAC, suggesting that elevated levels of FASN may be associated with a poor survival (114). Another enzyme that serves an essential role in FAS is acyl CoA synthetase, which converts long-chain fatty acids to acyl CoA, a critical step in phospholipid and triglycerol biosynthesis (115). Stearoyl-CoA desaturase-1 was demonstrated to exert an important role in the pathogenesis of PDAC by regulating the production of MUFAs (116). Alcohol and tobacco-related carcinomas, such as PDAC, have also been shown to overexpress the aldo-keto reductase family 1B10 (AKR1B10) enzyme, which catalyzes the production of aldehyde and NADPH from alcohol and $NADP^+$ (117). AKR1B10 is essential in FAS by regulating the stability of Acetyl CoA carboxylase, which is able to catalyze the biosynthesis of malonyl CoA, a FASN substrate. Fatty acids are esterified to phospholipids, which are required for membrane formation, and this pathway was indicated to be the most abundant in advanced pancreatic cancer (86). Cholesterol uptake was also identified to be elevated in PDAC, as pancreatic cancer cells are highly dependent on cholesterol (118).

A summary of the discussed metabolic pathways and how they influence immune cells is presented in Table I.

4. Recent treatment developments involving metabolic regulation

Recent treatment developments involving TCA inhibition in PDAC include phase II and III clinical trials investigating a TCA cycle inhibitor devimistat, also known as CPI-613®

(ClinicalTrials.gov.nos. NCT03435289 and NCT03504423). The combination of CPI-613 with gemcitabine, nab paclitaxel and FOLFIRINOX have been explored for unresectable, locally advanced and metastatic PDAC (119,120). In addition, the P13K-AKT-mTOR signaling pathway controls cell cycle, survival, metabolism and motility in cancer (121), therefore, studies targeting mTOR inhibition include phase I and II clinical trials (ClinicalTrials.gov.no. NCT03362412) investigating Sirolimus, an mTOR kinase inhibitor, for the treatment of patients with advanced pancreatic cancer (122). A combination of metabolic regulation and chemotherapy could be more effective than the use of chemotherapy alone.

5. Conclusion and future perspectives

The aggressive and unresponsive nature of pancreatic cancer highlights a requirement for an improved understanding of the mechanism of progression to provide effective therapeutic targets. Immunotherapy is a growing and promising treatment strategy in cancer; however, in pancreatic cancer, it is clear that further studies are required to investigate the effectiveness. The dysregulated interaction between the immune system and metabolic pathways in pancreatic cancer could provide greater insight into this disease. Furthermore, understanding these interactions may enable the development of effective therapeutic options that might increase the survival rate of patients. Targeting these pathways to enhance or elicit an immune response would be beneficial. Several studies have investigated the potential of targeting metabolic pathways and the effect on immune response in carcinogenesis (123-137), which are summarized in Table II. Future studies to determine these effects in pancreatic cancer and discover new targets may prove favorable.

Acknowledgements

Not applicable.

Funding

This study was funded by a grant from the South African Medical Research Council, which was awarded to the Wits Common Epithelial Cancer Research group. GPC was funded by the Cancer Association of South Africa (CANSA).

Availability of data and materials

Not applicable.

Authors' contributions

NE and EEN conducted the literature search. NE, PF, JOJ, GPC and EEN drafted the manuscript and critically revised the manuscript. EEN conceptualized the review article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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