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Amino Acid Metabolic Reprogramming in Pancreatic Cancer: Current Advances and Perspectives

Zhenhao Wang

School of Medicine, Jiamusi University, Jiamusi, China
2579369989@qq.com

Abstract. Pancreatic cancer is a highly aggressive digestive system tumor with a very poor prognosis. Initiation and progression of pancreatic cancer are closely associated with metabolic reprogramming. In recent years, more and more evidence shows that, apart from glucose metabolism, amino acid metabolism has an important role in pancreatic cancer cell proliferation, invasion, drug resistance, regulation of the tumor microenvironment and so on. This article summarizes the metabolic reprogramming of amino acid in pancreatic cancer and discusses the related influence to tumor biology behavior. Also points out the possible contribution of these amino acid metabolic reprogramming to targeted therapy and tumor marker and intends to introduce new ideas for basic and clinical studies of pancreatic cancer.

Keywords: metabolic reprogramming, amino acid metabolism, pancreatic cancer, tumor microenvironment

1. Introduction

Current pancreas cancer (PC) is one of the worst kinds of cancers in the digestive system. Pancreatic ductal adenocarcinoma (PDAC) takes up over 90% of PC cases in total [1]. Because PC often has no obvious symptom at the early stage, very quick clinical progression and poor effects of treatments, PC patients have a very poor prognosis and the five-year survival rate for patients is extremely poor. Thus, discovering molecular mechanisms of PC pathogenesis will be beneficial to identifying new diagnostic markers and therapeutic targets for PC. Metabolic reprogramming is now acknowledged as one of the core hallmarks of cancer. By restructuring intracellular metabolic pathways, tumor cells are able to support their rapid proliferation and resist hostile metabolism [2].

Although traditional research has largely centred on glucose metabolism defects, including Warburg effect, recent works have shown the paramount importance of amino acid metabolism in the whole tumor metabolic network. In addition to playing a basic role in protein synthesis, amino acids directly participate in nucleotide synthesis, maintenance of redox homeostasis, control of signal transduction, which all deeply affect the growth, proliferation and immune evasion of tumours [3]. In PC, the metabolic properties of several amino acids, such as glutamine, serine, methionine and branched-chain amino acids (BCAAs) are all altered. This metabolic reprogramming will provide metabolic energy and nitrogen for the growth of tumour cells and alter the tumour microenvironment (TME) and immune evasion, leading to the development of tumours. Furthermore, prevalent driver mutation in PC (such as KRAS mutations) can affect the expression of

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metabolic enzymes and metabolic transporters. Such genetic regulation would further remodel the amino acid metabolic network, meeting the biosynthetic demands and supporting the antioxidant capacity of cancer cells [4]. As such, amino acid metabolic reprogramming is not only a hallmark of PC pathology but also a potential target for the treatment of cancer.

Accordingly, this article reviews the recent advances of amino acid metabolic reprogramming in PC. We first highlight the pivotal metabolic pathways and related molecular regulatory mechanisms of reprogramming, and discuss their clinical role in the tumorigenesis, early diagnosis and targeted therapy of PC, and we believe that this review may provide a solid basis for future mechanistic studies and clinical treatment for PC.

2. Hallmarks of key amino acid metabolic reprogramming in PC

2.1. Enhanced dependency on glutamine metabolism

At the metabolic level, PDAC cells are powerfully dependent on glutamine, a situation ubiquitously referred to as 'glutamine addiction'. Glutamine is hydrolysed to glutamate by glutaminase (GLS) and enters the tricarboxylic acid cycle. This anaplerotic reaction of glutamine sustains cell energy supplies and provides the building blocks for the biosynthesis of lipids and nucleotides. Recent evidence identifies KRAS mutation—a pivotal driver event in PDAC—as a transcriptional activator of the transcription factor c-Myc and related metabolic regulatory pathways. Its up-regulation increases GLS expression and switches the glutamine pathway, which favors tumour cell proliferation and survival [5].

Furthermore, glutamine metabolism is also an important part of maintaining redox homeostasis. Glutamate is one of the important substrates for synthesis of glutathione (GSH), an important antioxidant molecule. High levels of GSH can scavenge ROS accumulated in the TME and help PC cells cope with high oxidative stress [6]. Obviously, the stromal cells in TME also participate in this metabolic rewiring. PSCs can synthesize glutamine from ammonia by GLS. PSC can export this newly synthesized glutamine into the TME as a metabolic substrate for cancer cells. This establishes a "metabolic symbiosis" between the two that further aggravates the tumor glutamine dependency.

2.2. Aberrant activation of the serine-glycine-one-carbon metabolic network

SGOC metabolic pathway is highly activated in PC and forms a critical metabolic axis that fuels rapidly proliferating tumour growth. Phosphoglycerate dehydrogenase (PHGDH), the rate-limiting enzyme of serine synthesis pathway (SSP), is highly expressed in many PDAC specimens. The expression of PHGDH is transactivated by both KRAS and the stress-responsive transcription factor ATF4 in a synergistic manner [7].

Serine has, besides being one of the amino acids indispensable for protein synthesis, also a substrate for nucleotide production through one-carbon metabolism. Importantly, serine fuels the production of reducing equivalents, in the form of NADPH, to maintain cellular redox balance. At the same time, one-carbon units are also used for DNA and histone methylation and for the modification of the epigenetic code and gene expression status of tumour cells to facilitate tumorigenesis. In addition, the GCS is upregulated in particular subtypes of PC. The degradation of glycine also contributes to replenishment of the one-carbon pool and production of NADPH and, in synergy with serine metabolism, contributes to the growth and antioxidant redox defence of the tumour cells.

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2.3. Arginine metabolic imbalance and immune regulation

Arginine metabolism is profoundly dysregulated in PC and is intimately involved in the tumor immune milieu. A subset of PC cells downregulates argininosuccinate synthetase 1 (ASS1), making them arginine auxotrophs and completely dependent on external arginine sources. This specific vulnerability of PC cells to arginine deprivation provides an excellent rationale for arginine deprivation therapy [8]. Simultaneously, the immune cells of the TME (that is, myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs)) tend to overexpress arginase 1 (ARG1) and to deplete the local abundance of arginine heavily. This arginine starvation leads to an impaired T-cell receptor (TCR) signalling response and T-cell proliferation, inducing T-cell exhaustion and driving tumour immune escape. Thus, arginine metabolism is emerging as an important link between tumour metabolic reprogramming and an immunosuppressive microenvironment.

3. How metabolic reprogramming drives PC malignancy

Amino acid metabolic reprogramming is also an essential part of the metabolic adaptation observed in pancreatic cancer (PC). By organizing multiple processes—such as biosynthesis, energy metabolism, redox metabolism and signal transduction—these metabolic adaptations drive proliferation of tumour cells and augment their response to multiple aspects of tumour microenvironments. In recent reports, it has been underlined that amino acids are not only metabolic metabolites for macromolecular synthesis, but also signalling molecules and epigenetic effectors, exerting multifactorial effects on tumour progression [9].

3.1. Sustaining biosynthesis and energy supply

As there is rapid growth of tumour cells, continuous production of biological macromolecules is demanded, and amino acid metabolic reprogramming plays a key role in this process. Metabolism of glutamine and serine provides the essential carbon and nitrogen sources for nucleotide biosynthesis, as the basis for DNA replication and proliferation. Glutamine has the role of amino acid donation for purine and pyrimidine nucleotide biosynthesis; and serine-glycine pathway provides methyl groups and carbon skeletons to cell energy and function through the one-carbon cycle to promote the nucleotide synthesis and cellular proliferation. Inhibition of the glutamine metabolism pathway causes nucleotide pool depletion and causes DNA replication stop and restricts tumour proliferation [10].

Furthermore, glutamine is essential for PC cells to maintain energy metabolism. Through glutaminase, PC cells hydrolyse glutamine to glutamate, which is then converted to α-ketoglutarate before entering the TCA cycle. This process replenishes metabolites (what is known as anaplerosis). This anaplerotic flux is particularly important when carbons from glucose are channelled towards biosynthesis, as it sustains mitochondrial oxidative phosphorylation and the continuous production of ATP, to meet the high needs of malignancy [11]. Thus, through integration of carbon and nitrogen metabolic networks, amino acid metabolism provides PC growth the necessary material and energy input.

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3.2. Maintaining redox homeostasis

PC tissues are mostly found in hypoxic and nutrient-poor microenvironments, often accompanied by an elevated level of reactive oxygen species (ROS). Appropriate ROS contribute to oncogenic signaling but too much ROS can promote cell damage and cell death. Therefore, the redox status should be maintained for tumor cell survival. Amino acid metabolism is an important regulator of redox status. Glutamine metabolism is one major pathway for maintaining the antioxidant capacity of cells. It produces glutamate, the most important precursor to generate glutathione (GSH). As one of the most important cellular antioxidants, GSH scavenges superfluous ROS and protects cells from oxidative damage. In PC, high levels of GSH in tumor cells allow them to tolerate oxidative stress and remain viable. There are studies that showed suppression of glutamine metabolism decreased the ratio of GSH/GSSG and triggers accumulation of ROS to cause cell death [12].

Meanwhile, the serine-glycine-one-carbon axis is a major source of cytoplasmic NADPH. In addition to playing a role in fatty acid synthesis, NADPH underpins antioxidant defences by maintaining the reduced status of GSH. Increased serine metabolism increases production of NADPH, thereby strengthening the tolerance of the tumour to oxidative stress [9]. Therefore, by affecting the pools of GSH and NADPH, amino acid metabolism is at the root of antioxidant defence in PC cells.

3.3. Modulating epigenetics and signaling pathways

Others than their metabolic functions, amino acids determine the behaviour of tumor cells through epigenetic regulation and cell signalling pathways. One carbon metabolism links amino acid metabolism to epigenetic regulation. S-adenosylmethionine (SAM), the ubiquitous donor molecule that is produced from serine metabolism, is the main substrate of DNA and histone methylation. Variations in SAM affect gene expression patterns directly and control the cell fate [13]. In PC, the serine metabolism flux variation reshapes the epigenetic profile by altering SAM generation, and finally, affects the aberrant transcription of tumor-associated genes [7].

Amino acids and their derivatives are signalling molecules. During amino acid starvation, cells can elicit the GCN2-ATF4 stress response pathway that upregulates genes for amino acid transport and metabolism and increases cellular plasticity. Under the conditions of nutrient-rich amino acid nutrient, branched chain amino acids robustly activate the mTORC1 signalling pathway. Activation promotes protein translation and cell growth, which amplifies cell proliferation of the tumour [14]. Their abnormal activation not only enhances the tumour potential of PC cells, but also leads to therapeutic resistance.

4. Therapeutic strategies targeting amino acid metabolism in PC

With emerging insights on the metabolic rewiring of pancreatic cancer (PC), targeting amino acid pathways represents an exciting new avenue for therapeutics. Because amino acids are important not only as nutrients but also as key signal transducing molecules, immune enhancers and epigenetic regulators, targeting amino acid dependencies yields a novel exciting direction for therapeutic interventions in PC. Yet, this clinical translation of these therapeutic concepts faces major hurdles, driven by strong complexity and heterogeneity of the tumor metabolic networks.

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4.1. Development of inhibitors against key metabolic enzymes

Small-molecule inhibitors of rate-limiting metabolic enzymes are currently major areas of research. For PC, considering the importance of the glutamine pathway, glutaminase (GLS) becomes a favourite target. Telaglenastat (CB-839) is one GLS inhibitor, and it displays strong anti-proliferative activity on many different tumour models. In PC, CB-839 suppresses tumour growth by attenuating glutaminolysis, and lowering anaplerotic influx in the TCA cycle; important, CB-839 also displays excellent synergistic effects against tumour growth when used in combination with conventional chemotherapy drugs such as gemcitabine [15, 16]. However, clinical trials show that its efficacious use as a monotherapy is limited, and combinatory strategies are required to increase clinical benefits.

Similarly, phosphoglycerate dehydrogenase (PHGDH), a rate-limiting enzyme for serine synthesis, is also a promising vulnerability. PHGDH inhibitors eliminate endogenous serine synthesis to eliminate nucleotide biosynthesis and redox balance. Trials in PC cells with high PHGDH expression have shown hypersensitivity to PHGDH inhibitors with selective toxicity. Indeed, PHGDH inhibitors also show synergy with antifolates, strongly amplifying the overall anti-tumour efficacy [7, 17].

Therapeutic strategies targeting arginine metabolism have also gained attention. PC cells expressing low levels of argininosuccinate synthetase 1 (ASS1) lack a sufficient endogenous arginine supply and thus depend totally on exogenous arginine. Indeed, by exploiting this quirk of metabolism, therapies that deplete arginine availability quench growth by depleting circulating arginine and are entering multiple clinical trials [8, 18, 19]. Unfortunately, tumour cells routinely resist these therapies by re-expression of ASS1 or by mobilization of alternative metabolic pathways, limiting long-term efficacy of this approach.

4.2. Exploration of combination therapy strategies

Given the poor effect of monotherapies of single metabolic nodes, combination strategies have become the most active research object. First, pairing of amino acid metabolic inhibitors with normal chemotherapy drugs is a viable strategy to overcome chemoresistance. For example, dampening glutamine metabolism can weaken the tumor antioxidant capacity and nucleotide biosynthesis, and sensitize PC cells to gemcitabine and enhance overall effect of chemotherapy [20].

Second, because amino acid metabolism is intimately involved with the tumor immune microenvironment, its regulation has fresh opportunities for immunotherapy. Although ICIs can deliver disappointing therapy effect on PC, rewiring of the metabolism of amino acids can alleviate the immunosuppression state. For instance, abolishing the function of arginase can rejuvenate the function of T cells and generate a more powerful anti-tumor immune response. Whereas a modulation of the tryptophan metabolism pathway can ameliorate the immune exhaustion of T cells, etc., eventually leading to better therapeutic effect of immunotherapy [21, 22].

Other metabolic combinations that are related to 'synthetic lethality' have great translational potential. For example, if cancer cells heavily rely on a certain exogenous amino acid, blocking the pathways of their amino acid synthesis pathway will result in cell death specifically in cancer cells. Such two-hit strategy exploits differential amino acid utilizations in malignant and normal cells, providing a therapeutic window where selective accumulation can be maximized, and healthy cells are spared.

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4.3. Existing challenges and future directions

Despite the tempting landscape of amino acid-targeted therapies, their clinical application remains burdened by several formidable challenges. The first is tumour metabolism which is highly plastic and redundant. If one specific metabolic pathway is pharmacologically blocked by an agent, malignant cells can, for instance, toggle on alternative pathways or upregulate take-up of other nutrients, blunting the effect of therapy. This means that future efforts need to take a multi-target approach to combinatory therapies or find drugs that hit specific junctures within the wider metabolic network. Another limitation is the lack of reliable biomarkers, hampering the precision application of metabolic therapies. At present, it is difficult to properly predict which patient subpopulations are most likely to benefit from a particular amino acid-targeted therapy. Advances in metabolomics, single-cell sequencing and molecular imaging will empower effective patient stratification and raise the efficacy and individualization of therapies.

Furthermore, the unique desmoplastic TME of PC is also a major challenge. PC is notorious for being enormously stroma rich. The stromal cells and immune cells in it have a complicated metabolic symbiotic balance with tumor cells through metabolite swapping. The metabolic balance not only feeds the tumor growth but also promotes tumor immunosuppression and resistance to anticancer treatments. Therefore, designing therapeutic regimens that can simultaneously disrupt the tumour cells and their metabolic crosstalk with the tumour microenvironment will be a major issue for future development [23].

5. Conclusion

As one of the pillars of overall tumor metabolic rewiring, amino acid metabolic reprogramming plays an essential role in the tumorigenesis and progression of PC. By heavily altering the pathways of glutamine, serine, branched-chain amino acid, tumor cells obtain the biosynthetic precursors and energy needed to support the incessant growth. By the same time, amino acid metabolism affects the tumor cell in a far-reaching manner through affecting redox state, enhancing antioxidant defense and promoting epigenetic and signal transduction regulation—leading to driving the PC malignant phenotype from a variety of different perspectives. Beneficially, targeting this dependence gives rise to new interventional therapies. Inhibitors for these metabolic enzymes, amino acid deprivation strategies and combine them together all exhibit promising potentials in preclinical studies and early clinical trials. However, the intrinsic plasticity and redundancy of tumor metabolism limit the potency of single-targeted interventions. And in many cases, compensation and TME factors elicit drug resistance.

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