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REVIEW

Bioenergetic alteration in gastrointestinal cancers: The good, the bad and the ugly

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Abstract

Cancer cells exhibit metabolic reprogramming and bioenergetic alteration, utilizing glucose fermentation for energy production, known as the Warburg effect. However, there are a lack of comprehensive reviews summarizing the metabolic reprogramming, bioenergetic alteration, and their oncogenetic links in gastrointestinal (GI) cancers. Furthermore, the efficacy and treatment potential of emerging anticancer drugs targeting these alterations in GI cancers require further evaluation. This review highlights the interplay between aerobic glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (OXPHOS) in cancer cells, as well as hypotheses on the molecular mechanisms that trigger this alteration. The role of hypoxia-inducible transcription factors, tumor suppressors, and the oncogenetic link between hypoxia-related enzymes, bioenergetic changes, and GI cancer are also discussed. This review emphasizes the potential of targeting bioenergetic regulators for anti-cancer therapy, particularly for GI cancers. Emphasizing the potential of targeting bioenergetic regulators for GI cancer therapy, the review categorizes these regulators into aerobic glycolysis/ lactate biosynthesis/transportation and TCA cycle/coupled OXPHOS. We also detail various anti-cancer drugs and strategies that have produced pre-clinical and/or clinical evidence in treating GI cancers, as well as the challenges posed by these drugs. Here we highlight that understanding dysregulated cancer cell bioenergetics is critical for effective treatments, although the diverse metabolic patterns

present challenges for targeted therapies. Further research is needed to comprehend the specific mechanisms of inhibiting bioenergetic enzymes, address side effects, and leverage high-throughput multi-omics and spatial omics to gain insights into cancer cell heterogeneity for targeted bioenergetic therapies.

Key Words: Energy metabolism; Mitochondria; Hypoxia; Oxidative phosphorylation; Glycolysis; Gastrointestinal neoplasms

Core Tip: This review discusses the bioenergetic alteration and metabolic reprogramming in gastrointestinal (GI) cancers, including the interplay between aerobic glycolysis, tricarboxylic acid cycle, and oxidative phosphorylation. The review also highlights potential strategies for targeting bioenergetic regulators for anti-cancer therapy in GI cancers, summarizing the efficacy and challenges of several drugs.

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INTRODUCTION

Cells require energy to carry out their functions, and the most common form of cellular energy is adenosine triphosphate (ATP). This energy is typically produced by oxidative phosphorylation (OXPHOS) in the mitochondria of normal cells[1]. However, in cancer cells, there is a shift in the way energy is generated. Instead of using OXPHOS, cancer cells use glycolysis, a process that results in increased uptake of glucose and secretion of lactate[2]. This phenomenon is known as the Warburg effect and is observed in many types of cancer[3,4]. By understanding the altered energy metabolism in cancer cells, researchers can gain new insights into cancer cell biology and identify potential targets for cancer therapy.

Glycolysis is the process by which glucose is broken down to produce ATP, and it does not require oxygen (Figure 1). Glucose enters cells through glucose transporters and is converted to glucose-6-phosphate (G6P) by hexokinase (HK). Glucose-6-phosphate isomerase (G6PI) converts G6P to fructose-6-phosphate (F6P), which is used in both the glycolytic pathway to generate pyruvate or lactate and the pentose phosphate pathway (PPP) to produce nucleotides and nicotinamide adenine dinucleotide phosphate (NADPH). Phosphofructokinase-1 (PFK1) converts F6P and fructose-2,6-bisphosphate (F2,6BP), a metabolite from a branch driven by fructose-2,6-biphosphatase 3 (PFKBP3), to fructose-1,6-bisphosphate (F1,6BP), which is further processed by aldolase to generate glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). G3P is converted by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) to 1,3-bisphosphoglycerate (1,3BPG), which is further converted to 3-phosphoglycerate (3PG) by phosphoglycerate kinase (PGK1). The 3PG is subsequently converted by phosphoglycerate mutase (PGAM) to 2-phosphoglycerate (2PG). The 2PG then serves as a substrate for enolase (ENO) to convert to phosphoenolpyruvate (PEP). Pyruvate kinase isozyme M1/M2 (PKM1/2) catalyzes the conversion of PEP to pyruvate, which can be converted to acetyl-CoA or lactate. This process generates NAD+ from NADH, which is important for the continuation of the glycolysis process. Although glycolysis itself does not require oxygen, the fate of the pyruvate produced by glycolysis depends on the availability of oxygen, and the overall efficiency of ATP production is much higher when oxygen is present[5].

Pyruvate, a product of glycolysis, enters the mitochondria where it is converted to acetyl-CoA. The resulting acetyl-CoA can then enter the tricarboxylic acid (TCA) cycle, also known as the Krebs cycle, which plays a pivotal role in generating ATP through the electron transport chain (ETC). The TCA cycle completes the breakdown of glucose by breaking down acetyl-CoA into carbon dioxide (CO_2) and water, releasing energy in the form of NADH and flavin adenine dinucleotide (FADH2). NADH and FADH2 donate their electrons to the ETC at Complex I and II, respectively. The ETC, specifically Complexes I-IV, transfers electrons from NADH and FADH2 to generate a proton gradient across the inner mitochondrial membrane. This gradient is then used by ATP synthase to produce ATP. Complex I, also known as NADH dehydrogenase or NADH ubiquinone oxidoreductase, is the largest of the five mitochondrial complexes and marks the initiation of the ETC[6]. Electrons are transferred from Complex I to coenzyme Q (CoQ) across the inner mitochondrial membrane and then from CoQ to Complex III, although an alternative pathway exists *via* Complex II, succinate dehydrogenase (SDH)[7,8]. Following reduction of succinate by Complex II, electrons are transported to CoQ and then transferred to Complex III. Complex III and cytochrome c transfer electrons to Complex IV, cytochrome c oxidase (COX). The ETC complexes act as proton pumps, creating an electrochemical gradient across the inner mitochondrial membrane, and this energy is harnessed by Complex V, ATP synthase, which generates ATP by using the energy from the movement of protons down their electrochemical gradient. This whole process is known as OXPHOS and is a time-consuming process compared to glycolysis, but is the most efficient way to generate ATP in the cell, producing up to 36-38 ATP molecules per glucose molecule. Complexes I-IV are known as the ETC, while Complex V (ATP synthase) does not (Figure 1). Except for Complex II, all OXPHOS-related complexes are partially encoded by mitochondrial DNA (mtDNA)[9]. Unfortunately, OXPHOS also produces reactive oxygen species (ROS) as a byproduct,

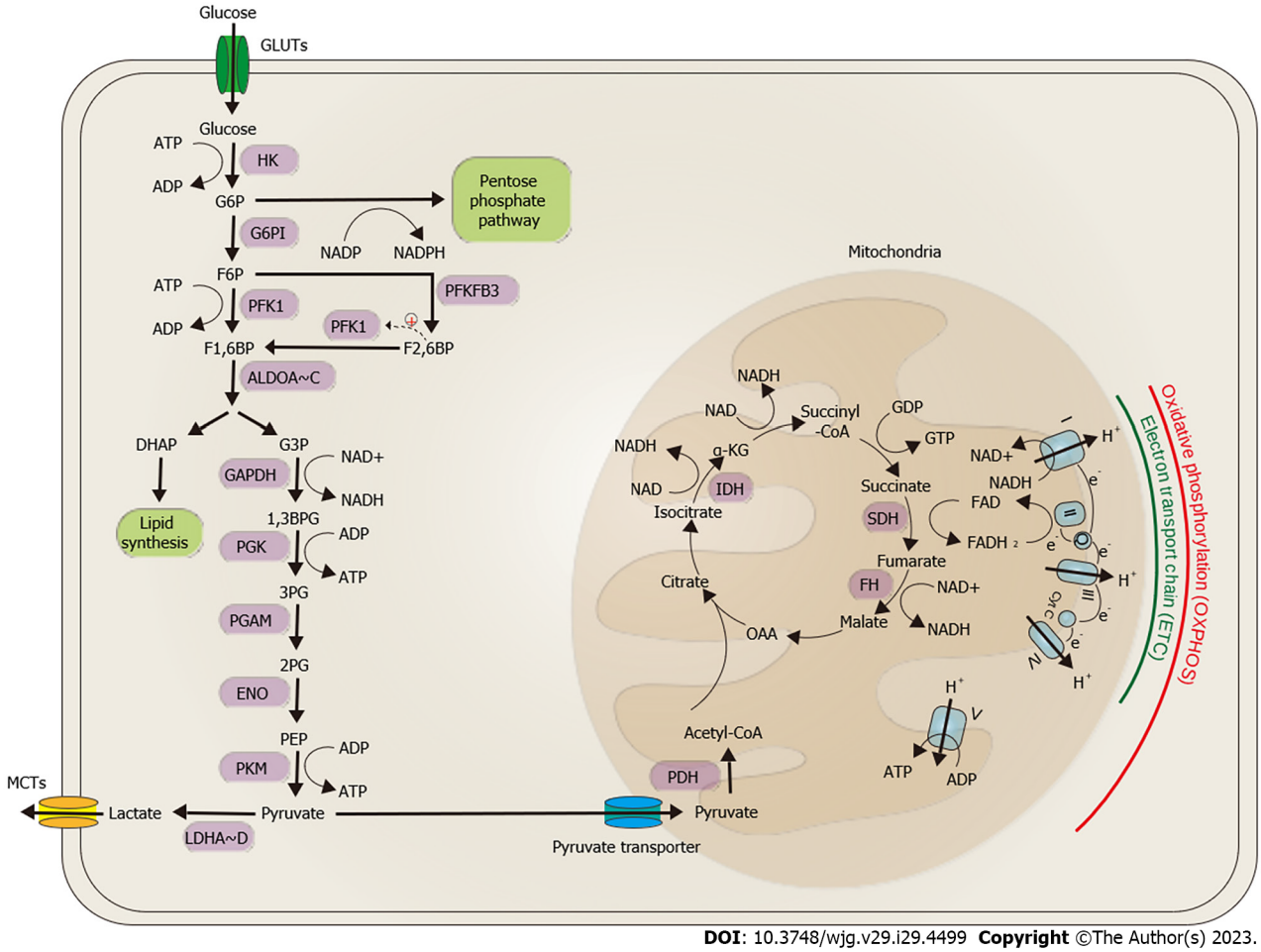

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Figure 1 Illustration of the pathway of glucose metabolism. Glucose is taken up by cells and undergoes a series of reactions to convert it to pyruvate *via* the process of glycolysis. Pyruvate can then enter the tricarboxylic acid cycle in the mitochondria to produce energy, or it can be converted to lactate in the cytosol under anaerobic conditions. The key enzymes involved in these reactions are highlighted in pale-purple, and linked pathways are depicted in pale-green. The mitochondrial complexes that are critical for oxidative phosphorylation and adenosine triphosphate production are shown in pale-blue. GLUT: Glucose transporter; HK: Hexokinase; G6P: Glucose-6-phosphate; G6PI: Glucose-6-phosphate isomerase; F6P: Fructose-6-phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; PFK1: Phosphofructokinase-1; F2,6BP: Fructose-2,6-bisphosphate; PFKBP3: Fructose-2,6-biphosphatase 3; F1,6BP: Fructose-1,6-bisphosphate; G3P: Glyceraldehyde-3-phosphate; DHAP: Dihydroxyacetone phosphate; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; 1,3BPG: 1,3-bisphosphoglycerate; 3PG: 3-phosphoglycerate; PGK: Phosphoglycerate kinase; PGAM: Phosphoglycerate mutase; 2PG: 2-phosphoglycerate; ENO: Enolase; PEP: Phosphoenolpyruvate; PKM1/2: Pyruvate kinase isozyme M1/M2; LDH: Lactate dehydrogenase; MCT: Monocarboxylate transporter family; PDH: Pyruvate dehydrogenase; IDH: Isocitrate dehydrogenase; α-KG: α-ketoglutarate; OAA: Oxaloacetate; SDH: Succinate dehydrogenase; FH: Fumarate hydratase; I: Mitochondrial complex I; II: Mitochondrial complex II; III: Mitochondrial complex III; IV: Mitochondrial complex IV; V: Mitochondrial complex V; Q: Co-enzyme Q; cyto C: Cytochrome *c*; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; FADH2: Flavin adenine dinucleotide; e⁻: Electrons.

which can cause damage to mitochondrial or nuclear DNA and activate oncogenic signaling pathways, potentially leading to diseases and carcinogenesis[10-12]. Mutations in mtDNA are also implicated in cancer[13]. Overall, the process of OXPHOS is vital for cellular energy production, but careful regulation is necessary to prevent the damaging effects of ROS production.

In cancer cells, certain enzymes and molecules involved in the conversion of glucose to energy are upregulated, which provides an attractive target for anti-cancer therapies[14]. Disrupting this process could prevent cancer cells from producing energy and lead to their death. In addition to the upregulation of these enzymes, alterations in certain mitochondrial enzymes and oncometabolites have been identified in cancer cells. Oncometabolites are small molecules that are produced in cancer cells and contribute to their growth and proliferation[15]. These alterations can be caused by genetic and epigenetic changes in the genes involved in energy production[13,16]. Recent research has focused on understanding these bioenergetic alterations in gastrointestinal (GI) cancers, such as esophageal cancer (ESCA), gastric cancer (GC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), pancreatic cancer (PAC), and colorectal cancer (CRC). Understanding these specific metabolic changes in cancer cells can provide insight into developing more effective targeted therapies for GI cancers. In addition to the potential for targeted therapy, these metabolic changes could also serve as biomarkers for cancer diagnosis and prognosis. By identifying alterations in the genes and molecules involved in energy production, clinicians may be able to more accurately diagnose and predict the course of the disease. Overall, understanding the bioenergetic alterations in cancer cells is a promising avenue for developing new therapies and improving cancer diagnosis and treatment. In this review, we summarize the latest findings on bioenergetic alterations in

various GI cancers, and discuss the potential therapeutic strategies that target these alterations. Such strategies may include inhibitors of specific enzymes or molecules involved in energy production, as well as interventions aimed at modulating the metabolic environment of cancer cells. Further research in this area could lead to new and more effective treatments for GI cancers.

BIOENERGETIC ALTERATION AND THE WARBURG EFFECT

The process of bioenergetic alteration in cancer involves changes in the way cancer cells generate energy. One well-known component of bioenergetic alteration is the Warburg effect. This phenomenon describes how cancer cells prefer to use glucose fermentation to produce energy even in the presence of oxygen[2]. This process, called aerobic glycolysis, is less efficient than mitochondrial OXPHOS in terms of ATP production[17,18]. However, it has been noted that respiration alone can maintain tumor viability, suggesting that glucose and oxygen must be eliminated to kill cancer cells by depriving them of energy[2]. The underlying mechanisms of the Warburg effect have been investigated for decades. Otto Warburg originally proposed that mitochondrial dysfunction could be responsible for aerobic glycolysis[19]. This theory was later confirmed and explored by another group that demonstrated the Warburg effect could be caused by an imbalance of intracellular pH and mitochondrial ATPase dysfunction[20]. Moreover, it was observed that aerobic glycolysis could be controlled by cascade signaling mediated by growth factors and oncogenes, questioning whether the Warburg effect was a mere bystander in the pathogenesis of cancer[21-24]. It was not until later that the Warburg effect was discovered to be crucial for tumor growth in genetic and pharmacological studies[25,26].

Scientists have been trying to understand why cancer cells prefer aerobic glycolysis to mitochondrial OXPHOS for decades, given that the ATP generated by aerobic glycolysis is much lower than that produced by mitochondrial OXPHOS[27-29]. Recent studies have shed light on this phenomenon. For example, when changes in the cellular environment increase ATP demand through alteration of ATP-dependent membrane activity, aerobic glycolysis increases rapidly and OXPHOS remains unchanged[30]. Another study showed high aerobic glycolysis as a metabolic strategy which cancer cells use to optimally respond to fluctuating energy availability[31]. Together, this literature suggests that the Warburg effect is a metabolic strategy that allows flexibility among cancer cells under an unpredictable tumor microenvironment.

THE DYNAMIC INTERPLAY BETWEEN OXPHOS AND AEROBIC GLYCOLYSIS

Not all pyruvate produced during glycolysis is converted to lactate. Indeed, a significant amount of pyruvate can enter the TCA cycle for oxidation and further metabolism. The intermediates generated during the TCA cycle, such as NAD+/NADH and NADP+/NADPH, can continue to enter the OXPHOS pathway, which can further generate bioenergy[32,33]. Although the role of the Warburg effect in cancers remains controversial, interfering with tumor metabolism and targeting both aerobic glycolysis and mitochondrial OXPHOS pathways have been shown to be necessary[34-37]. It is evident from current literature that there exists crosstalk between aerobic glycolysis, the TCA cycle, and coupled OXPHOS, suggesting cooperative and competitive roles in cancer. Interestingly, some studies suggest that targeting mitochondrial metabolism alone may not be sufficient to inhibit tumor growth, as cancer cells can redirect their metabolism to rely on other energy sources. In such cases, blocking both the glycolytic and mitochondrial pathways may be necessary to prevent cancer cell growth[34-37]. Therefore, a better understanding of the metabolic pathways in cancer cells and their interactions is required to develop effective cancer therapies.

Although the exact molecular mechanism that triggers the Warburg effect in cancer remains unclear, multiple hypotheses have been proposed, including the involvement of tumor suppressors (*e.g.*, p53) and oncogenes (*e.g.*, PI3K, AKT, mTOR), all of which appear to converge on the role of hypoxia-inducible transcription factors (HIFs), particularly HIF-1. HIF-1 is a transcription factor that regulates cellular responses to oxygen deprivation, and it was initially identified as a protein that is present only under hypoxic conditions[38-41]. However, it was later discovered that HIF-1 can also be stabilized under normoxia in a microenvironment with high lactate concentration[42,43]. Under normal conditions, HIF-1 α, a subunit of HIF-1, is targeted for degradation by prolyl hydroxylases (PHDs), which utilize molecular oxygen to hydroxylate HIF-1α, leading to its recognition by the von Hippel-Lindau tumor suppressor (VHL), and degradation *via* proteasome-mediated pathways[44-47].

HIF-1 regulates the expression of several key glycolytic enzymes, such as glucose transporter-1 (GLUT1), GLUT3, HK, aldolase A (ALDOA), PGK1, PKM1/2, ENO1, pyruvate dehydrogenase kinase (PDKs), and lactate dehydrogenase subunit A (LDHA), by directly promoting their expression[48-54]. This leads to an increased level of pyruvate, the final product of glycolysis. However, it is important to note that cancer cells with high glycolytic activity are not guaranteed to catabolize all pyruvate to lactate, as significant amounts of pyruvate can enter the TCA cycle for oxidation and metabolism. In cancer cells, it is suggested that the HIF-1 induced increased expression of PDKs can inhibit the function of pyruvate dehydrogenase (PDH), which blocks pyruvate entry into the TCA cycle and promotes lactate production. Since HIF-1 also promotes the expression of LDHA, an important subunit of LDH necessary for lactate biosynthesis from pyruvate, it is thought to be crucial in cancers affecting terminal lactate levels[55] (Figure 2). Therefore, HIF-1 plays a significant role in the Warburg effect, which may have implications for cancer diagnosis and treatment. While the precise molecular mechanism behind the Warburg effect remains to be elucidated, the involvement of HIF-1 is clear. Understanding the interplay between HIF-1, glycolysis, and OXPHOS in cancer cells may lead to the development of novel cancer therapies that target both pathways.

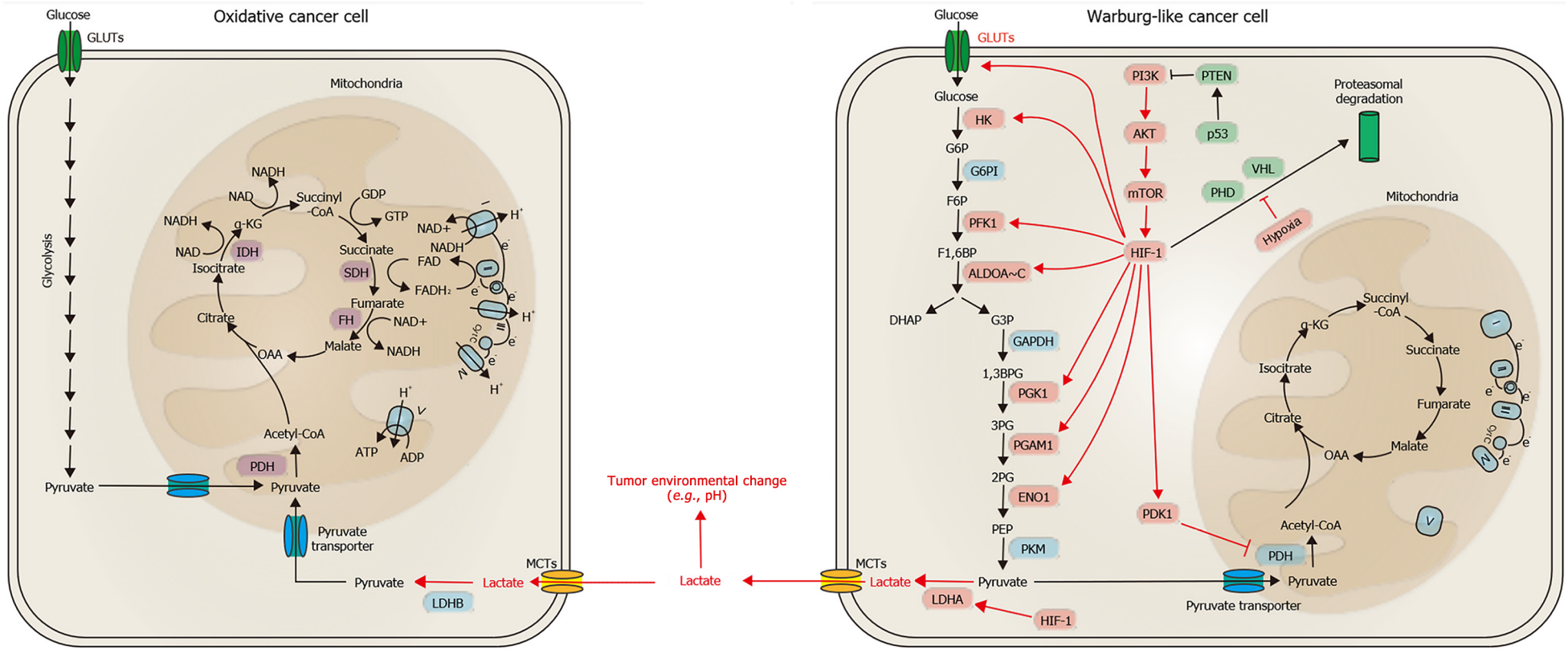

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Figure 2 The complex interplay between glycolysis and oxidative phosphorylation in cancer cells. This figure highlights the signaling networks and metabolic regulation in both Warburg-like and oxidative cancer cells. p53 induces PTEN and represses PI3K activity, which inhibits glycolysis and opposes the Warburg effect. Hypoxia and the subsequent activation of hypoxia-inducible factor 1 (HIF-1) play a crucial role in modulating various aspects of cancer cell metabolism, including glycolysis, lactate production, and the tricarboxylic acid (TCA) cycle. Hypoxia counteracts the degradation of HIF-1 by prolyl hydroxylases and von Hippel-Lindau, which stabilizes and activates HIF-1. HIF-1 then transcriptionally activates genes such as hexokinase, phosphofructokinase-1, aldolase A, PGK1, PGAM1, ENO1, and LDHA, as indicated by the red arrows. During glycolysis, excessive lactate can be exported to the extracellular environment, leading to microenvironmental changes such as a lower pH. Intracellular lactate can also be transferred to adjacent cells and re-converted to pyruvate, which can enter the TCA cycle and drive oxidative phosphorylation in oxidative cancer cells. GLUT: Glucose transporter; HK: Hexokinase; G6P: Glucose-6-phosphate; G6PI: Glucose-6-phosphate isomerase; F6P: Fructose-6-phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; PFK1: Phosphofructokinase-1; F2,6BP: Fructose-2,6-bisphosphate; PFKBP3: Fructose-2,6-biphosphatase 3; F1,6BP: Fructose-1,6-bisphosphate; G3P: Glyceraldehyde-3-phosphate; DHAP: Dihydroxyacetone phosphate; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; 1,3BPG: 1,3-bisphosphoglycerate; 3PG: 3-phosphoglycerate; PGK: Phosphoglycerate kinase; PGAM: Phosphoglycerate mutase; 2PG: 2-phosphoglycerate; ENO: Enolase; PEP: Phosphoenolpyruvate; PKM1/2: Pyruvate kinase isozyme M1/M2; LDH: Lactate dehydrogenase; MCT: Monocarboxylate transporter family; PDH: Pyruvate dehydrogenase; IDH: Isocitrate dehydrogenase; α-KG: α-ketoglutarate; OAA: Oxaloacetate; SDH: Succinate dehydrogenase; FH: Fumarate hydratase; I: Mitochondrial complex I; II: Mitochondrial complex II; III: Mitochondrial complex III; IV: Mitochondrial complex IV; V: Mitochondrial complex V; Q: Co-enzyme Q; cyto C: Cytochrome *c*; HIF-1: Hypoxia-inducible factor 1; PHD: Prolyl hydroxylases; VHL: Von Hippel-Lindau.

The concept of lactate as a metabolic waste product has been revised with the latest findings in lactate metabolism and transport. It is now known that lactate can serve as an alternative fuel for certain types of cells, including cancer cells[56,57]. In cancer, the excess lactate is transported between the intracellular and extracellular matrix by the monocarboxylate transporter family (MCT1-4), which depends on the gradients of the protons and monocarboxylate ions[58,59]. Imported extracellular lactate can be converted to pyruvate *via* LDH primarily composed by the LDHB subunit[60,61]. In oxidative cancer cells with a functional TCA cycle and OXPHOS, pyruvate can be further converted to acetyl-CoA through PDH, thus linking aerobic glycolysis and OXPHOS[62,63]. It has been demonstrated that HIF-1 and downstream oncometabolite lactate play causal roles in these regulatory events. Therefore, current findings provide a possible explanation for the Warburg effect and crosstalk of bioenergetic homeostatic transition between aerobic glycolysis and OXPHOS observed in cancer. The importance of lactate in cancer metabolism and its potential as a therapeutic target have been recognized by others in the field. Thus, a better understanding of the metabolic pathways and their interactions could lead to the development of new strategies for cancer treatment.

THE LINK BETWEEN HYPOXIA-RELATED ENZYMES, BIOENERGETIC CHANGES, AND GI CANCER: A GENETIC AND EPIGENETIC PERSPECTIVE

Cancer cells often undergo a metabolic shift characterized by increased glycolysis and decreased mitochondrial respiration, a phenomenon known as the Warburg effect. This metabolic reprogramming has been linked to the activity of HIF-1 under low-oxygen conditions[64,65]. Genetic and epigenetic alterations in HIF-1 regulatory genes contribute to the development of the Warburg effect in cancer. Methylation-induced epigenetic changes can drive transcriptional changes, leading to impaired expression of key enzymes involved in bioenergetic homeostasis. Additionally, mutations in nuclear and mitochondrial genomes may cause a loss of function or decreased expression of glycolytic/OXPHOS enzymes. Therefore, mutations, transcriptional changes, or epigenetic alterations that enhance HIF-1 stability or activity can lead to increased aerobic glycolysis, resembling the Warburg effect (Table 1).

Studies have found that alterations in PHD enzymes, which target HIF-1 for degradation, contribute to cancer development and progression. Reduced expression or loss-of-function due to PHD2 mutations lead to constitutive activation of HIF-1 and have been found to stimulate HCC and CC development and progression in mouse models[66,67]. In contrast, decreased PHD1-3 expression correlates with increased HIF-1 and vascular endothelial growth factor (VEGF) levels, invasive tumor behavior, and poor prognosis in certain GI cancers such as HCC[68], GC[69-71], and CRC[72]. Interestingly, the opposite effect has been observed in patients with PAC[73]. Another protein involved in HIF-1 stabilization, VHL, also plays a role in GI cancers. Mutations or promoter methylation within the *VHL* gene lead to increased cytoplasmic HIF-1 levels and an unfavorable prognosis in patients with PAC and CRC[74,75]. However, the general status of VHL protein expression in GI cancers remains unclear, with the exception of HCC, whose levels have been shown to decrease, and low levels correlate with poor prognosis[76]. Further investigation is needed to determine the impact of mutations, genetic, or epigenetic alterations in these hypoxia-associated enzymes on bioenergetic alterations in GI cancers, since understanding the mechanisms behind the Warburg effect and the role of HIF-1 regulatory genes could potentially provide new therapeutic targets for treating GI cancers.

THE LINK BETWEEN MITOCHONDRIAL AND NUCLEAR GENE EXPRESSION, BIOENERGETIC HOMEOSTASIS, AND THE PROGRESSION OF GI CANCERS

Cancer development and progression are often accompanied by changes in cellular metabolism that contribute to tumor growth and survival. In addition to genetic and epigenetic alterations in hypoxia-associated regulatory enzymes that promote aerobic glycolysis, emerging evidence suggests that changes in nuclear-encoded genes for enzymes and subunits involved in OXPHOS and the TCA cycle may also play a role in driving the switch to glycolysis and altering bioenergetic homeostasis in cancer. Studies have shown that changes in the expression of key enzymes involved in OXPHOS, such as cytochrome *c* oxidase (COX) and ATP synthase, as well as the TCA cycle enzymes isocitrate dehydrogenase (IDH), fumarate hydratase (FH), and succinate dehydrogenase (SDH), may contribute to glycolysis transition and cancer progression[77-80]. Furthermore, mutations and copy number alterations in mtDNA have also been identified as important factors in the development and progression of GI cancer by altering bioenergetic homeostasis[81]. These emerging factors and their potential contribution to the complex mechanisms underlying the progression of GI cancer are discussed in more detail in the following sections.

ROLE OF MITOCHONDRIAL-NUCLEAR ENCODED COX SUBUNITS IN BIOENERGETIC CHANGES AND PROGRESSION OF GI CANCERS

The COX complex, also known as respiratory chain complex IV, is a multi-subunit enzyme complex, consisting of 14 subunits, and a vital component of the final step in the mitochondrial ETC responsible for catalyzing the transfer of electrons from cytochrome c to oxygen, a crucial step in the process of OXPHOS[82]. Recent studies have shown that alterations in the expression of both mtDNA-encoded and nuclear-encoded COX subunits are associated with tumori-

Table 1 Genetic and epigenetic alterations in hypoxia-related enzymes correlated with the development and progression of gastrointestinal cancers

Cancer type	Gene	Type of change	Consequence	Model	Ref.
HCC and CCA	PHD2	Haplo-deficiency	Stabilized HIF-1 and promoted carcinogenesis and progression of HCC/CCA	Mice	[66, 67]
HCC	PHD3	Reduced tumor level	Correlated with elevated levels of HIF-1, aggressive tumor behavior, and a poor prognosis in HCC patients	HCC patient	[68]
GC	PHD3	Reduced tumor level	Correlated negatively with tumor size and stage, as well as HIF-1 and VEGF expression	GC patient	[69, 70]
GC	PHD2	Reduced tumor level	Correlated with shortened overall survival	GC patient	[71]
CRC	PHD1-3	Reduced tumor level	Although not correlated with HIF-1 expression, PHD2 was the only factor found to be associated with unfavorable overall survival	CRC patient	[72]
PAC	PHD1-3	Increased tumor level	PHD1-3 expression was elevated, and specifically PHD3 expression was found to be associated with unfavorable overall disease-specific survival	PAC patient	[73]
PAC	VHL	Promoter methylation or deletion of VHL	Correlated with decreased VHL expression and poor prognosis	PAC patient	[74]
CRC	VHL	*VHL* mutation	Elevated cytoplasmic expression of HIF-1 in tumors	CRC patient	[75]
HCC	VHL	Reduced tumor level	Negative VHL expression was correlated with an unfavorable prognosis	HCC patient	[76]

ESCA: Esophageal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; PAC: Pancreatic cancer; CRC: Colorectal cancer; PHD: Prolyl hydroxylase; VHL: Von Hippel-Lindau tumor suppressor.

genesis, cancer progression, and bioenergetic homeostasis in cancer. In GI cancers, alterations in the expression of the mitochondrial-nuclear encoded subunits of the COX complex have been implicated in driving disease progression. Studies have shown that the overall levels of the COX complex are increased in GI cancers, and higher levels have been associated with poor clinical outcomes[83,84]. Of the three mtDNA-encoded core subunits essential for the basic functions of the COX complex, including MTCO1, MTCO2, and MTCO3[85], MTCO1 is the most frequently investigated in GI cancers (Table 2). In ESCA, MTCO1 expression was found to be elevated but did not correlate with clinicopathological variables or survival[86]. On the other hand, elevated levels of MTCO1 were associated with diffuse GC types, suggesting a link between MTCO1 expression and GC carcinogenesis, de-differentiation, and distant metastasis[87,88]. In contrast, defective MTCO1 expression was observed in patients with HCC and CCA, while MTCO1 levels have been shown to predict postoperative survival in patients with HCC[89,90]. Elevated MTCO3 levels have been observed only in HCC, especially among patients with hepatitis B virus (HBV)-related HCC. This is likely due to the ability of the HBV X protein (HBx) to interact and increase MTCO3 expression[91,92]. Additionally, genetic variants identified within MTCO1 and MTCO3 are associated with increased carcinogenic risk in CRC[93,94], GC[95], and HCC[96], possibly due to reduced COX activity leading to intrinsic proton leak and a reduction in overall bioenergetic production efficiency[93,94]. However, studies on the expression or genetic variation of MTCO2 in GI cancers are relatively few and need further investigation.

While the three core mtDNA-encoded COX subunits have been extensively studied, 11 nuclear-encoded protein subunits are also required for the full functionality of the COX complex[97]. Of these 11 subunits, six can be replaced by isoforms, leading to heterogeneity in the composition and activity of this large complex[98]. In GI cancers, altered expression of nuclear-encoded COX subunits has been shown to play a crucial role in the switch to glycolysis and the promotion of tumor growth and progression (Table 2). For example, in ESCA, the silencing of COX4I1 and COX5B has been shown to promote bioenergetic changes and increased aggressiveness of ESCA cells *in vitro*[99]. In HCC and CRC, COX5B levels were found to correlate with prognosis, and changes in COX5B expression were associated with alterations in bioenergetics, cell proliferation, tumor growth, migration, and chemosensitivity. HCC and CRC, however, showed different COX5B expression patterns[100-102]. Similarly in CRC, increased COX4I2 has been shown to promote cell proliferation, migration, tumorigenesis, and angiogenesis[103]. COX6C and COX6B2 were also found to be increased in PAC, with changes in expression levels of COX6C affecting COX activity and cell growth *in vitro*. Meanwhile, COX6B2 levels were associated with prognosis, metastatic potential in PAC cells, and altered bioenergetic homeostasis[104,105].

The roles of remaining subunits in GI cancer are currently unknown, and studies focusing on the level of nuclear-encoded COX subunit in GI cancer largely suggest that altered expression leads to decreased OXPHOS activity in a Warburg effect-like phenotype. Increased GI cancer growth and/or progression is also suggested. Together, these findings highlight the crucial role COX subunits play in GI cancer progression and underscore the need for continued research. The identification of altered COX subunit expression and function may lead to the development of novel therapeutic targets for the treatment of GI cancers. Therefore, further research on the COX complex and its subunits is

Table 2 Defects in cytochrome c oxidase subunits correlated with bioenergetic alterations and the growth or progression of gastrointestinal cancers

Type	Gene	Type of defect	Consequence	Model	Ref.
GC	Full COX complex	Increased expression	Correlated with poor prognosis	GC patient	[83]
CRC	Full COX complex	Increased expression	May be involved in the initiation of carcinogenesis, but not in cancer progression	CRC patient	[84]
ESCA	MTCO1	Increased expression	There is no correlation with clinical variables or survival	ESCA patient	[86]
GC	MTCO1	Increased expression	Correlated with gastric tumorigenesis, dedifferentiation, and distant metastasis, but showed no significant correlation with prognosis	GC patient	[87,88]
HCC	MTCO1	Reduced expression	Correlated with postoperative prognosis	HCC patient	[89]
CCA	MTCO1	Reduced expression	Reduced MTCO1 correlates with increased VDAC1 expression but not with other clinicopathological factors	CCA patient	[90]
HCC	MTCO3	Increased expression	HBx interacted with MTCO3, leading to an increase in MTCO3 expression levels and an enhancement in OXPHOS activity	Cell line	[91,92]
CRC	MTCO1	Genetic variation	The Gly125Asp substitution in MTCO1 correlated with an increased risk of CRC and caused proton leak in COX	CRC patient	[93,94]
GC	MTCO3	Genetic variation	Polymorphisms at mtDNA positions 9540 and 9548 correlated with an increased risk of GC	GC patient	[95]
HCC	MTCO3	Genetic variation	Polymorphisms at mtDNA position 9545 correlated with an increased risk of HCC	HCC patient	[96]
ESCA	COX4I1	Expression silenced	Promotes alterations in cellular bioenergetics and increases cancer cell aggressiveness	ESCA Cell line	[99]
ESCA	COX5B	Expression silenced	Promotes alterations in cellular bioenergetics and increases cancer cell aggressiveness	ESCA Cell line	[99]
HCC	COX5B	Increased in tumor	Correlated with prognosis, regulated bioenergetic alterations, and influenced cell proliferation, tumor growth, and migration	HCC patient, cell line, mouse model	[100]
CRC	COX5B	Reduced in tumor	Correlated with prognosis, modulated COX activity, and controlled cell proliferation, apoptosis, and response to chemotherapy	CRC patient and cell line	[101,102]
CRC	COX4I2	Increased in tumor	Promoted cell proliferation, migration, tumorigenesis, and angiogenesis	CRC patient and cell line	[103]
PAC	COX6C	Increased expression	Modulated COX activity and cell proliferation	PAC cell line	[104]
PAC	COX6B2	Increased in tumor	Correlated with prognosis, and modulated cancer cell metastatic potential, and altered bioenergetic homeostasis	PCA patient and cell line	[105]

COX: Cytochrome *c* oxidase; GI: Gastrointestinal; ESCA: Esophageal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; PAC: Pancreatic cancer; CRC: Colorectal cancer; MTCO1: Mitochondrially encoded cytochrome *c* oxidase I; MTCO2: Mitochondrially encoded cytochrome *c* oxidase II; MTCO3: Mitochondrially encoded cytochrome *c* oxidase III; COX4I1: Cytochrome *c* oxidase subunit 4I1; COX4I2: Cytochrome *c* oxidase subunit 4I2; COX5B: Cytochrome *c* oxidase subunit 5B; COX6C: Cytochrome *c* oxidase subunit 6C; COX6B2: Cytochrome *c* oxidase subunit 6B2.

needed to fully elucidate their role in GI cancer.

THE ROLE OF ATP SYNTHASE SUBUNITS IN DRIVING BIOENERGETIC CHANGES AND GI CANCER PROGRESSION

ATP synthase, also known as Complex V, is a crucial mitochondrial protein complex that plays a vital role in cellular ATP synthesis. The F1 beta-catalytic subunit (ATP5F1B) is a critical component that has been extensively studied to find a significant reduction in various cancer types, including GI cancers[106] (Table 3). However, the expression patterns of ATP5F1B in patients with GC remain controversial. While one study reported increased ATP5F1B expression in tumors,

Table 3 Implications of defects in adenosine triphosphate synthase subunits on bioenergetic alterations and the development or progression of gastrointestinal cancer

Type	Gene	Type of defect	Consequence	Model	Ref.
GC	ATP5F1B	Increased in tumor	Higher ATP5B expression correlated with poor prognosis. Over-expression of ATP5F1B increased intracellular and extracellular ATP levels, cell proliferation, migration, and invasion	GC patient, cell line, and xeno-transplantation mouse model	[107]
GC	ATP5F1B	Reduced in tumor	Reduced ATP5F1B expression correlated with elevated glycolytic enzyme levels	GC patient	[108]
HCC	ATP5F1B	Reduced in tumor	Reduced ATP5F1B expression correlated with impaired OXPHOS	HCC patient	[109, 110]
ESCA	ATP5F1B	Reduced in tumor	Reduced ATP5F1B expression correlated with elevated glycolytic enzyme levels	ESCA patient	[108]
CRC	ATP5F1B	Reduced in tumor	Reduced ATP5F1B expression correlated with poor prognosis in CRC patients	CRC patient	[109]
PAC	ATP5F1B	Reduced in tumor	Unknown	PAC patient and cell line	[111]
CRC	ATP5F1A	Increased in liver metastasized tumor	Silencing of ATP5F1A inhibited cell invasion and reduced cell proliferation in CRC cancer cells	CRC patient and cell line	[112]
CRC	ATP5F1E	Increased in tumor	Higher ATP5E levels correlated with poor prognosis. Silencing of ATP5F1E inhibited cancer cell migration and invasion *in vitro*, and distal metastasis *in vivo*	CRC patient, cell line, and tail vein injected mouse model	[113]
CRC	ATP5F1D	Increased in liver metastasized tumor	Higher ATP5F1D expression correlated with poor prognosis, and silencing of ATP5F1D inhibited cell invasion	CRC patient and cell line	[112]

ATP: Adenosine triphosphate; GI: Gastrointestinal; ESCA: Esophageal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; PAC: Pancreatic cancer; CRC: Colorectal cancer; ATP5F1A: ATP synthase F1 subunit alpha; ATP5F1B: ATP synthase F1 subunit beta; ATP5F1D: ATP synthase F1 subunit delta; ATP5F1E: ATP synthase F1 subunit epsilon.

correlating with poor prognosis[107], consistent findings from other GI cancer studies indicate that decreased ATP5F1B expression results in reduced ATP production efficiency from OXPHOS and a subsequent shift towards the glycolysis-dependent Warburg effect phenotype[108-111]. These findings highlight the critical role of ATP synthase in GI cancer progression, suggesting that mitochondrial defects in ATP synthesis may contribute to the bioenergetic alterations observed in these cancers.

Apart from the F1 beta-subunit, other subunits of the ATP synthase F1 region have been implicated as crucial to CRC carcinogenesis/progression. Interestingly, in contrast to the finding that ATP5F1B generally decreases in tumors, ATP5F1A, ATP5F1E, and ATP5F1D were found to be increased in patients with CRC. Moreover, higher levels correlated with poorer prognosis as well as increased risk of CRC liver metastasis[112,113]. Currently, there are no reports on the expression patterns or role of ATP synthase subunits in CCA. The mechanisms underlying opposing expression patterns in ATP synthase subunits are thus unknown pending further investigation.

To provide more insight into the development of novel therapeutic targets for the treatment of GI cancers, further research on ATP synthase expression and function is necessary. In this regard, potential avenues of research may focus on clarifying the controversial findings regarding ATP5F1B expression patterns in GC and elucidating the mechanisms underlying these opposing expression patterns seen in differing ATP synthase subunits in CRC. Such research may uncover novel therapeutic targets, leading to improved treatment outcomes.

LINKING IDH, FH, AND SDH TO BIOENERGETICS AND GI CANCER PROGRESSION

Fumarate and succinate are critical metabolites that are produced during the TCA cycle, which is an essential process for energy production in cells. While these metabolites are important for normal cellular function, they have been shown to act as oncometabolites in various types of cancer by inducing pseudohypoxia[114]. Specifically, aberrant fumarate and succinate accumulation resulting from mutations or abnormal expression in FH and SDH, respectively, can impede the production of α-ketoglutarate in the TCA cycle, which is a key substrate in tumor suppression pathways. Similarly, mutations in IDH enzymes, which are responsible for α-ketoglutarate synthesis, can directly reduce the levels of α-ketoglutarate. This reduction in α-ketoglutarate can limit the availability of substrate for the hydroxylation of HIF-1 by PHDs for subsequent degradation by the proteasome. Consequently, stabilized HIFs activate the transcription of genes involved in cancer-related processes such as angiogenesis, glucose metabolism, and cell proliferation, thereby promoting cancer development and progression[114].

In addition to their effects on HIFs, high levels of fumarate and succinate have been shown to cause abnormal methylation of DNA and histones, leading to dysregulation of gene expression and cell function. This is due to

attenuation of enzymes responsible for DNA and histone demethylation such as tet-eleven translocation methyl-cytosine dioxygenase (TET) and lysine demethylase (KDM, also known as the Jumonji C domain-containing histone demethylase, JHDM)). Dysregulation of gene expression, increased carcinogenicity, and cancer progression can result from decreased α -ketoglutarate under high fumarate and succinate levels[115,116] (Figure 3).

The FH and SDH enzymes responsible for the catabolism of fumarate and succinate have been implicated as tumor suppressors[117]. Genetic variants in FH or SDH complex subunits, including SDHA, SDHB, SDHC, and SDHD, have been associated with increased risk of certain cancers such as hereditary leiomyomatosis and renal cell cancer (HLRCC) [118,119] as well as paraganglioma and pheochromocytoma[120-123]. Although there is limited evidence involving genetic mutants of FH or SDH complex subunit genes in GI cancer, an unusual mutation of the FH gene was found to be associated with the development of gastric leiomyoma following cutaneous and uterine leiomyomatosis[124]. Except for loss-of-function mutations, some researchers have revealed FH and SDH complex subunit gene single nucleotide polymorphisms (SNP) in patients with HCC and CRC[125,126]. Interestingly, FH was found to be downregulated in HCC patients with portal vein thrombosis due to currently unknown underlying mechanisms[127]. However, the role of FH and SDH in GI cancer remains largely unknown. Further investigation is thus necessary.

Understanding the role of oncometabolites in GI cancer could provide valuable insights into the development of novel therapeutic targets for the treatment of these cancers. Further research should be conducted to investigate the potential roles of FH and SDH in the development and progression of GI cancer and explore the possible therapeutic targets associated with the regulation of these enzymes. By gaining a better understanding of oncometabolites in GI cancer, we may be able to develop more effective therapies and improve patient outcome.

EXPLORING BIOENERGETIC REGULATORS AS TARGETS FOR GI CANCER THERAPY

Our current understanding of metabolic reprogramming and bioenergetic alterations in cancer has led to the emergence of several potential drugs that target the bioenergetics of cancer cells, offering a promising avenue for anti-cancer therapy. These drugs can be classified into two main categories based on their mode of action: targeting aerobic glycolysis/lactate biosynthesis and transportation, or targeting the TCA cycle and coupled OXPHOS (Figure 4).

To target aerobic glycolysis, several strategies have been developed including blocking glucose import by targeting GLUT1, reducing glycolysis activity by targeting hexokinase 2 (HK2), PKMFB3, and PKM2, inhibiting lactate biosynthesis by targeting LDHA and PDK, and blocking lactate transportation through targeting MCT1/2. Targeting the TCA cycle and OXPHOS involves PDH and mitochondrial complex inhibitors. Several bioenergetic-targeted drugs have provided pre-clinical or clinical evidence in treating GI cancers. Table 4 provides a summary of these drugs. In the following sections, we will discuss the details of such strategies and the drugs used to target bioenergetic regulators during GI cancer therapy.

UNLOCKING THE POTENTIAL OF GLUCOSE METABOLISM TARGETS IN GI CANCER THERAPY

Cancer cells typically rely on increased glucose uptake, a phenomenon known as the Warburg effect, to meet energy requirements, making glucose uptake a promising target for anti-cancer therapy. As a result, GLUT1 has been identified as a potential drug target for blocking glucose uptake. Several GLUT1 inhibitors, including genistein, apigenin, fasentin, WZB117, WZB27, WZB115, STF-31, and BAY-876 have shown an ability to block glucose uptake[14]. Genistein and apigenin are natural compounds belonging to the flavonoid group, and they have been shown to inhibit hypoxia-inducible factor 1A (HIF1A) mRNA and protein expression, which leads to inactivation of downstream genes such as GLUT1 and HK2, thereby attenuating glycolysis activity[128-130]. In GI cancers, these compounds have demonstrated the ability to inhibit cancer cell proliferation, cell cycle progression, colony formation, migration, invasion, angiogenesis, stemness, spheroid formation, EMT, and to enhance cell death[131-146]. Although the majority of evidence pertaining to efficacy comes from *in vitro* cell-based assays, genistein and apigenin have entered clinical trials as a combination anti-cancer therapy for patients with CRC (NCT10985763 and NCT00609310) and PAC (NCT02336087, NCT00376948 and NCT00882765). Moreover, dietary supplementation with apigenin has been shown to significantly prevent CRC recurrence in a prospective study[147]. Fasentin, WZB117, WZB27, WZB115, STF-31, and BAY-876 are synthetic chemicals with selective activity on GLUT1 inhibition. Fasentin, WZB27, and WZB115 have shown anti-cancer potential in other pre-clinical cancer models, although there is currently little to no research on GI cancers. WZB117 has been shown to reduce glucose uptake, inhibit cell proliferation/invasion, and enhance chemosensitivity in GI cancer cell lines, as well as in xenograft models[148-151]. STF-31 has been implicated in reducing cancer stem cell stemness, cell proliferation, viability, and tumor growth in PAC and CRC cell lines, as well as in xenograft models[152,153]. BAY-876 has been found to inhibit cell proliferation, tumor growth, glucose uptake, and promote chemosensitivity in ESCA, PCA, and CRC cell lines, and in xenograft mouse models[154-156]. Although these findings are promising, WZB117, STF-31, and BAY-876 are not currently in clinical trials for GI cancer. Thus, their safety, dosage, and therapeutic response in GI cancer patients remain to be determined in future studies.

Another strategy to block glycolysis is by targeting glycolytic enzymes or attenuating glycolytic activity. A well-studied example of this strategy is the use of 2-deoxy-D-glucose (2-DG), a glucose molecule with a 2-hydroxyl group replaced by hydrogen. 2-DG is taken up by cells with high glucose uptake ability, such as cancer cells, where it serves as a competitive inhibitor of glucose[157]. Once inside the cell, 2-DG enters the glycolytic pathway and is phosphorylated by HK2 to become 2-DG-6-phosphate (2-DG-6-P), which cannot be further processed by G6P isomerase and therefore

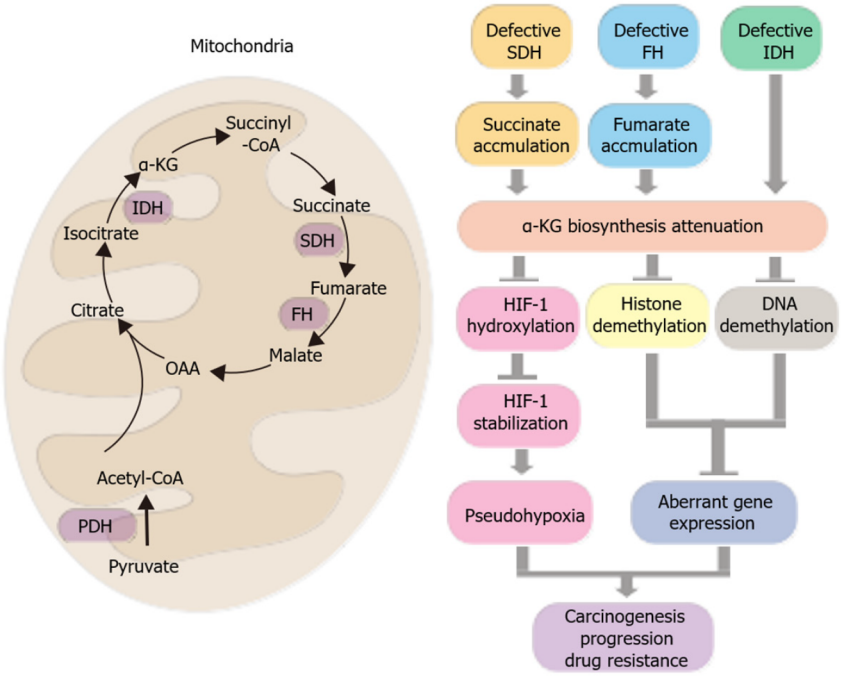

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Figure 3 Tricarboxylic acid cycle dysfunction in cancer and its role in carcinogenesis, progression, and anti-cancer drug resistance. The left panel depicts the tricarboxylic acid cycle, with succinate dehydrogenase and fumarate hydratase as key regulatory enzymes responsible for the formation of oncometabolites succinate and fumarate. The isocitrate dehydrogenase enzyme synthesizes α-ketoglutarate, which serves as a substrate for tumor suppressor pathways, such as hypoxia-inducible factor 1 hydroxylation for degradation, as well as histone and DNA demethylation. These processes can lead to pseudohypoxia and aberrant gene expression, promoting carcinogenesis, progression, and anti-cancer drug resistance. The right panel provides a summary of these relationships. OAA: Oxaloacetate; SDH: Succinate dehydrogenase; FH: Fumarate hydratase; PDH: Pyruvate dehydrogenase; IDH: Isocitrate dehydrogenase; α-KG: α-ketoglutarate; HIF-1: Hypoxia-inducible factor 1.

accumulates. Accumulated 2-DG-6-P reversely negatively inhibits HK2 activity, leading to a reduction in glycolytic activity. A derivative of 2-DG, fluorodeoxyglucose (18F-FDG), has been extensively employed in positron emission tomography (PET) to visualize the location and status of certain types of cancers[158]. In pre-clinical studies using GI cancer cell lines, as well as xenograft models and rat HCC and hamster PAC models, 2-DG has been shown to inhibit cell proliferation, tumor growth, and promote chemosensitivity[159-165]. Although 2-DG has entered clinical trials for other cancer types, only a phase I trial (NCT00096707) was conducted for patients with PAC, and the safety, dose, and efficacy of 2-DG in treating patients with other GI cancers are unknown.

Several other chemical drugs have been claimed to inhibit HK2 function, but their roles in GI cancers are unclear, with the exception of 3-bromopyruvate (3-BrPA) and lonidamine (LND). 3-BrPA is an analog of both lactate and pyruvate and shows an inhibitory effect on HK2, possibly due to its ability to induce protein alkylation[166,167]. In pre-clinical studies of GI cancers, 3-BrPA has shown its ability to inhibit cellular ATP generation, cell proliferation, tumor growth, induce mitochondrial depolarization, reduce animal serum VEGF levels, and promote cell death and chemosensitivity in GC, HCC, PAC, and CRC cell lines, as well as rabbit, transgenic mice, and xenograft mouse models[167-171]. Therapeutic efficacy and safety were only evaluated in a case report study, providing a safe and tolerable dose of 3-BrPA in patients with fibrolamellar HCC[172].

LND is an indazole derivative that was previously utilized as an anti-spermatogenic agent. In drug re-purposing studies, LND was found to have anti-cancer activity by affecting bioenergetic homeostasis, including the glycolytic pathway, through targeting HK2 *via* currently unclear mechanisms[173]. LND showed promising therapeutic efficacy by inhibiting cell proliferation, migration, invasion, cell cycle progression, and increasing chemosensitivity in HCC, CCA, and CRC cell lines, as well as in a hamster CCA model[174-179]. Encouraging results were observed in a clinical trial recruiting patients with GC, showing improved overall response rate and duration of disease progression[174]. Reversely, it was reported that administration of LND was ineffective and toxic in clinical trials recruiting patients with CRC[178, 179].

Targeting PFKFB3 is another approach to block cancer glycolysis, as it is considered an oncogene in cancers due to its high expression and role in glycolysis[180]. PFKFB3 is activated by multiple cancer-associated stimuli, including cytokines, chemokines, growth factors, and hypoxia, and then participates in glycolysis through catalyzing fructose-6-P to become F2,6BP, which can further positively enhance PFK1 activity and thus accelerate glycolysis[180]. Accordingly, PFKFB3 drugs have been identified and tested in pre-clinical and clinical studies. Among the list of candidate drugs that target PFKFB3, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO), 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK15), and 1-pyridin-4-yl-3-[7-(trifluoromethyl)-quinolin-2-yl]-prop-2-en-1-one (PFK158) have drawn more attention than others[181]. It was found that 3PO and PFK15 inhibit cell proliferation, reduce tumor growth, attenuate angiogenesis, prevent fibrogenesis, and increase cell death in pre-clinical studies using GI cancer cell lines, transgenic mice,

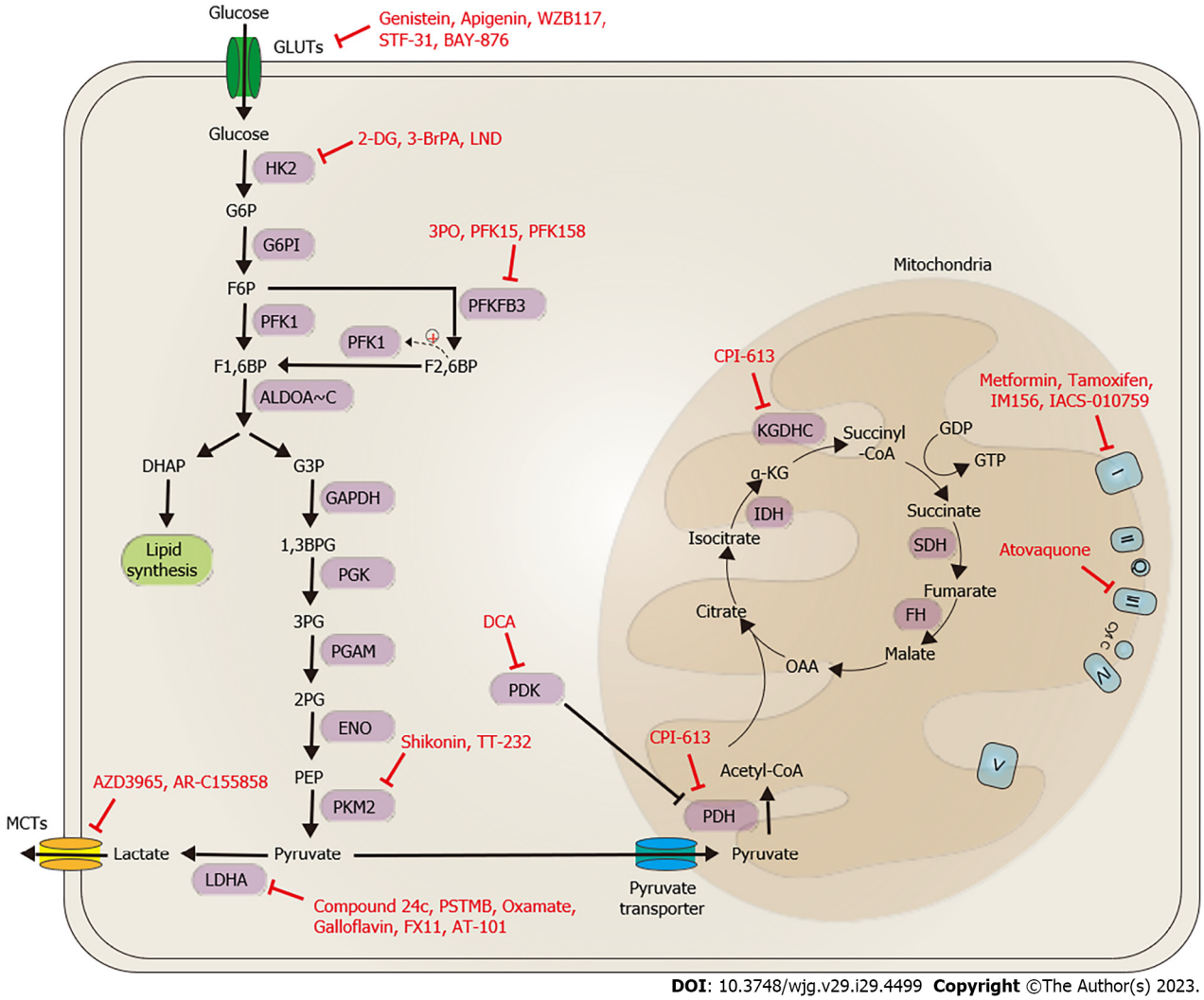

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Figure 4 Potent bioenergetic-targeting drugs for gastrointestinal cancers. Promising bioenergetic drugs for gastrointestinal cancers can be classified into two main categories based on their mode of action. The first category involves targeting aerobic glycolysis and lactate biosynthesis/transportation, while the second category involves targeting the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). Strategies to target aerobic glycolysis include blocking glucose importation through the targeting of glucose transporter 1 with compounds such as genistein, apigenin, WZB117, STF-31, and BAY-876, reducing glycolysis activity by targeting HK2 with compounds such as 2-DG, 3-BrPA, and LND, and targeting PKMFB3 and PKM2 with compounds such as 3PO, PFK15, PFK158, shikonin, and TT-232. Lactate biosynthesis can be inhibited by targeting LDHA with compounds such as compound 24c, PSTMB, oxamate, galloflavin, FX11, and AT-101, and PDK with DCA. Lactate transportation can be blocked by targeting MCT1/2 with compounds such as AZD3965 and AR-C155858. Targeting the TCA cycle and OXPHOS involves using inhibitors of pyruvate dehydrogenase, such as CPI-613, and mitochondrial complex I with metformin, tamoxifen, IM156, IACS-010759, and complex III with atovaquone. GLUT: Glucose transporter; HK: Hexokinase; G6P: Glucose-6-phosphate; G6PI: Glucose-6-phosphate isomerase; F6P: Fructose-6-phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; PFK1: Phosphofructokinase-1; F2,6BP: Fructose-2,6-bisphosphate; PFKBP3: Fructose-2,6-biphosphatase 3; F1,6BP: Fructose-1,6-bisphosphate; G3P: Glyceraldehyde-3-phosphate; DHAP: Dihydroxyacetone phosphate; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; 1,3BPG: 1,3-bisphosphoglycerate; 3PG: 3-phosphoglycerate; PGK: Phosphoglycerate kinase; PGAM: Phosphoglycerate mutase; 2PG: 2-phosphoglycerate; ENO: Enolase; PEP: Phosphoenolpyruvate; PKM1/2: Pyruvate kinase isozyme M1/M2; LDH: Lactate dehydrogenase; MCT: Monocarboxylate transporter family; PDH: Pyruvate dehydrogenase; IDH: Isocitrate dehydrogenase; α-KG: α-ketoglutarate; OAA: Oxaloacetate; SDH: Succinate dehydrogenase; FH: Fumarate hydratase; I: Mitochondrial complex I; II: Mitochondrial complex II; III: Mitochondrial complex III; IV: Mitochondrial complex IV; V: Mitochondrial complex V; Q: Co-enzyme Q; cyto C: Cytochrome *c*; KGDHC: α-ketoglutarate dehydrogenase complex.

xenograft mouse models, and HCC rat models[182-189]. Intriguingly, it was also found that 3PO suppresses glucose uptake *via* a 14C-2-DG tracing system[184]. Although there is no pre-clinical evidence of efficacy in GI cancers, the safety, tolerated dose, and therapeutic efficacy of PKF158 have been evaluated in a Phase I clinical trial (NCT02044861) that involved patients with solid tumors[190].

One strategy proposed to inhibit glycolysis activity is to target the last enzyme in the glycolytic pathway –PKM2. PKM2 targeting is based on its glycolysis role as well as aberrant expression in cancer-associated events[191]. While many drugs have shown the ability to inhibit PKM activity, only two, TT-232 and Shikonin, have been confirmed efficacious in pre-clinical studies. Both TT-232 and Shikonin have been found to inhibit GI cancer cell proliferation, migration, invasion, cell cycle progression, and tumor growth, as well as enhance cell death[192-200]. However, the efficacy of these drugs in treating GI cancers is still unclear and requires further investigation. Both drugs have entered clinical trials for specific cancers, showing promise as cancer therapy targets.

Table 4 Promising novel bioenergetics targeting drugs for gastrointestinal cancer therapy

Inhibitor	Target	GI model	Consequence	Clinical trial	Ref.
Targeting glucose transportation					
Genistein	HIF1A, GLUT1 and HK2	GC, ESCA, HCC, CCA, PCA, and CRC cell lines	Inhibited cancer cell proliferation, cell cycle progression, migration, invasion, angiogenesis, stemness, spheroid formation, EMT, and promoted apoptosis	CRC patient, phase I/II (NCT10985763), and PAC patient, phase I/II (NCT02336087, NCT00376948 and NCT00882765)	[131-140]
Apigenin	HIF1A, GLUT1 and HK2	GC, ESCA, HCC, CCA, PCA, and CRC cell lines	Inhibited cancer cell proliferation, colony-forming, cell cycle progression, migration, invasion, angiogenesis, and induced apoptosis	CRC patient, phase II (NCT00609310)	[141-146]
WZB117	GLUT1	HCC, CCA, PAC, and CRC cell lines, and xenograft models	Reduced glucose uptake, inhibits cell proliferation, and invasion, and enhanced chemosensitivity	None in GI cancers	[148-151]
STF-31	GLUT1	PAC and CRC cell lines, and xenograft model	Reduced cancer stem cell properties, such as stemness, and inhibits cell proliferation, viability, and tumor growth	None in GI cancers	[152, 153]
BAY-876	GLUT1	ESCA, PCA, and CRC cell lines, and xenograft mouse models	Reduced cancer cell proliferation, tumor growth, and glucose uptake, while also increased chemosensitivity	None in GI cancers	[154-156]
Targeting glucose metabolism					
2-Deoxy-D-glucose (2-DG)	HK2	GC, ESCA, HCC, PAC and CRC cell lines, xenograft models, and rat HCC and hamster PAC models	Inhibited cell proliferation, tumor growth, and promoted chemosensitivity	PAC patient, phase I (NCT00096707)	[159-165]
3-Bromopyruvate (3-BrPA)	HK2	GC, HCC, PCA, and CRC cell lines, and rabbit, transgenic mouse and xenograft mouse models	Inhibited cellular ATP generation, cell proliferation, and tumor growth. Also induced mitochondrial depolarization, reduced animal serum VEGF levels, and promoted cell death and chemosensitivity	HCC patient, case report[170]	[167-170]
Lonidamine (LND)	HK2	HCC, CCA, and CRC cell lines, hamster CCA model, and GC and CRC patients	Inhibited cell proliferation, migration, invasion, and cell cycle progression. Increased chemosensitivity, patient overall response rate, and duration of disease progression in GC patients. However, was ineffective and toxic in advanced CRC patients	GC patient, phase II[172], CRC patients, phase II[176,177]	[174-179]
3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO)	PFKFB3	HCC, PAC, and CRC cell lines, and transgenic and xenograft mouse models	Inhibited glucose uptake, cell proliferation, tumor growth, angiogenesis, fibrogenesis, and promoted cell death	None in GI cancers	[182-184]
1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK15)	PFKFB3	GC, HCC, PAC, and CRC cell lines, xenograft models, and HCC rat model	Inhibited cell proliferation, migration, invasion, cell cycle progression, tumor growth, and enhanced cell death	None in GI cancers	[185-189]
1-pyridin-4-yl-3-[7-(trifluoromethyl)-quinolin-2-yl]-prop-2-en-1-one (PFK158)	PFKFB3	None in GI cancers	None in GI cancers	Solid tumor patients, phase I (NCT02044861)	[190]
Shikonin	PKM2	GC, ESCA, HCC, CCA, PCA, and CRC cell lines, and xenograft mouse models	Inhibited cell proliferation, migration, invasion, cell cycle progression, tumor growth, and enhanced cell death	None in GI cancers	[192-197]
TT-232	PKM2	HCC, PAC, and CRC cell lines,	Inhibited cell proliferation, tumor growth, and enhanced cell death	None in GI cancers	[198-200]

		and xenograft mouse models			
Targeting lactate biosynthesis					
Dichloroacetate (DCA)	PDK	GC, ESCA, HCC, PAC, and CRC cell lines, xenograft models, and B6C3F1 mice	Reduced lactate production, cell proliferation, migration, and increased chemosensitivity. Showed synergistic anticancer effects in HCC. However, promoted hepatocarcinogenesis in B6C3F1 mice	CRC patient, phase I (NCT00566410)	[203-207]
Compound 24c	LDHA	PAC cell lines, and xenograft model	Suppressed cell proliferation, colony formation, enhanced cell apoptosis, arrested cell at G2 phase, repressed xenograft growth, and re-programmed cancer metabolism, with minimal impact on mouse weight	None in GI cancers	[210]
1-(Phenylseleno)-4-(Trifluoromethyl) Benzene (PSTMB)	LDHA	HCC and CRC cell lines	Inhibited cell proliferation, reduced cell viability, attenuated LDHA activity, lowered lactate levels, and induced mitochondria-mediated apoptosis	None in GI cancers	[211]
Oxamate	LDHA	GC, ESCA, HCC, PCA, and CRC cell lines	Suppressed LDHA activity, lactate production, cell proliferation, migration, MMP9 expression, pro-inflammatory cytokines, EMT transition, and AKT/ERK/mTOR signaling pathways, while enhanced apoptosis, senescence, protective autophagy, and metabolic rewiring	None in GI cancers	[212-218]
Galloflavin	LDHA	HCC, PCA, and CRC cell lines	Reduced ATPase activity and expression levels of heat shock proteins, inhibited cell proliferation, lactate production, pro-inflammatory cytokines, and EMT transition, while promoting apoptosis and senescence	None in GI cancers	[215, 218-220]
FX11	LDHA	HCC, PCA, and CRC cell lines, and xenograft mouse models	FX11 reduced lactate production and ATP levels, suppressed cell proliferation, migration, invasion, and xenograft tumor growth, while enhancing apoptosis. However, in a PCA patient-derived mouse xenograft model, FX11 was only effective in attenuating tumor growth in the presence of mutant TP53	None in GI cancers	[221-225]
Gossypol (AT-101) or its derivatives	LDHA	GC, ESCA, HCC, PAC and CRC cell lines, GC and xenograft mouse models, and ESCA patient	Reduced cell viability, suppressed cell proliferation, migration, and tumor growth, down-regulated cancer stem cell markers CD133, Nanog, LC3, and YAP-1, enhanced apoptosis, protective autophagy. and complete response rate/prognosis	ESCA patient, phase I/II (NCT00561197)	[226-240]
Targeting lactate transportation					
AZD3965	MCT1/2	GC, ESCA, HCC, CRC cell lines	Inhibited cell proliferation and tumor growth, while increasing intracellular lactate concentration, TCA-related metabolites, mitochondrial metabolism, and chemosensitivity. Also decreased intracellular pH	None in GI cancers	[242-246]
AR-C155858	MCT1/2	GC, PAC, and CRC cell lines, and xenograft mouse models	Inhibited cell proliferation, spheroid forming ability, and tumor growth, while decreased glycolysis and increased intracellular lactate concentration, TCA-related metabolites, mitochondrial metabolism, and chemosensitivity	None in GI cancers	[247-249]
Targeting mitochondrial OXPHOS					
Metformin	Mitochondrial complex I	GC, ESCA, HCC, CCA, PAC, and CRC cell lines, xenograft models, and ESCA, HCC, CCA, PCA and CRC patients	Suppressed cell proliferation, migration, cell cycle progression, and tumor growth while increasing chemosensitivity and cell death. Also re-programmed the tumor immune microenvironment in ESCA patients	ESCA patient, phase II (ChiCTR-ICR-15005940), HCC patient, phase I (CTRI/2018/07/014865), CCA patient, phase Ib (NCT0249674), PCA patient, phase II (NCT01210911 and NCT01167738), and CRC patient, phase II (NCT01312467, NCT03047837, and NCT01941953)	[252-265]

Tamoxifen	Mitochondrial complex I	GC, ESCA, HCC, CCA, PAC and CRC cell lines, CRC murine model, and ESCA, HCC and PAC patients	Inhibited cell proliferation, tumor growth, metastasis, and increased chemosensitivity. However, no prolonged survival benefits have been observed in HCC patients, and in some cases, there may even be a higher risk of death	ESCA patient, phase I (NCT02513849), PAC patient, phase II[272-274], and HCC patient, phase III (NCT00003424)	[267-273, 277]
IM156	Mitochondrial complex I	GC and CRC patients	Considered tolerable in human subjects, with stable disease being the most common response. Combinatorial therapy may be necessary for improved efficacy	GC and CRC patients, phase I (NCT03272256), and PAC patient, phase Ib (NCT05497778)	[278]
IACS-010759	Mitochondrial complex I	PAC cell lines, and CCA, PAC, and CRC patients	Reduced cell viability and generally well tolerated, but may induce neurotoxicity, peripheral neuropathy, and behavioral/physiological changes in mice. Increased blood lactate levels	CCA, PAC, and CRC patient, phase I (NCT03291938)	[279, 280]
Atovaquone	Mitochondrial complex III	GC, HCC, PAC and CRC cell lines, and xenograft models	Reduced OXPHOS, oxygen consumption rate, cell viability, cell proliferation, and cell cycle progression. Inhibited tumor growth and enhanced cell death	None in GI cancers	[283-285]
Targeting TCA cycle					
CPI-613	PDH and KGDHC	GC, ESCA, PAC and CRC cell lines, xenograft mouse models, and GC mouse model	Inhibited cell proliferation, cell viability, tumor growth, and metastasis, while increased cell death and chemosensitivity. In PAC patients, also increased the overall response rate	PAC patient, phase I (NCT01835041) and III (NCT03504423), HCC and CCA patients, phase I/II (NCT01766219), and CRC patients, phase I (NCT05070104 and NCT02232152)	[287-291]

GI: Gastrointestinal; ESCA: Esophageal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; PAC: Pancreatic cancer; CRC: Colorectal cancer; LDHA: Lactate dehydrogenase subunit A; MCT1/2: Monocarboxylate transporter family 1/2; HIF1A: Hypoxia inducible factor 1A; GLUT1: Glucose transporter 1; HK2: Hexokinase 2; PFKFB3: Fructose-2,6-biphosphatase 3; PKM2: Pyruvate kinase isozyme M2; PDK: Pyruvate dehydrogenase kinase; PDH: Pyruvate dehydrogenase; KGDHC: Alpha-ketoglutarate dehydrogenase complex; EMT: Epithelial-mesenchymal transition; OXPHOS: Oxidative phosphorylation.

EXPLORING LACTATE BIOSYNTHESIS AND TRANSPORT AS A POTENTIAL STRATEGY FOR GI CANCER THERAPY

As mentioned above, the Warburg effect is a common phenomenon in many cancers for which glycolysis is upregulated even in the presence of oxygen. This results in the accumulation of lactate, which is the last product of glycolysis. The PDK class of enzymes play a key role in deciding whether pyruvate is converted to lactate or enters the TCA cycle. Under hypoxia, PDKs are transcriptionally upregulated by HIF1A in cancers, promoting the inactivation of PDH through PDK-mediated phosphorylation. This leads to elevated lactate biosynthesis, resulting in excessive lactate levels that can promote carcinogenesis or progression[201]. Therefore, targeting PDKs is a potential strategy to inhibit lactate synthesis. Although several candidate drugs that target PDKs have been proposed, dichloroacetate (DCA) has been the most convincing inactivator of PDKs[202]. DCA has been shown in numerous pre-clinical studies on GI cancer to reduce lactate production, cell proliferation, migration, and increase chemosensitivity[203-207]. It has also shown synergistic anti-cancer activity in HCC despite concerns that it may promote hepatic carcinogenesis in B6C3F1 mice[205,208]. Despite promising pre-clinical results, clinical studies are still necessary to determine the efficacy and safety of DCA during cancer therapy. A clinical trial recruiting patients with CRC has been conducted to evaluate DCA as a potential anti-cancer drug (NCT00566410).

In previous studies on lactic acid inhibitors for anti-cancer therapy, the focus has been on inhibiting the enzymes responsible for lactate biosynthesis, namely LDH. TLDH complex composition has been investigated as a crucial factor in determining the fate of lactate biosynthesis or catabolism, and LDHA homo-tetramer (LDH5 or A4) has been considered the most effective complex for lactate biosynthesis. Accordingly, the currently established strategy is to identify LDH inhibitors with high selectivity against LDHA[209]. Although many candidates exist, including small peptides, small interfering RNAs (siRNAs), small chemical molecules, and natural compounds, only a few have progressed towards clinical use in anti-cancer therapy. Compound 24c and 1-(Phenylseleno)-4-(Trifluoromethyl) Benzene (PSTMB) are small compounds that have recently been identified as capable of selectively inhibiting LDHA, suppressing cancer cell aggressiveness, and enhancing cell death in both PCA cells and xenograft mouse models[210] as well as HCC and CRC cells [211]. Notably, Compound 24c has little effect on mouse weight, perhaps due to its relatively strong activity to reprogram metabolic profiling[210]. In contrast, oxamate, galloflavin, and FX11 have a longer history than Compound 24c and PSTMB in targeting LDHA. Pre-clinical evidence shows promise in suppressing GI cancer cell aggressiveness by targeting LDHA and other cancer-associated signaling pathways, suggesting possible treatment of GI cancers[212-225]. Despite this evidence, there is still a lack of clinical results to support the safety and efficacy of these LDHA-targeting drugs in GI cancer patients. An early natural compound, gossypol (AT-101), derived from the cotton plant, is one exception. Gossypol

and its derivatives have proven potent inhibitors of LDHA[226]. Gossypol not only reduces the aggressiveness of GI and other cancers, but also has a strong cytotoxic effect on cancer cells[226-240]. Most importantly, gossypol has entered a phase I/II clinical trial (NCT00561197) to evaluate its safety and efficacy in treating patients with esophageal cancer, showing significant improvement in complete response and survival rates[231]. Therefore, gossypol may be the most promising clinical drug targeting LDHA to date for use in GI cancers.

Excessive intracellular accumulation of lactate is a hallmark of many cancer types, which necessitates MCTs in transporting lactate from highly glycolytic cancer cells. Secretory lactate can acidify the extracellular microenvironment, which can impact the tumor microenvironment[241]. While secretory lactate was initially considered a waste product of cancer cells, recent evidence has suggested that it serves as an alternative fuel for oxidative cancer cells, leading to enhanced aggressiveness[56]. Therefore, MCT targets have emerged as an alternative strategy for anti-cancer therapy [241]. Among the various compounds proposed to target MCTs in cancer, AZD3965 and AR-C155858 have received more attention from researchers. Both drugs have demonstrated potential in targeting MCTs, inhibiting GI cancer cell aggressiveness, and stunting tumor growth both *in vitro* and *in vivo*[242-249]. While AZD3965 has entered the clinical trial phase, further investigation is needed to determine the safety and therapeutic efficacy of these drugs in patients with GI cancer. Notably, the development of MCT inhibitors has faced several challenges, including the presence of MCT isoforms and the need for inhibitors that selectively target cancer cells without affecting normal tissues[58,250]. In this regard, approaches and strategies to develop selective MCT inhibitors are being actively pursued. While MCT inhibitors hold promise as a potential anti-cancer therapy, further research is needed to fully understand their mechanisms of action and optimize their clinical applications.

TARGETING OXPHOS AS A POTENTIAL THERAPEUTIC STRATEGY FOR GI CANCER

Excessive OXPHOS activity has been observed in certain cancers and has been associated with more aggressive phenotypes/unfavorable clinical outcomes, making it a novel target for anti-cancer therapy[251]. Attenuating OXPHOS activity has been proposed as the best strategy to target OXPHOS, leading to the identification of a large number of candidate compounds that target mitochondrial complex I. Metformin, a compound that has long been used to treat diabetes, has been reported to exhibit mitochondrial complex I inhibition activity and can impact cancer cell aggressiveness/tumor growth in both GI cancer cell lines and xenograft models[252-265]. Metformin has advanced to clinical trials in combination with other anti-cancer regimens for patients with GI cancers, such as ESCA patients in Phase II (ChiCTR-ICR-15005940), HCC patients in Phase I (CTRI/2018/07/014865), CCA patients in Phase Ib (NCT0249674), PCA patients in Phase II (NCT01210911 and NCT01167738), and CRC patients in Phase II (NCT01312467, NCT03047837, and NCT01941953). It was found that metformin combination therapy can provide benefit to patients, perhaps through reprogramming the tumor immune microenvironment[258].

Recent studies have proposed several candidates as mitochondrial complex I-targeting compounds in addition to metformin. Among them, tamoxifen, IM156, and IACS-010759 have gained attention as potential anti-cancer agents. Tamoxifen is an anti-estrogen agent that has been clinically used to treat breast cancer patients with positive estrogen-receptor (ER) expression[266]. Interestingly, tamoxifen has also been shown to inhibit cancer cell aggressiveness, tumor growth, metastasis, and increase chemosensitivity in GI cancers[267-273]. This effect is thought to be through an ER-independent anti-cancer pathway[269]. Tamoxifen has been used as a monotherapy or combined therapy in several clinical trials, including an early phase trial in ESCA patients, Phase II trials in PAC patients[274-276], and a Phase III trial in HCC patients (NCT00003424). Tamoxifen has been found to be tolerable, safe, and with manageable adverse effects, while a Phase III trial in HCC patients found that tamoxifen monotherapy either offered no effect or decreased survival in patients with unresectable HCC[277]. This result has slowed the advancement of tamoxifen in GI cancers and requires further investigation.

IM156 and IACS-010759 are two novel mitochondria-targeting drugs that specifically inhibit mitochondrial complex I. While both compounds have shown promising results in pre-clinical studies against certain cancer cell lines, their potential in treating GI cancers involves limited evidence. Interestingly, IM156 has entered Phase I clinical trials in patients with GC, CRC and PCA (NCT03272256 and Janku *et al*[278]), demonstrating tolerability and safety. However, IM156 monotherapy in patients with GC and CRC offered only disease stabilization, indicating the need for further study.

On the other hand, IACS-010759 has shown significant cell viability reduction in PCA cell lines[279], leading to the initiation of a Phase I clinical trial (NCT03291938) to evaluate clinical efficacy and safety in patients with solid tumors due to CCA, PAC, and CRC. However, a recent publication reported that although IACS-010759 was tolerable and safe, it increased blood lactate levels and neurotoxicity while offering only limited anti-cancer efficacy. A reverse translational study using mice also found IACS-010759 to induce behavioral and physiological changes indicative of peripheral neuropathy, minimizing the possibility of combined therapy with specific anti-cancer compounds (*e.g.*, histone deacetylase 6 inhibitor). The development of mitochondrial complex I inhibitors is ongoing[280].

While the mitochondrial complex I inhibitors metformin, tamoxifen, IM156, and IACS-010759 hold promise as potential treatments for GI cancer, further studies are needed to evaluate their efficacy and safety, particularly in combination with other anti-cancer compounds. The development of more selective and potent mitochondrial complex I inhibitors may help overcome side effects and improve efficacy in cancer treatment.

The targeting of mitochondrial complexes other than complex I has also been proposed as a strategy for anti-cancer therapy[281]. One such compound of note is atovaquone, which was identified as a mitochondrial complex III inhibitor during a drug re-purposing study[282]. Pre-clinical studies have evaluated the potential of atovaquone as an anti-cancer agent in GI cancer cell lines and xenograft models, and have shown its ability to reduce OXPHOS, OCR, cell viability, cell

proliferation, cell cycle progression, and tumor growth, while enhancing cell death[283-285]. Despite promising results, atovaquone is currently in clinical trials for patients with non-small cell lung cancer (NCT04648033) and acute myeloid leukemia (NCT03568994) but not for patients with GI cancer. Further studies are needed to determine drug tolerability, safety, and therapeutic efficacy in patients with GI cancer. Nonetheless, the potential benefits of targeting OXPHOS make for a promising strategy in GI cancer therapy. However, the potential toxicity of these inhibitors in normal cells must be carefully evaluated before being considered as viable anti-cancer agents. In addition, the development of resistance to mitochondrial inhibitors, similar to the resistance seen with other anti-cancer agents, highlights the need for combination therapy.

POTENTIAL OF TCA CYCLE TARGETS IN GI CANCER THERAPY

The TCA cycle is a critical metabolic pathway that fuels bioenergetic processes in cells. Targeting the TCA cycle has emerged as a potential strategy for anti-cancer therapy[286]. Various agents have been tested for their anti-cancer efficacy, including AGI-5195, AG-221, AG-881, and CPI-613[286]. Among these compounds, CPI-613 is the only PDH and alpha-ketoglutarate dehydrogenase complex (KGDHC) dual targeting agent that has shown promising anti-cancer properties in GI cancer models both *in vitro* and *in vivo*[287-291]. The tolerability and safety of CPI-613, alone or in combination with other agents, has been evaluated or is currently being studied in patients with HCC, CCA, and CRC (NCT01766219, NCT05070104 and NCT02232152). However, a recent Phase III trial (NCT03504423) evaluating the anti-cancer efficacy of CPI-613 in patients with advanced PAC failed to improve survival rate but improved overall response rate[292]. This outcome is disappointing, combining CPI-613 with other drugs such as gemcitabine or nab-paclitaxel may provide better results.

The TCA cycle is a complex pathway, and there are multiple enzymes and metabolites that could be targeted for anti-cancer therapy. For example, the isocitrate dehydrogenase 1 and 2 (IDH1/2) enzymes play a crucial role in the TCA cycle, and mutations in these enzymes have been observed in several types of cancer, including gliomas and acute myeloid leukemia (AML)[293]. Enasidenib and ivosidenib are two IDH1/2 inhibitors that have been approved for the treatment of relapsed or refractory AML[294,295]. In GI cancers, however, the efficacy of IDH1/2 inhibitors is still under investigation [296]. In addition to IDH1/2 inhibitors, other TCA cycle inhibitors are being explored for anti-cancer therapy. For example, IDH1/2 mutant tumors are sensitive to glutaminase inhibitor CB-839, which targets glutamine metabolism [297]. Another TCA cycle inhibitor, BPTES, has shown anti-cancer efficacy in pre-clinical studies by blocking the activity of the glutaminase enzyme[298]. However, our understanding of these inhibitors in GI cancer treatment is still limited.

Targeting the TCA cycle and associated bioenergetic processes is a promising approach for anti-cancer therapy. While CPI-613 has shown some success in GI cancer models, the failure in Phase III trial underscores the need for continued research and combination therapy. Other TCA cycle inhibitors, such as IDH1/2 and glutaminase inhibitors, are being evaluated for their anti-cancer efficacy in GI cancers, offering hope for future treatments.

DISCUSSION AND FUTURE PERSPECTIVE

Cancer cells undergo significant metabolic changes which involve alteration to the nuclear and mitochondrial genomes as well as cell microenvironment. Understanding the molecular mechanisms behind these alterations is critical for the development of effective cancer therapies. Next-generation technologies such as metabolic profiling, single-cell sequencing, and metabolic tracing can provide insights into the regulation of mitochondrial metabolism in different cancer types. However, developing therapies based on altered metabolism is challenging due to the diverse metabolic patterns observed across different cancer cells.

Simply targeting a single bioenergetic enzyme or pathway may not be enough to effectively inhibit cancer cell growth, as metabolic symbiosis enables cancer cells to adapt to harsh tumor environments. One potential strategy is to treat the metabolic patterns of different cellular subpopulations in the tumor microenvironment to create a homogeneous metabolic population for targeting.

Bioenergetic enzymes have been explored as a way to inhibit cancer cell growth, with some small-molecule inhibitors of glucose metabolism showing significant inhibition in various cancers. However, clinical translation of these inhibitors has been limited by side effects. Other small-molecule inhibitors and natural products that regulate key bioenergy enzymes have also shown promise, but their specific mechanisms and targets require further investigation. Developing anticancer drugs targeting bioenergetic enzymes remains a significant challenge due to the unique metabolic features of cancer cells. Targeted drugs have shown anticancer effects in various tumor models, and combining them with conventional anticancer drugs is a promising strategy.

High-throughput multi-omics and spatial omics can help elucidate the heterogeneity of cancer cells and provide opportunities for therapeutic drugs targeting the bioenergetics of malignant tumors. Unbiased CRISPR-Cas9 synthetic lethality screening of metabolic genes that favor anti-cancer responses, particularly *in vivo*, could provide an avenue towards the identification of bioenergetic targets of interest. The ultimate goal is to develop drugs that simultaneously disable cancer cells while synergizing with targeted therapies.

However, while targeting bioenergetic pathways in cancer cells shows promise, it also has the potential to affect normal cells and tissues that rely on these pathways. Therefore, careful consideration and further research are needed to ensure that therapies targeting bioenergetics in cancer cells are specific and effective while minimizing potential side effects on normal cells and tissues. Additionally, combination therapies that target multiple pathways may be necessary

to achieve optimal therapeutic effects.

CONCLUSION

The metabolic reprogramming and bioenergetic alteration of cancer cells, particularly their utilization of glucose fermentation (the Warburg effect) for energy production, are well-known phenomena. However, comprehensive summaries of these alterations and their oncogenetic links in GI cancers are lacking. This review provides a summary of the interplay between aerobic glycolysis, the TCA cycle, and OXPHOS in cancer cells, including the molecular mechanisms that trigger these alterations. It also explores the role of HIFs, tumor suppressors, and the oncogenetic link between hypoxia-related enzymes, bioenergetic changes, and GI cancer. Additionally, this review details various anti-cancer drugs and strategies for treating GI cancers, along with the challenges associated with them. Understanding dysregulated cancer cell bioenergetics is critical for effective treatments, although the diverse metabolic patterns present challenges for targeted therapies. Further research is needed to comprehensively understand the specific mechanisms of inhibiting bioenergetic enzymes, address side effects, and utilize high-throughput multi-omics and spatial omics for insights into the heterogeneity of GI cancer cells in targeted bioenergetic therapies.

FOOTNOTES

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