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Review Article

Cancer and Glucose Metabolism: A Review on Warburg Mechanisms

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ABSTRACT

Modification of all four major classes of macromolecules metabolism in cancer tissues is a common feature. This alteration is a requirement for rapid proliferation as it provides quick energy generation, enhanced macromolecule biosynthesis and maintenance of the redox state. In tumour cells, there is increased glucose metabolism to lactate in the presence of oxygen, a phenomenon known as the "Warburg effect". Understanding the role of the Warburg effect in cancer progression and targeting this phenomenon as a possible target for cancer management has become paramount. Mechanisms such as acidification of tumour microenvironment, hypoxia-inducible factor (HIF) stabilisation, mutation of tumour suppressor genes and oncogenes, mitochondrial dysfunction, selected targeting by miRNA, altered glutamine metabolism and post-translational modifications have been found to induce the Warburg phenomenon. Other contributory mechanisms are isocitrate dehydrogenase gene mutation, mitochondria membrane transporters, and pyruvate dehydrogenase complex conditioning. Chemical compounds such as 2-deoxy-glucose, 3-bromopyruvate and dichloroacetic acid target this phenomenon to reverse altered metabolism. A better holistic understanding of these mechanisms will help uncover novel metabolism-based therapeutic strategies that may play a role in halting the Warburg effect and ultimately, cancer progression.

Keywords: Cancer, Warburg effect, Metabolism, 2-deoxy-glucose, Therapeutic strategies.

Introduction

Cancer is a group of diseases in which abnormal cells are rapidly produced and proliferated in addition to specific features such as invasion and metastasis.[1] This disease has become a public health problem accounting for about 10 million yearly deaths globally since 2018.[2] The initiation and progression of tumours require reprogramming of numerous metabolic pathways in cancer cells via autonomous flux alteration to meet the increased bioenergetic and biosynthetic demand while managing the build-up of reactive species to ensure proliferation and survival.[3] Cancer and altered metabolism link are established, as a change in metabolism is a reported characteristic found in cancerous tissues.[4] Intrinsic and extrinsic molecular mechanisms play a major role in not just altering metabolism but providing the basic needs of rapidly dividing cells, namely, quick ATP production and replenishment for energy condition maintenance, heightened macromolecule biosynthesis and strict upkeep of cellular redox status.[5] These molecular mechanisms a big challenge and have posed limitations in finding a cure for cancer.[6,7] In 1924, Otto Warburg discovered that tumour cells catabolise glucose via glycolysis to lactate in spite of normoxic conditions, a phenomenon later referred to as the "Warburg effect" (Figure 1).[8,9] The preference for glycolysis over oxidative phosphorylation enables the tumour cells to have a competitive advantage over normal cells.

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This preference has been attributed to relatively faster ATP generation and the provision of building blocks required for cell proliferation by glycolysis alone.[10-12] In the presence of excess glucose, pentose phosphate shunt is induced to generate NADPH, triggering glycolytic metabolism alone in the presence of oxygen for survival and rapid proliferation of these tumour cells.[13] Berg, Tymoczko[14] informs us on nucleic acids' importance in cell proliferation via the precursor ribose-5-phosphate, derived from glucose-6-phosphate, a glycolytic metabolite. Similarly, amino acid biosynthesis is derived from some precursors such as 3-phosphoglycerate (3-PG), phosphoenolpyruvate (PEP) and pyruvate, while dihydroxyacetone (DHA) is a precursor for lipid biosynthesis. Molecular techniques and high-level machines have led to a paradigm shift toward investigating the role of the Warburg effect in cancer, generating a lot of research on this phenomenon.[15] This review article aims to look at the role of the Warburg effect in cancer progression, some underlying mechanisms and target this phenomenon as a possible therapy for cancer management.

Mechanisms inducing the Warburg effect

The Warburg effect may be a consequence of adaptation to hypoxia, consequent mitochondrial damage or intentional shutting down of the mitochondria by cancer genes due to their involvement in apoptosis, a process deleterious to cancer cells. Some mechanisms have been strongly linked to this occurrence, as shown in Figure 2, despite the complete picture remaining elusive.[15]

Association of the tumour microenvironment and hypoxia inducible factor in inducing the Warburg effect

Glucose is catabolised by glycolysis, Kreb cycle, and electron transport chain under normal physiological conditions to yield energy in normal cells.[14] This ensures the complete breakdown of glucose to yield CO_2, H_2O and 38 ATP turnover in a slow but reliable process that ensures optimal proliferation. On the other hand, Tumour cells rapidly divide in such a way that they outgrow blood supply capacity,

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leading to hypoxia and corresponding acidic regions by metabolising glucose to lactate.[16-18] Increased lactate production and extracellular secretion lead to oxygen depletion, acidification of the tumour microenvironment, environmental acidosis and cellular toxicity.[17,19] This microenvironment induces several glycolytic enzymes and protects tumour cells from immune attacks.[20] Hypoxia-inducible factor 1 (HIF1) is utilised by cancer cells to adapt to hypoxic conditions.[15] HIF1α is a regulatory subunit of HIF1 which under normoxic conditions undergo proteasomal degradation resulting in a short half-life. During hypoxia, the mitochondria become deprived of oxygen, stifling pyruvate catabolism and inhibiting oxidative phosphorylation while activating glycolysis (Figure 3). HIF1 mechanism of action is induction of pyruvate dehydrogenase kinase 1 (PDK1), which then inactivates pyruvate dehydrogenase (PDH) activity. PDH inhibition leads to the inability of pyruvate to enter the mitochondria leading to the accumulation of cytosolic pyruvate, conversion to lactate and extracellular release into the environment by monocarboxylate transporter 4 (MCT-4).[21,22] This process regenerates NAD^+, which induces glycolytic enzymes and overexpresses glucose transporters (GLUTs) and glycolytic genes.[23] This induction enhances faster glucose metabolism to meet the ATP demands of tumour cells. Under hypoxic conditions, HIF induces the expression of selectin ligands (sialyl-Lewis x and a), fucosyltransferase VII (FUT7) and sialyltransferase facilitating and increasing the adhesion of cancer cells to endothelial cells.[24] These ligands are usually presented on surface proteins or lipid scaffolds of the microvasculature of the endothelial cells at inflammatory sites. This structure enables improved adherence to circulating tumour cells.[25]

Role of tumour suppressor genes and oncogenes in driving the Warburg effect

Oncogenes such as protein kinase B (Akt), Myc, Ras GTPases and tumour suppressors such as tumour protein 53 (p53) induce the Warburg phenomenon.[26] When the Akt-mediated signalling pathway is activated, there is an increase in the expression of GLUTs and direct phosphorylation of glycolytic rate-limiting enzymes through Akt oncogene implication activating glycolysis.[4,26,27] Mammalian target of rapamycin (mTOR) activation by Akt in tumour cells induces the synthesis of HIF1α in normoxic conditions, increasing glycolytic metabolism to support their rapid proliferation.

Myc oncogenes are transcription factors that induce pro-proliferative gene expression by binding and recruiting enhancer box sequences and histone acetyltransferases.[28]

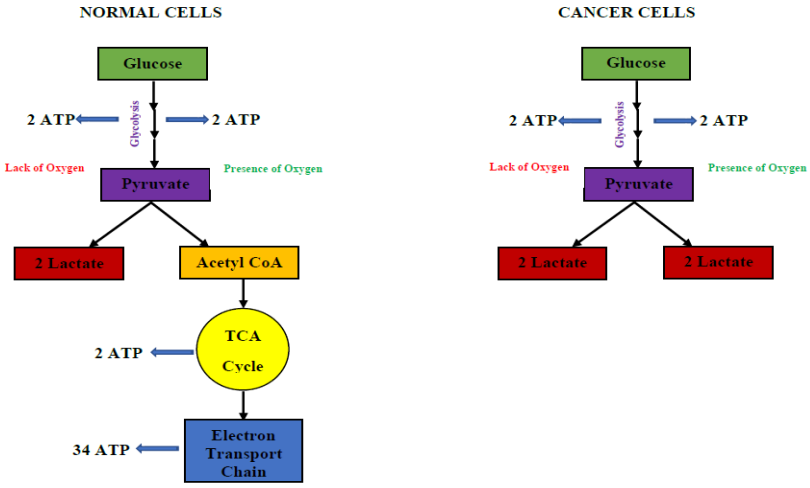

Figure 1: Observed differences in glucose metabolism under various oxygen states.

Figure 2: Mechanisms inducing the Warburg effect.

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They also regulate cell growth, apoptosis, differentiation, stem cell renewal, and nucleotide metabolism.[29] Onset of cancer triggers Myc oncogene, which in turn upregulates aerobic glycolysis by binding to glycolytic enzyme genes, activating them and inducing nicotinamide-phosphoribosyltransferase (NAMPT) for increased generation of NAD^+. Oncogenic Myc also activates the salvage pathway of purines and pyrimidines to match the demand for genetic matter. Ras, a group of small GTPase, play a role in cellular signal transduction and regulate diverse cell behaviours. Ras transduces signals received to other proteins to induce genes responsible for cell growth, differentiation, and survival in normal cells.[30] Like Myc, oncogenic Ras, is mutated in about 35 % of cancer cells, causing several metabolic disorders such as increased glucose uptake, glycolysis, lactic acid production and mitochondrial dysfunction (Figure 4).[30] p53 maintains a balance between glycolysis and oxidative phosphorylation by activating the expression of p53 induced glycolysis and apoptosis regulator (TIGAR), glutaminase 2 (GLS2) and synthesis of cytochrome c oxidase (CCO2) while downregulating phosphoglycerate mutase (PGM) expression.[15] TIGAR downregulates glycolysis by dephosphorylating and reducing the intracellular fructose 2,6-bisphosphate (F-2,6-biP) while upregulating hexose monophosphate shunt. A mutation on p53 leads to an alteration of the metabolic balance and redox status.

Mitochondrial dysfunction as an inducer of the Warburg effect

Fumarase (FH) and succinate dehydrogenase (SDH) are enzymes that catalyse tricarboxylic cycle (TCA) intermediates fumarate and succinate, encoded by FH and SDH genes, respectively.[31] When mutations arise in genes coding for FH and SDH, it leads to a loss of activity, accumulation of intermediates in the mitochondria and increase in intracellular NADH level, consequently shifting energy production to enhanced glycolysis.[32] Mitochondrial uncoupling, downregulation of β-F1-ATPase and accumulation of reactive oxygen species (ROS) are some mechanisms through which mitochondrial energy production is repressed and glycolysis is increased in tumours.[33-35] Mitochondrial DNA (mtDNA) and mitochondrial membrane, which play a key role in mitochondria function, are some targets of ROS leading to increased cell proliferation and migration, increased genetic lesions, truncated mitochondrial oxidative phosphorylation, loss of membrane potential and loss of ATP generation.[36]

Function of microRNA's as Warburg effect inducers

MicroRNAs (miRNAs) are small non-coding RNAs of about 20–23 nucleotides that function as oncogenes or tumour suppressor gene regulators. They also modulate gene expression by suppressing translation through gene silencing/degradation and translation of messenger RNA (mRNA) into proteins.[37] miRNAs induce the Warburg mechanism by targeting the metabolic pathway genes or genes linked to glycolysis. miRNA-223, -133, -19 and -150 regulate the expression of GLUT 1 and 4 while miRNA-200 isoforms, -326 and -143 target phosphoglucose isomerase (PGI), pyruvate kinase M2 (PKM2) and hexose kinase II (HKII) respectively.[38,39] miR-29 isoforms and -124 target MCTs regulating the extracellular secretion of lactate.[38,39] These individual molecular activities of miRNAs ensure the upregulation and maintenance of glycolysis with increased tumour environment acidosis.

Glutamine metabolism contribution to the Warburg phenomenon

Glutamine metabolism and intake in tumour cells are relatively higher than in normal cells. This observation has been attributed to the PKM2 dimeric form, which causes a shift from glucose metabolism to synthetic pathways providing an alternative source of energy.[40] The intermediates of glutamine metabolism are used to meet the increased proliferative demand of lipogenesis, nucleic acid biosynthesis and ATP provision in cancer cells.[41] In the course of glucose deprivation, ammonia-triggered autophagy provides energy for the tumour cells via glutamine hydrolysis. Glutaminolysis also prevents the entry of acetyl CoA into the Kreb cycle, making it readily available for lipid biosynthesis.[40]

Post-translational modifications inducing the Warburg effect

Phosphorylation of various rate-limiting enzymes in metabolic pathways due to oncogenic signalling network activation and post-translational modifications of non-histone proteins are also responsible for the shift in cellular metabolism favouring glycolysis in cancer cells. Phosphorylation of glycolytic enzymes such as lactate dehydrogenase (LDH) A, HK, pyruvate dehydrogenase (PDH) and PFK-2 promote expression of GLUTs and localisation of plasma membrane, stimulates the uptake of glucose and cell trapping in the cell, in the process switching from mitochondrial respiration to aerobic glycolysis.[9,42,43] De-SUMOylation of HIF-1*α*, modification of PFK1 to a shorter protein form, acetylation, oxidation and phosphorylation of PKM2 are some post-translational mechanisms tumour cells utilise to bring about the Warburg phenomenon (Table 1).[42,44,45]

Role of isocitrate dehydrogenase (IDH) mutations in activating the Warburg phenomenon

Isocitrate dehydrogenase (IDH) is the catalytic enzyme responsible for converting isocitrate to α-ketoglutarate (α-KG). Isoform 1 is located in the cytoplasm, while isoforms 2 and 3 are localised in the mitochondria.[46] Mutations of IDH isoforms occur due to arginine replacement at codon 132, resulting in new enzyme activity that further reduction of α-KG to 2-hydroxyglutarate (2HG).[47]

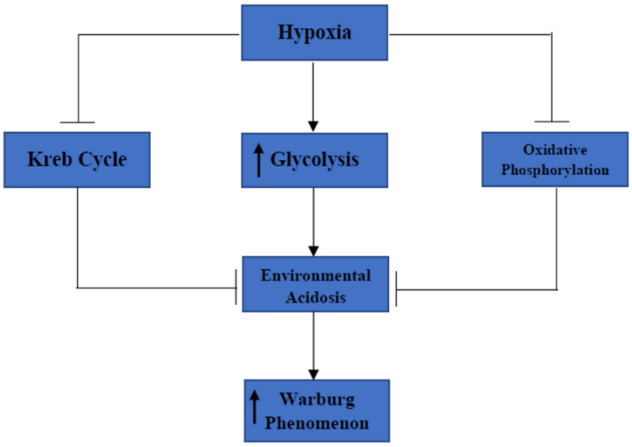

Figure 3: Role of hypoxia in inducing the Warburg phenomenon.

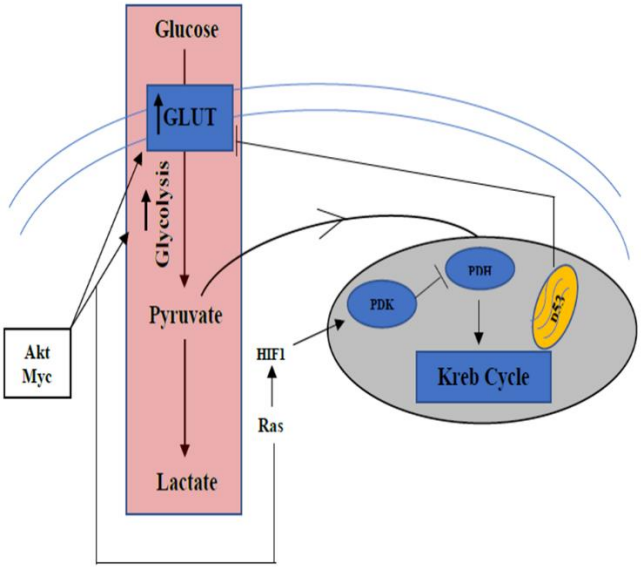

Figure 4: Role of oncogenic activation on glucose metabolism inducing the Warburg phenomenon (highlighted).

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Table 1: Post-translational modifications of proteins linked to the Warburg effect

Protein	Function	Modification	Effect
HK II	Glycolysis	Phosphorylation at T-473	Increases mitochondria hexokinase II Interaction
PFK-2	Activator of PFK-1	Phosphorylation at S-461	Activates PFK 1 in glycolysis
	Glycolysis, Coactivates HIF-1	Hydroxylation at P-403/408	Promotes transactivation of HIF-1
PKM2	Glycolysis	Phosphorylation at Y-105	Inhibits glycolysis and promotes other anabolic reactions required for tumour growth
	Glycolysis	Acetylation at K-305	Reduces PKM2 activity and decreases tumour growth
PDH	TCA Cycle	Phosphorylation at Y-243	Inhibits the TCA cycle and increases aerobic glycolysis
LDH-A	Glycolysis	Phosphorylation at Y-10/83	Promotes LDH tetramer formation and activates aerobic glycolysis
HIF-1α	Activates glycolysis	De-SUMOylation	Stabilises HIF-1α

HK – hexokinase, PFK – phosphofructokinase, PKM - pyruvate kinase muscle isozyme, PDH – pyruvate dehydrogenase, LDH - lactate dehydrogenase

This mutation leads to 2HG accumulation, which then inhibits histone demethylases, **α**-KG-dependent nuclear dioxygenases, collagen prolyl-4-hydroxylase**,** ten-eleven-translocation **(**TET) family of 5-methylcytosine hydroxylases and HIF prolyl hydroxylase domain (PHD), concomitantly, stabilising and activating of HIF1 while causing a genome-wide change of histone and DNA methylation (Figure 5).[31,48,49]

Pyruvate dehydrogenase complex hypothetical mechanism
When pyruvate accumulates in the cytosol, it is converted into acetyl-CoA or lactate. These processes are catalysed by pyruvate dehydrogenase complex (PDC) and LDHA.[14] During the synthesis of these enzymes, irrespective of the oxygen condition, PDC is three times more likely to encounter an error in the transcription process than LDH as the complex is made up of three enzymes. This hypothesis, where at least one of the enzymes is missing, may be responsible for developing cancer phenotype and switching from cellular respiration to aerobic glycolysis.[50] Studies have shown a higher incidence of cancer death in non-diabetic patients when compared with diabetic patients.[51-53] This has been attributed to the ability of cells in diabetics to maximise the relatively scarce glucose supplies by ensuring flawless PDC synthesis to avoid conversion of pyruvate to lactate.[50]

Metabolite exchange and mitochondrial membrane transporters
The sole transporter responsible for transporting anionic metabolites across the outer membrane of the mitochondria to maintain the mitochondrial energy homeostasis is the voltage-dependent anion channel (VDAC). Closure of VDAC favours aerobic glycolysis by lowering cytosolic ATP/ADP ratio and limiting oxidative phosphorylation.[54] Glutamate, protein kinase A, HK II, NADH, bcl2 family members, acetaldehyde, and free tubulin are some regulators of the VDAC transport mechanism.[55,56] The concentration of free tubulin in cancer cells is very high, inducing VDAC closure, in the process activating aerobic glycolysis.[54]
Adenine nucleotide transporter/translocator (ANT) moves ATP between the cytosol and mitochondria as ATP^{4-} and ADP^{3-} respectively. Among the four isoforms, ANT2 is responsible for ATP-ADP exchange and is highly expressed in all proliferating cells.[57] For every ATP cycle, the matrix expels one negative charge to the cytosol giving a negative mitochondrial membrane potential ($\Delta\Psi$), thereby making cytosolic proton motive force (ΔGp) greater than the matrix.[54,58] Interestingly, in cancer cells, an electroneutral ATP-Mg/Pi carrier is responsible for ATP mitochondrial transport despite ANT2 abundance.[59] The reason is due to ANT2 inactive nature and inability to maintain $\Delta\Psi$ after respiratory inhibition in the mitochondria. Hence, the preferred electroneutral carrier will bring about loss of ΔGp and lower cytosolic ATP/ADP ratios favouring aerobic glycolysis.[54]

Targeting Warburg phenomenon for cancer therapy

Aerobic glycolysis is the only metabolic pathway that can match ATP demand in cancerous tissues, making it a therapeutic target for anti-cancer therapy via inhibition.[60] Inhibiting the synthesis of glucose transporters and glycolytic rate-limiting enzymes, reducing blood glucose, membrane transporter effectors and diet modulation are also probable therapeutic mechanisms to reverse the Warburg effect.[12,61,62] Chemical compounds such as 2-deoxy-glucose, pimozide, 3-bromopyruvate and dichloroacetic acid target this phenomenon to reverse altered metabolism.

2-Deoxy-D-glucose (2-DG)
This compound is a synthetic analogue of glucose which competitively inhibits GLUTs and glycolysis. For its mechanism, upon cell entry by GLUTs, HK phosphorylates 2-DG into 2-deoxy-D-glucose-6-phosphate (2-DG-6-P), which cannot be metabolised further by phosphoglucose isomerase.[63] The accumulation of 2-DG-6-P, non-competitively and competitively inhibits HK and PGI, respectively, disrupting glycolysis and oxidative phosphorylation, leading to decreased intracellular ATP production, decreased cell growth, and blocked cell cycle and cell cycle death.[64] Low ATP production increases AMP/ATP ratio and AMP kinase (AMPK), induces phosphorylation of downstream targets, such as mTOR. It also induces tumour necrosis factor (TNF) binding to the transmembrane mediating apoptosis and death.[61] 2-DG treatment generates other metabolites which alter glucose metabolism in tumour cells and act as biological effectors of the Warburg phenomenon.[63]

Dichloroacetic acid (DCA)
Dichloroacetic acid (DCA) is a structural analogue of pyruvate which ensures PDC remains in its active unphosphorylated form by inhibiting PDKs and the complex turnover.[65] The activation of PDC by DCA is consistent with extended lowering of lactate in the microenvironment, degradation of HIF1, reduction of the hypoxic microenvironment and other dynamic effects which remain after systemic clearance of DCA.[61,66]
3-Bromopyruvate (3-BP): 3-Bromopyruvate (3-BP) is a structural analogue of lactate; thus, it is transported into the cells by lactate transporters as it cannot structurally differentiate it. 3-BP inhibits HK II upon cell entry, truncating glycolysis and ATP production.[67] Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) pyruvylation is another mechanism through which 3-BP reverses the Warburg phenomenon. This process makes GAPDH lose its enzymatic activity, disturbing aerobic glycolysis and tumour progression.[68,69] 3-BP has exhibited promising results against patients with advanced refractory epithelial ovarian cancer in clinical studies.[70]

Pimozide
The antipsychotic Pimozide elicits its anti-Warburg effect by hindering glucose uptake, ATP level, lactate production, reducing the extracellular acidification rate and suppressing PKM2 expression. These activities, both *in vitro* (MCF-7, MCF-10A and MDA-MB-231 cells) and *in vivo* (MCF-7 tumour xenograft model), were attributed to the increased expression of p53 via PI3K/Akt/MDM2 signalling pathway inhibition consequently downregulating PKM2 expression.[71]

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Novel promising compounds

BAY876, glupin, PFK-158, lonidamine and other small molecule candidates are novel therapeutic interventions that have been reported to show promising properties in targeting and reversing the Warburg phenomenon.[70]

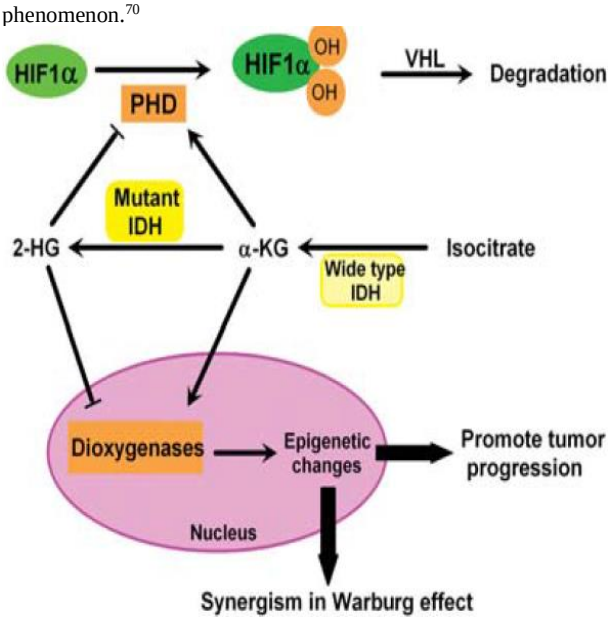

Figure 5: Role of isocitrate dehydrogenase (IDH) mutations in activating the Warburg effect. IDH - Isocitrate dehydrogenase, PHD - prolyl hydroxylase domain

Conclusion

In line with this review, most mechanisms induce the Warburg effect by overexpressing GLUTS, causing abnormal function and regulation of glycolytic enzymes, elevating glycolytic rate and diminishing electron transport chain. These processes favour the metabolic plasticity of tumours and may also be responsible for possible chemoresistance of the cancer cells. Understanding these mechanisms is required for clarity on abnormal components of tumour cell metabolism to uncover novel therapeutic targets, strategies and improved therapeutics. However, there might be little success translating the therapeutic strategy of targeting the Warburg phenomenon into clinical practice. This may result from significant toxicities posed by these molecules in inhibiting these metabolic enzymes in non-target cells, especially those of the immune system and stem cells that utilise aerobic glycolysis. Hence, future research should focus on bypassing these toxicities through techniques such as imaging technology for selective targeted delivery to the cancer cell or near the tumour intraarterially and micro-encapsulation. The development of therapeutic agents with high specificity for molecular targets that are overexpressed in cancer cells as well as alternative pathways utilised by these tumour cells for metabolic plasticity is worth exploring.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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