REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Role of Glycolysis in Breast Cancer

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Abstract

Breast cancer is one of the most common cancer types in women with a high death rate worldwide. Disturbance in glucose metabolism was proposed to be a pathogenetic mechanism of breast cancer. The Warburg's effect in cancer is considered an important cell metabolic reprogramming process. Tumor causes an increase in aerobic glycolysis uncoupled with glucose oxidation leading to rise in glucose uptake, lactate production and reduction in oxidative phosphorylation. Therefore, this reprogramming increases the persistence of cancer cells with low adenosine triphosphate (ATP) yield and this is associated with mitochondrial respiration inhibition. Consequently, this metabolic alteration provides cancer cell with a survival advantage because the high rate of aerobic glycolysis in cancer leads to increase of glycolytic branching pathways including PPP and SBP which supply cancer cell with NADPH, nucleotides and amino acids. Furthermore, the inhibition of mitochondrial GO supplies cancer cell with apoptosis resistance. The enhancing of PDC and GO (PDK inhibition) in cancer cells leads to increase in the mitochondrial membrane potential, that furthermore increases the threshold of activation of the mitochondrial permeability transition pore and mitochondrial dependent apoptosis.

Keywords: breast cancer; glucose oxidation; aerobic glycolysis; AKT; c-Myc; p53.

1. Introduction

Breast cancer is one of the most common cancer types in women, representing 11.7% (2.3 million) of new cancer cases in 2020 with a high death rate worldwide **(Sung et al., 2021)**. The Warburg's effect in cancer is considered an important cell metabolic reprogramming process. Tumor causes an increase in aerobic glycolysis uncoupled with glucose oxidation leading to rise in glucose uptake, lactate production and reduction in oxidative phosphorylation. Therefore, this reprogramming increases the persistence of cancer cells with low adenosine triphosphate (ATP) yield **(Warburg, 1952)**.

The aerobic glycolysis performed by cancer cells is associated with mitochondrial respiration inhibition **(Sutendra & Michelakis, 2013)**. This shift in metabolism provides the cancer cells with a higher ability to survive. Subsequently, glycolytic splitting pathways including hexose monophosphate pathway (HMP) and serine biosynthetic pathway (SBP) are activated to supply cancer cells with nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), nucleotides and amino acids **(Locasale et al., 2011)**.

Hypoxia inducible factor-1alpha (HIF-1α) is

upregulated in tumor cells. It is responsible for increasing the expression of GLUT-1, pyruvate dehydrogenase kinase 1 (PDK-1), pyruvate dehydrogenase kinase 4 (PDK-4), lactate dehydrogenase A (LDH-A) and glycolytic enzymes. PDK inhibits pyruvate dehydrogenase complex (PDC) activity leading to decrease in glucose oxidation **(Kooshki et al., 2022)**. Notably, it was reported that inhibition of PDK and increase of glucose oxidation in cancer cells could increase mitochondrial permeability and the intrinsic pathway of apoptosis **(Kim et al., 2006)**.

In normal cells, p53 regulates cell metabolism by suppressing the expression of both GLUT-1 and phosphofructokinase 1 (PFK1) and decreasing the rate of pentose phosphate pathway (PPP). It also enhances mitochondrial glucose oxidation and oxidative phosphorylation. On the other hand, p53 is mutated in cancer cells, acquiring modified metabolic profile **(Jacquier et al., 2022)**. The deficiency of functional p53 in cancer cells contributes to the metabolic shift towards aerobic glycolysis **(Lacroix et al., 2019)**.

In addition, c-Myc exerts a crucial role in oncogenic metabolism. It is overexpressed in cancer cells and it increases the liberation of GLUT-1, PDK-1 and LDH-A through aerobic glycolysis in cancer metabolism **(Hu et al., 2020)**. Also, PI3K/AKT signaling has an obvious up-regulatory effect on the transcription of GLUT-1 and hexokinase-2 (HK-2) leading to the increase in aerobic glycolysis. Additionally, phosphoinositide-3-kinase protein kinase P/AKT (PI3K/AKT) signaling promotes lipid synthesis in cancer cells **(Zhang et al., 2021)**.

Cellular storing of lipids is important for tumor development, where β-oxidation is an essential source of ATP in cancer cells **(Bensaad et al., 2014)**. Inhibiting β-oxidation can be considered as a potential anti-cancer strategy. Moreover, fatty acid oxidation inhibition could increase cellular deposition of long-chain fatty acids and death of cancer cells without affecting normal cells **(Halama et al., 2018)**.

2. Metabolism in cancer cells

Cancer disturbs cell growth and proliferation, and requires cellular building blocks, such as nucleic acids, lipids, and proteins. Cancer cells often have altered metabolism that allows them to accumulate metabolic intermediates as sources of these building blocks which maintain their proliferation and survival **(Currie et al., 2013)**.

The Warburg's effect is the most obvious metabolic alteration in cancer cells. The Warburg's effect in cancer is considered as an important cell metabolism reprogramming as tumor shows an increase in aerobic glycolysis uncoupled with glucose oxidation leading to increase in both glucose uptake and lactate production and decrease in both oxidative phosphorylation and mitochondrial respiration. Therefore, this reprogramming increases cancer cell survival although the small ATP yield **(Warburg, 1956)**.

Positron emission tomography (PET) imaging of a radioactive fluorine-labeled glucose analog uptake, 18F-fluorodeoxyglucose (18F-FDG) is successfully applied in the clinic for purpose of tumor diagnosis, staging and drug responsiveness monitoring **(Almuhaideb et al., 2011)**.

During normal cellular metabolism in the presence of oxygen, glucose undergoes glycolysis in the cytoplasm to produce pyruvate that oxidized to Acetyl-CoA into mitochondria then the last one enters the citric acid cycle to produce reducing equivalents for oxidative phosphorylation, so aerobic glycolysis here is coupled with glucose oxidation **(Vander Heiden et al., 2009)**.

When oxygen is limited, excess pyruvate is fermented to lactate in the cytoplasm. Proliferating cells typically use oxidative phosphorylation due to its efficiency; with one glucose molecule undergoing complete oxidation to yield ∼36 ATP molecules versus 2 ATP that are obtained from anaerobic glycolysis **(DeBerardinis et al., 2008)**; so that in cancer cell there is a high rate of ATP production during aerobic glycolysis compared to oxidative phosphorylation in normal cell **(Chandel, 2021)**. So, the Warburg's effect is the use of fermentation even in the presence of oxygen and is characterized by an increase in glucose consumption rate, a decrease in oxidative phosphorylation, and high generation of lactate **(Chandel, 2021) (Figure 1)**.

Cancer cell prefers converting excess pyruvate to lactate rather than transporting excess pyruvate into mitochondria to maintain OXPHOS because cancer cell has only a modest increase in its consumption of ATP relative to its need for precursor molecules and reducing equivalents such as NADPH. Glucose catabolism is important provider of these precursors and reducing equivalents. In contrast, tricarboxylic acid cycle (TCA) cycle activity (that

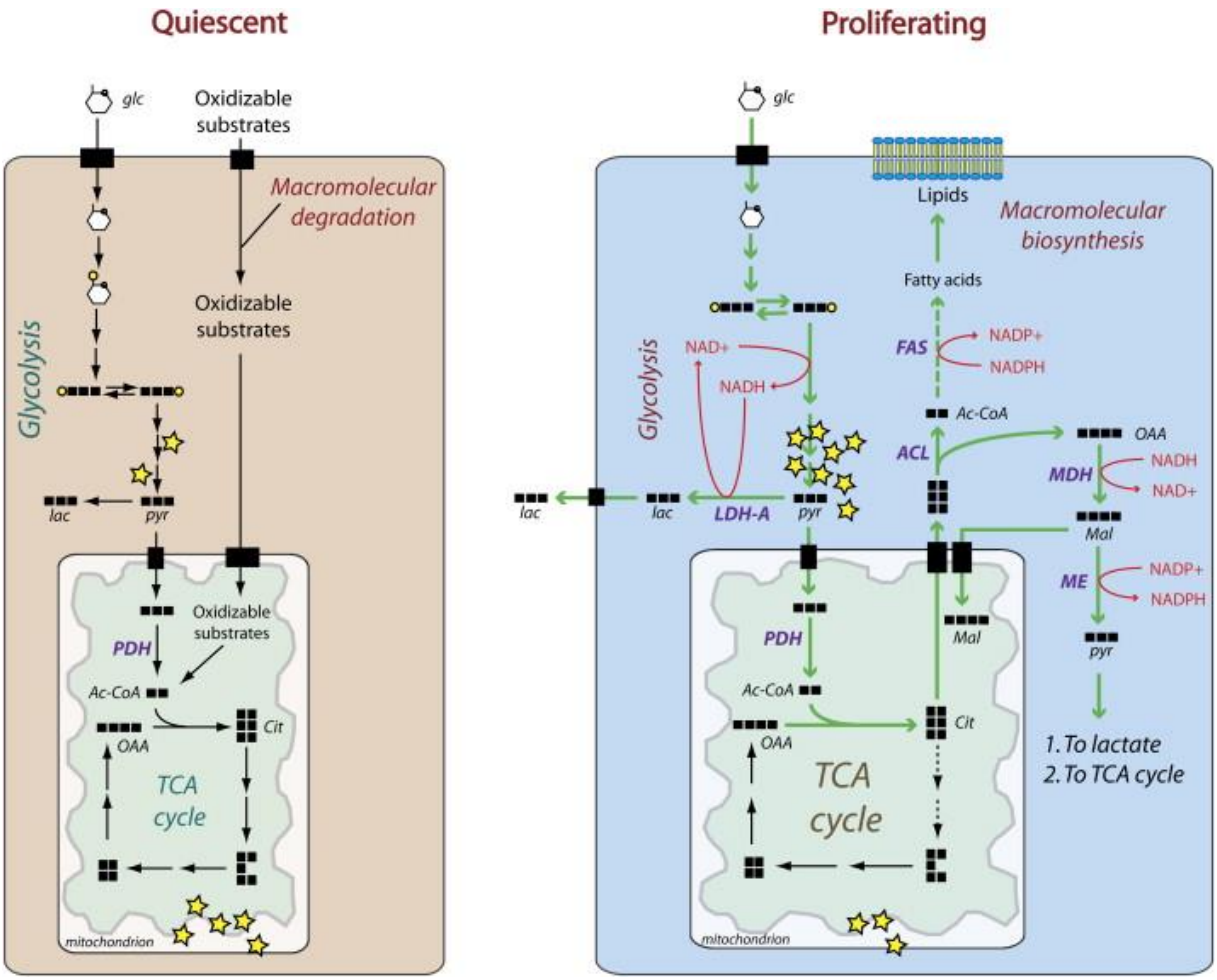

Figure 1: Aerobic glycolysis in proliferating cell or cancer cell versus normal cell glycolysis showing Warburg's effect in cancer cells **(DeBerardinis et al., 2008)**.

yields ATP & NADH) is the major negative factor of glucose metabolism. So, by converting excess pyruvate to lactate, cancer cells prevent high accumulation of NADH, decrease ATP yield and maintain continuous cytosolic glucose metabolism without feedback inhibition by excess ATP from mitochondria **(Pavlova & Thompson, 2016)**.

High glycolytic rate follows the decrease of mitochondrial activity in cancer cell leads to high tumor proliferation rate. Metabolism of pyruvate in the cytoplasm and impeding its oxidation in mitochondria has many results. Firstly, through preventing pyruvate entry into the mitochondria, cancer mitochondria are deprived of their building blocks thus inhibiting mitochondrial activity and consequently hindering mitochondrial-dependent apoptosis **(Shiratori et al., 2019)**. This process can happen as apoptosis is initiated via the pro-apoptotic mediators' efflux from the mitochondria to the MTP (a mega-channel which is voltage- and redox-gated) **(Zhou et al., 2022)**. The inhibition of mitochondrial activity in cancer cells increases mitochondrial hyperpolarization and inhibits the production of reactive oxygen species (ROS), this increases the opening threshold of the MTP that results in apoptosis inhibition in cancer cell **(Hernández-García et al., 2010)**. Secondly, through the metabolism of pyruvate in the cytoplasm by LDH producing lactate, acidosis resulting from this process can initiate the breakdown of the extra-cellular matrix, facilitating tumor proliferation and metastasis **(de la Cruz-López et al., 2019)**. Thirdly, by preventing pyruvate oxidation in the mitochondria, this facilitates its shunting through anabolic biosynthetic pathways (such as PPP and SBP) that are essential for the synthesis of many building blocks that are important for cancer cell **(DeBerardinis et al., 2008)**.

The GO produces ~36 ATP per one glucose molecule, compared to 2 ATP per one glucose molecule provided from aerobic glycolysis in

cancer. Thus, by increasing glycolytic rate, cancer cells can produce a sufficient amount of ATP. This is occurred by the increase of the transcription and the expression of glucose transporters and glycolytic enzymes, for enhancing the glucose uptake and glycolytic ATP production. This pathway shows the cause of the PET imaging (that measures glucose uptake in the cancer cell) that still the most sensitive tool for cancer diagnosis **(Sutendra & Michelakis, 2013)**.

3. Glycolytic pathway in cancer cells

Glycolytic Pathway **(Figure 2)** is a very critical target for cancer therapeutic promising agents. In cancer cell, glucose uptake into cells occurs by glucose transporters, after that it is phosphorylated by HK2 to form glucose-6-phosphate. Glucose-6-phosphate is converted to fructose-6-phosphate by glucose-6-phosphate isomerase to enter glycolysis or shunted into SBP for amino acid biosynthesis or into PPP by glucose-6-phosphate dehydrogenase (G6PDH) for nucleotide synthesis process. The PPP, moreover, combats oxidative stress by production of NADPH **(Cairns et al., 2011)**.

Fructose-6-phosphate is converted to fructose-1,6-bisphosphate by PFK-1. Fructose-1,6-bisphosphate is then transformed either to glyceraldehyde-3-phosphate to enter glycolysis or converted to dihydroxyacetone phosphate that is essential for lipid synthesis. In glycolysis, glyceraldehyde-3-phosphate is transformed to glycerate-2-phosphate through glucose-3-phosphate dehydrogenase (G3PDH) and then glycerate-2-phosphate is converted to phosphoenol pyruvate through enolase enzyme. Pyruvate kinase (PK) catalyzes step of an ATP-liberating in glycolysis where phosphoenol pyruvate is converted into pyruvate plus ATP production. Finally, through the glycolysis pathway, LDH-A converts pyruvate to lactate producing nicotinamide adenine dinucleotide (NAD+) from NADH; thus NAD+ is essential for constant flux in the glycolysis **(Lunt & Vander Heiden, 2011)**.

Cancer cells are highly dependent on aerobic glycolysis, and this presents a critical promising therapeutic targets as anti-cancer. On the other side, both of cancer cells and normal proliferating cells have the Warburg effect and it is a challenge to selectively target cancer metabolism not proliferating cell metabolism. Fortunately, a lot of parameters such as GLUT1, HK-2, PK, LDH-A and G6PDH are overexpressed in cancer and are a good target for cancer cell killing **(Zhang & Yang, 2013)**. GLUT1 is considered as the superior glucose transporter in several types of cancer **(Zambrano et al., 2019)**.

Lactate overexpression is one of critical hallmarks in cancer cell. The first cancer metabolic target therapy was LDH-A, an enzyme that produces lactate from pyruvate and produces NAD+ from NADH. Furthermore, enhancing continuous glycolysis, the overproduction of lactate result in an acidic tumor microenvironment associated with metastasis, recurrence of the tumor and poor survival **(Daverio et al., 2023)**.

Moreover, several of oncogenes are involved in the metabolic switch from OXPHOS to glycolysis in cancer cells, such as AMP-activated protein kinase (AMPK) **(Wu et al., 2007)**, HIF-1α **(Swietach et al., 2007)**, Myc **(Osthus et al., 2000)**, PI3K/Akt/mTOR **(Elstrom et al., 2004)** and rat sarcoma viral oncogene homolog (RAS) **(Telang et al., 2006)**. So, targeting of previous oncogenes can selectively kill tumor cells by repressing glycolytic pathway.

Warburg hypothesized that in cancer cells, mitochondrial respiration becomes defective, followed by high dependence on glycolysis for ATP yield **(Warburg, 1956)**, but this theory has been disputed recently and shall be reviewed. However, glycolysis is the well-defined metabolic pathway of tumors, it is not the only property of every human tumor. Indeed, in cancer cells with high glycolytic rate, there is no existence of mitochondrial oxidative metabolism defect **(Moreno-Sánchez et al., 2007)**. Fogal and colleagues showed that increased rates of glycolysis with no sufficient OXPHOS, may not be useful for breast cancer proliferation **(Fogal et al., 2010)**.

4. Factors regulating glycolytic pathway in cancer

There are important factors that regulate glycolysis in cancer cell **(Figure 3)**.

4.1. c-Myc

The c-Myc oncogene is overexpressed in cancer cells **(Miller et al., 2012)** and it has an important role in disturbing the mechanism of normal oxygen sensing and in regulation of glycolytic enzymes such as LDH-A, which converts pyruvate to lactate, GLUT1, HK2, phosphofructokinase-M (PFKM), and enolase 1 (ENO1) **(Mushtaq et al., 2015)**.

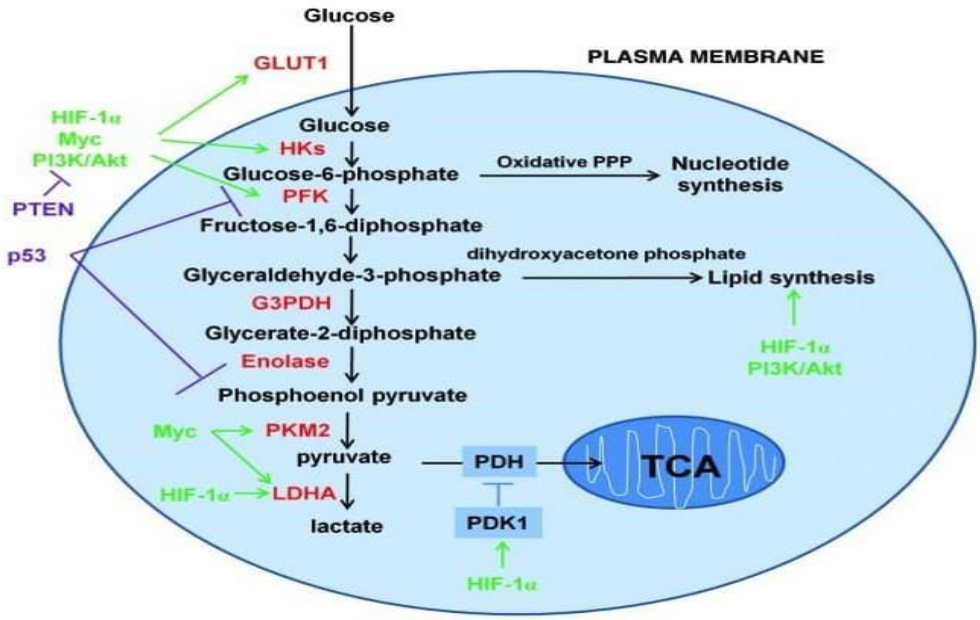

Figure 2: Glycolytic pathway in cancer cell with key modulator factors **(Zhang & Yang, 2013)**

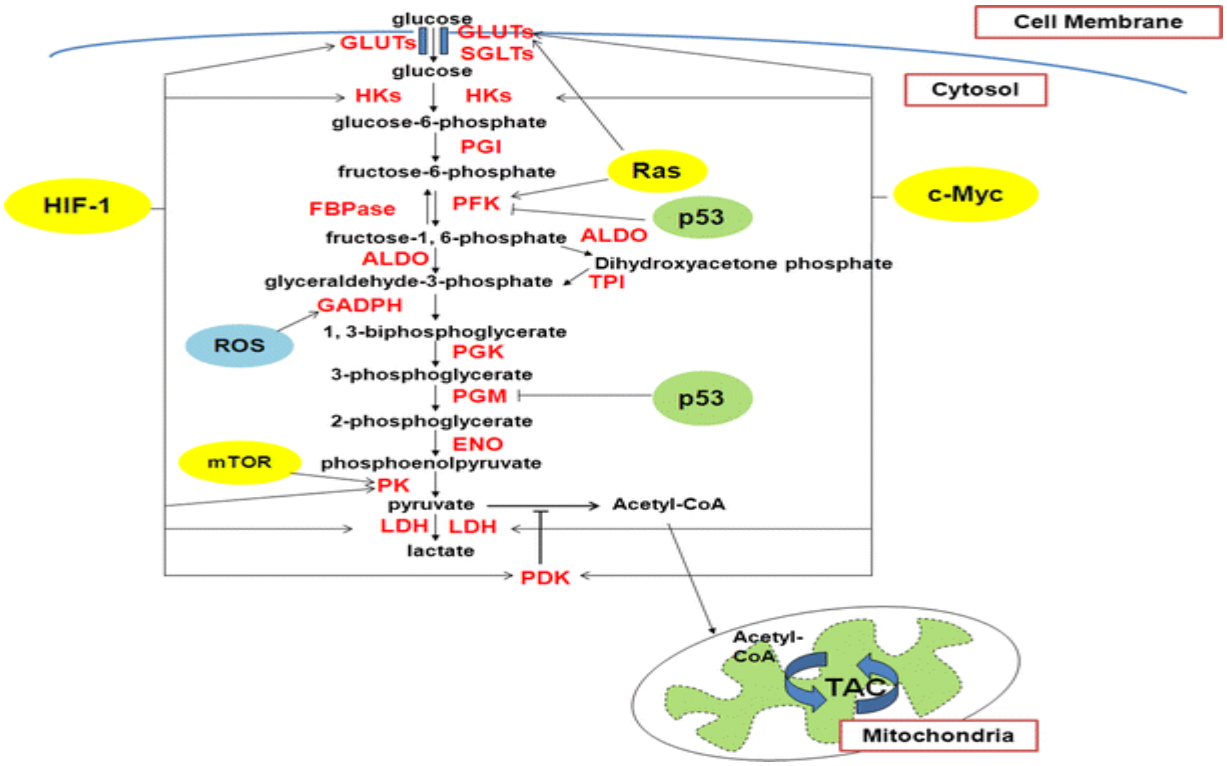

Figure 3: Significant glycolytic enzymes and oncoproteins regulating glycolytic pathway in cancer cells **(Hu et al., 2014)**

Through the up-regulation of these enzymes, c-Myc enhances the Warburg effect and the ability of cancer cells to convert glucose to pyruvate resulting in high rate of aerobic glycolysis uncoupled with GO **(Fadaka et al., 2017)**.

4.2. p53

p53 is a tumor suppressor gene and its expression in cancer cell is inactivated and converted to mutated one to avoid P53 inhibitory effect on many glycolytic enzymes especially GLUT-1 in cancer metabolism **(Li et al., 2022)**. p53 role in glycolytic pathway in normal cell is to block glycolysis by decreasing the expression of GLUT-1 and it also

decreases PPP by inactivating G6PD **(Bensaad et al., 2006)**. On another hand, PPP is important for cancer cell as it is activated to obtain NADPH and amino acids **(Patra & Hay, 2014)**. It was proved that loss of p53 activity mutation directly enhances the expression of PDK and induces HIF1α transcription, activity and stability **(Li et al., 2022)**.

4.3. PI3K/AKT signaling

PI3K/Akt signaling acts as a master regulator of glucose uptake because PI3K/AKT signaling activates both the glucose transporter GLUT1 mRNA expression and GLUT1 protein translocation from the endomembrane to the cell surface; increasing both glucose utilization and the rate of aerobic glycolysis **(Wieman et al., 2007)**. Additionally, AKT enhances the activity of the HK, which phosphorylates glucose molecules, so prevents glucose efflux back into the extracellular matrix, also AKT activates PFK enzyme, which catalyzes the key irreversible step of glycolysis **(Gottlob et al., 2001)**.

Furthermore, tumor 18F-FDG-PET signal intensity is highly dependent on the level of PI3K/AKT pathway activity and is deactivated by PI-3 kinase and receptor tyrosine kinase inhibitors **(Benz et al., 2011)**. Moreover, exogenous expression of an active form of Akt alone enhances glycolysis and this helps in restoring cell size, viability, mitochondrial potential and ATP levels in culture medium that is dependent on the presence of glucose with growth factor-deprived cells **(Plas et al., 2001)**.

The active form of AKT prevents a fall in ATP levels that is triggered by the loss of cellular attachment **(Schafer et al., 2009)**. Additionally, AKT signaling is essential to high glucose uptake in physiological remodeling of increased biosynthetic demand. For example, Akt1targeted deletion in the mouse mammary gland attenuates a lactation-induced increase of glucose uptake, leading to milk production insufficiency **(Boxer et al., 2006)**.

It has been documented that many tumors upregulate AKT for acquiring resistance to standard chemotherapies and targeted therapies. Inhibition of mammalian target of rapamycin complex (mTORC1) leads to the AKT pathway activation, showing the presence of a feedback loop **(Fresno Vara et al., 2004)**.

4.4. Ras

Rat Sarcoma Viral Oncogen Homology (Ras) is oncogenic stimulus that has an important role in facilitating glucose uptake. Ras upregulates GLUT1 mRNA expression and increases cellular glucose consumption. Ras with AKT together in cancer stimulate multiple growth signaling nodes that share an ability to increase cellular access to glucose **(Rajasekhar et al., 2003)**.

4.5. Human inducible factor 1α

The hypoxia inducible factor 1 is responsible for activation of glycolytic genes and this is considered as a critical for metabolic adaptation to hypoxia through enhancing glucose conversion to pyruvate and then to lactate. Moreover, HIF-1 decreases metabolism through the TCA by impeding the gene that encodes PDK1. PDK1 inactivates PDH, which converts pyruvate to Acetyl-CoA that enters the TCA cycle **(Kim et al., 2006)**.

High PDK1 expression in hypoxic cancer cells leads to high ATP production, diminishes hypoxic ROS liberation, and prevents hypoxia-induced apoptosis in cancer cell. Finally, this results in converting glucose metabolites from the mitochondria to aerobic glycolysis to maintain ATP levels and to prevent toxic ROS production **(Bonnet et al., 2007)**.

Glycolytic enzymes such as GLUT-1, LDH-A, PDK and the lactate exporter are over expressed in cancer while PDH is impaired leading to high glycolytic flux and reduced ability of pyruvate to enter oxidative phosphorylation resulting in high aerobic glycolysis uncoupled with GO **(Fadaka et al., 2017)**.

4.6. Lactate Dehydrogenase-A

The LDH-A is an enzyme that converts pyruvates to lactate and produces NAD+ from NADH. Furthermore, lactate and NAD+ are critical for enhancing continuous glycolysis, the overproduction of lactate leads to an acidic tumor microenvironment associated with metastasis, recurrence of the tumor and poor survival (**Daverio et al., 2023)**.

Moreover, lactate accumulation is involved in the promotion of angiogenesis. Thus, lactate enhances HIF1α stabilization and promotes activation of nuclear Factor Kappa-Light-Chain-Enhancer of activated B Cells (NF-κB) and PI-3K signaling in endothelial cells. It also increases the pro-angiogenic factor VEGF secretion from tumor-associated stromal cells **(Sonveaux et al., 2012)**. High lactate levels also stimulate hyaluronic acid production through fibroblasts, that can contribute

to invasiveness of tumor **(de la Cruz-López et al., 2019)**.

4.7. Pyruvate dehydrogenase kinase

The PDK attenuates activity of PDH; a gate keeper enzyme for GO that produces acetyl CoA from pyruvate. Therefore, PDK prevents the coupling of glycolysis with GO and glycolysis is accomplished in the cytoplasm, where pyruvate is metabolized to lactate without being oxidized in the mitochondria. This metabolic shift is a fundamental process in cancer cells **(Sutendra & Michelakis, 2013)**.

The regulation of PDK in cancer cell is activated by HIF1α as PDK is considered as a gate-keeping mitochondrial enzyme which regulates the flux of carbohydrates by pyruvate from the cytoplasm into the mitochondria, where GO process occurs **(Kim et al., 2006)**.

4.8. Hexokinase II

Hexokinase II is activated in cancer cell where it converts glucose to glucose-6-phosphate by phosphorylation thus initiates the glycolytic pathway, inhibiting MTP, suppressing apoptosis **(Mathupala et al., 2009)**. Hexokinase expression is increased by many oncogenic factors including HIF1α, AKT signaling and loss of function mutations to p53 **(Woldetsadik et al., 2017)**.

5. Conclusion

The current review provided a concise summary on the glycolytic pathway in cancer cells with different factors and oncogenes implemented in reprogramming of cancer cell metabolism. The present work also demonstrated a promising target of glycolytic pathway for many agents to reverse the cancer cell reprogramming causing cancer cell death.

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