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Review of Glucose Metabolism Dysregulation in Cancer

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Abstract of the Thesis

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It has been known for over 60 years that tumor metabolism is strikingly different than normal tissue metabolism. In this thesis, I review literature pertinent to cancer metabolism and how the altered regulation of metabolism helps tumors to meet their metabolic needs. Otto Warburg's pioneering studies on tumors first demonstrated that tumors rely on glycolysis even in the presence of oxygen. Warburg proposed that the high glycolytic rate in tumors was due to cancer cells' inability to perform mitochondrial oxidative phosphorylation (OXPHOS). Recent investigations do not support the idea of dysfunctional OXPHOS in cancer cells

A new understanding of Warburs'g original observations has emerged recently. The new working model has been termed two-compartment metabolism. This model underlines the extensive observed cooperation between non-transformed supporting stromal tumor cells and malignant cells within tumors. Evidence indicates that cancer cells condition stromal cells to secrete important metabolites (such as lactate) as byproducts of elevated glycolysis. Cancer cells import lactate and convert it to pyruvate, which enters the mitochondrion and drives OXPHOS.

This not only supplies ATP to cancer cells but provides crucial biosynthetic precursors for the synthesis of nucleotides, amino acids and lipids.

Cancer cells dysregulate the uptake of glucose and the regulatory enzymes in glucose metabolism as well. Some of the main enzymes include hexokinase, pyruvate kinase, lactate dehydrogenase, pyruvate dehydrogenase, and pyruvate kinase. Some of the changes in reconfigured cancer metabolism are due to the expression of specific isozymes of regulatory enzymes, others are due to changes in levels of expression. . The expression of particular isozymes presents the opportunity to create chemotherapeutics with higher specificity than currently available treatment regimens and hopefully better outcomes for patients. In the emerging field of therapies designed to target the aberrant tumor metabolisms some have shown promising potential.

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List of Abbreviations

ADP Adenosine diphosphate

Acetyl-CoA Acetyl-coenzyme A

α Alpha

AMP Adenosine monophosphate

AMPK AMP-activated protein kinase

ATP Adenosine triphosphate

β Beta

DCA Dichloroacetate

ETC Electron transport chain

$FADH_2$ Reduced flavin adenine dinucleotide

FBP Fructose 2,6-bisphosphate

G6P Glucose-6-phosphate

GLUT Glucose transporter

HIF-1 Hypoxia inducible transcription factor 1

HIF-1α Hypoxia inducible factor 1 α subunit

HIF-1β Hypoxia inducible factor 1 β subunit

HK Hexokinase

LDH lactate dehydrogenase

Myc Transcription factor

NADH Reduced nicotinamide dinucleotide

OSI Oncogene-induced senescence

PDC Pyruvate dehydrogenase complex

PDH Pyruvate dehydrogenase

PDK Pyruvate dehydrogenase complex kinase

PEP phosphoenolpyruvate

PK Pyruvate kinase

SGLT Sodium-dependent glucose transporter

siRNA small interfering RNA

TCA Tricarboxylic acid cycle (Krebs's cycle)

VDAC Voltage-dependent anion channel

Metabolism in Cancers

Normal cells derive most of their energy in the form of adenosine triphosphate (ATP) from oxidative phosphorylation at the end of the electron transport chain (ETC). Glycolysis is coupled with the Krebs cycle, which produces the reducing agents NADH and $FADH_2$. These reducing agents are then fed into the ETC to produce ATP. Based on earlier observation cancer tumor metabolism was determined to be intrinsically different from normal tissue metabolism. Earlier studies showed that tumors have an increased glycolytic rate and decreased mitochondrial oxidative phosphorylation activity. In tumor cells mitochondrial ATP production through oxidative phosphorylation accounts for 10-25% of glucose oxidized compared to 70% in non-transformed cells under normal conditions. (Moreno-Sanchez, Marin-Hernandez et al. 2014) (Zheng 2012). Accordingly, to satisfy the energetic needs tumors take up more glucose from blood than normal tissue (Warburg, Wind et al. 1927). This suggests a reconfiguration of the regulatory pathways in charge of glucose uptake and glucose metabolism. Studies with individual tumor cell lines showed that these tumor cells obtain most of their ATP through glycolysis even in the presence of oxygen. This has been termed aerobic glycolysis or the Warburg effect (Vander Heiden, Cantley et al. 2009).

The metabolic needs of cancer cells are very different compared to normal growing cells (Hanahan and Weinberg 2011). Cancer cells diverge crucial metabolites from glycolysis and the Krebs cycle for anabolic pathways to satisfy the production of biomolecules needed for cell growth, i.e. lipids, nucleic acids, and amino acids (Vander Heiden, Cantley et al. 2009). Thus cancer cells need the appropriate genetic configuration to successfully satisfy their metabolic requirements.

Recent investigations point towards a different model that explains phenomena observed by Otto Warburg. This new perspective has become known as two-compartment metabolism (Salem, Whitaker-Menezes et al. 2012) or reverse Warburg effect (Bonuccelli, Whitaker-Menezes et al. 2010). This model (see below) explains the increased glycolytic rate of tumors, and also underlines the importance of metabolic heterogeneity. It has been documented that cancer cells within a tumor possess remodeled metabolic circuitry, along with the support of stromal (non-transformed) tumor cells. This review will focus on some of the genetic adaptations of cancer cells needed for malignancy and proliferation, underlining the importance of mitochondrial glucose metabolism as a chemotherapeutic target.

Two-compartment Tumor Metabolism

Studies have shown a different behavior in cancer cells grown as isolated cell lines away from the tumor mass, than tumor cells grown in a tumor environment, suggesting that the interactions between cancer cells and non-transformed stromal cells play an important role in tumor growth and cancer progression (Warburg, Wind et al. 1927, Bonuccelli, Whitaker-Menezes et al. 2010). The investigations have shown that cancer cells *in tumors* secrete high levels of reactive oxygen species (Figure 1). This conditions the associated stromal cells to activate autophagy and switch to a more glycolytic production of ATP while secreting monocarboxylic acids such as lactate (Figure 2). Lactate in turn can be utilized by the malignant cells to derive ATP through oxidative phosphorylation (Op. cit.)

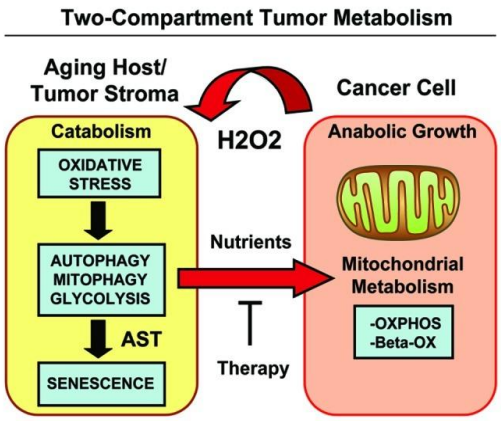

Figure 1. Tumor stromal cell metabolic conditioning by cancer cell.

A new interpretation had to be reached to explain the retained ability tumor cancer cells to use oxidative phosphorylation to produce ATP (Helmlinger, Yuan et al. 1997), along with the elevated glucose uptake of tumors. The two-compartment metabolism model suggests that reconfiguration of elevated glucose uptake in cancer cells is used to generate essential metabolites to satisfy growth requirements. Also, stromal cells produce lactate and glutamine

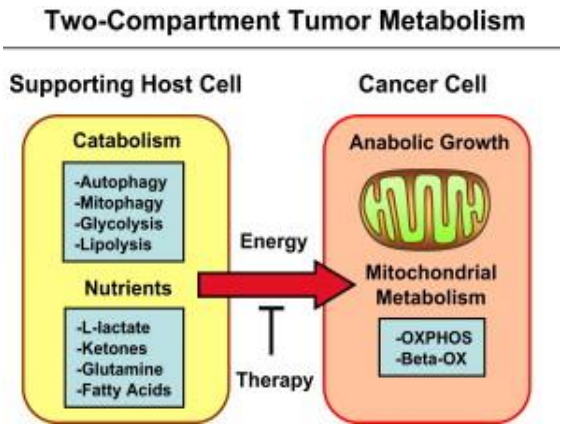

Figure 2. Cancer cell and tumor stromal cell metabolic interactions.

that are used to fuel mitochondrial oxidative phosphorylation in malignant cells. Current investigations suggest an active participation of tumor associated stromal cells in glucose uptake by tumors, while assisting the metabolism of transformed cells. The model builds on the tumor

metabolic behavior described by Otto Warburg, and provides new perspectives on the many phenotypes observed in either tumors or isolated cancer cells *in vitro*.

Tumors' nutrient microenvironment

One of the challenges presented to tumor cells is the availability of nutrients as the tumor grows in size. Cancer cells farther than 100-200 μm from blood supply end up in a hypoxic environment, and thus activate the innate mechanisms of cells to cope with situations with restricted access to oxygen (Helmlinger, Yuan et al. 1997). One of the mechanisms involves the

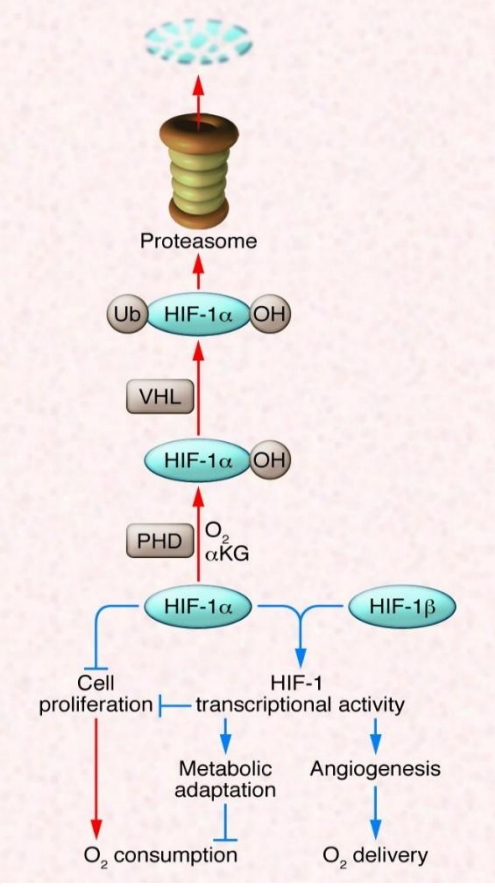

Figure 3. HIF-1α oxygen dependent regulation

hypoxia inducible factor 1 (HIF1). HIF1 is a heterodimeric transcription factor composed of an α and a β subunit. HIF1 regulates the response to cellular stress due to the lack of oxygen. Both HIF-1β and HIF-1α subunits are constitutively expressed, however HIF-1α is readily degraded in the presence of oxygen. Under normoxia HIF-1α is poly-ubiquitylated and tagged for protosomal degradation, this process is illustrated in figure 3 (Semenza 2013). When the availability of

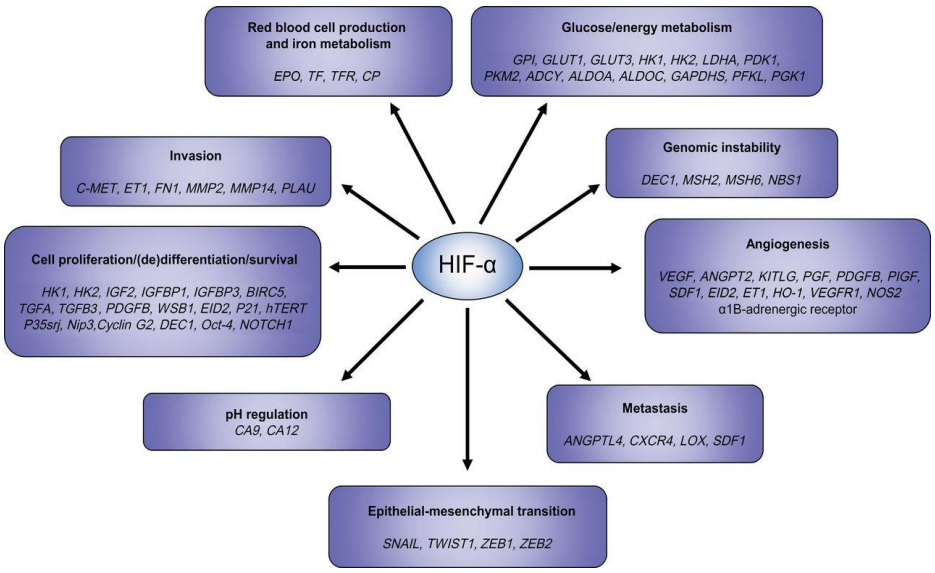

Figure 4 HIF-α Transcriptional regulation

Alteration in tumor	Molecular mechanism
Hypoxia	Decreased ubiquitination
VHL loss-of-function	Decreased ubiquitination
p53 loss-of-function	Decreased ubiquitination
PTEN loss-of-function	Increased synthesis
PI3K/AKT/FRAP signaling	Increased synthesis
SRC gain-of-function	Increased synthesis
$p14^{ARF}$ loss-of-function	Decreased nucleolar sequestration

Table 1 HIF-α regulation

oxygen decreases HIF1 can localize to the nucleus and control up to 60 genes involved in cell survival, angiogenesis, proliferation, glucose transport, and anaerobic glycolysis.

Some of the genes regulated by HIF1 are shown in Figure 4 (Jochmanova, Yang et al. 2013). There are many genetic alterations observed in cancer can perturb HIF-1α expression and stabilization. Table 1 shows tumor alterations that directly or indirectly perturb HIF-1α control, including some oncogenes and tumor suppressors (Semenza 2002). The ectopic expression of HIF-1α in tumor biopsies is associated with a poor prognosis and an increased malignancy (Opt. cit.). Also, the ectopic expression of genes regulated by HIF1 are indicators of advanced and aggressive tumors (Harris 2002). These genes include *GLUT1*, a glucose transporter; *HK2*, *PKM2,* two glycolytic enzymes and *PDK1* kinase regulating the entry of glucose into the TCA cycle and *LDHA*, enzyme which turns pyruvate into lactate. (Harris 2002, Chiavarina, Whitaker-

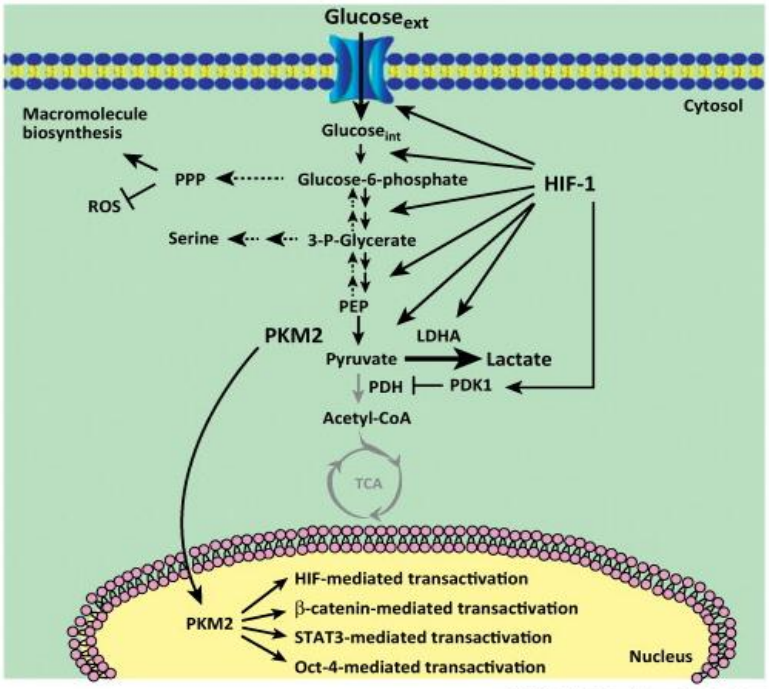

Figure 5. Glycolysis upregulation

Menezes et al. 2010). The context of these enzymes and how they are involved in cancer metabolism is shown in figure 5 (Luo and Semenza 2012).

The contrast of ATP derived from glycolysis or oxidative phosphorylation becomes a problem mainly when glucose is scarce. In this light, it is indispensable for cancer cells to increase the availability of glucose. It has been shown that angiogenesis is a necessary dysregulated process necessary for tumor progression in different cancers (Slominski, Kim et al. 2014). The ability of a tumor to grow depends partially on the recruitment of blood vessels and the regulation of endothelial mitogen signals. Cancer cells metabolic needs go beyond the production of ATP, they also include the anabolic precursors required for growth that can be derived from glucose metabolism (Moreno-Sanchez, Marin-Hernandez et al. 2014). HIF1 and its downstream regulatory molecules play an important role driving the molecular signaling design to overcome the metabolic hurdles presented to tumors.

Glucose uptake

It is known that tumors have an elevated uptake of glucose and an apparent elevated glycolytic rate (Warburg, Wind et al. 1927). It has been shown that tumors fulfill their need for glucose by up-regulating the hexose transporters. There are two families of such membrane proteins, Sodium-dependent glucose transporters (SGLT) and glucose transporters (GLUT). Analyses of tumors have revealed a tissue-dependent dysregulation and over-expression of the SGLT transporters. Also it has been shown that the GLUT1 transporter is over-expressed in multiple cancer cells (Osthus, Shim et al. 2000) (Szablewski 2013). Several studies have shown a relationship between GLUT1 expression and tumor development with poor prognosis

(Szablewski 2013). The uptake of glucose is the initial step in the dysregulation of cancer glucose metabolism. Many factors contribute to the regulation of glucose uptake in normal cells, AMP-activated protein kinase signaling pathway (AMPK) being one of them. Although some evidence suggest a relationship between AMPK and cancer progression, the data seems contextual and highly dependent on the accompanying genetic make-up of the cell (Hardie and Alessi 2013) (Liang and Mills 2013).

Glycolysis Dysregulation I (Hexokinase)

Glycolysis is a tightly regulated process in normal cells. Cancer cells have rewired these control mechanisms in a way to take advantage of these pathways to satisfy their metabolic needs. The first enzyme in the glycolytic pathway is hexokinase (HK). Shown in figure 6, is the highly energetically favorable conversion of glucose into glucose-6-phosphate (G6P).

Figure 6 Phosphorylation of glucose by hexokinase

G6P is the first key molecule in the metabolism of glucose. Once glucose is phosphorylated to G6P, it is unable to cross the plasma membrane thus driving the concentration gradient favoring the uptake of glucose. The possible fates of G6P include ribonucleotide biosynthesis by the pentose pathway, amino acid production by cataplerotic reactions, and ATP production by either substrate level phosphorylation in the cytosol, or oxidative phosphorylation in mitochondria. There are four isoforms of the enzyme hexokinase encoded by different genes, HK I-IV. The different isoforms exhibit different tissue dependent expression and varying

affinity for their substrates (ATP and glucose). HK IV is almost exclusively expressed in the liver with a higher apparent affinity for its substrates (Km= ~5mM) than HK I-III (Km= 0.02 mM) (Pedersen, Mathupala et al. 2002). During liver tumorigenic progression hepatic tissue switches from HK IV expression to HK II and to some extent, HKI. The switch involves the silencing of the HK IV gene by methylation of the promoter, and increased expression of HK II by promoter demethylation and gene amplification (Mathupala, Ko et al. 2006). It has been shown that HK II localizes at the outer mitochondrial membrane as a complex associated with other mitochondrial membrane proteins. One of these proteins is the Voltage-dependent anion channel (VDAC). Once HK II localizes to the mitochondrial membrane it has privileged access to mitochondrial generated ATP, favorable for glycolysis

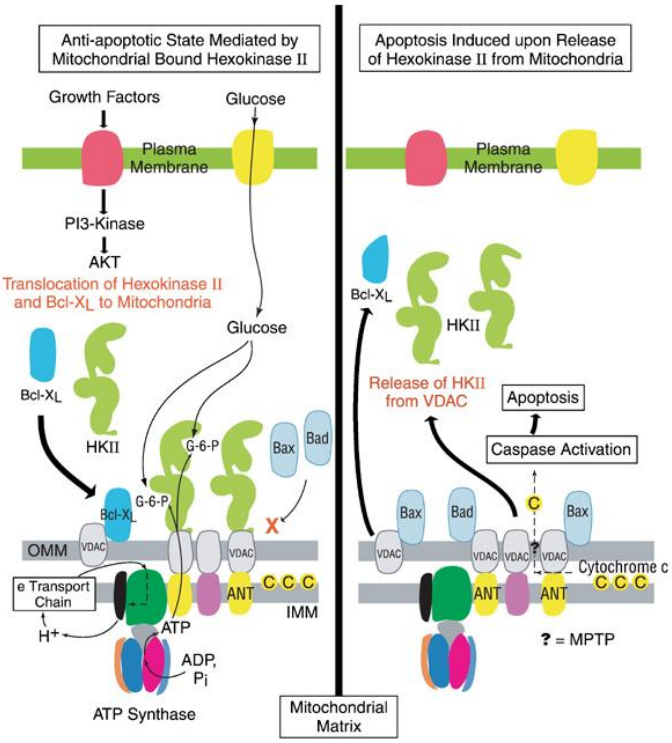

Figure 7. Hexokinase in cancer

By localizing to the mitochondria HK II also appears to escape the regulatory negative feedback loop by G6P that inhibits the hexokinases (Opt. cit.). The association of HK II and VDAC seems to be essential for cell survival. VDAC also functions as a regulator of apoptosis on the outer mitochondrial membrane (Schindler and Foley 2013). It has been suggested that the interactions between hexokinase and VDAC prevent the oligomerization of VDAC. VDAC oligomerization forms supramolecular structures which are likely associated with apoptosis mediation Figure 7 (Mathupala, Ko et al. 2009). Chemotherapeutics that disrupt the localization of HK II to the mitochondrial membrane such as bromo-pyruvate and methyl jasmonate induce apoptotic cell death Opt. cit. (Goldin, Arzoine et al. 2008).

Glycolysis Dysregulation II (Pyruvate Kinase)

Pyruvate kinase (PK) is a rate limiting enzyme and the last step of glycolysis. PK catalyzes the conversion of phosphoenolpyruvate (PEP) into pyruvate, with a payoff of two substrate level ATP produced per glucose molecule (Figure 8) (Mazurek 2011).

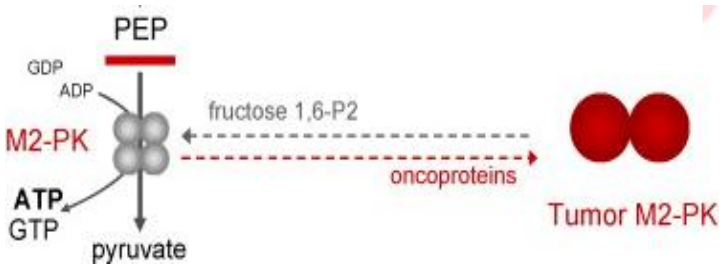

Figure 8. PKM2 activity linked to malignancy

Pyruvate in turn can be shuttled into the mitochondria to be oxidized further to produce more ATP in the presence of oxygen. In hypoxic conditions or high glycolytic rates, pyruvate is converted to lactate by lactate dehydrogenase (LDH). This regenerates the pool of nicotinamide adenine dinucleotide (NAD) consumed as an electron carrier during glycolysis (Figure 9) (Doherty and Cleveland 2013), allowing the cell to continue the glucose oxidation with lactate as byproduct being excreted (as discussed earlier, lactate can be used as fuel by adjacent cells, see below for LDH discussion).

There are four PK isozymes: PKR, PKL, PKM1, and PKM2. PKR and PKL are isozymes resulting from transcription from different promoters in the *PKRL* gene, while PKM1 and PKM2 are alternate exclusive splice variants of the *PKM* gene. The expression of PK isozymes is tissue specific, with PKR and PKL expressed in red blood cells and the liver respectively. PKM1 is predominantly expressed in muscle cells and PKM2 is expressed during embryonic and fetal development (Mazurek, Grimm et al. 2002). Various studies have shown the relationship between PKM and cancer. The transition between PKL to PKM2 has been observed in hepatocarcinogenesis (Hacker, Steinberg et al. 1998) and the switch between PKM1 to PKM2 is important for tumor growth and for the reconfiguration necessary to stablish aerobic glycolysis (Mazurek, Grimm et al. 2002).

PKM2 exists as a dimer or tetramer, with the dimer having a higher Km for the substrate and low catalytic activity. The dimer:tetramer ratio dictates the glycolytic rate of the cell. There are multiple factors that contribute to the oligomer state of PKM2. Fructose 2,6-bisphosphate (FBP) is a strong activator of PKM2 inducing tetramer formation (Iqbal, Gupta et al. 2014). Specific oncoproteins associate with the dimeric form preventing the tetramer formation (Figure 8). Finally post-translational modification of *PKM* gene products also affects the regulation of

PKM2 catalytic activity. The evidence suggests that PKM2 control, either at the translational level (as a HIF/Myc gene target) (Luo and Semenza 2012) or post-translational modification (Iqbal, Gupta et al. 2014); play a role in facilitating tumor formation and malignancy. It is also important to note that PKM2 in an entirely different role localizes to the nucleus and serves as a transcription factor interacting with β-catenin to induce cell survival and cell proliferation (Yang and Lu 2013). In this light PKM2 is an important regulator of metabolism, and the supporting evidence indicates that PKM2 favors tumor metabolism and as such presents a target to regulate tumor growth (Mazurek 2011).

Glycolysis Byproduct Buildup (Lactate Dehydrogenase)

As mentioned earlier LDH catalyzes the conversion of pyruvate into lactate for export and increase availability of NAD. Since tumors have an elevated glycolytic rate, it is not surprising that they also possess the necessary machinery to relieve the stress of pyruvate buildup and NAD depletion. LDH isozymes are tetramers composed of two subunits LDHA and LDHB encoded by the *LDHA* and *LDHB* genes respectively. The number of copies of each subunit determines the catalytic rate of the enzyme as a whole complex, also named after the ratios of LDH A:B units LDH1-5 (see Figure 9).

LDH isozymes with higher copy number of LDHA (LDH5) possess higher catalytic activities facilitating the production of lactate, conversely higher LDHB copies (LDH1) lead to an accumulation of pyruvate which can be used to feed the Krebs's cycle, and mitochondrial oxidative phosphorylation (top left Figure 9 (Doherty and Cleveland 2013)).

Imunohistochemical analysis of tumor biopsies has shown a higher LDHA expression in tumors than in the surrounding tissue. This makes LDHA expression compared to normal tissue. LDHA expression is a biomarker for multiple cancers (Miao, Sheng et al. 2013) (Yuan, Li et al. 2014). Some of the factors controlling the expression of *LDHA* include PKM2 and HIF/Myc transcriptional activation (Figure 5), ErbB2 signaling by activation of the Akt signaling pathway (Doherty and Cleveland 2013), and EGFR signaling (Miao, Sheng et al. 2013).

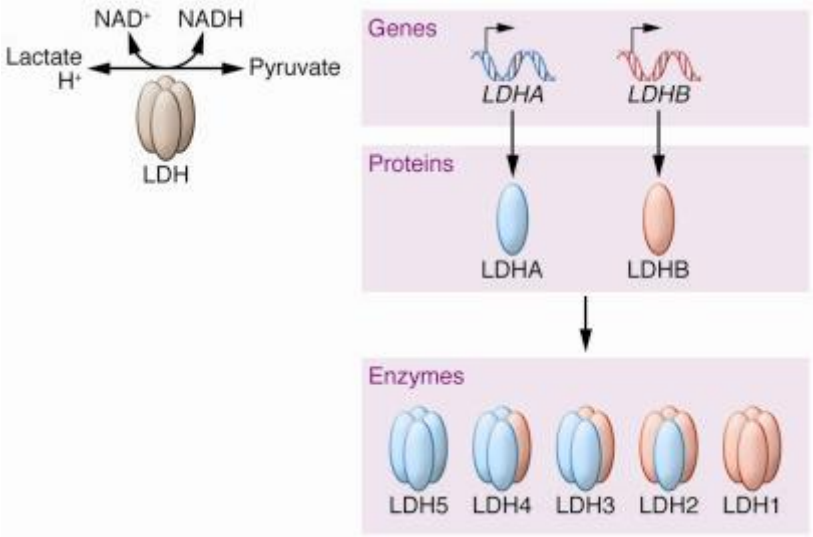

Figure 9. LDHA isozymes and NAD/NADH regeneration

Inhibition of LDHA by siRNA in cancer cells induces necrosis and apoptosis while limiting tumor growth and proliferation (Rong, Wu et al. 2013). This suggests that LDHA is central in the metabolic shift that allows for tumor aerobic glycolysis. LDH also regulates pyruvate levels, linking glycolysis and mitochondrial oxidative phosphorylation.

Regulation of Pyruvate Mitochondrial Oxidative Phosphorylation

The end product of glycolysis, pyruvate, can be further oxidized in the mitochondria to ultimately produce ATP. Pyruvate is converted to acetyl-coenzyme A (acetyl-CoA) which then enters the Krebs's cycle to fuel oxidative phosphorylation. The enzyme complex responsible for this task is pyruvate dehydrogenase (PDH or PDC), thus it is a chief regulator of glycolysis. PDH is a nuclear coded mitochondrial enzyme complex, composed of multiple copies of E1, E2, and E3 subunits. The subunits are responsible for decarboxylating pyruvate, creating and transferring the thioester bond to CoA, and regenerating thiols on a lipoic acid prosthetic group used in the transfer of an acetyl group to CoA, respectively. PDH is regulated mainly by an inactivating phosphorylation on the E1 subunit at three serines (Roche and Hiromasa 2007). The enzyme catalyzing the phosphorylation is pyruvate dehydrogenase kinase (PDK). There are four PDK isozymes, PDKs 1-4, whose expression varies in different tissues, with each kinase having different activity and site specificity.

PDKs' dysregulation of PDH has been observed as a necessary step in cancer metabolism. It has been reported that one of the most common type of gliomas, glioblastoma has a high PDK2 expression, and low PDH activity (Jha, Jeon et al. 2012). These findings support the observation that tumors partially suppress oxidative phosphorylation, accumulating pyruvate and eventually secreting lactate. In melanomas ectopic expression of PDK1 (also a HIF/Myc gene target) induces PDH inactivation and tumor progression, while depletion of PDK1 decreased oxidative phosphorylation of PDH (increasing PDH activity) and cells entered oncogene-induced senescence (OSI) (Kaplon, Zheng et al. 2013). Finally, studies in various tumor cell models

including non-small cell lung, breast , glioblastoma, and colon suggest that dichloroacetate (DCA), a PDK inhibitor, increased mitochondrial phosphorylation and induced apoptosis (Jha, Jeon et al. 2012) (Koukourakis, Giatromanolaki et al. 2005). These observations suggest a crucial role for PDH/PDK in tumor metabolic dysregulation.

Collectively, the evidence suggests that malignancy and tumor growth are closely intertwined with metabolic dysregulation. Transformed cells must acquire beneficial mutations to satisfy the metabolic needs and control the metabolism of stromal cells in the tumor mass. Recognizing the roles of these enzymes allows for the development of chemotherapeutics targeting specifically tumor metabolism. This in turn, has the potential to create more precise and effective clinical treatments.

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