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Understanding the Pathogenesis of Cancer as Metabolic Remodulations

Ibrahim Karidio Diori[1], Senay Hamarat Sanlier[1, 2]

[1]Department of Biochemistry, Faculty of Science, Block E, Ege University, ErzeneMahallesi, Bornova/Izmir 35040, Turkey
kardio_ib[at]outlook.fr

[2]ARGEFAR, Faculty of Medicine, Ege University, Bornova/ Izmir 35040, Turkey

Abstract: ***Cancer is a highly cell growing and proliferating pathological condition that hijacks cellular metabolism to fulfill its needs. In the early 1920's the Nobel laureate, Otto H. Warburg, defined aerobic glycolysis as the sine-qua-none characteristic feature of cancer cells. Lately, we are gaining awareness that the characteristic intratumoral heterogeneity is just like a reflection of intratumoral metabolic diversity. The metabolic phenotype of cancer stem cells (CSCs) differs from that of differentiated cancer cells. There from, the metabolic needs of cancer cells vary within a tumor. In fact, the overflow of glycolytic intermediates is reoriented toward alternative pathways. The pivotal interplay between the glycolytic pathway and other metabolic pathways prevails. Cancer metabolism ensures adequate energy supply, biomass production for rapid growth, prevents oxidative stress, epigenetic modulations, and immune assaults in a hostile tumor microenvironment. Warburg effect has long been considered as an insult to mitochondrial functions, especially the energetically more fruitful oxidative phosphorylation. Current understanding of cancer metabolic and signaling pathways has shown that mitochondrial functions do exist in cancer cells, but rather their metabolic functions are reprogrammed to favor rapid growth, proliferation, and less ROS production. Herein, we do revise the undersides of the Warburg effect and the metabolic shift of mitochondria with its associated signaling pathways.***

Keywords: cancer, Warburg effect, TCA cycle, electron transport chain, metabolic plasticity, signaling pathways, mitochondria, methylglyoxal, glyoxalases, oncometabolism

1. Introduction

Metabolism is an imperative property of a cell; it is the assembly of all the biochemical reactions that make life as we know it possible. Biochemical reactions taking place within the cellular environment are organized into metabolic pathways through which a specific molecule undergoes a series of interconnected chemical reactions in a predefined manner and steps to form a given product. Each of the steps of a metabolic pathway is usually catalyzed by a given enzyme. A metabolic pathway could be either anabolic that is, biosynthetic (thus endergonic), catabolic that is, biodegradation (exergonic), or amphibolic (either of the two). There is a rigorous control of the precursors, and products flow into/ from a metabolic pathway. Catabolic pathways are exergonic, thus release energy that could, if necessary, be used to fuel anabolic pathways that are endergonic in nature. Bioenergetics is concerned with the study of the energy metabolism of the cell. All the four macromolecules of a cell, namely carbohydrates, lipids, proteins, and nucleic acids, are both products and substrates of metabolic pathways. Abnormalities of metabolic pathways characterize many diseases conditions, as is the case in cancers, diabetes mellitus, among others (1-4). For the topic's purposes, in a brief discussion, we shall focus more on metabolic changes associated with cancer.

Cancer metabolism a.k.a. oncometabolism is concerned with the evolved / evolving adaptive tumorigenic alterations in metabolic pathways mostly encountered in cancer cells. These result in reactions that are either exclusive to cancer cells (thus absent in normal cells), or amplified in the diseases' conditions. Cancer being a highly proliferative pathological condition, to satisfy its needs in terms of energy and building blocks' demands, remodulates cells' metabolisms to survive even in depletion of nutrients supply and /or facing hostile microenvironment. The metabolic needs of each cancer cell's type vary with the tumor heterogeneity and progression stages. Both the genome and epigenome that characterize cancer determine which metabolic pathway (s) prevail (s) within each cell of a heterogeneous tumor, thereby determine the preferable substrate to fuel the prevailing metabolic pathway (s). There from knowing more about the prevailing metabolic pathway (s) of a given cancer would give ways to a targeted therapeutic strategy. The Nobel laureate Otto Heinrich Warburg was the first to make suggestions about the metabolic deviation of cancer cells, especially while describing aerobic glycolysis in cancer cells that grown to be the Warburg effect /Warburg hypothesis (5-8).

Warburg effect's significance to cancer cells' metabolism

Carbohydrates constitute the first source of metabolic energy in animals. Among monosaccharides, glucose is the major substrate for energetic metabolism. For a proper glucose supply into the intracellular environment in order to adequately fuel cell growth and division, Human cells have fourteen glucose transporters, among which four are specific to glucose (GluT1, GluT2, GluT3, GluT4). However, cells do not uptake glucose on need or self-command, but on instruction usually as a response to insulin stimuli that is, ininsulin-sensitive cells. Under appropriate oxygen supply, glucose is completely oxidized into carbon dioxide (CO_2) and water (H_2O) with a net production of 36 ATPs (**Figure 1**). The CO_2 is bound to H_2O *via* a reaction catalyzed by carbonic anhydrase to

form HCO_3^- which in turn helps in homeostatic pH regulation. In fact, the complete oxidation of glucose occurs in different cellular compartments and via distinct pathways. First, glucose goes through cytoplasmic glycolysis to give a net of two molecules of pyruvate, two NADH, H^+, and two ATPs. Each of the pyruvates enters the mitochondrion, where it feeds the tricarboxylic acid (TCA) cycle to produce three NADH, H^+ one $FADH_2$, and one GTP/ATP. The NADH, H^+, and $FADH_2$, along the mitochondrial respiratory chain, produce through oxidative phosphorylation respectively three and two ATP per molecule (9).

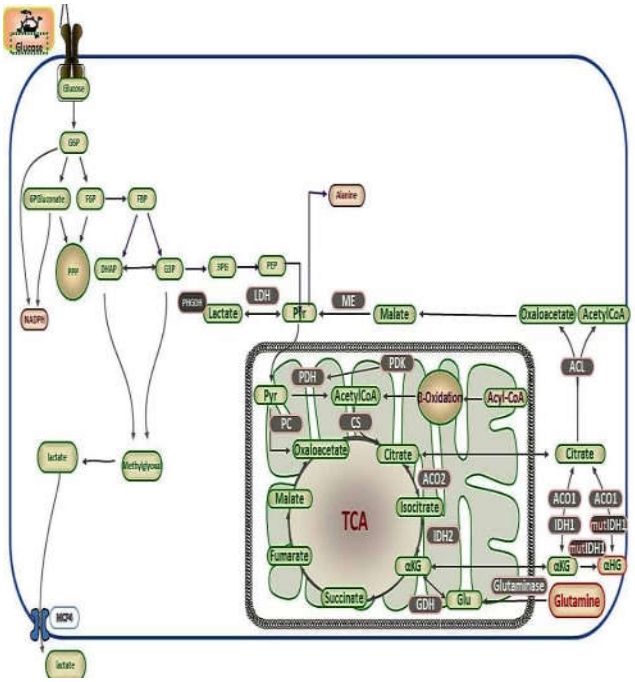

Figure 1: Cellular respiration. Upon intake, glucose is phosphorylated at C6 to form glucose-6-phosphate (G-6-P). The later, either enter the phosphate shunt, or feed the glycolytic pathway. At the fifth reaction of the glycolytic pathway i.e. interconversion of GAP to DHAP catalyzed by TPI, there could be a byproduct call Methylgyloxal. The highly electrophilic compound is detoxified by glyoxalase system to form D-lactate. Through this route glycolysis does not yield any ATP. The so formed D-lactate could be transported into the stroma and be used by oxidative phosphorylation competent cells within a tumor. As tumors are metabolically heterogeneous pyruvate produced through the normal glycolytic pathway could proceed to the mitochondria for complete oxidation through the TCA cycle.

Under insufficient oxygen supply, as it is the case during physical work/exercise, there is a relative hypoxic condition that is observed in muscles. Under such conditions, the cells could, unfortunately, not completely oxidize glucose. Instead, they go for an eighteen folds less energetic process that is, glycolysis coupled to fermentation. Oxygen supply to cells governs their bioenergetics. The two NADH, H^+ molecules produced through the glycolytic pathway are used to reduce the two pyruvates to two lactate molecules that are transported (via MCT4 out of the cell), onto the liver; thus they feed the "Cori cycle". There from, under anaerobic conditions, the glycolytic pathway leads to the net production of two ATP molecules. Under normal conditions, this process occurs especially in cells that lie far away from blood vessels/ hypoxic conditions. As cells usually are not more than five cells far away from a blood vessel so as to favor proper diffusion of oxygen and nutrients. Under this hypoxic condition, the cells, in parallel to immediate/short term solution that is, fermentation, respond in the long term by the production of two major transcription inducing factors namely Hypoxia Inducing Factor 1 alpha (HIF1-α), and Vascular Endothelial Growth Factor (VEGF), (we shall discuss the mitochondrial mechanisms that mediate the production and maintenance of HIF1 in more detail below). HIF1α, in turn, mediates the over expression of the enzymes of the glycolytic pathways. Over expression of these glycolytic enzymes, in turn, increases the metabolic rate of glycolysis. Besides that, the induction HIF1-α also induces over expression of the glucose transporters (GluT1 and GluT3) for more glucose uptake to feed the glycolytic pathway. Let's recall that; cells don't usually uptake glucose on self-command, but upon instruction generally by insulin. Other consequences to HIF1-α expression are Vascular Endothelial Growth Factor (VEGF) that promotes angiogenesis and MCT4 that export lactate from the cell (10-12).

However, glycolysis generates a byproduct from its fifth reaction, that is, the interconversion of dihydroxyacetone phosphate (DHAP) to glyceraldehyde-3-phosphate (GAP), catalyzed by triose phosphate isomerase (TPI). The byproduct produced is non-enzymatically formed and is named methylglyoxal / 2-oxopropanal/ pyruvaldehyde / or acetyl-formaldehyde. Methylglyoxal (MG) is a highly reactive and cytotoxic dicarbonyl compound cellularly detoxified by the glyoxalase system in the presence of glutathione and NADPH, H^+. Its detoxification leads to the production of D-lactate (**Figure 1**). Thus upon production of methylglyoxal glycolysis is less bio-energetically efficient ~ 0.05-0.1% glucotriose that is, about 5mmol produced per day (13-16).

Warburg's effect leading cancer metabolism

Biochemical changes associated with the initiation and progression of cancer that manifest as metabolic alterations with respect to those of normal cells are assembled under the scope of cancer metabolism. The well-known and leading edge of these metabolic alterations/cancer metabolisms is the Warburg effect. The Warburg effect characterizes cancer cells by their reliance upon aerobic glycolysis (followed by lactate fermentation), as a major source of energy. This has been long considered as an insult to the more energetically efficient mitochondrial oxidative phosphorylation. Although aerobic glycolysis is observed in some normal cells (embryonic tissues, proliferating cells, immune cells in response to infection.), but under homeostatic regulations, it is predominant and quasi-permanent in certain cancer cells. However, scientists that investigated the implications of the Warburg effect in cell metabolism support that it does not imply that the mitochondria become useless in the disease condition; instead, its hosted metabolic pathways are reprogrammed. The malady is

nothing else but a metabolic reprogramming that favors a rapid ATP synthesis for increased biomass production, amplification of biosynthesis of macromolecules that is, carbohydrates, proteins, nucleic acids, and lipids. Thus the Warburg effect is not an insult to mitochondria, but a strategy that promotes the conservation of the carbon biomass required for cell growth and proliferation (5, 17, 7, 8).

In fact, cancer cells by means of the Warburg effect move from catabolic to anabolic metabolism. It uses the pivotal interplay between the glycolytic pathway and other connecting pathways, the most prominent being the pentose phosphate pathway. This creates a condition with great advantages to the malady. First, it allows the tumor to withstand to a heterogeneous/ hypoxic condition in the tumor microenvironment (TME). Secondly, the efflux of lactate relatively lowers the pH in the TME to hinder the immune response. Thirdly increased glucose uptake has a relative impoverishment effect on the microenvironment, thus limits its access to lymphocytes that require glucose for their expansion and effect or functions; there from reduces the ability of lymphocytes to identify them and eventually mediate their destruction. Fourth, NADPH, H^+ is produced to detoxify the reactive oxygen *species* eventually generated by metabolic processes (18-21).

It is noteworthy to discuss the implication of the Warburg effect on pyruvate kinase (PK)'s activity. PK catalyzes the last step of the glycolytic pathway. In that, it mediates the phosphorylation of ADP through the transfer of high-energy-phosphate from phospho-enoyl-pyruvate (PEP), thereby occasioning the formation of pyruvate. In mammalian, there are four isoforms of PK, including PKL found in hepatocytes, PKR found in erythrocytes, PKM1 found in myocytes, cardiomyocytes, and neurons, and PKM2 found in most of the adult cells. Cells might express more than one isoform, but depending on their metabolic needs. PKM1 is widely involved in normal cell metabolisms, while PKM2 is widely referred to as promoting proliferative metabolism, thus potentially tumorigenic. PKM2 exhibits the particularities of having an allosteric activation site for F-1, 6-BP that is, fructose-1, 6-bisphosphate and sensitivity to growth factors while being potentially inhibited by ATP and/or alanine. It has been widely documented as associated with the Warburg effect.

PKM2 is the predominant form in cancer cells and is associated with high cellular content of lactate. In fact, as Warburg effect promotes glycolysis and the associated pseudohypoxic conditions mediated HIF-1α; HIF-1α, in turn, induces overexpression of glycolytic enzymes and glucose transporters namely: hexokinase, phosphofructokinase-2 (produces fructose 2, 6 bisphosphate that has an activating site on phosphofructokinase-1 to produce more fructose1, 6-bisphosphate), Pyruvate Kinase M-2 (PKM2), MCT4, lactate dehydrogenase (LDH), and Pyruvate Dehydrogenase Kinase-1 (PDHK-1). PDHK-1, in turn, inhibits Pyruvate Dehydrogenase (PDH) through phosphorylation, thus prevents the oxidative decarboxylation leading to the formation of acetyl-CoA from pyruvate. This generates an overflow of glycolytic intermediates that are eventually reoriented towards alternative pathways. There from, the pivotal interplay between the glycolytic pathway and other metabolic pathways prevails. Intermediates of the glycolytic pathways, namely glucose-6-phosphate, goes through the pentose phosphate pathway, and glyceraldehyde-3-phosphate serves for the synthesis of amino acids, e.g., serine. In fact, the pentose phosphate pathway provides to the cancer cells with NADPH, H^+ (for the biosynthesis of membrane lipids, nucleic acids), and ribose-5-phosphate-for nucleic acids synthesis, NAD, FAD (22, 23, 17, 24-26).

Warburg effect and the physiological role of the glyoxalase system

Warburg effect favors the excessive generation of glycolytic byproducts, the most prominent of which is the α, β-dicarbonyl electrophile, namely methylglyoxal (MG). The oxidative stress-inducing molecule is produced spontaneously-in a non-enzymatic reaction during the interconversion of DHAP and GAP (**Figure 1**). MG causes carbonyl stress with all the four types of macromolecules in non-enzymatic and irreversible reactions to form stable end products that is, Advanced Glycation Endproducts. In proteins, MG reacts with Arginine, thereby promoting receptor-mediated endocytosis, followed by a lysosomal degradation in macrophages/monocytes with the induction of cytokines and apoptosis. MG could also react with lysine (Lys) residues in proteins to form AGEs. The most frequent AGEs formed are CarboxyMethyl-Lysine (CML), CarboxyEthyl-Lysine (CEL), and pentosidine. In nucleic acids that is, DNA and RNA, MG forms AGEs by binding to the amine groups of guanylate and adenylate residues. The type of AGEs formed by MG with lipids is called Advanced Lipoxidation Endproducts (ALEs).

Besides forming AGEs with macromolecules, MG could also mediate inter-macromolecular crosslinking, especially protein-protein, DNA-protein, and DNA-DNA cross-linking. Thus, in general, MG exhibits the reaction potential of carbonyl compounds primarily because of its bifunctional properties. It has both an aldehyde and ketone functional groups. However, despite its carbonyl stress-inducing potential, one should bear in mind its physiological functions. In fact, MG has been reported to play an important role in cell physiology, especially in regulating cell growth and proliferation. Conversely, chronically increased concentrations beyond the physiological concentrations associated with impaired detoxification have been reported in pathophysiological conditions, such as diabetes, nephropathy, retinopathy, and neuropathy. Also, MG has been reported with cytotoxic activities in cancer cells (27-30).

It is noteworthy to mention similarities between diabetic hyperglycemia and the Warburg effect with respect to HIF-1α activities. HIF-1α is an essential transcription factor that mediates oxygen homeostasis, thereby functions to regulate the responsive, adaptive mechanisms of cells to hypoxia, namely neovascularization, metabolic

reprogramming, and survival. HIF-1α is sensitive to both hyperglycemia and hypoxia. Under normal cell physiological conditions, HIF-1α induces overexpression of glycolytic enzymes, GluT, and the Vascular Endothelial Growth Factor (VEGF). The latter mediates angiogenesis. However, diabetic hyperglycemia and Warburg effect as well, result in high effluxes of glycolytic intermediates, low/inappropriate mitochondrial oxidative phosphorylation, and high generation of MG.

MG interfere with the activities of HIF-1α, especially the induction of VEGF. It does so by binding to the Arg-17, 23 of respectively HIF-1α and HIF-1β preventing their heterodimerization. Moreover, MG binds covalently bind to the coactivator of HIF-1α, that is, p300 at its asparagine (Asn)-803, thereby preventing transactivation of HIF-1α. This results in an accumulation of HIF-1α associated with an impairment in its function, namely the subsequent induction of VEGF. This phenomenon promotes complications related to diabetes, especially sustained capillary rarefaction, diabetic foot ulcers, and also the anti-proliferative effect of MG in tumors characterized by the Warburg effect (31-33, 30).

However, in normal cellular physiology, there are detoxification pathways that eventually handle the dicarbonyl metabolite that is, MG remediation, the most prominent of which is the glyoxalase system; others include carbonyl reductase, aldose reductase, and aldehyde dehydrogenase pathways. Glyoxalase system refers to MG detoxifying system consisting of glyoxalase-1/Glox-1 (E.C.4.4.1.5.), and glyoxalase 2/ Glox-2 (E.C.3.1.2.6). These enzymes are dedicated to the remediation of the chronic and increased flux of MG in the presence of glutathione in a pathway that may also be an alternative for the production of D-lactate eventually for further catabolism. The first enzyme that is, Glox-1 uses glutathione as a cofactor in the conversion of MG to R- (S)-lactoylglutathione.

This is the most crucial step in the detoxification of MG for two main reasons: (i) R- (S)-lactoylglutathione is far less toxic than MG; (ii) it is the rate-limiting step of the detoxifying pathway. In cancer cells, especially carcinoma Glox-1 has been reported to be overexpressed nine (9) folds to prevent the accumulation of MG, while Glox-2 was overexpressed by three (3) folds. Glox-2 mediates the formation of D-lactate and regeneration of reduced glutathione at the expense of two (2) NADPH, H^+. Therefrom MG detoxification by glyoxalases is somehow linked to the pentose phosphate pathway as it uses the NADPH, H^+ (**Figure 2**). Overexpression of the glyoxalase system, especially Glox-1 overexpression is crucial to the proliferation and metastasis of many carcinomas characterized with Warburg effect e.g. Prostate carcinoma, bladder carcinoma, and colon carcinoma; it is reported to promote chemoresistance in breast and ovarian carcinoma (34-37).

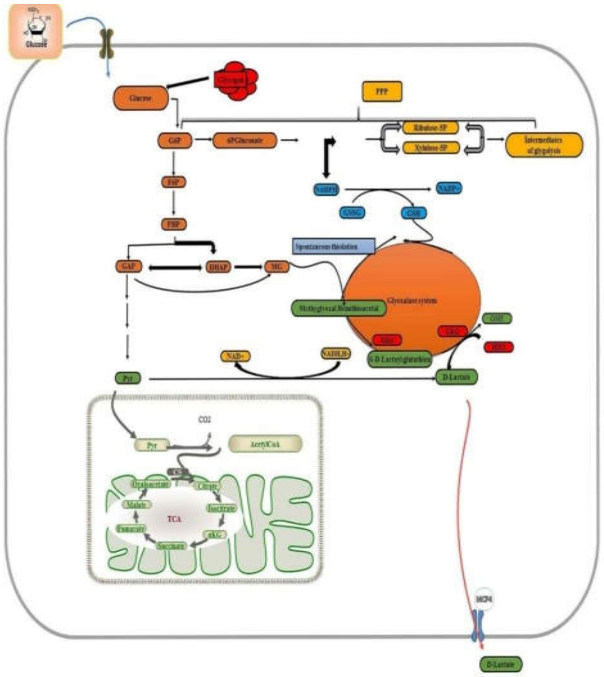

Figure 2: Formation, detoxification of methyl-glyoxal and its cytoplasmic detoxification by the glyoxalase system. Glycolysis produces a by-product non-enzymatically at its fith step i.e. the interconversion of GAP to DHAP. The highly electrophilic byproduct is detoxified within the cytoplasm by the enzyme system called glyoxalase system. Upon production and detoxification of methylglyoxal, glycolysis does not produce ATP. Upon detoxification MG is transformed into D-lactate.

Metabolic fates of lactate in Warburg effect characterized tumorigenesis

Accumulation of lactate in the Warburg effect characterized tumors has been widely reported. Lactate in this condition is generated mainly from pyruvate fermentation catalyzed by cytoplasmic lactate dehydrogenase, and by detoxification of MG by glyoxalase system. In contrast to the general wisdom, lactate is not just a toxic byproduct. Instead, lactate is a strategic metabolite to cancer cells with multifunctional features. The lactate shuttle hypothesis describes the most prominent known functions of lactate that could be enumerated as follows:

- The well-known fate of lactate as a precursor to the Cori cycle
- Cell-to-cell exchanges; lactate is secreted both in normoxic and hypoxic conditions in normal tissues as a response to substrate supply and equilibrium dynamics. In a heterogeneous tumor, cancer-associated fibroblasts have been reported to efflux onto the stroma lactate that would have a dual role; the first would be lowering the pH of the TME, while the second is to serve as a substrate to oxidative respiration in cancer cells of privileged niches, near blood vessels.
- In intracellular metabolism, per analogy to the malate/aspartate shuttles, lactate shuttle regenerate NAD^+ from NADH, H^+ formed in peroxisomal β-oxidation; while in the mitochondria it is converted back to pyruvate (by lactate dehydrogenase found on

the inner mitochondrial membrane), thereby generating NADH, H^+

- Lactate / lactormone is considered to play a role in the control, as a signal mediating molecule, of the redox status of the cell due to its inter-compartmental shuttle that involves NAD+/ NADH, H+.
- Cellular accumulation of lactate induces overexpression of MCT4 that transports it out-of-the cell, and *PPARG coactivator 1 alpha (*PGC1-α), that in turn induces mitochondrial biogenesis

In sum, for the cancer cell, the Warburg effect generated lactate accumulation serves a dual purpose, primarily the lowering of pH to acidic values in the TME, and secondly to serve as fuel to oxidative respiration in proliferating cancer cells (**Figure 3**), (38, 39, 9, 40-42).

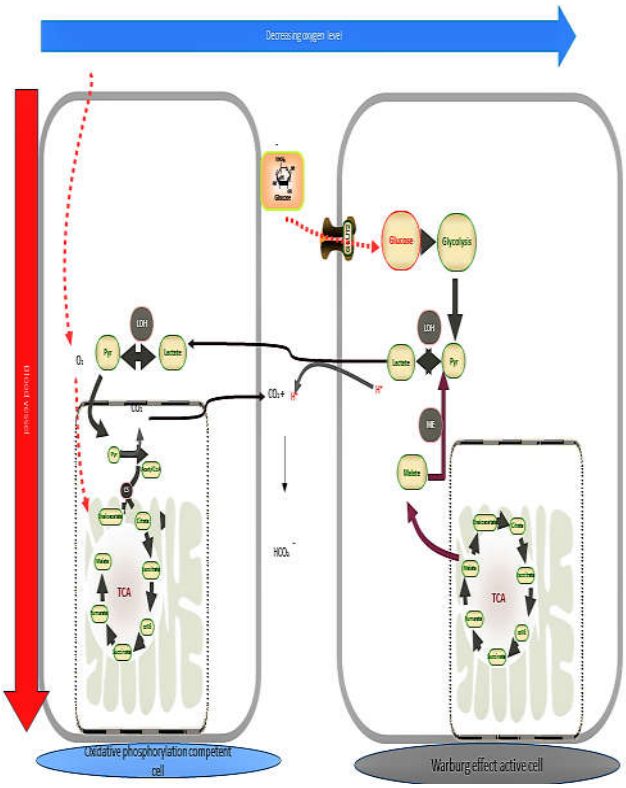

Figure 3: Intratumoral metabolic heterogeneity. Within a tumor, cells could have different metabolic phenotypes. Cells that lie close to blood vessels are usually oxidative phosphorylation competent. However, cells that lie far away from blood vessels are Warburg effect active cells; some of their produced lactate is transported into neighboring oxidative phosphorylation competent cells.

Metabolic fates of pyruvate in cancer

Pyruvate is a metabolite that plays a crucial role in cellular homeostasis and bioenergetics. It is a metabolic node to many pathways. Likewise, pyruvate is produced from diverse sources. The most common sources of pyruvate include: (i) Glycolysis, in which it is formed as the end-product and is formed from PEP in a reaction catalyzed by PKM2; (ii) In metabolically heterogeneous solid tumors, pyruvate could be imported into the cytosol from the TME by MCTs (MCT-1 and MCT-2); (iii) Pyruvate could be produced through the oxidation of cytosolic lactate or lactate imported from the TME by MCTs; (iv) Pyruvate could be produced from cytosolic alanine through transamination reaction catalyzed by ALT; (v) Pyruvate could be formed from malate in a reaction catalyzed by the cytosolic malic enzyme. Pyruvate is as well, a junction point to both mitochondrial anabolic and catabolic pathways (at least starting in the mitochondria), including gluconeogenesis, oxidative metabolism, *de novo* lipogenesis, TCA cycle and cholesterogenesis (43, 44, 41).

Obviously, all the mentioned pathways require mitochondrial pyruvate. Linking fates of pyruvate to the Warburg effect, the general wisdom of cancer metabolism would cite overexpression of PKM-2, PDHK-1, & LDH-A that ultimately down-regulates PDH. LDH-A, also known as LDH-M, is the isoform of LDH found in skeletal muscles, and that favors the formation of lactate from pyruvate. LDH-B or LDH-H is the isoform of LDH in cardiomyocytes that catalyzes the formation of pyruvate from lactate as the heart is a pyruvate-oxidizing organ. The down-regulation of PDH by overexpression of PDHK-1 has long been considered as the main blockage to mitochondrial pyruvate metabolism. However, there is a growing body of evidence supporting that Mitochondrial Pyruvate Carriers (MPC) activity determines the pyruvate's flux from the cytosol into the mitochondrial matrix. Ehrlich was the first to coin in 1977 that a carrier of the inner mitochondrial membrane, responsible for the transfer of cytosolic pyruvate into the mitochondrial matrix functions abnormally in cancer cells (17, 45-47).

However, there was no information with respect to the molecular identity of MPCs until 2012, when two groups of scientists, simultaneously reported their molecular characterization. There are two MPC, namely MPC1 and MPC2 (48, 49). Their molecular mechanistic pathway is still poorly understood. However, functional mutation (s) or down-regulation of either of them, result (s) in metabolic disease even if the activity of PDH is at its maxima as in the case of type 2 diabetes and cancer. The under-expression of MPCs has been characterized in many cancers, such as colon kidney carcinomas, prostate cancer, and squamous esophageal cancer, as it promotes the Warburg effect, thus cell growth and proliferation.

Conversely, induced overexpression or forced expression of MPC in cancer cells results in high survival and better outcomes for patients. Therefrom, some authors whisper the possibility that MPC is tumor suppressor genes: it is a functional antagonist to Warburg effect. MPCs transports pyruvate across the Inner Mitochondrial Membrane (IMM) by means of symport with protons, thus using a proton gradient per analogy to the Electron Transport Chain (ETC) (50, 46, 51-54).

As a matter of example, doxorubicin is a well-documented anticancer drug that has, among other side effects, cardiotoxicity. The mechanisms of its cardiotoxicity are believed, according to current evidence, to be due to its inhibitory effects on MPCs and carnitine transferase activity. The cardiac isoform of LDH is LDH-H; moreover, the heart's bioenergetics is commonly based on about 30% on carbohydrates (that is, pyruvate) and 70%

from lipid oxidation, thus a prolonged and/or exposure to a high concentration of doxorubicin obviously mediates induced heart failure. It is worth mentioning that another source of mitochondrial pyruvate flux is Alanine (Ala). Ala is transported into the mitochondrial matrix, where it is converted into pyruvate by mitochondrial alanine transaminase (ALT) (55).

Mitochondrial functions in cancer

Mitochondria are specialized cytoplasmic organelles found in most eukaryotic cells. They have their own DNA, independent protein synthesis machinery, and reproduce independently by fission through a process called mitochondrial biogenesis. They are very valuable dynamic organelles that bear the respiratory chain and host of many important metabolic and signaling pathways. Although they have general core functions in every cell, mitochondrial functions may vary depending on the cell type and include: (i) On a general basis cellular bioenergetic (degradation of fatty acids, TCA cycle, *etc.*), and biosynthesis of macromolecules as well as some specialized compounds (steroids, porphyrin, *etc.*); (ii) Oxidative phosphorylation along the respiratory chain embedded in the inner mitochondrial membrane; (iii) Ca^{2+} homeostasis; (iv) Detoxification of ammonia in hepatocytes; (v) Mediation of apoptosis. Abnormal mitochondrial functions, ranging from metabolic reprogramming to aberrant functional mutations, have been tightly associated with malignant features of cancer. Indeed, the Warburg effect suggests dysfunctional mitochondria as primordial tumorigenic fact (56-60).

In tumors, HIF-1α induced angiogenesis is anarchically tailored. Thus blood drainage is not uniform across tumors, and not even all tumor cells have access to areas covered by blood vessels. In normal tissues, cells are usually not farther than five cells away from blood capillaries. However, in tumors, this is somehow a privilege that all cells could not have due to their anarchic growth and anarchic angiogenesis. Thus concerning fluctuating phases of spatial and temporal blood irrigation across the tumor, cells that lie far away from a blood capillary constitutively reprogram their metabolism to set a Warburg effect. Conversely, those closer to blood supply continue oxidative metabolism. Therefrom, intratumoral heterogeneity could also be said to be metabolic, because all the ubiquitous variations of cancer etiology that support the three theories of intratumoral heterogeneity, could be gathered under the single, but broad-complex, the scope of biochemical abnormalities that manifest as a confined set of metabolic aberrations to support bioenergetics, biosynthetic and redox dynamics of malignancies. Indeed, the Warburg effect characterized tumor cells do not necessarily have defective mitochondria, but metabolically reprogrammed mitochondria. Mitochondria, in such cases, become biosynthetic organelles. Thus, although some mitochondrial defects could contribute to cancer's initiation, progression, and metastasis, functional mitochondria are required for both cancer growth and proliferation (61-64, 33, 65).

For their growth and proliferation, cancer cells, like normal cells, need adequate energy supply for cellular functions and duplication of vital structural components prior to cell division/proliferation. Mitochondria are host to bioenergetic, biosynthetic metabolisms and redox balance of the cell. In the animal cells, they are the unique organelles that host DNA that is, the mitochondrial (mtDNA). mtDNA is a small circular DNA of 16, 569 base pairs organized into 37 genes, that encode exclusively for 13 mitochondrial proteins, 22 tRNAs and 2 rRNAs. A cell might contain thousands of mtDNA copies as it has numerous mitochondria, and each mitochondrion could host dozens of mtDNA. Functional mutation (s) in each of these genes could manifest as a disease condition, but a total ablation of the mtDNA compromises cell growth and proliferation. The 13 proteins encoded by mtDNA are directly involved in oxidative phosphorylation, while other proteins/enzymes involved in mitochondrial functions are coded by nuclear DNA. Tumorigenic mutation of mtDNA would result in mechanisms that reprogram and reorient mitochondrial metabolism. With a compromised electron transport chain, exergonic redox metabolism that constitutes the major mitochondrial function in normal cells (that confers it with the name *powerhouse of the cell*), is shut down. Indeed, tumorigenic mutation of genes encoded by mtDNA that is, involved in the function of the respiratory chain, would hinder electron flow through the electron transport chain, and thus favors the production of ROS and reducing equivalence accumulation (NADH, H^+, and $FADH_2$). Increased ROS production increased the risk of nuclear DNA mutations, and mediate stable transcription of HIF, JUN, nuclear factor kappa-B transcription factor, while NADH, H^+ accumulation inhibits Isocitrate Dehydrogenase 3 (IDH3) activity. Conversely, the anaplerotic metabolisms of the mitochondria are increased. Thus the mitochondrial function in cancer cells is mostly biosynthetic. Tumorigenic mutations in the mtDNA have been characterized in many cancer types including brain cancer, breast cancer, colon cancer, gastric carcinoma, gingivobuccal oral cancer, liver cancer, lung cancer, penile cancer, prostate cancer, kidney cancer, ovarian cancer (66-71).

Functional mutation (s) in mtDNA generally generate (s) *heteroplasmism* that would probably vary among cells within the same tissue/organ/ organism. The most documented metabolic pathway hosted by mitochondria is probably the TCA cycle. All the enzymes involved in the TCA cycle are encoded by genes of the nuclear DNA (nDNA); however, with exception made to succinate dehydrogenase (SDH) located on the inner leaflet of the mitochondrial membrane facing the matrix, all operate within the mitochondrial matrix. Each of the enzymes involved in TCA has been characterized as mutated in various cancer types, and/or in various organs. Before going into details of the individual deficiencies observed in the enzymes of the TCA cycle and their related cancer, let's recall on the normal scenario in the regulation of the metabolic node that is, PDH and the allosteric regulatory enzymes of the TCA cycle namely Isocitrate De Hydrogenase (IDH) & α-Keto Glutarate Dehydrogenase (αKGDH). PDH is an enzyme complex regulated as

discussed above by covalent phosphorylation mediated by PHD-K, and the reverse by a phosphatase. The predominant enzymatic activities are mediated by pyruvate, insulin, acetyl-CoA, and NADH. Indeed, PDH-K is activated by a high cellular energy status that is, [ATP/ADP], redox status [NADH/NAD^+], and [acetyl-CoA/CoA], or inhibited by Ca^{2+}, and dichloroacetate. Activated PDH-K, in turn, inactivates PDH by phosphorylating it. Conversely, phosphor-pyruvate dehydrogenase phosphatase (pPDHP) is activated by Mg^{2+}, Ca^{2+}, and insulin to cause dephosphorylation of phospho-pyruvate dehydrogenase, thereby activating it to catalyze the oxidative decarboxylation of pyruvate into carbon dioxide (CO_2), and acetyl-CoA. So, a defective/non-properly functional respiratory chain, would not make NAD^+ available for this reaction as well as the reaction catalyzed by the two regulatory points of the TCA cycle, namely IDH and αKGDH. Therefrom, this could be an additional promoting reason to the Warburg effect and the anaplerotic function of TCA that is discussed below (72-74, 33).

TCA cycle is the final convergent pathway of cellular respiration. It involves the oxidation of acetyl-CoA residues coupled with the reduction of the coenzymes FAD^+ and NAD^+ into $FADH_2$ and NADH, H^+, that in turn go through the respiratory chain for oxidative phosphorylation to generate ATP. Several nutrients provide TCA cycle with acetyl-CoA, including carbohydrates, lipids, and proteins. The pathway is a set of eight enzyme-catalyzed reactions. Enzymes involved in the TCA cycle have been characterized in both sporadic and hereditary cancer types, some of which are discussed below.

Citrate synthase (CS) expression and citrate pool in cancer cells

Citrate synthase (E.C. 2.3.3.1.), catalyzes the generation of citrate, the first intermediate of the TCA cycle through a condensation reaction, the commitment step of the pathway that involves oxaloacetate (OAA), and acetyl-CoA. The so-formed citrate either continues through the TCA cycle or is transported into the cytosol by citrate-malate-antiporter/ mitochondrial citrate carrier (SLC25A1). Cytosolic citrate is acted upon by ATP-Citrate-Lyase (ACLY overexpressed in the stomach, urinary bladder, colon, breast, liver, and prostate cancer), to form OAA and acetyl-CoA. The so-formed acetyl-CoA in the cytosol could have several fates, including *de novo* lipogenesis/cholesterogenesis, and/or epimutation (s) on proteins that is, histone acetylation. OAA, as well, could have several fates, including its stepwise conversion into malate through reduction by malate dehydrogenase, then subsequently to pyruvate by malic enzyme (ME). The pyruvate could either be reduced to lactate or enter the mitochondria for reforming citrate. Another fate of the OAA could be nucleic acid (NA) biosynthesis. Overexpression of CS impaired with its consumption would lead to citrate acidosis, as observed in D2-/L2-hydroxyglutaric aciduria. Overexpression of CS has been observed in malignant ovarian and pancreatic cancers. Such types of cancers are believed to be lipogenic dependent. Underexpression /deficiency in CS as well has been characterized in cancers like cervical cancer (75-79, 65).

Aconitase (Aco) expression and the isocitrate pool in cancer

Aconitase (E.C. 4.2.1.3) is a Fe-S cluster that catalyzes the reversible and stepwise stereospecific isomerization of citrate into isocitrate. Aberrations in the activity of the enzyme have been observed in breast cancer, gastric cancer, prostate cancer, and pancreatic cancer. The pathophysiological conditions associated with the dysfunctionality of aconitase in the above-cited cancers have mainly been attributed to cellular zinc-dyshomeostasis. Zinc is a micronutrient involved mainly as a cofactor in various cellular processes. The cellular zinc-allostasis is mediated by zinc-transporters, namely Znt (SLC30) that export zinc into the extracellular environment, and *Zrt- and Irt- like protein* /ZIP (SLC39) that imports zinc into the cells. These transporters regulate cellular content of zinc depending on the cell type/tissue/organ and needs. For instance, in normal physiological conditions, prostatic cells' content of zinc is high such that it inhibits the activity of aconitase. Thus favors citrate's accumulation and *de novo* lipogenesis. Conversely, in prostate malignancies, a zinc-dyshomeostasis with respect to the desired conditions sets-in as a result of zinctransporter's functional aberrations manifested as depletion in the normally high cellular zinc content. This results inturn in regain of activity by aconitase, thus a depletion of citrate concentration due to its oxidation via the TCA cycle instead of the desired lipogenic route (80-84).

Isocitrate dehydrogenase (IDH)

Isocitrate undergoes a stepwise oxidative decarboxylation catalyzed by the allosteric enzyme IDH. In the cell, three isoforms of the enzyme have been characterized that is, IDH1, IDH2, and IDH3. IDH3 is exclusively located in the mitochondrial matrix and is the isoform related to the TCA cycle. It is the first regulatory point of the TCA cycle, while other isoforms catalyze the same reaction in different cellular compartments. The isoforms IDH1 and IDH2 have been localized in the mitochondria, cytosol, and peroxisomes. The oxidative decarboxylation of isocitrate leads to the formation of αKG with a concomitant reduction of cofactors NAD^+/$NADP^+$. IDH3 is the only isoform using the cofactor NAD^+ that, in turn, is the only cofactor related to the respiratory chain. The other isoforms, namely IDH1 and IDH2 use $NADP^+$ cofactor. Functional mutations observed in IDHs are the most common mutations in the two isoforms, namely IDH1 and IDH2. The well-known mutations on the isoform IDH1 have been observed in its Arg 172 or Arg 149, while IDH2 is generally mutated at its Arg 132 residues. These functional mutations generally manifest as neomorphism, in that, isocitrate is converted by the mutant-IDHs (*m*-IDH), into the (R)-or (s)-enantiomer called 2-hydroxyglutarate (2HG) that is an oncometabolite. Cancers in which these mutations have been characterized include pediatric glioblastoma,

malignant glioma, breast cancer, prostate cancer, thyroid carcinoma, AML, chondrosarcoma, colorectal cancer, intrahepatic cholangiocarcinoma. However, the isoform IDH3 has never been characterized by a tumorigenic mutation. Instead, an aberrant overexpression of its α-subunit has been characterized in various types of leukemia, brain cancer, and is used as a marker for diagnostic and prognosis (85, 86).

Neomorphic mutations and aberrant overexpression observed in the IDH isoforms modulate the cellular function of PHD, thus influences the stabilization of HIF-1α. The product of *m*-IDH1 and/ *m*-IDH2 catalyzed reaction that is, 2HG has two enantiomers, namely D-2HG and L-2HG (R or S), with controversial activities. The prolyl-hydroxylation of HIF-1α by PHD requires principally αKG, oxygen, ascorbate, and Fe^{2+}. Meanwhile, at high concentrations of L-2HG, its conformational similarities with αKG favor it's binding to PHD, thereby inhibiting the prolyl-hydroxylation of HIF-1α necessary for its degradation. Therefrom, L-2HG would promote stabilization of the angiogenic transcription factor HIF-1α. There reside the controversial effects of the enantiomers, as the D-form of 2HG promotes PHD activity, thus acts to degrade HIF-1α. The third isoform IDH3 could also, following aberrant overexpression of its α-subunit, interfere with PHD's activity by lowering the cellular content of αKG therefrom stabilizing the angiogenic transcription factor HIF-1α. Moreover, the enantiomers alter the normal epigenome of the cells by modulating the methylation scenery as they interfere individually with the activities of *Ten-eleventranslocation* (TETs) and KDMs proteins. They both act as competitive inhibitors to these demethylation enzymes thereby promoting activation of oncogenes e.g. Mechanistic Target of Rapamycin kinase (mTOR) (87-94).

Alpha-ketoglutarate dehydrogenase complex (αKGDH) and the cellular pool of αKG

Alpha-ketoglutarate dehydrogenase complex catalyzed the oxidative decarboxylation, converting αKG to succinyl-CoA. The reaction is very similar to that of PDH; in that, the equilibrium of the reaction is likely to favor the formation of succinyl-CoA that is, a high thioester similar to acetyl-CoA. This is the second site of control of the TCA cycle. As an allosteric enzyme, αKGDH is inhibited by a high concentration of the products of the reaction it catalyzes that is, NADH, H^+, succinyl-CoA. It is worth noting that αKG could also be produced via an oxidation or transamination reaction of glutamate. First, following the uptake onto the cell, glutamine is converted into glutamate by glutaminase with a release of ammonia, and then glutamate is subsequently converted to αKG. αKG is a hub to many metabolic pathways and signaling pathways as well. The so-formed αKG could serve as a substrate for both bioenergetic and biosynthetic pathways. Indeed, the particularity of glutamine metabolism with respect to that of glucose is that it used as both carbon and nitrogen source. The anaplerotic fate favors the generation of NADPH via malic enzyme and pyruvate that would subsequently be reduced to lactic acid. Therefrom the lactic acid accumulation in the tumor is not only due to the Warburg effect. At higher [αKG]: [citrate] conditions, especially induced by mitohormosis related HIF-1α inhibition of αKGDC or a defective ETC, the NADPH-dependent IDH2 converts αKG to isocitrate through a reductive carboxylation. αKG is also known to promote epimutations by triggering changes in the methylation patterns of DNA and histones via TETs and KDMs; this would lead to activation of some oncogenes. Another oncoactivation attributed to αKG is that of mTOR driven by PHD (95-99).

Succinate dehydrogenase activity and succinate pool in cancer cells

Succinate is a bio-energetically valuable intermediate of the TCA cycle formed from succinyl-CoA, the product of the αKGDC catalyzed reaction. Succinate, in turn, undergoes a dehydrogenation reaction catalyzed by Succinate Dehydrogenase (SDH) to form fumarate, with a concomitant formation of $FADH_2$ (the 3rd and final of TCA cycle). SDH, also known as complex II, is a *housekeeping* enzyme and the only enzyme of the respiratory chain fully encoded by mDNA. It is integrated into the inner leaflet of the inner mitochondrial membrane facing the matrix. SDH has four subunits, name from A through D. The subunits SDHA and SDHB are made up respectively of flavoprotein and iron-sulfur protein and constitute the catalytic frame, while SDHC and SDHD constitute the integrated portion of the enzyme in the inner membrane. Defects in SDHs result in a defective respiratory chain and cellular metabolic reprogramming to favor cell growth and survival through increased glycolysis, pyruvate carboxylation for aspartate synthesis, and reductive carboxylation following glutaminolysis. Functional mutations in each of the subunits would be tumorigenic, so SDH's subunits coding genes are referred to as Tumor Suppressor Genes (TSGs). *m*SDHs have been characterized in many chronical diseases, including inflammation, both sporadic and hereditary cancer types.Examples of *m*-SDH induced cancers include Breast Cancer (BC), Colorectal Cancer (CRC), Familial Pheochromocytomas (FPCC), Gastrointestinal Stromal Tumors (GISTs), mediastinal Paragangliomas (PGLs), neuroblastoma (NB), Ovarian Cancer (OC), Papillary, Testicular Seminoma (TS), Pituitary Thyroid Cancer (PTC), Renal Carcinomas (RCC) (100, 101, 92, 102-104).

Besides, the aberrant functional mutation, inhibition, or aberrant regulation of SDH results in similar disease conditions. The first consequence of SDH inactivity would be succinate accumulation. Upstream regulatory pathways of SDH mediated by the Tumor necrosis factor Receptor-Associated Protein 1 (TRAP1), has been often cited as an etiologic feature in many cancer types. TRAP1 is a highly conserved regulatory mitochondrial chaperone of the *heatshockprotein*-90 (HSP90) family. It is a multifunctional protein involved in various regulatory pathways, including redox control, proteostasis, energy homeostasis, as well as cell maturation, proliferation, motility, and apoptosis. The exact role of TRAP1 could sometimes be controversial as research groups reported it as both oncogenic and oncosuppressive depending on the cell's status. TRAP1 functions as a proteostatic regulator

for SDH / complex II and complex IV / ATP synthase of the mitochondrial respiratory chain. TRAP1 is a cellular metabolic modulator that drives its dynamic switch between mitochondrial respiration and the Warburg effect. TRAP1's overexpression leads to the low activity of the respiratory chain as it would downregulate two of respiratory chain's components, thus lessen oxidative phosphorylation, while it promotes the Warburg effect. This condition has been reported in lung cancer, hepatocellular carcinoma, breast cancer, glioblastoma, colorectal cancer, gastric cancer, thyroid cancer, prostate cancer, and esophageal squamous cell cancer. Conversely, an under-expression / downregulation of TRAP1 has been found to be tightly associated with renal, ovarian, and urinary bladder cancer. In such cases, tumor cells are oxidative cells, but that would generate ROS, thereby disturb mitochondrial homeostasis triggering metabolic reprogramming in cancer (105-108).

Tumorigenic functional mutations that manifest as reduced activity/inhibition of SDHs are usually associated with tumorigenic functions of dicarboxylic transporters. Succinate, malate, and αKG, being charged molecules need to be transported across the mitochondrial and/or plasma membrane (s) by specific carrier proteins that they happen to share in common. The mitochondrial ones are of the family of SoLute Carrier 25 (SLC25) and the subfamily 10, thus otherwise called SLC25A10. These are phosphate dependant carriers that mediate succinate homeostasis across the mitochondrial membrane. The plasma membrane carriers are of the sodium-dependent type, that monitors succinate, or dicarboxylate pool in general across the plasma membrane. They are called Na^{2+}-Dependant Carrier /NaDC, and they are of three (3) common subfamilies, including NaDC1, NaDC2, and NaDC3 (109-111).

Overexpression of these carriers has been widely documented in various cancer types. Of concern, succinate has valuable extramitochondrial functions that benefit tumorigenesis and metastasis. Overexpression of SLC25A10 has been associated with succinate mediated tumor growth and metastasis, while its inhibition would force oxidative phosphorylation in intact, but metabolically reprogrammed mitochondria or oxidative stress in ETC altered mitochondria. Accumulated succinate inhibits functional activity of PHD, therefrom stabilizes HIF-1α. Besides that, another recently documented function of succinate is its *epimutational* potential through post-translational succinylation. NaDC1 (SLLC13A2) transports succinate onto the extracellular/ interstitial space/ stroma, where it: (i) participates in maintaining acidic TME; (ii) plays its hormone-like function by binding to its receptor i.e. the G-protein coupled receptor-91 (SUNCR1/GPR91) thereby activating angiogenesis through STAT3 and ERK pathways or; (iii) is uptaken by oxidative competent tumor cells (112-114, 102, 115, 116).

Fumarate hydratase expression in cancer

SDH catalyzes the conversion of succinate to fumarate, an α, β-unsaturated electrophilic metabolite of the TCA cycle, that upon accumulation would have similar effects with those of succinate and 2HG e.g. inhibition of PHD among others. Besides that, even at moderate physiological concentrations, the electrophilic nature of fumarate confers it with the potential to *succinate* cysteine residues of proteins, therefrom altering their functions as observed in pathological conditions, that evolve subsequently to alterations in fumarate metabolisms such as succination of aconitase, and *Kelch-like ECH-associated protein 1 (*Keap1). Keap1 is a Cys-rich (27 residues) cytoplasmic regulatory protein that inhibits the activity of the Nuclear factor (Erythroid-derived2)-like 2 (Nrf2), that functions to upregulate a broad set of cytoprotective proteins against various stresses. Upon sensing of potential stress inducers, including oxidants, xenobiotics, radiation, and electrophiles through its Cys-151 of BTB domain, and Cys 273/288 of Intervening region (IVR)-domain, keap1 derepresses Nrf2. Defects in Keap1 activity has been characterized in many cancer, including NSCLC, prostate cancer (117-119, 33).

Fumarate accumulation usually occurs as a result of mutation (s) in Fumarate Hydratase (FH), the enzyme that catalyzes its reversible conversion to malate. Cellular FH isoforms are of two types, namely cytosolic and mitochondrial, but that are both encoded by the same gene. Homozygous functional mutation (s) in FH has been observed in a rare form of a lethal autosomal recessive syndrome called fumaric aciduria. Heterozygous germline mutation in FH has been characterized as various tumorigenic cancer, including Leydig cell tumors, uterine leiomyoma, breast cancer, type 2 papillary renal cancer, renal cancer cells, and ovarycystadenomas. It is worth noting that the activation of the Nrf2 pathway has been characterized in cancers with tumorigenic mutations in the genes that encode for SDH, FH, and IDH (120-125).

2. Future Outlook

Warburg effect has often been erroneously interpreted as a substitute to mitochondrial respiration in cancer cells. Indeed, the heightened aerobic glycolysis favors a momentous benefit, as metabolic remodulations drive biomass production for rapid growth and proliferation. Warburg effect exhibiting tumors are also mitochondrial oxidative phosphorylation competent entities. They exhibit aerobic glycolysis while retaining mitochondrial respiration due to the intratumoral metabolic heterogeneity.

Due to the anarchic vascularization, tumor niches are heterogeneous. Thus cells within privileged niches oxidize while others ferment. In privileged niches, tumor cells' mitochondria are essentially biosynthetic. They oxidize pyruvate gleaned from the Warburg effect exhibiting tumor cells.

Therefrom, the lofty goal for cancer biologists is to hinder the metabolic plasticity that drives the synthesis of building blocks for biological infrastructures and the bioenergy that fuels biological processes. A wealth of evidence unveiled the benefit of nutritional ketosis's propensity to lower blood glucose and interferes with

insulin's signaling. Either physiologically produced in the liver or through consumption of Ketogenic Diets (KDs), Ketone Bodies (KBs), traditionally considered as metabolic garbage are used today in the treatment of a broad spectrum of diseases (epilepsy, coronary artery disease, diabetes, arthritis, multiple sclerosis, *etc.*). This is surely due to the role they play in cell signaling, interference with inflammation, modulation of cellular biochemistry, metabolomics, and epigenetics. Thereof, the use of KDs as metabolic therapy to cancer is an evolving research domain. The resulting ketosis has the advantage of targeting not only a single feature of cancer cells but directly impinges a broad scope of oncometabolism while fostering immunometabolism. Undoubtedly, further development of KDs cancer therapy would decipher the undersides of oncometabolism and gives new opportunities to targetable and more efficient therapeutic outcomes.

3. Highlights

- The genome and epigenome of cancer cells determine their respective metabolic phenotype within a metabolically heterogeneous tumor
- There are Warburg effect active cells and oxidative phosphorylation competent cells within a tumor with respect to glucose metabolism.
- Mitochondrial functions in cancer cells exist but are reprogrammed to meet the specific need of the cells with respect of their types and niches within a tumor.

4. Competing Interest

The authors declare no competing interest

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