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Review article:

Cancer Cell Metabolism: Past, Present and Future

Dr. Abhishek Ghosh , Dr. Sanjeet Kumar Das , Prof Dr. Sk. Abdul Mahmud , Prof Dr. Mousumi Pal

Dept of Oral Pathology, Guru Nanak Institute of Dental Sciences & Research. 157/F, Nilgunj Road, Panihati, Kolkata-700114, W.B.

Corresponding author : Dr. Abhishek Ghosh

Abstract

Carcinogenesis is a complex process involving several steps, requiring the elimination of many cell-imposed barriers such as anti-proliferative responses, apoptosis inducing mechanisms and cellular ageing. This occurs mostly through mutations in oncogenes and tumor suppressor genes. These mutated cancer cells are characterized by their ability to rapidly grow and divide, and to undergo uncontrolled proliferation. There are six distinctive hallmarks that a cell acquires during its progression into malignancy: limitless replicative potential, sustained angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals and tissue invasion and metastasis. These hallmarks have been studied extensively. Two characteristics have recently been added to the list: evasion of immune destruction and reprogramming of energy metabolism.To carry out mitotic division, a cell must duplicate its genome, proteins and lipids and assemble these elements into daughter cells. Tumor cells undergo metabolic reprogramming, which are characterized by changes in the metabolic processes, to satisfy large demands for ATP, NADPH, NADH and carbon skeletons. A detailed understanding of tumour cell metabolism will not only throw light for early detection and screening of cancerous lesions, but will also pave paths for targeted therapy with better patient compliance.

Key-words: Crabtree effect, Warburg effect, hypoxia-inducible factor, Glucose transporters, Reactive Oxygen Species.

Introduction

"Cancer" is a constitutive term explaining a 'biostructure disorder'—uncontrolled cell division, invasive cell growth into adjacent tissues and metastatic implantation to other body sites. One of the most important biochemical hallmarks in tumor cells is the shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis, mainly controlled by specific transcriptional pathways. Activation of Hypoxia Inducing Factor (HIF) due to mutation, stimulating expression of glycolytic enzymes; then evading reliance on mitochondrial oxidative phosphorylation, even under aerobic conditions, thus converts pyruvate to lactate, effect known as Warburg Effect/ Aerobic glycolysis. This acidification of tumor microenvironment often is a strategy to escape drug effectivity. A better understanding of this metabolic reprogramming will lead to identification of important control points that may help in diagnosis or that may be specific targets for the control of the disease.

Overview of normal metabolism

Cells in our body produce energy through a series of chemical reactions or metabolism. Metabolism is considered as a balance between anabolism (building up) and catabolism (breaking down). The food we intake (carbohydrates, proteins, and fat) are converted to energy (or adenosine Triphosphate [ATP] through these metabolic pathways. Carbohydrates are broken down to glucose that is converted to pyruvate and acetyl-coenzyme A (CoA) in glycolysis

or Embden Meyerhof (EM) pathway. Acetyl-CoA is metabolized to a number of intermediate products in the tricarboxylic acid (TCA) cycle, or "Krebs cycle," releasing ATP and high-energy molecule nicotinamide adenine dinucleotide phosphate [NADPH] that result in additional ATPs in oxidative phosphorylation (OXPHOS). Energy is produced in the form of ATPs during aerobic glucose oxidation to carbon dioxide and water.

Protein is broken down to amino acids that help to build pyruvate and acetyl-CoA molecules. Fats are catabolized to a small-chain three-carbon molecules, glycerol and fatty acids. Both anabolism and catabolism pathways are regulated by several hormones (glucagon, glucocorticoids, insulin, and growth hormone).[1]

Metabolizing pathways in cancer

Genetic mutations increase the number of growth factor receptors in cancer cells. Intracellular signaling pathways that promote cellular proliferation may be constantly up-regulated or amplified, allowing malignant cells to self-stimulate growth and proliferation. To sustain this continuous cell proliferation, the biosynthetic capabilities of tumor cells are enhanced, including fatty acid and nucleotide synthesis. On the other hand, beta-oxidation of fatty acids is suppressed and futile cycles are minimized. These changes promote metabolic autonomy of the transformed cells and allow them to acquire an enhanced anabolic phenotype. [2]

The Crabtree effect

Crabtree made a unique observation on the utility of carbohydrates by cancer cells. It was noticed that, for normal cells, the presence of glucose increased respiration a little or had no effect on oxygen consumption. In contrast, glucose decreased oxygen uptake by cancer cells. This respiratory inhibition is known as the Crabtree effect. It is now known that this metabolic transformation of cancer cells is not a specific feature of cancer cells, but is a requirement of rapidly dividing cells such as proliferating hematopoietic progenitor cells, spermatozoa, intestinal mucosal cells, renal cells and embryonic stem (ES) cells.[3]

The Warburg phenomenon

What kind of metabolic reprogramming occurs in cancer cells? In order to sustain the uncontrolled growth rate, cancer cells have adopted a separate mechanism to derive energy from outside. Normal cells do not metabolize glucose to lactate with the availability of oxygen. Only when the oxygen is absent or limiting , normal cells resort to anaerobic glycolysis or metabolism of glucose to lactic acid. On the contrary, cancer cells metabolize glucose to lactate even in the presence of oxygen (aerobic glycolysis). The idea that cancer cells exhibit an altered metabolism was originally conceived by Otto Warburg nearly 100 years ago.

The propensity of cancer cells under well-oxygenated conditions to metabolize glucose to lactate (aerobic glycolysis) is known as the *Warburg effect*. Most cancer cells depend on glycolysis, even in the presence of plenty of oxygen, to generate a considerably lesser amount of ATP with a decreased use of the OXPHOS mechanism.[4]

Usually, cancer cells are highly glycolytic (glucose addiction) in nature and have a "sweet tooth" that avidly take up more glucose than do normal cells from outside. The increased uptake of glucose is facilitated by the overexpression of several isoforms of membrane glucose transporters (GLUTs) as in case of hepatocarcinomas, breast cancer, neuroendocrine carcinomas,

lymphoblastic leukemia and others.[5]

However, the reasons for increased glycolysis in cancer cells (the Warburg effect) are not totally clear. Warburg hypothesized that defects in mitochondrial function might be the reason for dependence of cancer cells on glycolysis for their survival. However, subsequent studies have clearly emphasized a robust role for mitochondrial metabolism in cancer cells. Recent research suggests that the major advantage of the Warburg effect is not the generation of glycolytic ATP but is production of many glycolytic intermediates that are precursors to many anabolic processes such as pentose phosphate pathway; generating NADPH, ribose-6-phosphate, amino acid, lipids, and other cellular sources of energy. [6]

Rapidly proliferating tumor cells not only require high levels of ATP for growth and proliferation, but they also require carbon skeletons for biosynthesis of macromolecules. When these cells use and increase aerobic glycolysis process to obtain ATP, they also conserve carbon skeletons because there is no CO_2 production in glycolysis. If tumor cells were mainly generating ATP through Krebs cycle and OXPHOS mechanism, they would lose more carbon molecule in the form of CO_2. However, the Krebs cycle must function to some extent in tumour cells to fulfill its anabolic role.

The Warburg effect was used in cancer diagnosis and in evaluating the drug response in cancer treatment. Experimental confirmation for the higher uptake of glucose in tumor proper and metastasis sites came from positron emission tomography (PET) imaging, one of the most commonly used imaging techniques for diagnosing tumor growth and response to therapy. The most frequently used PET tracer is fluorinated deoxyglucose (18-FDG). FDG, an analog of glucose, is not metabolized in the glycolytic pathway; rather it is transported by glucose transporters (GLUT 1, GLUT 3, etc.), that exhibit differing affinity for glucose located in the plasma membrane. The increased uptake of FDG indirectly measures the glucose metabolism of tumour cells and other proliferating cells; therefore, it can be used as an imaging biomarker for glucose metabolism and the metabolic capability of cancer. [7]

Metabolism in hypoxic conditions

The micro environment of premalignant epithelial cells inevitably develops hypoxia and acidosis and the partial pressure of oxygen (pO2) inside the tumor is seen to be lower than the surrounding normal tissue.[8] Metabolic reprogramming of tumor cells changes the metabolic processes, increasing glycolysis and reorganising the Krebs cycle in response to the reduced availability of oxygen. One of the main regulatory mechanisms underlying aerobic glycolysis involves hypoxia-inducible factor (HIF-1). [9]

The activation of HIF-1 involves an altered expression of approximately 450 genes regulating the glycolysis, lactate production and lactate/proton extrusion, angiogenesis, metastasis and iron metabolism. In tumor cells, HIF-1 induces the upregulation of some isoforms of glycolytic enzymes that are different from those found in normal cells. These are glucose transporters (GLUT1, GLUT3), glycolytic enzymes (HKI, HKII, PFK-1) and enzymes related to lactate production (LDH-A, MCT4). There is increasing evidence of association HIF-1 function with metastatic characteristics, such as the epithelial to mesenchymal transition (EMT), cell detachment, invasion and tumor cell seeding; HIF-1 overexpression and prevalence is also correlated with the severity of the cancer.[10]

Tumor cell populations are heterogeneous from the point of oxygen concentrations, because tumors contain well-oxygenated (aerobic) and poorly oxygenated (hypoxic) regions. There is evidence that a tumor cell can experience oxygen oscillations, changing from hypoxic to normoxic conditions and vice versa in short periods of time.[11] The

existence of a "metabolic symbiosis" between aerobic and hypoxic cancer cells has also been reported. When tumor cells are cultured under hypoxic conditions, there is over-expression of the glucose transporter GLU-1, which is activated by HIF-1. The enhanced glycolytic carbon metabolism, in turn, increases lactate production. Tumor cells, growing under normoxic conditions, take up lactate instead of glucose supporting the concept of a tumor metabolic symbiosis. In aerobic cancer cells, the monocarboxylate 1 transporter (MCT1) draws lactate inside, which is converted into pyruvate by the lactate dehydrogenase B enzyme (LDHB). Pyruvate then enters the Krebs cycle and intermediaries are used by the OXPHOS pathway for energy production.

When MCT1 is inhibited, aerobic tumor cells tend to consume more glucose than lactate, breaking the metabolic symbiosis. Thus the anaerobic tumor cells die out from glucose deprivation. It has also been found that MCT1 expression is exclusively found in aerobic regions of human tumor cells from head, neck, breast and colon cancers. This result is consistent with the over-expression of LDHB for utilizing lactate as an energy substrate. [12] This phenomenon is of particular clinical importance because the hypoxic zone is known to be especially resistant to chemotherapy and radiation, resulting in treatment failure, disease relapse or finally, mortality of the patient.

Effect of acidic micro-environment

When tumor cells enhance glycolysis and produce large quantities of lactic acid, they generate an acidic environment that is more toxic to the adjacent normal cells than to the malignant cells because tumor cells have developed survival mechanisms. In addition to lactic acid, CO_2 is a significant source of acidic extracellular pH (pHe) in the tumor microenvironment; in the reaction catalyzed by carbonic anhydrase (CA), CO2 is hydrated, producing bicarbonate (HCO_3-) and H+. Hypoxia is usually associated with acidosis, but acidosis can also be seen in the tumor microenvironment under normoxic conditions due to the Warburg effect.

Acidosis promotes the alteration of both cell cycle checkpoints and apoptotic mechanisms.[13] As a result, tumor cells undergo cycles of cellular quiescence and proliferation, depending on nutrient concentrations and pH. Acidosis also promotes extracellular matrix degradation, allowing invasiveness. [14]

Glucose metabolism and cancer cell survival

Glucose deprivation can lead to energy stress and to the selective death of cancer cells in comparison with normal cells. However, the energy stress per se may not be the main cause of this selective cell death. Glucose deprivation reduces the intracellular redox power of cancer cells because it decreases the production of NADPH from the Pentose Phosphate Pathway and from glucose-derived one-carbon metabolism. Thus, glucose deprivation markedly increases the intracellular level of Reactive Oxygen Species (ROS). As highly metabolic cancer cells have higher levels of ROS than normal cells, they may be more prone to ROS-induced cell death.[15]

Glucose transporters. The transport of glucose into cells is facilitated by a family of membrane-bound channels called GLUTs. There are multiple forms of GLUT proteins (GLUT 1, GLUT 3, etc.,) that are up-regulated in several cancers and, in most cases, increased expression of GLUTs is associated with poor prognosis and survival of cancer patients. Thus targeting GLUTs by blocking their glucose transport channel with small molecules might be a viable mechanism of nutrient deprivation in tumors. Currently, there are several GLUT inhibitors, including cytochalasin B and selected tyrosine kinase inhibitors. Some of these compounds are relatively less toxic to normal cells, showing good promise in tumor treatment. [16]

Hexokinases. The utility of the FDG–PET scan to selectively detect cancer cells is not solely due to the high level of glucose transporters in cancer cells, because the reversible glucose transporters might export FDG unless it is phosphorylated and trapped inside the tumour cells. The phosphorylation of FDG is catalysed by enzyme hexokinases. As cancer cells have higher hexokinase activity than most normal cells, the FDG–PET scan could be an indirect proof for the high hexokinase activity of cancer cells.

The high hexokinase activity in cancer cells is due to the induction of HK2 expression. As HK2 is not expressed in most normal adult cells, its systemic ablation could selectively target cancer cells.[17] Importantly, no compensatory induction of HK1 expression was observed. However, because of the structural similarities between HK1 and HK2 , developing small-molecule inhibitors that preferentially inhibit HK2 could be challenging.

2-DG. One of the first antiglycolytic antitumor strategies is the use of 2-deoxyglucose (2-DG). The compound 2-DG acts as a competitive inhibitor of glucose metabolism. 2-DG is taken up into cells through the same transporters and phosphorylated by HK to 2-DG-P. 2-DG-P cannot be further metabolized by phosphohexose isomerase to the fructose-6-phosphate. As a result, glycolysis is inhibited and the net result is lowered ATP levels in cancer cells treated with 2-DG and thus resulting in decreased proliferation. One of the side effects of 2- DG is toxicity to normal cells like skeletal muscles and neuronal cells, which are dependent on glucose for energy. 2-DG only partially blocks glucose utilization; consequently, glycolysis is only partially inhibited. 2-DG as a single chemo-therapeutic agent in cancer treatment has not been successful but has shown promise in multimodal cancer therapy. [18]

Pyruvate oxidation. Pyruvate is considered as a "hub" metabolite (being at the interface of glycolysis and TCA cycle) in cell metabolism and especially plays a crucial role in regulating metabolic reprogramming in cancer cells. Several forms of Pyruvate Kinases (PKM1, PKM2, etc.) are over-expressed in tumor cells.[19] Dichloroacetate (DCA), a drug that has shown promising chemotherapeutic effect in preclinical tumor xenograft studies and in humans with glioblastoma (an aggressive form of brain tumor), presumably inhibits pyruvate dehydrogenase kinase (PDK), thereby shifting the glucose metabolism from a glycolytic to oxidative pathway.[20] Several clinical trials for testing DCA as an anticancer agent are going on.

Lactate dehydrogenase A. LDHA is a major glycolytic enzyme responsible for converting pyruvate to lactate coupled with NAD+ recycling. LDHA is overexpressed in several tumor cells.[21] Inhibitors of lactate metabolism are being developed. LDHA inhibitors deplete NAD+ and therefore inhibit glycolysis. The mechanism of action of LDHA inhibition is more or less similar to that of DCA in that pyruvate is "forced" to enter the mitochondria for undergoing decarboxylation to acetyl-CoA, finally resorting to enhanced mitochondrial activity.

Fatty acid oxidation/role of fat on tumor metabolism

If glucose consumption does not increase proportionately to keep up with the energy demands of rapidly proliferating cancer cells, the cells move to fatty acid oxidation (FAO). Normal cells typically acquire fatty acids from dietary sources. On the other hand, tumor cells exhibit a marked increase in *de novo* fatty acid synthesis. Thus, some tumor cells (ovarian tumor tissues) have increased monoacylglycerol lipase (MAGL) activity.[22]

This enzyme hydrolyzes monoglycerols and releases glycerol and free fatty acids (FFAs). Aggressive cancers utilize this mechanism to acquire FFAs. MAGL is shown to promote tumorigenesis by increasing the FFA levels. *De novo* lipogenesis involves conversion of acetyl-CoA to palmitate, which is catalyzed by fatty acid synthase. The newly

synthesized FFAs are converted into neutral lipid stores and released by MAGL. In addition to glycolysis, which serves as a predominant mechanism, the oxidation of fatty acid provides an alternate route for meeting the energy needs of tumor cells. Studies suggest that MAGL is a promising target for therapeutic cancer treatment.[23]

The metabolic relationship between tumour and stroma: symbiotic or parasitic ?

The trade in metabolites between stromal cells and the cancer cells themselves is considered as an important facet of tumour metabolism, and often involves the transport of amino acids. Bidirectional relationship between cancer-associated fibroblasts (CAFs) and cancer cells was recently reported. In this model, it was depicted that CAFs provide aspartate to cancer cells, which is taken up via the transporter named SLC1A3 (also known as the excitatory amino acid transporter 1 [EAAT1]) to support nucleotide biosynthesis, while tumour cells reciprocate with glutamine-derived glutamate to the CAFs through the same transporter. [24]

Interestingly, the expression of SLC1A3, a transporter originally described in regulating extracellular glutamate levels in neuron synapses, was more recently described as being regulated by p53 in cancer cells, providing the cells with aspartate during glutamine deprivation.[25] This metabolic relationship is of utmost benefit for the cancer cell and may lead to less reliance on the oxidative TCA cycle for proliferation, given that glutamate is swapped for aspartate rather than oxidatively metabolised to synthesise it.

The two examples given above show two relationships between cancer and stromal cells: one in which both cells are benefited, and another in which the cancer cells take advantage of the stromal activity. This is also the case when the cell providing the required amino acid and the cancer cell are physically more distant. For example, the process of tumour-associated cachexia, in which muscles and adipose tissue are progressively catabolised, is often observed in late-stage cancer patients as their tumours continue to require nutrients in excess of what is contained in the diet.

An alternative route by which cancer cells can take up amino acids en masse, comes in the form of macropinocytosis. Described as ‘cell-drinking’, it is a process in which cells take up materials of their microenvironment, shown by a number of cell types under non-pathological conditions. These proteins are catabolised through the autophagy by the cancer cells, providing free amino acids for new protein synthesis, or catabolism to produce ATP. [26]

This process helps the cancer cells to survive in relatively nutrient-poor environments, taking up a number of different macromolecules derived from both the periphery (such as accumulating in oedema) and necrotic areas of the tumour. It may also play an important role in hypoxic tumour regions, where not only the exogenous nutrients are limiting, but also necrotic areas are juxtaposed to the malignant cells.

Tumours have therefore developed diverse mechanisms to provide themselves a supply of the amino acids that are required for malignant progression. It is also the case that many of these mechanisms are probable targets for novel therapy. However, care will need to be taken to avoid on target side effects.

Conclusions

Throughout this review, we have described how tumor cells change their metabolism in comparison to the normal cells. Tumor cells undergo metabolic reprogramming to modify their metabolic processes in response to large demands for, not only ATP, but also NADPH, NADH and carbon skeletons for housekeeping, growth and proliferation, depending on the changes in their microenvironment. However, not all tumor cells go through the

same metabolic states at the same time, and they do not stay in that state indefinitely. The changing tumor microenvironment (e.g., nutrient and oxygen availability and acidosis) seems to exert selective pressures on tumor cells, modifying their metabolic pathways to survive. Hypoxia has been the best seen selective force that directs this metabolic adaptation. Moreover, acidosis has also been shown to promote metabolic reprogramming in tumor cells, leading to the inhibition of glycolysis and the use of OXPHOS as the main pathway of ATP production. Although the Warburg effect was originally associated with mitochondrial dysfunction, it is now proved that tumor cells need to maintain functional mitochondria to reprogram their metabolism in the ever-changing microenvironment.

Hypoxia/HIF-1-targeting gene therapy is a newer tumor-specific approach with few side effects in normal tissues, and has the potential to enhance the effect of radiation therapy. Some approaches are now in clinical trials and are expected to make breakthroughs in cancer therapy. The study of the metabolic reprogramming processes that support tumor development will allow us to find specific markers to establish an early diagnosis, to make prognostic tools and to find selective and targeted treatments for limiting or preventing tumor growth. Thus, survival and quality of life will definitely be improved for cancer patients.

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