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THE METABOLIC YELLS IN CANCER CELLS

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ABSTRACT

Cancer is the disease that has become the most catastrophic threat to human survival. Although researchers have been in constant search of novel diagnostic, prognostic and therapeutic strategies with might and main; yet the evil paves its way by diverse mechanisms. A growing tumor requires energy for its survival and metastasis. Till a certain point of time, the cells derive it from their external environment, but when the environmental conditions worsen due to the continuous growing of tumor, oxygen and nutrients in their vicinity are depleted. In such conditions of hypoxia and the seemingly 'draught' like situations for these tumor cells, the cells themselves start metabolizing the constituents within them or at times around them, but more judiciously. This implies that the cancer cell exhibit metabolic events that are different than those that occur in healthy cells of the body. Moreover, due to the constant replication and other cellular processes, the tumor cells need to get rid of the toxic metabolites more efficiently for survival. All these circumstances, justify that the cancer cell metabolic pathways need to be explored further in order to effectively exploit the elements of the same for the targeting of the tumors. Thus a brief review of literature has been compiled here to acknowledge such targetable insights in the tumor biology, with a vision to evoke more effective diagnostic, prognostic and therapeutic protocols in cancer.

KEYWORDS: tumor, oxygen and nutrients.

INTRODUCTION

Cancer is one of the deadliest threats to human survival, and despite vast research in its pathologic, diagnostic and therapeutic fields, it still remains to claim a number of lives. This is because of the diverse adaptations adopted by the tumor cells that help them to become such devastating. Unfortunately these are the mechanisms that mostly stay unexploited during the formulation of diagnostic and therapeutic strategies. Growing tumors face two major metabolic challenges; first one as how to meet the bioenergetic and the biosynthetic demands of the increased cell proliferation and the second one being how to survive the environmental fluctuations in external nutrient and oxygen deprivation when tumor growth outpaces the delivery capabilities of the existing vasculature. The persistent appeal of cancer metabolism as a line of investigation lies both in its ability to uncover the fundamental aspects of malignancy and in the translational potential of exploiting cancer metabolism to improve the way we diagnose, monitor, and treat cancer.

It is now well established that the process of carcinogenesis, involves a profound change in the metabolic scenarios of the cancer cells and the pioneer for the proposal of the same was Otto Warburg, in 1930, where he derived the relationship between the altered glucose metabolism and the proliferating cancer cells. He showed that highly proliferating cells experience a shift from oxidative metabolism to increased anaerobic glucose consumption.[1] The trigger factors for such an alteration can be attributed to the various oncogenes such as ras, wnt, or AKT, cell cycle regulators such as the CDK4-E2F1 axis, as well as some viral gene products and this has well been documented.[2]

Likewise, metabolic changes have been now reported in recent past, with respect to the other metabolic pathways like the proteins, lipids, vitamins, minerals, etc. Thus an attempt has been made to compile all of them with an intention to broaden the insight into the subject of cancer cell metabolism.

Glucose Metabolism

Glycolysis is a catabolic process that converts one molecule of glucose to two pyruvates with the production of two ATP and two reduced nicotinamide adenine dinucleotide (NADH) molecules. Pyruvate in the presence of oxygen undergoes oxidation to CO_2 and H_2O in the oxidative phosphorylation pathway, resulting in the production of 36 molecules of ATP. Alternatively, in the absence of oxygen, pyruvate is transformed into lactic acid in the anaerobic glycolysis pathway. Cancer cells, pose an alteration here, and that is, they convert glucose to lactic acid even in the presence of oxygen, the well known concept of Warburg effect or aerobic glycolysis.[3]

Most cancer cells produce large amounts of lactate regardless of the availability of oxygen.[4] This increases glycolysis is considered by some as the seventh hallmark of cancer[5] (others initially proposed by Hanahan and Weinberg[6], being limitless replicative potential, self-sufficiency in growth signals, resistance to apoptosis, insensitivity to antigrowth signals, sustained angiogenesis, and tissue invasion and metastasis).

In the early phase of carcinogenesis, uncontrolled cell proliferation moves the tumor cells away from the blood vessels and thus from the oxygen and nutrient supply. Thus the partial oxygen pressure drops to very low values 100µm away from the blood vessels.[7] This implies that hypoxia and glucose shortage are rapidly generated in the inner mass of a growing tumor. Paradoxically it is known since 1920 that the tumor cells have a much higher rate of glucose consumption through a glycolysis pathway that does not send pyruvaye to krebs cycle but rather converts pyruvate to lactate : the so called Warburg effect[8] . In fact many tumors use this glucose to lactate pathway even in the presence of oxygen, explaining why the term aerobic glycolysis is frequently used to substitute the term 'Warburg effect'.
It is important to note that this glycolytic switch is not accompanied by a reduction in oxidative phosphorylation[9] and this implies that a targeted therapy protocol is possible for cancer without hampering the metabolism of normal cells.

The metabolic intermediates of the Warburg phenomenon like the glucose 6-phosphate and pyruvate are utilized by the dividing cells in the production of nucleic acid and lipid synthesis respectively which are further essential for DNA replication and macromolecules formation needed by the dividing cells.[10] The final product, lactate, additionally serves by acidification of tumor microenvironment and thus ushering many deleterious effects by creating a favourable niche for the cancer cells.

Lactate metabolism in tumors mainly involves a cell to cell or cell lactate shuttle. The lactate dehydrogenase (LDH) reaction is a rapid, near equilibrium reaction that lies heavily in the direction of lactate; any time glycolysis is active, lactate is formed and equilibrates with local lactate gradients. Lactate equilibrates mainly by diffusing across membranes via monocarboxylate transporters (MCTs). In lactate-producing tissues or situations, this often means exporting lactate into circulation, where both local and distant tissues can take it up and use it as a fuel.

Lactate and the hallmarks of malignancy

1. Contribution to immune escape

One major reason for tumor development is the inability of the immune system to adequately eliminate aberrant cells. Several escape mechanisms of tumor cells have been elaborated, including upregulation of inhibitory molecules, production of immunosuppressive cytokines, and downregulation of co-stimulatory molecules. Besides these mechanisms, tumor metabolism largely contributes to the immunologic escape. Recently, extracellular lactate was found to inhibit the differentiation of monocytes to dendritic cells(DC)and to inactivate the cytokine release from DCs[11] and cytotoxic T cells, the key player in antitumoral response.

Furthermore activated T cells themselves use glycolysis as their main energy source.[12] When the tumor cells release high amounts of lactate to the extracellular space, the immune cells cannot rid themselves of their own lactate, because cellular lactate secretion is dependent on the ratio of intra- to extracellular concentration. Ultimately, leukocytes may be asphyxiated by lactate. Because cellular lactate secretion via the MCTs is accompanied by H^+ transport, a decrease in extracellular pH results in a reduction of cytotoxic T-cell function.[13]

2. Influence on cell migration

In classic Boyden chamber experiments, the addition of exogenous lactate led to a concentration-dependent increase in random migration of various cancer cell lines.[14] This was true for lactate levels that are relevant for solid tumors in vivo (i.e., 0–40 mmol/L). Furthermore, the lactate-mediated enhancement of tumor cell motility was seen not only in single-cell motion but also in enforced bulk migration by means of time-lapse videomicroscopy.[14] Although lactate induced changes in signaling protein levels and their activation status, such as β1-integrins, have been registered, the molecular mechanisms involved in the impact of lactate on cell motility are still not understood. Recent data support the TGF-β2 signaling pathway as being a mediator of the lactate-associated effects on migration of cancer cells .

Employing the same experimental setup as that used for cancer cells, Goetze and colleagues[14] showed that exogenous lactate invariantly inhibited the migration of monocytes. This finding was paralleled by a concentration-dependent reduction of cytokine release, such as that of IL-6 or TNF-a.

Furthermore, these experiments showed that lactate stimulates VEGF production by endothelial cells (EC),

leading to enhanced migration and resulting in lactate-induced angiogenesis independently of O2 conditions.[15]

Also, lactate added to cultured fibroblasts increases their hyaluronan production and leads to elevated expression of CD44, a transmembrane glycoprotein and the predominant hyaluronan receptor on cell surfaces. The stroma that surrounds carcinomas has increased hyaluronan produced by tumor associated fibroblasts (TAF), providing an environment that promotes the growth and motility of cancer cells.[16,17]

3. Contribution to radioresistance

Anticancer therapies, such as ionizing radiation and several chemotherapeutic drugs, induce oxidative stress in targeted cells. Overproduction of reactive oxygen species (ROS) leads to DNA and RNA damage, lipid peroxidation, and genomic instability. ROS are required for the fixation of radiation-induced DNA damages; therefore, an accumulation of antioxidants (e.g., lactate) may induce or enhance resistance to radiation and may cause chemoresistance.[18]

Results from a study group on experimental tumors, including more than 1,000 individual xenografts of human HNSCC, showed that lactate concentrations are positively correlated with radioresistance.[19]. This correlation could be due, at least in part, to the antioxidant properties of lactate as revealed in various such studies.[20]

Applications

1. The augmented glycolytic activity of the tumor cells is exploited by Positron Emission Tomography for the identification of metastatic lesions. This technique takes advantage of the increased ability of the tumor cells to take up and metabolise glucose compared with the normal tissues.[10]
2. Assessing the concentration of LDH (by induced metabolic bioluminescence imBI technique) for the prognosis.[21] Because lactate has been shown to decrease after chemotherapy or radiotherapy in animals,[22] and thus monitoring this metabolite in human tumors may allow for the prediction of therapeutic responses. Besides lactic acid, it has been recently hypothesized that the pyruvic acid levels in serum and saliva can serve the same.[23]
3. Therapeutically, drugs can be formulated that are weakly acidic rather than the conventional weakly basic to avoid the protonation of drugs and hasten their uptake. Moreover studies have shown that the addition of sodium bicarbonate in drinking water increased the uptake of the weakly basic drugs while addition of glucose decreased it. Thus, the need for dietary modulations is justified.[10] Also, recently researchers have been introducing drugs that target the enzyme specific reactions in the altered glucose metabolism and thus limiting the same.[24,25]

Protein Metabolism

Among all the essential and non-essential amino acids, glutamine and proline metabolism in cancer cells has been studied extensively in the recent past. The importance of glutamine as a nutrient in cancer derives from its abilities to donate its nitrogen and carbon into an array of growth-promoting pathways (Figure 1). At concentrations of 0.6–0.9 mmol/l, glutamine is the most abundant amino acid in plasma.[26] Although most tissues can synthesize glutamine, during periods of rapid growth or other stresses, demand outpaces supply, and glutamine becomes conditionally essential.[27] This requirement for glutamine is particularly true in cancer cells, many of which display oncogene- dependent addictions to glutamine in culture.[28] Glutamine catabolism begins with its conversion to glutamate in reactions that either donate the amide nitrogen to biosynthetic pathways or release it as ammonia. The latter reactions are catalyzed by the glutaminases (GLSs), of which several isozymes are encoded by human genes GLS and GLS2.[29]

Glutamate, the product of the GLS reaction, is a precursor of glutathione, the major cellular antioxidant. It is also the source of amino groups for nonessential amino acids like alanine, aspartate, serine, and glycine, all of which are required for macromolecular synthesis. In glutamine-consuming cells, glutamate is also the major source of α-ketoglutarate, a TCA cycle intermediate and substrate for dioxygenases that modify proteins and DNA. These dioxygenases include prolyl hydroxylases, histone demethylases, and 5-methylcytosine hydroxylases. Their requirement for α-ketoglutarate, although likely accounting for only a small fraction of total α-ketoglutarate utilization, makes this metabolite an essential component of cell signaling and epigenetic networks.[30]

Conversion of glutamate to α-ketoglutarate occurs either through oxidative deamination by glutamate dehydrogenase (GDH) in the mitochondrion or by transamination to produce nonessential amino acids in either the cytosol or the mitochondrion. During avid glucose metabolism, the transamination pathway predominates.[31] When glucose is scarce, GDH becomes a major pathway to supply glutamine carbon to the TCA cycle, and is required for cell survival.[31,32] Metabolism of glutamine derived α-ketoglutarate in the TCA cycle serves several purposes: it generates reducing equivalents for the electron transport chain (ETC) and oxidative phosphorylation, becoming a major source of energy;[33] and it is an important anaplerotic nutrient, feeding net production of oxaloacetate to offset export of intermediates from the cycle to supply anabolism.[32] Glutamine oxidation also supports redox homeostasis by supplying carbon to malic enzyme, some isoforms of which produce NADPH. Under conditions of mitochondrial dysfunction, glutamine-derived α-ketoglutarate is reductively carboxylated by NADPH-dependent isoforms of isocitrate dehydrogenase to produce isocitrate, citrate, and other TCA cycle

intermediates. These conditions broaden glutamine's utility as a carbon source because it becomes not only a major source of oxaloacetate, but also generates acetyl-CoA in what amounts to a striking rewiring of TCA cycle metabolism.

Glutamine and the hallmarks of malignancy

1. Deregulated energetic

One hallmark of cancer cells is aberrant bioenergetics.[34] Glutamine contributes to a phenotype conducive to energy formation, survival, and growth. In addition to its role in mitochondrial metabolism, glutamine also suppresses expression of thioredoxin interacting protein, a negative regulator of glucose uptake.[35] Thus, glutamine contributes to both of the energy-forming pathways in cancer cells: oxidative phosphorylation and glycolysis.

2. Sustaining proliferative signaling

Pathological cancer cell growth relies on maintenance of proliferative signaling pathways with increased autonomy relative to non-malignant cells. Several lines of evidence argue that glutamine reinforces activity of these pathways. In some cancer cells, excess glutamine is exported in exchange for leucine and other essential amino acids. This exchange facilitates activation of the serine/threonine kinase mTOR, a major positive regulator of cell growth.[36] In addition, glutamine-derived nitrogen is a component of amino sugars, known as hexosamines, that are used to glycosylate growth factor receptors and promote their localization to the cell surface. Disruption of hexosamine synthesis reduces the ability to initiate signaling pathways downstream of growth factors.[37]

3. Enabling replicative immortality

Some aspects of glutamine metabolism oppose senescence and promote replicative immortality in cultured cells. Studies have shown that, silencing either of two NADPH-generating isoforms of malic enzyme (ME1, ME2) rapidly induced senescence, while malic enzyme overexpression suppressed senescence.[38] Malic enzymes thus have been suggested as potential therapeutic targets.

4. Resisting cell death

Glutamate due to a constant supply of TCA cycle intermediates, resists apoptosis and help in cell survival.[38]

Apart from glutamine, proline is another important amino acid that has been studied experimentally in cancer cells. It is used for signaling as well as an alternate source of ATP. During nutritional plenty, proline is stored in collagen, the main component of ECM. This reservoir of proline can be mobilized during conditions of nutritional stress. It is frequently converted to glutamine, to serve the further functions, thereby releasing energy or synthesizing purines and pyrimidines de novo. [40] In addition to this it has also been suggested to maintain the pluripotency of embryonic stem cells and inducing within them a mesenchymal phenotype.[41]

Thus, by using collagen as a 'dump' for reducing equivalents in the form of proline, tumors can optimize conditions for metabolism and growth.

Applications

1. Glutamine analogs infusion may be used for the positron emission tomography, thereby helping in the diagnosis and the screening of tumor lesions. C^{11}, N^{13} or F^{18} may be used as the radioisotopes for glutamine imaging.[30] This application has also been used for monitoring the therapeutic outcome in cancer patients.
2. Various selective and non-selective inhibitors of glutamine metabolism have been tried as therapeutic agents. The outcome largely depends upon the extent of glutamine metabolism by a particular tumor.[30]

Lipid metabolism

Lipids encompass a vast class of biomolecules of unique chemical structure in terms of fatty acid (FA) chain length, number and location of double bonds as well as backbone structures. Important changes in lipid composition (saturated (SFA) vs unsaturated FA) and abundance severely alter membrane fluidity and protein dynamics. For example, an increase in saturated phospholipids (PLs) markedly alters signal transduction, protects cancer cells from oxidative damage such as lipid peroxidation and potentially inhibits the uptake of chemotherapeutic drugs.[42,43] In addition to their structural roles, lipids orchestrate signal transduction cascades and can also be broken down into bioactive lipid mediators, which regulate a variety of carcinogenic processes, including cell growth, cell migration and metastasis formation.[44,45,46]

The lipid reprogramming in tumors has been studied by tumor-specific gene expression profiling and tumor specific lipid profiling. It has been identified that there is an up regulation of transcripts involved in lipogenesis and cholesterol synthesis pathways, which are essential for the development and progression if various tumors. Increased expression of lipogenic enzymes, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), and ATP citrate lyase (ACLY) that promote cholesterol synthesis, represent a nearly-universal phenotypic alteration in most tumors.[47,48] FASN overexpression predicts poor prognosis in cancer patients.[49] Also, FAO-limiting enzymes, the carnitine palmitoyltransferase 1 isoforms A and C (CPT1A and C) are overexpressed in many human tumors.[50]

Lipid profiling indicated a striking increase in membrane phosphatidylcholine and phosphatidylethanolamine which was enriched in saturated fatty acid (SFA); and this composition was correlated with high tumor grade and poorer overall survival. This membrane lipid saturation, a feature shared by all lipogenic tumors,[42] reduced membrane fluidity and dynamics and increased chemotherapy resistance.[51]

Lipids and the hallmarks of malignancy

1. Increased lipid rafts

Cell membranes contain different classes of lipids, some of which, in particular cholesterol and sphingolipids, form specific planar microdomains known as lipid rafts.[52] In cancer cells, a wide range of signaling proteins and receptors regulating pro-oncogenic and apoptotic pathways during the early, advanced and metastatic stages of carcinogenesis reside in lipid rafts.[53] Moreover, lipid rafts and their main component, cholesterol, are enhanced in membrane of multiple cancer cells as well as in membranes of tumor-released exosomes.[54]

2. Cancer-stroma interplay through free FAs

Numerous tumors grow in the vicinity of adipocytes or metastasize to adipocyte rich host environment which constitutes an important reservoir for triglycerides(TG). Hydrolysis of these TG provides free FA (FFA), which are taken up and used as energy source by the metastatic cancer cells. Lipoproteins, serum albumin and exosomes play a key role as carriers of FAs for the same.[55]

3. Tumor–stroma crosstalk orchestrated by prostaglandins

Moreover, an increase in prostaglandins(PG), the tumor derived PGE_2 promotes tumor growth by the pro-angiogenic activity and evasion of immune response[45] Also, tumor-derived PGE2 activates the CAF-dependent secretion of a tryptophan catabolite, the kynurenine, which in turn increases cancer cell invasiveness.[56]

4. Sphingolipid derivative as a mediator of tumor–stromal cell crosstalk

Sphingosine-1-phosphate (S1P), another bioactive lipid secreted by cancer cells, induces angiogenesis and lymphangiogenesis through its binding on S1P receptor 1, and facilitates tumor growth and metastasis formation.[57]

Together, these findings highlight the crucial role of lipids in supporting the tumor-tumor microenvironment crosstalk, which is essential for tumor cell proliferation and dissemination.

Applications

1. The levels of certain intermediates or enzymes involved in the lipid metabolism may be assessed for the purpose of diagnosis and prognosis. For example, levels FASN and FAO-limiting enzymes have been correlated with the prognostic outcome in many cancers.[49,50]
2. Therapeutically, drugs may be formulated that help limiting the supplies of FAs, blocking fatty acid synthesis, blocking expression of FA synthesis genes, increasing FA degeneration, diverting FA to storage and blocking FA release from the storage to limit cancer cell proliferation.[58]
3. Additionally, the lipid and cholesterol dependence of the cancer cells may be targeted by using inhibitor agents directed against lipogenic enzymes like FASN and others.[59]
4. As seen above the role of lipid rafts, these can also be considered as the targets for therapy and thus anticancer drugs that disturb membrane cholesterol content can be used to impair lipid raft-dependent cell survival or cell death pathways.[60]
5. Targeting either the lipid messengers or their carriers between stromal and tumor cells willdisrupt the tumor-stroma crosstalk. Also has been reported that the use of COX-2 enzyme inhibitor, Celecoxib, to disrupt PG synthesis has revealed its strong antitumoral and antimetastatic effect in various preclinical models.[61]
6. Any disruption in the lipid homeostasis, eventually ushers in the endoplasmic reticulum stress induced apoptosis and thus may help as a therapeutic strategy.[62]

Mitochondria: From Engine to Biosynthetic Hub

The majority of macromolecules required for proliferation (i.e., lipids, proteins, and nucleic acids) are generated de novo from glucose. The remaining pyruvate from aerobic glycolysis that is not converted to lactate (10% of total) enters the mitochondrion and is extruded from the TCA cycle at various steps for use in biosynthetic pathways. Thus, in addition to its role as cellular energy center, the mitochondrion takes up a new role as a biosynthetic hub to meet the increased biosynthetic demand during proliferation, converting metabolites such as pyruvate and glutamine into intermediates utilized by other biosynthetic pathways.

Vitamins and the cancer cell metabolism

Besides the metabolic alterations in the above macronutrients, certain micronutrients like vitamins and minerals also have an altered story to narrate regarding their metabolism in cancer cells. Amongst the many, thiamine (Vitamin B1) and Vitamin A have been researched with respect to cancer cell metabolism.

Thiamine is classified as an essential water-soluble vitamin requiring continuous dietary intake to support carbohydrate metabolism. Thiamine is critical for the activity of four key enzymes in cellular metabolism, pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (α-KGDH) in the tricarboxylic acid (TCA) cycle, transketolase (TKT) within the pentose phosphate pathway (PPP), and branched chain alphaketo acid dehydrogenase complex (BCKDC) involved in amino acid catabolism.[63] This implies that excess thiamine will help the cancer cells proliferate by hastening the activity of the required enzymes.

Studied have revealed a low thiamine status in cancer patients and have attributed the finding to the fact extensive accumulation and/or utilization of thiamine by the cancer cells thereby depleting it from the peripheral blood.

Although the impact of thiamine supplementation on tumor growth has received negligible attention, it has been hypothesized that the over-the-counter availability of multivitamin supplements may be hazardous in the unsuspecting manner. Also is hypothesized that a

Western diet characterized in part by excess thiamine supplementation , may be a factor for increased cancer incidence compared to other countries.[65]

Disturbance in vitamin A metabolism seems to be an important attribute of cancer cells. Retinoids, particularly retinoic acid, have critical regulatory functions and appear to modulate tumor development and progression. The key step of vitamin A metabolism is the esterification of all-transretinol, catalyzed by lecithin/retinol acyltransferase (LRAT). In a study published in 2012, it was proposed that ATRol esterification by LRAT and the subsequent isomerization of all-trans-retinyl esters to 11 cis Retinol could be an important feature of vitamin A metabolism in melanoma cells leading to a disturbance in the cellular retinoid level by removal of all-trans-retinol. Consequently, the decreasing cellular amount of all-trans-retinoic-acid and its precursor molecules should result in a change of gene regulation. The data thus implicated that aberrant vitamin A metabolism may be involved in the process of melanomagenesis.[66]

Drug Metabolism

Anticancer or chemotherapy drugs are powerful chemicals that kill cancer cells by arresting their growth at one or more checkpoints in their cell cycle. Their main role is thus to reduce and prevent the growth and spread of cancer cells. In vivo, after absorption in the organism, xenobiotics (including anticancer drugs) are typically metabolized through a number of parallel and/or sequential reactions. Metabolism occurred through two distinct consecutive phases named “phase I” and “phase II”. Phase I reactions are most commonly described as “functionalization” reactions and include oxidations, reductions, and hydrolysis[67]. Phase II reactions are most commonly described as conjugation reactions and include glucuronidation, sulfonation, glycine/glutamine conjugation, acetylation, methylation, and glutathione (GSH) conjugation.[68]

The enzymes Cytochrome p-450s (CYP) and glutathione transeferases (GST) are the key enzymes belonging to the phase I and phase II reactions respectively.[69]

In cancer, alterations in drug pharmacokinetic and metabolism, modification of drug target expression or function, drug compartmentalization in cellular organelles, altered repair of drug-induced DNA damages, changes in apoptotic signaling pathways or expression of proteins directly affecting cellular drug transport are responsible for anticancer drug resistance.

The newer drug strategies need to acknowledge the alterations that take place in the drug transporters, and attempt at reducing the transporters that cause efflux of drugs out of the cells.[70] The alterations in the drug metabolizing enzymes must also be given a due consideration. Besides this, the surrounding environmental pH that falls due to the presence of lactate also hampers the drug metabolism and thus must be considered and the therapeutic strategies be modulated accordingly.[13]

The Possible Mechanisms for the altered metabolism in the cancer cells

Primary defect in OXPHOS have been invoked to explain the Warburg phenomenon because tumor mitochondria are often relatively small, lack cristae and are deficient in the β F1 subunit of the ATP(synth)ase.[71] Besides this, a mutant mtDNA encoded NADH dehydrogenase subunit 2 concomitantly stimulates aerobic glycolysis, reactive oxygen species(ROS) production and tumor growth.[72]

One of the principal mechanisms of aerobic glycolysis resides in the activation of hypoxia inducible factor α(HIFα), a transcription factor that is activated by hypoxic stress, but also by oncogenic, inflammatory, metabolic and oxidative stress. It stimulates the conversion of glucose to pyruvate and lactate by upregulating the glucose transporter isofoem 1 (GLUT1). Hexokinase 1 and 2 and lactate dehydrogenase A as well as the lactate extruding enzyme monocarboxylate transporters 4.[73]

Besides the central role of HIF 1 activation, oncogenes and tumor suppressor genes like p53 also determine the metabolic reprogramming of cancer cells.[74]

The Possible Advantages of altered metabolism to cancer cells

1. Cells can survive in the conditions of fluctuating oxygen tensions with the help of aerobic glycolysis.[75]
2. The principal end product of aerobic glycolysis, the lactic acid, conditions the tumor environment and favor tumor invasion and evasion of the immune response. The lactate so produced can be used by the surrounding stromal cells to refuel the cancer cells by generating pyruvate.[76]
3. By metabolizing glucose through the pentose phosphate pathway, cancer cells can generate NADPH that ensures cells’ antioxidant defences. Moreover this NADPH acts as a source of fatty acid generation.[77]
4. The intermediates of the glycolytic pathway are utilized for the anabolic reactions. For example, glucose 6- phosphate for glycogen synthesis, dihydroxyacetone phosphate for triglyceride and phosholipid synthesis and pyruvate for alanine and malate synthesis.[77]

Hallmarks of Malignancy fulfilled?

1. Self sufficiency in growth signals

Cancer cells partially inhibit the pyruvate kinase isoform PKM_2 which allows theintermediates of glycolysis to divert towards the anabolic reactions. To add on, there is a general increase in the glycolytic flux. This helps

sustaining a constant nutrient supply and thus a self sufficiency in growth signals.[78]

2. Evasion of apotosis

Hexokinase(HK), an enzyme in the glycolytic pathway is associated with the voltage dependent anion channels(VDACs) which in cancer cells is tightly associated to the outer membrane of VDACs. This is attributed in part to the Akt gene which induces translocation of HK to the outer mitochondrial pathway by phosphorylating it. This reduces in turn the mitochondrial membrane permeability which is required for effective apoptosis.[79]

3. Limitless replicative potential

p53, a tumor suppressive gene, gets inactivated in an hypoxic environment and this inactivation leads to the occurrence of Warburg effect. The exact pathway still remains to be unclear but this provides a limitless replicative potential to the tumor cells.[74]

4. Sustained angiogensis

Expression of vascular endothelial factor (VEGF) is induced by HIF1-α. Thus, a constant blood and nutrient supply is attempted to be sustained even in the conditions of hypoxia.[80]

5. Tissue invasion and metastasis.

HIF1-α activation causes the loss of E-cadherins which is required for the maintenance of intercellular contacts within the epithelia and the loss of it results into epithelial mesenchymal transition(EMT). Also the proteins like chemokine receptor proteins (CXCR4) and lysyl oxidase(LOX) are activated by HIF1-α. Both of these favour invasion and metastasis.[74] In addition to this, the acidification of the tumor microenvironment due to the excess production of lactic acid, help the activation of cathepsins and metalloproteinases thus degrading the extracellular matrix and basement membranes.[25]

6. Escaping the immunosurveillance.

HIF1-α increases the infiltration of tumor associated macrophages that exert an immunosuppressive effect.[81] Also as already seen, acidification of the tumor microenvironment results into asphyxiation of the killer T cells and reduced differentiation of monocytes to the dendritic cells. This helps the cancer cells in escaping the immune surveillance.[25]

CONCLUSION

Alterations in the cancer cell metabolism pose to be the drivers of a malignant process. The cancer cells utilize the macro and the micro nutrients available to them both exogenously or due to their own synthetic pathways to obtain energy and synthesize products required for uncontrolled proliferation. Although therapeutically, conventional measures attempt at restoring the complete health of a cancer patient by vigorous nutritional supplementation, care must be taken that the same doesn't turn out to be a bane in disguise.

Conflict of interest statement

None

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