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Cancer Cell Metabolism: A Review

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ABSTRACT

It has been known for decades that cancer cells exhibit enhanced rates of Glucose uptake and glycolysis. Rapidly growing Tumor cells display remarkably different metabolic autonomy from the tissues which they are derived. Tumor cells alter their metabolism to support growth and proliferation. In this study, we have re-examined the metabolism in tumor cells and have made an attempt to bring together the major contributions made to this topic till date. This review in particular highlights the altered metabolism in the high energy demanding tumour cells, genetic changes that alter tumour cell metabolism and the role of metabolic microenvironments that may promote malignant progression.

Keywords: Crabtree, Warburg, Metabolic microenvironments, Hypoxia, pH,

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INTRODUCTION

Over the past few decades, increased researches related to the metabolic adaptations of the cancer cells has resulted in the augmentation of evidences that suggest an association of the several pathways of human metabolism with the cancer cells[1,2,3]. Tumour cells are less specialised than the normal cells[4] which help them ignore signals to sustain an uncontrolled division[5] and defy apoptosis mediated particularly by oxidative damage[6]. For a cell to divide rapidly, it must be nutrient hungry of the major metabolically demanding macromolecules viz. carbohydrates, proteins, lipids and nucleic acids. However, these essential nutrients are only present in concentrations that are spatially and temporarily heterogenous[7]. Therefore, it is required that the cancer cells adapt to this stressful microenvironment of the growing tumour. It is this anabolic drive that redesigns the tumour cell's metabolic pathway for its better survival and growth.

Carbohydrate come from nearly all food sources in our diet and is eventually broken down into glucose by enzymes in the small intestine; which are later absorbed into the blood stream through the intestinal walls by the villi. Glucose being the body's main energy source, most of the calories are derived from the carbohydrates. The catabolism of carbohydrates to yield ATP in a normal cell is associated with pathways such as Glycolysis or Embden-Meyerhoff Pathway, Oxidation of pyruvate, the Citric acid cycle or the Kerb's Cycle, Pentose Phosphate Pathway, Glycogenolysis, Glycogenesis and Gluconeogenesis.

The application of computer-aided tomography (CAT) in combination with positronemission tomography (PET) imaging technique using the glucose analogue tracer fluorodeoxyglucose (FdG) has demonstrated that most cancer cells show significantly increased glucose uptake[8-13].This is because anabolic pathways branching off from glycolysis produces some biosynthetic intermediates such as amino acids, lipids and nucleotide precursors[14]. In a cancer cell, the demand for these products is relatively high owing to its nature of rapid growth. When glycolytic flux through these pathways increases, glucose uptake must also increase alongside to maintain normal ATP levels. As per reports, by the time a normal cell would take to produce 36 ATP from per glucose, the normoxic cancer cell would utilize 11 molecules of glucose to produce 56 ATP from it, whereas the anoxic cancer cell would generate 26 ATP from 13 glucose molecules[15].

This review aims to describe the role of altered glucose metabolic pathway in the high energy demanding tumour cells as described by the Warburg effect with a particular

emphasis on the role played by hypoxia inducible factor (HIF1), pH and high lactate concentration in tumour cell metabolism. It is rather interesting to know how tumour cells shift from normal cellular respiration to an inefficient glucose metabolism for meeting their ATP needs. To look at it from a different perspective, the increased uptake and altered metabolism of glucose is actually a solution to the constraints put by the environment on the growth of tumour cells.

The Crabtree effect

English biochemist Herbert Grace Crabtree asserts that the presence of glucose in normal cells increases the rate of respiration or has no effect on oxygen consumption. However, in the cancer cells, the presence of glucose decreases the oxygen uptake. This inhibition in respiration is known as the Crabtree effect.

The mechanism by which the Crabtree effect operates is unknown. Yet, several mechanisms have been suggested to explain the Crabtree effect in tumour cells.

- P_i levels tend to decrease after the addition of glucose in tumour cells[16]. It has been proposed that a decrease in P_i triggers the Crabtree effect in some tumour cells[17].
- A decrease in the cytosolic pH can decrease the rate of synthesis of ATP by the mitochondria thereby inducing the Crabtree effect[18].
- Increased mitochondrial Ca^{2+} uptake in response to glucose may lead to the inhibition of the ATP synthase inducing a decrease of respiration[19,20,21]. An increase in calcium levels in mitochondria can increase the association of the inhibitory subunits of F_1F_0 to the ATP synthetase thereby inhibiting coupled respiration [22].
- It is reported that the metabolite Fructose-1, 6-biphosphate participates in the e stablishment of the Crabtree effect. It links glycolysis to the inhibition of respiration by inhibiting mitochondrial respiratory rate at the level of respiratory complexes III and IV[23].
- The metabolism of glucose increases the production of reactive oxygen species that depresses respiration by damaging the mitochondrial membranes[24].
- The overproduction of a particular hexose monophosphate viz. Glucose-6-phosphate releases the mitochondria-bound hexokinase II. The dissociation of it promotes the acceleration of adenine nucleotide fluxes from the outer membrane of mitochondria thereby inhibiting respiration[25].
- When glycolysis is overactive, the enzymes phosphoglycerate kinase and pyruvate kinasecompete with the mitochondria for free cytosolic ADP uptake[26,27]. ADP being a substrate of the oxidative phosphorylation, would limit the ATP synthase and consequently respiration would be decreased.

The Warburg effect

Otto Heinrich Warburg worked on glycolysis and showed that the cancer cells exhibited a reversed Pasteur effect i.e., in a tumour cell, a substantial amount of pyruvate is reduced to lactate even in the presence of oxygen instead of being directed into the mitochondria to produce ATP by oxidative phosphorylation [28]. Cancer cells are, therefore, compelled to rely on inefficient mode of synthesizing ATP as it produces only 2 ATPs per molecule of glucose rather than the conventional respiration that produces approximately 36 ATPs per molecule of glucose. It is ironic to realise that the tumour cells that require a huge supply of ATP for its rapid growth, would switch to aerobic glycolysis that produces significantly lesser molecules of ATPs than that is required. As a result, to meet their increased energy needs, biosynthesis and redox needs more glucose molecules are taken up. A possible reason as to why cancer cells re-programme their metabolic pathway is to produce other metabolic end products to support their uncontrolled growth and proliferation in low oxygen tension during the process of tumour progression.

Warburg misinterpreted his own early observations stating that respiration must be damaged in cancer cells as even high levels of O_2 are unable to suppress lactic acid production in them[29]. Warburg hypothesized that cancer cells develop a defect in mitochondria that leads to impaired aerobic respiration and a subsequent reliance on glycolytic metabolism[30]. However future work has shown that mitochondrial function is not always impaired in cancer cells[31]. However, in later studies it was reported that mitochondrial defects are rare[32].

Metabolic pathways in cancer cells

MYC - HIF- VHL

With respect to glycolysis, overexpressed MYC have shown to collaborate with HIF in the activation of several glucose transporters and glycolytic enzymes such as LDHA and PDK1.MYC induces the splicing factors that produce PKM2[32]. PKM2 converts PEP to pyruvate in aerobic glycolysis thereby further underscoring the role of MYC in the aerobic glycolysis process. In RCCs, MYC appears to collaborate with activated HIF2α to confer tumorigenicity.

The HIF1 and HIF2 complexes are the major transcription factors that are responsible for the gene expression changes during the cellular response to low oxygen conditions. They are heterodimers that are composed of the constitutively expressed HIF1β (also known as ARNT) subunit, and either the HIF1α or the HIF2α (also known as EPAS1) subunits, which are rapidly stabilized on exposure to hypoxia. HIF1α is ubiquitously expressed, whereas the expression of HIF2α is restricted to a more limited subset of cell types[33]. HIF1 can also be activated under normoxic conditions by oncogenic signalling pathways, including PI3K[34,35] and by mutations in tumour suppressor proteins such as VHL[36,37], SDH [38] and FH[39]. Once activated, HIF-1 amplifies the transcription of genes encoding glucose transporters and most glycolytic enzymes, increasing the capacity of the cell to carry out glycolysis[40]. In addition, HIF-1 transactivates the gene encoding pyruvate dehydrogenase kinases 1(PDK1), which inactivate the mitochondrial pyruvate dehydrogenase complex and thereby reduce the flow of glucose-derived pyruvate into the tricarboxylic acid (TCA) cycle[41,42,43]. HIF-1 induction can also be triggered by the mitochondria themselves. Accumulation of krebs cycle substrates might serve as a signal for stimulation of glycolysis when mitochondrial respiration in tumor cells downregulated [44].

Under normoxic conditions HIF1α subunits undergo oxygen-dependent hydroxylation by prolyl hydroxylase enzymes, which results in their recognition by the tumour suppressor protein VHL. VHL is an E3 ubiquitin ligase that normally mediates proteosomal degradation of HIF1α. In RCCs, the loss of VHL results in the non-hypoxic expression of HIF1α and HIF2α[45].

The role of HIF1 is not restricted to upregulation of the enzyme stimulating glucose utilization. HIF1 stimulates the conversion of glucose to pyruvate and lactate by upregulating glucose transporter (GLUT) isoform 1(GLUT1) hexokinase and lactate dehydrogenase A (LDHA) as well as the lactate extruding enzyme monocarboxylate transporter 4 (MCT4)[46,47].

PI3K - ATK1 – mTOR

Augmentation of this pathway by mutations activating PI3K or eliminating negative regulators like PTEN comprises a prevalent category of mutation in human cancer[48]. The PI3K pathway is activated by mutations in tumour suppressor genes, such as PTEN, mutations in the components of the PI3K complex itself or by aberrant signalling from receptor tyrosine kinase [49].

AKT1 is an important driver of the tumour glycolytic phenotype and stimulates ATP generation through multiple mechanisms, ensuring that cells have the bioenergetic capacity required to respond to growth signals[50,51]. AKT1 stimulates glycolysisby increasing the expression and membrane translocation of glucose transporters and by phosphorylating key glycolytic enzymes, such as hexokinase and phosphofructokinase 2 (also known as PFKFB) [52]. The increased and prolonged AKT1 signalling that is associated with transformation inhibits forkhead box subfamily O (FOXO) transcription factors, resulting in a host of complex transcriptional changes that increase glycolytic capacity [53]. AKT1 also activates ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5), an enzyme that supports increased protein glycosylation in the endoplasmic reticulum and indirectly increases glycolysis by creating an ATP hydrolysis cycle [54]. Although AKT function independently of HIF1 to induce aerobic glycolysis [55,56], it can also increase the activity of HIF1, further enhancing induction of glycolysis[57].

AKT1 strongly stimulates signalling through the kinase mTOR by phosphorylating and inhibiting its negative regulator tuberous sclerosis 2 (TSC2; also known as tuberin[58]. mTOR functions as a key metabolic integration point, coupling growth signals to nutrient availability. Activated mTOR stimulates protein and lipid biosynthesis and cell growth in response to sufficient nutrient and energy conditions and is often constitutively activated during tumorigenesis[59]. At the molecular level, mTOR directly stimulates mRNA translation and ribosome biogenesis, and indirectly causes other metabolic changes by activating transcription factors such as HIF1 even under normoxic conditions.

AMPK

The tumour suppressor gene STK11 codes for liver kinase B1 (LKB1) which in turn activates AMPK. Biochemically, AMPK opposes the effects of AKT1 and functions as an inhibitor of mTOR. The loss of AMPK signalling allows the activation of mTOR and HIF1, and therefore might also support the shift towards glycolytic metabolism. AMPK functions as a metabolic checkpoint, regulating the cellular response to energy availability. During periods of energetic stress, AMPK becomes activated in response to an increased AMP/ATP ratio. Tumour cells must overcome this checkpoint in order to proliferate in response to activated growthsignalling pathways, even in a less than ideal microenvironment[60].

Activated RAS

It was recently reported that depriving colon carcinoma cells of glucose increases the mutation rate of RAS, which, thus activated, facilitates glucose import through induction of GLUT1 (also known as SLC2A1), an important glucose transporter[61]. In a multistep, multigene transformation of human breast epithelial cells, it was documented that the initial transformation of normal epithelial cells by viral oncogenes and telomerase reverse transcriptase is associated with increased mitochondrial function; with activated KRAS as the final reaction step in this model, the transformed cells exhibit the Warburg effect through high conversion of glucose to lactate [62]. It is notable that activated RAS has been proposed to induce MYC activity and enhance non-hypoxic levels of HIF1, although the precise mechanisms remain to be established [63,64].

p53 and OCT1

p53 is a cellular regulator and transcriptional factor with tumour suppressor properties which is an important regulator of cell death and replicative senescence in response to oncogenic stress[65]. p53 activates the expression of hexokinase 2 (HK2), which converts glucose to glucose-6-phosphate (G6P)[66]. G6P then either enters glycolysis to produce ATP, or enters the pentose phosphate pathway (PPP).Activation of SCO2 (which regulates the cytochrome c oxidase complex) by p53 increases the efficiency of mitochondrial respiration[67]. Conversely, p53 suppression of phosphoglycerate mutase 2 (PGAM2) and activation of tumour protein 53-induced glycolysis and apoptosis regulator (TIGAR), which has 2,6-fructose bisphosphatase activity and depletes PFK1 of a potent positive allosteric ligand, suppresses glycolysis and favours increased NADPH production by the pentose phosphate pathway[68,69]. Wild-type p53 also supports the expression of PTEN, which inhibits the PI3K pathway, thereby suppressing glycolysis[70].

OCT1 (also known as POu2F1) is a transcription factor, the expression of which is increased in several human cancers, and it may cooperate with p53 in regulating the balance between oxidative and glycolytic metabolism[71]. Data from studies of knockout mice and human cancer cell lines show that OCT1 regulates a set of genes that increase glucose metabolism and reduce mitochondrial respiration. One of these genes encodes an isoform of PDK (PDK4) that has the same function as the PDK enzymes that are activated by HIF1[72].

Tumour microenvironment

Hypoxia – Although a pre-malignant lesion such as a polyp or carcinoma are often characterised as highly vascularised, the hyperplastic epithelia are physically separated from their blood supply by a basement membrane. In the early phases of tumour formation, uncontrolled cell proliferation shifts tumour cells away from the blood vessels and therefore are deprived from the supply of oxygen and nutrients. At this stage, it is only through diffusion across the basement membrane and through the peripheral tumour-cell layers that oxygen and nutrients reach the inner cells of a non-vascularised tumour. This diffusion and consumption process were modelled through reaction-diffusion equations which proved that as the distance from a blood vessel increases, the oxygen concentration decreases such that oxygenated cells were limited to a distance of less than 150 µm from a blood vessel[73]. In neoplastic cell populations, low concentrations of oxygen seem to be the first substrate limitation, as reaction-diffusion models have proved empirically that the decline of $pO_2$is more rapid as the distance from the blood vessels increases [74-77].

In studies with tumour xenografts using a magnetic-resonance imaging technique that is sensitive to oxygenation status[78] and using microelectrodes[79], it was shown that oxygen delivery to tumours is inconsistent. Oxic-hypoxic cycles in tumours may occur at intervals of minutes[80], hours [81] or even days[82]. These cycles are probably due to a range of physiological mechanisms. It has been suggested that oxic-hypoxic fluctuations in the penumbral region of pre-malignant tumours favours maintenance of metabolic activities in the absence of oxygen.

A hypoxic microenvironment induces tumour growth by activating the transcription factor hypoxia-inducible factor 1 (HIF1). HIF1 regulates genes that are responsible for the expression of most glycolytic enzymes such as hexokinases, regulation of tumour pH, angiogenesis and the expression of glucose transporters GLUT1 and GLUT3[83]. Angiogenesis is brought about by the expression of vascular endothelial growth factor (VEGF) when induced by HIF1. This facilitates the formation of new blood vessels in the tumour cells previously separated by the basement membrane thereby establishing a link for the supply of essentials for their growth.

Under normoxic conditions the ODD (Oxygen-dependent degradation) domain of HIF1α is hydroxylated by prolyl hydroxylases (PHDs) followed by subsequent ubiquitination by Von-Hippel Lindau (VHL), thereby degrading HIF1α and rendering it inactive[84-86]. Also, several factors inhibiting HIF1 (FIH1) gets activated under normoxic conditions. FIH1 hydroxylates an asparagine residue of HIF α following which, anasparaginyl hydroxylation blocks the interaction of HIF1α with transcriptional factors p300 and CBP, thereby suppressing HIF1α's transactivational activity. However, under hypoxic conditions, HIF1α becomes stable. Since oxygen is a substra te of both FIH1 and PHDs, an oxygen deprived condition activates HIF1[87]. Upon which, HIF1α interacts with HIF1β and forms a heterodimer HIF1[88]. HIF1 binds to its cognate DNA sequence, the hypoxic responsive element (HRE) and ultimately initiates the expression of glycolysis, metastasis, angiogenesis[89- 91].

Hypoxia also inhibits mTOR signalling[92,93]. Albeit mTOR inhibition results in tumour suppression, evidences assert that mTOR inhibition increases the tolerance to hypoxia and promotes tumour cell survival during metabolic stress. In certain microenvironment, tumour cells have been found to benefit from moderate mTOR activity[94]. mTOR inhibition have been found to induce autophagy in tumour cells[95].

pH:

An increase in the rate of glycolysis results in the increase in the production of glycolytic byproducts such as lactate and H^+. This makes the intracellular environment of the tumour cells highly acidic and shown to induce apoptosis[96]. In order to overcome this and maintain homeostasis, cancer cells efflux lactate and $H^+$by monocarboxylate transporters (MCTs) and Na^+/H^+ exchangers (NHEs) respectively[97,98], making the extracellular pH now highly acidic. Numerous studies have shown that the extracellular pH of tumour cells can reach a pH value as low as ≤ 6.[99,100]. Only through adaptations to this low pH microenvironment will an avascular pre-invasive tumour transform into a malignant invasive tumour with patent vasculature [101]. The low extracellular pH values under some conditions induces migration and invasion [102,103]. Such an induction mechanism might involve the metalloproteinases and cathepsins, which promote the degradation of the extracellular matrix and basement membranes[104,105].

Fate of lactate produced in cancer cells

An increase in the rate of glycolysis in cancer cells increases the production of glycolytic byproducts viz. lactate and H^+ making the intracellular region highly acidic. Hypoxic cells produce enormous amounts of lactate using two key enzymes: pyruvate dehydrogenase kinase (PDK1) that inhibits pyruvate dehydrogenase (PDH) from converting pyruvate to acetyl-CoA; and Lactate dehydrogenase kinase A (LDHA) which converts pyruvate to lactate[106] . In order to maintain homeostasis, these products need to be exported to the extracellular space. The cell exports lactate and $H^+$by monocarboxylate transporters (MCTs) and Na^+/H^+ exchangers (NHEs) respectively, making the extracellular environment of the tumour acidic. The oxygenated cells in the vicinity then removes lactate from the extracellular fluid using MCT1. Lactate is now converted back to pyruvate for further oxidation using the LDBH isoform, thereby conserving glucose for use by the hypoxic cells.

Redox balance of cancer cells

The net physiological balance between reducing and oxidizing equivalents within the cell is maintained due to reduction/oxidation (redox) homeostasis in it [107]. In a normal healthy tissue, the production of Reactive oxygen species (ROS) and Reactive Nitrogen Species (RNS) are well-regulated to help maintain homeostasis [108].

ROS are tumorigenic by their ability to increase cell proliferation and migration, but also by inducing genetic lesion that can initiate tumorigenicity and sustain subsequent tumor progression [109]. ROS at low levels have been reported to increase cell proliferation and survival through the post-translational modification of kinases and phosphatases[110,111]. At moderate levels, ROS induces the expression of stress-responsive genes such as HIF1A, which in turn trigger the expression of proteins providing prosurvival signals, such as the glucose transporter GLUT1 (also known as SLC2A1) and vascular endothelial growth factor (VEGF)[112,113]. At high levels, ROS can cause damage to macromolecules, including DNA; induce the activation of protein kinase Cδ (PKCδ), triggering senescence[114,115] and/or cause permeabilization of the mitochondria, leading to the release of cytochrome c and apoptosis[116,117] and activate pathways such as PI3K andmitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK)] and transcription factors such as HIF and nuclear factor kB (NF-kB) necessary for tumorigenesis.

To counter such oxidative stress, a cell uses antioxidants that prevent ROS from accumulating at high levels.The primary antioxidant enzymes in cells include superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). Other antioxidant enzymes such as thioredoxin (TRX), glutaredoxin (GRX), and peroxiredoxin (PRX) also contribute to cellular protection against oxidation[118].

Mitochondria and cytosolic NADPH oxidases (NOXs)produces O_2^- from the one-electron reduction of oxygen [119] and convert it into H_2O_2 by the enzymatic activity of superoxide dismutase 1 or 2 (SOD), which are localized to the cytosol or mitochondrial matrix, respectively.The dismutation of superoxide produces hydrogen peroxide. Hydrogen peroxide is a more stable ROS and it is permeable to cellular membranes. Despite being a relatively weak oxidizing agent; H_2O_2at high levels

can generate hydroxyl radicals through the Fenton reaction [12ǫ] and prove to be cytotoxic.H_2O_2 is subsequently detoxified to water by the enzymatic activity of mitochondrial and cytosolic peroxiredoxins (PRXs), which, as a consequence, undergo H_2O_2-mediated oxidation of their active-site cysteines[121]. Thioredoxin (TRX), thioredoxin reductase (TR), and the reducing equivalent NADPH reduce oxidized PRXs to complete the catalytic cycle[122]. Glutathione peroxidases (GPXs) can also convert H_2O_2 to water in the mitochondrial matrix and cytosol through H_2O_2-mediated oxidation of reduced glutathione (GSH) [123]. Glutaredoxin (GRX) can directly reduce H_2O_2 in a catalytic manner, using reducing power provided by NADPH, GSH, and glutathione reductase [124] . Glutathione reductase (GR) and NADPH reduce oxidized glutathione (GSSG) back to GSH. Additionally, catalase (CAT), an abundant antioxidant in peroxisomes, can detoxify H_2O_2 to water without any cofactors.

During the process of tumorigenesis, loss of the tumour suppressor gene TSC2 makes mTOR hyperactivated [125]. A hyperactivated mTOR leads to the upregulation of translation and increased ROS production. Loss of tumour suppressor retinoblastoma (RB) fails to counter ROS due to lack of antioxidant response and the cell undergoes apoptosis[126]. Similarly, loss of tumour suppressor gene PTEN hyperactivates AKT1 which inactivates FOXO and increases oxidative stress[127].

NRF2 is an antioxidant transcription factor which upregulates the expression of several antioxidant and detoxifying molecules. p53 has been reported to promote the stabilization of the transcription factor nuclear factor (erythroidderived 2) -related factor-2 (NRF2) through its target gene cyclin-dependent kinase inhibitor 1A (CDKN1A). When ROS levels are low, NRF2 binds to Kelch-like ECH-associated protein 1 (KeAP1)[128]. Critical cysteine residues within KEAP1 can undergo oxidation, succination, and glutathionylation, thereby inhibiting the KEAP1-NRF2 interaction, leading to the proteasomal degradation of NRF2[129]. However, under oxidative stress, p53 is activated and stimulates expression of p21 by CDKN1A. Once activated, NRF2 induces the transcription of many antioxidant proteins including GPXs and TXNs as well as enzymes involved in GSH sy nthesis and cysteine import through the cysteine/ glutamate antiporter. Furthermore, to maintain the antioxidant capacity of GPXs and TXNs, NADPH is required. NRF2 plays an important role in activating enzymes that increase cytosolic NADPH levels. NRF2 also regulates the serine biosynthesis pathway, generating NADPH in the mitochondria, which is critical for redox balance under hypoxic conditions[13ǫ,131]. Therefore, inactivating NRF2 or disabling antioxidant proteins in cancer cells would allow for the accumulation of excessive amounts of ROS to levels that initiate toxicity and reduce tumorigenesis[132,133].

In neurodegenerative diseases such as Parkinson's disease, DJ1 promotes antioxidant responses by stabilizing NRF2[134,135]. Loss of DJ1 function leads to elevated oxidative stress in the brain and neuronal cell death and also to regulate the tumour suppressor PTEN and in turn stimulate AKT1 activity [136].

GSH is another important antioxidant that controls the redox balance of sub-cellular components[137]. Although glutamine is not an essential amino acid in a normal cell, as mentioned earlier, cancer cells are critically dependent on it. MYC has been reported to promote the uptake of glutamine by inducing the expression of glutamine transporters SLC5A1 and SLC7A1. MYC also inhibits the expression microRNA-23A and microRNA-23B to increase glutaminase 1 (GLS1); the first enzyme of glutaminolysis[138]. MYC also enhances the antioxidant capacity by producing NADPH with the expression of the PKM2 isoform via. Pentose Phosphate pathway (PPP) and by the synthesis of GSH through glutaminolysis.*De novo* synthesis of GSH is also achieved through the upregulation of Glutaminase 2 (GLS2) by p53[139].

CONCLUSION

Despite the myriad of adaptations that the tumour cells undergo for its faster growth and better survival, there lies one distinct difference between the normal cells and the tumour cells that makes them resort to the Warburg effect and aerobic glycolysis. In the presence of growth factors, a normal cell would undergo quiescence when deprived of nutrients but a cancer cell, on the other hand, in the presence of growth factors is stimulated in a way that demands the supply of ATP and an upregulation of nutrients along with it. The three important steps that balance the metabolic adaptations of these tumour cells are: increased ATP production, ample macromolecular biosynthesis and maintaining a redox balance. The basis of the resistance that a tumour cells exhibits to both radiotherapeutic and chemotherapeutic agents lies in its unsual metabolic pathway. To which, a reversion to a normal metabolic pathway would make these cells slows in progression and increase its response to these agents. HIF-1 and PI3K/Akt/ mTOR pathways have an important role in cancer metabolism and the Warburg effect.

Development of cancer cells depends on various factors. So it is very difficult to establish a generalized cancer treatment. But our understanding of cancer cell metabolism evolved continuously because of advances in technologies. Thus, survival and quality of life will be improved for cancer patients.

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