**Low Sugar Diet: A New Tool in War Against Tumorigenesis**

*Nupur Rani Agarwal,1* Nancy Maurya2*

1 Transcriptional Regulation Group, International Centre For Genetic Engineering And Biotechnology, Aruna Asaf Ali Marg, New Delhi, India 110067
2 School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, M.P., India 462033

Corresponding Author. Email: Nupur Rani Agarwal, nupurrani23@rediffmail.com; Nancy Maurya, nm_7582@rediffmail.com

Received: 26 April 2018, Accepted: 25 June 2018, Published Online: 26 June 2018


**INTRODUCTION**

Cancer is a metabolic disease. Their typical characteristic is high consumption of glucose as these cells mostly have defective mitochondria. They primarily derive energy through aerobic glycolysis even in presence of abundant oxygen. Cancer cells thus are heavily dependent on ample and continuous availability of glucose for growth, proliferation and invasion. These cells adopt various strategies to satisfy their high demand for sugar which includes modification in signalling pathways and abnormally high expression of glucose transporters. Glucose uptake is favoured by alteration in PI3K-Akt-mTOR pathway. High glucose condition creates conducive environment for cancer cells to flourish. The H+ ion secreted as by-product of glycolysis helps in invasion and metastasis. Other by products of glycolysis which includes ATP, NADP and NADPH also aids in growth of cancer cells. Glucose restriction puts break on speedy multiplying tumor cells as unlike normal cells of the body they are unable to metabolize any other source of fuel. Lower glucose level induces changes in level of cleaved caspase 3, Bcl-2, p53 and p21 which prompts senescence and apoptosis in rapidly proliferating tumor cells. Various strategies can be employed to cut down glucose accessibility to cancer cells such as inhibition of glucose transporters, adoption of keto diet. Combining glucose restriction with either chemo or radiotherapy increases their effectiveness; lower CHO levels also provide protection to normal healthy cells of the body against toxic effect of anti-carcinogens. Carbohydrate restriction is a non-toxic, easily impeccable, economical and safe tactic which may be utilized as weapon in war against cancer.

Cancer cells are notorious as they are endowed with the ability to divide uncontrollably and generate multitudes of new tumor cells. Most of the fuel consumed by these rapidly proliferating cells is glucose, a type of sugar. Cancer and sugar are best friends. It is indeed said that “Sugars feed cancer cells.” In multicellular organisms, most cells in tissues have a constant supply of nutrients via circulating blood. There are control systems in an organism that prevent proliferation of cells even when nutrient availability is surplus. Unrestricted cell division does not occur in mammals under normal circumstances as cells do not take up nutrients from their environment unless they are encouraged to do so by growth factors. Cancer cells bypass growth factor regulation as they acquire genetic mutations and thus exhibit altered signalling pathways which aids in constitutive uptake and metabolism of nutrients which promote cell survival and fuel cell growth. Oncogenic mutation within cancer cells favours the intake of comestibles, in particular glucose which is a monosaccharide for uncontrolled cell proliferation.

Glucose consumed by cells enters Glycolysis which is a series of metabolic pathway by which one molecule of glucose is catabolized into two molecules of pyruvate with net gain of two ATP molecules. The whole process of glycolysis occurs in cytosol. In presence of oxygen pyruvate enters tricarboxylic acid cycle and oxidized to CO₂ and H₂O in the mitochondria but under anaerobic circumstances pyruvate is reduced to lactic acid by lactate dehydrogenase. Cancer cells prefer aerobic fermentation even in the presence of oxygen however as it generates only 2ATP per molecule of glucose consumed were as energy generation by oxidative phosphorylation ends up producing 36 ATP per molecule of glucose utilized but less production of ATP is not a concern for cancer cells as they readily take up nutrients from circulating blood and apart from that cancer cells induces angiogenesis which helps them satisfy their energy demands. The shift toward glycolysis during tumorigenesis, occurs because cancer cells have lesser number of mitochondria and moreover most of them are non-functional [1], activation of oncogenes also results in upregulation of glycolytic genes [2]. Unrestrained multiplication of cells during cancer progression elicits a strong hypoxic response which switches off oxygen-dependent respiration in particular during the early avascular phase of tumour development; glycolytic metabolism arises as an adaptation to hypoxic conditions, as it allows ATP production even in the absence of oxygen [3].

Preferential adoption of aerobic glycolysis in cancer cells
helps them to generate ATP at a higher pace than oxidative phosphorylation and so this would be advantageous as long as glucose supplies are not limited. The H+ ions secreted as the end product of glycolysis diffuses into the surrounding environment of cancer cells and supports enhanced invasiveness [4]. The increased glucose consumption frequency associated with high rate of glycolysis also supports the bio-synthetic requirements as carbon source for anabolic processes required for unconfined proliferation of cancer cells [5]. Anomalous expression of certain metabolic enzymes also supports Warburg effect.

Cancer cells have bad table manners. Normal cells of the body require a balanced diet for their growth and multiplication. They can also utilize amino acids and fatty acids as a source of fuel for energy production. Unlike them, cancer cells are habituated to glucose. It serves as a principal source of energy to these ill-famed cells. High sugar consumption rate is also helpful in Darwinian selection as feasting and metabolism of glucose produces several by-products which encourages increased cancer progression and metastasis.

Cell survival depends on the activity of numerous proteins including Akt, pERK, PTEN etc. PI3K/AKT is amid the most often mutated web in cancer. To facilitate rapid uptake of sugar, glucose transporters are deregulated in cancer cells. On signalling level glucose uptake is facilitated by PI3 kinase/ AKt which promotes expression of GLUT’s. Constitutive expression of growth factors in cancer cells leads to the stimulation of signalling pathways which enhances the expression of Glucose transporters, encourages glucose uptake and thus ensures high glycolytic flux.

Here we review available evidence which support the notion that elevated glucose levels supports carcinogenesis and lowering carbohydrate levels can be an effective adjuvant therapy in slowing down cancer progression.

HIGH CARB DIET LINKED TO INCREASE RISK OF CANCER

Cancer cells grow and multiply profusely for which they require a lot of energy. Thus they consume sugar 10-12 times faster rate than the healthy cells. This is the basis of PET (positron emission tomography) scans. It is one of the most accurate tools for detecting cancer growth. High level of glucose exposure increases proliferation of Human colon cancer cell [6]. Cholangiocarcinoma (CCA) cells cultured in high glucose (25 mM) media showed significantly higher rates of cell proliferation, adhesion, migration and invasion as compared to those cultured in normal glucose (5.56 mM). Activation of STAT3, increase in level of p-STAT3 and nuclear translocation of p-STAT3 along with up-regulations of cyclin D1, vimentin, and matrix metalloproteinase 2 were responsible for growth progression in response to high glucose condition. These observations were verified not only in CCA cell lines but were also found to be true in CCA patient tissues [7]. High glucose (HG) also encouraged migration and Invasion of CCA cells and the effect was found to be more pronounced in the highly metastatic sublines. Global O-GlcNAcylated proteins were upregulated along with increase in expression levels of vimentin, hexokinase, glucosamine-fructose-6-phosphate amidotransferase and O-GlcNAc transferase in CCA cells [8]. Human epithelial lung cells (A549) cultured in high glucose medium showed epithelial mesenchymal-transition and oncofetal fibronectin production [9]. HG also causes increase in level of [10] ROS which are oxygen-containing species that can react with nucleic acids, proteins and lipids. It occurs when the balance between its production and destruction gets disturbed. Compared to the normal tissues cancer cells have characteristically increased amounts of ROS. The elevated level of oxidative stress helps in tumor progression as it supports unsuppressed cell proliferation, alteration in genomic material, metastasis and angiogenesis. Increase in invasive and migratory activity of pancreatic cancer cells BxPC-3 and Panc-1 was observed in 25 and 55 mM glucose containing media as compared to 5 mM glucose media [11]. This increased tumorigenic behaviour was due to increase in the level of ROS which is supported by HG in the media (Figure 1).

Hyperglycaemia is condition in which blood glucose level shoots up. It occurs either when the pancreas secretes less insulin or cells in the body become less reactive to insulin. High blood glucose weakens immune response against malignant cells as it impairs transport of ascorbic acid which is required for phagocytosis hence weakening immune response against transformed cells. It also supports increased production of inflammatory cytokines by monocytes and macrophages that help in increased cancer progression [12]. This situation also leads to oxidative stress by attenuating activity of antioxidant enzymes. It is able to augment the metastatic activities of cancer cells [11].

Hyperglycemia often gives rise to diabetes Mellitus. It is well studied that people with type II diabetes have an increased risk of several cancers [13]. On the contrary cancer patients are more prone to diabetes than general people. A close relationship exists between these two disease states as they share common etiologic factor.

SIGNALLING PATHWAYS ALTERED ON GLUCOSE RESTRICTION

![Figure 1](image-url). Cancer development processes cell growth; division, adhesion and invasion all are retarded in low glucose condition owing to increase in oxidative stress.
Cells have devised various mechanisms to recognize nutrient status. Availability of glucose is sensed by adenosine monophosphate-activated protein kinase (AMPK). ATP is the most commonly used energy currency of the cell. Its hydrolysis into ADP and phosphate fuels energy for most of the biological actions. AMPK is triggered upon decrease in ATP/adenosine monophosphate ratio. Activation of AMPK enhances catabolic processes and declines anabolic pathways which results in increase in ATP synthesis. Signaling pathways are affected on glucose scarcity in cancer cells. Upon glucose shortage, AMPK stabilities cell cycle inhibitor p27 via activation of p53. This leads to cell cycle arrest [14] which helps to conserve ATP. Another important target of AMPK is the mammalian target of rapamycin (mTOR) which dictates cell growth and multiplication. In proliferating cells mTOR is expressed constitutively. The major function of mTOR is translation of mRNA i.e. protein synthesis. The whole process of translation is divided into three major steps initiation, elongation and termination. mTOR mainly supervise the initiation and elongation stages of protein synthesis. Stimulation of mTOR is under the control of the PI3-kinase/Akt pathway. Glucose starvation inhibits PI3-kinase/Akt and its downstream effector mTOR resulting in termination of protein synthesis [14]. Decline in NADH/NAD+ ratio is also viewed under low glucose condition. This leads to activation of sirtuin SIRT1 which is accountable for chromatin compaction and thus represses gene expression. SIRT1 also supresses transcription of ribosomal RNA [15] and therefore inhibit translation of proteins. Cutting down glucose availability also has an impact on post translational modification of proteins including inhibition of acetylation [16]. Inadequate glucose supply also hampers folding of newly synthesized proteins and elicits endoplasmic reticulum stress (ER stress) in cancer cells. During ER stress assembly of misfolded or unfolded proteins occurs inside the endoplasmic reticulum which excites unfolded protein response (UPR). UPR evolved as a pro-survival mechanism as it promotes autophagy, angiogenesis and inflammatory response to protect cell but under severe stress conditions it leads to cell death [17] (Figure 2).

Upregulation of glucose metabolism in cancer cells also helps in combating hydroperoxide induced oxidative stress through production of more pyruvate and NADPH via glycolytic pathway. Glucose starvation prompts supra-physiological levels of phospho-tyrosine signaling and cell death through enhanced oxidative stress in cells dependent on glucose for existence [18]. CHO shortage thus induces cytotoxicity through alteration in signalling pathways triggered by enhanced ROS production.

**KETO DIET**

![Figure 2](image-url)  
*Figure 2.* Glucose deprivation causes shortage of ATP leading to mTOR inactivation and activation of AMPK which leads to cell cycle arrest, through p53 and p27 stimulation. CHO scarcity induces UPR and subsequently stimulates induction of BH3-only proteins and cell death. Autophagic and necrotic cell death pathways are triggered on ATP depletion. Synthesis of ribosomes, protein translation is affected due to decline in NADH/NAD+ ratio. Post translation modification of protein is also hindered upon glucose shortage in cancer cells.
Normal cells of the body are able to derive energy for survival through various fuels including glucose, fatty acids, and ketones. Unlike them cancer cells which mostly have defective mitochondria are unable to catabolize oxygen dependent fuels such as fatty acids and ketones to generate ATP. Instead they mostly depend on glucose as energy source. Thus higher the glucose available to cancer cells more they flourish. This makes them more susceptible to glucose shortage than normal healthy cells of the body. In this scenario, food modification such as intake of keto diet is helpful. This diet contains high fat, with moderate to low protein and very small amount of carbohydrates. In ketogenic regime with high fat content, Oxidation of fatty acids occurs in the liver which generates ketone bodies such as acetooacetate, β-hydroxybutyrate and acetone. Theses ketone bodies are carried in the blood stream and catabolized by citric acid cycle. Carbohydrate content being low in keto diet causes reduction in blood glucose level [19].

Appetite with lot of carbohydrate content causes blood glucose levels to rise sharply. When an individual suffering from cancer is put on ketogenic diet, amount of glucose consumed is curtailed due to which blood glucose levels drops. Decline of glucose in blood causes cancer cells to starve as they are mostly dependent on it for energy generation, survival and growth. Ketogenic diet also increases oxidative stress inside cancer cells as they are forced to derive energy mainly from lipid and protein, since cancer cells have defective mitochondria it ends up in production of ROS. Cancer cells selectively experience oxidative stress rendering normal cells unharmed. VM-M3 mouse model of metastatic cancer were fed on keto diet to compare tumor progression. Mouse on Keto diet showed lowered blood Glucose level, elevated blood Ketones and decreased Body Weight and declined tumor growth. Keto diet increased mean survival time in mice with systemic metastatic cancer [20]. Cancer Patients on keto diet showed tumor shrinkage [21].

Adoption of keto diet is an economical, easily implementable, and may be an effective tactic to selectively target cancer cells as they are more vulnerable to any diet which sharply lowers blood sugar level.

### INHIBITION OF GLUCOSE TRANSPORTER

Glucose metabolism plays an important role in cancer biology. Sugar molecules are polar in nature, their movement across plasma membrane, composed of phospholipid bilayer, occurs with the help of carrier proteins. Sugar transporters are divided into two major families on the basis of energy usage during transfer of sugars: Na⁺-independent sugar transporters (GLUT) are facilitative, they depend on sugar gradient for its movement and Na⁺–dependent sugar cotransporters (SGLT) require energy for transfer of sugars across membrane. SGLT transports glucose in concurrence with sodium ions. It depends on sodium concentration gradient produced by the sodium–potassium ATPase as the source of energy. It encompasses 14 transmembrane helices in which both carboxyl and amino terminus are towards the extracellular space. Molecular weight of SGLT family ranges between 60-80KDa whereas GLUT proteins have 12 membrane-traversing regions with both amino and carboxyl terminus positioned intracellularly. GLUTs are further classified into three categories based on structural and sequence studies [22].

To meet their high metabolic demand cancer cells hijack glucose transporters. Glucose transporters are among the substrates targeted by PI3K-Akt pathway. Studies suggest increased level of glucose transporters in various cancers including gastric cancer [23], squamous cell carcinomas [24], meningioma [25], and glioblastomas [26] and its suppression leads to initiation of apoptosis [27].

Inhibition of glucose transporters reduces growth of cancer cells by a mechanism similar to glucose deprivation. Phloretin (Ph) a phytochemical found in Apples and Pears is known to have glucose transporter (GLUT) inhibitory activity. It impedes growth of human leukaemia [28] and B16 Melanoma 4A5 Cells by hindering transmembrane glucose transport [29]. Inhibition of GLUT2 by Ph induces apoptosis in HepG2 cells [30]. Another important inhibitor of Glucose transporter is WZB117. It inhibits GLUT1 which is a predominant transporter of glucose found in pancreatic, ovarian, and glioblastoma Cancer stem cells. It retards self-renewal and tumor-initiating capacity of the Cancer stem cells. Exposure of cancer cells to WZB117 showed decrease in the level of both intracellular ATP as well as enzymes of Glycolysis, along with concomitant decline in the level of GLUT1 protein [31]. Cutting down fuel supply via an indirect approach of inhibition of glucose carrier can be a hopeful approach to check cancer growth.

### APOPTOSIS INDUCTION ON GLUCOSE DEPRIVATION

Glucose is an essential nutrient for all mammalian cells. Cancer cells in particular shows high avidity for glucose and thus are more sensitive to cell death by glucose shortage than non-transformed cells. The tendency of cancer cells to proliferate irrepressibly is associated with the hyperactivation of oncogenes and inactivation of tumor suppressors, most of which also regulate glucose uptake and utilization. Deficiency of glucose in these cells may lead to depletion of ATP which induces mitochondrial death pathway. It also promotes cell death by two other pathways namely the oxidative stress-related cell death pathway, and induction of hypoxia-inducible factor-1α with concomitant activation of the p53-induced cell death pathway.

Culture of glioblastoma multiforme in glucose free medium encourages apoptosis in transformed cells but not in normal astrocytes [32]. Glucose deprivation is able to induce cell death in Bac-Bak- deficient cancer cells by apoptosis through cleavage and activity of caspase, phosphatidyl-serine exposure and cleavage of caspase substrates [33]. Immortality is attributed to cancer cells because of heightened activity of telomerase in these cells. Restricted glucose conditions are able to decrease Telomerase activity by more than 75% in Breast cancer MDA-MB 231 and MCF-7 cells. Further treatment of triple negative breast cancer cell with telomerase inhibitor BIBR 1532 in low glucose medium is able to induce cell death [34].

Endometrial cancer cell lines ECC-1 and Ishikawa were cultured in three different media conditions: low (1mM), normal (5mM) and high glucose (25mM) containing medium. Low glucose in the culture medium inhibits adhe-
sion and invasion, induces cell cycle arrest and apoptosis. Glucose starvation thus retards growth of endometrial cancer cells, affects AMPK and AKT/mTOR/S6 pathways and drives cells towards apoptotic pathway [35]. Tumor cell lines Human U937 myeloid leukemic, SKW6.4 B-lymphoblastoid, HeLa cervical carcinoma, and MCF-7 breast carcinoma cells were exposed to glucose free media. Glucose shortage boosted Caspase activation, mitochondrial depolarization, and release of cytochrome c [36]. Glucose shortage hence is able to impede cancer growth and induce programmed cell death.

**LOW GLUCOSE AVAILABILITY INSTIGATE SENESCENCE**

Cells cannot divide uncontrollably and it is under the control of “internal Biological clock”. This definitive proliferative capacity of somatic cells is known as the “Hayflick Limit” [37]. When cells reach their proliferative limit, they start displaying signs of ageing such as large flat morphology, increased granularity, and a vacuole-rich cytoplasm. They also show increased intrinsic fluorescence which is caused by the accumulation of oxidatively damaged proteins and lipids and senescence-associated β-galactosidase activity [38]. This growth arrested metabolically active state is known as senescence.

Senescent cells are found prevalent in premalignant tumours but as cancer progresses towards malignancy, cells escape the process of senescence. Immune cells of the body are able to remove senescent tumour cells and thus aids in effectual tumor suppression. Since senescence slows down cancer progress, induction of senescence can be an effective strategy to overcome cancer advancement. Various approaches are used for induction of sleep in cancer cells such as anticancer agents, γ-irradiation, or UV light. Stimulation of senescence using these approaches causes harm to neighbouring non tumorogenic cells of the body but initiation of senescence in cancer cells through glucose shortage leaves neighbouring non transformed cells of the body unharmed. HeLa cells are routinely cultured in high glucose medium (25Mm) but change of media having physiological glucose content in studies by Agarwal et al. showed signs of ageing such as enlarged flat morphology, increased granularity, enhanced auto-fluorescence and increase in level of ageing such as anticancer agents, γ-irradiation, or UV light. Stimulation of senescence using these approaches causes harm to neighbouring non tumorogenic cells of the body but initiation of senescence in cancer cells through glucose shortage leaves neighbouring non transformed cells of the body unharmed. HeLa cells are routinely cultured in high glucose medium (25Mm) but change of media having physiological glucose content in studies by Agarwal et al. showed signs of ageing such as enlarged flat morphology, increased granularity, enhanced auto-fluorescence and increase in level of p53 and p21. Low glucose condition forces HeLa cells to undergo nap [39]. Scarcity of glucose metabolism also induces senescence. Gitenay et al. constitutively expressed Glucose-6-phosphatase in immortalized Human mammary epithelial cells. These cells were cultured in media having 8mM glucose which is near to the normal physiological levels. Constitutive expression of glucose-6-phosphatase mimic with decrease of glucose consumption. It resulted in reduction in level of proliferative markers and induction of senescence as confirmed by SA-β-Gal activity and enhanced levels of various senescence markers [40]. Therefore in absence of adequate glucose availability cancer cells undergoes sleep even though they remain metabolically active. Initiation of senescence via glucose deprivation may be an important therapeutic strategy to win battle against cancer as surrounding cells might not be influenced.

**DISCUSSION**

Glucose is the basic fuel that generates energy in every single cell of our body. As glucose enters in the cell it is

**GLUCOSE RESTRICTION SENSITIZES CANCER CELLS TO TREATMENT**

High glucose in the culture medium creates cancer friendly niche for the rapid growth and proliferation via activation of proliferative pathways in tumor cells. They mainly use glucose for production of metabolites especially nucleic acid and fatty acids [41]. Constant availability of glucose reduces the effect of stress experienced by cancer cells due to anti-carcinogens. Numerous studies suggest that glucose restriction itself is able to slow down cancer cell growth [33, 39, 42]. Combining glucose restriction with anti-carcinogen make cells more responsive to drugs. Exposure of 0.35 ± 0.12 μM Rotenone to HeLa cells for 24 h arrests 50% of the cells in mitosis [43] whereas treatment of same cell line with Rotenone on glucose deprivation induced apoptosis at a much lower concentration of 1nm, even though exposure time was increased to 72 h [39]. Comparison of these two studies shows that combining glucose depletion with rotenone treatment to as low as 1nm can check HeLa cell growth. Such low concentrations of 1nm might not affect surrounding cells. Metformin exposure to different cancer cells shows variation in sensitivity. Human cancer cell lines MDAMB231 and SKBR3 are resistant to metformin when grown in high glucose medium (25 mM glucose). Reduction of glucose levels to 2.5 mM or less induces a cytotoxic response to metformin treatment. Calorie restricted low carbohydrate ketogenic diet which reduced serum glucose levels to 3mM in Balb/c mice treated with metformin exhibited sluggish tumor growth whereas metformin treatment had no effect on mice having normal diet. Dropping glucose levels in vivo is able to enhance metformin’s toxicity to cancer cells [44]. Bikas et al. found similar results on treatment of thyroid cancer cell (FTC133 and BCPAP) with metformin. Anti-cancer efficacy of metformin was enhanced in FTC133 and BCPAP cells cultured in low glucose medium (5 mM) [45]. Activation of UPR supports tumor growth as it stabilizes ER folding under ER stress but it depends entirely on the context. UPR can either be cytotoxic or cetotoxic depending on cell situation. Interference of UPR with macrocyclic compound, versipelostatin in glucose deprived Human colon cancer HT-29 and fibrosarcoma HT1080 cells induced toxicity [46]. Presence of Glucose analogue 2-deoxy-D-glucose (2-DG) in the culture medium mimics glucose deprivation. As 2-DG enters the cell hexokinase phosphorylate it to 2-deoxy-D-glucose-6-phosphate (2-DG-6-P) but it is not further metabolized which results in reduced yield from both glycolysis and the pentose phosphate pathway [45]. Combination treatment using both Glucose analogue 2-DG and irradiation (IR) or chemotherapy enhances the rate of improvement [47]. Low carbohydrate diet acts as a speed breaker which decelerates rate of fast dividing cancer cell. Further exposure to irradiation or chemotherapy slows down cancer progression at much higher rate as compared to treatment alone with anti-carcinogens.
metabolized by glycolysis and oxidative phosphorylation to generate ATP. Cancer cells are cells gone wrong. They live on the edge of what is metabolically attainable. They have strong desire for glucose laden food. To satisfy their abnormal high glucose demand they adopt various skills. Enhanced expression of glucose transporter accompanied with an increase in the translocation of the transporter to the plasma membrane are key features which cancer cells use and maintain to fulfil energy demands. Glucose withdrawal causes alteration in signalling pathways including activation of AMPK that leads to activation of catabolic processes with simultaneous inhibition of anabolic pathways with ultimate aim of ATP conservation.

There is an indirect link between cancer risk and sugar. Individuals having lots of sugar in their diet are at an increased risk of being obese. They have greater chances of developing Diabetes which favours development of solid malignancies such as pancreatic, bladder and liver [13]. An excessive sweet tooth assists onset of cancer. Enhanced expression of glucose transporters in non-malignant human breast cells stimulated oncogenic signalling pathways and loss of tissue polarity. Concentration of glucose and its uptake from the culture medium determined whether breast cancer cells form colonies with malignant or non-malignant phenotypes. On the other hand decline in glucose availability or uptake re-established formation of organized structures, inhibited oncogenic signalling and halted growth [48].

Cancer cells are mostly cultured in medium having 20mM-25mM Glucose. Depletion of glucose in the culture medium in vitro to 2.5mM-5 mM induces sleep in rapidly dividing cancer cells. Unlike normal cells, cancer cells solely depend on glucose for energy demands. Glucose deprivation thus induces a stronger stress response leading to induction Apoptotic cell death due to exhaustion of ATP which leads to activation of various death pathways.

Cutting down sugar availability to cancer cells inhibit glucose transporters and slows down progression of tumor. Numerous strategies are used for inhibition of glucose transporters such as treatment with nutraceutical Genistein, quercetin, myricetin, morin, rhamnetin and isorhamnetin [49-51]. Implementation of keto diet is another approach to curtail glucose availability to cancer cells. Switch to this regime with high fat content, reasonable quantity of protein and very little carb, makes cancer cells more susceptible to growth restriction leaving normal healthy cells of the body unharmed. Cancer treatment mainly relies on chemotherapy and irradiation. But both these approaches have toxic side effects. Despite hindering cancer progression chemo and radiation therapy also harm normal cells of the body. Strategies that target transformed cells without impairing normal cells of the body will be a better choice. Glucose reduction is an effecter therapeutic strategy to put check on endlessly proliferating cancer cells. Since normal and transformed cells behave differently to glucose depletion. Normal cells of the body show enhanced expression of glucose transporter either by increased synthesis of mRNA and protein or through change in glycosylation pattern of glucose transporter. Increased translocation of glucose transporter to the plasma membrane also boosts glucose uptake by normal cells. On the contrary transformed cells undergo stress response that leads to cell death [52] (Figure 3). Glucose scarcity also protects normal cells but not transformed cells from toxic effects of anti-carcinogens [53]. Uniting glucose depletion along with treatments with anticarcinogens makes cancer cells more susceptible to treatment.

All these studies have laid the foundation for further research on integration of glucose restriction with other approaches to reexplore cancer treatments and give new ray of hope for patients to smile again.

CONCLUSION

Dependency of tumor for excess glucose is exploited in diagnostics. As an indirect link exists between cancer progression and sugar, targeting metabolic machinery along with traditional chemo and radiotherapies may prove helpful. However further research is needed in future for better understanding of tumor metabolism. Thus affecting metabolic pathways by focusing on the potential of dietary approaches to contain the disease might be a decent approach.

Acknowledgment

NRA is grateful to SERB, DST, India for providing NPDF for research and for the financial support. NM acknowledges Prof. Archana Tiwari, Professor and Head, School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya (RGPV), Bhopal, M.P. (India). No financial support has been availed for publication of this article.

Notes

The authors declare no competing financial interest.

References


[16] S. Zhao; W. Xu; W. Jiang; W. Yu; Y. Lin; T. Zhang; J. Yao; L. Zhou; Y. Zeng; H. Li; Y. Li; J. Shi; W. An; S. M. Hancock; F. He; L. Qin; J. Chin; P. Yang; X. Chen; Q. Lei; Y. Xiong; K. L. Guan, Regulation of cellular metabolism by protein lysine acetylation. Science. 327(5968), 1000 (2010). doi: 10.1126/science.1179689


[18] N. A. Graham; M. Tahmasian; B. Kohli; E. Komisopoulou; M. Zhu; I. Vivanco; M. A. Teitell; H. Wu; A. Ribas; R. S. Lo; I. K. Mellingerhoff; P. S. Mischel; T. G. Graeber, Glucose deprivation activates a metabolic and signaling amplification loop leading to cell death. Molecular Systems Biology. 8(1), 589 (2012). doi: 10.1038/msb.2012.20


[31] Y. Liu; Y. Cao; W. H. Zhang; S. Bergmeier; Y. R. Qian; H. Akbar; R. Colvin; J. Ding; L. Y. Tong; S. Y. Wu; J. Hines; X. Z. Chen, A small-molecule inhibitor of glucose transporter 1 down-regulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth in vitro and in vivo. Molecular Cancer Therapeutics. 11(8), 1672 (2012). doi: 10.1158/1535-7163.MCT-12-0131


[38] Y. Li; J. Hu; F. Guan; L. Song; R. Fan; H. Zhu; X. Hu; E. Shen; B. Yang, Copper induces cellular senescence in human glioblastoma cells through downregulation of Bmi-1. Oncology Reports. 29(5), 1805 (2013). doi: 10.3892/or.2013.2333


Open Access
This article is licensed under a Creative Commons Attribution 4.0 International License.
© The Author(s) 2018