HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 3 (2022)

Molecular Mechanisms of Cancer Metabolism and Their Cellular Cycles

Harshita Ganga[1] and Raj Appavu[#]

[1]William Mason High School, Mason, OH, USA
[#]Advisor

ABSTRACT

Cancer is a prevalent disease, with 1,752,735 new cases reported to the CDC in 2019. The disease is characterized by uncontrolled growth and spread of abnormal cells. Current treatments for cancer can affect the whole body and have detrimental effects. Cancer cells are often programmed metabolically. In recent years, treatments to undermine this metabolic reprogramming have come to the forefront. In this review, we explore some of the molecular mechanisms underlying certain dietary interventions and critical metabolic pathways. Dietary interventions such as chronic calorie restriction (CR) and fasting have been shown to aid in adjusting metabolic reprogramming to help in reducing cancer progression. Other dietary interventions target amino acid (AA) metabolism. Essential AAs are only consumed from the diet and their restriction has been shown to work as a treatment in mice. Lastly, central carbon metabolism includes the TCA cycle and glycolysis, both commonly reprogrammed pathways in cancer cells. Other dietary interventions and the reprogramming of these pathways can be used to treat cancer in other ways, such as knocking out genes and cell cycle arrest.

Introduction

Cell proliferation is an attribute of cancer cells that leads to tumor formation and cancer progression.[1] Cancer cells may exhibit changes in cellular metabolism, a biological process that consists of all the chemical reactions in the human body. Metabolism is a series of biochemical reactions using nutrients and converting them into products such as energy, biomass precursors, and antioxidants.[1] The metabolism of cancer and normal cells are very different from each other. Cancer cell metabolism is characterized by enhanced uptake and utilization of glucose, a phenomenon known as the Warburg effect. This difference is partly due to tumor suppressor genes and oncogenes.[2] Mutations of oncogenes and tumor suppressors can change metabolism to keep up with the survival requirements of cancer cells.[3] Signaling pathways may also have clear changes in the case of cancer. Mutations in signal transduction pathways (transcriptional programs) alter gene expression and activity through post translational modification on essential proteins and enzymes in key metabolic reactions.[2] Metabolic reprogramming in tumor cells includes enhancing glycolysis to fill the higher ATP demands of the tumor cell. This can lead to many integral changes in the microenvironment of the cell itself, such as acidosis.[3]

Dietary interventions such as chronic calorie restriction (CR) and fasting have been shown to aid in adjusting metabolic reprogramming to aid in the reduction of cancer progression. These dietary interventions can slow down aging in many models by enhancing stem cell function, metabolic flexibility, and DNA repair.[4] All of these qualities play a role in inhibiting cancer progression, as well. Other methods include balancing the macronutrient environment and fasting (or time-restricted feeding). In this review, I will be exploring the signal transduction pathways underlying these dietary interventions for cancer treatments.

Dietary Changes

Calorie Restriction

As mentioned above, CR is a dietary intervention commonly used on cancer patients and has many different molecular mechanisms (See Figure 1). CR induces weight loss without malnutrition and inhibits cancer progression, as shown in experimental models.[5] The diet for CR consists of a 20% to 40% reduction in the average daily caloric intake. CR causes a metabolic adaptation in mammals. Circulating glucose concentration is the first to decline. The organism will need to break down stored glycogen to use as a main energy source. Once the glycogen stocks are depleted, glycerol and fatty acids are mobilized from adipose tissue. Therefore, ketone bodies become the main fuel, leading to decreased body weight.[6] CR works to increase lifespan and protect against cancer by reducing the levels of anabolic hormones, growth factors, and inflammatory cytokines. CR can also reduce oxidative stress and cell proliferation, evidently decreasing tumor growth and metastasis, among other things. In addition, CR enhances autophagy and several DNA repair processes.[7]

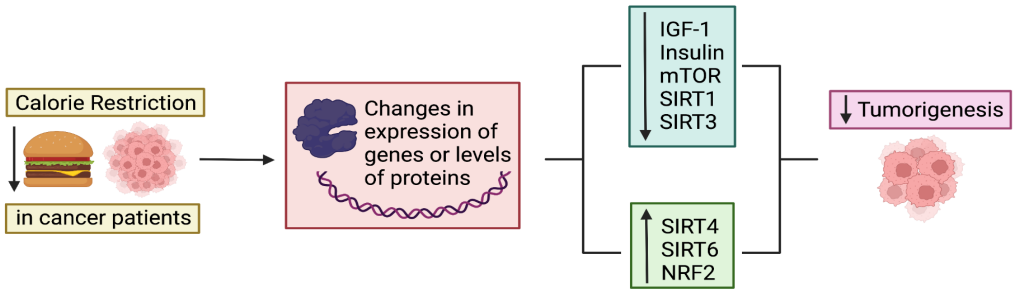

Figure 1. Possible molecular mechanisms of CR. This figure splits the molecular mechanisms of CR into upregulating and downregulating key cancer-related genes and their overall effect on tumorigenesis.

CR can cause a dysregulation of growth factors. One example of a growth factor is insulin-like growth factor 1 (IGF-1).which is an endocrine protein produced by the liver that promotes tumor formation by inhibiting apoptosis.[9] IGF-1 is a strong nitrogen, which means that it stimulates the development and growth of several tumors.[7] IGF-1 found in the blood is IGF binding proteins (IGFBPs). When IGF-1 binds to its receptor, insulin-like growth factor 1 receptor (IGF-1R), the AKT signaling pathway is triggered. Activation of this pathway results in cell growth, proliferation, and inhibition of apoptosis (programmed cell death).[9] As the concentration of IGF-1 increases, tumor formation is more likely, which is detrimental for a cancer patient. In CR, the concentration of IGF-1 decreases since growth hormone (GH) concentration is decreased; in turn, GH cannot stimulate the release of IGF-1 (See Figure 2). In addition, IGF-1R is a commonly activated pathway in epithelial cancer, which means that CR is an effective treatment, in part because it decreases the levels of IGF-1.[10, 11]

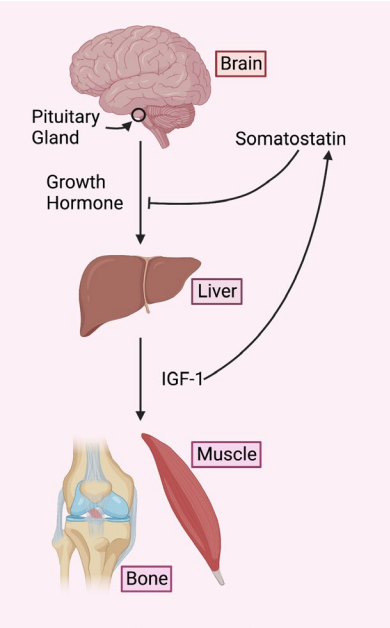

Figure 2. Relation between IGF-1 and GH. This figure shows the effects that this pathway may have on the body, such as increasing bone and muscle growth.

In addition to decreasing IGF-1 levels, CR plays a role in depleting levels of adiponectin, a peptide protein secreted by the white visceral adipose tissue. Adiponectin can counter obesity-related metabolic perturbations. through decreasing mTOR signaling in the AMP activated protein kinase (AMPK) pathway.[10] This pathway has a role in tumor suppression, which is regulated by the inhibition of mTOR.[8] mTOR in the AMPK pathway controls autophagy, a process in which the cell degrades unnecessary proteins and organelles to use them as building blocks for the necessary molecules.[5, 12] Autophagy is critical in the success of a tumor cell, which wants to maintain a favorable environment for its daughter cells.[12] CR causes AMPK pathway stimulation which can increase autophagy.[5] Both of these mechanisms can explain CR's effectiveness against cancer,

A third key player in metabolic action of CR is the sirtuin pathway. Sirtuins are a family of proteins that are NAD^+-dependent and play a role in modifying protein. There are seven genes in the sirtuin family (SIRT 1-7).[13] SIRT1 represses the p53 gene, which is a tumor suppressor. This means that SIRT1 can cause tumor formation.[14] SIRT2 has a role in tumorigenesis, however what exactly it does is not clear. It can increase tumor formation and suppress it.[15] SIRT3 can regulate levels of reactive oxygen species (ROS). SIRT3 is found primarily in the mitochondria and can cause increased expression of hypoxia-inducible factor 1 (HIF1) genes, which increases glycolysis and can cause tumor formation or growth. SIRT4 regulates glutamine metabolism by inhibiting glutamate dehydrogenase (GDH). SIRT4 is also in the mitochondria; a loss of SIRT4 increases glutamine catabolism, which promotes tumor growth.[14] As SIRT5 is expressed, tumor proliferation decreases.[16] SIRT5, on the other hand, has not been implicated in cancer. Next, SIRT6 is chromosome-bound as a protein and acts as a repressor of MYC and nuclear factor-κB (NF-κB). A loss of SIRT6 favors tumor proliferations, since it causes an increase in the expression of glycolysis and ribosomal genes.[14] It has been shown that metastasis and larger tumor size are more likely to occur as SIRT7 is expressed.[17] CR has been shown to increase life span, while sirtuin levels and activity change accordingly.[5] However, it is unclear if we can use the sirtuins for chemotherapy or a related treatment in the future due to the many roles of each of the sirtuins.

Transcription factor NF-E2-related factor (NRF2) regulates several metabolic pathways. NRF2 knockout in mice has shown that CR mimetics induce the NRF2 pathway.[18] In addition, NRF2 is responsible for many of the anticarcinogenic effects of CR.[19] The NRF2 protein acts as a transcription factor and is potent enough to activate the target 100-fold. However, NRF2 is a very unstable protein and is induced by oxidative stress, which

is harmful to many cells in the body. CR mice with knocked out NRF2 are characterized by low cancer protection. This implies that NRF2 may play a key role in the protective ability (as a treatment) of CR for cancer. [18]

Fasting

In addition to chronic calorie restriction, fasting is a dietary restriction that plays a role in reducing tumorigenosis.[20] There are other methods of diet restrictions that reduce tumorigenesis. One of these methods is fasting. 3 types of fasting methods that can be used to combat cancer– short-term fasting (STF), intermittent fasting (IF) and periodic fasting (PF). STF is a mechanism that has been tested in rodents. Unlike CR, STF works to protect the patient (rodents, in this case) from the harmful effects of chemotherapy. CR, on the other hand, works to combat tumorigenesis without the help of chemotherapy.[20] STF induces differential stress resistance (DSR) in both tumor and normal cells.[21]

We can compare STF to CR, since they both have similar molecular mechanisms (See Figure 3). For example, IGF-1 is also a regulator of STF. IGF-1 levels decrease as a patient goes through STF. Similar to CR, this decreases GH levels in the liver, which can prompt many things such as stress resistance in healthy cells.[20] This can help the healthy cells survive when being treated with chemotherapy. AMPK is also activated during STF, but has different molecular mechanisms. It inhibits energy consuming processes, such as cell proliferation.[20] DSR protects healthy cells from chemotherapy due to reinvestment of energy into maintenance and repair. This is critical to cancer patients, since chemotherapy still works on tumor cells.

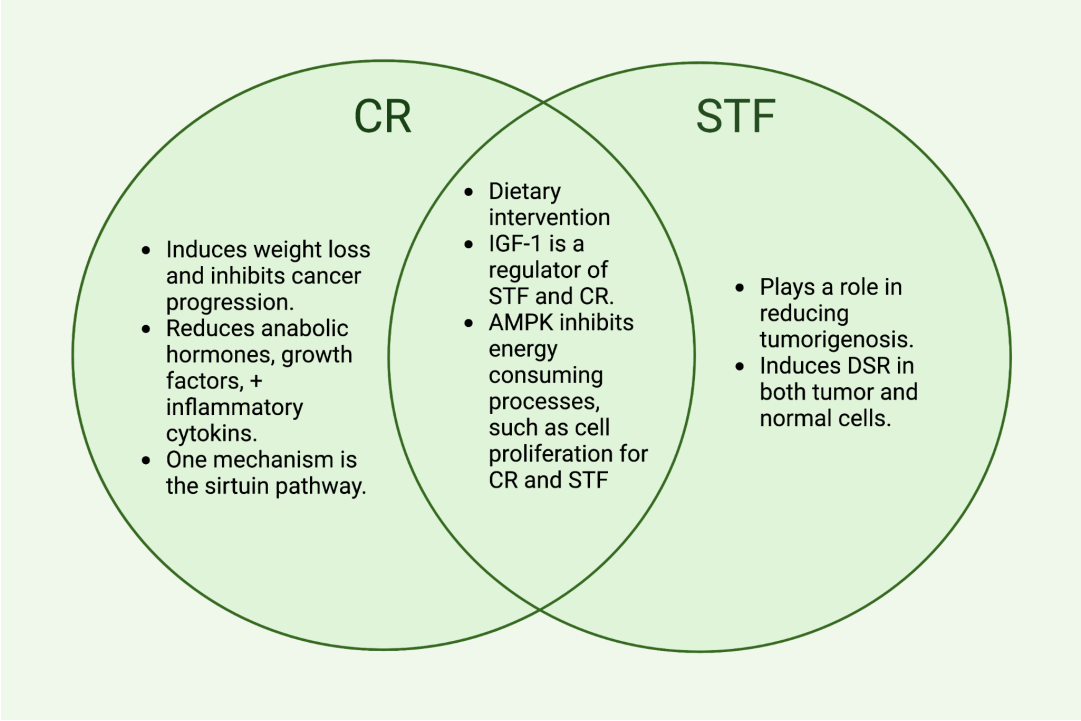

Figure 3. Similarities and differences in the molecular mechanisms of CR and STF. This figure compares and contrasts CR and STF, which are both dietary interventions that can be used to treat cancer. They both share similar molecular mechanisms.

Secondly, IF, a reduction in calorie intake over intermittent time periods, reduces tumorigenesis. IF is.[22] IF has recently become one of the most popular ways to fast, both generally and among cancer patients. There are many different types of IF (See Table 1). The most popular being time-restricted feeding (TRF),

which involves fasting 12-20 hours a day, and having daily food intake in a specific time during the remaining 4-12 hours.[24] Some benefits of IF include weight loss and reduced risk of cardiovascular disease.[22] IF also is correlated with cancer prevention. TRF has been tested in mice and it has been shown to stop tumor initiation, decrease progression, and inhibit metastasis.[23]

Table 1. Types of IF. This table details the different types of IF and their regimens. The different types include TRF, ADF, modified fasting regimens, and religious fasting. The table explores Ramadan fasting, a type of religious fasting.

TRF	This version involves a restricted time window of calorie intake, each day. This window is usually between 4 to 12 hours.[24]
Alternate Day Fasting (ADF)	This version involves alternate fasting with eating days. An eating day is defined as a day when energy containing beverages or foods are consumed.[25]
Modified Fasting Regimens	This version is a basis for the 5:2 diet. On fasting days, it involves a calorie intake of 20-25% of the normal daily calorie intake.[25]
Religious Fasting - ex. Ramadan fasting	Religious fasting can be undertaken for a variety of reasons and are very different in principle as well. One example of religious fasting is during Ramadan. In Ramadan, a meal is eaten either before dawn or after sunset. Generally, there is a heavy meal after sunset and a light one before dawn. This results in 12 hour fasting periods.[24,25]

We can explore the underlying mechanisms of IF; however, just like STF, they are very similar to those in CR. Studies in mice have shown that this fasting regimen can decrease levels of IGF-1.[25] This can lead to a decrease in cell proliferation because IGF-1 can inhibit apoptosis, which means that it increases genomic instability, and therefore cell proliferation. Autophagy has also been implicated in the mechanisms of IF. Autophagy is a lysosome-degradation pathway that is very important in the regulation of both tumor suppressor genes and oncogenes.[23]

The third type of fasting is PF. PF involves fasting for 2-7 days once a month. Unlike IF, PF can be carried out as needed.[26] PF can also be called a fasting-mimicking diet. Some of the molecular mechanisms that have been associated with PF are also seen in CR. These include lower insulin, leptin, and IGF-1 levels in the blood, and inhibiting AKT–mTOR.[27]

Amino Acid (AA) Metabolism

In addition to CR and fasting, other types of metabolism can be explored to find dietary interventions. As tumor cells continue to proliferate, their metabolic demands increase. One way that tumor cells keep up with increased demand is by altering AA metabolism.[2] AAs play roles in a wide range of metabolic activities such as redox balance, energetic regulation, biosynthetic support, and homeostatic maintenance, on top of their role as protein building-blocks.[28,29] AAs have also been used for other purposes in tumor cells. For example, tumor cells often use the synthesis of glutathione from glutamate, glycine, and cysteine to reduce reactive oxygen species (ROS).[28] AA can be used in dietary interventions for cancer patients by inhibiting certain amino acids.

Methionine Metabolism

Methionine is an essential amino acid that cannot be produced in the body, and is therefore consumed in a meal. Methionine is a necessary source of sulfur for tumor cells. Dietary interventions for cancer can target methionine. [30] Methionine restriction (MR) is a dietary restriction of methionine that has been shown to extend lifespan in mice. Healthy cells have no need for methionine, in the case that homocysteine is present, therefore MR works on just cancer cells. MR works by reducing oxidative stress, altering autophagy, improving insulin sensitivity, and decreasing adiposity.[31] MR has a greater effect on cancer cells and has potential as a treatment for cancer or to prolong the patient's life.

Methionine has three major functions in relation to cancer: glutathione formation, polyamine synthesis, and methyl group donation.[30] Glutathione is tripeptide that reduces ROS, leading to a decrease in oxidative stress.[31] MR can increase levels of glutathione. Polyamines are small cations that occur naturally, and polyamines help preserve chromatin structure.[30] Spermine and spermidine are two polyamines that require methionine to form. Both of these polyamines have important roles in nuclear and cell division.[32] Inhibition of polyamines has been shown to disrupt the cell cycle and DNA synthesis, which can lead to oxidative damage. Polyamines can induce apoptosis in healthy cells. It is clear that since polyamines have a far-reaching role in the cell cycle, MR or a similar dietary restriction can be used to treat patients. Thirdly, methionine plays a role in methyl group donation. Methyl groups can be given to many molecules, one of which is DNA. DNA methylation is one of the most studied epigenetic changes.[30] DNA methylation can stabilize chromatin structure and decrease its sensitivity, making it a valuable tool for tumor cells.[32] MR can increase global DNA methylation as shown in studies of mice livers.[30]

Serine and Glycine Metabolism

Serine is involved in a side-branch of glycolysis and if often dysregulated in cancers.[33,34] Serine can support cell proliferation by facilitating folate metabolism and redox homeostasis as they relate to cancer.[34] Folate metabolism is related to one-carbon molecules. Folate metabolism networks play a major role in redox maintenance and integrate nutritional components such as the amino acids, including serine and glycine. Folate metabolism intersects with methionine metabolism as well. [2] Serine starvation leads to p-53 dependent metabolic remodeling in the cell and an upregulation of a serine synthesis pathway and oxidative phosphorylation (both independent of p53).[36,37] This means that serine can be used to treat any cancer in which p53 has been mutated. Glycine, on the other hand, does not have the same detrimental impact as serine when restricted in the diet but has been shown to stop the growth of certain tumors, such as liver and melanoma tumors.[36]

Branched-chain Amino Acid (BCAA) Metabolism

The next type of AAs that can be used in dietary interventions are BCAAs. The BCAAs are leucine, isoleucine, and valine (See Figure 4). These are essential AAs for mammals and have roles in protein synthesis, nutrient signal sensing, and energy production.[2,38,39] Tumors are quick to take in BCAAs and use them for protein synthesis or oxidize them for energy purposes. Two enzymes, cytosolic branched-chain aminotransferase 1 (BCAT1) and mitochondrial branched-chain aminotransferase 2 (BCAT2), convert BCAAs into branched-chain α-keto acids. The genes coding for these enzymes are often overexpressed in cancer, but not always.[38] The epigenetic regulation of the genes that code for BCAT1 comes from a mutated form of IDH1/2.[40] BCAAs can provide an alternate pathway to glucose utilization.[2] During tumorigenesis, some studies found that there is a flux in the shutdown in BCAA catabolic pathways through down-regulation of the gene that codes for BCAT2. On the other hand, BCAT1 expression is increased in certain tumors, which increases the intake of BCAAs.[40]

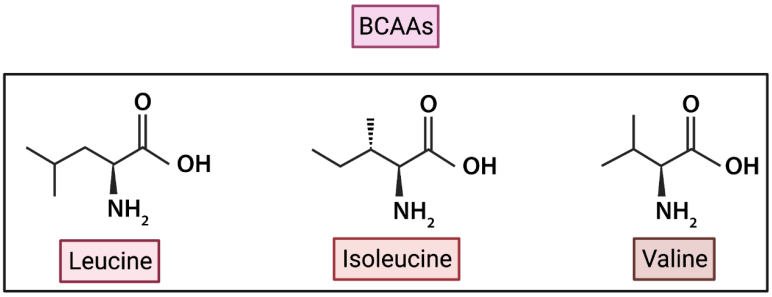

Figure 4. Structure of the three BCAAs. This figure draws out the chemical structure of the three BCAAs: leucine, isoleucine, and valine. The aliphatic side chain is clear in the figure; however, it is important to note that similar structure doesn't mean similar hydrophobicity nor biological effects.[41]

Given the correlation of the expression of BCAT1/BCAT2 and tumorigenesis, dietary manipulation or knocking out a gene are two possible therapeutic treatments.[2,40] BCAT1 is upregulated in cancers, so knocking out the gene has been shown to have a positive effect on mice. This is a useful treatment for BCAT1-dependent tumors or cancers.[40] However, there have been few studies on these topics and even the correlation is not clear, because certain studies have shown contrasting results.

Metabolism of Other AAs

There are many other AAs that are dysregulated in cancer. One of these is arginine, a semi-essential AA that is a precursor for many vital molecules, such as polyamines and nitric acid. Arginine is taken into a cell by a member of the cationic amino acid transporter (CAT) family, specifically CAT-1 (SLC7A1). It has been shown that in L-arginine dependent tumors, when SLC7A1 is knocked out, apoptosis is induced in tumor cells. Another AA that is significant in cancer is glutamine. Glutamine is a semi-essential AA that is a major nitrogen source for many different macromolecules. When tumors are in a state of hypoxia or the mitochondria is functioning irregularly, glutamine is used to create lipids or other sources of energy. Asparagine is also commonly used by cancer cells to the point that some tumor cells can be considered asparagine-addicted.[39]

Central Carbon Metabolism

Other types of metabolism are also used for dietary interventions. An example is central carbon metabolism, which is also important for some possible mechanisms of CR. In the 1920s, Otto Warburg proposed that the cause of cancer may be metabolic defects.[42] It is clear that cancer cells rewire their metabolic pathways in order to increase proliferation and survival. The Warburg effect occurs when this rewired metabolism involves the increased uptake of glucose and an increase in fermentation, which leads to an increase in lactate.[43] Of the metabolic pathways related to cellular respiration, two pathways are more likely to be dysregulated in cancer: the tricarboxylic (TCA) cycle and glycolysis. This is called central carbon metabolism.[1]

TCA Cycle

The TCA cycle plays a central role in oxidative phosphorylation. Cancer cells initially don't utilize the TCA and go through aerobic glycolysis, instead. As we see from the increased amount of lactate, cancer cells do switch to an anaerobic pathway. Cancer cells can switch to the TCA cycle, which plays roles in production and macromolecule synthesis.[44] The TCA cycle occurs in the mitochondria after the initial oxidation of glucose into

2 pyruvate molecules (See Figure 5). Pyruvate is then converted to lactate by the cancer cell and secreted from the cell. The TCA cycle also produces electron carriers.[45]

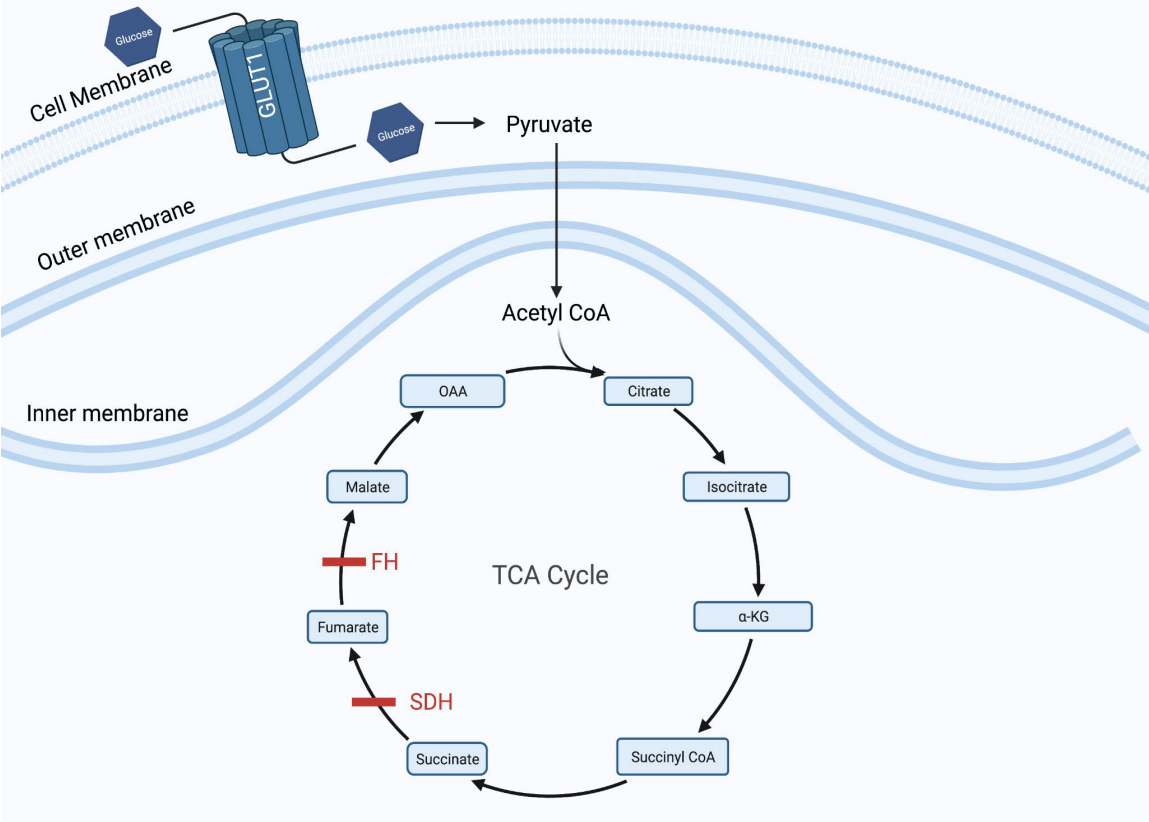

Figure 5. Steps of the TCA cycle. This figure details the different steps of the TCA cycle, and it shows the location of these steps. Two enzymes are labeled at certain steps in the cycle. Mutations of the genetic codes that codes for these enzymes have been implicated in cancer.[45]

There are three critical molecules in TCA that are most affected by mutations: isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH). All of these molecules have been implicated in different cancers.[45] IDH is a member of the dehydrogenase family. It produces CO_2 and 2-oxoglutarate (α-KG) in the TCA cycle. Mutations of IDH are seen in blood cancers, such as acute myeloid leukemia and angioimmunoblastic T-cell lymphoma. Secondly, SDH is a highly conserved tumor suppressor with 2 catalytic parts and 2 hydrophobic parts. In the TCA cycle, SDH catalyzes the oxidation of succinate to fumarate. Thirdly, FH catalyzes the hydration of fumarate to L-malate. A loss of a wild-type allele of this gene can lead to aggressive cancers in the kidney.[46]

Phosphoenolpyruvate carboxykinase (PEPCK) is a key regulator of the TCA cycle's flux. The primary function of PEPCK is to limit the rate of gluconeogenesis. PEPCK catalyzes the conversion of oxaloacetate (OAA) to phosphoenolpyruvate (PEP). In addition, it has been shown that a decrease in PEPCK can also lead to a decrease in the activity of the TCA cycle. This decrease is a lot more drastic than the corresponding decrease in gluconeogenesis.[47] Dietary interventions can be used to intervene in the TCA cycle. Other therapeutic interventions may include knocking out a gene or upregulating it (i.e. SDH).

Glycolysis

Warburg predicts that the aerobic glycolysis exhibited by cancer cells originates from damaged mitochondria.[48] Another reason that cancer cells use aerobic glucose may be because it is the most efficient pathway for beginning the breakdown of glucose, after which, the two pyruvate molecules are converted to lactate and secreted from the cell.[45] This works because electron carriers (NAD^+, specifically) have already been generated and can go to the ETC to produce more ATP. Around 10% of the pyruvate produced from glycolysis is not converted into lactate, and instead sent to the mitochondrion (into the TCA cycle).[49]

Glycolysis is very important to meet the anabolic needs of cell growth. There are three important transcription factors that scientists have studied in glycolysis in cancer cells: hypoxia-inducible factor 1 (HIF-1), cellular Myc (c-Myc), and the tumor suppressor p53. There are changes in concentrations of these transcription factors that occur in hypoxia. The TCA cycle and glycolysis interact; metabolites in the TCA cycle, fumarate and succinate, can lead to the upregulation of HIF-1. As tumor cells use the TCA cycle more, these metabolites accumulate. This can lead to an upregulation of HIF-1, which means that the cell believes that it is in a state of hypoxia. Overall, metabolic reprogramming of tumor cells may be induced by HIF-1, c-Myc, and p53.[50]

Discussion

Cancer is a prevalent disease in the United States and around the world. In the US alone, there are 1,752,735 new cancer cases reported in 2019.[51] Current treatments of cancer, such as chemotherapy and radiation therapy, can be used in conjunction with dietary interventions. Molecular mechanisms of the metabolism of cancer cells can be mitigated through possible dietary interventions. Dietary interventions can relate to whole calorie intake, time periods, or certain molecules, such as amino acids. For example, calorie restriction involves decreasing the daily calorie intake of a patient. This can create an environment that mimics starvation in tumor cells, which can increase the efficiency of treatments, such as chemotherapy. On the other hand, mechanisms underlying AA metabolism can show us what genes are upregulated or downregulated or the effect of an AA on cancer progression. Essential AAs are only obtained from diet, which makes them a key focus for dietary interventions. For example, methionine is an essential AA and MR has been shown to increase lifespan. Although this paper focuses mainly on the application of molecular mechanisms of cancer metabolism on dietary interventions, there are many other ways that we implement molecular mechanisms of cancer metabolism, such as knocking out genes (leading to metabolic reprogramming) and cell cycle arrest.[52,53]

There are some limitations on using dietary restrictions. Chronic CR can lead to a substantial weight loss in a patient, which means it can be used for a long time. AA restriction, similarly, cannot be used in the long term as well. Therefore, exploring metabolic reprogramming of cancer cells would be the next step to look into. From Warburg's principle, we know that the metabolism of cancer cells is different from healthy cells, which means we can target certain pathways or molecules.

Conclusion

Cancer is a disease characterized by the proliferation and uncontrolled growth of cells, which leads to tumor formation. There are some treatments available for cancer patients, such as chemotherapy. However, the current treatments can be detrimental to the patient's body. Certain dietary interventions can help reduce the effects of chemotherapy and other current treatments. These interventions have been found by studying the molecular mechanisms of cancer cells. Some dietary interventions affect the body as a whole and have greater effects on cancer cells, such as chronic CR. Fasting, on the other hand, has many different types and generally involves a time period where food and energy-containing drinks are not consumed. Fasting and CR have some molecular mechanisms. Dietary interventions can also focus on AA metabolism. AAs play many different roles in the

body, the main one being protein synthesis. This means that AAs have a huge effect on the entire body and essential AA restriction can be utilized against tumor cells. Lastly, central carbon metabolism plays a big role in the generation of energy for the body. It is clear that there is metabolic reprogramming of central carbon metabolism (among other pathways) in cancer cells. Thus, dietary interventions in conjunction with other cancer treatments, provide a more effective solution to combat the growth and metastasis of cancer.

Acknowledgments

I would like to thank my mentor, Dr. Rajagopal Appavu, for all his guidance. I also wish to show my appreciation to Biorender.com, where I generated my figures.

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