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Pathology

CANCER: ETIOLOGY, CONTROL AND NUTRITION

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ABSTRACT Cancer is the leading cause of death in the world; and cancer treatments are becoming more expensive and there are not resources available in any institution or government for their cure. In 2020, there were 19.3 million new cases and around 10 million deaths and 28.4 million cases are expected by 2024. The most common types of cancer are breast, lung, colon and rectum and prostate; approximately 30% are due to tobacco use, alcohol consumption, low fruit and vegetable intake, and lack of physical activity; as well as infections caused by hepatitis viruses or human papillomaviruses. Cancer in children and adolescents is one of the leading causes of death in the worldwide. Each year, more than 400,000 children are diagnosed globally. In children, leukemias are more common, then brain tumors, and then lymphomas. This makes it a public health problem in Mexico and the worldwide. Amino acids stimulate cell growth and development cellular. Polyamines are the integrated part of the cellular and genetic metabolism and help in transcription, translocation, signaling and post-translational modifications. Polyamines binding to RNA leads to structural changes which stimulate and increase the protein synthesis along the amino acids may influence the conditions of various diseases. Several diseases can be controlled to a higher extend via maintaining the metabolism of amino acids and polyamines. On the other hand, a controlled diet is a way to maintain the level of amino acids and polyamines in the body. Present review highlights to etiology of cancer, also discusses functions and metabolism of polyamines in human and also highlights the nutritional role of amino acids and polyamines in the prevention and control of various diseases.

KEYWORDS : Cancer Metabolism, Amino Acids, Polyamines, Canavanine, Sulforaphane

INTRODUCTION

Cancer can affect any part of the body and is characterized by a rapid growth of abnormal cells that can invade adjacent parts of the body or spread to other organs (metastasis). The complex cellular mechanisms and inter-related pathways of cancer proliferation, evasion and metastasis remain as emerging field of research. These alterations are due to the interaction between genetic factors of the affected person and some external agents such as:

Physical carcinogens: Ultraviolet and ionizing radiation.

Chemical carcinogens: Tobacco smoke, aflatoxins that contaminate food, arsenic in drinking water

Biological Carcinogens: Viruses, Bacteria and Parasites

The incidence of cancer increases with age, possibly because risk factors accumulate and, on the other hand, the effectiveness of cellular repair mechanisms that occurs with increasing age is lost. Tobacco use. Alcohol, unhealthy diet, physical inactivity and air pollution are risk factors for cancer.

Cancer treatments are becoming more expensive. Lately it has been observed that when biological medications or other compounds are added to conventional treatments, a faster recovery of cancer patients occurs. In this article, after reviewing the mechanism of action of some compounds, they are proposed as additional compounds (1).

Multiple pieces of evidence suggest that dietary and lifestyle habits are related to cancer risk. In general, a low-fat, low-calorie diet is recommended; populations accustomed to meat consumption and low fruit and vegetable content have a higher risk of cancer, especially colon cancer. Routine physical exercise is also recommended. Various factors considered to be carcinogenic to different tumors and their possible mechanisms of action are mentioned below. This review provides a comprehensive review of the cancer metabolism, dietary interventions used during cancer treatment and metabolic drugs and their impact on nutritional deficiencies.

Types of Cancer

The type of cancer is usually defined by the tissue or organ in which it has originated and are grouped by the tissue that gave rise to them.

Carcinomas:

They originate from epithelial cells; they represent more than 80% of all cancers including the most common ones such as lung, breast, colon, prostate, pancreatic, stomach among others.

Sarcomas: These form from connective tissue, bones, or fatty tissue. The most common are bone sarcomas.

Leukemias: These originate in the bone marrow, which is the tissue that produces erythrocytes, leukocytes, and platelets. Alterations in these cells can lead to anemia, infections, and blood clotting disorders.

Lymphomas: Develop from lymphatic tissue

Causes

DNA is the code of instructions that each cell has to program its functions, including cell growth and division. Cancer is the result of damage to DNA and/or DNA regulation mechanisms (epigenetic damage), causing uncontrolled cell proliferation. DNA damage can be inherited from parents or caused by external agents. External factors are responsible for 90% of cancers.

Proteins are the elements that give structural support to cells, control chemical reactions, transport other proteins into or out of cells, activate or inactivate genes. DNA condenses in the nucleus of the cell to form chromosomes. The regions of chromosomes that govern the individual production of a protein are called genes, and the collection of 30,000 found on our chromosomes is called the genome.

Mutations are processes in which the nucleotide sequence of a gene is altered, inducing errors in protein production and therefore programmed cellular functions. Epigenetics refers to the study of the mechanisms that alter the expression (functioning) of genes without altering the sequence (without mutations) in DNA (2).

Any carcinogen that damages genes can lead to cancer. There are a number of stages in the genesis of cancer (carcinogenesis) that develop over a variable time that can even last for several years. The first step in carcinogenesis consists of the action of an initiating agent that causes damage (mutation) in the DNA, which may be due to internal causes of the organism such as hormones, infections or chronic inflammation. External factors such as radiation or chemical agents can also be the cause. The second step is induced by exposure to a promoter agent that stimulates cells to divide, which is initiated by the mutation. This promoting agent can be congenital, acquired, or external. A third step leads to epigenetic changes that lead to invasion and metastasis. The tumor destroys the basement membrane and extracellular matrix to make its way into blood and lymphatic vessels to metastasis.

In addition, in order to have its own supply of nutrients, it develops a system of its own blood vessels (angiogenesis).

Apoptotic genes induce cell suicide and, when they stop working,

contribute to the development of cancer by allowing genetically damaged cells to survive. Thus, the "p53" protein acts as a cell gatekeeper, recognizes DNA damage and can induce apoptosis in the cell.

The identification of the causes of cancer has been carried out through population-based studies of geographic incidences of cancer and lifestyle habits. A long period of It is time to complete the stages of carcinogenesis, and several years may elapse from exposure to the carcinogen to the clinical onset of cancer. Smoking is the leading environmental carcinogen known for lung cancer and an important factor for cancers of the head, neck, esophagus, and stomach. Alcohol consumption is also associated with cancer of the oral cavity, larynx, esophagus and breast cancer in women. Other external chemical agents have been associated with the risk of cancer, such as asbestos and lung cancer; the benzenes (petroleum) and leukemias, radon gas in coal mines and lung cancer; vinyl chloride and liver cancer, **etc**. Exposure to radiation such as ultraviolet radiation present in the sun's rays is associated with skin cancer (3). There are more than 100 distinct types of cancer but sharing common hallmarks, including sustaining proliferative signaling and evading growth suppressors.

Most cancer studies have focused on the disease from a genetic standpoint; However, cancer also includes biochemical alterations. These are mentioned below. Breast cancer metastasis is the main cause of cancer death in women so far, no effective treatment has inhibited breast cancer metastasis.

LEUKEMIA

Leukemia is characterized by an abnormal controlled proliferation and process of malignant transformation of one of the hematopoietic cells, usually white blood cells (leukocytes). Etiology of acute myeloblastic leukemia (AML), myelocytic leukemia (M3) or acute promyelocytic-leukemia (APL) includes a genetic predisposition to instability in the genes located on the long of chromosomes 15 and 17. The genes translocate due to DNA brockage most likely caused by exposure to X-rays, smoking and chemicals e.g. benzene and aromatic organic solvents. Obese persons and children with Down´s syndrome have an increased risk of developing leukemia. The first symptoms of AML, these include, fatigue, malaise, fever, pallor, loss of appetite, anemia, easy bruising, petechiae, purpura, hemorrhage, bone and joint pain, epistaxis, headaches, nausea and vomiting.

Leukemia is the most common kind of cancer in children. Leukemia also causes more deaths than any other form of cancer in children. Fortunately, improved treatment methods, have greatly reduced deaths from leukemia. Leukemia rates are higher for white children than black children. There are several forms of leukemia two of which are particularly important in children. There are usually known acute lymphoblastic leukemia (ALL) and acute myelocytic leukemia (AML). Acute lymphoblastic leukemia is the most common form in children and represents 78% of cases of leukemia; the incidence rate was 59 cases per million children under five, up to 80 cases per million children by year at ages 3 to 4; rates then decline to age 20.

Acute non-lymphocytic leukemia is the second most common form of leukemia in children and represents 19% . It is the form of leukemia most commonly diagnosed in children less than one year old.

Leukemia remission is when there is no evidence of the disease during treatment; in other words, it is a period when leukemia is in state of minimal or undetectable disease activity. However, this mean not a complete cure, as some cancer cells may remain in the body and can cause disease the return. Refractory ALL is a type of leukemia characterized by the failure to achieve complete remission or the recurrence of the disease after initial treatment. In other words, it is a form of ALL that does not respond to standard treatment or comes back after treatment. Treatment options for refractory ALL may include high dose chemotherapy, immunotherapy clinical trials or palliative care to manage symptoms and improve quality of life (5).

Known and suspected causes of leukemia

Both prenatal and pos-natal exposure to ionizing radiation and (particularly X-rays) can cause leukemia in children. Prenatal exposure to ionizing to X-rays has been greatly reduced with the adoption of ultrasound for screening in pregnant women.

Leukemia is linked to the production of final toxic metabolites such as quinones, semi-quinones, and free radicals. Quinones and free radicals damage hematopoietic stem cells (HSCs) through oxidation and adduct formation, damaging cell cycle arrest mechanisms at the DNA level. This genomic damage creates changes in the HSCs, including proto-oncogene activation, gene fusion, and inactivation suppressor gene. These changes give rise to leukemic clones observing that the absence of the tumor suppressor gene p53 causes: 1) cell damage by benzene and its metabolites, 2) continuous cycle of damaged cells without DNA repair, 3). inhibition of apoptosis, and 4). suppression of DNA damage repair genes. Reactive benzene metabolites mutate a critical gene or set of genes related to proliferation and differentiation in HSC causing chromosomal aberrations (6).

CML is characterized by the presence of BCR-ABL gene fusion, the result of a reciprocal translocation between chromosomes 9 and 22 cytogenetically visible as a shortened chromosome 22 known as the Philadelphia chromosome (Ph). Such a fusion is the cause of the pathogenesis of CML and that tyrosine kinase activity is central to the transformation of hematopoietic stem cells. This fusion, increases proliferation, reduces apoptosis, and other manifestations which lead to the clinical manifestations of CML. Hence, current efforts are focused on the molecular target that is BCR_ABL fusion. The ABL gene contains a DNA-binding domain and an α-kinase domain, while the BCR gene contains an autophosphorylation domain, when the BCR-ABL fusion takes place, it results in a tyrosine kinase-like protein with autophosphorylative capacity, promoting cell survival and proliferation signals

Several studies link pesticide exposure by both parents and children to leukemia. Children born of parents employed in certain occupations that have chemical exposures are more likely to have leukemia. Chemicals specifically including benzene have been shown to cause leukemia in adults. Also was observed that parents, exposure to chemicals other than pesticides and childhood leukemia was for solvents paints and employment in motor vehicle-related occupations. Exposure to X-rays after birth also increased the risk of leukemia. Infants receiving diagnostic X-rays had 60% more leukemia than other children (6).

PESTICIDES.

Several studies found than leukemia was more likely in children whose fathers were exposed to pesticides at work than other children. Risks for children are often reported to be greater than risks for adults. Herbicide use during pregnancy was associated with a 50% of increased in risk. A study of childhood leukemia cases in Shangai city found more than three times increase in risk for children whose mothers were exposed to pesticides at work. Children regularly exposed to pesticides in the house hold had 3.5 times greater risk of leukemia than those not exposed. In others studies have been found that the risk of childhood leukemia increased nearly four times when pesticides were used within the house at least once per week and more than six times when garden pesticides were used at least once per month.

SOLVENTS.

Chemicals where risks are elevated include solvents, in general chlorinated solvents, benzene, carbon tetrachloride. A study of nearly 2,000 children found that the risk of ALL was increased in the children´s mothers were exposed to solvents, paints or thinners before conception or during pregnancy or to last after birth. Also was found that parents, exposure to petroleum products increased the risk of AML. Petroleum products usually contain benzene (7).

Benzene is a hematotoxin and carcinogen. The hepatic metabolism of benzene is thought to be a prerequisite for its bone marrow toxicity. Chronic exposure causes aplastic anemia in humans and animals and is associated with increased incidence of leukemia in humans and lymphomas and certain solid tumors in rodents.

Benzene evaporates quickly when exposed to air; is among the most widely used chemical in world. It is used mainly as a starting material in making other chemicals as: plastics, lubricants, rubbers, dyes, detergents, drugs and pesticides.

Also is a natural part of crude oil and gasoline (and therefore motor vehicle exhaust) as well as cigarette smoke. The main way people are exposed is by breathing in air containing benzene. People can be exposed to benzene: at work; in the general environment through the use of some consumer products. The higher exposures have typically been in the workplace.

Benzene exposure, 99% of which is inhalational, diffuses easily into the lung; It is then distributed throughout the body and deposited in the fatty tissue. During distribution, benzene reaches the liver, which is the main organ responsible for metabolism. In the liver, benzene is hydroxylated by cytochrome P450ZEI producing benzene oxide, which is transformed by epoxide hydrolase into benzene dihydrodiol, which undergoes another oxidation producing catechol that by means of myeloperoxidase (MPO) produces 1,2-benzoquinone. In a non-enzymatic way, benzene oxide is converted to phenol; which is oxidized and hydroquinone (HQ) is formed, followed by 1,2,4-trihydroxybenzene. Alternatively, MPO metabolizes HQ to form 1,4-benzoquinone (BQ). In addition, benzene metabolites are also metabolized by other enzymes, which contribute to its detoxification. In the presence of glutathione-S-transferase (GST), benzene oxide is transformed into S-phenylmercapturic acid (S-PMA), which is less toxic and easily excreted. On the other hand, phenol, catechol, HQ, and 1,2,4-trihydroxybenzene can be conjugated with sulfotransferases (SULT) and UDP-glucuronosyltransferases (UGTs) to form sulfate and glucuronic acid conjugates respectively, which ultimately detoxifies benzene and allows its elimination from the body. In addition to hepatic metabolism, benzene has a secondary metabolism in bone, so bone marrow plays an important role in hemato-toxicity. Especially HQ, BQ, catechol alone or in combination are the main metabolites responsible for toxicity in the hematopoietic system (8).

ACTION OF BENZENE IN THE BLOOD

HEMATOPOIESIS. Hematopoietic stem cells (HSCs) play a crucial role in the long-term maintenance and production of all mature blood cell lineages, which have mechanisms to protect themselves from environmental stress as well as oxidative stress. In the case of benzene poisoning, the cytotoxic effect is due to metabolites that affect bone marrow cells; BQ and muconaldehyde are the ones that most affect HSCs in their differentiation process. It has been observed that at concentrations below the occupational exposure limit of 1 ppm, a lower that normal erythrocyte, leukocyte and platelet count occurs. Long-term exposure can lead to an increased risk of acute myeloid leukemia, aplastic anemia, and myelodysplastic syndrome (MSD). MSD It is a group of neoplastic diseases in which an alteration of the functions and morphology of cells is observed, which can evolve into AML.

ACUTE INTOXICATION.

Acute toxicity is related to CNS impairment after exposure to 250 to 500 ppm resulting in headache, dizziness, confusion, fatigue, loss of coordination, muscle tremors, convulsions, etc. Repeated exposures to 1 ppm of benzene cause damage to the bone marrow, leading to leukopenia, erythropenia and thrombocytopenia, leading to aplastic anemia, immunosuppression and MDS (9).

CHRONIC INTOXICATION. Cytopenia also occurs, and chronic myelogenous leukemia can occur. Leukemia develops after 1.5 to 5 years of exposure.

HEAVY METALS

Exposure to heavy metals represents significant health concerns; heavy metals induce a number of adverse health effects, but one of their more serious actions is their role in carcinogenesis.

ALUMINUM. exposure has been documented in contaminated food, vaccines to elicit a more powerful immune response and aluminum salts used in industrial processes and commercial products. Aluminum exposure has been strongly correlates with carcinogenesis in the breast tissue. Mice subjected to AlCl3 the same aluminum salt used in antiperspirant deodorant displayed malignant growth of mammary gland epithelial cells. This same result was observed in studies performed on samples of human breast cells. One study determined that subjecting human breast cells to aluminum had the potential to induce uncontrolled growth. Aluminum was observed to act as a metallo-estrogen, which behaves as an against for estrogen receptors and represents a known risk for carcinogenesis in the breast. On the other hand, analyzed samples of bladder carcinoma displayed statistically higher levels of aluminum, among other heavy metals. Standard therapy following aluminum poisoning has been the use of chelators (10).

ARSENIC.

Arsenic exposure includes smelting and arsenic based pesticide industries. This heavy metal has been detected in an extensive variety of malignant growth. Research strongly supports role of arsenic in the development of lung, bladder and skin cancer, colon, gastric, kidney and nasopharingeal. Carcinogenic mechanisms for this heavy metal include generation of reactive oxygen species (ROS), epigenetic alterations and damage to the dynamic DNA maintenance system. Key epigenetic changes induced by arsenic include alterations to the status of DNA methylation, histones and mRNA. Further examination of arsenic revealed its ability to reduce intracellular concentrations of glutathione a natural antioxidant. The use of chelators has remained the most effective way to eliminate arsenic from the body. Rice and apple juice have been recognized as two common sources of exposure (11).

CADMIUN.

Cadmiun is an immensely toxic heavy metal; soil pollution in a serious issue from cadmiun emissions and human exposure typically occurs from inhalation, smoking and ingesting contaminated food and water. Exposure to cadmiun has been associated with carcinogenesis in multiple tissues including breast, esophagus, stomach, intestines, prostate, lungs and testes, and gallbladder; additionally, this metal has been associated with the development of chronic myeloid and lymphoblastic leukemia (12).

LEAD. One common source of environmental pollution has been found in the soil, which can enter the human food cycle through contaminated produce. Lead is associated with any form of cancer as kidney cancer, gallstones, lung, larynx and bladder tissues. Chelation therapy is the recommended course of action for individual with lead poisoning (13).

MERCURY. Although this element can be found in trace amounts in mineral form most present in the environment is due to human induced pollution from processed mercury. Several sources of this heavy metal have been identified as thermometers, fossil fuel emission, dental fillings, certain batteries and burning medical waste. Mercury exposure is associated with renal cancer, hepatic cancer and gastric cancer. Mercury has the potential to generate free radicals as well as disrupt DNA molecular structure; in reducing the body´s concentration of glutathione, a natural antioxidant, elevated rates of lipid peroxidation, can disrupt cellular division. The use of chelators is the common therapeutic strategy for eliminating mercury from the body. One of most effective chelators is dimercaptopropane sulfonate (DMPS) (14).

NICKEL. There are a variety of cancers that have been associated with nickel exposure with lung, nasal and sinus tissues, breast cancer, acute myeloid and lymphoblastic leukemia and hepatic cancer. Nickel can generate free radicals, which contributes to the carcinogenic process; also has the ability to alter the regulation status for the transcription of various mRNA and microRNA; additionally has the potential to induce epigenetic changes such as alterations in DNA methylation. Compared to other heavy metals, the use of chelators involving nickel has been markedly different. Still has not been recommended the use of chelators to nickel cancer. It was determined that CaNaEDTA reverses the damage induced by nickel chloride (15).

Heavy metals exhibit an immense range of toxic effects in humans with regard to carcinogenesis, it is clear that a refined understanding of carcinogenic mechanisms is necessary. (13).

TRACE ELEMENTS

Trace elements are crucial for the functioning of several enzyme systems. Trace elements are so called because they constitute less than 0.01% of the weight of human body. Recently it has become apparent that human beings can suffer adverse effects from nutritional deficiencies of essential trace elements including Zinc and copper.

Zinc.

Zinc is a constituent of DNA and RNA polymerase; it is required as a catalytic structural and regulatory ion for enzymes, protein and transcription factors and thus is key trace element in any homeostatic mechanisms of the body including immune responses. Signs and symptoms of zinc deficiency includes depressed growth with stunting, increase incidence of infection, possibly related to alteration in immune functions, diarrhea, skin lesions. Excessive dietary intake of zinc has been linked with declining CD4 counts and reduced survival (15).

Selenium.

This element is essential for normal functioning of the immune system. Selenium also serves as a factor for glutathione peroxidase. An important enzyme in the antioxidant cascade and cellular protection, the low levels of selenium found in some cases of cancer may reflect long -term impairment of cell protection capacity. Selenium deficiency has been directly associated with the development of cancer, cardiovascular disease and hepatic lesions. Decreases in selenium, Zinc and a high copper status have been demonstrated in leukemia patients (15).

Manganese.
Manganese deficiency has been associated with cancer, rheumatic conditions, rickets, morning sickness, jaundice and diabetes. Manganese poisoning has been found among workers in the battery manufacturing industry. Symptoms of toxicity mimic those of Parkinson´s disease (tremors, stiff muscles) (15).

AMINO ACIDS

A seminal discovery in the field of cancer metabolism was made in the 1920s by Otto Warburg, who observed that tumor tissues consume glucose much more rapidly than surrounding healthy tissue and ferment glucose to lactate regardless of oxygen availability (aerobic glycolysis or Warburg effect). Subsequently was observed that optimal proliferation of certain cultured mammalian cell lines requires a several fold molar excess of glutamine over any other amino acid. Indeed, glucose and then glutamine are the most rapidly consumed nutrients by many cultured cancer cells lines; although altered metabolism of fatty acids, acetate, nucleotides, folate, proteins and several amino acids besides glutamine has also been reported. The antifolate aminopterin in 1940s was used to reduce remission in pediatric acute lymphoblastic leukemia (ALL) patients. Aminopterin supplanted in the cases antifolate by the related drug methotrexate competitivity inhibits dihydrofolate reductase and thereby blocks recycling of tetrahydrofolate a carrier of one carbon units that has essentials roles in amino acid and nucleic acid metabolism. Today antifolates along with anti-pyrimidines and antipurines are routinely used to treat a range of cancers illustrating the feasibility of targeting metabolism for cancer therapy (16, 17).

Amino acids provide both carbon and nitrogen for nucleic acids synthesis; purine biosynthesis requires formate, bicarbonate and three amino acids, aspartate, glycine and glutamine. While glutamine and aspartate act as the nitrogen source for both nucleobases from aspartate and N3 and N9 from glutamine and the amino group of purines (glutamate for adenine and aspartate for guanine). Amino acid catabolism produces metabolic intermediates affecting tumor cell growth and survival. Some of the earliest cancer therapies and antimetabolites to disrupt tumor metabolism and there is now renewed interest in developing drugs that target metabolic dependences. (18, 19)

Leucine

Leucine is an essential amino acid. Leucine acts as a signaling molecule activating mechanistic target of rapamycin (mTOR). Leucine is one of branched chain amino acid (BCAA), which is not first catabolized in the liver due to the low activity of BCAA-aminotransferase, Therefore, leucine increases rapidly in circulation after meal, and be really available as an essential nutritional signal to reduce food intake via mTOR. Although leucine is the highest enrichment BCAA in proteins, leucine deprivation showed modest effects on human breast cancer cells. Among BCCAs, leucine is important for melanoma cell survival. Leucine deprivation in melanoma cells fails to appropriately activating autophagy subsequently leading to apoptotic death.

Serine

Serine is a non-essential amino acid. The enhanced serine synthesis pathway could make significant contribution (50%) to the anaplerosis of glutamine to α-ketoglutarate for mitochondrial TCA cycle. Under the starvation of serine, the upregulation or enhancement of the novo serine synthesis pathway and oxidative phosphorilation were independent of p53. Serine starvation might have a potential role in the treatment of p53-deficient tumors. Serine and glycine are closely related and can be interconverted by serine hydroxymethyl-transferase (SHMT 1 and 2), SHMT is one of the key enzymes in folate-mediated one-carbon metabolism. One carbon metabolism encompasses both the folate and methionine cycle and provides methyl-groups for the one-carbon pools that are required for the novo nucleotide biosynthesis and DNA methylation. Serine is also involved in GSH synthesis via the folate cycle. Thus, it is not surprising that serine depletion results in glutathione reduction. In addition to the inhibition of serine biosynthesis, dietary restriction of serine and glycine has been explored in mice and was shown to be effective at limiting tumor growth in certain conditions where the novo serine synthesis activity is low. (20)

Glycine

Glycine restriction alone didn´t have the same detrimental effect on cancer cells as serine starvation which might be explained by the inter-conversion between serine and glycine in one-carbon metabolism by serine hydroxymethyl transferase. On the other hand, dietary supplement of glycine was also reported to inhibit the growth certain types of tumors, such as liver tumors and melanoma tumors. Glycine lowers cortisol levels.

In almost all indigenous cultures, they don´t eat muscle meat. Muscle meat is very low in glycine; but all the rest of the animal is high in glycine. Glycine is a glucogenic amino acid which help to regulate blood levels released in your liver and it supplies glucose in body tissue for energy. This is why L-glycine can help those who are suffering from chronic fatigue, anemia, hypoglycemia. Glycine helps to build muscle strength and tissue; athletes increase their muscle mass using glycine. Glycine prevent melanoma from forming.

Lysine

Kwashiorkor is a severe protein malnutrition disease of childhood associated with lysine deficiency in normal corn diet. Normal maize has low levels of lysine and tryptophan which lead to the imbalance of amino acid and malnutrition. In 1983 five cases were described in detail, all cases had a history of lacking breast-feeding and were only fed with the food prepared from normal maize, it took 4 to 12 months for the development of the kwashiorkor disease in those children. Thus, Lysine is an important amino acid than play indispensable roles in homeostasis, proliferation, differentiation and diseases including malnutrition and cancer. Intermittent dietary lysine restriction with normal maize as an intermittent staple food for days or weeks, might have the value and potential for cancer prevention or therapy (19).

Tryptophan

The metabolism of tryptophan is complicated and was involved in the regulation of immunity, neuronal function and intestinal homeostasis. Majority (95%) of absorbed tryptophan degraded via kynurenine pathway. Besides the usage for protein synthesis a small fraction was catabolized by tryptophan hydroxilase for the production of serotonin and melatonin.

Methionine

Methionine is essential for the initiation of protein synthesis. S-adenosyl-methionine (SAM) provides the methyl group for epigenetic modification. The methionine cycle and folate cycle are two functional modules connected and involved in one-carbon metabolism. The one-carbon metabolism of cancer cell may mobilize multiple carbon sources including glucose, serine, threonine, glycine, histidine and choline. The synthesis of pyrimidine and purine nucleotides require carbon and nitrogen sources, which rely on amino acid metabolism and the folate cycle; THF is an essential factor for nucleotide synthesis and the survival of cancer cells. Interestingly, the dietary supplementation of histidine upregulated the histidine degradation pathway to deplete THF and then enhanced the sensitivity of cancer cells to methotrexate, an inhibitor of dihydrofolate reductase for THF synthesis. (21)

GLUTAMINE

Glutamine is antagonized physiologically by lactulose. The drug may be less effective in patients with seizures. It is contraindicated in cases of renal and hepatic insufficiency and metabolic acidosis. A guideline was not possible in relation to glutamine for all cancers except in hematopoietic stem cell transplantation, where the recommendation was against the use of glutamine for the prevention of mucositis based on level II evidence. In cancer cells glutamine is the major amino acid that serves as an anaplerotic metabolite and drives the tricarboxylic acid cycle (TCA) to sustain mitochondrial ATP production. Similarly, under hypoxia or in cancer cell with mitochondrial dysfunction the direction of metabolic flow and utilization of glutamine is drastically changed. Upon glutamine deprivation asparagine plays a critical role in suppressing apoptotic cell death. Glutamine is a substrate for asparagine synthetase (ASNS), providing amide nitrogen to aspartate to produce asparagine (22).

Hidroxyproline.
The hidroxyproline has implications for tumor aggressiveness. Hydroxyproline provides a direct bridge between the TCA (glutamate and α-KG) and urea cycle (ornithine). It is correlated with hepatocellular carcinoma (HCC) clinical pathogenesis.

Asparagine.
Exogenous asparagine completely restored cell survival under glutamine-depleted conditions whereas silencing asparagine synthetase (ASNS) lead to apoptosis even in the presence of glutamine. These observations highlight the potential importance of ASNS during tumor cell accumulation and progression (when glutamine availability is limited) indeed ASNS expression is associated with prognosis in brain tumors, such as glioma and neuroblastoma.

Interestingly cumulating research findings have demonstrated that amino acid restrictions play roles in cancer interventions including glycine restriction serine starvation, leucine deprivation glutamine blockade, asparagine and methionine. Since the consumptions and metabolisms of amino acids are the most demanding biological processes for cancer cell growth. As demonstrated leucine is the more heavily amino acid, serine is the second ranked and tryptophan is the least used amino acid in the human proteoma. Specifically, leucine is one of branched chain amino acids, which are not first catabolized in the liver due to the low activity of BCAA aminotransferases, therefore increases rapidly in circulation after meal and are readily available as an essential nutritional signal to reduce food intake via mTOR. Although leucine is the highest enrichment amino acid in proteins, leucine deprivation showed modest effects on human breast cancer cells.

Arginine.
Arginine participates in synthesis of polyamines by the action of arginase producing ornithine and this with (ODC) becomes putrescine (23). There are two different isotypes of arginase; arginase l and arginase ll. Arginase l is found in the liver and macrophages and account for 20% of the total conversion of arginine to ornithine.

Arginase ll is mitochondrial, found in kidney, brain, small intestine, mammary gland and macrophages; and is the main one in synthesis of ornithine and synthesis of polyamines. In intestinal tissue it has been observed that the decrease of polyamines due to inhibition of ODC inhibits the proliferation of intestinal epithelial cells. (23)

Starvation of tumor cells from the amino acid arginine has recently gained particular interest become of the down regulation of the limiting enzyme arginine-succinate synthetase in various cancer entities (ASSl). ASSl-deficient cells can´t resynthetize arginine from citrulline and are therefore considered arginine auxotrophic. The natural arginine analogue canavanine can compete with arginine for arginyl-tRNA binding sites and consequently be incorporated into nascent proteins instead of arginine; therefore, could disturb intracellular protein homeostasis, especially under arginine deprivation. Arginine starvation alone led to delayed induction of apoptosis (e.g. 35% cell death9 after 72h of treatment. Addition of 100 mmol canavanine strongly increased cell death specifically in the context of arginine deficiency (e.g. cell death 87% after 24h, 100% after 48h) while it was non-toxic and not effect on cell viability under physiological arginine conditions. (24)

Arginine plays an important role in various molecular pathways regulating cell division, wound healing, neurological and immune functions and hormone synthesis. It is also a key precursor in the synthesis of cancer-associated compounds such as nitric oxide (NO) and polyamines. Arginine deprivation is considered as nontoxic and selective since it decreases viability and allows the control of the growth of malignant tumors. Due to specific metabolic shifts in subsets of glioblastomas, the strategy of arginine deprivation could also be a promising approach for the treatment of these devastating cancers. (25)

POLYAMINES
Polyamines are organic polycationic alkylamines which are synthesized from L-ornithine or by the decarboxylation of amino acids. They are found in all living cells and mammalian cells. Polyamines have been found to be involved in various important biochemical roles such as synthesis, functioning maintenance and stability of nucleic acids (DNA and RNA) and proteins and other functions.

Polyamines (spermine, putrescine and spermidine) might be the best-known metabolites to promote tumor proliferation and aggressiveness. Polyamine synthesis starts from arginine conversion to ornithine through the action of arginase which is then decarboxylated by the rate limiting step enzyme, ornithine decarboxylase (ODC) to produce putrescine. Elevated polyamines levels have been observed in patients with cancer. Polyamines and their metabolites in urine and plasma can be useful in both cancer diagnosis and as markers of tumor progression in lung and liver cancer. Polyamines affect numerous processes in tumorigenesis in part by regulating specific gene expression transcriptionally. As charged cations at physiological pH, polyamines can associate with nucleic acids which in turn can affect global chromatin structure as well as specific DNA-protein interactions, leading to impacts on gene transcription. (26)

Polyamines are formed by decarboxylation of amino acids, and they activate cell growth and development via different cellular responses. Polyamines are the integrated part of the cellular and genetic metabolism and help in transcription, translation, signaling and post-translational modifications. Polyamines concentrations may influence the conditions of various diseases for instances a high polyamines level patients suffering from aging, cognitive impairment and cancer.

There are three ways to maintain the polyamine pool in the body: intestinal microorganisms, of novo biosynthesis (endogenous) and supply through diet (exogenous). These mechanisms simultaneously regulate the synthesis, catabolism and transport of intracellular polyamine concentration. However, the exogenous diet provides the maximum quantity of polyamines than the process of endogenous biosynthesis. A controlled diet solely or with clinical applications can be used as an effective treatment against various cancer, cardiovascular diseases, Huntington´s disease, Alsheimer´s disease and Parkinson´s disease. (27)

Polyamines are produced in the cell cytoplasm. In vivo production of polyamine begins with the intake of amino acids (arginine, lysine and methionine)) through food serving as substrates for polyamine synthesis through the action of micro-organisms/enzymes. In the mammalian gut, the enzyme arginase first decomposes the amino acid arginine to produce ornithine. The accumulated ornithine is then decarboxylated by the action of the ornithine decarboxylase (ODC) enzyme to produce the polyamine putrescine, (28)

Excess of polyamines can be toxic and can cause skin cancer, colon cancer and increased oxidative stress due to the formation of abnormal cells and peroxides. It has been demonstrated that cancer cell proliferations have high polyamine transport activity and the transport system holds relevance as a target site for selective drug delivery. In cancer polyamine metabolism is frequently dysregulated and elevated polyamines have been shown to promote tumor growth and progression, suggesting that targeting polyamines is an attractive strategy for therapeutic intervention.

Prostate cancer is known to have high degree of polyamine metabolic flux and therefore PCa is highly sensitive to changes in polyamine levels. In addition to polyamine synthesis, methionine is also an upstream precursor for cysteine synthesis. Cysteine is a non-essential amino acid, yet serves as a precursor for anabolic and antioxidant pathways (e.g. glutathione) synthesis that promote cell survival and proliferation and that are in high demand in cancer cells. Finally, the methionine salvage pathway can also affect AMD1 and polyamine levels in cancer. (29).

Conversely hyperactive arginine metabolism and excessive polyamine production have been observed in psoriasis an incurable chronic inflammatory disease. Prolonged intake of dietary polyamines could potentially increase risk for some cancer types. (29).

CANCER METABOLISM
Over the last several decades, nutritional research has prominent role in identifying emerging adjuvant therapies in our fight against cancer. Nutritional and dietary intervention are being explored to improve the morbidity and mortality for cancer patients worldwide. The last decade seems to have witnessed a surge of interest in the role of diet and its effects on cancer metabolism. The World Cancer Research Fund

estimates that 30%-40% of cancers can be prevented by healthy dietary regimens, improved physical activity and maintenance of appropriate body weight. Prostate cancer studies have shown results where certain lifestyle factors are associated with the progression of malignancy. Vegan diet has been shown to decrease tumor markers and inhibit tumor cell growth in prostate cancer studies.

As a special case, cancer-induced cachexia is described as a multifactorial metabolic disorder seen in 50% of cancer patients. The exact mechanisms remain unclear, but it is thought to be typified by an increase in energy expenditure, hepatic gluconeogenesis, fat lipolysis and skeletal muscle proteolysis leading to progressive weight loss throughout therapy. (30)

Acute leukemia patients are at a high risk of malnutrition because of poor nutrients intake metabolic abnormalities related to disease and side effects of treatment, including chemotherapy radiotherapy and hematopoietic stem cell transplantation. The negative interaction between nutritional status and chemotherapy effects is common. Malnutrition can impair tolerance to chemotherapy and decrease response to treatment leading to severe toxic side effects decreased quality of life and ultimately shorter survival. On the other hand, malnutrition can be exacerbated by the side effects of chemotherapeutic drug such as anorexia, nausea, vomiting, taste problems. (31)

Weight loss is a common manifestation of malnutrition and has been recognized to have adverse effects on chemotherapy and survival. Has been observed than average weight loss of 4.28% after induction chemotherapy. However, body weight did not change significantly during consolidation chemotherapy. Studies have shown that both cancer and its treatment exacerbate muscle loss and that patients suffer continuous muscle mass loss during treatment. Low muscle mass often means fatigue, asthenia, impaired physical function, increased chemotherapy toxicity and reduced survival.

In the absence of oxygen, pyruvate is instead converted to lactate for energy production via non-oxidative pathways such as ketosis, which produces far less ATP than oxidative phosphorilation (**two** ATPs per one glucose molecule). ATP is essential for driving the metabolic machinery in all cells, phosphorylation especially for malignant cells. Malignant cells are thought to utilize a unique metabolic pattern termed the Warburg effect, where anaerobic glycolysis is preferably utilized instead of oxidative phosphorylation for ATP production, regardless of oxygen status. As described above, a diet low in carbohydrates will result in an initial increased rate of glucose metabolism forcing the cells to utilize glycolysis as their primary energy source. Some studies have shown that glucose uptake and lactate released by tumors is 30-to-43fold that of non-malignant cells, suggesting that tumor cells will utilize both pathways, including ketosis to compensate for lack of glucose availability for oxidative phosphorylation. (32)

TREATMENT

Historically, leukemia, being an incurable disease, has been treated in various ways, from the palliative form, then the transplantation of hematopoietic stem cells and then tyrosine kinase inhibitors, through the use of arsenic, irradiation, bisulfan, hydroxyurea, interferon, etc. Transplantation is potentially curative for patients with CML, but the good results with imatinib have changed the role of allogeneic transplantation as a first-line therapy. The 60-month follow-up showed complete remissions in up to 87% of patients and overall survival was 89% at 60 months for patients who received treatment as a first line and it has been observed that there is a decrease in the risk of relapse.

The main goal of treatment management in leukemia patients is support the immune system, which enables the patient to cope better with treatment. The genes translocate in APL normally code para retinoic acid receptor; treatment with retinoic acid induces differentiation in the majority of patients cells which leads to a cure. The first goal in treating AML with chemotherapy is to achieve complete remission by reducing the number of leukemic cells to an undetectable level i.e. < 5% blasts on bone marrow biopsy. There are three stages of chemotherapy, namely induction (one six-weeks cycle) consolidation (three cycles) and maintenance (two years). (33)

IMATINIB. It is an inhibitor of tyrosine kinase activity by competitive inhibition of ATP binding to BCR-ABL with high selectivity. The compound inhibits proliferation and induces apoptosis in Philadelphia -chromosome-positive leukemia and lymphoid leukemia; Inhibits platelet growth factor. In vivo studies, concentrations >-1uMol were required for normalization of hematologic parameters. 95% binds to proteins, is metabolized in the liver and CNS and has a half-life of 19 hours. 81% of the dose is eliminated within 7 days. Side effects can lead to nausea, edema, vomiting, muscle cramps, neutropenia, and thrombocytopenia. Imatinib is teratogenic so it should not be taken during pregnancy. Despite its effectiveness, resistance develops in several patients (33).

Cancer chemotherapy regimen target rapidly dividing by either inhibiting DNA or protein synthesis or restricting essential micronutrients, thus leading to cellular death. Further, studies show that between 30% and 90% of patients have inadequate dietary regimens. Chemotherapies that affect the nutritional status of patients include anti-metabolites such as, folate, purine and pyrimidine analogs. Due to the broad mechanism of action of these drugs, many organ systems are adversely affected.

Methotrexate is an anti-metabolite folate analog that is used in standard therapy protocols for leukemia, lymphoma and osteosarcoma. Although methotrexate is associated with favorable mortality outcomes in combination with other chemotherapies, it is difficult to predict one´s toxicity after treatment; therefore, dose reductions are often necessary due to severe side effects from inhibition of DNA synthesis and cellular proliferation.

5-fluorouracil (5-FU) blocks thymidine synthesis and inhibits DNA and RNA replication; is widely used in colorectal, breast and head and neck cancers. Interaction between metabolites suggests that optimal nutrition can improve chemotherapy effects in specific cancer groups. In pancreatic cancer, it has been shown that intravenous omega-3 fatty acids, along with gemcitabine, improve quality of life scores with regard to chemotherapy-induced side effects. Platinum-based chemotherapy drugs are used in the treatment of cancers such as testicular, ovarian, lung cancer, osteosarcoma and neuroblastoma. After drug is incorporated into the cell, it binds at the guanine, causing cross-linking between adjacent guanine. This leads to failed DNA repair mechanisms and eventually cellular apoptosis. Selenium supplementation when given during cisplatin therapy, reduced myelosuppression and nephrotoxicity, suggesting that optimal levels of selenium could aid in the toxicity profile related to platinum-based therapies (34).

THERAPEUTIC STRATEGIES

Amino acids as epigenetic and posttranscriptional regulators

Epigenetic alterations are inheritable features that affect cellular phenotypes by modifying gene expression independent of the DNA sequence. Epigenetic control of gene expression is fine turned by a balance between enzymes that “write” regulatory marks Into DNA and histone proteins (e.g. DNA and histone-methyltransferases and histone-acetyltransferases) and other enzymes that “erase” these some marks (e.g. histone-demethylases, histone-deacethylases and DNA dimethylases). Histone methyltransferases (HMTs) catalyze the transfer of mono-to tri-methyl groups to lysine and arginine residues of histone proteins. Methionine by serving as the methyl group donor for methylation, is the major amino acid that contributes to epigenetic regulation.

The enhanced methionine cycle leads to an excess supply of S-Adenosylmethionine (SAM). This in turn causes DNA hyper methylation and inappropriate gene silencing as well as aberrant histone methylation and enhanced tumor growth. It has been observed that the tumor has a preference for some amino acids; In addition, the tumor cells appear to have completely lost their ability to maintain the cycle of methionine into homocysteine. This implies that the tumor cell is completely dependent on the exogenous supply of methionine and seems to be a typical feature of metabolism in all neoplasms. The idea of an analogue of this amino acid that cannot be used by neoplastic cells to proliferate is very attractive due to its therapeutic potential. In summary, the therapeutic strategies that can be deduced from the study of amino acids can be: 1).- Deprive the tumor of a key piece /(AA) either by dietary restriction or by using a drug that empties the reserves of that amino acid. 2).- Give the tumor a structural analogue of that amino acid but that can be metabolized. Add other molecules that are cytotoxic or that act in the metabolic process of the amino acid (35). For Cancer control the maintenance of hematopoietic stem cells

(HSCs) the essential amino acid valine is indispensable and depletion of valine decreases the number of native HSCs. (36)

L-asparaginase has produced excellent results in the treatment of ALL and is a component of the standard of care. Arginine has been classified as a semi-essential amino acid because healthy individuals can synthesize arginine from other amino acids, such as glutamine, glutamic acid and proline. In pathologic conditions however the human body becomes dependent on arginine intake. Arginine is also the major precursor for synthesis of cancer associated compounds such as polyamines, nitric oxid (NO) and NO-synthetase itself.

Several studies have tested the effect of arginine-deiminase (ADI) monotherapy in melanoma and advanced hepatocellular carcinoma; despite the transient drop of arginine levels observed, tumor progression was sustained and a neutralizing antibody was detected in the patient´s plasma. The other arginine-depleting strategy is arginase, a catabolic enzyme that converts arginine to ornithine in the urea cycle. With this treatment diminished the proliferation of OTC and ASS1 deficient cancer cells. This was observed on AML blasts. (37)

Asparagine starvation is a potential strategy to induce apoptosis on cancer cells that express a low level or are deficient in ASN synthetase (ASNS). Examples of the tumors lacking ASNS are leukemia and lymphoma which depend on external sources of asparagine. Asparagine are monotherapy has been an effective approach to treat ALL and some cases of lymphomas and the combination of vincristine and prednisone with ASNase has resulted in a remission rate of >90% in children with ALL. Resistance to ASNase is currently though to follow 1 of 4 patterns as follows: 1) normal and leukemic lymphoblasts may eliminate the ASNase enzyme through immune responses, secreting a neutralizing anti-ASNase antibody and blocks the drug activity. 2) Leukemia blasts rapidly may develop resistance to ASNase. 3) Cancer cells inhibit glutamine synthetase. 4) on stromal cells release Asparagine where leukemia blasts are treated with ASNase (36)

Antimetabolites that interrupt amino acid synthesis have also been developed and are undergoing clinical trials as cancer therapeutics. However, the lack of antimetabolite specificity often leads to undesirable side effects. Therefore, drug combination is being studied extensively to optimize amino acid-targeted enzyme therapy. Combination of an inhibitor with a hypomethylating agent acts to inhibit amino acid uptake and catabolism has been shown to be effective against LSCs, which depend on amino acid metabolism for survival. (38)

Glioblastomas are the most frequent and aggressive form of primary brain tumors with no efficient cure. However, they often exhibit specific metabolic shifts that include deficiency in the biosynthesis and dependence on certain exogenous amino acids. Therefore, it was evaluated in vitro a novel combinatory anti-glioblastoma approach based on arginine deprivation and canavanine, an arginine analogue of plant origin. The combinatory treatment profoundly affected cell viability, morphology, motility adhesion, destabilizing the cytoskeleton and mitochondrial network and induced apoptotic cell death. Importantly the effects were selective toward glioblastoma cells, as they were not pronounced for primary rat glial cells. (39)

The effects of arginine deprivation on glioblastoma cells were reversible after arginine re-supplementation. In the majority of tumors, arginine deprivation affects only cell growth and does not promote cell death, therefore bringing the danger of cancer recurrence after stopping the treatment. To overcome this problem is propose combining arginine deprivation-based treatment with an arginine antimetabolite L-canavanine. importantly, the effect of the combination of enzymatic arginine deprivation with canavanine does not depend on the permeability of the brain-blood barrier, as canavanine is transported by the same carriers as arginine. It was observed that under arginine deprivation, canavanine stimulated pleiotropic mechanisms leading to apoptotic cell death only in cancer cells but not in normal cells. It was observed that preincubation with canavanine at concentration above 50 μM essentially blocked such growth restoration. Furthermore, the number of dead cells was noticeably increased after 48 h of treatment with 100 uM canavanine it was observed that canavanine augmented alterations in the focal contact morphology evoked by arginine deprivation in both studied cancer cell lines. We observed that 68.3% of all arginine sites were occupied by canavanine after culturing cells in media with 100 uM canavanine for 48 h. (39).

Lack of arginine in combination with canavanine profoundly impairs migration and adhesion of human glioblastoma cells lines. (40)

DEPLETION OF SERUM AMINO ACIDS.

Mammalian cells can generate asparagine from aspartate and glutamine via the enzyme asparagine synthetase (ASSNS). However, some cancer cells including leukemic lymphoblast lack expression of ASSNS and therefore rely on blood serum asparagine supply (i.e. they are asparagine auxotrophic). L-asparaginases catalyze the deamidation of asparagine resulting in a rapid depletion of this amino acid in serum.

Like lung tumors, gliomas accumulate glutamine which they produce from glucose carbon via the TCA cycle and GLDL. Glutamine in these tumors is used to fuel de novo purine synthesis rather that for TCA cycle anaplerosis. Even different cancer subtypes show distinct metabolic phenotypes. Thus, basal breast cancer cells are typically glutamine dependent and sensitive to GLS inhibition. Whereas most luminal breast cancer cells express GLVL are resistant to GLS inhibitors, and are capable of glutamine independent proliferation.

From the standpoint of energy expenditure and anabolism for cell growth, amino acid restriction might be an effective metabolic intervention for cancer since the energy expenditure (ATP) metabolism is up to 58% for protein and nucleotide synthesis. The magnitude of lysine value was demonstrated by that lysine restriction completely blocked the proliferation of cancer cells and that lysine deficiency caused human childhood malnutrition disease kwashiorkor. It is possible to gain time for tipping the scale of the battle in favor of anticancer immune responses by an effective metabolic intervention to inhibit the proliferation of cancer cells. Therefore, intermittent dietary lysine restriction might have the value and potential as a practically available dietary strategy for cancer therapy. Immuno-nutrition has been investigated for decades including arginine, cysteine, fatty acids, nucleotides and trace elements. However, according to the latest systematic review and meta-analysis, immune-nutrition alone didn´t reduce all-cause mortality of cancer patients although reduces postoperative infection complications. (19). Several studies have shown promising results using combination treatment of immunotherapeutic agents with metabolic inhibitors (41).

DIETARY STRATEGIES FOR CANCER THERAPY

Let your food be your medicine and medicine be your food. Hipocrates The controlled diet of polyamines can also reduce the growth of tumor cells in cancer patients. The elimination of intestinal microbiota is necessary without compromise metabolic enzymes along with the regulated supply of exogenous polyamines in diet. A diet with the decreased level of dietary polyamines and intestinal decontamination were found beneficial for the controlling of pain in the patient of prostate cancer. It has been observed that the dietary polyamines level might be a strategy to prevent colon cancer chemotherapy, also reduced the pain and enhanced the health of patients with prostate cancer and colorectal adenoma. Various health disorders can also be cured via targeting polyamines during the metabolic process. As a future therapeutic tool, polyamines and their analogs may be applied along with clinical applications against fatal diseases for maintaining good health (29). Therefore, a controlled diet is an easy way to maintain the level of polyamines in the body and several diseases can be controlled.

Arginine deprivation and low doses of the natural arginine analog canavanine can enhance radio-response. The novel combinatorial targeting strategy of metabolic-chemo-radiotherapy has great potential for the treatment of malignancies. Missing incorporated canavanine disrupted the proper folding of the hydrophobic nascent polypeptides within the exit tunnel or while being inserted into the inner mitochondrial membrane. Canavanine can mistakenly incorporate into the nascent protein chains in place of arginine leading to irreversible disruption of protein conformation; several studies found that canavanine inhibited protein synthesis in rat liver and brain mitochondria.

The therapeutic potential of arginine deprivation has been established in clinical trials for melanomas and hepatocellular carcinomas, also other malignancies are underway like leukemia, lymphoma, prostate cancer, **etc**. It had been proposed to co-apply arginine deprivation with

a natural arginine - analog canavanine, as such combination supposedly preserves the cytotoxic potential of canavanine with a selectively high anti-cancer efficacy in vitro as indicated in an early study. In absence of arginine canavanine 0.1 mM not only completely abrogated spheroid growth, but also caused a severe spheroid disintegration. Majority of the cells (80%), which had detached from the spheroids, was membrane-defect in all experimental settings (32).

Canavanine.

Canavanine is an arginine antagonist able to manifest antimetabolic effects interfering with DNA and RNA synthesis (34). When canavanine was administered in rats was observed that the amount of canavanine that is incorporated into the protein is equal to the amount of arginine. The substitution occurs in all proteins that contain arginine altering the structure of the proteins. Canavanine is incorporated into the nucleus of cells and cytoplasm; it also interferes with the helix of DNA and RNA in formation. Furthermore, canavanine can inhibit any enzymatic reaction that uses arginine as a substrate. When canavanine was administered 20 mg injected every hour for 24 hours; the DNA synthesis was reduced by 86% compared to the control level and up to 70% of canavanine is included in the protein (42).

L-canavanine serves as a substrate in virtually every enzyme mediated reaction that employs L-arginine. Canavanine also affects the charged surface membrane properties of cells; such alterations may be associated with an abnormal immune response (43). L-canavanine is a substrate for arginyl tRNA synthetase and replace L-arginine during protein synthesis; this substitution can occur in every arginine-containing proteins and results in the production of structurally aberrant canavanyl proteins (40). The result is a disruption of enzymatic activity in a rapid degradation of enzymatic activity and a rapid degradation of the protein. It has been observed that when canavanine is consumed accumulates in the human organism when is consumed for a long time (44).

Sulforaphane.

Sulforaphane is an isothiocyanate found in stored form as glucoraphanin in cruciferous vegetables as cabbage, cauliflower and kale and at high levels in broccoli especially in broccoli sprouts. Sulforaphane is metabolized through mercapturic acid pathway being conjugated with glutathione and further biotransformation. It has been shown that sulforaphane may protect against various types of cancer, may also decrease the risk of cardiovascular disease and help in autism and osteoporosis. Glucoraphanin (sulforaphane precursor) occur in particularly high concentrations in young broccoli plants (**Brassica oleracea**). The content of glucoraphanin in extract from broccoli sprouts was 16umol per gram of fresh weight. (45)

Sulforaphane is an isothiocyanate with multiple biomedical applications; broccoli sprouts are the chief source of sulforaphane and are 20 to 50 times richer than mature broccoli as they contain 1.15g/100g. It is a potent anticancer phytochemical that is safe to consume with minimal side effects. Whereas in mature broccoli is 44-171 mg/100g. Sulforaphane is effective because of its high bioavailability (80%) due to its lighter molecular weight. When SFN was evaluated its potential in an "in vitro" study on liver hepatocellular carcinoma, breast adenocarcinoma, lung adenocarcinoma, neuroblastoma and human colon cancer, showed here enhanced anticancer activity by a inhibiting of cancer cell proliferation arresting the cell cycle and enhancing the process of apoptosis; additionally the consumption of broccoli sprouts causes the inhibition of histone acetylation and downgrading the process of angiogenesis. (46)

Sulforaphane can also be used with conventional cancer treatments to achieve an enhanced effect was observed that in combination with other compound is more effective in enhancing the process of apoptosis than compound alone. The investigators found that the combined therapy also caused an increase in the down regulation of cell migration. One study showed that sulforaphane significantly reduced the progression of prostate cancer and disease severity; also prevent the risk of melanoma. Other study disclosed that sulforaphane is highly effective in reducing serum prostate specific antigen (PSA) levels.

Conventional chemotherapeutic drugs such as paclitaxel, fluorouracil, tamoxifen, imitanib are a few commonly used chemo-preventive medications, but such chemotherapy poses several harmful effects. Sulforaphane (SFN), including its two isomers of R-SFN and S-SFN, significantly inhibited TGF-P1-induced migration and invasion in breast cancer cells. Proteomic and phosphoproteomic análisis showed that SFN affected the formation of the cytoskeleton. SFN inhibit the formation of actin stress fibers thereby inhibiting breast cancer cell metastasis. Due to the high rate of metastasis, the mortality of young women (<45 years) with breast cancer especially with TNBC type has increased significantly recently. (46).

In several studies, it had been shown that sulforaphane may protect against various types of cancer including pancreatic cancer, colon, leukemia, prostate. Benzene metabolites can be conjugated with sulfas to form sulfates which ultimately detoxifies benzene and allows its elimination from the body. (47). Sulforaphane which is found in cruciferous vegetables has been reported to have anti-inflammatory, antioxidant and antitumor activities. Sulforaphane has therapeutic effects on inflammatory or autoimmune skin diseases including psoriasis.

Dietary approaches

Chemotherapy is the first therapeutic option for all patients. Malnutrition has an accepted association with chemotherapy-related toxicity. which not only impacts chemotherapy efficacy, but leads to a significant deterioration in patients nutritional and performance status. The relapses of cancer patients are due to the fact that they do not change their eating habits or their microenvironment. No attention is paid to the diet of cancer patients and relapses occur with some frequency, despite the fact that antineoplastic drugs are very effective against cancer. (48)

The role of diet in cancer metabolism is certainly an area of popular interest. The World Cancer Research Fund estimates that 30-40% of cancers can be prevented by healthy dietary regimens; it has been shown in epidemiological studies of breast cancer, prostate cancer and colon cancer that migration to different countries influences overall risk of the development of these cancers; misleading to hypotheses that changes in dietary habits may alter cancer risk. Several epidemiologic studies suggest that changes in life style and dietary influences play a role in determining the risk of various cancers. Caloric restriction is a well-established dietary intervention for preventing cancer and increasing lifespan in experimental animal models. Another diet of interest is the vegan diet, which has been shown to decrease tumor markers and inhibit tumor cell growth in prostate cancer studies. Here we present a brief mention about the interactions between nutrition, diet and the course of malignant neoplasms. (15).

Environmental and lifestyle factors, including diet, are hypothesized to influence risk of malignancy. The western diet, which consists of a high intake of fats, processed meats, dairy and carbohydrates and low intakes of fibers. This composition has been suggested to contribute to tumorigenesis. Over the last few decades, the western diet has been epidemiologically associated with an increased incidence of many cancers, including prostate cancer, breast cancer, colorectal cancer, among many others.

Caloric restriction

Caloric restriction (CR) is defined as a reduction in dietary intake by approximately 30% to improve metabolic profile, without causing malnutrition. In murine models, CR has been shown to reduce IGF-1 by about 30%-40% in mice. Mice receiving CR along with radiation therapy, required a longer period to develop breast cancer metastasis to the lung and had increased overall survival. Angiogenesis and inflammation have been shown to be related to tumor proliferation and CR has been shown to module these processes to exert anti-neoplastic effects. CR decreases levels of chronic inflammation by reducing absolute quantity of adipose tissue.

Ketogenic diet

The ketogenic diet (KD) is a high-fat, moderate-protein and low carbohydrate diet. The proposed effectiveness of the KD relies on the many metabolic differences between normal cells and cancer cells, especially in the metabolism of glucose. Under normal oxygen-rich conditions, glucose is broken down to pyruvate via glycolysis, which is then converted to Acetyl CoA, which enters the mitochondria to initiate the citric acid cycle to produce energy for the body in the form of ATP (36 ATP per one glucose molecule) In the absence of oxygen, pyruvate is instead converted to lactate for energy production via non-oxidative pathways such as ketosis, which produces far less ATP than

oxidative phosphorylation (two ATPs per one glucose molecule). The KD seeks to shift the metabolism toward ketosis to limit anabolism, therefore inhibiting growth and proliferation pathways in malignant cells. When glucose is limited, the body is forced to utilize stored adipose tissue instead of glucose for ATP production. After prolonged periods of glucose restriction, the body preferentially enters ketosis where fat is metabolized via fatty acid oxidation to produce ketone bodies and those are then converted to acetyl CoA for use in the citric acid cycle for ATP production. This is an important underlying principal in the KD, where glucose availability is limited, creating an environment where non-malignant cells are able to utilize ketones for survive during ketosis, while cancer cells are "starved" of an energy source due to a lack of glucose availability. Fatty acid oxidation in the KD provides energy that is primarily utilized by non-malignant cells, since cancerous cells are poor metabolizers of ketones.

There are a wide variety of studies that illustrate the possible anti-neoplastic effects of the KD. The majority of the papers revealed a beneficial effect seen across a variety of tumor types including prostate, gastric, neuroblastoma and lung in animal models. In a colon carcinoma murine model, mice fed with a ketogenic formula showed cancer suppression. However, this regimen risks potential side effects including hypoglycemia and other side effects along various chemotherapies.

Mediterranean diet.
(MedD). The MedD has gained attention as a healthy diet to reduce the risk of cancer; it is common in countries bordering them Mediterranean Sea, Higher fruit and vegetable consumption affects inflammation, redox reactions and various metabolic processes that may exert anti-cancer effects and promote healthy weight management. Whole grains contain phytic acids and fiber that bind and neutralize carcinogens in the gastrointestinal tract. Olive oil contains polyphenols, which contribute anti-inflammatory and anti-oxidant effects.

Japanese diet.
Individuals from Japan have a lower incidence of various cancers, especially those termed fat-related cancers of the colon, breast, prostate and ovary. For Japanese individuals who moved from Japan to Hawaii, the incidence of stomach cancer decreased while the rates of breast, colon and prostate cancer increased in just one generation. In the last 40 years, the incidence of colon cancer has increased 9.4 times for male and 4.7 times for females as Japanese have adopted a more Western dietary pattern. Individual components of the Japanese diet are hypothesized to establish the protective roles of this dietary regimen in cancer risk.

Vegan diet.
A vegan diet removes all animal products, including dairy or eggs. The vegan diet has been associated with a wide variety of health benefits, including lower risk of cardiovascular disease, obesity and type II diabetes. Individuals who follow a vegan diet, the risk of obesity-related cancers, such as colorectal, breast and prostate cancers is decreased. Vegan diets consist of a higher proportion of fruits and vegetables, which contains phytochemicals and anti-oxidants. Fibers, flavonoids and vitamin C, which are all proposed to have protective effects against the development of malignancy. In animal models, phytochemicals have been shown to induce apoptosis, arrest cell growth and decrease angiogenic potential.

A cancer patient must carefully plan his diet to address two conflicting problems: the need to maintain healthy muscle tissue and adequate protein synthesis and at the same time restrict the anabolic capacity of tumor tissue. There is not common agreement on how to plan the best dietary strategy, removing or limiting the consumption of some foods according to their composition. Thus, a recommended food is natural corn because it does not contain lysine and good results have been observed after several weeks of consumption, either as a preventive or as a therapy.

Many studies confirm the role of diet, mainly in cancer prevention. A diet including high amounts of vegetables such as broccoli, lettuce, tomatoes, soya, alfalfa and celery has been proven to reduce the risk of developing proliferative diseases. Table number one shows some foods with their respective concentrations of canavanine and methionine that can be considered to reduce the production of polyamines.

Benzene is metabolized by the liver and excreted through urine in approximately two days. The elimination of benzene occurs 75% through the kidney and 25% through the lungs through exhalation. The intriguing study focused on 300 Chinese adults exposed to benzene and acrolein. They drunk a beverage made with broccoli sprouts every day for 3 months, leading to high excretion rates in the urine of the two harmful chemicals. Among the people consuming the broccoli sprout beverage the rate of benzene excretion increased by 61% throughout the duration of the clinical trial. (48, 50).

CONCLUSION

Several attempts have been made to stop the progression of the disease with the limitation of some amino acids as a strategy for its cure. However, there is no common agreement on how to plan the best dietary strategy, removing or limiting the consumption of some foods according to their composition. Thus, a recommended food is natural corn because it does not contain lysine and good results have been observed after several weeks of consumption, either as a preventive or as a therapy. A controlled diet solely or with clinical applications can be used as an effective treatment against various cancer, cardiovascular diseases, Alsheimer´s disease and Parkinson´s disease.

Several studies have shown promising results using the combination of chemotherapy drug treatment with canavanine or sulforaphane at various doses without showing toxicity with enormous benefits for the cancer patient. In this way, the side effects are reduced because the doses of chemotherapy drug can be reduced and the patient heals faster because in this way cell division decreases and apoptosis increases at lower doses. On the other hand, when eliminating some foods that contain methionine and polyamines the patient recovers faster.

Table Number 1
Foods with canavanine, methionine and polyamines

Food	g %
Foods with canavanine	
Lentils	1.30
Soybean	1.10
Chickpea	0.70
Foods with methionine	
Sesame	1.68
Walnut	1.10
Roasted chicken	0.80
Parmesan cheese	0.80
Foods with polyamines	
Sausages	……
Smoked meats	……

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