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Relationship between Restrictive Diet and Autophagy in Preventing Cancer Cells

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ABSTRACT

In elderly people, cells can show DNA mutations and the accumulation of protein aggregates that impair physiological processes in the body. Several studies have shown that the activation of autophagy slows down the ageing process. The study groups included the materials, which published data on the relationship between restrictive diet and autophagy that prevent early ageing, chronic metabolic diseases and degenerative cells until cancer diseases.

Disturbances in the autophagy process can lead to chronic metabolic diseases, such as Parkinson's disease, type 2 diabetes, cancer and other diseases that occur with ageing. Reduction of Beclin 1 protein, a product of the ATG-7 gene, an autophagy promoter molecule, results in decreased levels of phagocytic receptors recycling and phagocytosis, example being Alzheimer's disease (AD), with the stored peptide β-amyloid (Aβ) inter--neuronal brain. A better regeneration of the body takes place during the black fast, in which senescent cells, (dead cells that no longer exercise any function, but instead produce inflammation in the body), are eliminated by autophagy and in their place the cells are stimulated by the stem cells of tissues from human body.

Aging and its associated conditions of illnesses, are due to genomic instability caused by DNA damage, telomere shortening, and epigenomic changes that modulate gene expression. Activation of autophagy delays the ageing process and maintains more time in a healthy human organism.

Keywords

Apoptosis, Autophagy, Adenosine triphosphate (ATP), Atg gene, Beclin-1 protein, mTOR enzyme complex, Isoform p53 protein, The family genes, SIRT genes, P53 gene.

Abbreviations

Apoptosis: The programmed death of cells, Atg: Autophagy-related genes, AMPK, 5'-AMP: Activated protein kinase, MAPK: Mitogen-activated protein kinases, mTOR: Mammalian target of rapamycin, PI3K: Phosphatidyl inositol-4,5-bisphosphate-3-kinase, Protein p-53: Protein of the suppressor gene P-53, ULK1: UNC-51-like kinase 1.

Introduction

The retrospective study in genetic research was undertaken purpose for the emphasise autophagy benefits to people until aging which followed a healthy lifestyle, preventing the carcinogenesis process. A restrictive diet represents a period of self-discipline designed to purify the body from a physical and spiritual point of view. It is well known that when special genes are activated, either through low-calorie or low-amino acid diets or through exercise, the body becomes healthier and more resistant to disease.

The nutritional advantages of fasting on health are explained by the more effective detoxification of tissues and the regeneration of the

body. Whether you choose to fast for religious reasons or health reasons, (there are some "fasting" diets, with longer or shorter periods of not eating), self-initiated fasting can be an effective great way to revitalize the body, mind, and soul. In general, it is recommended that certain people do not fast, such as children, pregnant women, and the elderly with health problems, do not fast. A person without health problems can create a diversified menu and, in principle, can follow the fast without worries. Following these simple rules, there are a multitude of benefits for our health. Through autophagic processes, the body cleans toxins and recycles the components of the damaged cells. Not only do autophagy levels decrease with age, but Atg gene activity and overexpression of (Atg) protein also contribute to improved lifespan in a human model of ageing. Beclin-1, the product of the Atg-7 gene, which allows the activation of autophagy, is a positive regulator of autophagy due to its ability to create a link between cytoskeletal motor proteins and the cytoplasmic complex phosphatidylinositol triphosphate kinase (PI3K), a class III protein that triggers the autophagy process. Depending on nutritional conditions, the activities of the ULK-kinase enzyme complex, the product of the ATG-7 gene, can be regulated by the mTOR enzyme complex.

Method

In this study were included the materials which published data on the relationship between restrictive diet and autophagy which prevent early ageing, chronic metabolic diseases and degenerative cells until cancer diseases. The article highlights the four main longevity genes important in life pathways, mTOR, AMPK, PTEN, and SIRT genes which protect the body during periods of adversity and cellular stress by activating survival mechanisms.

Results

The process of Autophagy refers to the ability of cells to destroy their contents, which they then transport in sac-shaped vesicles to a recycling compartment, the lysosomes, where the actual destruction of the cellular material occurs. Through autophagic processes, the body also cleans toxins and recycles the components of the damaged cells. Cells create membranes that hunt down the debris of dead, diseased, or worn-out cells and use the resulting molecules for energy or to regenerate other cells [1].

Disturbances in the autophagy process can lead to chronic metabolic diseases, such as Parkinson's disease, type 2 diabetes, cancer, and other diseases that occur with ageing. Reduction of Beclin 1 protein, an autophagy promoter molecule, results in decreased levels of phagocytic receptor recycling and phagocytosis, such as an example being Alzheimer's disease (AD), with the stored peptide β-amyloid (Aβ) inter-neuronal [2].

The release of ATP stimulates the microglial cells and the release of auto-page-lysosomes into the extracellular space. In cancer cells from solid undernourished tumors, the response to radiotherapy or DNA-damaging chemotherapy triggers ATP production by autophagy, which may play an essential role in DNA repair. The addition of pyruvate rescued ATP levels and prevented mitotic catastrophe, suggesting that autophagy, sustained ATP generation, could be employed by mechanisms that promote genomic integrity, such as DNA repair. Autophagy is essential for the maintenance of intracellular ATP levels, which in turn is required for the secretion of lypo-phosphatidyl-choline (LPC). Secretion of LPC is associated with the acute phase of the inflammatory response and is involved in the development of chronic inflammation. Autophagy acts also through different mechanisms to decrease inflammation.

Has been shown that autophagy-deficient cells fail to generate phosphatidylserine on the outer membrane surface, an important anti-inflammatory pro-apoptotic marker. This explains how defects in autophagy can stimulate inflammatory response subsequently to insufficient clearance of dead cells. The efficacy of autophagy in favoring cell death has been demonstrated in many other cancer models, such as breast cancer, leukemia, prostate cancer, and myeloma. Currently, protocols targeting autophagy induction instead of autophagy blockade are under intense investigation in oncology research [3,4].

Discussion

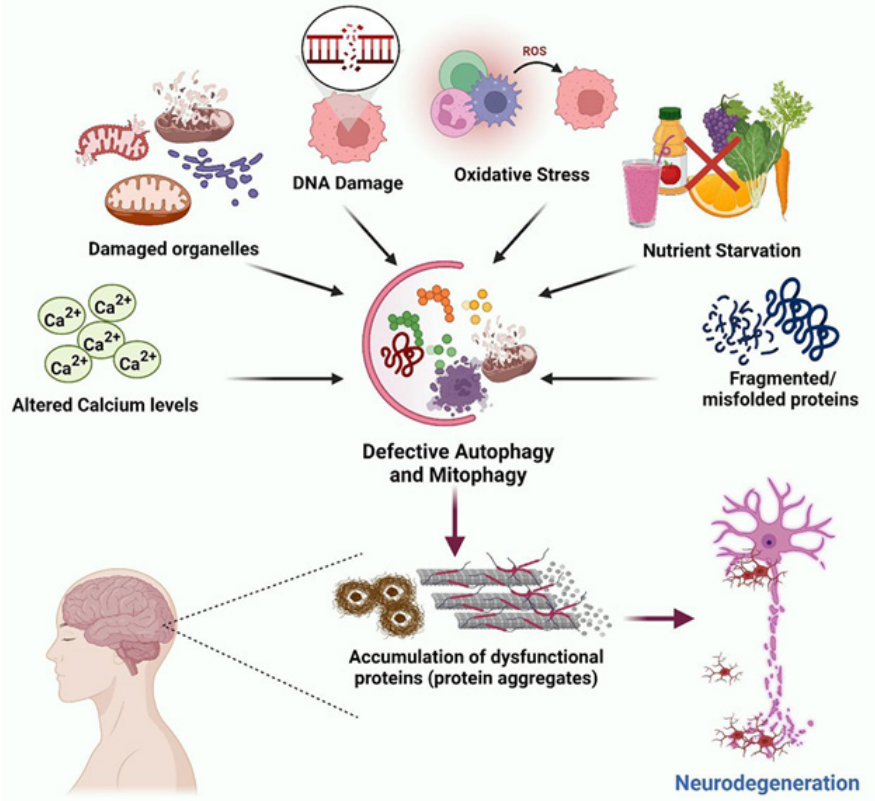
A diet rich in red meat and poor in fruits and vegetables can hinder the body's ability to detoxify, therefore, an alternative vegetarian diet maintained over a certain period determines the elimination of excess toxins and accumulated residues, helping the body to regenerate and recharge with energy.

In preclinical studies, dietary restriction, (DR), has been shown to extend the lifespan and reduce the development of age-related diseases, such as diabetes, cancer, and neurodegenerative and cardiovascular diseases. DR promotes metabolic and cellular changes in organisms, from prokaryotes to humans, that allow adaptation to periods of limited nutrient availability [5], [Scheme 1].

The main changes include decreased blood glucose, levels of growth factor signaling, [P2] and the activation of stress resistance pathways affecting cell growth, energy metabolism, and protection against oxidative stress, inflammation, and cell death.

Nutrient starvation also activates autophagy in most cultured cells and organs, such as the liver and muscles, as an adaptive mechanism to stressful conditions. Studies have demonstrated that dietary interventions can reduce tumor incidence and potentiate the effectiveness of chemotherapy- and radiotherapy in different tumor models, highlighting dietary manipulation as a possible adjunct to standard cancer therapies. Among the many diet regimens that are assessed, caloric restriction (CR) and fasting are the methods under intense investigation in oncology.

CR is defined as a chronic reduction in the daily caloric intake by 20-40% without the incurrence of malnutrition and with the maintenance of meal frequency. In contrast, fasting is characterized by the complete deprivation of food, but not water, with intervening periods of normal food intake. Based on the duration, fasting can be classified as (i) intermittent fasting as alternate day fasting (≥16 hours) or 48 hours of fasting/week) or periodic fasting minimum



Scheme 1: Multiple risk factors include increased ROS production, nutrient deprivation, oxidative stress, DNA damage, accumulation of misfolded proteins, damaged organelles etc., representing the complex nature of chronic diseases.

of 3 days of fasting every 2 or more weeks. The specific diet called the Bredesen diet, is a method that combines intermittent fasting, eating healthy foods and avoiding sugar. In a weight loss treatment, the recommendation for a restrictive diet can include 2 meals/day, in intermittent time, according to a well-established plan, with a fixed schedule after 16 hours of the last meal, from the previous day, more precisely breakfast at 10 a.m., and the next meal at 6 AM, on the same day. In the weight loss diet, we must avoid losing muscle mass, but we must have the main objective of a vegetarian diet, with white meat consumption, especially for people over 65 years of age. A total fast of 24-48 hours, once a year, with daily hydration, 30 ml/Kg body, approximately 2.5 L/day, triggers the beneficial mechanisms of autophagy to prevent carcinogenesis [6].

There is an evolutionarily conserved and serves as a self-degradative catabolic process that removes long-lived, damaged molecules and organelles, aggregated proteins, and intracellular pathogens. Autophagy is required for the fulfilment of cellular metabolic demands, preservation of genomic integrity and adaptive immune processes, and regulation of proinflammatory mediators for cell survival [7].

Metabolism refers to all the biochemical and energetic transformations that take place in the tissues of the living organism. Metabolism is a complex process, which involves exchanges of matter and energy, and includes two (simultaneous) opposite processes: catabolism, which represents the totality of the chemical processes of degradation of substances in the body by breaking the bonds between carbon atoms, from the molecules of different substances with the release of energy (exothermic reaction) and anabolism, which includes the chemical processes of biosynthesis of the substances that make up living matter (endothermic reaction). Anabolic reactions involve an increase in the biological structure and in the second law of thermodynamics there is an increase in the entropy of the system as energy is needed. In contrast, catabolic reactions involve a decrease in entropy and a release of energy. Catabolic pathways generate metabolites (amino acids, proteins, fatty acids, glucose) and large, intermediate energies used in anabolism.

The role played by autophagy in the maintenance and function of stem and progenitor cells is still quite empty field. Embryonic as well as tissue stem and progenitor cells are essential players during development, tissue renewal and in some disease processes. The peculiar characteristic of stem cells resides in the fact that they are persistent in adult organisms and they should possess a highly effective system for controlling their quality and homeostasis. Bearing this in mind, autophagy should play a crucial role in the normal function of stem and progenitor cells, while its impairment could be associated with some diseases [8].

More and more evidence is emerging for autophagy playing an active role which is crucial for embryonic stem cells (ESCs), for various tissue stem cells, such as hematopoietic stem cells, (HSCs), and for cancer stem cells (CSCs). Autophagy activation seems to be important not only for the maintenance of stem cells

but also for their progenies during differentiation processes, such as erythrocyte maturation.

The different types of autophagy include macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. Autophagy is used for the removal of damaged organelles, including mitochondria (mitophagy), the endoplasmic reticulum (ER), (ER autophagy) and lysosomes (mitophagy). The mitochondria are central to the model linking autophagy. Normal mitochondrial activity generates ROS, which may cause damage to cell components, including the DNA. Direct ROS-mediated damage to the mitochondria may result in mitochondrial DNA damage, alterations in the mitochondrial membrane permeability (MMP) and uncoupling of the respiratory chain, resulting in even more ROS generation in a vicious [9]. Mitophagy of injured organelles has a central role in impeding this vicious cycle, a process in which the protein parkin has a central role. Macro-autophagy applies to subcellular organelles within cytosolic double-membrane-bound autophagosomes fused with lysosomes. Micro-autophagy and micro-ER autophagy can occur with high precision by allowing specific cargoes to be captured before they enter the invaginations of endo--lysosome membranes, (self-eating) By such [10].

Protein aggregates are removed by macro-autophagy and lipophagy to maintain the energy balance by the breakdown of lipids. The core proteins that regulate autophagosome biogenesis of autophagosomes have not yet been identified, and it is not yet clear how these structures are assembled. The lysosomal compartment is a key element of the autophagic machinery that, accounts for the exhaustive degradation of the engulfed substrates. First characterized as the main degrading organelles, lysosomes now have granted complex regulatory functions in both normal and pathological conditions, including cancer development and progression [11].

Lysosomes are known to account for the lower susceptibility of cancer cells to chemotherapeutics, and they are weak bases that favor their intra-lysosomal sequestration and ensuing removal from the cell by exocytosis. This lysosome could be a potential target for cancer therapy. This was mainly linked to evidence that the lysosomes play a significant role in cell death, as well as their ability to fuel cancer cells' energy needs.

Previous studies have shown that activated B cells release antibodies and label tumor cells for recognition to be recognized and attacked by other cells in the immune system, which may suggest a stronger anti-tumor relationship between lysosomes and the presence of immune cells. Furthermore, the study found that higher levels of type interferon-2 (IFN), response, HLA and (human leukocyte antigen (HLA), as a major histocompatibility complex (MHC) product in humans, modulate the immune response to cancer by presenting antigens. It has been shown that type-2 IFN can directly trigger apoptosis and cell cycle arrest by impairing autophagosome-lysosomal fusion in cancer cells, which plays an important role in tumor development, and which may be related to immune cells and cytokines [12]. However, the intracellular intra-lysosomal accumulation of drugs at high concentrations, when not followed by their extracellular release, has also been reported to trigger lysosomal membrane permeabilization and the activation of lysosomal death pathways. Thus, in this view, lysosomal destabilization may represent both a putative intrinsic mechanism of action of these drugs and an effective strategy for increasing the susceptibility of cancer cells to anticancer therapy.

The beclin-1 gene refers to the centromeric region of BRCA1 on chromosome 17q21, which is generally deleted in 75, 50%, and 40% of ovarian, breast, and prostate cancer cases, respectively. Depending on nutritional conditions, the activities of the ULK-kinase enzyme complex, the product of the ATG-6 gene, can be regulated by the mTOR enzyme complex. Beclin-1, the mammalian ortholog of Atg7, is cloned as a Bcl-2 interacting protein. In starved cells, Beclin-1 delivered from Bcl-2 protein induces signals for the autophagic process [13].

Beclin-1 protein, which allows the activation of autophagy, is a positive regulator of autophagy, because due to its ability to create a link between cytoskeletal motor proteins and the cytoplasmic complex phosphatidyl-inositol triphosphate kinase, (PI3K), a class III protein that triggers the autophagy process. Defective autophagy is implicated in tumorigenesis, and an essential autophagy regulator, the Beclin-1 gene, is mono-allelically deleted in human breast, ovarian, and prostate cancers [14].

The molecular interactions between the p53 protein and autophagy, in cells with damaged DNA, lead to cell apoptosis. In addition to mitigating DNA damage by controlling ROS production, autophagy can also influence the dynamics of DNA repair by recycling key proteins involved in the processing of lesions. Autophagy may also provide metabolic precursors for the generation of ATP, which is employed in several steps of DNA repair**.** The tumor suppressor protein p53, the product of the P53 gene, is a critical control protein in mammalian cells that is activated under conditions of genotoxic stress, including DNA damage, hypoxia, and oncogene activation, and responds by initiating tumor suppressor mechanisms, such as cell cycle arrest, senescence, and apoptosis [15].

The tumor suppressor gene, p53, which is uniformly activated in response to DNA damage by radiation, can induce autophagy through the activation of autophagy-inducing genes, particularly ULK1 and ULK2. Activation of gene complexes, ULK1 and ULK2, as a result of DNA damage, causes increased levels of autophagy and contributes to the triggering of apoptosis. Under the appropriate circumstances, mammalian rapamycin target protein complex 1 (mTOR1) can phosphorylate ULK1 and Atg13, preventing ULK1 from binding to Atg13, FIP200, and Atg101, therefore suppressing autophagy. Activation of the ULK1 gene inhibits the mTOR gene and, promotes the autophagy process [16].

Conversely, deletion of the PTEN gene is followed by an increase in mTOR activity, which leads to an increase in clonogenic survival. Studies have suggested that inhibition of mTOR signaling could be an effective strategy for increasing the radiosensitivity of malignant

tumors. By another mechanism, the p53 protein, the product of the P53 gene, in the isoform state, accelerates the progression forms of cancer from the mild form to the severe form., [Scheme 2] [17].

The native protein p53 is a control protein in the normal functioning of the cell and is activated by cellular stress, including DNA damage, hypoxia, and a restrictive diet, which thus contributes to the inhibition of malignancy, by stopping the cell cycle in the Go-1 phase, as a rest before cell division. The p53 protein has been shown to contribute to and trigger the autophagy process by inhibiting the mTOR protein, and AMP gene-activated protein kinase (AMPK) [18], [Scheme 3].

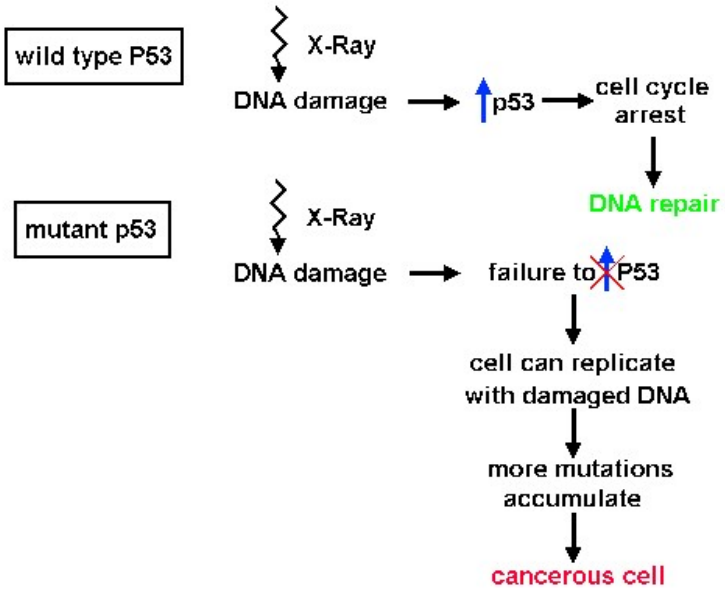
Simultaneously the same time, genetic or pharmacological inactivation of cytoplasmic p53 protein triggers autophagy, indicating that the non-nuclear p53 protein pool is a potent autophagic repressor. Thus, autophagy is activated as a stress-mitigation mechanism, both by stress-intermediated p53 protein induction and by stress-exacerbated p53 loss.

In this context, the nuclear protein p53 has been shown to protect the cell from a malignant process, and only the cytoplasmic protein p53, through its isoforms, phosphorylated in multiple sites, in a modified cytoplasmic environment, through a high concentration of anaerobic ATP, leads to cancer. In Chronic Lymphocytic Leukemia, (CLL), blocked apoptosis due to malignant diseases may be due to a high ATP concentration originating from an anaerobic metabolism. The difference of energy between anaerobic ATP in B lymphocytes from CLL and aerobic ATP in activated T lymphocytes from normal status and non-malignant diseases was 2.68 μM ATP, as an energetic transfer between T and B cells initiates carcinogenesis by suppression of anti-oncogene proteins, especially p53 protein [19].

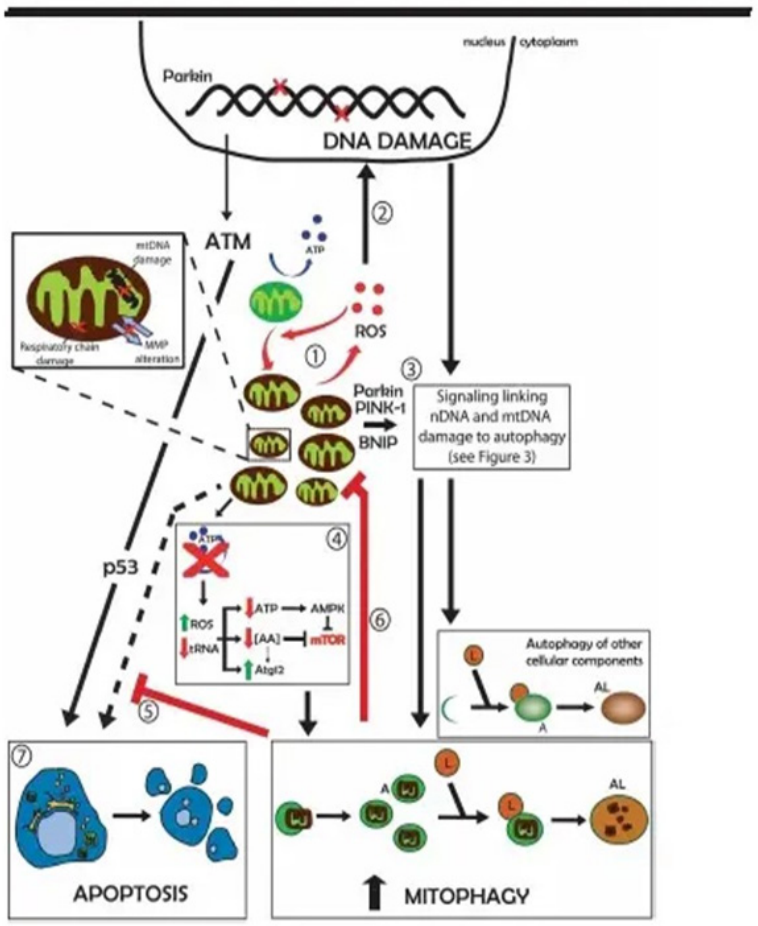
Through genetic research for longevity, the family genes, SIRT1 to SIRT7 have been discovered for the development of drugs, to extend the life span of humans. The SIR2 gene was discovered in animal tissues. The Sirtuins in the mitochondria, such as SIRT3, SIRT4, and SIRT5, are among the seven mammalian sirtuins. SIRT3 is a deacetylase that regulates mitochondrial activity and is one of the most significant deacetylases in mitochondria. SIRT3 deacetylates the PDC (pyruvate dehydrogenase complex (PDC) in glycolysis, allowing pyruvate to participate in the Krebs cycle and increasing glucose absorption by triggering protein kinase B [20].

Through the process of visualizing DNA and grouping it into tight bundles of proteins, marking genes with chemical tags called methyl and acetyls made up of carbon, oxygen, and hydrogen atoms, the epigenome can use the genome to create the music of our lives. Sirtuins are not the only long-lived longevity proteins. Two other sets of genes currently under study perform similar roles, which have also been shown to be manipulable in how one can live up to 113 years with a healthier life. Currently, the life expectancy in the developed world is just over 80 years, To anticipate a cancer diagnosis, with the genes still "silent", the Whole Genome Sequencing Genetic Test (WGS) can be performed, which identifies in the patient's DNA the genetic mutations of multiple genes that are responsible for the carcinogenesis process followed by, Next Generation Sequencing (NSG) and Single Nuclear Polypeptide, (SNG) techniques, for the analysis of epigenetic variations [21].

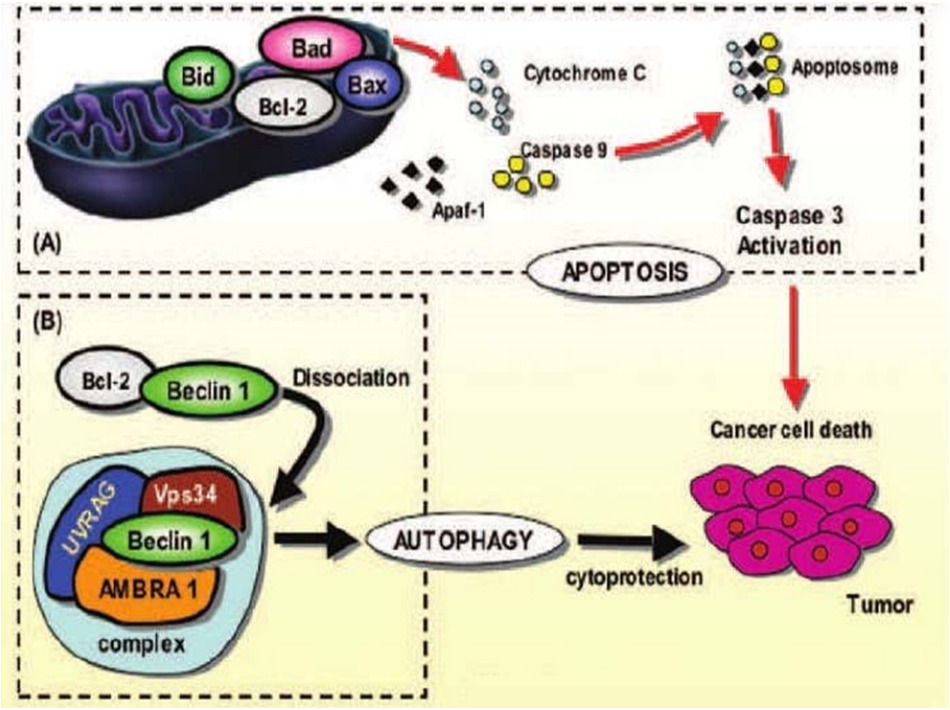
The other pathway involved in autophagy is a metabolic control enzyme known as AMPK, which is activated at low-energy levels. The AMPK enzyme contributes to preventing cell damage and sustaining apoptosis, under conditions of a low-calorie diet, combined with certain types of physical exercise and exposure to intermittent hot and cold temperatures, called hormesis. The pro-apoptotic proteins Bad, Bid, and Bax can activate on the cell membrane, triggering apoptosis with the release of cytochrome C and, promoting autophagy by dissociation of Beclin-1 from the molecular complex [22], [Scheme 4].



Scheme 2: P53 protein in the isoform state amplifies DNA damage and even accelerates forms of cancer.



Scheme 3: Molecular interaction between p53 proteins and autophagy in cancer cell.



Scheme 4: Autophagy, apoptosis and Beclin-1 protein in cancer.

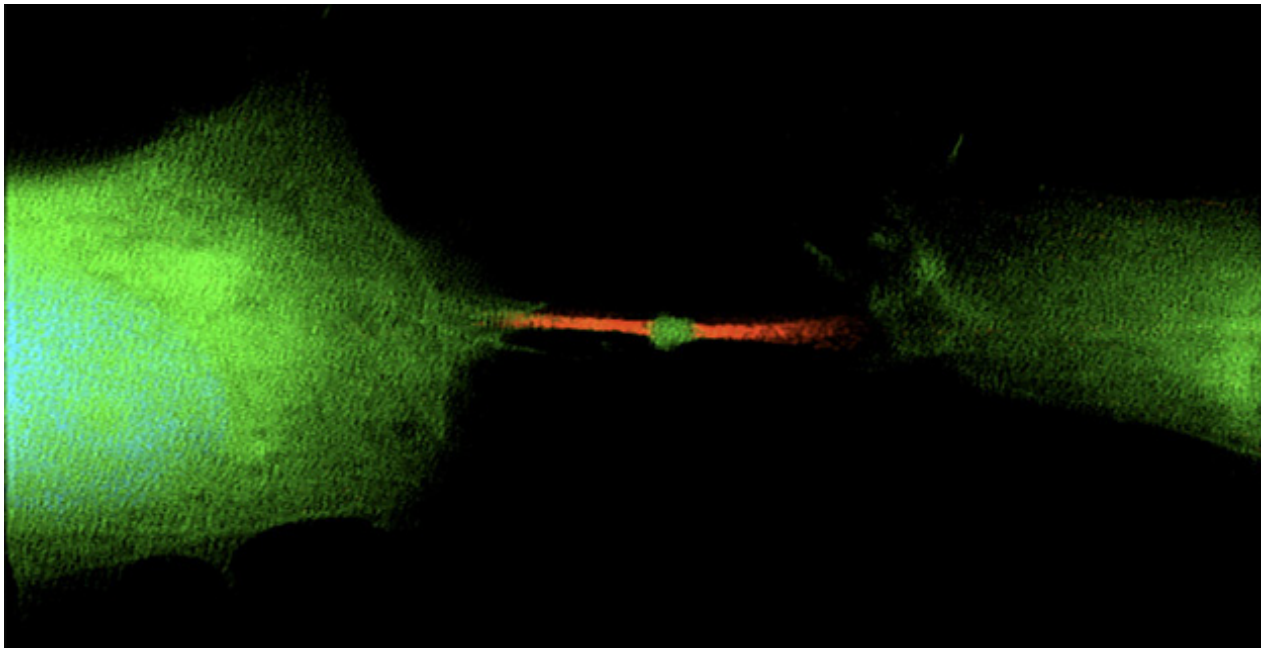
Autophagy confers stress tolerance, limits damage, and confers a survival advantage on cancer cells. In addition, autophagy may allow for a quiescent state in residual cancer cells after treatment, which may contribute to cancer recurrence and metastasis. Autophagy is one of the most important survival mechanisms under stress conditions and is involved in cellular homeostasis and proliferation. Several studies have demonstrated links between autophagy and carcinogenesis, highlighting the dual role of autophagy in cancer. Depending on the tumour model and/or tumor state, autophagy may have pro- or anti-tumor effects. In the initial stages of cancer, autophagy protects normal cells from tumorigenesis by preventing DNA damage and mutations [23].

The PTEN gene demonstrates a tumor-suppressive role in autophagy when considering its genetic inactivation, either indirectly through constitutive activation of the PI3K/AKT pathway by activating PI3K m mutations, AKT amplifications, or PTEN gene mutation. Multiple mutations in the PTEN gene, or loss of function, affect lipid phosphatase activity, leading to the development of a variety of cancers. Of the three residues in the PTEN component, the R-335 mutation is the most important for interaction with the cell membrane, similar to several other germline mutations, and has been associated with inherited cancer [24].

One of the greatest technological advances of this century has been the discovery of precise and programmable 'genome editing',' CRISPR technology, (short regularly spaced palindromic repeats) with the DNA strand scissor enzyme Cas9, which can introduce healthy genes or edit mutated genes, Researchers have identified a gene, called Arc, which that plays a role in modulating cell activity. This gene packs functional genetic material with the power to change the fate of other cells by transferring genetic information, including transforming turning them into cancer [25] (Figure 1).

Many studies of hematological malignant diseases have demonstrated that autophagy allows T and B lymphocytes to survive under nutrient-deprivation conditions or during stress stimuli. Since cytoplasmic calcium levels are essential for activation of TCR signaling pathways, autophagy-dependent regulation of calcium flux could influence lymphocyte activation. Inhibition of autophagy causes defects in T-cell activation. Deletion of the Atg7 gene results in decreased levels of IL-2 mRNA, interleukin-2, and ATP generation, suggesting that autophagy is required to provide an adequate level of energy for cell activation T. Similar data were obtained in B lymphocytes, demonstrating that autophagy is essential for the maturation process and the subsequent maintenance of the lymphocyte repertoire in the periphery [26]. Molecules that alter these pathways, such as metformin, and resveratrol, boost the enzyme nicotinate deaminase (NAD), which is responsible for cellular respiration. For example, resveratrol activates autophagic cell death in prostate cancer cells via the downregulation of STIM1 and the mTOR pathway. Metformin is a well-known mitochondrial inhibitor that has shown beneficial effects on animal models of neurodegeneration by inducing autophagy through AMPK activation. It has been shown that modulating cyclic AMP and Inositol 3 –phosphate (cAMP/IP3) positively regulates the autophagy process [27,28].

The autophagy process can effectively remove the misfolded and damaged proteins that can drive, starvation, tumor development, and suppression. Autophagy is a kind of intracellular degradation process, and it can be initiated in the presence of poor nutritional and hypoxic conditions or upon the exposure of cancer cells to chemotherapy. When autophagy-related proteins such as ATG7 and ATG5 were knocked down, both autophagy and apoptosis have been reported to play an important role in protection against cellular damage [29].



The Signal transducer and activator of transcription 5 (STAT5) plays have been known to play a significant role in the regulation of cellular survival and homeostasis. However, its aberrant activation has been reported to mediate tumorigenesis. The different STAT family members, including STAT5, can promote the development of various cancers such as solid tumors and hematological malignancies. Activation of the STAT5 signaling pathway is initiated upon its phosphorylation by intracellular kinases such as JAK1, JAK2, and Src genes. Additionally, previous studies have suggested that pharmacological inhibition of STAT5 gene phosphorylation could induce programmed cell death mechanisms (s) like autophagy and apoptosis, in human lung and mesangial cancer cells. Autophagy is a type of cellular autolysis initiated by various stimuli, including one of which is cytoplasmic deprivation, which allows cells to eliminate cytoplasmic components. An understanding of autophagy as a mechanism of resistance to metabolic stress-inducing therapies or as a means of cell death, is rapidly fast developing, indicating that a new therapeutic starvation paradigm is emerging [30].

Physical activity may positively influence lysosomal disintegration and mitochondrial quality control, thereby reducing age-related cognitive decline. Exercise is a well-known physiological therapy that can preserve tissue integrity, reduce inflammation, and activate the direct signaling pathways for cellular responses. It has also been shown that significantly enhance diverse mitochondrial gene transcripts and autophagy-associated genes, promote mitophagy in the mitochondria, and increase autophagy and mitophagy flux.

The ideal weight, (IW), is recommended to be calculated according to height in centimetres (H) and age in years (A), using the EMBED method, for men, IW = 50 + 0.75(H – 150) + [(A – 20) / 4], and for women, IW x 0.9. In an overweight person or with degrees I-IV obesity, a physical exercise program must be accompanied by a daily reduction in energy intake from the diet. A previous study of sedentary subjects proved that walking at a self-selected pace (10,000 steps per day, (6Km), 3 days/week, in the open air, with a consumption of 400 Kcal, showed lipoprotein profiles improved and an expression of genes involved in the reverse transport of lipids, (leptins).

In an intense muscular effort, the degradation of glucose takes place anaerobically with the reduction of pyruvic acid to lactic acid and the accumulation of lactic acid proportional to the degree and duration of the effort. Pathological changes in lipid metabolism are correlated with those of carbohydrate and proteolytic metabolism and depend on the functional state of the main organs involved in the metabolism of these compounds.

At a moderate muscular effort, glucose degradation is done aerobically, it is done by oxidizing pyruvic acid resulting from glycolysis via tricarboxylic acids. The energy consumption per minute for jogging can be calculated as E (kcal) = 0.8 x + 0.5, where v is the jogging speed (3.5-6.5 km/h) [31].

Metabolic equivalents (METs) are useful when walking exercise is recommended by clinicians (American College of Sports Medicine (ACSM). By definition, a MET is the energy or oxygen level used at rest (1 MET = 3.5 VO2 mL/kg)./min). Recent studies indicate that the mean resting MET level in subjects with coronary artery disease is 23–36% lower than the standard value of 3.5 ml/kg/min. The total energy consumed, Q (kcal), can be calculated by the theoretical equation Q (kcal) = oxygen consumption (VO2) x isocaloric coefficient, (4.83 kcal) = [(5.8 x W) + (151 +10 .1 x P) x 4.83], where W represents the patient's weight (kg) and P is the power to pedal on a treadmill, (Watt/sec). Lipid energy consumption, QL (kcal) can be estimated using the equation Q1 = VO2 – [17.35 x 4.83 x total body muscle mass (TSM)].

For effective physical exercise, the consumption of lipid energy exceeds 7 kcal/min. Target heart rate (THR), which determines the intensity of exercise, was generally recommended based on resting heart rate (HR) and a heart rate during physical effort (HRP), which had to be 60-80% of the values characteristics of aerobic metabolism. For a value of 60% of aerobic metabolism, the THR is 136 bpm. Periodically order the control of risk factors.

The prevention of Metabolic Syndrome is possible by optimizing the lifestyle, applied both at the population level and to people at risk in essence, it refers to the prevention of cardiovascular risk factors by allocating at least half an hour a day of physical exercises to maintaining a normal body weight [BMI] [32].

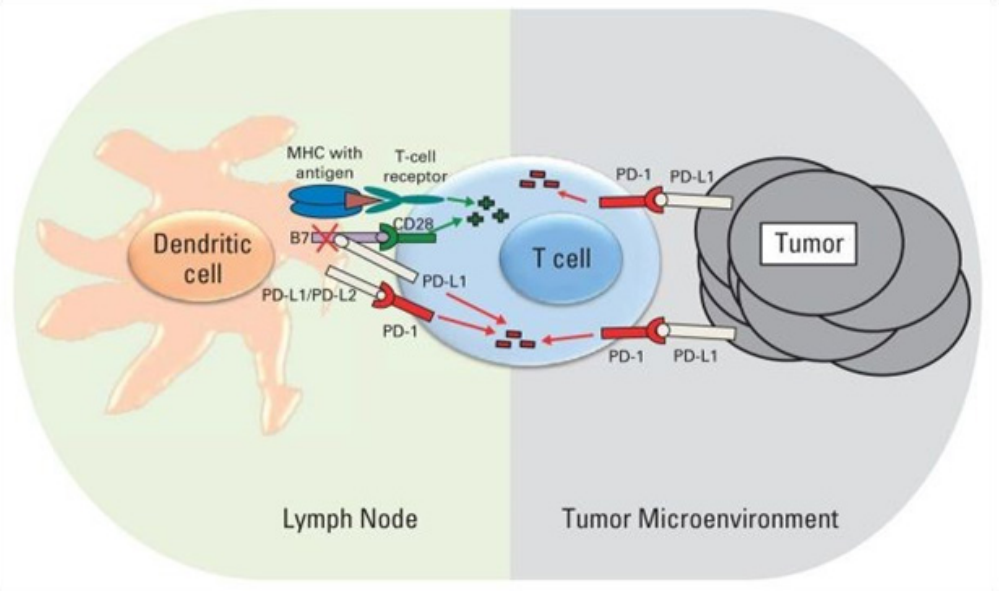
Nutrition affects all physiological processes, including those that regulate our immune system1. The link between nutrition and host immunity represents an important opportunity to develop therapeutic nutritional interventions in the context of various disease states, such as cancer or chronic inflammatory disorders. In support of a link between diet and disease state, a low-fat vegan or vegetarian diet has been previously associated with decreased inflammation, reduced risk for cardiovascular diseases and reduction in overall mortality.

Autophagy inhibition in the status of malignant cells, concurrently with chemotherapy or radiotherapy, has emerged as a novel approach in cancer treatment because of the tumor cells' survival under drug- and radiation-induced stress. Based on the fact that approximately 70% of clinical trials focus on the role of autophagy in cancer, indicates that the potential for autophagy modulation in cancer treatment is promising. Clinical studies involving autophagy modulation in cancers have been designed to evaluate the effect of autophagy inhibition in combination with other conventional therapies. The use of autophagy inhibitors in combination with chemotherapy can suppress tumor growth and trigger cell death at a higher percentage than alone chemotherapy alone [33].

According to multiple clinical trials, activation or inactivation of autophagy may contribute differently to tumorigenesis, depending on the type of tumor and its stage of development, activation or inactivation of autophagy may contribute differently to tumorigenesis. In this regard, if increased autophagy confers tumor resistance to death-inducing agents, its inhibition will

allow an improved response to treatment. In established solid tumors, autophagy has been shown to favor tumor development by enhancing tumor growth, cell survival, resistance to platinum-based chemotherapy, and metastasis. Notably, change in diet itself, independent of diet order, induced significant changes, including a significant decrease in the level of naive CD8 T cells and a significant increase in the level of activated CD4 T cells, effector CD4 T cells and effector CD8 T cells following both ketogenic/vegan versus baseline diet [34].

Autophagy may also interfere with immunotherapy, as some studies have shown a link between autophagy and immune checkpoint activity and/or expression, including CTLA-4, IDO, and PD1/PD-L1. Autophagy also plays a critical role in tumor immune cells and the tumor immune response, promoting the immunogenic cell death of tumor cells and favoring immune cell activation and proliferation. Autophagy in cancer-associated fibroblasts (CAFs) promotes tumorigenesis by providing nutrients to cancerous cells and favoring epithelial-to-mesenchymal transition, angiogenesis, and stemness, [Scheme 5].



Scheme 5: Tumor antigens are taken up by antigen-presenting cells (APCs) and presented in the context of CD28 co-stimulatory molecules inhibits receptors represented of PD-1 and PD-L1, or ligand.

There are two types of autophagy inhibitors: the early stage, which blocks the formation of autophagosomes (3-methyladenine-3 MA, wortmannin, and LY294002), and late-stage inhibitors present in the auto-phagosome lysosome fusion and degradation phases (hydroxychloroquine- HCQ). Pharmacological manipulation of autophagy for cancer prevention and treatment will depend on the ability of doctors to successfully recognize the functional status of autophagy in tumors and on the availability of specific autophagy modulators, [35].

Conclusions

Autophagy levels decrease with age, but the activity of Atg gene complexes, through autophagic proteins (Atg), may contribute to improving lifespan by delaying ageing. In principle, the four longevity genes, mTOR, AMPK, PTEN, and SIRTUINS, protect the body during periods of cellular stress by activating survival mechanisms.

Prospective Strategy for Cancer Therapy: When these genes are activated, either through diets with fewer calories or a low content of fatty amino acids and carbohydrates, combined with physical exercise, the body becomes healthier and more resistant to disease. The study of preclinical models for the promotion of autophagy, through genetic or pharmacological means, revealed the possibility of destroying malignant tumor cells and triggering apoptosis with the eventual regeneration of cell vitality.

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