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RESEARCH ARTICLE

Interrelations between Apoptosis and Autophagy in Autoimmune and Malignant Diseases

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ABSTRACT

The lifespan of a cell in the body oscillates between two fundamental processes, Autophagy, which ensures cell survival, even under conditions of cellular stress, and Apoptosis, which programs the end of cell life, not before the renewal of a new cell in a tissue. Overall, there is a continuation of daily life until a specified date of highlighting the length of the telomeres, in the chromosomal analysis of the cell.

Apoptosis, in the scheduling of cell life, is a normal process which is different from cell necrosis that occurs as a result of physical or chemical aggression. The decision to activate a suicide process is made based on intrinsic or extrinsic apoptotic messages. The intrinsic inducers of apotheosis come from the mitochondria or nucleus. Extrinsic inducers of apotheosis are ligands, cytokines for death receptors, (DR-Death receptors) on each cell surface.

Autophagy: is a homeostatic and catabolic processes that allows the sequestration and lysosomal degradation of cytoplasmic organs and proteins, important for maintaining genomic stability and cell survival. Autophagy is regulated by the Beclin 1 protein, which forms a complex with a class III enzyme, phospho-inoside 3-kinase (PI3K), and serves as a platform for the recruitment of other proteins critical for autophagosome formation.

Conclusions: The most important regulatory mechanism in autoimmunity and oncogenesis process are death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogenes and tumor suppressor gene P53. Pharmacological manipulation of autophagy for cancer prevention and treatment will depend on our ability to successfully recognize the functional status of autophagy in tumors, and the availability of specific autophagic modulators.

Keywords: apoptosis, autophagy, autophagy inhibitors, autophagy activators, cancer, death receptors, inflammation, inflammatory cytokine; nuclear factor-κB, P-53 Gene, Tumor Necrosis Factor.

Introduction

It is recently revealed that apoptosis process is functioning to induce cell death. In contrast, the autophagy in mammalian cells, which has been characterized in past decades, appears to be much more complex. In mammalian cells, primary function of autophagy is thought to be cell survival mechanism. However, autophagy can induce cell death or alternatively, mammalian cells are dying associated with autophagy in certain conditions, Autophagy may enhance cell death caused by apoptosis; alternatively, it may induce cell death independently of apoptosis or necrosis.

In contrast to autophagy, apoptosis is characterized in the apoptotic pathways, starting from the activation of the death receptor, which is followed by a downstream signaling cascade including the involvement of mitochondria, subsequent caspase activation, and DNA cleavage. However, pro-apoptotic signals apoptosis receptors, such as TNF-related apoptosis-inducing ligand, (TRAIL), Tumor Necrosis Factor, (TNF) and Fas receptor, also known as APO-1 or CD95, [FAS-associated protein with death domain, (FADD)], is the key adaptor protein transmitting apoptotic signals mediated by the main death receptors (DRs). are also known to induce autophagy. Pro-apoptotic signals, which is promoting or causing apoptosis, participate in a cascade that leads to culminate in cleavage of a set of proteins, resulting in disassembly of the cell for apoptosis [1].

Mitochondria are shown to be playing an important role in the induction of apoptosis through the cytochrome c release via the disruption of mitochondrial outer membrane potential. Mitochondria would provide an ideal molecular platform of counter regulation of autophagic cell death vs. apoptotic cell death. In this regard, mitochondria-associated proteins may also be responsible for interactions between the autophagic and apoptotic pathways. **(Figure 1).**

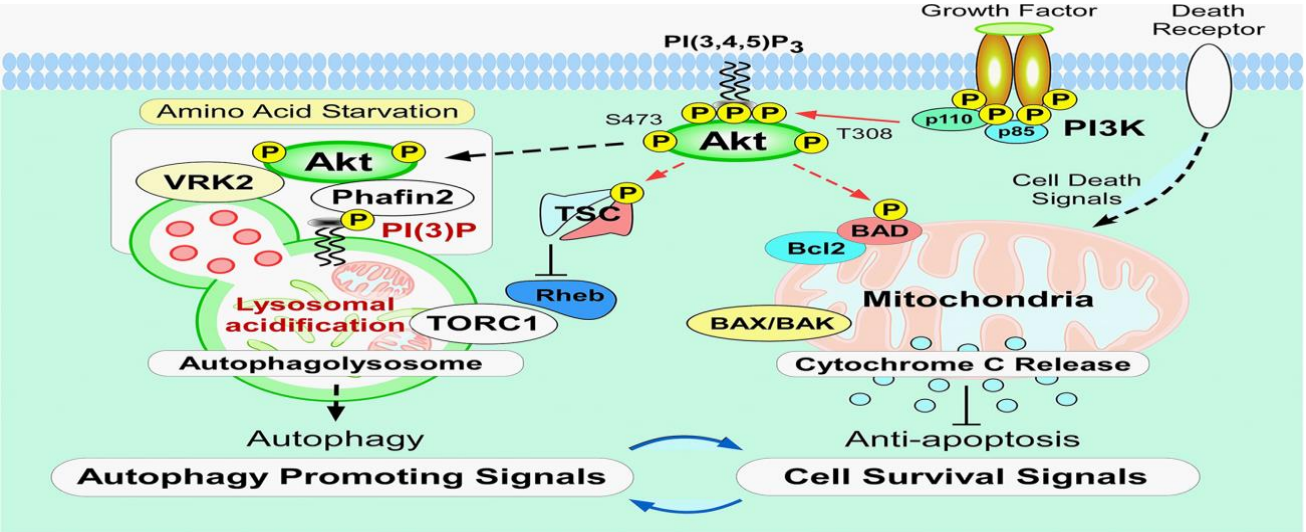

Figure 1. The major mechanisms for cell death have been identified in mammalian cells: apoptosis (type I), autophagic cell death (type II), *(Noguchi, M., Hirata, N., Tanaka, T. et al. Autophagy as a modulator of cell death machinery. Cell Death Dis* ***11****, 517 (2020).* https://doi.org/10.1038/s41419-020-2724-5).

1.Apoptosis and autoimmunity

Apoptosis is a normal process, while autoimmunity is not. The "decision" to activate a suicidal process is made on the basis of intrinsic or extrinsic apoptotic messages. Intrinsic inductors come from mitochondria or nucleus. Extrinsic inductors are ligands, cytokines for death receptors on the cells surface. In the case of systemic lupus erythematosus (SLE), more than 40 such genes have been identified. A characteristic hallmark of lupus is increased production of anti-nuclear antibodies. (ANA). There may be three different groups of genes responsible for this. One category of genes codes for molecules that have an impact

of the clearance of apoptotic cells. When apoptotic cells are accumulated, the production of ANA by auto-reactive lymphocytes is stimulated.

The second group codes for molecules that may act for the deletion of self-reacting B and T cells. The third group codes for molecules that amplify or modulate lymphocytes signal and expansion. The fact that many different molecules can all lead to SLE suggest that the different mechanisms that keep nuclear antigen-reactive lymphocytes in check are all equally vulnerable, and show not only how immensely complicated the human immune systems is but also how fragile it can be.

The action of these genes is controlled by the native P-53 gene, which by its product, the p-53 protein, inhibits the Nk-beta nuclear factor, which is susceptible to protein synthesis in inflammation of autoimmune diseases. Mutations of the P-53 gene will lead to insufficient action of p53 protein and trigger autoimmunity. I this kind, autoimmunity become an interface at malignancy by central element, P-53 gene [2].

In systemic auto-immune diseases, especially in (SLE), auto-antibodies against of a palette of intra-cellular antigen are found. It has been suggested that humoral response may be driven by the products of apoptotic cells with central importance of the nucleosomes as potential auto-antigens. In this circumstance anti-nuclear antibodies, (ANA), can appear as response of body to antigens as: double stranded (ds) DNA, extractable nuclear antigen Sm (UI RNP), nucleosome (mixture of DNA +histone), H2A, H2B, H3, H4 molecules, nucleoplasma and nucleo-matrix, antigens: SS-A, SS-B. Auto-reactive of B and T cells, which escaped from natural apoptosis, might represent additional necessary condition, [3].

The link between apoptosis and TNF activity shows why abnormal production of TNF plays in important role in several autoimmune diseases: rheumatoid arthritis, multiple sclerosis, diabetes mellitus, ulcerative colitis. The supplementary mutations in these diseases will drive cells toward cancer diseases. Mitochondria has a fundamental position in executing apoptosis induced by intracellular signals. When cells are stressed due to physical signals, chemical stimulus, hypoxia or cytokines, mitochondria release pro-apoptotic proteins, including cytochrome C. This binds to an adapter, protein Apaf-1, and thus activates pro-caspase-9 and enzymatic cascade, [4],
(**Figure 2**).

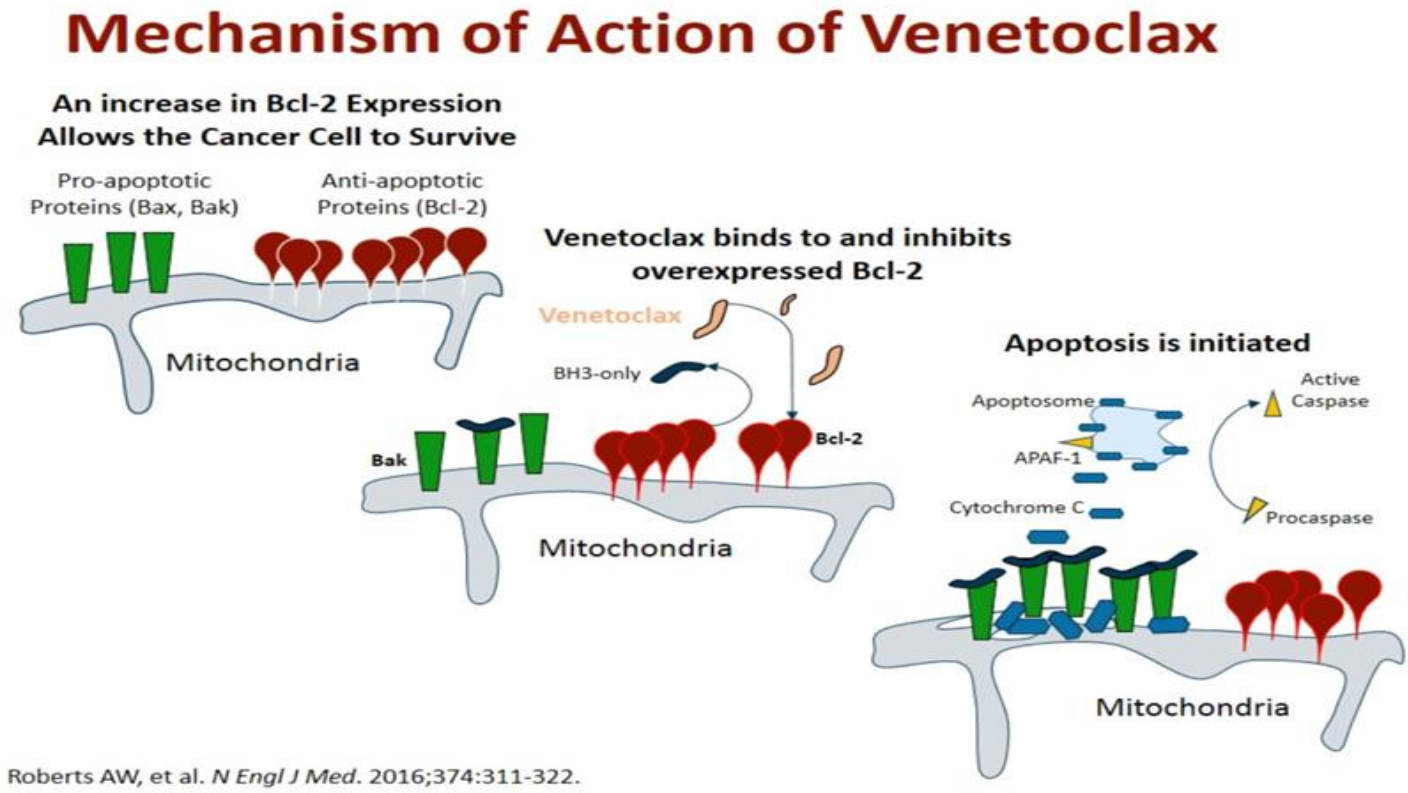

Figure 2. Additional, mitochondrial activities leading to apoptosis provide the disruption of transport of membranes cells and the cellular reduction-oxidation potential *(www.Medscape.org, Navigating New Oral Treatment Algorithms in CLL, LLC, New York, accessed in 11/05/2022)*.

2.Receptors of autoimmunity

An individual cell requires multiple signals for to survive, otherwise it will undergo a programmed cell death. The main death receptors (DR) are CD95 (Fas), CD 120a, (TNF-R1), DR3, DR4, DR5, DR6, which are responsive to cytokines belonging to the tumor necrosis factor (TNF-alpha, lympho-toxin, Fas-L, Apo-TNF 13). It has been proposed that possible increased sensitivity to CD95 can provoke apoptosis and for the epithelial cells. The death of cells is mediated by CD95 expressing lamina proper lymphocytes. High levels of soluble CD95 were found in rheumatoid arthritis (RA and this contribute to inhibition of synoviocytes and inflammatory cells apoptosis.

Simultaneously expressed CD95 and its ligand causes apoptotic cells death by paracrine or autocrine mechanisms and during inflammation interleukin-1 beta and interferon-1 alpha induce massive CD up-regulation. The studies from last 10 years suggested that the neonatal wave of beta cells apoptosis might activate auto-antigens necessary for triggering beta cells in diabetes mellitus. In the animal models, increased TNF-alpha mediated apoptosis has been found, which has been explained by selective nitric oxide-mediated up-regulation of functional of functional CD95 molecule which is subsequently killed by CD95L-producing T cells. Inhibitor of apoptosis family (IAP) inhibits the apoptosis by deference of activity of same caspases, and by prevention of activation of some pro-caspases [5].

3.Apoptosis and malignancy

The most important regulatory mechanism in autoimmunity and oncogenesis process are death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogenes and tumor suppressor gene P53. Metabolic changes in malignant cells are caused by a higher demand for ATP levels

and these develop the chemo-immune resistance of conventional specific treatment, in malignant diseases. The P-53 gene is a tumor suppressor gene and its activity stop the formation of tumors. The P-53 gene has been mapped to chromosome 17. In the cell, p53 nuclear protein binds DNA, stimulating another gene, CDKN-IA, to produce a protein called p21 that interacts with a cell division stimulating protein (cdk2). When p21 protein forms a complex with cdk2 protein the cell cannot pass through to the next stage of cell division, G1-S. Mutant gene P-53 products a p-53 protein which can`t longer binds DNA in an effective way and as a consequence the p21 protein is not made be available to act as the stop signal for cell division. The cells divide uncontrollably and form tumor, [6]. **(Figure 3).**

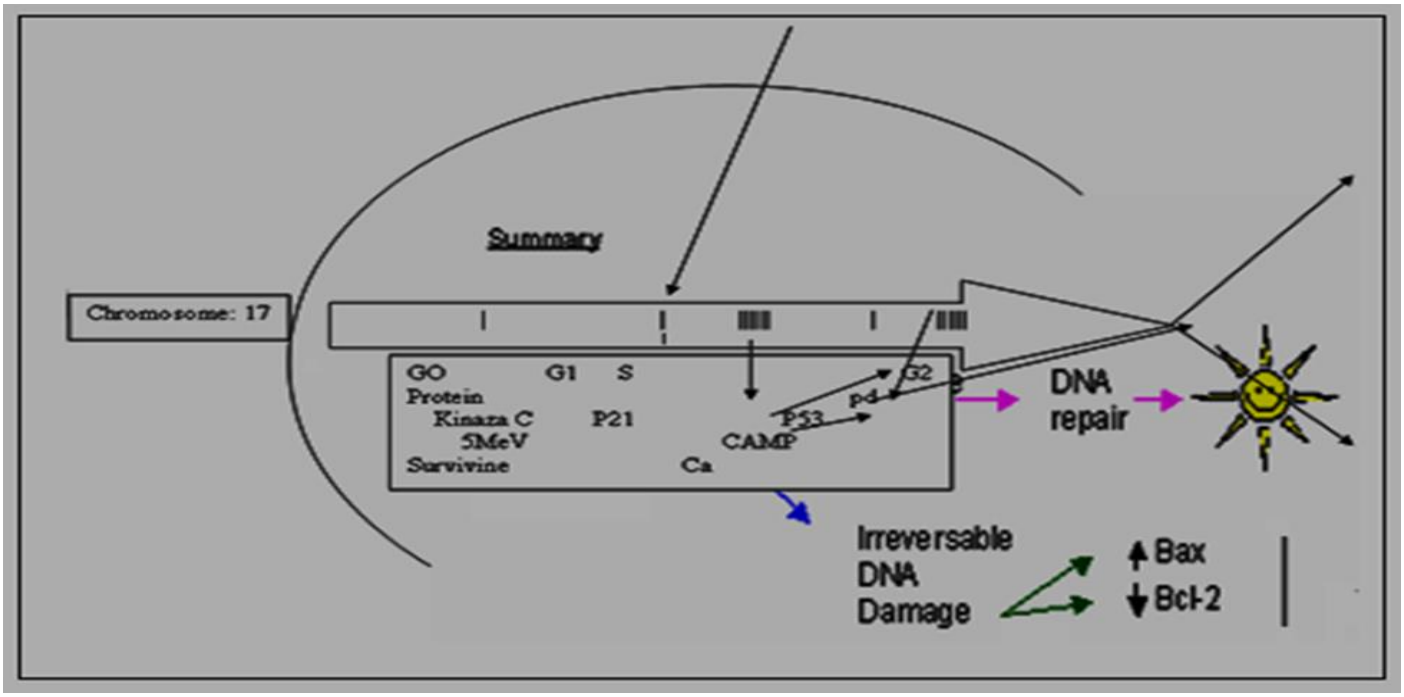

Figure 3. Current models are useful for modeling protein isoforms of p53 mutations and their effects of oscillation. (*Udristioiu A, Florescu C, Popescu MA, Cojocaru M. High Concentration of anaerobic ATP implicated in aborted apoptosis from CLL. LabMed 2010; 41: 203-08*).

Increased frequency of amplification of the MDM2 gene in presented in many human cancers as a mechanism for the down-regulation of p53 activity through ubiquitin-dependent proteosomal degradation of intra-cytoplasmic p53. Intrinsic DNA damage in tumor cells may result in elevated levels of post-translationally modified p-53 protein, (for example phosphorylation at Ser-46 and Ser-392) ineffective in repaired damaged DNA [7], Similarly, methylation at the CDKN-2A gene, (INK4a/ARF locus) can epigenetically silence the expression of the p14-ARF protein, and block the ability of activated oncogenes, to stabilize the p53 response. In experimental models, disrupting the MDM2–p53 interaction restored p53 function and sensitized tumors to chemotherapy or radiotherapy. This strategy could be particularly beneficial in treating cancers that do not contain P-53 mutations or other specific genetic mutations or deletions (chromosome 11-q, 13-q, 13-14q deletion, deletions 11q22-q23, 7q21 -g23 or trisomy 12); for example, in hematologic malignancies such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL) with the 17-p chromosomal short arm present and with p-53 genes present, acute lymphoblastic leukemia (ALL), acute myeloid leukemia and Hodgkin's disease.

In the presence of gene P-53 mutations, immune treatments with p-53 anti-peptide antibodies are being tested. In these tumor types, the induction of p53, using a small-molecule inhibitor of MDM2, nutlin, can induce apoptosis in malignant cells, [8]. A large cohort study of primary CLL were examined samples from more than 100 patients for response to MDM2 inhibition and found direct correlation between wild-type P-53 status and MDM2 inhibitor (nutlin-3 and MI-219) induced cyto-toxicity across various CLL subtypes. This response was not predicted by other biomarkers used clinically in CLL, including expression of ZAP70, expression of CD38 receptor on malignant B cells, un-mutated immunoglobulin variable genes, IGHV and mono-allelic ATM gene loss, [9], (**Figure 4).**

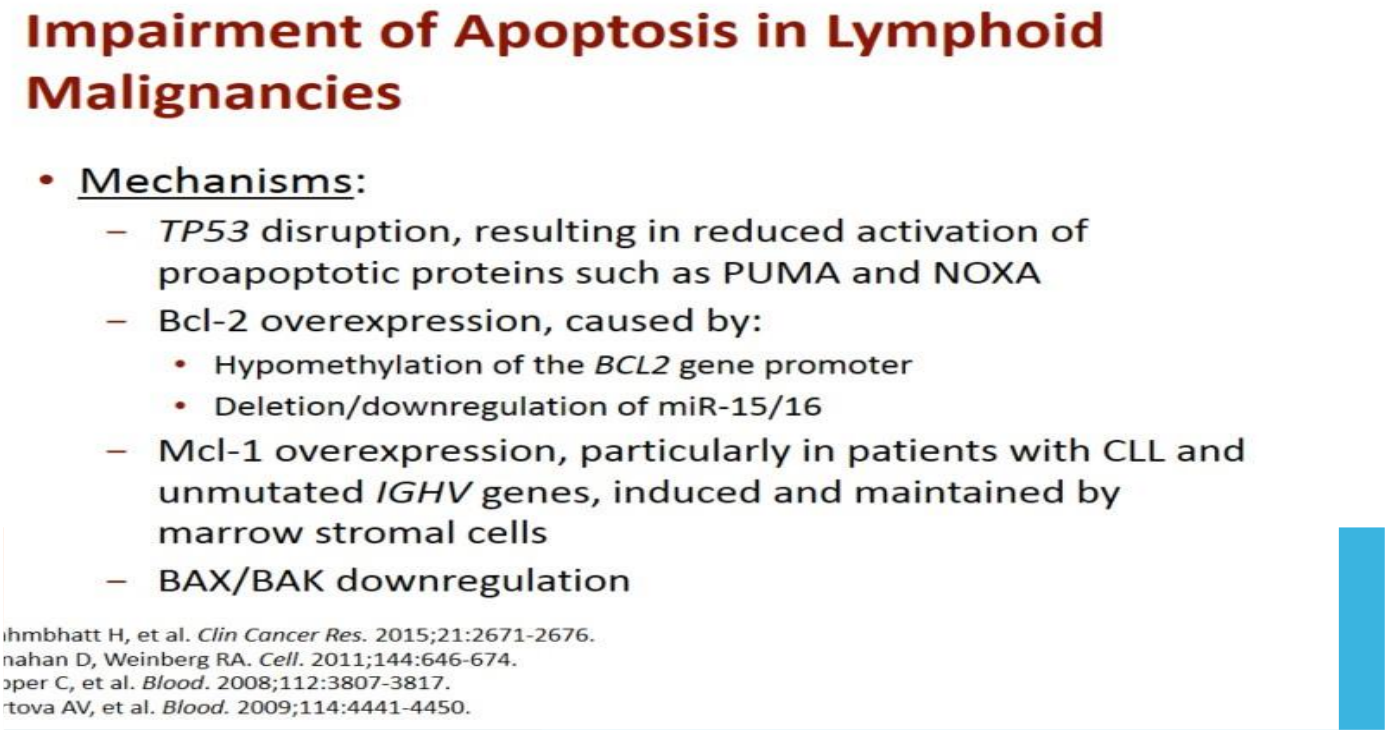

Figure 4. Apoptosis impaired in presence of anaerobic metabolism in malignant cells

Antibodies specific for total p-53 and for p-53 reactive phosphorylated at three different sites within the activation domain were used in parallel analyses in cancer diseases. Mutation of Ser-15 in p-53 protein, to alanine, results in partial failure of p53 to inhibit cell cycle progression. In this context the nuclear p-53 protein was showed that protect the cell of a malignant process, and only cytoplasmic p-53 protein, by its isoforms, phosphorylated in multi-sites, into modified cytoplasmic medium, by high concentration of anaerobic ATP, drives at cancer. Intracellular ATP levels are a core determinant in the development of acquired cross-drug resistance of human cancer cells that harbor different genetic backgrounds.

Autophagy is a fundamental physiological process, given its role in the production of ATP during nutrient deprivation and in the control of organ and protein metabolism. Drug-resistant cells were characterized by defective mitochondrial ATP production, elevated aerobic glycolysis, higher absolute levels of anaerobic intracellular ATP and enhanced HIF-1α-m.

In this regard, we revealed the different levels of anaerobic ATP concentration in leukemic cells, T and B lymphocytes, of certain categories of this disease. The energy difference from anaerobic ATP in B lymphocytes in CLL and aerobic ATP in T lymphocytes in the same case of CLL was 2.68 pM ATP and this level can initiate the carcinogenesis

process by suppressing anti-oncogenic proteins, especially p53 protein. Further studies should also be needed to detect high concentrations of patients with mutated and translocated ATP or deletions of the P-53 gene on chromosome 17, where this gene is located, [10].

When the cellular concentrations of ATP are high, typically 1–5 mM it was thought that a high concentration of drug would be needed for efficacy with ATP-competitive inhibitors, bringing potential toxicity problems. A large number of patients with cancer produce p-53-reactive phosphorylated T cells; more than 40% of patients with breast cancer have p53-reactive CD-4 and CD-8 T cells in their peripheral blood. These responses occur most frequently in patients with high p53 protein expression in their tumors. The current study showed that the level of p-21 is strongly correlated with the activity of Mammalian Target Rapamycin (m-TOR).

The study was published in the February 2, 2016, online edition of the Journal Nature Communication, (www.cnio.es). By the Warburg effect, glucose maintains stability mutant P-53 gene and promotes cancer cell. Most researches seem to indicate that, in line with its role as tumor suppressor p53 is able to fall glycolysis. The mTORc2/Akt complex controls mitochondrial metabolism and physiology, through the phosphorylation of the glycolytic enzyme hexokinase 2, thus promoting cancer cell's aerobic glycolysis (Warburg effect) and preventing mitochondrial apoptosis, [11].

Another concern was that the large number of protein kinase enzymes, all sharing a common cofactor and similar three-dimensional structure of the catalytic site, might confound attempts at developing adequately selective drugs. As small-molecule inhibitors of protein kinases are now well established as clinically useful drugs, particularly for the treatment of cancer. Metabolic shift driven by higher ATP demand is also applicable to the progression of acquired chemoresistance of cancer cells [12, 13].

Aurora kinases, enzymes A and B, also play critical roles in regulating spindle assembly, chromosome segregation, and cytokinesis to ensure faithful segregation of chromosomes during mitotic cell division cycle. Aberrant expression of Aurora kinases, on the other hand, cause defects in mitotic spindle assembly, checkpoint response activation, and chromosome segregation leading to chromosomal instability. In contrast, the effect of Aurora-A phosphorylation on p-53 activity and stability, Aurora-B phosphorylation of p-53 at serine-269 and threonine- 284 inhibit p-53 transactivation activity, whereas phosphorylation at serine-183, threonine-211, and serine-215 accelerates the degradation of p53 through protease enzyme [MDM2], [14, 15].

4.Roles of Autophagy in Human Pathology

As already mentioned, one of the most important functions of autophagy is the degradation of misfolded proteins, so in neurons, the failure of autophagy can contribute to neurodegeneration [16]. It can occur in Parkinson's disease, a neurodegenerative disorder characterized by α-synuclein accumulation in the brain. Recently, in a study, was demonstrated that autophagy inhibition by 3-methyladenine (3-MA) and by Atg5 knocking down in lymphocytes lead to a significant increase of α-synuclein levels [17]. The removal of mitochondria, source of reactive oxygen species (ROS), performed by autophagy, certainly protects cells from DNA mutations and prevents cellular transformation. It has also been demonstrated that deletion of the autophagic gene Beclin-1 may cause development of various malignancies in mouse models [18].

Furthermore, it has been demonstrated that autophagy-deficient tumors are more sensitive to several chemotherapeutic agents [19]. In this case, autophagy promotes the survival of cancer cells and protects them from the action of drugs that induce apoptosis. Although research in this field is just at the beginning, an encouraging number of works suggest that defects in the autophagy mechanism may be involved in the pathogenesis of autoimmune diseases.

In systemic lupus erythematosus (SLE), showed that factors present in the serum of SLE patients, probably antibodies, are able to induce autophagy in T lymphocytes from healthy donors, but not in T lymphocytes from patients with SLE. We speculated that chronic exposure to specific

autoantibodies, as occurs in SLE, could lead to the selection of autophagy-resistant T lymphocytes [20, 21].

Considering the crucial role of autophagy in the maintenance of cellular homeostasis, it is not surprising that several signaling-related molecules are involved in the perfect functioning of this process. Genetic screens in yeasts allowed the discovery of at least 37 autophagy-related genes (Atg) [22]. Many of these genes, encoding proteins involved in autophagy and its regulation, are evolutionarily conserved in humans.

The mammalian target of rapamycin (mTOR) complex 1 (mTORC1) regulates the activation of autophagy machinery, acting as a sensor of energy levels and integrating upstream signals deriving from other pathways, including the phosphoinositide 3-kinase (PI3K). In the presence of amino-acids and growth factors, mTORC1 represses autophagy by inhibition of Vps34 and ULK1 complexes. On the contrary, in low nutrients state, defined as starvation, the dissociation of mTORC1 from the induction complex triggers autophagy [23, 24, 25].

Regulation of HIF-1α pathway at different levels. (a) Growth factors related pathways; (b) pVHL related pathways; (c) FIH-1 pathway; (d) Mdm2-p53 mediated ubiquitination and proteasomal degradation pathway, [26], **(Figure 5).**

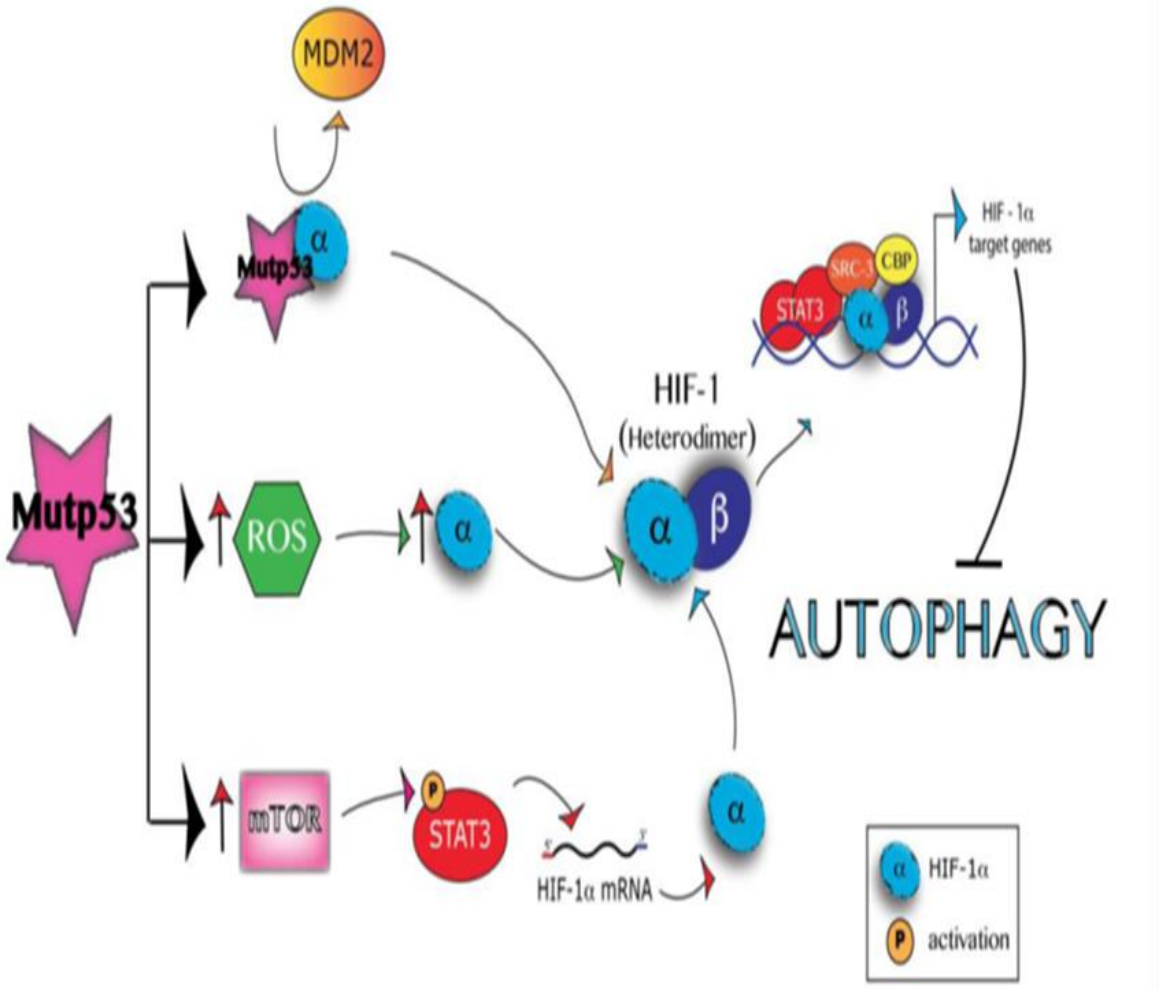

Figure 5. Schematic representation of the mechanisms at the basis of the stimulation of HIF-1 and HIF1- target genes by mutp53 resulting in autophagy inhibition. Regulation of HIF-1α pathway at different levels. (a) Growth factors related pathways; (b) pVHL related pathways; (c) FIH-1 pathway; (d) Mdm2-p53 mediated ubiquitination

and proteasomal degradation pathway, (Cordani M, Butera G, Pacchiana R, Donadelli M. Molecular interplay between mutant p53 proteins and autophagy in cancer cells. BBA - Reviews on Cancer 2016; 8: 133-134. doi:10.1016/j.bbcan).

5.Role and regulation of autophagy in cancer

Increasing evidence reveals that autophagy dysfunction is associated with human diseases, such as cancer. Paradoxically, although autophagy is well recognized as a cell survival process that promotes tumor development, it can also participate in a caspase-independent form of programmed cell death. Induction of autophagy cell death by some anticancer agents highlights the potential of this process as a cancer treatment modality, [27].

Dysfunctional autophagy contributes too many diseases. Large-scale genomic analysis of human cancers indicates that the loss or mutation of core autophagy genes (Atg) is uncommon, whereas oncogenic events that activate autophagy and lysosomal biogenesis have been identified. Thus, the role of autophagy in cancer is determined by nutrient availability, microenvironment stress, and the presence of an immune system, [28].

Defective autophagy is implicated in tumorigenesis, as the essential autophagy regulator *Beclin 1* is mono-allelically deleted in human breast, ovarian and prostate cancers, and *Beclin* $1^{+/-}$ mice are tumor-prone. Cell-autonomous mechanisms, involving protection of genome integrity and stability, and a non-cell-autonomous mechanism, involving suppression of necrosis and inflammation, have been discovered so far. Autophagy inhibition concurrently with chemotherapy or radiotherapy has emerged as a novel approach in cancer treatment, as autophagy-competent tumor cells depend on autophagy for survival under drug- and radiation-induced stress [29].

Lower Beclin 1 protein expression, as compared to Beclin 1 levels in normal adjacent breast tissue, was confirmed in a small series of human breast tumors but any correlation between allelic Beclin 1 loss, and thus defective autophagy, and clinical outcome in breast cancer remains to be investigated [30]. The mechanism by which autophagy defects lead to accelerated tumorigenesis is not readily apparent, especially given the well-documented pro-survival function of autophagy, which prolongs both normal and tumor cell survival under metabolic stress, [31].

A number of upstream intracellular signaling pathways are involved in the regulation of converging autophagy and include the complex enzymatic pathway, PI3K-protein-kinase B, (AKT) and mammalian target rapamycin, (mTOR class I), which is frequently implicated in human cancer. Activation of m-TOR may occur due to loss of tumor suppressors (ex, PTEN enzyme) or by mutations in p-53 protein after high concentrations of anaerobic adenosine-three-phoshate, (ATP), in cancer cells. Regulators of apoptosis, such as anti-apoptosis protein Bcl-2/Bcl-xL and the pro-apoptosis protein family, BH3-only proteins, interact with Beclin 1 and can modulate autophagy. The anti-apoptotic protein Bcl-2 binds to Beclin 1 under non-stress conditions and inhibits autophagy in the ER, whereas the BH3-only protein Bad, BNIP3 and BH3 mimetics, such as ABT737 competitively inhibit the interaction between Beclin 1 and Bcl-2/Bcl-xL and stimulate autophagy. Constitutive activation of the PI3K/AKT/mTOR axis is a prototypic survival mechanism commonly encountered in human cancer [32].

Diverse cellular events, such as loss of the tumor suppressors phosphatase and tensin-homolog deleted on chromosome 10 (PTEN) and tuberous sclerosis complex (TSC) 1 and TSC2, amplification or mutation of class I PI3K, overexpression of AKT, constitutive activation of tyrosine kinase growth factor receptors and exposure to carcinogens, can all result in abnormal activation of this pathway and, ultimately, in autophagy suppression [33], **(Figure 6)]**.

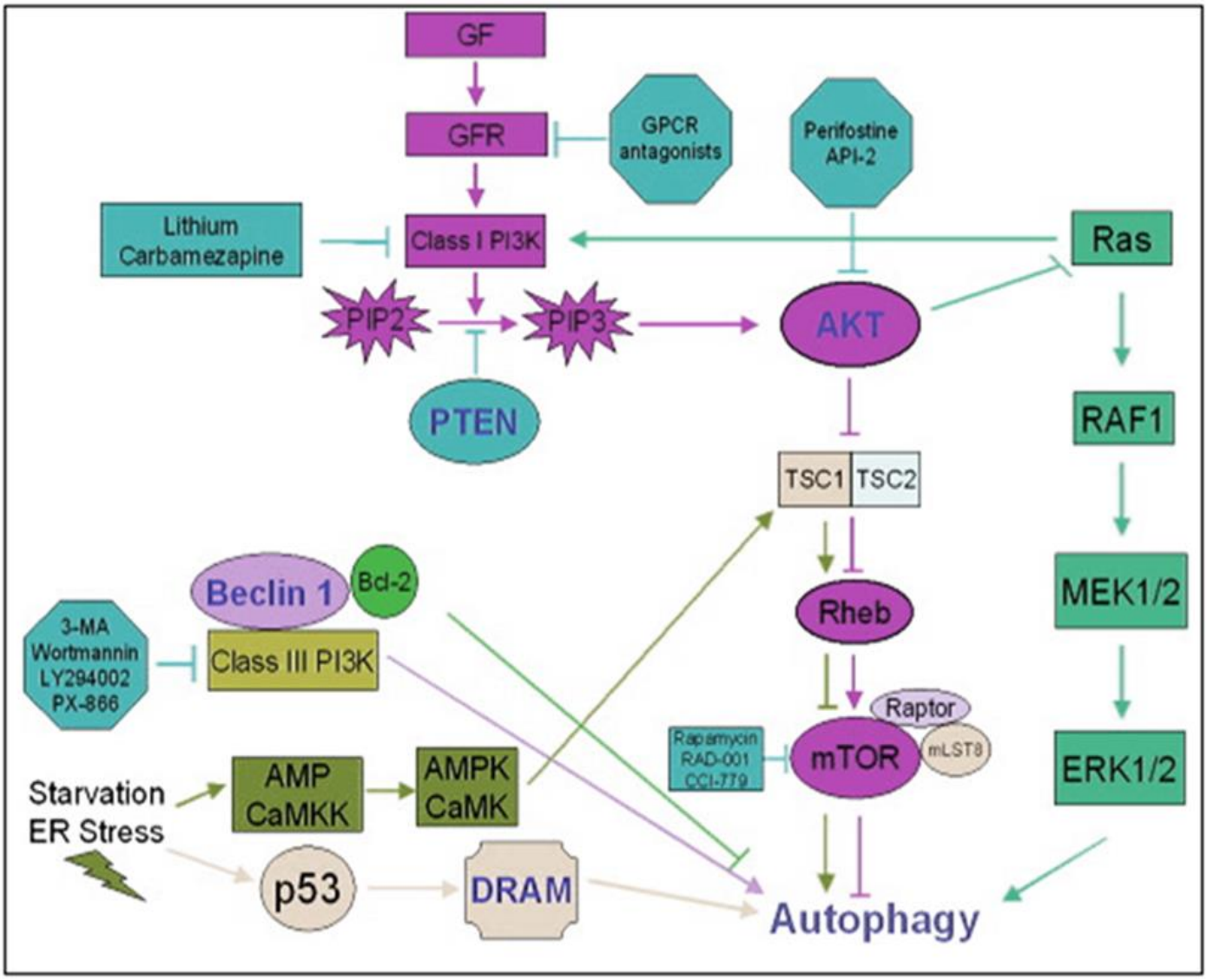

Figure 6. A first group of protein kinases belongs to the MAPK family (JNK1-3, ERK1-2, p38 MAPK), which is known to respond to several types of stress, such as membrane damage, oxidative stress, osmotic shock, heat shock, (*Chen V, Karantza-Wadsworth V. Role and regulation of autophagy in cancer. Biochim. Biophys. Acta. 2009; 1793(9): 1516–1523).*

6.Autophagy in Immunological Tolerance

Many studies demonstrated autophagy's contribution to the presentation of cytosolic antigens in association with MHC class II molecules, playing an important role not only in the acquired immune response but also in the maintenance of self-tolerance Mechanisms of central (in the primary lymphoid organs) and peripheral tolerance (in peripheral tissues) physiologically prevent immune responses to self-antigens [34].

During T cells development in the thymus, the recognition of peptide–MHC molecules on the surface of thymic epithelial cells (TECs) ensures that only thymocytes restricted to MHC molecules, and specific for non-self (foreign) antigens, will survive and continue their maturation. Emerging evidence indicates that autophagy contributes to the maintenance of the central tolerance mechanism [35].

Was recently revealed that there had been an alteration in the selection of the T cell receptor

(TCR) restricted to MHC class II in mice transplanted with Atg5−/− thymus. Autophagy defects, in association with a consequent loss of self-tolerance, could be the reason of multiple signs of autoimmunity reported in these animals. These two opposite results probably depend on the different approach used to inhibit autophagy in the thymus, thus further investigations are necessary. The involvement of autophagy in the presentation of self-antigens to immature T cells in the thymus was first analyzed by Kasai and colleagues, who showed a colocalization of LC3-II with the lysosomal compartment in which MHC–peptide complexes are formed. More recently was demonstrated that autophagy is essential for endogenous antigen-loading onto MHC class II of TECs for negative selection [36].

7.Autophagy in Lymphocytes Homeostasis

Many studies demonstrated that autophagy allows T and B lymphocytes to survive in conditions of nutrients deprivation or during stress. Mice lacking Atg5 do not survive and have a reduction of peripheral T cells, showing how autophagy is essential for their survival. Since cytoplasmic calcium levels are essential for TCR-signaling pathways activation, autophagy-dependent calcium flux regulation could influence T lymphocytes activation. It has been demonstrated that CD4+ and CD8+ Atg5−/− cells are not able to properly proliferate following TCR stimulation [37].

Moreover, the inhibition of autophagy causes defects in T cell activation. In fact, deletion of Atg7 results in decreased in IL-2 mRNA level and ATP generation, suggesting that autophagy is required to ensure appropriate energy level for T cell activation. Similar data were obtained also on B lymphocytes, demonstrating that autophagy is essential for the maturation process and for the subsequent maintenance of B lymphocytes repertoire in the periphery [38].

Peripheral immune cells play an important role in the perpetuation of autoimmunity by sustaining systemic inflammation status and by participating in the extension of joint destruction mechanisms. Many studies demonstrated that autophagy allows T and B lymphocytes to survive in conditions of nutrients deprivation or during stress stimuli. Mice lacking Atg5 do not survive and have a reduction of peripheral T cells, showing how autophagy is essential for their survival. Since cytoplasmic calcium levels are essential for TCR-signaling pathways activation, autophagy-dependent calcium flux regulation could influence T lymphocytes activation. It has been demonstrated that CD4+ and CD8+ Atg5−/− cells are not able to properly proliferate following TCR stimulation. Moreover, the inhibition of autophagy causes defects in T cell activation. In fact, deletion of Atg7 results in decreased in IL-2 mRNA level and ATP generation, suggesting that autophagy is required to ensure appropriate energy level for T cell activation. Similar data were obtained also on B lymphocytes, demonstrating that autophagy is essential for the maturation process and for the subsequent maintenance of B lymphocytes repertoire in the periphery [39, 40].

8.Autophagy inhibits inflammation in tumor

Inflammation can contribute to tumor development and proliferation. Chronic inflammation is in fact a common future for the development of early cancer. Also, autophagy has been suggested that different mechanisms can modulate these inflammatory reactions, as autophagy-deficient tumors show an increased necrosis and inflammation. Autophagy activation in tumor cells has been reported to be able to inhibit necrotic cell death. In contrast to apoptotic cell death, necrosis-dying cells stimulate a strong inflammatory response, Impairment of both autophagy and apoptosis has been reported to promote in vitro and in vivo necrotic cell death associated with an inflammatory response and an increased tumor growth. Autophagy has been suggested to participate in the regulation of cell death caused by necrosis and therefore in subsequent inflammation, [41].

Paradoxically, although autophagy is well recognized as a cell survival process that promotes tumor growth, it can also participate in an independent form of programmed cell death. Induction of autophagic cell death by some

anticancer agents highlights the potential of this process as a treatment for cancer. Large-scale genomic analysis of human cancers shows that the loss or mutation of basic autophagic genes (ATGs) is less common, while oncogenic events that triggered autophagy and lysosomal biogenesis have been identified. Thus, the role of autophagy in cancer is determined by the availability of nutrients, the stress of the micro-environment and the presence of an immune system, [42].

9.Conclusions

The most important regulatory mechanism in autoimmunity and oncogenesis process are death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogenes and tumor suppressor gene P53. The frequencies of gene mutations, deletions or translocations of P-53 gene, in CLL, can be classified as biomarkers of individual proteomic and genomic profile in cancer diseases.

Inhibition of autophagy, along with specific chemo-immunotherapy treatment, may increase antitumor activity and thus the effectiveness of cancer drugs. Pharmacological manipulation of autophagy for cancer prevention and treatment will depend on our ability to successfully recognize the functional status of autophagy in tumors, and the availability of specific autophagic modulators. Personalized treatments in cancer diseases, will be applied by combining diagnostic tools, knowledge databases and therapeutic medicines.

Authors' Disclosures of Potential Conflicts of Interest

Manuscript "Interrelations between Apoptosis and Autophagy in autoimmune and malignant diseases" is a original research that has not been published and is not under consideration elsewhere. No authors declared any potential conflicts of interest.

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Abbreviations

Atg-Autophagy-related gene
AMPK 5'-AMP -activated protein kinase
GATE-16-Golgi-associated ATPase enhancer of 16 kDa
HIF-1α, hypoxia-inducible factor-1α;
MAP- kinase interacting kinase;
MAPK- mitogen-activated protein kinases;
MEK, -MAPK/ERK kinase;
mTOR-mammalian target of rapamycin
mTORC1-mTOR complex 1
mTORC2-mTOR complex 2
Mdm2-mouse double minute 2 homolog;
PI3K-phosphatidyl inositol-4,5-bisphosphate-3-kinase; TGF-α, transforming growth factor α;
PKB-protein kinase B
TGF-β3-transforming growth factor beta3
ULK1-UNC-51-like kinase 1
ULK2- UNC-51-like kinase 2
VEGF-vascular endothelial growth factor

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