



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Therapeutic Implications of Autophagy

Kiran M.Kulkarni¹, Sachin G. Lokapure¹, Kirti S.Patil¹, S.A.Tamboli¹

*Department Of Pharmaceutical Chemistry, Appasaheb Birnale College of Pharmacy, Sangli,
Maharashtra, India*

ABSTRACT

Autophagy is an intracellular process that has demonstrated that autophagy plays a wide variety of physiological and pathophysiological roles, which are sometimes complex. Autophagy consists of several sequential steps: sequestration, transport to lysosomes, degradation, and utilization of degradation products and each step may exert different function. In this review, the process of autophagy is summarized, and the role of autophagy is discussed in various diseases like Cancer, Neurodegenerative disease etc.

Keywords: Autophagy, Lysosomes, Degradation

*Corresponding Author Email: Kirankulkarni_1986@rediffmail.com

Received 20 April 2018, Accepted 27 April 2018

Please cite this article as: Kulkarni KM *et al.*, Therapeutic Implications of Autophagy. American Journal of PharmTech Research 2018.

INTRODUCTION

Autophagy (or *autophagocytosis*) (from the Ancient Greek *autóphagos*, meaning “selfdevouring” and *kýtos*, meaning “hollow” is the natural, regulated, destructive mechanism of the cell that disassembles unnecessary or dysfunctional components.

From the Greek words, auto "self" and phage in "to eat". It is a catabolic process through which the cell recycles its own constituents .It is a Pathway that lead to the elimination of cytoplasmic components by delivering them into lysosomes.

Autophagy allows the orderly degradation and recycling of cellular components. In macroautophagy, targeted cytoplasmic constituents are isolated from the rest of the cell within a double-membraned vesicle known as an autophagosome. The autophagosome eventually fuses with lysosomes and the contents are degraded and recycled. Three forms of autophagy are commonly described: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA).

In disease, autophagy has been seen as an adaptive response to stress, which promotes survival, whereas in other cases it appears to promote cell death and morbidity. In the extreme case of starvation, the breakdown of cellular components promotes cellular survival by maintaining cellular energy levels. . Unlike other cellular degradation machineries, autophagy removes long-lived proteins, large macro-molecular complexes and organelles that have become obsolete or damaged. Autophagy mediates the digestion and recycling of non-essential parts of the cell during starvation and participates in a variety of physiological processes where cellular components must be removed to leave space for new ones. In addition, autophagy is a key cellular process capable of clearing invading microorganisms and toxic protein aggregates, and therefore plays an important role during infection, in ageing and in the pathogenesis of many human diseases.

History & Chronology^[3]

Autophagy was first observed by Keith R. Porter and his student Thomas Ashford at the Rockefeller Institute. In January 1962 they reported an increased number of lysosomes in rat liver cells after addition of glucagon, and that some displaced lysosomes towards the centre of the cell contained other cell organelles such as mitochondria. They called this autolysis.

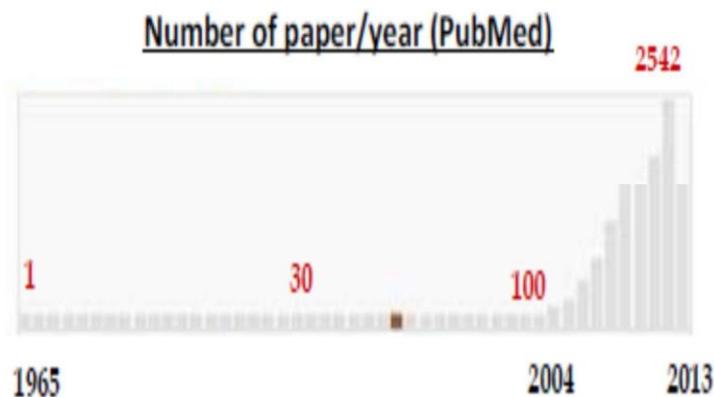


Figure 1: Chronology Graph

The **2016 Nobel Prize** in Physiology or Medicine is awarded to **Yoshinori Ohsumi** for his discoveries of mechanisms for autophagy. Macroautophagy (“self-eating”, hereafter referred to as autophagy) is an evolutionarily conserved process whereby the eukaryotic cell can recycle part of its own content by sequestering a portion of the cytoplasm in a double-membrane vesicles that is delivered to the lysosome for digestion

Although autophagy was recognized already in the 1960’s, the mechanism and physiological relevance remained poorly understood for decades. The work of Yoshinori Ohsumi dramatically transformed the understanding of this vital cellular process. In 1993, Ohsumi published his seminal discovery of 15 genes of key importance for autophagy in budding yeast. In a series of elegant subsequent studies, he cloned several of these genes in yeast and mammalian cells and elucidated the function of the encoded proteins. Based on Yoshinori Ohsumi’s seminal discoveries, the importance of autophagy in human physiology and disease is now appreciated.

The mystery of autophagy

In the early 1950’s, Christian de Duve was interested in the action of insulin and studied the intracellular localization of glucose-6-phosphatase using cell fractionation methods developed by Albert Claude. In a control experiment, he also followed the distribution of acid phosphatase, but failed to detect any enzymatic activity in freshly isolated liver fractions. Remarkably, the enzymatic activity reappeared if the fractions were stored for five days in a refrigerator. It soon became clear that proteolytic enzymes were sequestered within a previously unknown membrane structure that de Duve named the **lysosome**. Comparative electron microscopy of purified lysosome-rich liver fractions and sectioned liver identified the lysosome as a distinct cellular organelle. **Christian de Duve and Albert Claude, together with George Palade**, were awarded

the **1974 Nobel Prize in Physiology or Medicine** for their discoveries concerning the structure and functional organization of the cell.

Recognizing that the structures had the capacity to digest parts of the intracellular content, Christian de Duve coined the term **autophagy** in 1963, and extensively discussed this concept in a review article published a few years later. At that time, a compelling case for the existence of autophagy in mammalian cells was made based on results from electron microscopy studies. Autophagy was known to occur at a low basal level, and to increase during differentiation and remodeling in a variety of tissues, including brain, intestine, kidney, lung, liver, prostate, skin and thyroid gland. It was speculated that autophagy might be a mechanism for coping with metabolic stress in response to starvation and that it might have roles in the pathogenesis of disease. Furthermore, autophagy was shown to occur in a wide range of single cell eukaryotes and metazoa, e.g. amoeba, *Euglena gracilis*, *Tetrahymena*, insects and frogs, pointing to a function conserved throughout evolution.

During the following decades, advances in the field were limited. Nutrients and hormones were reported to influence autophagy; amino acid deprivation induced, and insulin stimulation suppressed autophagy in mammalian tissues. A small molecule, 3-methyladenine, was shown to inhibit autophagy. One study using a combination of cell fractionation, autoradiography and electron microscopy provided evidence that the early stage of autophagy included the formation of a double-membrane structure, the **phagophore**, that extended around a portion of the cytoplasm and closed into a vesicle lacking hydrolytic enzymes, the **autophagosome** (*Figure 1*).

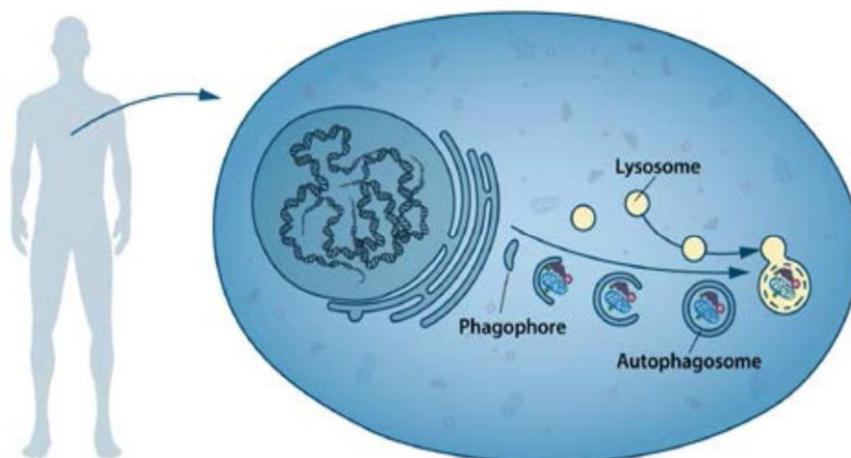


Figure 2: Formation of the autophagosome.

The phagophore extends to form a double-membrane autophagosome that engulfs cytoplasmic material. The autophagosome fuses with the lysosome, where the content is degraded.

In the early 1990's, almost 30 years after de Duve coined the term autophagy, the process remained a biological enigma. Molecular markers were not available and components of the autophagy machinery were elusive. Many fundamental questions remained unanswered: How was the autophagy process initiated? How was the autophagosome formed? How important was autophagy for cellular and organismal survival? Did autophagy have any role in human disease?

Discovery of the autophagy machinery

In the early 1990's Yoshinori Ohsumi, then an Assistant Professor at Tokyo University, decided to study autophagy using the budding yeast *Saccharomyces cerevisiae* as a model system. The first question he addressed was whether autophagy exists in this unicellular organism. The yeast vacuole is the functional equivalent of the mammalian lysosome. Ohsumi reasoned that, if autophagy existed in yeast, inhibition of vacuolar enzymes would result in the accumulation of engulfed cytoplasmic components in the vacuole. To test this hypothesis, he developed yeast strains that lacked the vacuolar proteases proteinase A, proteinase B and carboxy-peptidase¹⁹. He found that autophagic bodies accumulated in the vacuole when the engineered yeast were grown in nutrient-deprived medium¹⁹, producing an abnormal vacuole that was visible under a light microscope. He had now identified a unique phenotype that could be used to discover genes that control the induction of autophagy. By inducing random mutations in yeast cells lacking vacuolar proteases, Ohsumi identified the first mutant that could not accumulate autophagic bodies in the vacuole²⁰; he named this gene autophagy 1 (*APG1*). He then found that the *APG1* mutant lost viability much quicker than wild-type yeast cells in nitrogen-deprived medium. As a second screen he used this more convenient phenotype and additional characterization to identify 75 recessive mutants that could be categorized into different complementation groups. In an article published in *FEBS Letters* in 1993, Ohsumi reported his discovery of as many as 15 genes that are essential for the activation of autophagy in eukaryotic cells. He named the genes *APG1-15*. During the following years, Ohsumi cloned several *ATG* genes and characterized the function of their protein products.

Process and Pathways of Autophagy^[4-6]

How Autophagy Takes Place in a Cell

The process of autophagy is initiated in response to molecular triggers that indicate damage, starvation, oxidative stress, or pathogenic invasion. The components to be recycled are marked and targeted for degradation by lysosomes. These are small spherical organelles that comprise an acidic interior containing a set of digestive enzymes.

Once the autophagosome is formed, the proteins that participated in building the membrane are released into the cytosol. These proteins are then free to assist the formation of new phagophores, whenever required.

The function of this autophagosome is to fuse with, and deliver the cargo into the lysosomes. The outer layer of the autophagosome membrane fuses with the lysosomal membrane, thus, releasing a single-layered vesicle into the lysosome. The digestive enzymes present in the lysosomes degrade the single-layered membrane, and the lysosome is now termed as **autolysosome**.

The inner cargo is now exposed to the lytic enzymes, like proteases, lipases, and hydrolases. These enzymes break down the cargo into basic building blocks, like amino acids, sugars, other carbohydrate moieties, as well as certain lipid molecules. These are then released into the cytosol for building new molecules, and they are used as an energy source to fuel metabolic processes of the cells.

Microautophagy

This mechanism of autophagy involves the direct entry of targeted cellular components into the lysosomes. Cytosolic molecules, like glycogen, protein aggregates, misfolded proteins, and organelles may be degraded through microautophagy.

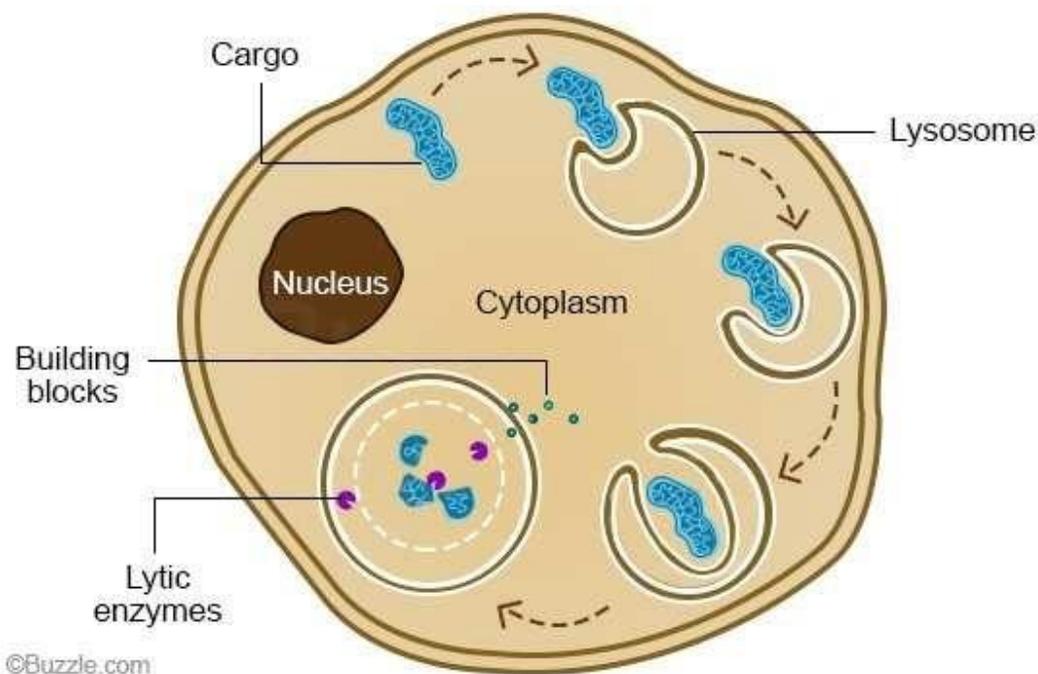


Figure 4: Microphagy

The process begins with the formation of tubular invagination of the lysosome. The lysosomal membrane forms tube-like projections that surround the targeted molecule or organelle. The surrounding membrane projections fuse together to form an intralysosomal vesicle that contains

the cargo. The lytic enzymes can now degrade this cargo, and the building blocks are released into the cytosol. A special case of microautophagy is micronucleophagy or piecemeal microautophagy of the nucleus, during which a part of the nucleus is sequestered and degraded.

Role

Microautophagy together with macroautophagy is necessary for nutrient recycling under starvation. as one of the mechanism of glycogen delivery into the lysosomes. it plays role in membrane proteins turnover. Microautophagy is also connected with organellar size maintenance, composition of biological membranes, cell survival under nitrogen restriction.

Chaperone-mediated Autophagy (CMA)

This route of autophagy functions to degrade only a specific set of misfolded, or erroneously formed cytosolic proteins. The proteins are identified and guided into the lysosome through cytosolic molecular assistants called chaperone.

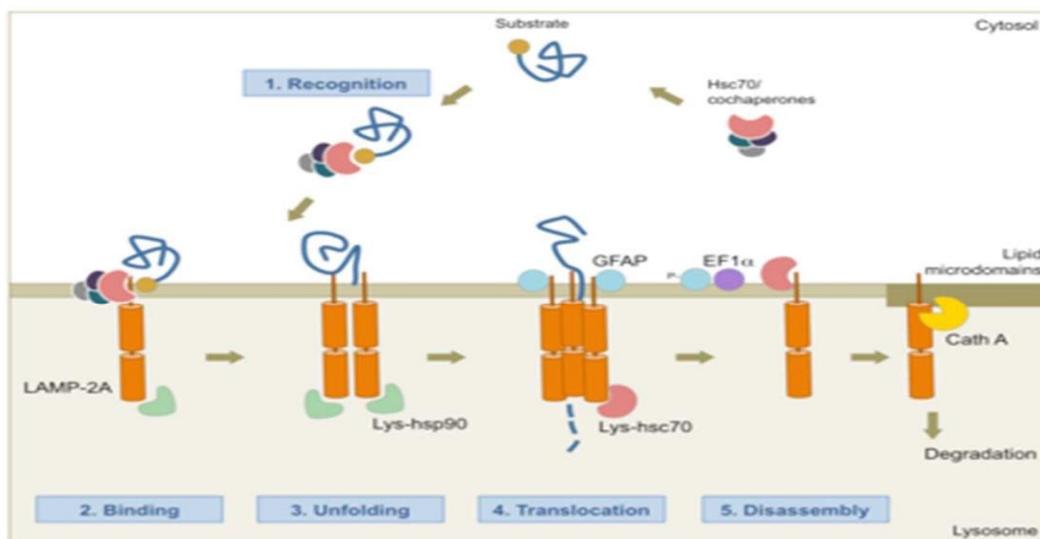


FIGURE 1. Steps of CMA. 1) Recognition of KFERQ-motif bearing substrate proteins by hsc70/cochaperones in the cytosol. 2) Binding of substrate-chaperone complex to LAMP-2A monomer. 3) Unfolding of the substrate. 4) LAMP-2A multimerization, substrate translocation and subsequent degradation. 5) Disassembly of LAMP-2A multimer/translocon. LAMP-2A monomers are degraded in lipid microdomains.

The proteins to be degraded through the CMA contain a unique motif that is biochemically related to the pentapeptide KFERQ. When the protein is not correctly folded, or is damaged, this motif gets exposed and is recognized by a molecular chaperone called hsc70 (heat shock cognate protein of 70KDa). Hsc70 binds to this unique motif and guides the protein, or CMA substrate, to the lysosomal surface.

The lysosomal surface has a protein called lysosome-associated membrane protein type 2A (LAMP-2A), embedded into its membrane. This protein serves as a receptor for the substrate-hsc70 complex.

Once the substrate-hsc70 complex binds to the LAMP-2A monomer, hsc70 as well as other membrane molecules and chaperones, like hsp90 (heat shock protein 90) unfold the substrate protein. Also, the LAMP-2A protein undergoes conformational changes and multimerization to form a hollow, cylindrical transport structure called CMA translocation complex.

The unfolded substrate passes through the translocation complex and enters the lysosomal lumen. A variant of the hsc70, called lysosomal hsc70, is present in the lumen of the lysosome. It helps in pulling the substrate inside the lysosome, and it also prevents it from returning to the cytosol. Once the substrate passes into the lysosomal lumen, the CMA translocation complex is immediately disassembled by hsc70, hsp 90, and other proteins present at the lysosomal membrane. The substrate is degraded by proteases present in the lumen, and the resultant amino acids are released into the cytosol.

Role

- energetic cellular balance
- to cellular quality control
- CMA is essential for T cell activation through the degradation of negative regulators of T cell activation (Itch, RCAN1)

Mitophagy

It is the selective degradation of mitochondria by autophagy. It often occurs to defective mitochondria following damage or stress. Mitophagy promotes turnover of mitochondria and prevents accumulation of dysfunctional mitochondria which can lead to cellular degeneration. It is mediated by Atg32 (in yeast) and NIX and its regulator BNIP3 in mammals. Mitophagy is regulated by PINK1 and parkin proteins. The occurrence of mitophagy is not limited to the damaged mitochondria but also involves undamaged ones.

APPLICATIONS OF AUTOPHAGY^[7]

Autophagic degradation of cytoplasmic components is essentially non-selective, but can also be selective. Non-selective (bulk) autophagy is important for starvation adaptation, whereas selective autophagy may be more important for maintaining homeostasis of cytosolic proteins and organelles, although these two categories are not mutually exclusive. Autophagy has also been implicated in pathological conditions including neurodegenerative diseases, cancer, and inflammatory diseases. Modulation of autophagy has become a potentially interesting therapeutic target in human diseases.

Autophagy in Cancer^[8]

Autophagy and Cancer

Dual Role:

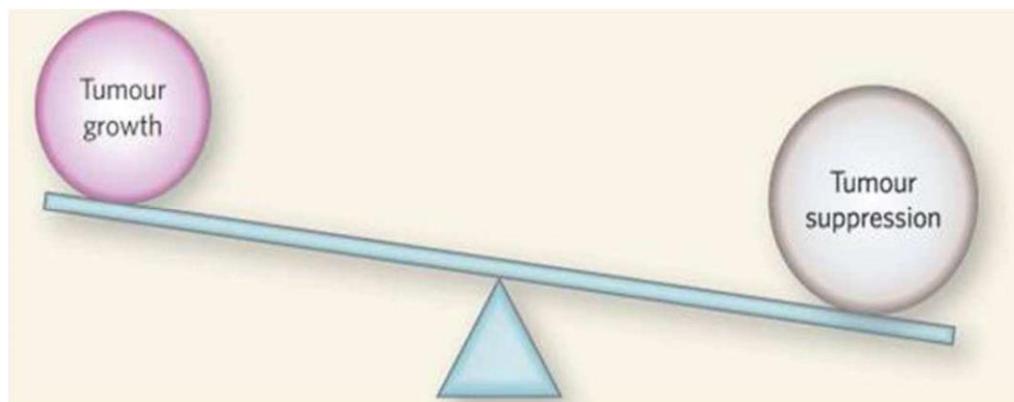


Figure 6: Autophagy Role

Autophagy act in twofold way that is it promote Tumour growth as well as shows mechanism of Tumour suppression.

Autophagy in tumor suppression

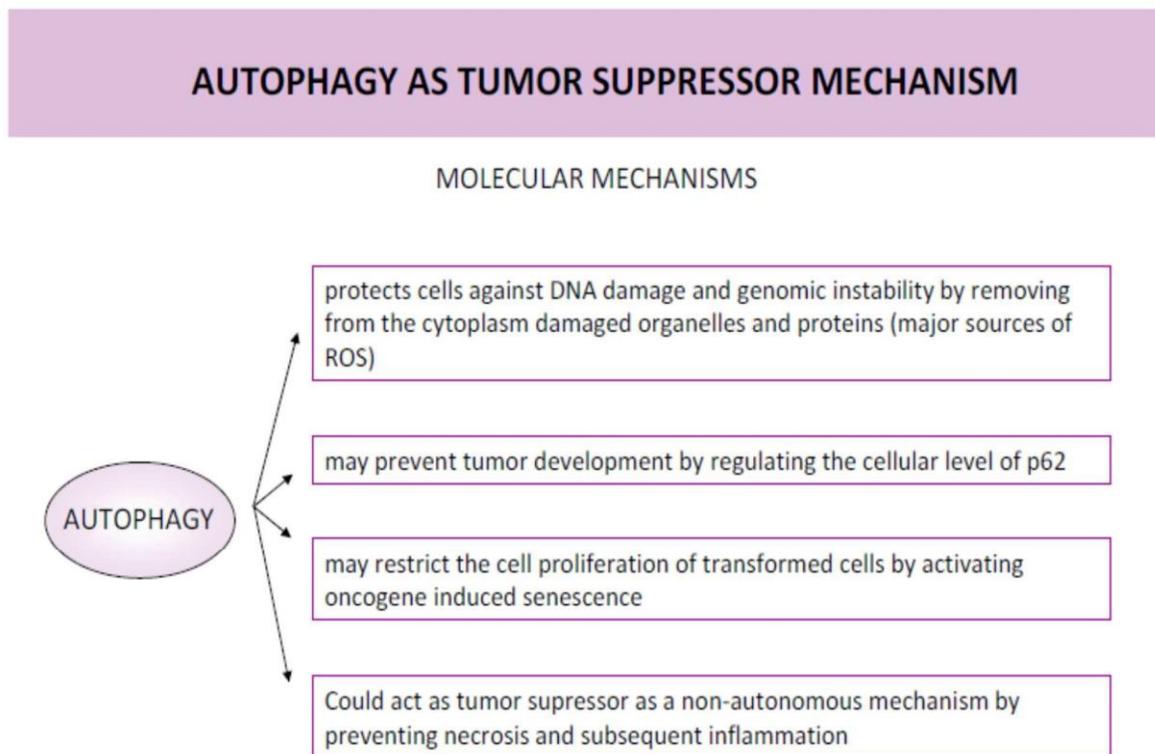


Figure 7 Autophagy Mechanism

Autophagy is a homeostatic mechanism that when disrupted, can promote and accelerate tumorigenesis. Autophagy functions as a tumor suppression mechanism by removing damaged

organelles/proteins and limiting cell growth and genomic instability. Beclin 1 is a protein required for autophagy induction and *Beclin 1*^{+/-} mice were shown to be tumor-prone indicating that *Beclin 1* is a haplo insufficient tumor suppressor gene. In contrast, excessive stimulation of autophagy due to Beclin 1 over expression can inhibit tumor development. A potential molecular link between defective autophagy and tumorigenesis involves the accumulation of p62/SQSTM 1 protein aggregates, damaged mitochondria, and misfolded proteins that lead to the production of reactive oxygen species (ROS) to cause DNA damage that can lead to genomic instability. Knockdown of p62/SQSTM 1 in autophagy defective cells prevented ROS and the DNA damage response. The relationship between defective autophagy and p62/SQSTM 1 accumulation with tumorigenesis was also shown in *p62/SQSTM 1*^{-/-} mice were protected from *Ras*-induced lung carcinomas compared to wild-type animals. Autophagy may also protect against tumorigenesis through limiting necrosis and chronic inflammation that are associated with the release of proinflammatory HMGB1. Together, these findings establish a role for autophagy as a mechanism of tumor suppression.

Autophagy Modulation for Cancer Therapy

Autophagy inhibitors

Multiple studies have shown that genetic knockdown of autophagy-related genes (Atgs) or pharmacological inhibition of autophagy can effectively enhance tumor cell death induced by diverse anti-cancer drugs in preclinical models. Inhibition of autophagy in preclinical models improves response to alkylating agents in tumor cells. In apoptosis-defective leukemic and colon cancer cell lines, inhibition of autophagy was shown to sensitize resistant cells to TRAIL-mediated apoptosis. Furthermore, inhibition of autophagy enhanced apoptosis induction by cetuximab, an antibody against the epidermal growth factor receptor (EGFR).

Pharmacological inhibitors of autophagy can be broadly classified as early versus late stage inhibitors of the pathway. Early stage inhibitors include 3-methyladenine (3-MA), wortmannin, and LY294002 that target the class III PI3K (Vps34) and interfere with its recruitment to the membranes. Late stage inhibitors include the anti-malarial drugs chloroquine (CQ) or hydroxychloroquine (HCQ), bafilomycin A1, and monensin. Bafilomycin A1 is a specific inhibitor of vacuolar-ATPase while monensin and CQ/HCQ are lysosomotropic drugs that prevent acidification of lysosomes whose digesting hydrolases depend on low pH. Auto phagosomes and lysosomes move along microtubules and microtubule disrupting agents (taxanes, nocodazole, colchicine, vinca alkaloids) inhibit fusion of auto phagosomes to lysosomes. Other inhibitors of

autophagy that block autophagosome degradation include the tricyclic antidepressant drug, clomipramine, and anti-schistosome agent, lucanthone.

The ability of autophagy inhibition to enhance chemo sensitivity and tumor regression has been confirmed in animal models. In a Myc-induced murine lymphoma model, inhibition of autophagy by CQ was shown to enhance cyclophosphamide-induced tumor cell death to a similar extent as did shRNA knockdown of *Atg5*, and delayed the time-to-tumor recurrence. In a colon cancer xenograft model, the addition of CQ to vorinostat was shown to significantly reduce tumor burden and to increase apoptosis. Similarly, CQ enhanced the therapeutic efficacy of the Src inhibitor, saracatinib, in a prostate cancer xenograft mouse model. Saracatinib decreased tumor growth by 26% compared to control-treated mice, and CQ plus saracatinib further inhibited tumor growth by 64%. This combination also led to at least a 2-fold increase in the number of apoptotic tumor cells in the group treated with saracatinib plus CQ, suggesting that suppression of autophagy drives cells into apoptosis. Autophagy inhibition by 3-MA increased apoptosis induction by 5-fluorouracil (5-FU) in association with tumor regression in colon cancer xenografts. These data indicate that autophagy inhibition can enhance the antitumor efficacy of chemotherapeutic agents that utilize diverse cellular mechanisms. Of the known autophagy inhibitors, only CQ/HCQ have been evaluated in humans given their common usage as anti-malarial drugs and in autoimmune disorders. These drugs cross the blood-brain barrier, and HCQ is preferred to CQ in humans given its more favorable side effect profile.

Based upon preclinical data, several phase I/II trials are ongoing that evaluate the combination of HCQ with cytotoxic drugs in a variety of tumor types. Challenges include the long half-life of HCQ and the need for micromolar concentrations to inhibit autophagy that may limit its efficacy in human studies. A recently reported Phase I trial of HCQ in combination with adjuvant temozolamide and radiation in patients with glioblastoma found that the maximum tolerated dose (MTD) of HCQ was 600 mg a day and this dose achieved concentrations of HCQ required for autophagy inhibition in preclinical studies. In this trial, dose-dependent autophagy inhibition was observed as indicated by increases in autophagic vesicles (by electron microscopy) with confirmatory elevations in LC3-II detected in peripheral blood mononuclear cells (PBMCs). In a phase I trial of 2-deoxyglucose, an agent that blocks glucose metabolism, autophagy occurred in association with a reduction in p62/SQSTM1 in PBMCs. These biomarker data suggest the potential for evaluating autophagy modulation during therapy and to correlate with treatment outcome.

Intracellular proteins are degraded within lysosomes during autophagy and by the ubiquitin-proteasome pathway. Given the primary role of these pathways in protein degradation, it has been postulated that their combined blockade may lead to ER stress-induced cytotoxicity through the accumulation of unfolded protein aggregates that can activate autophagy through JNK or PERK/eIF2 α . The combination of bortezomib and CQ was shown to suppress tumor growth to a greater extent than did either drug alone in colon cancer xenografts. Phase I/II clinical trials evaluating this combination are ongoing in patients with relapsed/refractory multiple myeloma.

Targeting Autophagy for Cancer Prevention

Since autophagy plays a role in tumor suppression, the induction of autophagy may be an important strategy for cancer prevention. PI3K-AKT-mTOR signaling is frequently dysregulated in human tumors and the inhibition of mTOR signaling can induce autophagy. In accordance with this observation, treatment with the mTOR inhibitor rapamycin was associated with a 90% reduction in carcinogen-induced lung tumors in a murine model. In another study, inhibition of mTOR signaling by metformin attenuated tumorigenesis in the same tumor model. Furthermore, continuous, low dose rapamycin treatment in APC^{Min/+} mice with enhanced AKT-mTOR signaling was shown to markedly inhibit intestinal neoplasia. Defective autophagy has been linked to colonic tumor formation through a mechanism involving the aberrant activation of Wnt signaling from impaired degradation of disheveled (Dvl) by autophagy. Other pharmacological activators of the autophagy may also be of potential benefit for cancer chemoprevention and further studies are awaited.

AUTOPHAGY IN PARKINSON'S DISEASE [8]

Great progress has been made toward understanding the pathogenesis of Parkinson's disease (PD) during the past two decades, mainly as a consequence of the discovery of specific gene mutations contributing to the onset of PD. Recently, dysregulation of the autophagy pathway has been observed in the brains of PD patients and in animal models of PD, indicating the emerging role of autophagy in this disease. Indeed, autophagy is increasingly implicated in a number of pathophysiological conditions, including various neurodegenerative diseases. Here in this point the connection between autophagy and PD by introducing the concept and physiological function of autophagy, and the proteins related to autosomal dominant and autosomal recessive PD, particularly α -synuclein and PINK1-PARKIN, as they pertain to autophagy will come to know.

There seem to be various causes of Parkinson's disease (PD), yet the pathogenesis of this disease appears to be converging on common themes—oxidative stress, mitochondrial dysfunction, and protein aggregation—all of which are tightly linked to autophagy, a highly conserved cellular

homeostatic process essential for bulk degradation of cytoplasmic contents. In particular, the recent identification of autosomal dominant and autosomal recessive mutations in familial PD has revealed the involvement of the corresponding gene products in autophagy. Although autophagy has commonly been regarded as an adaptive response to nutrient deprivation, increasing evidence indicates that basal, constitutive autophagy is essential for neuronal survival and that its dysregulation leads to neurodegeneration

Physiological Functions and Connections to PD

Although autophagy is primarily a starvation response in yeast, in higher eukaryotic organisms, autophagy is involved in a wide range of physiological and pathological processes, including responses to nutrient deprivation, development, intracellular clearance, suppression of tumor formation, aging, cell death and survival, and immunity. As a primary protective mechanism that maintains nutrient and energy homeostasis in response to stress, dysregulation of autophagy underlies the pathophysiology of many diseases. Increasing evidence suggests that dysregulation of autophagy results in the accumulation of abnormal proteins and/or damaged organelles, which is commonly observed in neurodegenerative diseases, such as Alzheimer, Huntington's, and Parkinson's diseases. Of note, autophagy is the only known mechanism that eukaryotic cells possess to degrade protein aggregates and damaged organelles that cannot be processed by the proteasome. Recent studies from transgenic mice, animal, and cell models of PD suggest the involvement of proteins genetically linked to autosomal dominant PD, particularly α -synuclein and LRRK2, in the autophagy pathway. In addition, proteins related to recessive PD, such as PINK1 and PARKIN, have an important role in the process of mitophagy.

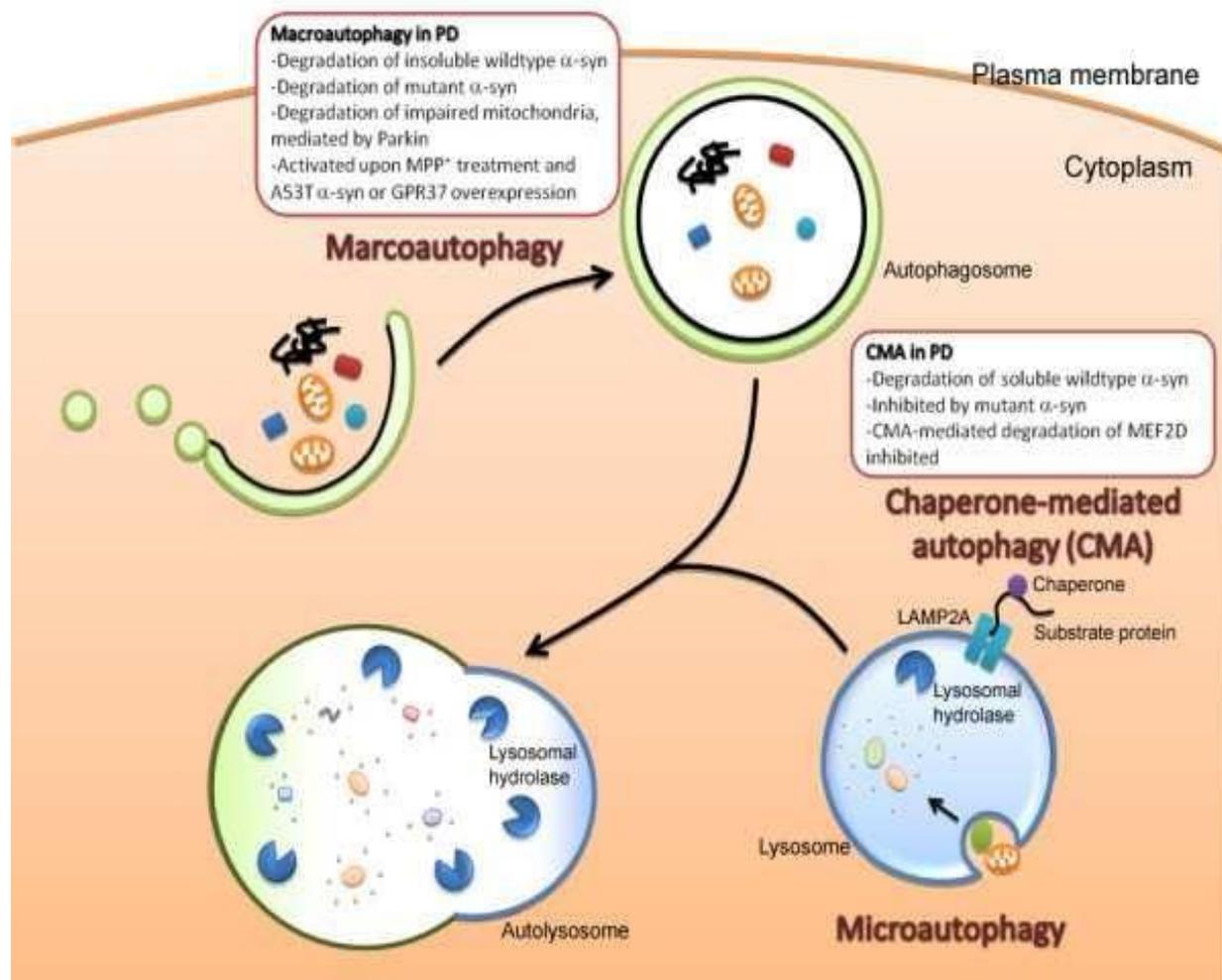


Figure 10 : Autophagy in Parkinson's disease

α -Synuclein and PD

α -Synuclein was found to localize to the presynaptic terminals in the central nervous system and is involved in vesicular release. It is a natively unfolded protein, but can be found in several abnormal conformational states including an oligomer, a protofibril, and an amyloid fibril. α -Synuclein was identified as a component of Levy bodies, cytosolic inclusions that are a pathological trait of PD. Studies of familial cases of autophagy reveal two separate autosomal dominant mutations in the α -synuclein gene: A53T and A30P. In addition to the point mutations, several post translational modifications such as phosphorylation, ubiquitination, nitration, oxidation, and dopamine-dependent adduct formation also create toxic forms of the pro

FUTURE PROSPECTS ^[9]

EARLY DISCOVERIES: α -SYNUCLEIN AND AUTOPHAGY

α -Synuclein and Autophagy

As noted previously, inhibition of CMA by aberrant α -synuclein leads to an increase in autophagy. This appears to be a compensatory response, but rather than leading to cell survival, the induction of autophagy can be harmful causing autophagic cell death. Blocking autophagy by knocking down the autophagy protein Atg5 in cells expressing the A53T α -synuclein mutant can rescue the cell from toxicity-induced cell death. However, autophagy-induced neuronal death is not always the outcome. One study suggests that the signaling pathway for activation of autophagy may be important as to whether or not autophagy will be protective or harmful. Autophagy is mainly initiated through the mTOR signaling pathway either directly or indirectly through the autophagy protein Atg1. An additional signaling pathway for initiation of autophagy is the Vps34-Beclin 1 complex. It is this secondary signaling pathway that appears to promote cell survival. For example, a reduction in α -synuclein accumulation is seen when Beclin 1 is overexpressed. In addition, Beclin 1 overexpression decreases cell death and increases autophagy activity observed through enhanced lysosomal degradation.

Recent Studies: Controversies Abound

In this section, we will discuss new yet controversial areas of research with regard to PD and autophagy. Recent studies have focused on the hypothesis of mitochondrial dysfunction as a cause of the disease. These studies have resulted in some interesting data, but to doubt there is no clear indication as to whether mitochondrial dysfunction is a cause of Parkinson or is rather correlated with the progression of the disease.

Basic Science Research and Clinic Treatment

Based on the significant roles of mitochondria and autophagy in PD, maintaining and stabilizing mitochondrial function or promoting the degradation of damaged mitochondria might benefit the protection of dopaminergic neurons. Data on the possible connection between defects in mitophagy and PD suggest that modulation of autophagy might be one avenue for treating some types of this disease. However, autophagy is described as a double-edged sword, because both reduced and excessive autophagy can be harmful; therefore, simply upregulating autophagy is not a practical course of action, and the application of autophagy-inducing drugs must be undertaken.

CONCLUSION

Autophagy serves a dual role as a mechanism of tumor suppression and as an adaptive stress response in tumor cells to maintain their survival in the setting of increased metabolic demands, a hypoxic microenvironment, or cancer therapy. Maintenance of cell survival by autophagy can

promote the growth of established tumors. Abundant preclinical evidence indicates that stress-induced autophagy in tumor cells is predominantly cytoprotective and that inhibition of autophagy can enhance tumor cell death by diverse anti-cancer therapies. These data establish autophagy as a novel therapeutic target whose modulation presents new opportunities for cancer treatment. While several drugs can inhibit autophagy, most lack specificity and anti-tumor activity. Chloroquine is the most widely tested in preclinical models and multiple ongoing phase I and II clinical trials are evaluating hydroxychloroquine alone or in combination with cytotoxic chemotherapy or targeted agents, mostly in patients with solid tumors. Targeting autophagy in cancer provides new opportunities for drug development since more potent and specific inhibitors of autophagy are clearly needed. High-throughput screening of chemical libraries to identify small molecule inhibitors of autophagy is ongoing. Biomarkers to measure autophagy modulation during treatment should be an important component of drug development efforts. While important strides have been made, several key questions remain unanswered and include how autophagy is regulated in tumor cells, its interplay with apoptosis, and the specific mechanism by which autophagy confers treatment resistance. An increased understanding of autophagy in cancer is important for its optimal exploitation for therapeutic advantage. Given the role of autophagy in tumor suppression, activation of autophagy may be an important strategy for cancer chemoprevention with extreme caution.

REFERENCES:

1. Kobayashi S (2015). "Choose Delicately and Reuse Adequately: The Newly Revealed Process of Autophagy". *Biological & Pharmaceutical Bulletin*. **38** (8): 1098–103. doi:10.1248/bpb.b15-00096. PMID 26235572
2. Arstila, A.U., and Trump, B.F. (1968) Studies on cellular autophagocytosis. The formation of autophagic vacuoles in the liver after glucagon administration. *Am J Pathol* 53, 687–733.
3. Matsuura, A., Tsukada, M., Wada, Y., and Ohsumi, Y. (1997) Apg1p, a novel protein kinase required for the autophagic process in *Saccharomyces cerevisiae*. *Gene* 192, 245–250.
4. Harding, TM; Hefner-Gravink, A; Thumm, M; Klionsky, DJ (26 July 1996). "Genetic and phenotypic overlap between autophagy and the cytoplasm to vacuole protein targeting pathway". *The Journal of Biological Chemistry*. **271** (30): 17621–4. doi:10.1074/jbc.271.30.17621. PMID 8663607.

5. Česen MH, Pegan K, Spes A, Turk B (July 2012). "Lysosomal pathways to cell death and their therapeutic applications". *Exp. Cell Res.* **318** (11): 1245–51. doi:10.1016/j.yexcr.2012.03.005. PMID 22465226.
6. Bandyopadhyay U, Kaushik S, Varticovski L, Cuervo AM (September 2008). "The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane". *Mol. Cell. Biol.* **28** (18): 5747–63. doi:10.1128/MCB.02070-07. PMC 2546938 . PMID 18644871.
7. Banerjee R, Beal MF, Thomas B 2010. Autophagy in neurodegenerative disorders: Pathogenic roles and therapeutic implications. *Trends Neurosci* 33: 541–549.
8. Lynch-Day MA, Bhandari D, Menon S, Huang J, Cai H, Bartholomew CR, Brumell JH, Ferro-Novick S, Klionsky DJ 2010. Trs85 directs a Ypt1 GEF, TRAPPIII, to the phagophore to promote autophagy. *Proc Natl Acad Sci* 107: 7811–7816.
9. Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P, Rizzuto R 2009. Mitochondria, calcium and cell death: A deadly triad in neurodegeneration. *Biochim Biophys Acta* 1787: 335–344.

AJPTR is

- Peer-reviewed
- bimonthly
- Rapid publication

Submit your manuscript at: editor@ajptr.com

