Autophagy related genes mediated mitophagy in yeast, mammals and higher plants

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Article Info

Abstract

Autophagy is classified into macro-autophagy and micro-autophagy. Two major types of autophagy in the complex eukaryotic organism are microautophagy and macroautophagy. During microautophagy, cytoplasmic components that need to be degraded are taken up by lysosomes in animals and by vacuole in yeast and plants via the invagination of tonoplast. While macroautophagy is initiated after the formation of a cup-shaped membrane structure, a phagophore develops at cargo that grows in size and is sealed by double-membrane vesicles to form autophagosome; a generalized mechanism for degradation of the organelle. Autophagic removal of damaged mitochondria is a conserved cellular process to maintain a healthy mitochondrion called Mitophagy. In plants and animals, mitophagy has crucial roles in stress responses, senescence, development, and programmed cell death. Mitophagy appears in mammals, fungi, and plants but many genes that controlled mitophagy are absent from plants. Numerous studies have been conducted by using ATG mutants for the identification of functional roles of Autophagy Related Genes (ATG) required during the autophagy process at various steps like; auto phagosome formation, ATG protein recruitment, etc. The role of more than 25 ATG genes in mitophagy has been discussed in this review paper. The main parameters, reviewed and summarized in this review paper, are the name of species, common name, function, domain, deletion, induction, and localization of these autophagy-related genes in the cell. This review will facilitate the students, researchers, and academics for their further research insights.

Keywords: Mitochondria, Autophagy, Proteins, Mitophagy.

1. Introduction

Autophagy is a natural conserved regulated mechanism of the higher cellular organisms that degrade and removes unnecessary and dysfunctional organelles and alerts the degeneration of cytoplasmic components which results in the regulation of the physiological functions of the cell [1-3]. When cells suffer stress conditions or any damage occurs to organelle, those cytoplasmic components are identified and isolated within double membraned vesicles called autosomes from other cellular constituents [4]. For identification of the genetic mechanism involved in the formation of autophagosomes major event of autophagy initiation, the first research was conducted in Saccharomyces cerevisiae which leads to the identification of the first ATG gene [5-7]. Today 36 ATG proteins belonging to the core machinery of autophagy have been identified and grouped on the basis of their functional role in autophagy [8]. In general, autophagy is induced upon exposure to starvation conditions to support cell survival after generating biomolecules from the degradation of cell organelles and protein aggregates [2, 9]. Based on the cause of induction autophagy is classified into two categories selective autophagy or non-selective autophagy. Cells undergo non-selective autophagy during stress conditions of nutrient starvation and adverse environmental effects to provide cells with nutrients by degrading cytoplasmic components. Whereas selective autophagy is a normal cellular mechanism of clearance during which degradation of misfolded protein aggregates, damaged, degraded and excess cytoplasmic organelle occurs [10]. During the 1990s in yeast, a comprehensive mechanism of autophagy induction has been deduced by the researcher after the identification of several ATG proteins [11-13]. Discovered genes upon their specific role in autophagy were abbreviated as ATG following unified nomenclature by the researcher [14]. In yeast species, only, more than 40 ATG genes have been discovered through mutant analysis (deletion). Homology-based studies also revealed that several ATG genes are conserved in yeast and plants and a few ATG mutants are also developed through exploiting forward genetic techniques in Arabidopsis thaliana [15].

The major event in autophagy is the formation of autophagosomes that translocate membraned cargo bodies to lysosome or vacuole where it is degraded by lysosomal enzymes. Furthermore, mutant analysis studies of the ATG genes showed that several ATG genes were found to

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have a specific role in the formation of autophagosomes [9]. Upstreaming signaling elements for elucidation of the molecular regulation of plant autophagy is still lagging [16]. Carl Benda discovered mitochondria in 1898, a double membrane-bounded organelle present in most eukaryotic organisms that supplies adenosine triphosphate (ATP) in most of the cells, used as a source of chemical energy. In addition to ATPs, mitochondria are also involved in the synthesis of reactive oxygen species (ROS), the highest level of which was found to facilitate aging and several disease processes [17, 18]. Therefore, the health of mitochondria is the key factor that determined the level of ROS production. Any comptonization in mitochondrial health affects cellular bioenergetics, disrupts signalling pathways, and increases ROS production [17]. In yeast and mammalian cell, several proteins of the ATG series (ATG11) were found to interact with mitochondria during oxidative stress and cellular differentiation to facilitate mitochondrial degradation [19-21].

2. Mitophagy in yeast, animals and plant cells

The mitochondrial selective deterioration process by self-eating is called Mitophagy. Following damage or stress, it exclusively happens to faulty mitochondria. Wassen Horman Lewis first described it over a hundred years before. The term mitophagy was coined by John Lemasters, who analyzed that depolarized mitochondria entered into acidic lysosomal compartments of cells in hepatocytes [22, 23]. Maintenance of a healthy quantity and quality of mitochondria is a conserved cellular process in many organisms as in fungi, plants, and animals achieved via the process of autophagic removal of degraded mitochondria [10].

In yeast, deficiency of the mitophagy process was found to associate with the production of ROS species and dysfunctional mitochondria on exposure to nutrient starvation conditions [24, 25]. For example, in S. pombe, nitrogen starvation causes proteasome inactivation that leads to autophagy-dependent mitochondrial degradation [26]. In yeast regulation of mitochondrial quality and quantity is necessary to maintain the balance of energy production and to suppress the production of ROS via mitophagy. As in the ATG32 deficient mutants that grew under starvation conditions resulted in the shortening of the life span of yeast cells [27]. Therefore, mitophagy involves in the maintenance of a healthy population and the longevity of mitochondrial life. Some of these genes that involve mitophagy in yeast species are given in Table 1.

Human mitophagy has an important role in the pathogenesis of several diseases like cancer, diabetes, atherosclerosis, muscular dystrophy, alzheimer’s, and hepatic steatosis diseases [76]. Mitophagy plays a key role in regulating mitochondrial quality and quantity by eliminating the damaged mitochondria. Any defects in the process of mitophagy result in the accumulation of dysfunctional and damaged mitochondria in the cells which leads to aging and aging-related disorders in mammals [77-79]. Whereas, the accelerated rate of mitophagy effectively ameliorates mitochondrial dysfunction and toxicity of cells in diseases like diabetes and Parkinson’s disease [80, 81]. Using Caenorhabditis elegans (C. elegans) and mouses as modal organisms various studies showed that enhanced activity of mitophagy successfully increased the health and life span of animals [82, 83]. Furthermore, studies also revealed that impaired mitophagy is the reason of several diseases of the liver including both alcoholic and nonalcoholic, drug-induced and liver cancer [84-86]. The latest molecular studies of the ATG13-ATG101 structure revealed various unique sites of interaction like conserved WF fingers and hydrophobic pockets specific to animals [87]. In Table 2 list of ATG genes that are involved specifically in mitophagy is given with their functions and structural domains.

In plants mechanism of autophagy is strictly regulated by the nutritional status, upon exposure to nutrient starvation, the concentration of phosphoproteins of ATG proteins declines dramatically and rises when nutrients are added. These fluctuations occur due to the inhibition of the ATG system, suggesting the significance of ATG complexes in autophagy (34). In plant species, carbon starvation causes mitophagy through the breakdown of the mitochondrial network which results in punctuated mitochondria; this mitophagy is specifically mediated by ATG proteins (44). In Table 3, ATG genes that are specifically related to mitophagy and found in plant species are given their important features.

3. ATG genes dependent mechanism of mitophagy

Macro autophagy is the principal mechanism of removing damaged and aged cellular organelles in which the damaged organelle are engulfed by phagophore following the formation of double-membrane vesicles autophagosomes around it; this autophagosome then degraded by lysosomal The autophagosome then transferred to the vacuole in yeast and plants, or to lysosome in animals [100-102]. Two organelles fuse within the lysosome vacuole/vacuoles and connect to the autophagosome, which is degraded by lysosomal enzyme hydrolase [103].

Various natural compounds are involved in controlling mitophagy through the regulation of proteins which intern involved in the modulation of mitochondrial oxidative phosphorylation, ROS production and transcriptional factors activation [76]. Mitophagy, a conserved bulk degradation system in eukaryotes retains the cell healthy and stops the gathering of dysfunctional mitochondria that can level to cell for degeneration and boost the ratio of mitochondria. The process of autophagy is a bulk degradation system that is conserved in all eukaryotes [97]. For example, ATG16 as a multimeric complex that is required in the biogenesis of autophagosomes in mammals. During bulk and starvation-induced autophagy, ATG5 binds to specific N-terminal sites of the ATG16L1 and ATG16 in mammals and yeast respectively [104]. Moreover, a single-nucleotide variant of ATG16 was also found to have an association with the development of Crohn's disease during a pathogen attack [98]. The process of macro-autophagy not only removes damaged mitochondria it can also degrade and removes healthy mitochondria [105]. ATG genes with their respective role in the mechanism of mitophagy are reviewed in the following section.

3.1. Mitophagy receptor

In yeast, it has been observed that ATG32 place an essential role in mitophagy as a receptor protein [49, 50]. ATG32 protein localizes on the outer mitochondrial
### Table 1. ATG genes function during mitophagy in Yeast.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Species</th>
<th>Common Name</th>
<th>Function</th>
<th>Domain</th>
<th>Deletion</th>
<th>Induced</th>
<th>Localized</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG11</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Recruit the autophagosome to mitochondria &amp; adaptor linking cargo to the autophagosome</td>
<td>Third coiled coil</td>
<td>Does not abrogate the delivery of n-Rosella to vacuole cytoplasm POMC (pro-opiomelanocortin) neurons autophagy-deficient</td>
<td>Glucose starvation-induced autophagy</td>
<td>Protein localization to the phagophore assembly site</td>
<td>(28-31)</td>
</tr>
<tr>
<td>ATG12</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Apoptosis</td>
<td>C-terminal 40 amino acids</td>
<td></td>
<td>DNA damaged suppressor</td>
<td>Phagophore membrane</td>
<td>(31-33)</td>
</tr>
<tr>
<td>ATG13</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Protein kinase regulator activity</td>
<td>Containing HORMA forms a heterodimer with ATG101</td>
<td>Growth retardation and myocardial growth defects</td>
<td>Self-dimerization enhances kinase activity</td>
<td>Cytosol</td>
<td>(34, 35)</td>
</tr>
<tr>
<td>ATG17</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Enables molecular adaptor &amp; protein kinase activator activity, SNARE binding</td>
<td>Lack dimerization</td>
<td>Leading to a model for the PAS</td>
<td>Efficient induction of nonselective autophagy</td>
<td>PAS</td>
<td>(27, 36-38)</td>
</tr>
<tr>
<td>ATG20</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Fine-tuned by phosphorylation and acetylation Uses membrane-binding modules</td>
<td>Contain putative BAR, (Bin-Amphipysin-Rvs)-domain,</td>
<td>Reduction, but not complete loss, of Atg11.</td>
<td></td>
<td></td>
<td>(39-41)</td>
</tr>
<tr>
<td>ATG23</td>
<td>G. zeae</td>
<td>Wheat head blight fungus</td>
<td>Regulation of filamentous growth</td>
<td>AAA</td>
<td>Reduction in amount of mature Ape1</td>
<td></td>
<td>Stimulation of starvation Phagophore assembly site (IMP)</td>
<td>(5, 42, 43)</td>
</tr>
<tr>
<td>ATG24</td>
<td>T. brucei</td>
<td>Rice Blast Fungus</td>
<td>Autophagic degradation of organelles, which can physiologically add to the diversity in filamentous fungi</td>
<td>GRGRAM 2AM 1, PH.</td>
<td>Degradation of methanolpersuaded large and intermediate peroxisomes.</td>
<td></td>
<td>PAS and VSM (vacuolar sequestering membrane)</td>
<td>(1, 44)</td>
</tr>
<tr>
<td>ATG31</td>
<td>S. cerevisiae</td>
<td>Baker's yeast</td>
<td>Autophagic degradation of organelles, which can physiologically add to the diversity in filamentous fungi</td>
<td>Domains within the other proteins</td>
<td>Reduced survival of cells, nitrogen starvation due to inhibition of autophagy</td>
<td></td>
<td></td>
<td>(45-47)</td>
</tr>
<tr>
<td>ATG32</td>
<td>S. cerevisiae</td>
<td>Baker’s yeast</td>
<td>Selectivity for mitochondrial sequestration as a cargo &amp; recruit autophagy machinery for mitophagy.</td>
<td>Single transmembrane spanning the OMM (outer membrane of mitochondria)</td>
<td>Mitophagy completely inhibited in cells</td>
<td></td>
<td></td>
<td>(48-51)</td>
</tr>
<tr>
<td><strong>C. glabrata</strong> Budding Yeast</td>
<td><strong>ATG33</strong></td>
<td>Selective degradation of mitochondria</td>
<td>N- and C-terminal</td>
<td>Blocks mitophagy to half level of wild type when induced by starvation</td>
<td>Blocks Mitophagy completely when induced at stationary phase</td>
<td>Mitochondrial outer membrane (52-54)</td>
<td></td>
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<tr>
<td><strong>S. cerevisiae</strong> Baker’s Yeast</td>
<td><strong>ATG34 S. cerevisiae</strong></td>
<td>Cargo-receptor protein involved in the cytoplasm to vacuole transport (Cvt) and in autophagy</td>
<td>C-terminal</td>
<td>No participation in the Cvt pathway</td>
<td>Protein expression, isopropyl β-dithiogalactopyranoside</td>
<td>Cvt complex (55, 56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ATG43 S. pombe.</strong> Fission yeast</td>
<td><strong>ATG43 S. pombe.</strong></td>
<td>Mitophagy receptor to bridge mitochondria with phagophore</td>
<td>Transmembrane</td>
<td>Leads growth defects</td>
<td>Starvation induced mitochondrial Mitocondrial outer membrane (57, 58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DNM1 S. cerevisiae</strong> Baker’s Yeast</td>
<td><strong>DNM1 S. cerevisiae</strong></td>
<td>Permits GTPase activity &amp; identical protein binding</td>
<td>GTPase, middle, insert B and GED (GTPase effector Domain)</td>
<td>Mitochondrial morphology flaw constant with condensed fission</td>
<td>Persuaded by separation of membranes nucleate at the prec</td>
<td>Restricted in mitochondrial inside (59-61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FZO1 S. cerevisiae</strong> Baker’s Yeast</td>
<td><strong>FZO1 S. cerevisiae</strong></td>
<td>Involves mitochondrial fusion, mitochondrial genome maintenance, protein transport</td>
<td>Intact N-terminal</td>
<td>Mitochondrial fusion and lesion creation.</td>
<td>Separation of membrane nucleate at preautophagosome arrangements' PAS</td>
<td>Endoplasmic reticulum membranes (62-66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UGO1 S. cerevisiae</strong> Baker’s Yeast</td>
<td><strong>UGO1 S. cerevisiae</strong></td>
<td>Involved in mitochondrial fusion (IMP) molecular function unknown (ND)</td>
<td>Interacts with FZO1 (fuzzy onions) through its cytoplasmic domain and with MGM1 (Dynamin-related GTPase) through its mitochondrial intermembrane space domain.</td>
<td>Mitochondrial I Fusion</td>
<td>Precisely Intricate in vitality Deprivation-Persuaded Autophagy Choufei Wu1</td>
<td>Ugo1p colocalizes with a mitochondrial protein (6, 7, 12, 67, 68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ZFC3 M. oryzae</strong> Rice Blast Fungus</td>
<td><strong>ZFC3 M. oryzae</strong></td>
<td>ATP synthesis and as a negative regulator of mitochondria.</td>
<td>Displays faster early-stage hypha infiltration, MAP1-mediated pathogenicity mitochondrial fission in host rice.</td>
<td>Disruption of Mitochondrial dynamics, inhibition of mitochondrial fission</td>
<td>Mitochondria, subcellular (44, 69-72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fis1 M. oryzae</strong> Rice blast fungus</td>
<td><strong>Fis1 M. oryzae</strong></td>
<td>Encourages fission OMM protein, with a single trans membrane</td>
<td>Caused by the absence of Fis1, but rather by a secondary mutation in the stress-response</td>
<td>Mitophagy expected persuaded to degrade mitochondria in initial phases of formation of blast disease</td>
<td>Mitochondria (73-75)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. ATG genes function during mitophagy in animals.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Species</th>
<th>Common Name</th>
<th>Function</th>
<th>Domain</th>
<th>Deletion</th>
<th>Induced</th>
<th>Localized</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG3</td>
<td>D. melanogaster</td>
<td>Fruit Fly</td>
<td>Autophagy, Protein transport, Transport, Ubl conjugation pathway</td>
<td>N-terminal, catalytic and C-terminal</td>
<td>Lipodystrophy and Metabolic Dysregulation</td>
<td>Caspase-independent cell death</td>
<td>Autophagy-related membranes</td>
<td>(88)</td>
</tr>
<tr>
<td>ATG6</td>
<td>D. melanogaster</td>
<td>Fruit fly</td>
<td>Cytoprotective, Tumor suppressor</td>
<td>Coiled-coil</td>
<td>Gametophytic Mutation</td>
<td>Hypersensitive response PCD (programed cell death)</td>
<td>ER (Endoplasmic reticulum) network and nuclear envelope region</td>
<td>(89, 90)</td>
</tr>
<tr>
<td>ATg10</td>
<td>D. melanogaster</td>
<td>Fruit fly</td>
<td>Adenovirus-mediated lysis</td>
<td>Autophagy-related protein 3</td>
<td>Impaired autophagy-flux</td>
<td>Complete autophagic flux</td>
<td>Compartments Subcellular</td>
<td>(91, 92)</td>
</tr>
<tr>
<td>ATG24</td>
<td>T. brucei</td>
<td>Parasitic flagellate protozoa, Sleeping sickness parasite</td>
<td>Endocytosis and autophagy. Differentiation to amastigotes, Lead to rise in autophagosome no.</td>
<td>Dominant-negative influence.</td>
<td>Functional autophagy pathways are pathogenic and could be induced by starvation stress.</td>
<td>Endocytic membranes</td>
<td></td>
<td>(93-95)</td>
</tr>
</tbody>
</table>

Table 3. ATG genes function during mitophagy in plants.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Species</th>
<th>Common Name</th>
<th>Function</th>
<th>Domain</th>
<th>Deletion</th>
<th>Induced</th>
<th>Localized</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG7</td>
<td>E. uniflor a</td>
<td>Surinam cherry</td>
<td>Essential protein for cell degradation and its recycling</td>
<td>CTD (C-terminal domain) andCell Death &amp; mild Growth Retardation</td>
<td>recruiting E2 enzymes</td>
<td>Autophagy without starvation</td>
<td>Nucleoplas m &amp; plasma membrane.</td>
<td>(96)</td>
</tr>
<tr>
<td>ATG16</td>
<td>Arabidops is thaliana Mouse-ear cress</td>
<td>Auto phagosome assemblyCentral coiled-coil protein transport.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(97, 98)</td>
</tr>
<tr>
<td>Iga2</td>
<td>U. maydis</td>
<td>Maize</td>
<td>Lga2 overexpression as a trigger aimed at mitochondrial dysfunction, monitored by Mitophagy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(99)</td>
</tr>
</tbody>
</table>
membrane and plays a crucial role in the selective type of mitophagy via association with ATG11 which works as an adapter protein, where after recruitment imported to the vacuole along with mitochondria. Therefore, ATG32 specifically involves mitochondrial sequestration and is essential for the staffing of mitochondria via autophagy [48-51]. It is localized at the outer mitochondrial membrane, after initiating mitophagy ATG32 interacts with ATG11 and ATG32 and this association with mitochondria then transported to the vacuole (Figure 1). Silencing of the ATG32 gene results in the retardation of protein recruitment during autophagy that impaired mitochondrial degeneration and is not involved in the degradation of other forms of autophagy pexophagy or nuclease [99, 106]. Whereas in fission yeast upon nitrogen starvation autophagy of mitochondria and ER is induced by the interaction of three proteins (ATG20, ATG24, and ATG24b) as in plants and animals, ATG8-interacting motifs act as receptor proteins during mitophagy [10, 40]. In fission yeast, ATG43 localized to the mitochondrial outer membrane function as a receptor during mitophagy and interacts with a ubiquitin-like ATG8 protein. Whereas this protein was found to have no similarity with mitophagy receptors proteins in other organisms suggesting that it has evolved from mitophagy receptors and works in mitophagy independent manner [58]. This protein also directly forced the recruitment of ATG8 to mitochondria and tether expanding of isolation membrane to mitochondria. As a mitophagy-independent protein, it also facilitates vegetative growth during stress conditions [57].

3.2. Formation of autophagosomal membranes

Ubiquitin-like protein, ATG8 is required for the synthesis of autophagosomal membranes at Cvt pathways and is essential for autophagy in eukaryotes such as S. cerevisiae [107]. During normal cellular conditions, this protein localized at the PAS in the cytoplasm whereas under nutrients starvation conditions when autophagy is induced this protein is found to be associated with autophagosomal membrane and performs important functions in pexophagy, mitophagy, and nuclease [108]. ATG31 is localized to PAS, after interaction with ATG17 it plays a critical role in the proper autophagosome biosynthesis [47]. During starvation-induced mitophagy, ATG17, ATG29, and ATG31 form a scaffold that is involved in the recruitment of the ATG1-ATG13 protein kinase complex to the site of autophagosome formation. Suggesting that the autophagy-specific scaffold and mitophagy platform complex ATG11-ATG32 both collaborate during the formation of autophagosome-like membrane structure around mitochondria [45]. Phosphorylation of ATG31 is required for its proper functioning when the phosphorylated aminoamides are replaced by alanine or deletion mutation analysis reveals impaired autophagy [46].

3.3. ATG protein Recruitments

As a scaffold protein ATG11 plays an important role in selective autophagy as it is involved in the recruitments process of fission components in mitochondria via interaction with ATG32 during starvation, leading to mitophagy and also in the recruitment process of ATG proteins to the pre-autophagosomes where the formation of the autophagosome occurs. In addition to mitochondria, this protein also involves in the degradation of other organelles like the nucleus, peroxisomes and Cvt. Moreover, during the process of autophagy ATG11 after binding with the Cvt activates dimerization that results in the regulation of other ATG components like ATG1 and ATG17; for the transportation of ATG9 anterograde and ATG19-prAPE1 complex from mitochondria to PAS; in the expansion of cell life [28-30]. ATG24 with other ATG-proteins (ATG20, ATG24, and ATG24b) is required for organelle autophagy (ER and mitochondria) and general autophagy when cells are subjected to nitrogen starvation [40]. MoATG24 plays a specific role in the direct recruitment of mitochondria to autophagy bodies and in stress response and was not involved in pexophagy and macroautophagy [109]. Localization of ATG24 is near the endophytic membrane and after interaction with ATG20 it plays a critical role in the formation of Cvt vesicles in the mutually dependent way and the deletion of ATG24 results in the loss of basal activity and it was found that the number of autophagosomes doubled upon gene silencing [93-95].

3.4. Regulation of apoptotic pathway

ATG12 another protein that involves in the apoptosis of mitochondria, as a mediator binds and inactivates prosurvival Bcl-2 family members (Bcl-2 and Mcl-1) which results in the direct regulation of the apoptotic pathway [33]. ATG12 also performed a unique role in the E3 activity of ATG3, as it was found that when a conjugate molecule of ATG12-ATG5 associated with the ATG3 its affinity to bind with complex on exposure to the specific location of ATG12 enhanced [32]. Mutation in ATG12 in mice renders the cells autophagy-deficient [31]. ATG6 protein in fission yeast was found to have a multifunctional role in the cell related to autophagy as this protein is an essential component of autophagy-specific vps34 PI3-kinase complex I which involve in macroautophagy of nucleus and mitochondria, Cvt and recruitment of ATG8-phosphatidylinositol and ATG12-ATG5 conjugated molecules to autophagosomes structures [89]. Localized to PAS, this protein in S. cerevisiae and A. thaliana
forms a complex with VPS30 protein and is required for autophagy and during the sorting of vacuolar hydrolases such as carboxypeptidase. In Arabidopsis cells, disruption of the AtATG6 gene by T-DNA insertion renders the cells male sterile [90].

3.5. Mitophagy regulation via interacting with other proteins

ATG14 protein is the essential component of the complex Ptdlns 3-kinase which is required for the phosphorylation of phosphatidylinositol (Ptdlns), a crucial process in autophagy where the role of ATG14 is to target the specific site for the autophagosomal formation either as a basal or inducible. Collectively, ATG14 plays a significant role in macro-autophagy of mitochondria and Golgi apparatus, response to mitochondrial depolarization, endosomes to lysosome transport, and positive and negative regulation of protein phosphorylation [110, 111]. Like ATG32, ATG33 is also an outer mitochondrial membrane protein required in the regulation of mitochondria amount by degrading damaged or aged mitochondria in the cells during general stress conditions. ATG33 requires phosphorylation for efficient mitophagy, therefore, activity and localization of kinase protein phosphatase ATG33 [52, 53]. During the stationary phase, deletion of ATG33 leads to complete blockage of the mitophagy, suggesting that ATG33 is required for the selective degradation of aged mitochondria when cells reach to stationary phase [3]. Zinc finger protein (ZFC3) is a transcriptional factor protein that localizes to mitochondria where it interacts with mitochondrial ATP-reliant protease (MAP1) and maintains mitochondrial integrity and functions by regulating the expression of ATP synthesis genes. In Magnaporthe oryzae interaction of MAP1 and ZFC3 mediate the pathogenicity and also plays a critical role in cell longevity and stress response [69, 71]. In plants, C3H versions of ZF proteins CpCZF1 and CpCZF2 are found highly expressed in flowers and regulate the flower organs development and functions. During pathogen attack, oxidative and metabolic stresses it also involves in the regulation of mitochondrial fragmentation in yeast and plants [44, 70, 72]. In plants, the mechanism of autophagy is strictly regulated by the nutritional status, upon exposure to a nutrient starvation concentration of phosphoproteins of ATG1a and ATG13a declines dramatically and rises when nutrients are added. This fluctuation occurs due to the inhibition of the ATG system, suggesting the significance of the ATG1/13 complex in autophagy [34]. In plant species, carbon starvation causes mitophagy through the breakdown of the mitochondrial network which results in punctuated mitochondria; this mitophagy is specifically mediated by MoATG24 [44]. In S. cerevisiae, ATG42 localized to the vacuole lumen is required for the proper functioning of the vacuole which is a terminal step in autophagy and for the degradation of the autophagic body. As the yeast vacuole is home to many proteins, ATG42 also plays an important role during the proteolytic processing of the vacuole [112].

3.6. Mitochondrial fission and fusion

Fission and fusion of mitochondria regulate the morphology and size of mitochondria in response to intra and extra-cellular environmental changes [113]. Dynamin 1 (DNM1) is localized at the ends of mitochondrial tubes and function specifically as a mitochondrial fission factor during mitophagy and promote mitochondrial fragmentation leading to cell death; and work epistatic to that of Fzo1 that regulate mitochondrial fusion [60, 99]. Mutant analysis of DNM1 showed that upon point mutation or completely lacking GTP binding domain cells fail to rescue mitochondrial morphology defects [28, 60, 61]. DNM1 protein was also found to oppose mitochondrial fusion during sexual development [99]. During endocytosis, vesicles originated from the membrane after dynamin protein undergoes conformational changes. Mitochondrial fission and fusion processes regulate copy number and variation in mitochondrial morphology such as spherical to branched organelles [114].

In S. cerevisiae Fzo1 is an important mitochondrial integral protein involved specifically in the fusion of outer membranes which promotes mitochondrial fusion. Initiation of membrane fusion in other organelles requires small GTPases and SNAREs whereas in mitochondria dynamin-like large GTPases and the mitofusins (Mfn1 and Mfn2 in mammals; Fzo1 in yeast) are required [62, 63, 115, 116]. Like Dnm1, Fis1 (fission 1) proteins have been shown to be essential for mitochondrial fission after forming a complex with each other to induce mitophagy and promote cell apoptosis [73, 117]. Fis1 also mediates the regulation of mitochondrial size and distribution as the downregulation of the mammalian Fis1 gene results in elongated mitochondria. Furthermore, deletion analysis revealed that loss of Fis1 impairs respiration and mediates non-selective macroautophagy [118] Another outer mitochondrial membrane protein, Ugo1p interacts with Fzo1p to form a complex that plays a critical role in mitochondrial DNA maintenance, shape formation and ultimately in mitophagy through the fusion of mitochondria [67] In yeast, a fusion of mitochondria required machinery consisting of Fzo1, Ugo1, Mgm1, and Pcp1 genes where Ugo1 function as an adaptor in linking other genes [114]. IgA1 and IgA2 are subclasses of immunoglobulin A glycoproteins that vary in their glycosylation profiles and involve in the mediation of various autoimmune diseases. During selective autophagy, IgA2 also plays a critical role in inducing mitophagy but this role is facilitated by ATG8 and ATG11 and depends strongly on DNM. IgA2-induced macroautophagy of mitochondria is mechanistically different from starvation-induced mitophagy as the former renders the mitochondria dysfunction through exhaustion of transcripts of mitochondrial RNA [99] (Figure 1). In changing environmental conditions, the mitophagy process may play a vital role in the adaptation by regulating the quantity and quality of mitochondria [20].

4. Conclusion

Current research progress in identifying the role of autophagy-related genes in mitophagy has enabled researchers in understanding molecular mechanisms that regulate mitochondrial health in yeast, animals, and higher plants. This review summarized the role of autophagy-related genes in the mitophagy of yeast, animals and plants; among the discussed ATG proteins, ATG32, and ATG11 play a key role in inducing mitophagy. By investigating several nutrient starvation conditions, phosphorylation and dephosphorylation, lipid metabolism in yeast will help better understanding of regulation of mitophagy. In plants, mitophagy is necessary not only under nutrient-deficient conditions but also during the
normal development process. But the mechanism of mitophagy regulation is not clear in plants as limited information is available about the functions of ATG genes in plants. Investigating the mechanism of mitophagy may contribute to the understanding of the role of mitophagy in premature plant senescence and plant response under stressful environmental conditions. Through exploitation of ATG mutant analysis for dissecting their role in mitophagy and factors that regulate the expression of ATG genes might allow a comparative analysis of turn off and on of mitophagy at a molecular and physiological level in animals and plants.

Conflict of interest
The authors declare no competing interests.

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Authors contribution
Muhammad Riaz: Conception, and supervision; Razia Sultana (Review writeup from own study/research); Javed Ahmad (Helped in data collection); Azhar Mehmoon (Helped in writeup); Saira Sattar (Helped in writeup); Muhammad Hamad Tanveer (Data collection); Muhammad Zulkiffl (Data collection); Muhammad Sarwar (Data collection).

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Autophagy related genes mediated mitophagy


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