Chapter 2

Aging-Related Diseases and Autophagy

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Additional information is available at the end of the chapter

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Abstract

Autophagy is fundamental, evolutionary conserved physiological process at molecular level which targets long-lived cytosolic proteins and organelles to be recycled through lysosomal degradation. Diminished autophagic activity caused cellular stress in many organisms following aging, and inhibition of autophagy in model organisms causes degenerative changes and pathologic diseases observed with high incidence ratio generally in older ages. Consequently the delayed senescence or increased longevity in model organisms often stimulate autophagy, and autophagy inhibition compromises anti-aging effects. The cytoprotective function of autophagy is presented in various human diseases such as lung, liver, cardiovascular diseases, neurodegeneration, myopathies, cancer, stroke, infections and metabolic diseases which are found associated with autophagic targets. These pathologies are defined with their age-dependent characteristics, is not fully understood that how autophagy network regulates metabolism and may cause diseases in age-related manner. In this book chapter, we are going to discuss the autophagy and aging relationship in three different parts. In the first section autophagy and aging relationship is going to be presented through explaining responsible signalling network. The autophagy and age-related neurological disorders, genetic basis of age-dependent diseases and the functional role of autophagy is going to be discussed in the second and third part of the chapter.

Keywords: autophagy, aging, metabolism, diseases, sirtuins, AMPKa

Definitions [1]:

Macroautophagy: Macroautophagy is a complex process that involves the formation of subcellular and typically double membrane vesicles. These subcellular compartments are

called as autophagosomes, which is used for sequestration of cytoplasmic materials and cargo them into lysosomes to be recycled. The process of macroautophagy starts with the initiation of the formation of the phagophore. The growth of the phagophore terminates in completion of the autophagosome.

Chaperone-mediated autophagy (CMA): Chaperone-mediated autophagy is the only type of autophagy in mammalian cells that able to selectively degrade cytosolic proteins in lysosomes. All CMA substrates contain in their amino acid sequence a motif biochemically related to the pentapeptide KFERQ required for their selective recognition by the CMA cytosolic chaperone complex. These proteins are recognized by a chaperone complex and are translocated into the lysosome through a specific receptor called the lysosome-associated membrane protein (LAMP)-2A. Reduced CMA activity has been observed in many cell types and tissues of old rodents, as well as in cells derived from aged individuals. This mechanism is also linked to "lipophagy."

Lipophagy: Cellular lipid stores are also targeted for lysosomal degradation through a process termed "lipophagy." Therefore during lipophagy, autophagy and lipases can act together to mobilize lipids stored in lipid droplets. According to *Caenorhabditis elegans* studies, less fat content may promote longevity through inactivating mTOR downstream targets.

Microautophagy: During microautophagy, cytoplasmic content is sequestered into lysosomes through direct invagination of lysosomal membranes. This process can be observed in different organisms: yeast and mammalians. However, there are less information about microautophagy in mammalians compared to other distinguished autophagic processes.

Mitophagy: The process of removal of damaged mitochondria through autophagy is called mitophagy. Accumulating evidence points that the maintenance of mitochondrial homeostasis is strongly associated with the onset and the progression of several age-associated neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease.

Moreover, the selective degradation of endoplasmic reticulum, mitochondria, ribosomes, and peroxisomes are referred to as ERphagy, mitophagy, ribophagy, and pexophagy, respectively.

1. Introduction

Autophagy is an evolutionary conserved process, characterized by massive degradation of cytosolic contents [2]. The typical autophagy process is finalized by fusion of autophagosome to endosomes and lysosomes, which engulf cytoplasmic contents within a double-membrane vacuole [3]. Autophagy process has important physiological functions including the degradation of misfolded proteins and organelle turnover [4]. Recent studies also showed that there is a functional role between autophagy and apoptosis, which has been introduced as an important regulation of cell death in response to chemotherapeutic drugs [5]. The process is regulated by several proteins such as Atg protein family, essential for the initial building of the autophagosome, and phosphoinositide-3 kinase (PI3K) important in the early stages of

autophagic vesicle formation. This complex is called autophagosomes, which are specific cytoplasmic compartments to degrade useless cellular components to reutilize in cellular processes. It is well established that a number of molecular targets are critical in autophagosome complexes [2]. One of the most remarkable autophagic marker, Beclin-1, has Bcl-2 homology (BH) 3 domain and it is a linker protein between apoptosis and autophagy due to its interaction with antiapoptotic Bcl-2 family members. Therefore, forced expression of Bcl-2 renders autophagy-related processes and thereby prevented autophagy as well as apoptosis [6].

In addition, LC3, a cytosolic soluble protein, is cleaved during autophagic induction and involved in the autophagic vacuole membrane formation. When autophagic process starts, LC3-I (16 kDa) is converted to LC3-II (14 kDa). Recent studies showed that another autophagic key molecule, p62, is integrated in the autophagosome complexes during autophagy and reduced level of cytoplasmic-free p62 level could be accepted as an autophagic marker in the cells. Autophagy is also classified as the second type of cell death. A number of reports showed that drug-induced apoptosis mechanism could be postponed in cancer cells by activating autophagy [5]. Recent reports showed that inhibition of autophagy by the treatment of specific inhibitors for autophagic regulators, 3-MA, or suppression of autophagy regulatory pathways [7, 8] may provoke apoptotic efficiency of chemotherapeutic agents in prostate, breast, colon, lung, and HeLa cancer cells [9–11]. Mammalian target of rapamycin (mTOR) signaling pathway is one of the leading pathways that orchestrates autophagy in the cells [12]. Normally, mTOR is activated and autophagy is suppressed in the presence of insulin. Insulin binds to its specific receptor and caused autophosphorylation by the recruitment and phosphorylation of its major substrates insulin receptor substrate 1 and 2 (IRS1 and IRS2). Phosphorylated partners then recruit class I PI3K. Rapamycin is a lipophilic, macrolide antibiotic which has been shown to induce autophagy by inactivating mTOR [13, 14]. Therefore, rapamycin-mimicking agents, rapalogs, are natural autophagy inducers through inhibiting mTOR downstream signaling cascade.

Autophagy is also referred as a catabolic process, which involves the formation of a double membrane structure around damaged organelles and cellular compartments which lead to growth arrest [4]. It has been shown that mTOR negatively regulates autophagy in response to cellular conditions and environmental stress [15]. mTOR consists of two complexes: mTOR complex I (mTORC1) and mTOR complex II (mTORC2). mTORC1 has specific protein, raptor, which is sensitive to rapamycin. mTORC2 associates with Rictor, which is considered to be insensitive to rapamycin (**Figure 1**).

The PI3K/Akt pathway is an important intracellular signaling pathway in the regulation of cell survival through activating mTOR. Its downstream targets are translational regulators: p70S6K and eukaryotic initiation factor 4E (eIF4E) binding protein-1 (4EBP1) [12]. Raptor binds to mTOR substrates, including 4E-BP1 and p70 S6 kinase, through their TOR signaling (TOS) motifs and is required for mTOR-mediated phosphorylation of these substrates. Furthermore, the Rictor-mTOR complex has been identified as the previously elusive PDK2 responsible for the phosphorylation of Akt/PKB on Ser473, facilitating phosphorylation of Akt/PKB on Thr308 by PDK1 and required for the full activation of Akt/PKB [16]. The PI3K/Akt signaling proteins

also interfere with apoptotic regulators, Forkhead box O (FoxO) and glycogen synthase kinase 3 (GSK3β), to inhibit apoptosis and autophagy in cancer cells [17, 18].

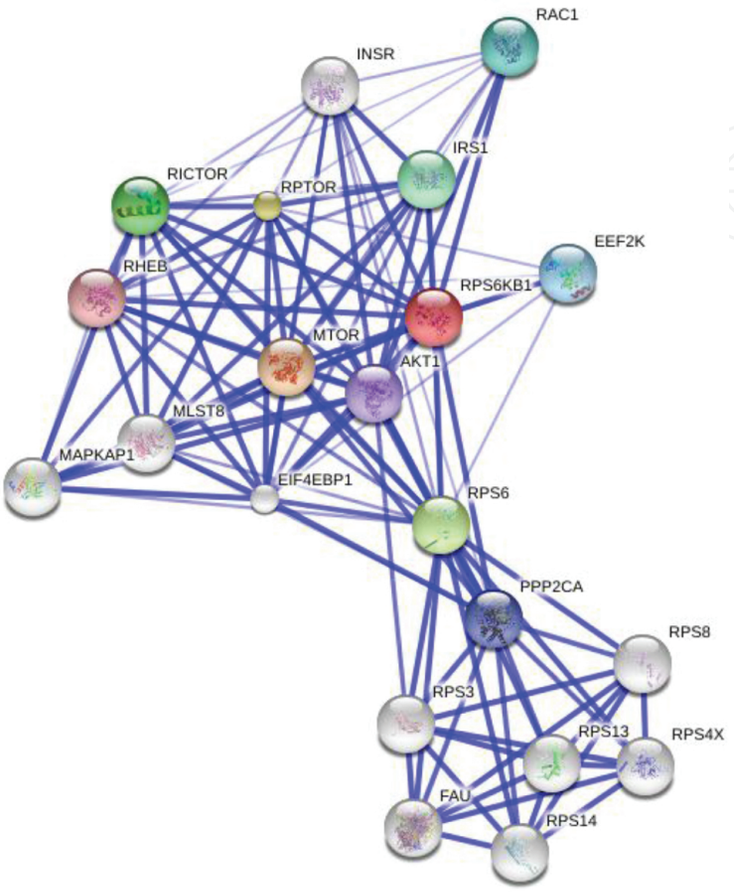

Figure 1. STRING mTOR interacting partner analysis.

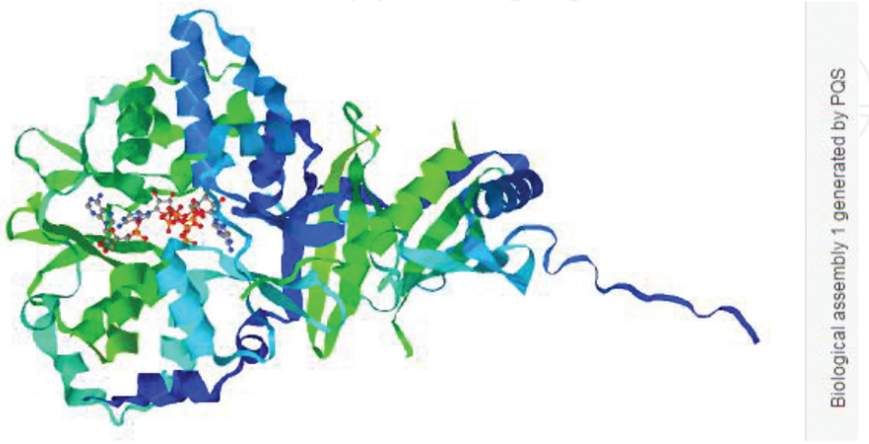

Figure 2. Crystal structure of regulatory fragment of mammalian AMPK in complexes with ATP-AMP through PDB database ribbon presentation.

All the mentioned molecular targets are well documented with their autophagy-related characteristics in different cells or organisms. Beside these highlighted targets, there are other important regulators, which also act as stress sensors in the cells [19]. One of the leading targets is AMP-activated protein kinase (AMPK), energy-sensing kinase, which is a downstream target of mTOR (**Figure 2**). AMPK is a heterotrimeric protein complex that is regulated by different modulators in the cells. This serine/threonine kinase is a heterotrimer composed of a catalytic (AMPKα) subunit and two regulatory (AMPKβ and AMPKγ) subunits. The phosphorylation of a conserved threonine residue (T172) in the activation domain of catalytic α-subunit by a number of kinases is crucial for the activity of AMPK [20]. Activated AMPK typically phosphorylates TSC2 tumor suppressor and leads to inactivation of Rheb, which is an interacting partner of mTORC1. Alternatively, it is shown that AMPK can regulate mTOR signaling by phosphorylating Raptor at Ser722 and Ser792, which leads to 14-3-3 binding to Raptor, and induces cell-cycle arrest triggered by impaired energy balance [21].

Since the ratio of AMP to ATP exerts the intracellular energy measurement, these substrates determine the AMPK activity in the cells [22, 23]. AMPK can be also activated by metabolic stress factors, hypoxia or ATP consuming catabolic processes in the cells [17, 24, 25]. For this purpose, it can be emphasized that there is strong relationship between energy balance and autophagy regulation in the cells. To point this relationship, it is critical to put forward AMPK activation status in different conditions. In a brief presentation, AMPK is referred as a central metabolic sensor found in a variety of organisms that regulates glucose and lipid metabolism in response to alterations in nutrients and intracellular energy levels [23, 24]. However, the functional role of autophagy in energy balance conditions is not fully understood.

As an example for this issue, although glucose starvation can activate AMPK-mediated signaling route and trigger autophagy through phosphorylating Ulk1 at Ser 317 and Ser 777, nutrient deficiency in high mTOR activity can also prevent Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. In addition, an established marker for autophagy, p62, can accumulate in AMPK-deficient livers [26]. Since p62 is involved in mitochondria clearance, the defects in selective degradation of mitochondria by autophagy (mitophagy) and a corresponding mitochondria accumulation was also shown in the same study with presence of severe abnormalities in AMPK- or ULK1-deficient hepatocytes.

Therefore, there is still need to evaluate the AMPK activation status in autophagy-related issues. The supporting data for this manner are also observed in the treatment of type 2 diabetes (T2D). The well-known T2D treating drugs, metformin, thiazolidinediones, etc., can activate AMPK and improve insulin sensitivity and metabolic health [27–29]. It can be concluded that AMPK as a critical autophagy regulator has a great impact on human metabolic diseases. Thereby, diminished cellular energy capacity can stimulate glucose uptake in skeletal muscles or fatty acid (FA) oxidation in tissues through modulating AMPK.

AMPK is a central molecular target that orchestrates metabolic stress and energy balance in the cells. One of the critical mechanisms regulated by AMPK is fatty acid synthesis, which is generally age-related problem due to nutritional habits or genetic background. When activated AMPK acetyl-CoA carboxylase (ACC) is phosphorylated at Ser79 (an inhibitory site), it

prevents the conversion of acetyl-CoA to malonyl CoA. This action allows long-chain FAs to enter the mitochondria for oxidation. Concomitantly, HMG-CoA reductase leads to the inhibition of cholesterol synthesis, peroxisome proliferator-activated receptor-gamma coactivator (PPARα) 1α, which stimulates mitochondrial biogenesis and many others [19, 23]. The inhibition of FA synthase (FAS) expression due to AMPK was previously reported in primary cultured hepatocytes [30, 31]. Supporting this finding, it was shown that AMPK can suppress FAS gene expression either by AMPK activating AICAR or an antidiabetic drug metformin treatment in liver cells [29]. Indeed, activation of AMPK by either AICAR or rosiglitazone reduces expression of FAS and ACC resulting in the suppression of proliferation of prostate cancer cells [32]. Of note, physical exercise and calorie restriction (CR) may exert similar beneficial effects on metabolic health and reduce risk of several diseases, including T2D and cardiovascular diseases via targeting previously mentioned pathways [33]. Both exercise and CR are shown as the frequently observed metabolic stresses that increase the AMP: ATP ratio in an organism's cells, which led to activation of AMPK. Similar to AMPK, silent information regulator 1 (SIRT1) signaling pathways are evolutionarily conserved energy sensors in cells responding to the increase in cellular AMP and NAD^+ concentrations, respectively [34–36]. SIRT1 is a member of sirtuins, which is discussed later in detail to evaluate the autophagy and aging relationship.

2. Aging: energy balance and stress management

It is well studied that over 30 proteins orchestrated autophagy-related processes in the cells, which differ due to stress stimuli or depends on intrinsic molecular mechanism. Autophagy is a complex process in development, metabolism, and aging. In order to evaluate the potential characteristics of autophagy in aging, researchers pointed out that energy balance and stress factors should be discussed. Both factors are critical initiators of autophagy and play a role in cell decision signaling routes. For this reason, in this part, we will discuss the energy metabolism-related signaling cascades and stress-related cellular responses.

Aging is strongly correlated with autophagy in different organisms from fungi to humans. It is well documented that protein degradation ratio is decreased due to aging [35, 36], which presents similar observations of diminished levels of age-related autophagic/proteolytic activity [37]. Therefore, it can be emphasized that there is strong relationship between autophagy, aging, and lifespan. The genetic basis of this connection was established in *C. elegans* daf-2 mutants, which have diminished insulin-signaling cascade and extended lifespan. Similar to this finding, mTOR or p53 mutants show lifespan extension [38–40].

It is well documented that CR or late findings also showed the potential effect of resveratrol or spermidine treatment causing upregulation of sirtuins and led to increased lifespan in the cells. Similar findings were also shown for *Caenorhabditis elegans* and *Drosophila melanogaster* species [33, 41–44]. For this reason, sirtuins (mammalian protein family members 1–7) are also termed as antiaging proteins, class III histone deacetylases (HDACs), exerting function as protein deacetylases/ADP ribosyltransferases that target a wide range of cellular proteins in

the nucleus, cytoplasm, and mitochondria for posttranslational modification by acetylation (SIRT1, -2, -3, and -5) or ADP ribosylation (SIRT4 and 6). Sirtuins have conserved NAD+-dependent deacetylase domain, which is known to regulate cellular senescence and lifespan. SIRT1 is generally found in nucleus, but there are remarkable data about its presence in cytoplasm. SIRT2 is the dominant member found in cytoplasm. SIRT3, SIRT4, and SIRT5 are localized to the mitochondria with different enzymatic activities. SIRT6 is a chromatin-associated nuclear protein and SIRT7 is found in nucleoli. Early data about involvement of sirtuins in autophagy-related longevity was shown with CR experiments [43, 44]. The reduced food intake without malnutrition caused increased autophagy via upregulation of AMPK and SIRT1 and inhibition of insulin/insulin-like growth factor (IGF) signaling. mTOR inhibition also has a remarkable data with these alterations [45]. Rapamycin is an mTOR complex I inhibitor that altered sirtuins and caused autophagy responses in the cells [46]. In a similar way, researchers highlighted that increased levels of acetate, acetyl-CoA, could inactivate autophagy in yeast models [47, 48]. These substances are generated through mitochondrial energy regulator networks such as acetyl-CoA hydrolase-1 (ACH1) and mitochondrial pyruvate carrier-1 (MPC1)-dependent pathway and the acetyl-CoA synthetase-2 (ACS2)-dependent nucleo-cytoplasmic pathway. The hyperactivation of these targets led to hyperacetylation of histones and ATG genes [48]. Similar findings were also shown for a number of pharmacological drugs, such as rapamycin, spermidine, or resveratrol, in different organisms.

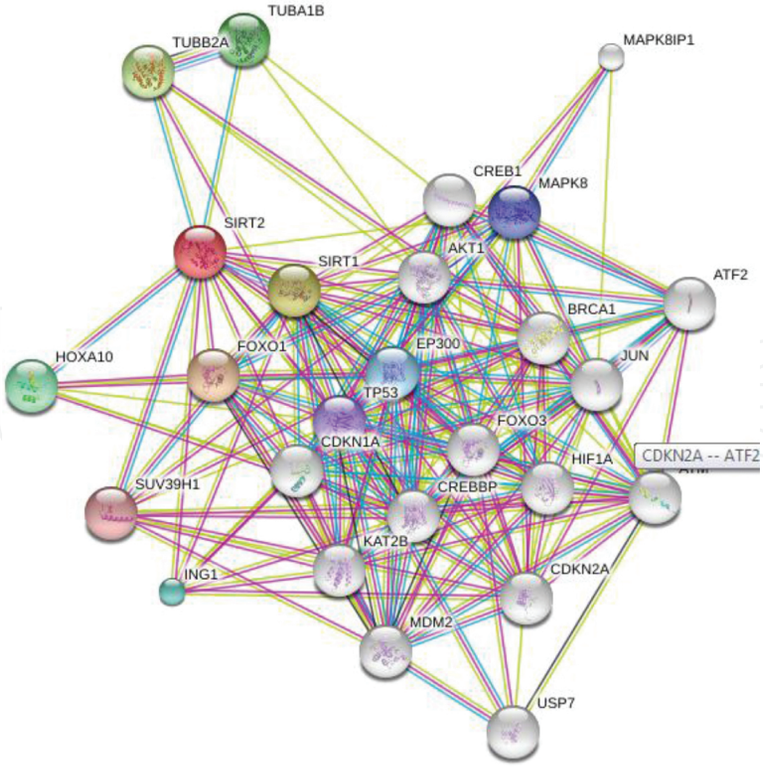

Figure 3. STRING analysis of *Homo sapiens* SIRT2.

The supporting data are observed within 25 years of experiment with primates. CR reduced mortality rates and age-related diseases in Rhesus monkeys [49]. Therefore, the identification of CR-altered molecular mechanisms has gained importance to evaluate the main reason of human diseases arisen during aging. *In viv*o and *in vitro* evidences highlighted that CR or fasting without malnutrition upregulated SIRT1, which regulates several transcription factors that regulate stress responses, energy metabolism, and endocrine signaling, including peroxisome proliferator-activated receptor (PPAR)γ, PPARγ coactivator 1 (PGC1)-α, forkhead box transcription factors (FOXOs), liver X receptor (LXR), and p53 [50]. In addition to these observations, we search SIRT2 on STRING (**Figure 3**). The analysis results showed that SIRT2 and SIRT1 have strong interactions with cellular dynamic proteins tubulins, cell survival, and death decision maker proteins: p53, MDM2, FoXO1, FoXO3, DNA repair proteins (BRCA1), and PI3K/AKT/MAPKs signaling axis proteins [51]. For this reason, it can be suggested that longevity, which is a final destination of sirtuins, is a complex cellular decision.

When we checked protein atlas database for cancer-related SIRT1 and 2 expression profiles, we observed that SIRT1 is the most critical target in a number of cancer cases (**Figure 4A** and **B**). Overexpression of SIRT1 is regulated at the transcriptional level through p53 binding sites, as SIRT1 promoter normally repress SIRT1 expression. However, in the absence of nutrients, FoXO3a translocates to the nucleus, interacts with p53, inhibits its suppressive activity, and leads to increased SIRT1 expression [52]. Moreover, double knockout p53 mice show increased basal expression of SIRT1 in selective tissues, including adipose tissue, but SIRT1 levels were not further elevated upon nutrient withdrawal [52]. The loss of functional p53 in carcinogenesis might increase SIRT1 levels [53].

It is noteworthy that the clarification of several indicators is required to determine critical molecular factors in disease progression related to autophagy in age-dependent manner. The well-established models in this concept are nutrient deficiency with CR or physical exercise, a metabolic stress inducer. According to previous results both CR and physical exercise exert beneficial effects on metabolic health and reduce risk of several diseases, including T2D and cardiovascular diseases through targeting previously mentioned pathways. These factors are also accepted as metabolic stressors that increase the AMP: ATP ratio in an organism's cells, which led to activation of AMPK [54].

A number of studies showed that AMPK activation may slow aging [55, 56]. In contrary, the decline in AMPK activation with aging causes diminished autophagic regulation, increased oxidative stress, endoplasmic stress, apoptotic resistance, inflammation, fat deposition, hyperglycemia, and finally metabolic disorders. The key molecule AMPK gains more importance in age-related disease progression. While AMPK stimulates energy production from glucose and FA during metabolic stress and depress energy consumption for macromolecule synthesis [57, 58], it is not a new paradigm that nutritional overload breaks the functional AMPK status and induces insulin resistance which trigger metabolic syndromes such as obesity, diabetes, and cardiovascular diseases [59]. According to the findings obtained from model organisms, metformin treatment increases lifespan of *C. elegans* model organism [60]. The AMPK ortholog, AAK-2, can be activated through metformin treatment. Similar findings were also observed in *Drosophila* model organism [61]. However, all findings indicate that there

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is a clear deficiency in the sensitivity of AMPK activation in aged tissues. This might be a reason of systemic alterations such as function of protein phosphatases, which could be involved in the suppression of AMPK activation with aging.

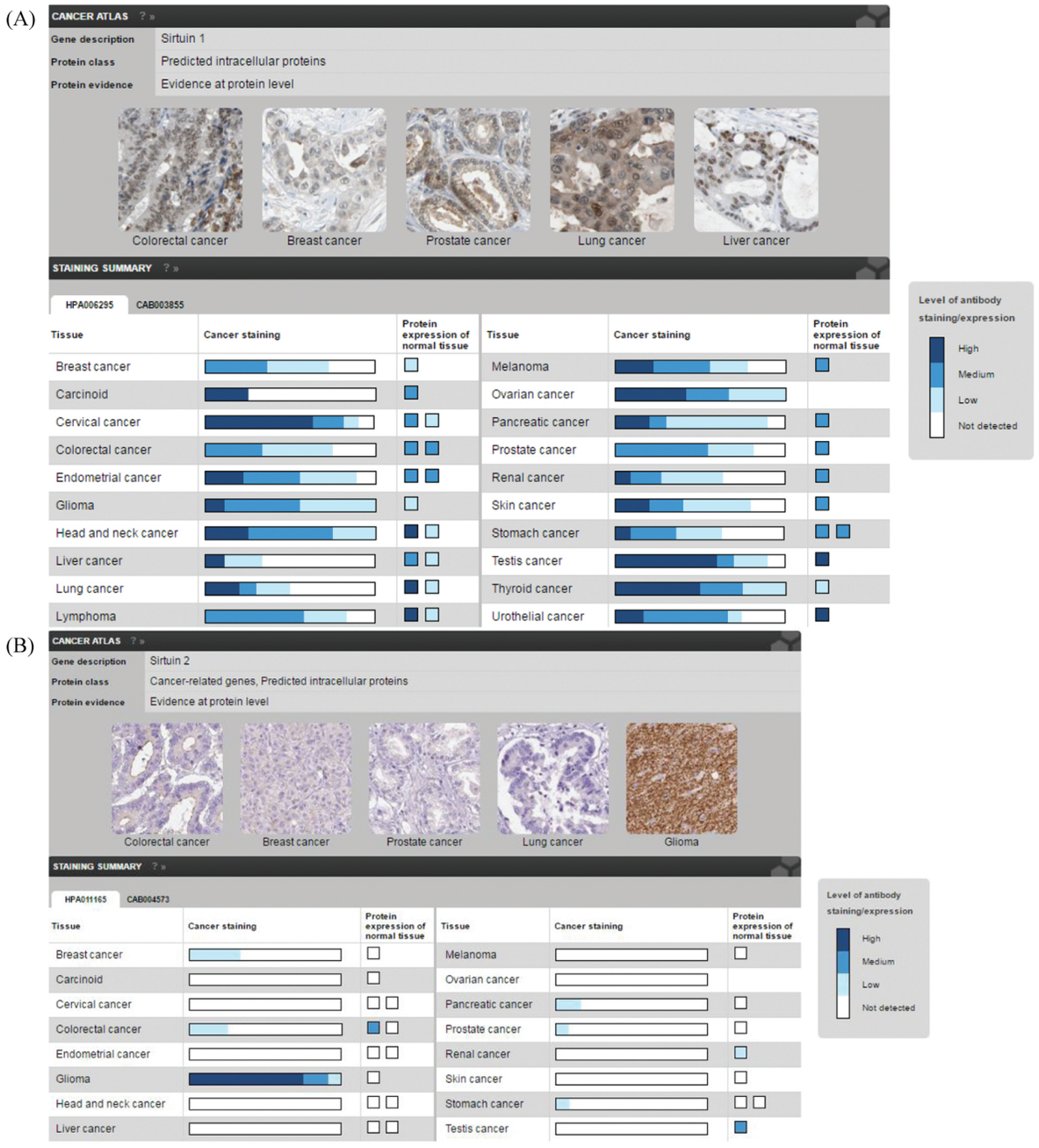

Figure 4. Human protein atlas database query results for SIRT1 (A) and SIRT2 (B). http://www.proteinatlas.org/.

Since it is well established that CR might reduce the tumor weight, the energy balance mechanism is investigated by cancer researchers. Supporting this observation, it is highlighted that cancer is a disease of aging, and the incidence of most of the cancers are increased with age due to genomic stability problems in genome [62–64]. DNA replication errors, reactive

oxygen species (ROS) generation due to intrinsic cellular stress factors, or extrinsic stress inducers increased genomic instability. In correlation, in a number organisms which have lower reactive oxygen species are shown with increased lifespan. Therefore, increased lifespan may be causative factor for cancer development.

In contrary to CR, high fat diet or increased calorie intake leads to obesity with a number of comorbidities, including cancer, cardiovascular diseases, and diabetes [65–68]. The main idea is to understand energy balance and human diseases relationship through investigating molecular targets in the cells (**Figure 5**). High calorie intake or fat oxidative stress cause metabolic dysfunction of critical pathways. During aging, slow rate of autophagy decision mediates a number of pathogenesis related to functional status of mTOR, AMPKa, and sirtuins, which are cellular stress and nutrient sensors.

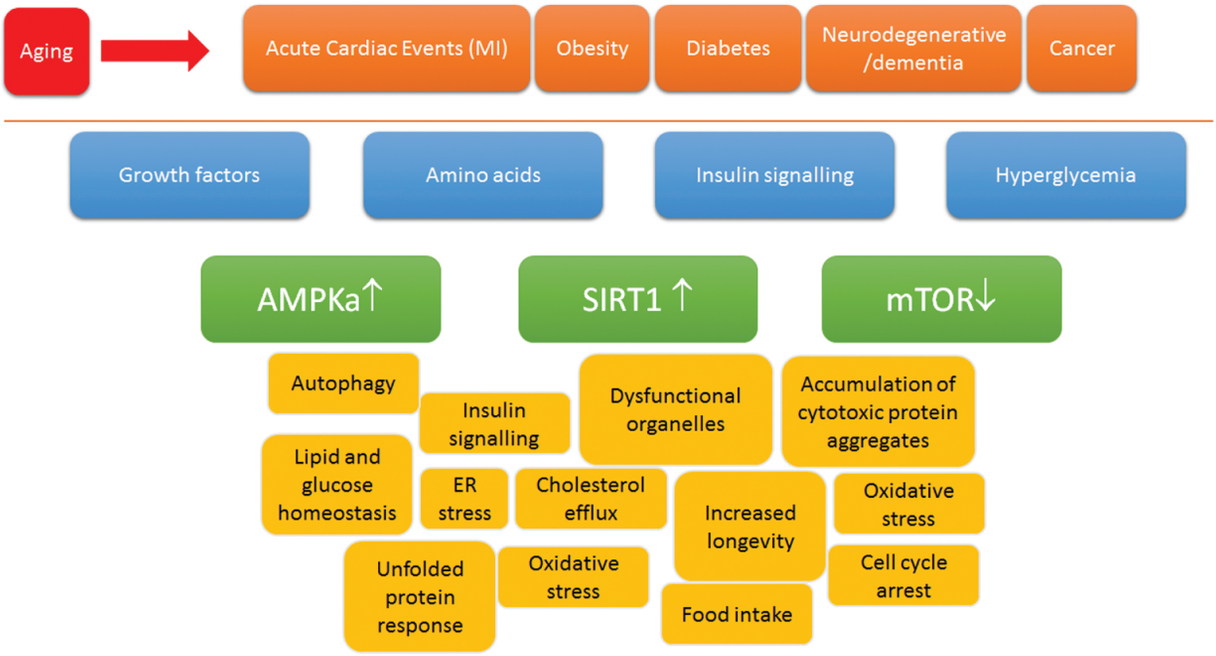

Figure 5. Aging-related diseases and autophagy-related molecular signaling cascades.

3. Aging and related neurological disorders

Human aging, the gradual harmful effect of time on an organism, is comprised of physiological changes leading to senescence and inability to adapt to metabolic stress. Although aging has been considered as a natural process, age-associated diseases are found as leading causes of death. The dramatic increase in average life expectancy in the last century has been accompanied by an equivalent increase in age-related disease diagnosis, such as cancer, neurodegenerative diseases, type II diabetes, and cardiovascular diseases.

The basis of aging process is examined under several hypothesis: the free radical, the immunologic, the inflammation, and the mitochondrial theories [69–72]. However, aging seems more

likely a multifactorial process rather than a single cause [73, 74]. In this context, studies on longevity focus more than one target at a time, and animal models showed that aging rates and life expectancy can be modified by multitarget modulators. The consensus among researchers in the field indicates that aging can be retarded by dietary and pharmaceutical interventions, which let to delays in age-related diseases.

Aging is an occasional process in different individuals in contrast to the programmed events in early development. Although recent studies indicate that *klotho* gene mutation could cause premature aging or telomeres are tightly linked to senescence, the variation of aging initiation pose an obstacle to interfere to the progress.

The promising strategies to slow aging have suggested suppressing glucose production by the liver, inhibition of inflammation, and protein restriction [75]. The prevention of high glucose production, hyperglycemia, the condition in which excessive amount of glucose is found in the blood plasma, by metformin is under investigation for its potential effect on slowing aging in different organisms such as *C. elegans* [76]. Studies indicate that worms treated with metformin have stable body volume with reduced deformation of cuticle [76, 77].

One of the possible mechanisms of metformin to decrease hyperglycemia is the activation of AMPK. AMPK is the primary activator of cellular response to lowered ATP levels [78]. As mentioned in previous section, AMPK targets mTOR signaling pathway, which affects transcription and translation through effector proteins 4E-BP1 and p70S6. The involvement of AMPK/mTOR axis in the suppressing glucose production strategy also overlaps with the inhibition of inflammation and protein restriction targets against aging. mTOR signaling regulates inflammatory responses after bacterial stimulation in monocytes, macrophages, and primary dendritic cells [79]. mTOR following tuberous sclerosis complex 2 activation (TSC2) has been shown to diminish proinflammatory cytokines production through nuclear factor (NF)-κB [79]. On the other hand, mTOR inhibition by AMPK is also a critical step in the control of translation attenuation [80]. In normal cellular conditions, nutrients induce mTOR and its downstream target S6K to promote growth and proliferation. However, in nonproliferating cells, this signaling axis has been shown to initiate cellular senescence, the phenomenon by which cells cease to divide. mTOR inhibitor rapamycin has been proposed for decelerating aging and age-related pathologies in *D. melanogaster, C. elegans*, and yeast [81–83].

Therefore, the inhibition of mTOR is a critical phenomenon to balance cell survival and death signaling in eukaryotic organisms. Nutrient starvation can directly cause mTOR inhibition and induction of autophagy, a process that optimize the usage of limited energy supply. Autophagy is generally referred as a catabolic process during which autophagosomic-lysosomal degradation of cytoplasmic proteins, macromolecules, and damaged or aged organelles occur.

The hallmarks of neurogedenerative diseases are generally described with the accumulation of abnormal proteins forming aggregates. These aggregates usually cause toxic effects, such as defective axonal transport, inactivation of transcription factors, reactive oxygen species generation, and consequently neuronal death [84]. Since differentiated neural cells lose their ability to divide, except the granule cell layer of the olfactory bulb, and the dentate gyrus of the hippocampus, a well-organized protein quality-control complex is needed in neural cells.

Autophagy, as a process of cellular recycling for aggregated proteins, might be a critical target in the treatment of neurodegenerative diseases; however, altered autophagic activity has also been implicated in their pathogenesis [85].

3.1. Alzheimer's disease

The main manifestations of Alzheimer's disease (AD) are selective memory impairment and degenerative dementia in the elderly people. AD is characterized by the formation of neurofibrillary tangles and extracellular senile plaques. Tau protein and amyloid beta-peptide (Aβ) are involved in these two processes, respectively. Tau is a soluble microtubule-associated protein playing a role in microtubule stabilization and vesicle transport along the axon. Tau proteins have six isoforms with different size of amino acid chain. All isoforms are present usually in central nervous system, and upon hyperphosphorylated, they paired as helical filaments, a characteristic feature of AD. The hyperphosphorylation might be due to mutations in tau isoforms that alter their function and expression or in tau-kinases capable of phosphorylating tau such as glycogen synthase kinase 3 β (GSK3β), cyclin-dependent kinase 5 (CDK5), the mitogen-activated protein kinase (MAPK) extracellular-regulated kinases 1 and 2 (ERK1/2), p38, and the c-Jun NH2-terminal kinases (JNKs) [86–88]. Hyperphosphorylated tau disassembles microtubules and aggregates with MAP 1 (microtubule-associated protein1), MAP 2, and ubiquitin forming tangles. These aggregations are insoluble and cause neuronal dysfunctions in axonal transport resulting in cell death [89].

Apart from Tau protein, amyloid plaques, which consist of aggregates of Aβ peptide, are responsible for AD development. Neurotoxic Aβ42 peptide is generated by the irregular proteolytic cleavages of transmembrane amyloid precursor protein (APP) extracellular domain by β- and γ-secretases. The cleaved intracellular parts form fibrils due to protein misfolding and can induce tau hyperphosphorylation, disruption of proteasome, mitochondria, and synapses as well [90, 91].

Both tau and Aβ neurotoxicity exhibit altered protein aggregate formation, therefore the clearance of these structures is extremely important in neurons which are unable to eliminate them by dilution through cell division [92]. Thus, a protein quality-control system is needed in neural cells. Autophagy, due to its role of degrading nonfunctional proteins, is one of the candidates to process against neurodegenerative disorders. The increasing autophagosome formation augmented Aβ42 in autophagy-deficient conditions and reduced Beclin1 expression, which provided evidence for the importance of autophagy in AD [93–95]. However, autophagy might not always be the answer. The effect of autophagy is divided into two stages during neurodegenerative disorder: the acute and the chronic condition. Although acute autophagy helps neurons to eliminate neurotoxic aggregates, studies showed that chronic autophagy may be implicated in AD pathogenesis [96]. When autophagy is induced by rapamycin, due to mTOR inhibition γ-secretase activity and Aβ production was found increased by two fold compared to autophagy suppressed mouse fibroblasts [97]. Similar results were also found by serum starvation, where threefold increase in Aβ levels was also observed in human neurons [98].

Consequently, the role of the autophagy is elusive for AD at the initial steps; however, later stages of the same pathway might affect the prognosis negatively. Therapies based on autophagy will require attentive targeting of specific steps of the process for efficient digestion of the aggregates without worsening the disease stage.

3.2. Parkinson's disease

The loss of dopaminergic neurons in the substantia nigra of the central nervous system is the primary cause of Parkinson's disease (PD). The pathology of the disease requires characteristic Lewy bodies in the nuclei of neurons [99]. Lewy bodies contain insoluble α-synuclein aggregates. α-synuclein, in nonpathological conditions, has the ability to bind membrane phospholipids and involved in presynaptic membrane procedures during neurotransmitter release, especially dopamine [100, 101]. The accumulation of α-synuclein occurs due to two missense mutations during PD: A53T and A30P [102]. A small percentage of the aggregates carrying these two mutations have been shown to recycle by the proteasomal degradation or CMA in dopaminergic neurons. During CMA, pathologic α-synucleins are directly targeted to lysosomes by HSC70 due to their Lys-Phe-Glu-Arg-Gln (KFERQ) amino acid sequence without involvement of vesicle formation apart from macroautophagy [103]. Mutated α-synucleins can accumulate with extra phosphate groups which led to the loss of the recognition sequence for CMA. In this case, the accumulation cannot be tolerated by CMA and dopaminergic neurons die via apoptosis [104]. Other than α-synuclein, parkin and PINK1 (PTEN-induced putative kinase 1) are PD promoting molecules.

Parkin is an ubiquitin E3 ligase, located in mitochondria, which regulates variety of cellular processes in neural cells. Loss of parkin has been suggested as the second most common cause of PD. On the other hand, PINK1, with parkin, manage mitochondrial quality control. Recent studies indicate that upon mitochondria membrane potential loss, PINK1 cannot be imported to mitochondria and it accumulates in the cytoplasm where it recruits parkin to induce mitophagy [105]. Therefore, dysfunctional mitochondria are degraded under normal cellular conditions. However, when PINK1 is mutated, altered parkin activity leads to autophagy impairment and mitochondria imbalance which has been reported for animal models of PD [106, 107]. In addition, PINK1 also interplays with Beclin1. PINK1 mutation during PD cause defective or loss of PINK1-Beclin1 interaction and thus resulted in insufficient autophagic activity [108]. Taken together, PD promoting proteins having a role in either cell membrane or mitochondria integrity are also involved in the induction of autophagy. Therefore, mutations in their genes cause defective autophagy process and leads to the accumulation of both α-synuclein and unhealthy mitochondria leading to the apoptotic cell death of dopaminergic neurons in the substantia nigra.

3.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons resulting in paralysis. ALS patients suffer from muscle weakness, atrophy, and spasticity. Denervation of the respiratory muscles and diaphragm is the fatal event of ALS. Although most incidences of ALS are sporadic, 20% of all

cases are hereditary and caused by mutations in the superoxide dismutase 1 gene (SOD1) [109]. SOD1 is responsible to convert the natural byproduct of respiration, superoxide, to water and hydrogen peroxide. Therefore, defective SOD1 is not able to work properly causing loss of detoxification in motor neurons [110]. The alanine-to-valine substitution at position 4 of SOD1 is responsible for most of the cases, and patients carrying the mutation have a mean survival of 1 year after onset. Mice having the mutant SOD1 gene have been shown also to develop progressive motor neuron degeneration [111, 112]. ALS mice expressing mutant SOD1 have defective protein folding, mitochondrial dysfunction, oxidative stress, inflammation, and toxicity. More importantly, these mice exhibited aberrant neuronal aggregates composed by insoluble forms of SOD1 in their motor neurons, which suggested a pathological hallmark of ALS. These aggregates, also detected in sporadic ALS patients, were shown to carry not only SOD1 but also neurofilaments, peripherin, an intermediate filament subunit, and ubiquitin [110, 113, 114]. Therefore, it is concluded that although cells are willing to eliminate aggregates following ubiquitination through proteasomal degradation, misfolding due to mutations provides an obstacle for this process, which prevents them from degrading. In addition, proteasome malfunction has been implicated in motor neuron death during ALS [115]. The experimental models of ALS suggested that the above aggregates are cleared by autophagy. When autophagy was inhibited by 3MA or bafilomycin, cell viability was found further decreased in *in vitro* ALS models [116]. In contrary, autophagy inducer lithium increased the number of Renshaw cells, interneurons found in the spinal cord, which are affected early during experimental ALS [117]. Therefore, it is concluded that a proper autophagy mechanism is needed for the elimination of the aggregates for ALS treatment.

3.4. Multiple sclerosis

Studies on age-related diseases revealed that there is a relationship between age and the rate of disability progression of multiple sclerosis (MS). Although MS patients are usually diagnosed between the ages of 20 and 50, the relapse-remitting form of MS exhibits active symptomatic period by the age, indicating a faster rate of disease progression in older patients. MS is the most common autoimmune inflammatory demyelinating disease of the central nervous system. Demyelination occurs due to T cells and activated microglia attack to myelin proteins resulting in axonal injury and loss of oligodendrocytes. Findings also indicate that MS patients have increased T and B lymphocyte levels in demyelinated areas due to blood-brain barrier disruption [118]. In addition, dysfunction of mitochondria is one of the important factors in the pathogenesis of MS [119]. The decreased expression of cytochrome *c* oxidase impairs the function of mitochondria [120]. Dysfunction of mitochondria induces reactive oxygen species generation, contributing demyelination, and axonal loss [121]. Recent studies revealed that autophagy plays a role in the progress of MS and experimental autoimmune encephalomyelitis (EAE), which is accepted as the mouse model of MS. Studies indicated that depolarized mitochondria is engulfed and degraded in autophagic vacuoles to reduce the excessive production of ROS, which was supported by the increase of Beclin1 and Atg4 expression in MS brains [122]. On the other hand, exposure of rapamycin, mTOR inhibitor, prevented relapsing-remitting EAE.

It was also shown that Atg5 was increased, whereas Atg16L2 is reduced in T cells in EAE and relapsing-remitting MS brains [123]. Atg-5-deficient mice were reported to have impaired T-cell function and survival [124]. All these data suggest that autophagy relates to both prevention of MS by degrading defective mitochondria and inducer of MS through Atg5 to extend T-cell survival [125].

3.5. Huntington disease

Huntington disease (HD) is an autosomal-dominant neurodegenerative disorder with a distinct phenotype, including cognitive decline, muscle incoordination. The HD symptoms are noticeable between the ages 35–45; however, the case gradually worsens at the old age with dementia, pneumonia, and heart diseases. HD develops due to a mutation in huntingtin protein, an expanded CAG repeat leading to a toxic polyglutamine strand of variable length at the *N*-terminus. Normally associated with vesicle and microtubule function, mutated huntingtin accumulates in tissues causing undegradable molecules by proteosomal degradation [126]. In this step, macroautophagy acts as a compensatory mechanism for the elimination of huntingtin [127]. Studies indicated that HD is associated with impaired degradation process of autophagosomes resulting in the accumulation of highly ubiquitinated aggregates of huntingtin in the endosomal-lysosomal organelles. Moreover, mutations in Atg genes, especially in Atg7 (V471A), have been linked to disease onset [128].

4. Genetic basis of autophagy-related genes and diseases

Since Human Genome Project is completed in 2003 and HapMap Project in 2005, valuable bioinformatics data were gained and published for research interested tools. Instead of classical Sanger-type DNA sequencing, next-generation DNA sequencing equipment accelerated the human gene-related alteration and human disease among ethnic population all around the world [129, 130]. While Mendelian-mediated monogenic and multifactorial-induced polygenic genes responsible for diseases were determined and localized within the human genome, association mediated regression analysis of human population genetics revealed some specific genes related with various cellular process involved in diseases has been assumed. One of the essential cellular processes, autophagy, is the process of long-lived proteins and organelles that are nonfunctional or damaged, maintaining the cellular homeostasis mediated by autophagosome and autolysosome formation [131]. Autophagy is demostrated as a protective event against oxidizable substrates, various pathological processes such as aging, neurodegeneration, cancer, diabetes, obesity, cardiac disease infection, and immunity [132–136]. These diseases are linked with various autophagy process key elements expressing genes via etiology of them. All the mutated autophagy-related genes and linked disease are presented in **Table 1**.

Aging slows autophagy and prevents cellular defense mechanism against metabolic stress factor. However, all findings indicate that the functional role of autophagy differs in conditional manner.

Genes	Mutation type	Associated human disease	Ref.
Gene products required for autophagosome formation			
ATG5	Polymorphism	Asthma and risk of systemic lupus erythematosus	[137]
ATG16L	T300A	Crohn's disease	[138]
BECN1	Monoallelic deletion	Risk and prognosis of human breast, ovarian, prostate and colorectal cancer	[139–142]
EI24/PIG8	Mutations and deletions	Risk of early breast cancer	[143]
TECPR2	Frameshift mutation	Hereditary spastic paraparesis	[144]
UVRAG	Deletion mutation	Static encephalopathy of childhood with neurodegeneration in adulthood	[145]
Gene products required for autophagosome maturation/degradation			
EPG5	Recessive mutations	Vici Syndrome	[146]
IRGM	SNPs, deletions	Risk of Crohn's disease	[147]
ZFYVE26/SPG15	Mutations	Hereditary spastic paraparesis type 15	[148]
Gene products required for induction of mitophagy			
PARK2/Parkin	Mutation	Autosomal recessive or sporadic early-onset Parkinson's disease	[149]
PARK6/PINK1	Mutations	Autosomal recessive or sporadic early-onset Parkinson's disease	[150]
Gene products involved in autophagosomal sequestration, movement or maturation			
SQSTM1/P62	Mutations	Paget disease of bone and amyotrophic lateral sclerosis	[151]
CLN3	Mutations	Batten disease	[152]
LAMP-2	Mutations	Danon disease	[153]
Dynactin subunit p150	Mutations	Spinal or bulbar muscular atrophy	[154]

Table 1. Germline and somatic mutations in human diseases-related with autophagy.

4.1. Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA)

SENDA begins with early childhood intellectual impairment. Unlike the other forms of NBIA, however, the cognitive dysfunction remains nonprogressive, sometimes for decades, after first being recognized. Then, in adulthood, affected patients develop severe dystonia-parkinsonism and later exhibit signs of a progressive dementia. Although no etiology has yet been identified for SENDA, autophagy is focused on the pathogenesis of the disease [155, 156]. The neuroimaging of SENDA is distinct. In addition to iron deposition in the globus pallidus and substantia nigra, SENDA features T1 hyperintensity of the substantia nigra with a central band

of T1 hypointensity. Significant cerebral and milder cerebellar atrophy also occur in elder age [157].

Recent studies about autophagy-related genes has been identified, *de novo* mutations within WD Repeat-Containing Protein 45 (WDR45) gene [158]. WDR45 is a member of WD repeat protein family, encodes WD repeats which has minimally 40 amino acid conserved region leads to heterotrimeric or multiprotein complex generation [159]. WDR family member proteins are involved in cell-cycle progression, signal transduction, apoptosis, and gene regulation [160]. WDR45 gene is located at Xp11.23 band, and 25.9 kb length gene composed of 12 exons and 11 introns [161]. WDR45 gene expressed one of the four mammalian homologs of yeast Atg18 protein. Besides, Atg18 is the major autophagosome formation-related protein, with WIPIs proteins Atg18 belonging to PROPPIN family proteins [162]. Atg18/WIPIs protein complexes interact directly with Atg2 and this complex cross-talk with class III PtIns 3-kinase during autophagosome formation [163]. Homologs of Atg18 are ATG-18 and EPG-6 in *C. elegans*. Although *C. elegans* needs each homolog proteins at the same time to form autophagosome, homology of WDR45/WIPI4 in human shows powerful correlation with EPG-6 than ATG-18 [164]. Next-generation whole-exome sequencing results revealed that static encephalopathy of childhood with neurodegeneration in adulthood is classified as a subtype of neurodegenerative disease category. The etiology of this disease is mainly related to iron accumulation in brain leading to paraplegia and mental retardation at early onset. Other symptoms of this disease are aggressive behavior, abnormality of eye movement, absent speech, cerebellar atrophy, cerebral atrophy, dementia, dystonia, neurodegeneration, parkinsonism, and spastic paraparesis [165]. Lymphoblastoid cell lines derived from SENDA patients highlighted the reduced level of WIP14 expression compared to healthy control cases. In affected patients lymphoblastoid cell lines demonstrated abnormal accumulation of ATG9A and LC3-double positive components leading to autophagy blockage [159]. As both WDR45 and WIPI4 genes are localized within the same locus at chromosome X. Although the gender-dependent gene expression through X inactivation has not been determined yet, female-type mosaics and male-type hemizyotic lethally confused the molecular processes [166].

4.2. Vici syndrome

Vici syndrome is a very rare and severe congenital multisystem disorder characterized by the principal features of agenesis of the corpus callosum, cataracts, oculocutaneous hypopigmentation, cardiomyopathy, and combined immunodeficiency. The pathogenesis of Vici syndrome is related with autophagy because of the putative role of autolysosome formation gene, EPG-5 [Ectopic P-Granules Autophagy Protein 5 Homolog (*C. elegans*)] [167]. EPG-5 is a metazoan-specific autophagy gene that encodes a large coiled coil domain-containing protein that functions in autophagy during starvation conditions. Note that 5.9 kb long EPG-5 gene is localized in the Xp11.23 band and it is composed of 16 exons and 15 introns. Mutations within EPG-5 reported to be autophagy defective profile in *C. elegans* [146]. Moreover, lack of *C. elegans* EPG-5 demonstrated an accumulation of nondigested autolysosome in mammalian cells. Accumulation of SSTM/P62 and NBR1 are the leading cause of autophagy flux blockage in *in vitro* culture of fibroblasts from Vici syndrome patients [168]. In addition, the role of EPG-5 in

Vici syndrome also indicated by reporting of dysregulation in endocytic pathway. In addition, EPG5$^{-/-}$ mice displayed some of the symptoms of Vici syndrome such as facial dysmorphism and cataracts [167].

4.3. Danon disease

Danon disease is a X-linked recessive disease characterized by weakening of the heart muscle (cardiomyopathy); weakening of the muscles used for movement, called skeletal muscles (myopathy); and intellectual disability [169]. Age and gender are the main risk factors for Danon disease as males develop Danon disease earlier than female and the symptoms come up in childhood or adolescence in most affected males and in early adulthood in most affected females. Heart-related signs and symptoms, including a sensation of fluttering or pounding in the chest (palpitations), an abnormal heartbeat (arrhythmia), or chest pain are the symptoms of Danon disease [170]. The association between autophagy and Danon disease is dependent on the gene that is responsible for Danon disease formation, LAMP2. LAMP2 gene encodes integral lysosomal membrane proteins that is an essential protein involved in the autophagosome vesicle formation *via* interaction with LAMP-2A [171]. The gene responsible for Danon disease is lysosomal-associated membrane protein 2 (LAMP2) that is localized at Xq24 band [172]. LAMP2 protein is a member of a family of membrane glycoproteins, which provides selectins with carbohydrate ligands and it may also function in the protection, maintenance, and adhesion of the lysosome. Alternative splicing of this gene results in multiple transcript variants encoding distinct proteins [173]. LAMP2 gene is composed of 9 exons and 8 introns, 43.2 kb in length. GLN174TER, VAL310ILE, and TRP321ARG mutations within the LAMP2 gene lead to Danon disease [174].

4.4. Liver disease

Both liver disease and lung disease may be developed with the deficiency of alpha-1 antitrypsin gene [175]. Alpha trypsin deficiency prevalence is 1/1500–3500 individuals among European ancestry population. The disease onset varies at age range among individuals. First signs of lung disease in alpha-1 antitrypsin deficiency are generally observed between ages 20 and 50 [176]. Among alpha-1 antitrypsin deficiency patients, 10% of them develop liver disease, which can be diagnosed by yellowing of the skin and whites of the eyes (jaundice). Approximately 15% of adults with alpha-1 antitrypsin deficiency develop liver damage (cirrhosis) due to the formation of scar tissue in the liver [177]. Since liver disease is a multifactorial polygenic disease and alcohol and hepatotoxic agents are the major environmental risk factors for liver disease causing cirrhosis include a swollen abdomen, swollen feet or legs, and jaundice. The most common genetic risk factor for liver disease is the alpha-antitrypsin gene deficiency [178]. The protein encoded by SERPINA1 [serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin)] is secreted as a serine protease inhibitor. It has a number of targets including elastase, plasmin, thrombin, trypsin, chymotrypsin, and plasminogen activator. The mutations on SERPINA1 can cause emphysema or liver disease. Several transcript variants encoding the same protein have been found for this gene. SERPINA1 is composed of 7 exons and 6 introns with a length of 13.9 kb that is located in the 14q32.1 band [179]. SERPINA1 gene product plays

an essential role in the hepato-detoxification process of ZZ genotype of alpha antitrypsin deficiency syndrome diagnosed by PCR amplification and RFLP analysis [180]. By using 19-mer synthetic oligonucleotide probes, SZ phenotype is reported to be associated with M/S difference in exon 3 and M/Z difference in exon 5, whereas phenotype of MZ heterozygotes showed a low Z expression [181]. By routine isoelectric focusing of affected Z type and MZ (her husband genotype) of an obligate carrier mother of PI(M)/PI(null), heterozygote showed atypically low concentrations of circulating Z peptides, which were demonstrated by Harrison et al. [182]. Accumulation of ZZ peptides as intracellular inclusion bodies was reported by Lomas [183] in the ZZ homozygote. Moreover, it was shown that only about 15% of the AAT protein is secreted in the plasma in ZZ homozygotes and the rest of 85% of the protein is not secreted and accumulates in the endoplasmic reticulum (ER) of the hepatocyte. Thus, about 10% of newborn ZZ homozygotes develop liver disease that often leads to fatal childhood cirrhosis. Antitrypsin is an acute phase protein and undergoes a manifold increase in association with temperature elevations during triggered inflammation. Regulation of triggered inflammation and pyrexia symptoms in ZZ homozygote infants is found critical [183]. Wild-type protein primarily degraded by proteosomal activity, mutant alpha-ATZ protein, is reported to be digested autophagy-mediated degradation. According to Yorimitsu and Klionsky et al [1], depletion of Atg-5 in hepatocytes leads to the formation of insoluble aggregates of ATZ proteins and increased production of inclusion bodies. Although the protective or tumor suppressor effect of ATZ protein via autophagy regulation has not demonstrated yet, general evidences support the role of ATZ as a protection against alcohol and hepatotoxic agents [184] (**Figure 6**).

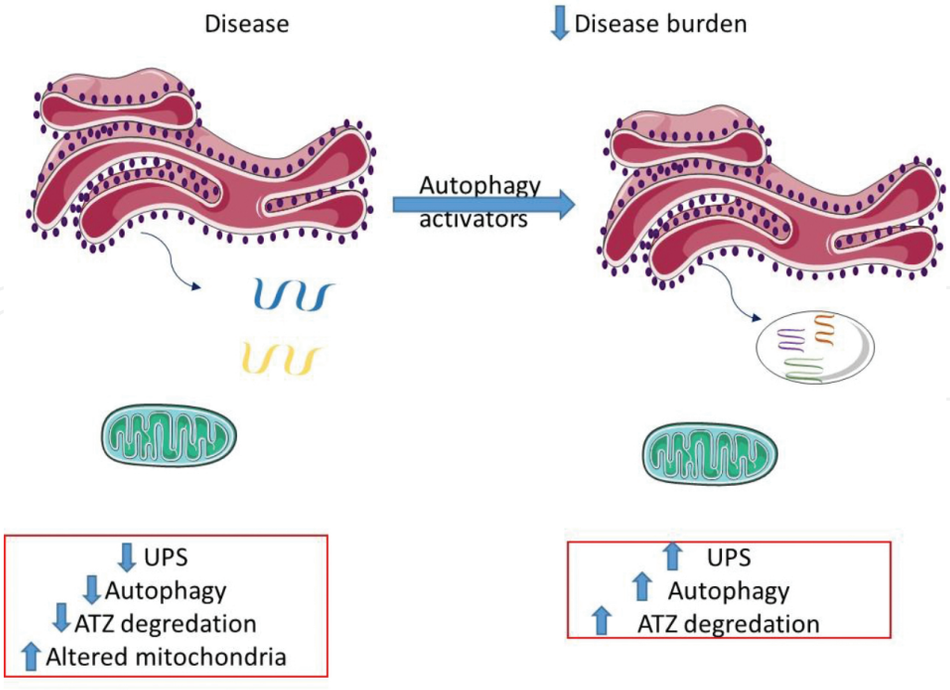

Figure 6. The role of autophagy in alpha antitrypsin deficiency syndrome etiology.

4.5. Myopathy

Myopathies are neuromuscular disorders in which the primary symptom is muscle weakness due to dysfunction of muscle fiber. As different genes are responsible for various types of myopathy, the symptoms of myopathy can include muscle cramps, stiffness, and spasm [185]. Moreover, myopathies can be inherited as the muscular dystrophies or acquired as common muscle cramps [186]. Congenita (developmental delays in motor skills; skeletal and facial abnormalities are occasionally evident at birth), muscular dystrophies (progressive weakness in voluntary muscles; sometimes evident at birth), mitochondrial myopathies (such as in Kearns-Sayre syndrome, MELAS, and MERRF), glycogen storage diseases of muscle (Pompe's, Andersen's, and Cori's diseases), dermatomyositis (inflammatory myopathy of skin and muscle), myositis ossificans (bone growing in muscle tissue), polymyositis, inclusion body myositis, and related myopathies (inflammatory myopathies of skeletal muscle), neuromyotonia (alternation episodes of twitching and stiffness), tetany (characterized by prolonged spasms of the arms and legs is defined as myopathy), and major symptoms of Danon disease is linked with myopathy. There are also various autophagy-related myopathic disorders such as X-linked congenital autophagic vascular myopathy and adult onset vacuolar myopathy with multiorgan involvement that the etiology machinery has not been highlighted [187–190]. All these emphases disorders are predicted to be associated with autophagosome-lysosome fusion. Among muscle diseases sporadic inclusion body myositis, limb girdle muscular dystrophy type 2B, and miyoshi myopathy are shown to be associated with autophagy *via* clearance of the disease causing proteins during molecular pathogenesis [191].

4.6. Cardiac disease

X-linked Danon disease or lysosomal storage disorder and Pompe diseases are rare hereditary diseases of heart, and they are associated with imperfect autophagy processes due to impaired autophagosome lysosome fusion. Patients with coronary artery disease, hypertension, aortic valvular disease, and congestive heart failure are associated with autophagy [135, 192]. The cardiomyocytes isolation from cardiac disease rodent models showed that an obvious accumulation of autophagosomes is distinguishable [193]. Although it is not well clarified that autophagy might exert cytoprotective effects in these models via regulating ATP production, protein, and organelle quality control, or other mechanisms [136]. Atg5 knockout heart tissue models in adult mice results cardiac hypertrophy and contractile dysfunction. The heart consumes more energy per gram than any other tissue in the body. Therefore, energy turnover mechanisms are strictly orchestrated in normal heart tissue. In contrary, cell homeostasis is not properly regulated in a number of cardiac disorders such as cardiac ischemia and heart failure, which are characterized by a reduction in the availability of energy substrates [194]. Furthermore, long-term cardiac stress may remodel in myocytes through inducing elongation and hypertrophy to adapt to stress factors [195]. According to previous data, it is well established that heart tissue required more energy substrates under stress conditions. Therefore, active autophagy may increase the survival of heart cells when they were exposed to stress. Cardiac-specific Atg-5 knockout models did not exert any physiological change under normal conditions. However, stress induction caused more severe pathophysiological processes. Therefore,

these data suggest that upregulation of autophagy in failing hearts is an adaptive response that protects against hemodynamic or neurohormonal stresses. Furthermore, it was shown that Beclin-1 protects contractile functions in the myocytes after stress overload [196]. While heterozygous disruption of Beclin-1 mediated decrease in the size of the myocardial infarction after ischemia/reperfusion, Beclin-1 overexpression decreased cell injury in an *in vitro* model of cardiac ischemia/reperfusion. Dominant-negative Atg5 overexpression increased cell injury, suggesting a protective effect for both ATG genes in ischemia/reperfusion [196].

5. Conclusion

Under physiological conditions, autophagy-related processes are important to provide unique cell homeostasis. In addition, when the cells are exposed to a number of environmental or cellular stress factors, full functional autophagy may protect cells against stress factors. However, as we discussed in previous parts, aging is a multifactorial process, which renders functional regulatory pathways and cause a pathophysiological problems in the cells. Aging in the presence of metabolic diseases causes the impairment of a number of critical genes, which orchestrates autophagy. For this reason, the determination of potential role of autophagic processes in aging-related diseases has potential to provide better therapeutic strategies in the treatment of diseases.

Briefly all mentioned signalling cascades related to aging are altered during autophagic processes. As shown in **Figure 5**, the incidence of orange-colored diseases is increased in an age-dependent manner. Under normal conditions physiological energy balance is orchestrated by several factors placed in blue boxes. Intracellular stress and nutrient sensors labeled in green exert their functional roles through modulating different signaling cascades, which produce a variety of cellular responses as placed in yellow boxes.

The functional role of autophagy in diseases is controversial. Also nutritional status, oxidative stress, and genetic basis of autophagy-related molecular targets determine the disease progression. In this section, we discuss the functional role of autophagy in genetic manner in common diseases and rare diseases (Vici syndrome, SENDA, and Danon disease).

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