Alteration in Autophagic-lysosomal Potential During Aging and Neurological Diseases: The microRNA Perspective

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Abstract Macroautophagy (hereafter referred to as autophagy) is an evolutionary conserved degradation pathway that targets cytoplasmic substrates, including long-lived proteins, protein aggregates and damaged organelles, and leads to their degradation in lysosomes. Beyond its role in adaptation to cellular stresses, such as nutrient deprivation, hypoxia and toxins, recent studies attributed a central role to autophagy in aging and life span determination. Moreover, alterations and abnormalities of autophagy may contribute to a number of important health problems, including cancer, myopathies, metabolic disorders and, the focus of this review, aging-related neurodegenerative diseases. Some disease-related, mutant and aggregation-prone proteins may be cleared by autophagy; on the other hand, dysregulation of the autophagy pathways may also contribute to neurotoxicity observed in degenerative pathologies. microRNAs (miRNAs) are endogenous regulators of gene expression, and their dysregulation was reported in several aging-related conditions. Studies in the last few years introduced miRNAs as novel and potent regulators of autophagy. In this review article, we will summarize the connection between autophagy, aging and Alzheimer's, Parkinson's and Huntington's diseases, and discuss the role of autophagy-related miRNAs in this context.

Keywords Autophagy · Mitophagy · microRNA · Neurodegenerative diseases · Ageing · Pathobiology

Introduction

Aging is an evolutionarily conserved and biologically regulated natural phenomenon, leading to changes that eventually result in the death of organisms. As the human life span is increasing due to higher living standards, medical care and preventive measures, aging-related diseases have become widespread in societies. Therefore, a better understanding of molecular, cellular and organismal changes accompanying aging and aging-related diseases is required.

Recent studies underline the importance of changes and abnormalities in autophagy pathways during aging and disease [1]. In fact, autophagy is a cellular recycling mechanism and a key biological phenomenon in cell survival and death. Two major types of autophagy were involved in aging and related diseases, namely macroautophagy and chaperone-mediated autophagy (CMA). Macroautophagy is characterized by sequestration in double membrane vesicles (autophagic vesicles or autophagosomes) of cytosolic components, such as long-lived proteins, organelles (e.g., mitochondria) and abnormal aggregates, followed by their delivery into lysosomes (now becoming autolysosomes) [2, 3]. Once degraded by lysosomal enzymes, the building blocks (e.g., amino acids from proteins) are recycled for reuse by the cell. On the other hand, CMA directly delivers a subset of cytosolic proteins into lysosomes. Abnormalities in both macroautophagy and CMA were reported in aging-related phenomena and diseases, but in this article, we will mainly focus on macroautophagy (autophagy herein) pathways and recent studies about the importance of microRNAs (miRNAs) as novel regulators of autophagy.

miRNAs are endogenous regulators of gene expression [4]. They regulate important biological processes, including

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Fig. 1 Biogenesis and mechanism of action of microRNAs (miRNA) in mammals. miRNA are transcribed from miRNA genes by RNA polymerase II, and primary-miRNAs (pri-miRNAs) are processed by Drosha and precursor miRNAs (pre-miRNAs), which are produced and exported from nucleus to cytoplasm and processed by the Dicer complex to form the miRNA duplex. The mature miRNA strand of the duplex is then loaded onto the RISC (The RNA-induced silencing

complex). Depending on the complementarity of the mature miRNA sequence (including the seed sequence marked in bold) and target mRNA sequence (miRNA response elements, MRE), the end result is a translational repression (partial complementarity) and/or cleavage of the target mRNAs (near perfect complementarity). Both mechanisms result in the downregulation of target protein levels

differentiation, proliferation and apoptosis [5]. microRNAs are transcribed by RNA polymerase II as pri-miRNAs and processed by a Drosha-DGCR8 complex in the nucleus to produce hairpin-shaped pre-miRNAs (Fig. 1). Following transport to the cytoplasm, DICER protein further cleaves the hairpin, leading to the formation of a ~21–22-nt-long mature miRNA/miRNA* duplex. One of the mature miRNA strands is loaded onto Argonaute protein containing the RISC complex, which guides the miRNA to its target transcripts, while the other strand is usually degraded [4, 5].

Imperfect matching between a functionally important region of the miRNA, namely “the seed sequence” consisting of around 6–8 nucleotides, and complementary “miRNA response elements” (MRE) on the target mRNA sequences (mainly in the 3'UTR regions) determines the target specificity of the miRNA [6, 7].

miRNAs and especially their functional sequences, such as the seed sequence and sequences responsible for proper folding, were highly conserved between species, including those commonly used as animal models for human disease

(e.g., mice, rats, zebrafish, *C. elegans*, *drosophila*) [8]. So far, there are approximately 1,500 miRNAs described in humans. miRNA names are denoted as a combination of letters and numbers [7]. Prefixes (3–4 letter) in miRNA names indicate the species (e.g., *Homo sapiens*: hsa-miR-181). Mature miRNA sequences are denoted with ‘miR’; however, primary-miRNAs are denoted with ‘mir’. miRNAs conserved between species are usually given the same number (e.g., hsa-miR-181 and mmu-miR-181). miRNAs with closely related mature sequences are marked with letter suffixes (e.g., hsa-miR-10a and hsa-miR-10b) and they usually belong to the same family [9]. In the mature miRNA/miRNA* duplex, the complementary arm of the predominant strand is indicated with a star (*), and it may sometimes be functionally relevant.

In this review article, we will first summarize changes and abnormalities occurring in the autophagy pathways during aging and common aging-related diseases, namely Alzheimer’s, Parkinson’s and Huntington’s diseases, and then discuss the relevance and importance of autophagy-related miRNAs in this context.

Role of Autophagy in Aging and Neurodegenerative Diseases

Autophagy is tightly controlled by various signaling pathways and protein complexes (see Fig. 2 for a summary) [2, 3], and is an important determinant of the well-being and life span of an organism [1]. Limitation of oxidative stress through degradation of damaged mitochondria, abnormal proteins and disease-related protein aggregates include beneficial effects of autophagy in health and disease. Yet, the overcrowding of cytosol by autophagosomes does not necessarily reflect autophagic clearance, and might sometimes be a sign of perturbation of autophagy mechanisms. Resulting inefficient autophagy and autophagic flux abnormalities may even contribute to pathological changes in cells and tissues. Intricate connections exist between autophagy, aging and aging-related neurodegenerative diseases.

Aging and Autophagy

The autophagic responses of cells and tissues decline with age and this decrease correlates with the accumulation of abnormal proteins and organelles [1, 10]. Data complementing these observations came from anti-aging studies. It was shown that drug-mediated or long-term, caloric restriction-related life span extension correlated with increased autophagic activity, and that autophagy inhibition neutralized the anti-aging effects [1]. The rate-limiting function of autophagy in life span extension was documented by genetic studies performed in the model organism *C. elegans*. Knockdown of

autophagy genes compromised life span prolongation by insulin receptor mutation, drugs or dietary restriction [11, 12]. Therefore, autophagic activity is important for healthy aging and possibly life span determination as well in higher organisms (Fig. 2).

Alzheimer’s Disease and Autophagy

Alzheimer’s Disease (AD) is characterized by cognitive impairment, memory loss and dementia [13]. Histopathologically, extracellular plaques of amyloid-beta and intracellular neurofibrillary tangles in neurons are considered to be pathognomic findings [13]. Amyloid plaques result from abnormal processing, excessive production, aggregation and improper clearance of the amyloid precursor protein (APP) [13, 14]. Accumulation of the amyloid-beta peptide is a result of a sequential proteolytic cleavage of the APP protein by BACE1 and gamma-secretase enzymes. Following BACE1 cleavage, APP fragments sAPPbeta and B-CTF are formed. sAPPbeta has a role in neuronal death, however B-CTF is further cleaved by the gamma-secretase enzyme complex, resulting in the release of amyloid-beta fragments: amyloid beta-40 (physiological role in synapse formation) or amyloid beta-42 (pathological aggregate-prone form). In contrast, alpha-secretase cleavage occurs within the amyloid-beta fragment, preventing amyloid generation [14]. ADAM9, ADAM10 and ADAM17 were shown to possess alpha-secretase activity, whereas gamma-secretase activity resides in a protein complex including Presenilin-1 and -2 (mutated in some familial AD patients). Microtubule defects also contribute to vesicular traffic abnormalities observed during AD, and hyperphosphorylation of the microtubule stabilizing protein tau is involved in the origin of microtubule dysfunction and organelle transport defects [15]. Hyperphosphorylated tau has a tendency to form large filaments, leading to pathological aggregates of neuronal tangles that cause microtubule instability [15]. Other factors playing a role, especially in the sporadic forms of AD, include high blood cholesterol and overexpression of an e4 variant of the cholesterol receptor apolipoprotein (ApoE e4) [16]. In neurons affected by AD, cholesterol and ApoE e4 were proposed to stimulate endocytosis, causing an increase in the number of Rab5- and Rab7-containing vesicles [17]. Reactive oxygen production and mitochondrial changes were also seen in diseased neurons.

Protein accumulations, organelle transport defects, mitochondrial problems and increases in ROS levels create a vicious cycle of aggravating neuronal dysfunction, and according to some studies, stimulating autophagosome generation in AD. Amyloid-beta and tau were targeted by autophagosomes for degradation, yet autophagosomes may also be a site of amyloid-beta generation [18, 19]. Moreover,

Fig. 2 Autophagy activating stress signals converge at the mTORC1 complex. Suppression of the activity of mTOR kinase in the complex relieves the ULK1/2 complex from an inhibitory phosphorylation, and triggers autophagy. Class III phosphatidylinositol 3-kinase Vps34 is regulated by partners including the beclin 1 protein and phosphorylates phosphatidylinositol (PI) molecules on membranes, and marks the autophagosome formation sites. These PI3P-rich membranes nucleate a formation of cup-shaped structures (omegasomes or cradles) that serve as templates for autophagic “isolation membranes”. Elongation and completion of “autophagosomes” depend on two ubiquitination-like conjugation systems, namely Atg12–Atg5–Atg16L1 and Atg8/MAP1LC3 (LC3). The end result is covalent conjugation of LC3 to the lipid phosphatidylethanolamine (PE). Other Atg proteins contribute to reaction steps as well, but the Atg12–Atg5–Atg16L1 complex serves as an E3-ligase for LC3. LC3 priming by

Atg4 through the cleavage of a short C-ter peptide is a prerequisite for lipid conjugation. Moreover, during selective autophagy, the interaction of LC3 with autophagy receptor proteins (e.g., SQSTM1/p62) is critical for the recruitment of various types of cargos, including protein aggregates into autophagosomes. Atg9 and Atg2 proteins shuttle between other membrane compartments (such as Golgi) and autophagosome formation sites, and transport lipids and proteins. Completed autophagosomes are transported by microtubules to the vicinity of acidic compartments, and fuse with late endosomes and lysosomes forming “autolysosomes”. Proteins such as LAMP2 and RAB7 play a role in the fusion. Cargos carried by autophagosomes are degraded by lysosomal hydrolases, and their building blocks (such as amino acids from proteins) are recycled back to cytosol for reuse by the cell

amyloid-beta itself impaired autolysosomal degradation in disease models. Strikingly Presenilin-1 was necessary for targeting of the vacuolar ATPase to lysosomes and acidification, affecting the lytic enzymatic activity in this organelle [20]. Therefore, mutant Presenilin-1 may also lead to autolysosomal function impairment. To further complicate the picture, abnormalities of endocytosis and microtubular transport machinery have repercussions on the closely related autophagy and autophagic degradation pathway. Endocytic maturation, proper lysosomal pH, lysosomal

enzymatic activity, and intact microtubules are required for autophagosomes to reach into and fuse with lysosomes, a prerequisite for autophagic degradation of substrates, including pathological protein aggregates. As a result of disease-related events, autophagosomes that fail to mature into autolysosomes and clear protein aggregates will overcrowd AD neurons. This situation might contribute to the progression of the neurodegenerative pathology through defects of abnormal protein and organelle turnover, further increases in ROS levels, as well as metabolic disturbances

due to insufficient cellular building block recycling and perturbances of energy homeostasis. Hence, accumulation of autophagic vesicles in AD brains seems to be a negative and aggravating factor, rather than a sign of protein aggregate clearance.

Parkinson's Disease

Parkinson's Disease (PD) is another age-related neurodegenerative disease. PD causes movement disorders, including muscle rigidity, akinesia and resting tremor. Selective death of dopaminergic neurons in substantia nigra are in the origin of the symptoms [21]. Intracytoplasmic inclusions called Lewy bodies, mainly consisting of aggregates of alpha-synuclein protein (a product of the *PARK1/SNCA* gene), are a pathological trait of the disease. Other genes that are mutated in the familial forms of Parkinson's disease include *PARK2* (parkin), *PARK5* (*UCHL1*), *PARK6* (*PINK1*), *PARK7* (*DJ-1*) and *PARK8* (*LRRK2*) [22]. Moreover, chemicals leading to mitochondrial dysfunction and oxidative stress, such as MPTP and rotenone, were shown to result in parkinsonian phenotypes in PD animal models [22].

Native alpha-synuclein plays a role in vesicle release in synaptic junctions [23]. Mutation, multiplication or post-translational modifications (e.g., ubiquitination, oxidation, dopamine-related adducts or nitration) of alpha-synuclein cause its aggregation [22]. In contrast, native alpha-synuclein was a target of CMA-mediated proteolysis; mutant alpha-synuclein perturbed lysosomal translocation and degradation of CMA substrates, including itself [24, 25]. Another PD-related protein, mutant *UCH-L1*, physically interacted with *LAMP-2A* lysosomal receptor for chaperone-mediated autophagy (CMA) and blocked the CMA pathway [26]. Under these conditions, autophagy was upregulated to compensate the CMA pathway and excessive autophagy was toxic to cells [27]. Indeed, autophagy inhibition improved the survival of cells expressing mutant alpha-synuclein [28]. It was first demonstrated that in an MPP(+)-induced cellular model of PD, stimulation of beclin 1-independent autophagy was associated with neuronal cell death [29]. Conversely, beclin 1-dependent autophagy was seen to protect neurons from cell death, when observed in mutant alpha-synuclein PD models [30].

In fact, alpha-synuclein itself was described as an autophagy target by several independent studies (for example [30, 31]). Yet, alpha-synuclein might impair autophagy by sequestering TFEB [32]. In summary, as in the case of AD, unperturbed autophagy and CMA pathways might have some beneficial effects against PD, yet, abnormal protein accumulations and perturbation of normal degradative functions seem to contribute to disease progression.

Recent studies link PD-related proteins, such as parkin, *PINK1*, *DJ-1* and *LRRK2*, to “mitophagy”, i.e., autophagy of mitochondria. Mitophagy protects cells, including neurons, by eliminating damaged mitochondria, controlling ROS production and preventing cell death. Parkin, a ubiquitin ligase that is recruited to damaged mitochondria through the *PINK1* protein, led to degradation of outer mitochondrial membrane proteins by the ubiquitin-proteasome system (UPS), and triggered autophagy of the organelle [33]. Mutations of parkin caused accumulation of its substrates and led to disturbances of mitophagy. Furthermore, other PD-related proteins might also affect mitophagy. *DJ-1* was linked to ROS management in cells, while *LRRK2* was shown to play a role in mitochondrial fission/fusion dynamics [34]. Moreover, *LRRK2* mutants were recently shown to promote mitophagy in neurons [35]. Both events have an impact on the efficiency of mitophagy in cells. As another link between mitophagy and PD, mutant alpha-synuclein was shown to massively promote autophagy of even healthy and polarized mitochondria [36]. Therefore, dysfunction of UPS, protein misfolding and mitochondrial dysfunction might play an important role in the pathogenesis of PD [22].

Huntington's Disease

Abnormally long polyglutamine repeats (polyQ) in the Huntingtin (Htt) protein cause its misfolding and aggregation, leading to Huntington's Disease (HD) [37, 38]. Degeneration of neurons in the striatum and other regions of the brain are responsible for symptoms such as motor dysfunction, cognitive difficulties and dementia. Native Htt containing less than 35 polyQ repeats has a role in diverse biological processes, including vesicle transport, clathrin-mediated endocytosis, neuronal transport and postsynaptic signaling. However, more than 36 polyQ repeats in the N-terminal region of the protein defines the disease-associated allele. Htt may be cleaved by caspases/calpains, and N-terminal cleavage products containing the polyQ stretch were shown to be even more toxic than the full-length protein [39, 40].

Mutant Htt perturbs various cellular processes. Although aggregates were also observed in the nucleus in rare juvenile onset cases of HD, cytosolic aggregates predominate in the adult-onset disease [41]. Cytoplasmic insoluble full-length Htt or its N-terminal fragments accumulated as ubiquitinated inclusions, impaired the UPS system that normally degrades the soluble forms of the protein, and stimulated autophagy [42]. Furthermore, postmortem analyses revealed a dramatic increase in the number of autophagosome-like structures in the brains of HD patients [43]. A number of studies introduced autophagy as a clearance mechanism, especially for insoluble Htt

aggregates, and inhibition of autophagy in affected cells decreased viability [38, 44]. In line with these observations, the mTOR inhibitor and autophagy activator drug rapamycin and its derivatives decreased Htt aggregates and toxicity in HD animal models [44]. mTOR itself was sequestered within mutant Htt aggregates, decreasing its activity, and possibly contributing to autophagy stimulation [45•]. Importantly, Jeong et al. showed that clearance of mutant Htt by autophagy depended on its acetylation at K444 [46]. Acetylation was also observed in the brain of HD patients, and it was important for targeting mutant Htt for degradation by autophagy in mouse models of the disease [47]. All these studies and others indicate that autophagy activation might be beneficial in HD patients through clearance of pathological Htt aggregates.

Regulation of Autophagy by miRNAs

Changes in miRNA levels were observed in pathologies such as cancer and neurodegenerative diseases [48]. Recent studies introduced miRNAs as new players in the regulation of autophagy. mRNAs of several key proteins in various steps of autophagy, from proteins functioning in the upstream signaling pathways to the later stages of autophagic degradation, were shown to be targeted by miRNAs.

Upstream Pathways, mTOR and Atg/ULK Complexes and miRNAs

miRNAs regulate the mTOR complex and its upstream components. In adult pancreatic β -cells, miR-7 negatively regulated mTOR, and inhibition of the miRNA resulted in mTOR pathway activation and cell proliferation [49]. miR-199-3p targeted both mTOR and cMet in hepatocellular carcinoma [50]. miR-101 was another miRNA targeting mTOR in vascular endothelial cells [51]. Several studies showed the role of miR-21 on the mTOR pathway [52–54]. Upstream regulators of mTOR, PIK3CD and IGF1R were other targets of the miR-7 [55, 56]. Additionally, miR-30a also targeted PIK3CD to suppress cell migration and invasion of colorectal carcinoma cells [57].

The Atg1/ULK1-2 autophagy complex that operates downstream to mTOR was subject to regulation by miRNAs. miR-20a and miR-106b controlled leucine deprivation-induced autophagy in C2C12 myoblast cells through direct targeting of the ULK1 protein [58]. ULK1 was also regulated by miR-290/295 in melanoma cells, where the miRNAs inhibited autophagic cell death and gave selective advantage for tumor cell survival [59]. The second mammalian Atg1 protein, ULK2, was a target of miR-885-3p [60].

Beclin 1 as an miRNA Target

Beclin 1 was described as a common target of a number of autophagy-related miRNAs. miR-30a was reported to control rapamycin-induced autophagy by targeting beclin 1 [61•]. Further studies confirmed the role of miR-30a in autophagy regulation [62–65]. Zou et al. [62] showed that miR-30a blocked cisplatin-induced autophagy and sensitized tumor cells to death. Again, miR-30a augmented imatinib treatment efficacy in chronic myeloid leukemia, and Atg5 and beclin 1 level changes caused by the miRNA contributed to the observed effect [63]. Additionally, two other studies provided evidence about the importance of miR-30a in autophagy of cardiomyocytes [64, 65]. In both cases, suppression of miR-30a resulted in beclin 1 protein accumulation and stimulated cardioprotective autophagy. Another member of the miR-30 family, miR-30d, blocked starvation and rapamycin-induced autophagy through modulation of several autophagy-related genes, including beclin 1, bnip3L, Atg12, Atg5 and Atg2 [66].

Beclin 1 function was controlled by other miRNAs as well. An unbiased screen of miRNAs blocking starvation-activated autophagy led us to discover miR-376b as a novel regulator of autophagy [67•]. In addition to starvation, mTOR inhibition-related autophagy was also blocked by the miRNA in cancer cells. Beclin 1 and Atg4C were direct and rate-limiting targets of miR-376b for autophagy inhibition [67•]. Later, another miRNA, miR-199-5p was reported to control irradiation-induced autophagy in cancer cells, through its inhibitory effects on both beclin 1 and DRAM1 (a p53-induced modulator of autophagy and DNA damage-induced cell death) [68, 69].

Components of Ubiquitination-like Systems and miRNAs

Other targets of miRNAs in the autophagy pathway were the components of the ubiquitination-like systems. Studies from independent groups showed that Atg5 was a target of miR-181a and miR-30a [63, 70]. Autophagy activated by starvation or mTOR inhibition was blocked by the overexpression of miR-181a in cancer cells from different tissues, and direct targeting of Atg5 3'UTR by the miRNA was crucial for this outcome [70]. In addition to beclin 1, targeting of Atg5 by miR-30a played a role in the imatinib-induced cytotoxicity in leukemia cells [63].

Another component of the ubiquitination-like reactions, Atg7, was reported as an miRNA target. miR-375 downregulated Atg7 and inhibited the cytoprotective autophagy that was activated under hypoxic conditions in liver cancer cells, resulting in their demise [71, 72]. In line with this study, cisplatin-induced downregulation of miR-199-5p in liver cancer cells enhanced autophagy and cell proliferation

through increased expression of Atg7 [69]. Lastly, miR-290-295 cluster miRNAs targeted Atg7 to inhibit autophagic cell death of melanoma cells, giving them a selective advantage for tumor cell survival [59].

Atg4 family members were controlled by at least two miRNAs, including miR-376b and miR-101 [67, 73]. miR-376b, which controlled beclin 1 levels, also regulated Atg4C during starvation and mTOR-dependent autophagy [61]. A luciferase-based functional miRNA screen performed by Frankel et al. [73] led to the characterization of miR-101 as an autophagy regulator. In fact, the effects of miR-101 on Atg4D, STMN1 and RAB5A levels were critical for autophagy regulation and sensitization of breast cancer cells to the cytotoxic effects of tamoxifen.

Additionally, the autophagy adaptor and ubiquitin-binding protein P62/SQSTM1 was a target of several miRNAs, including miR-17, miR-20, miR-93 and miR-106 [74].

Rab Proteins and miRNAs

Rab family proteins play a role in vesicular transport, endosome maturation and lysosome-autolysosome formation. miR-101 was shown to affect the levels of the early endosome-related protein Rab5A [73]. Similarly, miR-501 and miR-130a targeted Rab5A and Atg2B, respectively, in leukemia cells [75]. TBC1D2/Armus, a GAP of the late endosome-associated Rab7, was described as a novel target of miR-17 [76]. Furthermore, miR-502 inhibited autophagy through regulation of another Rab protein, Rab1B, that is involved in the formation of Atg9-autophagosome precursors [77].

Other miRNAs Targets

In addition to Atg genes and proteins that are directly related to canonical autophagy pathways, other proteins involved in autophagy-related events were also controlled by miRNAs. For example, the gene of the Crohn's disease (CD)-associated autophagy protein IRGM was targeted by miR-196 [78]. miRNA was overexpressed in CD-affected bowels and selectively downregulated the disease-protective IRGM allele, but the risk-associated allele was spared. Targeting of IRGM by the miRNA blocked autophagic clearance of bacteria in the intestine, hence contributing to the pathology [79]. Interestingly, IRGM was necessary for autophagy-dependent survival of neurons in a stroke model [80].

Martinez-Outschoorn et al. [81] observed that autophagy-related gene expression as well as miR-31 and miR-34c levels were upregulated in caveolin-null stroma cells. Autophagy was stimulated in the tissues of caveolin-null mice, and the authors speculated that this was a result of

FIH (factor-inhibiting HIF) downregulation by miR-31 and activation of HIF-1 α , a central regulator of hypoxia-induced autophagy. Yet, Yang et al. [82] showed that miR-34c inhibited Atg9A expression and autophagy activation in *C. Elegans*.

Telomerase-specific oncolytic adenovirus studies provided additional evidence about the involvement of miR-7 in autophagy pathways. Virus infection upregulated miR-7 and stimulated autophagy; furthermore, overexpression of the miRNA gave similar results [83]. The authors correlated the observed effect on autophagy with a decrease in the epidermal growth factor receptor following miR-7 expression.

A study on Waldenstrom macroglobulinemia (WM) (a low-grade B cell lymphoma) led to the analysis of the role of miR-9* in cell death and autophagy. WM cells had low miR-9* levels and introduction of the miRNA into the cells stimulated autophagy and death [84]. miRNA-9*-related targeting of histone deacetylases HDAC4/HDAC5 or inhibition of HDAC activity might be the cause of Rab7 and LC3B upregulation in this context, and induction of autophagy.

miRNA enrichment analyses give insight to complex miRNA networks regulating gene expression. Jegga et al. followed a systems biology approach and reported that several miRNAs, including miR-130, let-7/miR-98, miR-124, miR-204 and miR-142, could play a role in the regulation of autophagy pathways [85].

Autophagy miRNAs in Aging and Neurodegenerative Diseases

Analysis of the literature concerning miRNAs deregulated during aging or neurodegenerative diseases revealed the existence of an overlap with miRNAs implicated in autophagy regulation. Yet, to our knowledge, so far there is no report directly connecting an miRNA abnormality to an autophagy deregulation during aging or neurodegenerative diseases. Therefore, here we will summarize available data about the role of those autophagy miRNAs that were linked to aging and neurodegenerative diseases and discuss their contribution to the pathology. Autophagy miRNAs that were implicated in aging-related conditions are listed in Table 1.

Aging and Autophagy miRNAs

Several miRNAs regulating autophagy were differentially expressed in the aging brain. Li et al. showed that, in addition to miR-22, 720 and 721, the autophagy blocking miRNA miR-101a was increased in the brain during aging [86, 87]. In contrast, miR-130a levels were lower in elderly

Table 1 List of autophagy-related miRNAs involved in aging or neurodegenerative diseases

miRNA	Species	Chromosome	miRNA gene	Disease	Autophagy targets	Effect on autophagic target	References
let-7b	Human, mouse	Human: chr22(q13.31) mouse: chr15(qE2)	let7 cluster	AD, HD	N.D.	Indirect evidence	[120]
miR-7	Mouse	Human: chr9(q21.32) mouse: chr13(q B1)	miR-7 cluster	PD	EGFR	Induction of autophagy	[83]
miR-9	Human, mouse	Human: chr1(q22) mouse: chr3(qF.1)	miR-9 cluster	AD, HD	HDAC4, 5	Induction of autophagy	[84]
miR-9*	Human	Human: chr1(q22) mouse: chr3(qF.1)	miR-9 cluster	HD	HDAC4, 5	Induction of autophagy	[84]
miR-17-5p	Human	Human: chr13(q31.3) mouse: chr14(qE4)	miR-17 cluster	AD	ATG7	Inhibition of autophagy	[121]
miR-20a	Human	Human: chr13(q31.3) mouse: chr14(qE4)	miR-17 cluster	AD	ULK1	Inhibition of autophagy	[58]
miR-30b	Human	Human: chr8(q24.22) mouse: chr15(q D2)	miR-30 cluster	PD	ATG5, BECN1	Inhibition of autophagy	[61•–63]
miR-30c	Human	Human: chr1(p34.2) mouse: chr4(qD2.2)	miR-30 cluster	PD	ATG5, BECN1	Inhibition of autophagy	[61•–63]
miR-30e	Mouse	Human: chr1(p34.2) mouse: chr4(qD2.2)	miR-30 cluster	Aging	N.D.	Indirect evidence	[61•–63]
miR-34a	Rat, mouse	Human: chr1(p36.23) rat: chr5(q36) mouse: chr4(qE2)	miR-34 cluster	Aging, AD	HIF1 α	Inhibition of autophagy	[81]
miR-34b	Human	Human: chr11(q23.1) mouse: chr9(qA5.3)	miR-34 cluster	HD, PD	HIF1 α	Induction of autophagy	[81]
miR-34c	Human	Human: chr11(q23.1) mouse: chr9(qA5.3)	miR-34 cluster	PD	HIF1 α	Induction of autophagy	[81]
miR-93	Human	Human: chr7(q22.1) mouse: chr5(qG2)	miR-17 cluster	Aging	P62	Inhibition of autophagy	[74]
miR-101	Mouse, human	Human: chr1(p31.3) mouse: chr4(qC6) chr19(qC1)	miR-101 gene	Aging, AD, PD	ATG4C, STMN1, RAB5A	Inhibition of autophagy	[73•]
miR-106b	Human	Human: chr13(q31.3) mouse: chr14(qE4)	miR-17 cluster	AD	ULK1	Inhibition of autophagy	[58]
miR-106b	Human, mouse	Human: chr7(q22.1) mouse: chr5(qG2)	miR-17 cluster	AD, Aging	ATG16L1	Inhibition of autophagy	[122]
miR-122a	Human	Human: chr18(q21.31) mouse: chr18(qE1)	miR-122 cluster	AD	N.D.	Indirect evidence	[123]
miR-124a	Human	Human: chr8(p23.1) mouse: chr14(qD1)	miR-124 cluster	HD	N.D.	Bioinformatic evidence	[85]
miR-124a	Mouse	Human: chr8(p23.1) mouse: chr14(qD1)	miR-124 cluster	AD	CAPN1, CAPN2	Indirect evidence	[85]
miR-125b	Human, mouse	Human: chr11(q24.1) mouse: chr9(qA5.1)	miR-10 cluster	HD	PI3KCD	Indirect evidence	[124]
miR-128a	Human, rat	Human: chr2(q21.3) mouse: chr1(qE4) rat: chr13(q12)	miR-128 cluster	PD	TFEB	Inhibition of autophagy	[32]
miR-130a	Human	Human: chr11(q12.1) mouse: chr2(qD)	miR-130 cluster	Aging	ATG2B, DICER	Inhibition of autophagy	[75]
miR-132	Mouse, rat	Human: chr17(p13.3) mouse: chr11(q B5) rat: chr10(q24)	miR-132 cluster	HD	FOXO3a	Inhibition of autophagy	[125]
miR-142	Chick	Human: chr17(q22) mouse: chr11(qC)	miR-142 gene	AD	ATG7	Inhibition of autophagy	[59]
miR-181a	Human, mouse	Human: chr1(q31.1) mouse: chr1(qE4) chr2(qB)	miR-181 cluster	Aging, AD	ATG5	Inhibition of autophagy	[70]
miR-195	Rat	Human: chr17(p13.1) mouse: chr11(qB3) rat: chr10(q24)	miR-15 cluster	AD	ATG14	Induction of autophagy	[100]
miR-199-5p	Human	Human: chr19(p13.2)	miR-199 cluster	PD	ATG7, BECN1	Inhibition of autophagy	[126]
miR-374	Human	Human: chrX(q13.2)	miR-374 cluster	PD	ATG5	Inhibition of autophagy	[60]
miR-470	Mouse	Human: – mouse: chrX(q A7.1)	N.D.	Aging	N.D.	Activation of autophagy	[127]

Table 1 continued

miRNA	Species	Chromosome	miRNA gene	Disease	Autophagy targets	Effect on autophagic target	References
miR-669b	Mouse	Human: – mouse: chr2(q A1)	N.D.	Aging	N.D.	Activation of autophagy	[127]
miR-681	Mouse	Human: – mouse: chr12(qC2)	N.D.	Aging	N.D.	Activation of autophagy	[127]

N.D. Not determined

individuals, while the expression of miR-93 and miR-106b were increased during aging [88, 89]. Proteins that are related to aging and known to inhibit the autophagy pathway, such as IGF1R and Akt, were controlled in long-lived mutant mice by a number of miRNAs, including miR-470, miR-669b and miR-681 [90]. These miRNAs showed an age-dependent increase possibly correlating with autophagy activation in these models. In other studies, longevity was correlated with a decrease in miRNAs, including miR-30e, 34a and 181a, all reported to be blockers of the autophagic activity [91]. Therefore, changes in autophagy miRNA levels generally favored autophagy activation in this context and might have contributed to longevity.

Alzheimer's Disease and Autophagy miRNAs

miRNA expression profiling studies documented that several autophagy miRNAs were dysregulated in AD. Downregulation of a group of miRNAs, including autophagy-related miR-101 [92, 93], miR-106b [94], miR-181a and miR-181c [95], and upregulation of let-7 [96] and miR-34a [97], was found in various AD studies. Indeed, AD-related genes and proteins were direct targets of several miRNAs. Hebert et al. [98] provided evidence that miRNAs of the miR-20a family (miR-20a, miR-17-5p, miR-106b), which are endogenous regulators of APP expression and inhibitors of autophagy, were downregulated in AD cell line models and in samples from patients. Moreover, polymorphism in the 3'UTR of APP mRNA was a risk factor for AD, and an A454G variant allele modified the efficacy of miR-20a binding to this mRNA [99]. Similarly, miR-101 was reported as an miRNA controlling the expression of the APP protein [92]. Another important gene in AD pathology, BACE1, was targeted by several miRNAs, including the autophagy-related miR-195, leading to a decrease in amyloid-beta generation [100–102]. miR-195 expression affected APP expression as well. Interestingly, plasma levels of the miRNA were lower in patients with dementia, and lentiviral delivery of miR-195 reduced dementia vulnerability in a carotid artery occlusion model of dementia in a rat model [102]. Fang et al. studied the role of the putative autophagy miRNA, miR-124, in an AD mice model [103]. In fact, miRNA targeted the 3'UTR region of BACE1 mRNA and regulated its expression, resulting in a decrease in amyloid-beta neurotoxicity and

preventing neuronal death. Autophagy-related miRNAs were reported to control some other AD susceptibility genes and gamma secretase modulators as well. miR-122 regulated ADAM10, ADAM17 and IGF1R gene expression [104, 105]. miR-142 that might directly or indirectly affect autophagy protein levels was shown to regulate ADAM9 expression [59, 85, 106]. All these studies provide evidence that modification of autophagy and disease-related proteins might affect the course of AD and influence prognosis.

Parkinson's Disease and Autophagy miRNAs

miRNAs play important roles in the dopaminergic system. For example, Kim et al. [107] showed that mir-133b and homeodomain transcription factor PITX3 defines a pivotal negative feedback loop during dopaminergic neuron differentiation. Screens of differentially expressed miRNAs revealed that a subset of autophagy-related miRNAs, namely miR-30b, miR-30c, miR-101, miR-199-5p and miR-374, were underexpressed in PD patients [108]. Similarly, downregulation of mir-34b and mir-34c was observed in advanced-stage PD [109]. Here, the decrease in mir-34b and c levels correlated with mitochondrial dysfunction, ROS production, and the depletion of DJ1 and parkin expression. It is possible that changes in above-mentioned autophagy-related miRNAs affected the course of the disease through contribution of autophagy defects and resulting protein aggregate and mitochondria clearance abnormalities.

Not surprisingly, the expression of some PD-related genes were controlled by miRNAs. Alpha-synuclein had a long 3'UTR that was directly regulated by at least two miRNAs: miR-153 and the autophagy miRNA, miR-7 [110, 111]. Moreover, these miRNAs and alpha-synuclein were expressed in similar brain regions [111]. A consequence of miR-7-induced downregulation of alpha-synuclein was protection of cells against oxidative stress and death [110]. In line with these observations, miR-7 levels were decreased in an MPTP-induced mice model of PD [110]. Since, miR-7 was previously shown to activate autophagy, in addition to its effect on alpha-synuclein levels, autophagy-mediated clearance of aggregates and abnormal mitochondria might have contributed to the observed antioxidant and cell protective effects. Another

autophagy-related miRNA was miR-128, which was shown to target a major transcriptional regulator of lysosome biogenesis and autophagy genes, called TFEB. Decressac et al. [32] reported that a decline in the autophagic-lysosomal function was observed in animal models of PD or in affected patient brains. Downregulation of TFEB by miR-128 aggravated alpha-synuclein toxicity in neuronal cells, pointing to a role for autophagy inhibition by the miRNA in PD pathogenesis.

Huntington's Disease and Autophagy miRNAs

In a study comparing the outcome of mutant Htt exon1 versus non-toxic variant protein expression, Gaughwin et al. [112] identified upregulation of the autophagy-related miR-34b as well as miR-1285 in cells expressing mutant Htt. Since plasma levels of miR-34b were elevated even in HD carriers compared to controls, the authors introduced miR-34b as an easily detectable marker of the disease. Other studies analyzing samples from mice using miRNA microarrays revealed that a number of miRNAs, including autophagy-related miR-132, were downregulated in HD transgenics compared to controls [113, 114]. Surprisingly, mutant Htt expression in mice led to changes in central miRNA pathway protein levels, and showed abnormal miRNA biogenesis [115]. Moreover, the Htt protein physically interacted with Argonaute, a key protein in miRNA function. As a consequence, mutant Htt expression attenuated global miRNA-mediated silencing activity in cells [115]. In line with these findings, Htt knockdown caused a defect in the function of the autophagy-related miRNA, let-7b [115].

Several miRNAs were shown to target the Htt mRNA. A direct interaction between the 3'UTR of Htt mRNA and miRNAs, including the autophagy-related miR-125b, was reported [116]. miR-125b could downregulate Htt levels in cells. Levels of two other HD-related genes, transcriptional repressor REST, and its partner coREST, were modulated by miRNAs. REST and coREST are master regulators of the expression of a number of neuron-specific genes, and they are key to neural cell fate decisions. REST was sequestered in cytoplasm, in part through its interaction with Htt, and to perform its transcriptional repressor function, it needed to translocate into the nucleus [117]. Mutant Htt failed to control REST translocation [117]. Gene promoters of miR-9/9*, autophagy-related miRNAs with decreased levels in HD patients, contained REST-responsive RE1 sequences. Conversely, REST and coREST 3'UTRs had miR-9/9*-responsive elements and overexpression of the miRNAs attenuated their protein levels, forming a regulatory loop [114]. A similar feedback mechanism was also documented for REST and autophagy-related miR-124a [118]. miR-124a levels were

found to be decreased, while its cellular targets were upregulated in HD models and patient brains [114, 118, 119].

Conclusion

Studies summarized here and elsewhere underline the importance of autophagy abnormalities in aging and aging-related neurodegenerative conditions. The number of reports on miRNAs involved in autophagy regulation is exponentially increasing, and providing new evidence about the connection between autophagy defects and human diseases. Although systematic studies are lacking to date, autophagy-regulating miRNAs that were shown to be upregulated or downregulated during aging and neurodegenerative diseases (listed in Table 1) possibly contribute to disease-related abnormalities observed in the autophagy pathway. Autophagy may clear protein aggregates, limit oxidative stress and provide stress-resistance, or conversely autophagy abnormalities may aggravate disease burden to cells secondary to metabolic and intracellular transport-related defects. Therefore, the autophagy pathway plays a critical role in the course of aging and degenerative conditions, and miRNAs affecting its function and efficacy should be considered as determining factors in disease progression. Analysis and manipulation of these miRNAs might open new avenues in the diagnosis, follow-up and even treatment of various pathological conditions, including aging-related neurodegenerative diseases.

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Compliance with Ethics Guidelines

Conflict of Interest Kumsal Ayse Tekirdag, Deniz Gulfem Ozturk, and Devrim Gozuacik declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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