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Endosomal-lysosomal dysfunction in metabolic diseases and Alzheimer's disease

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Abstract

The endosomal-lysosomal pathways and related autophagic processes are responsible for proteostasis, involving complexes between lysosomes and autophagosomes. Lysosomes are a key component of homeostasis, involved in cell signaling, metabolism, and quality control, and they experience functional compromise in metabolic diseases, aging, and neurodegenerative diseases. Many genetic mutations and risk factor genes associated with proteinopathies, as well as with metabolic diseases like diabetes, negatively influence endocytic trafficking and autophagic clearance. In contrast, health-improving exercise induces autophagy-lysosomal degradation, perhaps promoting efficient digestion of injured organelles so that undamaged organelles ensure cellular healthiness. Reductions in lysosomal hydrolases are implicated in Alzheimer's, Parkinson's, and lysosomal storage diseases, as well as obesity-related pathology, and members of the cathepsin enzyme family are involved in clearing both A β 42 and α -synuclein. Upregulation of cathepsin hydrolases improves synaptic and memory functions in models of dementia and in exercising humans, thus identifying lysosomal-related systems as vital for healthy cognitive aging.

1. Introduction

The endosomal-lysosomal pathways and related autophagic responses are critical for proteostatic regulation involving dynamic, membrane-bound organelles that function as the primary catabolic compartment of cells. The pathways maintain cell homeostasis through the control of vital processes (e.g., nutrient sensing, protein and other substrate trafficking, cellular migration), processes that experience compromise during metabolic diseases, aging, and neurodegenerative diseases (Condon and Sabatini, 2019; Wang et al., 2018; Xu and Ren, 2015). Table 1 provides a list of diseases that exhibit endosomal-lysosomal compromise and dysfunction. Lysosomal storage diseases (LSDs) are rare metabolic diseases that typically present at infancy and young ages by disrupting the function of one or several of the over 60 different hydrolytic enzymes that break down proteins, lipids, glycoconjugates, and nucleic acids (Parenti et al., 2015; Platt, 2018). The heterogeneous group of over 70 LSDs is characterized by lysosomal dysfunction and substrate accumulation, with progressive

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neurodegeneration common among LSDs, as well as frequent defects in other organ systems.

More prevalent are age-related diseases of which numerous pathways are involved, regulating cell and system processes that influence aging and age-related risk factors for neurodegenerative diseases (see Carmona-Gutierrez et al., 2016; López-Otín et al., 2013; Mattson and Arumugam, 2018). Age-related neurodegenerative diseases, which increasingly are complicated by metabolic perturbations like obesity and diabetes, often involve intracellular or extracellular aggregate formations, due to dysfunction among the endo-lysosomal pathways and impaired clearance of biological polymers. The substrates are delivered to lysosomes through endocytic trafficking and pathways of autophagy, and the cross-talk between these trafficking routes provides efficient substrate clearance. Cross-talk between distinct protein clearance systems—the autophagy lysosomal and the proteasome pathways—also functions as a complimentary network to ensure cellular homeostasis, involving balanced regulation of the pathways and their compensatory responses to govern protein accumulation stress (see Farizatto et al., 2017; Pandey et al., 2007; Pohl and Dikic, 2019).

In this review, we will focus on endosomal-lysosomal dysfunction that plays a role in lifestyle-induced metabolic perturbations, as well as Alzheimer's disease (AD) and other protein accumulation pathologies.

2. Metabolic energy balance

In recent years, it has become clear that whole body metabolic state can profoundly influence the risk of acquiring and the progression of neurodegenerative diseases. Energy balance is of particular importance, where excessive caloric intake is a principle driver of obesity and diabetes, which can impede normal endosomal-lysosomal function in the brain. Enhancing energy expenditure via physical activity, however, has a restorative effect and offers insights into treatment options.

2.1 Diabetes and obesity

Insulin resistance, Type 2 diabetes mellitus (T2DM) and obesity lead to an increased risk of cognitive decline and development of AD (Jayaraman and Pike, 2014; Neth and Craft, 2017; Ryu et al., 2019; Thambisetty et al., 2013). In fact, the connection between T2DM and AD etiology overlaps to the extent that the term “type 3 diabetes” has been used to describe AD induced by insulin resistance and T2DM (Steen et al., 2005), although this nomenclature is not officially accepted by the World Health Organization or the American Diabetes Association. While there are conflicting studies, in general, obesity and T2DM tend to decrease autophagy, and a decrease in autophagic flux appears to facilitate the progression from obesity to T2DM (Levine and Kroemer, 2019). Mitochondrial dysfunction associated with reduced autophagy (including mitochondria-specific autophagy known as mitophagy), as well as mitochondrial fusion, fission, and biogenesis, appears to be a central driver of the responses to high circulating glucose and insulin resistance in the brain (Cardoso and Moreira, 2019).

Carvalho et al. (2015) found that the autophagy related 7 protein (ATG7) and the glycosylated form of the lysosomal-associated membrane protein 1 (LAMP1) were downregulated in brains of mouse models of both diet-induced T2DM and a transgenic model of AD. Furthermore, these disease models had compromised mitochondrial function and biogenesis, as well as synaptic damage. In non-obese diabetic mice, Santos et al. (2014) observed a decrease in autophagy in the brain, indicated by a reduction in the autophagy protein microtubule-associated protein 1A/1B-light chain 3 (LC3, particularly its lipid-modified form LC3II) and an increase in phosphorylation of the mechanistic target of rapamycin complex 1 (mTORC1). These findings are consistent with decreased autophagy, which Santos et al. (2014) proposed was part of an adaptive strategy to maintain mitochondrial quality and preserve cellular energetics during the early stages of T2DM. In contrast, shifting the balance toward net energy expenditure via calorie restriction and/or exercise can restore insulin sensitivity, increase brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB), reduce mTORC1 activation, and thus restore autophagy and mitochondrial function (Mattson et al., 2018; also see Fernandez et al., 2018).

Tramutola et al. (2015) examined post-mortem human inferior parietal lobule in patients with pre-clinical AD, mild cognitive impairment (MCI), and late AD. There was an increase in the amyloid β protein (A β) in all three groups, which was associated with decreases in the autophagy-initiating proteins Beclin-1 and LC3, consistent with a reduction in autophagy. Furthermore, the PI3K/Akt/mTORC1 pathway, which inhibits autophagy, was hyper-activated and associated with increased insulin receptor substrate 1 (IRS1), an indicator of insulin resistance. Tramutola et al. (2015) proposed that even in pre-clinical AD the elevated A β levels induce insulin resistance that exacerbates disease progression. Consistent with these findings, Han et al. (2017) demonstrated that the neuroprotective agent, humanin, improved insulin sensitivity by inducing an upregulation of autophagy, which led to enhanced learning and memory in the APP/PS1 mouse model of AD. Other studies have similarly found that treatment with insulin or insulin-sensitizing agents, such as metformin, leptin or glucagon-like peptide-1, restores autophagy in AD models and enhances cognition, and the PI3K/Akt/mTORC1 pathway appears to be a central mediator of these effects (de Mello et al., 2019; Gabbouj et al., 2019; Hölscher, 2019).

The central role of autophagy in both T2DM and AD was recently evaluated by Caberlotto et al. (2019). A transcriptomic analysis of post-mortem T2DM and AD human brains, followed by a network analysis revealed overlap of 158 genes among the two disease states. Within the network, overlap was a strong involvement of autophagy genes, and this was confirmed in AD mouse models, indicating the fundamental importance of autophagy dysregulation in both T2DM and AD (Caberlotto et al., 2019). While the causative mechanisms of insulin resistance in the brain are yet to be determined, the linkage to autophagy, cognitive impairment and AD has become well established (de Mello et al., 2019).

2.2 Exercise and exercise mimetics

Exercise has positive effects on synaptic plasticity, cognition and memory, and affords protection against neurodegeneration (Cotman et al., 2007; Mattson, 2012). In older adults,

the level of physical activity and frailty influence learning and the progression of AD and other neuropathologies (Buchman et al., 2019; Wallace et al., 2019). Two recent clinical trials demonstrated that a healthy lifestyle, including physical activity, had positive outcomes for the progression of AD (Isaacson et al., 2019) and heritable frontotemporal degeneration (Casaletto et al., 2020). While it is well established that in skeletal muscle, exercise induces an increase in autophagy, and elevated autophagic flux and lysosomal activity appear to be a prerequisite for muscle protein and mitochondrial turnover associated with exercise training effects, the effects of exercise on brain autophagy and lysosome function are only recently coming into focus.

He et al. (2012) demonstrated that exercise induces autophagy in the brain, using wild-type and B-cell lymphoma 2 (BCL2) mutant mice that lacked the capacity for exercise- and starvation-inducible autophagy but not basal autophagy. In wild-type transgenic mice expressing green-fluorescent protein (GFP) conjugated to the autophagy marker LC3, fluorescence microscopy images revealed an increase in GFP-LC3 puncta following acute exercise in the cerebral cortex, which is consistent with elevated autophagic activity. In addition, sequestosome 1 (SQSTM1/p62) was decreased in cerebral cortex in response to acute exercise in wild-type mice, while BCL2 mutant mice lacked this response. SQSTM1/p62 is degraded during autophagy, so a decrease in protein levels is generally associated with elevated autophagic flux, while SQSTM1/p62 accumulation is indicative of autophagy impairment.

Zhao et al. (2018) found that exercise reduced A β plaque deposition in the APP/PS1 transgenic model of AD, which has reduced autophagy activity relative to wild-type mice as indicated by the combination of increases in LC3II and SQSTM1/p62, as well as an overabundance of the lysosomal protein LAMP1. While an increase in LC3II expression typically is thought to be associated with upregulation of autophagy, when it accumulates in concert with increases in SQSTM1/p62, it is indicative of a decrease in degradation of autophagosomal substrates (Yoshii and Mizushima, 2017). Furthermore, Zhao et al. (2018) argue that the elevated LAMP1 in APP/PS1 mice suggests an accumulation of lysosomes and reduced clearance of autophagic substrates and is consistent with prior findings in this AD model. In contrast, exercise in APP/PS1 mice led to a further increase in LC3II expression and decreases in both SQSTM1/p62 and LAMP1, which are results consistent with an increase in autophagic flux that likely explains, at least in part, the reduction in A β plaque accumulation.

The mechanisms by which exercise enhances synaptic plasticity and provides neuroprotective effects, and the linkage to autophagy remain to be fully elucidated. Recent work has identified the myokine, irisin, which is a cleavage product of fibronectin type III domain-containing protein 5 (FNDC5), as a key factor that is released from muscle during exercise and mediates some of the positive effects of exercise on brain function (Lourenco et al., 2019; Munoz et al., 2018).

Genetic and pharmacological reduction of FNDC5/irisin in mouse brain impairs synaptic plasticity and memory, while increasing FNDC5/irisin rescues these functions in wild-type and AD models (Lourenco et al., 2019). Swimming protected against A β oligomer-induced

memory loss in an AD mouse model and increased FNDC5/irisin in the brain, whereas these beneficial effects were lost when irisin was inhibited. In addition, peripheral treatment with FNDC5/irisin had the same beneficial effect, suggesting potential therapeutic approaches to treating AD and related diseases. These authors further showed that irisin stimulated the cAMP-PKA-CREB signaling pathway, which is known to be involved with memory formation. In addition, CREB has been shown to induce autophagy by upregulating the autophagy genes *ATG7*, UNC51-like autophagy activating kinase 1 (*ULK1*) and transcription factor EB (*TFEB*) (Füllgrabe et al., 2016), providing a potential mechanistic link between exercise, FNDC5/irisin and autophagy.

FNDC5/irisin triggers the expression of BDNF, which is involved in neuronal growth, memory and learning (Wrann et al., 2013). Choi et al. (2018) evaluated the effects of genetic and pharmacological induction of adult hippocampal neurogenesis (AHN), elevations of BDNF, and exercise in a mouse AD model. Exercise induced AHN, as well as an increase in BDNF and FNDC5, all of which led to cognitive improvement. While artificial elevation of AHN or BDNF alone did not improve cognition, activating AHN and BDNF in concert led to cognitive improvements comparable to those seen following exercise. Moon et al. (2016) found that running exercise induces the release of secretory cathepsin B, a candidate exercise myokine, in mice and humans. In cathepsin B knockout mice the exercise-induced increases in BDNF, hippocampal neurogenesis, and spatial memory were blocked, suggesting that like FNDC5/irisin, cathepsin B is also an important mediator of the beneficial effects of exercise on brain health.

Neuroprotective effects of exercise can also be mediated through the AMP-activated protein kinase (AMPK)-sirtuin1 (SIRT1)-TFEB pathway, independently of mTORC1. Bayod et al. (2011) showed in rat brain that exercise reduced levels of phospho-tau, and this was associated with the activation of AMPK and upregulation of SIRT1. Kim and Leem (2016) found that stress-induced memory deficits could be offset by exercise, which led to an increase in BDNF in an AMPK-dependent manner. Huang et al. (2019) further demonstrated that exercise activated AMPK in brains of mice, and this was associated with phosphorylation of ULK1 and an increase in LC3II. The phosphorylated modification of AMPK, in turn, led to an increase in NAD⁺ and activation of SIRT1, which increased TFEB in the brain and induced expression of lysosomal proteins.

While exercise has clear functional benefits in brain, some of which are mediated by autophagy enhancement, there is also evidence that exercise mimetic drugs can improve brain function, which may provide useful treatment options for patients who lack the capacity for physical exercise. The AMP analog 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) activates AMPK and leads to whole body training effects and improves endurance in mice. Kobil et al. (2014) found that AICAR treatment led to improved spatial memory and motor function, and increased gene expression in brain similar to the patterns seen in muscle that lead to the endurance phenotype. The poor capacity for AICAR to cross the blood-brain barrier suggests that these effects are indirect, and skeletal muscle may be a key contributor to the effects seen in brain.

In a follow up study, Guerrieri and van Praag (2015) found that AICAR induced positive short-term effects on brain in an AMPK-dependent manner, but unlike in muscle, the AICAR treatment led to long-term cytotoxicity in the brain, suggesting that it is not a suitable substitute for exercise. Hill et al. (2016) showed that traumatic brain injury reduces AMPK activity, and pharmacological stimulation of AMPK with AICAR or metformin improved spatial memory. Likewise, the creatine analog and known AMPK activator, β -guanidinopropionic acid (β -GPA), led to an upregulation in brain mRNA for genes associated with mitochondrial biogenesis and oxidative stress, as well as behavioral changes (Gureev et al., 2018).

While these and other exercise mimetic drugs target AMPK, which can activate autophagy and lysosomal activity, the role of these treatments in autophagic processes and lysosomal activity is yet to be determined (Guerrieri et al., 2017).

3. Alzheimer's disease and related dementias

Alzheimer's disease is an irreversible and progressive diseases, noteworthy as possibly the biggest challenge in medicine today with millions of the aging population facing an impending epidemic if effective strategies to prevent or slow the disease are not discovered. Alzheimer's disease is one of many age-related protein accumulation diseases. Compromised clearance of protein aggregates is implicated in several proteinopathies, and lysosomal instability is a feature of brain aging that decreases clearing efficiency and thereby disrupts the balance between protein synthesis and protein degradation/recycling (Colacurcio and Nixon, 2016; Miquel et al., 2018; Peng et al., 2019). This altered balance increases the risk of AD and related dementias as abnormal accumulations of A β peptides and tau form long before signs of memory impairment (see Bateman et al., 2012).

Altered levels of lysosomes, autophagosomes, and autolysosomes occur in AD, and familial AD and polymorphisms linked to sporadic AD exhibit the indications of endo-lysosomal and autophagic disturbances (see Wang et al., 2018). The gradual, age-related lysosomal instability leads to gradual deposition of pathogenic protein species, slow disruption of microtubule-based transport processes, and progressive synaptic decline (see Bahr et al., 2012; Bendiske et al., 2002; Dourlen et al., 2019; Forner et al., 2017). This cascade of synaptopathology is notable as synapse loss stands out as a strong correlate of cognitive deterioration in both AD and aging.

Several risk factors for Alzheimer-type pathogenesis have also been linked to protein clearance machinery including autophagic-lysosomal functions. Two examples of AD-associated genes are involved in autophagic initiation and autophagosome formation, namely phosphatidylinositol-binding clathrin assembly protein (*PICALM*) and the Beclin-1 component of autophagy biogenesis (*BECN1*) (Bonam et al., 2019; Wang et al., 2018). Reduction in *BECN1* in certain cells is linked to reduced trafficking of retromer, a complex involved in endo-lysosomal sorting which is impaired in familial AD (Caglayan et al., 2014). Apolipoprotein E4 (ApoE4) promotes the trapping of its lipidation controlling protein ATP-binding cassette transporter subfamily A member 1 (ABCA1) in late-endosomes and alters its membrane trafficking in astrocytes (Rawat et al., 2019). In addition to other

avenues toward abnormal sorting, recycling, and trafficking that are linked to AD (see Wang et al., 2018), lysosomal organelles themselves exhibit impairment of their axonal transport, maturation, and hydrolase trafficking in AD mice (see Gowrishankar et al., 2015; Hwang et al., 2019), events that occur at early time points of the AD-type proteinopathy.

Lysosomes play a key role in governing AD-type protein accumulation events since increasing lysosomal biogenesis reduces amyloid deposits and neurofibrillary pathology in APP/PS1 and tauopathy models, respectively (Polito et al., 2014; Xiao et al., 2015). Altered tau secretion in tauopathies has been linked to impairment in the autophagy-lysosomal pathway, thereby enhancing the spreading of the protein (Chen et al., 2020). In addition, lysosomal cathepsins B and L, members of the papain-family of cysteine endopeptidases, have been found to be involved in the fragmentation and clearance of the A β peptide (Butler et al., 2011; Mueller-Steiner et al., 2006; Wang et al., 2012) and tau isoforms (Bendiske and Bahr, 2003; Wang et al., 2009). The autophagic-lysosomal and proteasomal systems for protein clearance display concerted regulation and cross-talk with regards to the governance of A β pathology (e.g., see Farizatto et al., 2017), perhaps comprising a complimentary network that maintains a balance between the two clearance pathways through compensatory responses. Evidence indicates that the lysosomal component of the compensatory action is compromised with age as shown by different studies (Gavilán et al., 2015; Mueller-Steiner et al., 2006; Torres et al., 2012), thus pointing to an unprotected protein clearance system as an aging risk factor for the development of proteinopathy.

Protective compensatory responses by the autophagic-lysosomal system are related, at least in part, to exercise-mediated induction of the autophagy-lysosomal degradation pathway as discussed above. Epidemiological studies reported that exercise reduces the risk of age-related cognitive decline, as well as the likelihood of developing AD (Hamer et al., 2018; Livingston et al., 2017). Eight of thirteen randomized controlled trials found that exercise improves cognitive function in people with AD (Du et al., 2018), and high levels of physical activity were associated with slower clinical decline in autosomal dominant frontotemporal dementia (Casaletto et al., 2020). In healthy humans and monkeys, regular treadmill exercise increased systemic levels of cathepsin B and improved learning and memory (Moon et al., 2016), thus further indicating the neuroprotective potential of the autophagy-lysosomal pathway for healthy brain aging (also see Bayod et al., 2011; Chen and Gan, 2019; He et al., 2012; Zhao et al., 2018). Endurance exercise was also found to be protective in a mouse model of MPTP-induced parkinsonism (Jang et al., 2018), similar to Moon et al. (2016) as being associated with increased autophagy and cathepsin proteins. Exercise also elicits new synapse formation/repair, which is clearly relevant since gradual synaptic decline is a significant correlate of cognitive deterioration (Chen et al., 2018; Spire-Jones and Hyman, 2014).

Broadening the importance of compensatory actions through the autophagy-lysosomal pathway, note the contrast between lysosomal dysfunction, including reduced cathepsin B and L activities recently linked to obesity-related pathology (Mizunoe et al., 2019) versus evident lysosomal enhancement by exercise-induced cathepsin B levels that correlate with improvements in the type of memory encoding lost in AD (see Moon et al., 2016). In addition to the hippocampal-dependent recall ability in humans, the treadmill training in the

Moon et al. (2016) study also detected a positive correlation between aerobic fitness change and the change in cathepsin B plasma levels.

Cathepsin B has been shown to significantly lower levels of A β ₄₂ amyloid peptide when positively modulated by genetic and pharmacological strategies in AD transgenic mouse models, leading to reductions in both neuronal and behavioral disease parameters (Butler et al., 2011; Hwang et al., 2019; Mueller-Steiner et al., 2006; Viswanathan et al., 2012; Wang et al., 2012; Yang et al., 2011). It is also of interest that, cilostazol, a positive modulator of the autophagy-lysosomal system, enhanced cathepsin B activity and reduced A β ₄₂ accumulation via sirtuin 1 (SIRT1)-coupled AMPK signaling in neuroblastoma cells (Park et al., 2016)—note that SIRT1 is widely considered a crucial component for proteostasis. Cathepsin B indeed degrades A β ₄₂ through carboxy-terminal truncation, resulting in proteolytic detoxification of the peptide (Butler et al., 2011; Hwang et al., 2019; Mueller-Steiner et al., 2006; Wang et al., 2012). In addition, the hydrolase promotes the clearance of α -synuclein, including the A53T α -synuclein variant linked to familial Parkinson's disease (Hwang et al., 2019; McGlinchey and Lee, 2015). The McGlinchey–Lee study found that cathepsin B cleaves α -synuclein in such a way that circumvents pathogenic fibril formation.

The regulation of cathepsin B has been extensively studied and the enzyme shown to be modestly enhanced in response to different types of protein accumulation pathology (see Bonam et al., 2019; Farizatto et al., 2017) as compared to the level produced by direct pharmacological enhancement. Such findings suggest the involvement of endogenous compensatory signals that explain the slow nature of disease progression in many dementias. In addition to the synaptic and behavioral protection by cathepsin B upregulation in several transgenic AD models (see above), similar enhancement of the hydrolase improved memory performance and synaptic integrity in models of MCI (Hwang et al., 2019).

In striking contrast to the manner of protection the cysteine protease cathepsin B produces when enriched in lysosomes, inhibition of the non-lysosomal cysteine protease calpain has long been suggested as a neuroprotective avenue (see Hassen et al., 2017; Romine et al., 2017). Together, such protective avenues may act in a concerted manner since the calcium-activated calpain generates fragments of cytoskeletal components and membrane receptors during excitotoxic events, including the hyperexcitability and seizure episodes identified during early stages of AD and in a model of frontotemporal dementia (García-Cabrero et al., 2013; Vossel et al., 2013, 2016), thus exacerbating proteostatic stress on autophagic-lysosomal processes working to clear the accumulating break-down products. It is also of interest here that neuronal excitability has been found to increase with age, and inhibition of excitatory neurotransmission increases longevity (Zullo et al., 2019).

Through the recent lines of research, a clearer understanding has evolved regarding the autophagy-lysosomal pathway and the role it plays in cellular quality control for healthy brain aging. Accordingly, regulators of protein clearance activity are being pursued to identify candidate therapeutic drugs, peptides, and natural products, following the proof-of-concept studies on both the positive modulation of cathepsins (Bendiscke and Bahr, 2003; Butler et al., 2011; Mueller-Steiner et al., 2006), as well as the down-regulation

of endogenous inhibitors of lysosomal cysteine proteases that leads to cathepsin-dependent reduction of proteinopathy (Wang et al., 2018; Yang et al., 2011). Exercise mimetics may be among the candidates as recent drug discovery efforts equaled the exercise-mediated benefits to neuronal networks and brain function, with exercise widely accepted as a health-improving lifestyle factor that can prevent a variety of diseases.

4. α -Synucleinopathies

The α -synuclein protein is the major component of proteinaceous inclusions found in neurodegenerative diseases called α -synucleinopathies, and it appears to contribute to the protein accumulation stress in 50% of AD patients. Parkinson's disease (PD) is the second most common, late-onset neurodegenerative disease, behind only AD. The accumulation of α -synuclein is the main pathological hallmark of PD and PD-related disorders. It is notable that α -synuclein is a regulator of the autophagic network (Winslow et al., 2010) in addition to being a substrate of the autophagy-lysosomal pathway (Hwang et al., 2019; McGlinchey and Lee, 2015).

Parkinson's disease-associated genes and evidence from model systems strongly implicate intracellular trafficking and protein clearance systems as playing a major role in α -synucleinopathy. Several PD-associated genes are related to endo-lysosomal/autophagy pathways, such as *ATP13A2*, *PINK1*, *PRKN*, *TMEM175*, *VPS35*, *LRRK2*, *GBA1*, *SMPD1*, *GALC*, *ASAHI*, *SCARB2*, *CTSD*, *CTSB*, and *GLA* (see Table 2), thus in support of dysfunction in these and related pathways as being a contributing or even primary cause of PD (Bellomo et al., 2019; Bento et al., 2016; Wallings et al., 2019; Wang et al., 2018). *GBA1* and *LRRK2* genes harbor some of the most common PD-associated mutations and they are linked to autophagic-lysosomal processing. Note that mutations in the glucocerebrosidase gene *GBA1* also cause Gaucher disease, an autosomal recessive lysosomal storage disease, and Mullin et al. (2020) recently reported that amroxol, a drug known to increase glucocerebrosidase activity and reduce α -synuclein levels, can positively target the glucocerebrosidase pathway in PD patients with and without *GBA1* mutations.

Leucine-rich repeat kinase 2 (*LRRK2*) regulates autophagy, perhaps through vesicle sorting and/or lysosomal positioning. Using generated lines of *C. elegans* expressing *LRRK2* and α -synuclein in dopaminergic neurons, PD-causing mutations in *LRRK2* were found to inhibit autophagy and accelerate age-related failure of autophagic function, while wild-type *LRRK2* improved autophagy throughout the *C. elegans* lifespan (Saha et al., 2015). The relationship between autophagic-lysosomal dysfunction and the pathogenesis of α -synuclein aggregation/propagation points to positive modulatory agents of the protein clearance pathway as a potential disease-modifying avenue.

Disturbances in the endo-lysosomal system play a prominent role in PD pathogenesis (see Wang et al., 2018), including the dysfunction of endo-lysosomal sorting and trafficking. Mazzulli et al. (2016) established that α -synuclein accumulation disrupts lysosomal hydrolase trafficking in human midbrain dopaminergic neurons, finding a significant reduction in cathepsin B activity in PD and Gaucher disease neurons. They also showed that overexpression of an endoplasmic reticulum-Golgi trafficking regulator improved

hydrolase maturation and activity in patient neurons, and the lysosomal enhancement reduced pathological α -synuclein in neurons and improved their viability.

Note that a mutation in *VPS35*, a component of the large retromer complex for endo-lysosomal sorting and trafficking, causes late-onset PD (Zimprich et al., 2011) and thereby implicates retromer dysfunction in PD, as well as AD (see Caglayan et al., 2014). A retromer-like heterotrimer called retriever was also identified and found to mediate recycling of $\alpha 5\beta 1$ integrins and other signaling receptors from endosomes to the plasma membrane (McNally et al., 2017). Such transport machineries may be involved in compensatory responses important for neuronal homeostasis and synapse integrity, as a neurotoxic insult enhanced $\beta 1$ integrin levels at synaptic contacts and promoted integrin-cofilin signaling (Farizatto et al., 2019).

The protein accumulation stress from α -synuclein inclusions and associated transport deficiency may explain the synaptic decline in transgenic mouse models of PD (Batey et al., 2005; Hwang et al., 2019). Enhancing the autophagy-lysosomal system with a small-molecule modulator (*Z*-phenylalanyl-alanyl-diazomethylketone), which appears to act as an inhibitory chaperone to promote transport to lysosomes and elution of active cathepsin B (Butler et al., 2011), was found to reduce α -synuclein levels in PD mice, similar to the decreased proteinopathy the positive modulator produced in AD mouse models (Butler et al., 2011; Hwang et al., 2019). Such enhancement led to the positive relationship between improved clearance of α -synuclein and the extent of synaptic marker recovery.

Related compensatory signaling was evident in response to protein accumulation stress and autophagic compromise in Huntington's disease mice, with activation of chaperone-mediated autophagy (CMA) resulting in constitutive upregulation (Koga et al., 2011). Interestingly, an autophagy-inducing peptide (Shoji-Kawata et al., 2013) and LC3 linker compounds that target mutant huntingtin protein for degradation using an autophagosome-tethering approach (Li et al., 2019) also reduced the polyglutamine proteinopathy related to Huntington's disease. Chaperone mediated autophagy works to control cellular energy through involvement in glucose metabolism and recycling amino acids from lysosomal degradation of substrate proteins. Tapping into CMA compensatory responses is key for therapeutic routes since dysfunctional CMA occurs with age, thus the development of CMA activators has been progressing. For example, in the lysosomal storage diseases cystinosis, which exhibits CMA defects and impaired trafficking of the CMA receptor LAMP2A, the developed small-molecule CMA activator QX77 (*N*-[4-(7-chloro-2H-1, 4-benzoxazin-3-yl)phenyl]acetamide) improved LAMP2A localization to lysosomes and increased cell survival (Zhang et al., 2017). As with lysosomal-targeted cathepsin modulation, CMA upregulation is a potential strategy to treat a variety of diseases exhibiting defective CMA.

5. Conclusion

Lysosomes are clearly a core component of proteostasis with multiple types of substrates of extracellular and intracellular origin being delivered for degradation through endocytic trafficking and autophagic events. Several related metabolic and genetic cascades influence aging and longevity, and the aging process and many disease states weaken the proteostasis

network of mechanisms that works to maintain (i) the integrity of the proteome, (ii) complex glycoconjugates and glycans, and (iii) posttranslational modifications that influence functionality. Vital compensatory responses for the maintenance of cellular and subcellular homeostasis (to include pre- and postsynaptic moieties) involve lysosomal maturation, autophagic regulation, as well as cross-talk with the ubiquitin-proteasome system (Bahr et al., 2012; Bonam et al., 2019; Colacurcio and Nixon, 2016; Farizatto et al., 2017; Scrivo et al., 2018; Wang et al., 2012). These distinct restorative outlets are related due to shared components or due to having correlative activation events in response to proteinopathy. Together they represent an intimate circle of potential therapeutic targets for neurodegenerative diseases, with lysosomes at the hub of each avenue.

Abbreviations

ABCA1

ATP-binding cassette transporter subfamily A member 1

AD

Alzheimer's disease

AHN

adult hippocampal neurogenesis

AICAR

5-aminoimidazole-4-carboxamide ribonucleotide

ApoE4

apolipoprotein E4

ASAH1

N-acylsphingosine amidohydrolase 1

ATG7

autophagy related protein 7

ATP13A2

ATPase cation transporting 13A2

A β

amyloid β protein

BDNF

brain-derived neurotrophic factor

BECN1

Beclin 1

CMA

chaperone mediated autophagy

CREB

cAMP response element binding protein

CTSB

cathepsin B

CTSD

cathepsin D

FNDC5

fibronectin type III domain-containing protein 5

GALC

galactosylceramidase

GBA1

glucosylceramidase β 1

GLA

galactosidase α

IRS1

insulin receptor substrate 1

LAMP1

lysosomal-associated membrane protein 1

LC3

microtubule-associated protein 1A/1B-light chain 3

LC3II

the lipid conjugated form of LC3

LRRK2

leucine-rich repeat kinase 2

MCI

mild cognitive impairment

mTORC1

mechanistic target of rapamycin complex 1

PD

Parkinson's disease

PI3K

phosphoinositide 3-kinase

PICALM

phosphatidylinositol-binding clathrin assembly protein

PINK1

phosphatase and tensin homolog (PTEN) induced putative kinase 1

PKA

protein kinase A

PRKN

Parkin RBR (RING between RING-RING) E3 ubiquitin protein ligase

SCARB2

scavenger receptor class B member 2

SIRT1

sirtuin 1

SMPD1

sphingomyelin phosphodiesterase 1

SQSTM1/p62

sequestosome 1/p62

T2DM

Type 2 diabetes mellitus

TFEB

transcription factor EB

TMEM175

lysosomal K⁺ channel transmembrane protein 175

ULK1

UNC51-like autophagy activating kinase 1

VPS35

vacuolar protein sorting-associated protein 35 retromer complex component

β-GPA

β-guandinopropionic acid

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Table 1

Disease states that exhibit endosomal-lysosomal dysfunction.

• Lysosomal storage diseases
• Type 2 diabetes mellitus
• Obesity
• Aging
• Alzheimer’s disease
• Parkinson’s disease
• Huntington’s disease
• Pick’s disease
• Chronic traumatic encephalopathy
• Sporadic multiple system tauopathy with dementia
• Amyotrophic lateral sclerosis/frontotemporal dementia
• Frontotemporal dementia and parkinsonism linked to chromosome 17

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Table 2

Summary of genes with mutations associated with familial PD and linked to the autophagy-lysosomal pathway.

Symbol	Name
<i>ATP13A2</i>	ATPase cation transporting 13A2
<i>PINK1</i>	Phosphatase and tensin homolog (PTEN) induced kinase 1
<i>PRKN</i>	Parkin RBR E3 ubiquitin protein ligase
<i>TMEM175</i>	Transmembrane protein 175
<i>VPS35</i>	Vacuolar protein sorting-associated protein 35 retromer complex component
<i>LRRK2</i>	Leucine-rich repeat kinase 2
<i>GBA1</i>	Glucosylceramidase β 1
<i>SMPD1</i>	Sphingomyelin phosphodiesterase 1
<i>GALC</i>	Galactosylceramidase
<i>ASAHI</i>	<i>N</i> -acylsphingosine amidohydrolase 1
<i>SCARB2</i>	Scavenger receptor class B member 2
<i>CTSB</i>	Cathepsin B
<i>GLA</i>	Galactosidase α