expert reviews
in molecular medicine

Autophagic pathways in Parkinson disease and related disorders

Maria Xilouri[1] and Leonidas Stefanis[1,2,*]

Macroautophagy and chaperone-mediated autophagy (CMA) are the two main mammalian lysosomal proteolytic systems. In macroautophagy, double-membrane structures engulf organelles and other intracellular constituents through a highly regulated process that involves the formation of autophagic vacuoles and their fusion with lysosomes. In CMA, selected proteins are targeted through a nonvesicular pathway to a transport complex at the lysosomal membrane, through which they are threaded into the lysosomes and degraded. Autophagy is important in development, differentiation, cellular remodelling and survival during nutrient starvation. Increasing evidence suggests that autophagic dysregulation causes accumulation of abnormal proteins or damaged organelles, which is a characteristic of chronic neurodegenerative conditions, such as Parkinson disease (PD). Evidence from post-mortem material, transgenic mice, and animal and cellular models of PD suggests that both major autophagic pathways are malfunctioning. Numerous connections exist between proteins genetically linked to autosomal dominant PD, in particular α-synuclein and LRRK2, and autophagic pathways. However, proteins involved in recessive PD, such as PINK1 and Parkin (PINK2), function in the process of mitophagy, whereby damaged mitochondria are selectively engulfed by macroautophagy. This wealth of new data suggests that both autophagic pathways are potential targets for therapeutic intervention in PD and other related neurodegenerative conditions.

Autophagy derives from the Greek words auto (self) and phagia (eating) and is a term that quite aptly describes the process of self-eating, or consumption and digestion of the cell's own constituents (Ref. 1). If in anthropomorphic terms apoptosis is used as a term to describe cell suicide, by analogy, autophagy could be envisioned as a form of self-cannibalism.

[1]Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

[2]Second Department of Neurology, University of Athens Medical School, Athens, Greece

*Corresponding author: Leonidas Stefanis, Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens (BRFAA) 4, Soranou Efesiou Street, Athens 11527, Greece. E-mail: lstefanis@bioacademy.gr

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

Autophagy is but one of the mechanisms the cell has at its disposal to degrade intracellular proteins. Although there are many protein degradation (proteolytic) systems in cells, the two major ones are the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway (ALP). These degradation systems are important for the normal turnover of cell components both under normal housekeeping conditions and under conditions of stress. Such turnover is important for the renewal of the cell and the removal of potentially damaging constituents, but also for fine-tuning the cell phenotype, so that it can respond more readily to changes in its environment and its own metabolic changes.

The ALP differs from the UPS in a number of ways, most notably because degradation through the ALP is relatively more important for long-lived proteins, and because the ALP can also degrade cellular organelles through the process of macroautophagy, not only smaller proteins. Macroautophagy is one of the three major avenues through which the ALP degrades intracellular constituents, the other two being chaperone-mediated autophagy (CMA) and microautophagy. All three pathways result in delivery of intracellular components to the lysosomes; within this acidic environment, and through the effects of lysosomal hydrolases, they are digested into their composite parts, which can then be reused by the cell. In this way, the cell can reorganise its arsenal to best fit its needs.

What distinguishes the different types of autophagy is the manner in which the cellular constituents reach the lysosomes. In microautophagy, invaginations are formed at the level of the lysosomal membrane; such invaginations engulf neighbouring areas of the cytosol, which may include organelles, lipids or proteins (Ref. 2). The invaginations eventually round up into vesicles that are digested within the lysosomes, together with their engulfed constituents. The lysosomal membrane itself can be engulfed in this manner, leading to the adjustment of the size of the vacuole. Very little is known about microautophagy in mammalian systems, in particular regarding its possible role in neurodegenerative disease; therefore, it will not be discussed further here. It should be noted, however, that it could conceivably have an important role in protein degradation in neuronal systems, especially if other proteolytic systems are dysfunctional.

Macroautophagy

Macroautophagy is sometimes used synonymously with autophagy, although it is clear that it just represents a subset of autophagic pathways in mammalian systems (Refs 3, 4). In macroautophagy, cup- or rod-shaped isolation double-membrane structures, called phagophores, are first formed within the cell (Fig. 1). The origin of this isolation membrane is still under investigation, but so far the endoplasmic reticulum, Golgi, mitochondria and the plasma membrane are all proposed to be the membrane source (Refs 5, 6, 7). These structures gradually form the so-called autophagosome or autophagic vacuole (AV), which is characterised by the external boundary of the double membrane. Within this structure, there are engulfed cytosolic constituents such as organelles, proteins and lipids. The autophagosome fuses with lysosomes, creating a structure called the autophagolysosome, wherein the vesicular components are eventually degraded. This process, similarly to microautophagy, involves delimitation of cytosolic constituents by a vesicular membrane. A major difference, however, is that such autophagosomes can be formed anywhere within the cell, and not necessarily within close proximity to the lysosomal membrane (Ref. 8). In fact, on many occasions such structures, especially in neurons, can be found at long distances from the perinuclearly located lysosomes, for example along neuronal processes (Ref. 9). It follows that an important aspect of macroautophagy involves the movement of autophagosomes from such remote areas to a perinuclear location, hence the importance of the cellular transport machinery in the efficient functioning of this system. The endosomal system also converges on macroautophagy. Vesicular structures from the late endosomal pathway and multivesicular bodies fuse with autophagosomes to create amphisomes, which enable full maturation of the vesicle and subsequent fusion with lysosomes. Therefore, a dysfunction of either the late endosomal system or the cellular transport machinery may secondarily cause macroautophagy impairment.

Macroautophagy is a highly regulated process and has been studied in great detail in yeast,

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

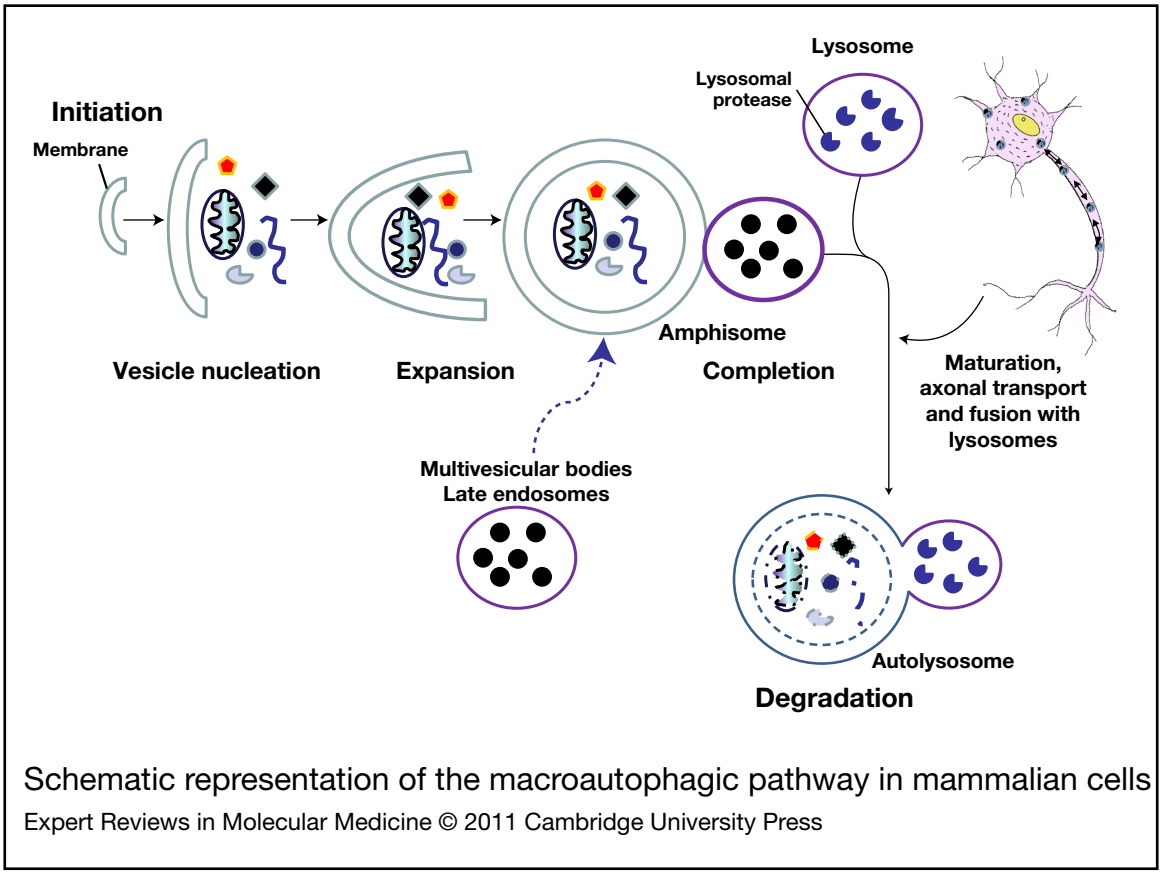

Figure 1. Schematic representation of the macroautophagic pathway in mammalian cells. The macroautophagy pathway can be divided into several sequential steps. The first step is the formation of autophagosomes, a process that includes initiation, nucleation, cargo recognition and expansion events that result in completion of the autophagosomes. The completed autophagosomes undergo multiple maturation steps and fusion events with multivesicular bodies or endosomes (amphisomes). An important feature of the process is the movement of autophagosomes (axonal transport) from neuronal axons to a perinuclear location and vice versa (bidirectional transport). Finally, degradation of the cargo takes place in the acidic environment of the autolysosomes by lysosomal proteases, and the constituents of the outer membrane are available for reuse.

and more recently, has also been described in mammalian systems. The process of autophagosome formation and maturation in particular includes a series of separate steps: initiation, nucleation, cargo recognition, expansion and completion of the autophagosomes (Fig. 1). Several autophagy-related genes involved in induction and completion of macroautophagy have been well characterised in yeast and in mammals (Refs 10, 11). Macroautophagy occurs constitutively in cells, but is markedly induced under certain circumstances. The classical example is that of starvation or relative nutrient deprivation. In mammalian cells, this can be mimicked by deprivation of amino acid or insulin or growth factor signals, which leads to inactivation of the serine/threonine kinase mTOR (mammalian target of rapamycin), the master regulator of nutrient signalling (Ref. 12). Therefore, the mTOR inhibitor rapamycin is the usual agent used to activate macroautophagy. It should be noted, however, that in mammalian cells there are indications that macroautophagy can also be induced by mTOR-independent pathways (Refs 13, 14). Regulation of autophagy downstream of mTOR is not yet fully understood, but the protein complex made up of ULK1 (yeast Atg1), Atg13

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

and FIP200 has a pivotal role (Ref. 12). Recently, a novel Atg protein, Atg101, was identified, which interacts with the mammalian ULK1–Atg13–FIP200 complex and localises to the isolation membrane or phagophore (Ref. 15). The nucleation phase of initial phagophore formation requires the interaction of ULK1 with complexes of Vps34 and PI3K class III, which are made up of beclin-1 (Atg6), p150/Vps15, AMBRA1, Atg14L and UVRAG (UV irradiation resistance-associated gene) proteins (Refs 16, 17, 18, 19, 20). Other beclin-1-binding proteins include Rubicon (RUN domain, a cysteine-rich domain containing beclin-1-interacting protein), Bcl-2, Rab5, AMBRA1 and Bif-1 (Refs 19, 20).

The classical pharmacological inhibitors of macroautophagy, 3-methyladenine (3-MA) and wortmannin, act at this stage of the pathway as PI3K class III inhibitors. The further expansion of autophagosomes is mediated by two ubiquitin-like conjugation systems. One is the conjugation of Atg5 with Atg12 and the other is the covalent linkage of MAP1LC3 (microtubule-associated proteins 1A/1B light chain 3; Atg8) to phosphatidylethanolamine. This linkage leads to two changes that are useful as specific indices of macroautophagy: the change of LC3 labelling from a diffuse to a punctuate pattern, which can be detected by immunostaining, and a shift of the molecular mass of the protein, which can be detected on western immunoblots as LC3-II. Another marker that is potentially useful (although experience is still rather limited, and there may be issues of specificity) is p62 (sequestosome 1, SQSTM1). This appears to be a substrate for macroautophagy; hence its levels increase when macroautophagy is inhibited, and decrease when macroautophagy is induced (Ref. 21). p62 binds directly to LC3 through a specific sequence motif at the same time as it binds to polyubiquitylated proteins. Thus, p62 provides a link between macroautophagy and the UPS; it is thought to sequester polyubiquitylated proteins away from the UPS and direct them towards macroautophagic-dependent lysosomal degradation (Refs 22, 23). In combination with LC3-II, it can provide an index of autophagic flux, as explained in detail in Table 1. It should be noted that electron microscopy evidence is still ideally required to conclusively show autophagosome accumulation, although because of the biochemical tools now available, it is not always performed (Ref. 24).

Recently, macroautophagy has been shown to mediate selective degradation of various targets such as aggregated proteins and damaged organelles. In this process, p62 and perhaps HDAC6 proteins have a vital role. HDAC6 has the capacity to bind both polyU misfolded proteins and dynein motors, thus targeting polyubiquitylated aggregates and damaged mitochondria to aggresomes for degradation (Ref. 25). Moreover, several other proteins that link the autophagic machinery to its substrates have been identified in mammalian systems. These are designated 'autophagy receptors' and are involved in the cytosol-to-vacuole targeting pathway (Atg19) (Ref. 26) and in the degradation of ubiquitylated bacteria (NDP52) (Ref. 27), mitochondria (Nix-1, Atg32) (Refs 28, 29) and protein aggregates (NBR1) (Ref. 30). All proteins contain an LC3-interacting region and a substrate-recognition domain. Recently, it has also been shown that Alfy (autophagy-linked FYVE protein, also known as WDFY) is required for the macroautophagic elimination of aggregated proteins, but not for macroautophagic elimination of bulk cytosol in response to starvation (Ref. 31).

Macroautophagy in the nervous system

The fact that constitutive macroautophagy is essential for neuronal homeostasis was highlighted by two landmark studies which showed that genetic ablation of essential macroautophagy genes (*Atg5* or *Atg7*) in the mouse control nervous system (CNS) led to neuronal degeneration within the first few months of life (Refs 32, 33). This was surprisingly accompanied by extensive accumulation of ubiquitylated inclusions, which would have been expected only with UPS dysfunction; in fact, enzymatic proteasomal activity was found to be unaffected in these mice. Two additional pieces of work seem to provide an answer to this conundrum. Mating of Atg7-deficient mice with p62-knockout mice leads to drastic diminution of the inclusions, although neurodegeneration per se is not affected (Ref. 34). Furthermore, p62 is upregulated following impairment of macroautophagy and leads to enhanced recruitment of ubiquitylated substrates away from the UPS, thus impeding their degradation (Ref. 35). It appears therefore that p62 has a key role in this respect, and its regulation may be

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

Table 1. Alterations in the number of autophagosomes and LC3-II and p62 levels in neurons under physiological and pathological conditions

	Autophagosomes	LC3-II	p62	Overall lysosomal function
Homeostasis	↓	↓	↓	Normal
Impairment of macroautophagy upstream of autophagosome formation	↓↓↓	↓↓↓	↑	May be ↓
Impairment of macroautophagy downstream of autophagosome formation	↑↑↑	↑↑↑	↑	↓
Excessive induction of macroautophagy	↑	↑	↓↓	May be ↑

Under physiological conditions (top row), in healthy neurons the number of AVs and the levels of LC3-II and p62 are relatively low, indicating a rather rapid autophagic flux. In this setting, the whole process of the generation of autophagosomes and their fusion with lysosomes is rapid, so that substrates, such as p62, are efficiently cleared, leading to low steady-state levels of p62. Because autophagosomes rapidly fuse with lysosomes and are degraded, the number of autophagosomes at any given point in time and the levels of LC3-II, biochemically reflecting the autophagosome step, are low. When macroautophagy is impaired (second row) upstream of autophagosome formation, the number of autophagosomes and the levels of LC3-II are decreased, whereas p62 accumulates, because it is not efficiently degraded through this pathway. If macroautophagy is impaired to a significant enough degree, and if macroautophagic-dependent degradation represents a significant proportion of total lysosomal degradation, this could lead to an overall decrease of lysosomal function. On blockade of any step of macroautophagy downstream of autophagosome formation (third row), such as the maturation, axonal transport and fusion of autophagosomes with lysosomes, autophagosomes, LC3-II and p62 rapidly accumulate because the normally rapid flux is compromised. This is accompanied by overall lysosomal dysfunction. Finally, excessive macroautophagy induction (bottom row) occurs, characterised by increased AVs and LC3-II levels but reduced p62 levels, because p62 will be cleared even more rapidly than normal; this may eventually lead to enhanced lysosomal degradation ('productive' macroautophagy) and could be deleterious to neuronal homeostasis.

important for a variety of situations where ubiquitylated inclusions accumulate in neurodegenerative conditions.

From the above-mentioned studies it became clear that post-mitotic neurons rely heavily on macroautophagic machinery to degrade cellular components as part of their normal physiological function. A number of additional studies in a variety of organisms have shown that elimination of components of the macroautophagic pathway leads to neuronal degeneration and lysosomal abnormalities (Refs 36, 37, 38, 39, 40). In fact, it seems that healthy neurons normally have an increased autophagic flux compared with other cells, meaning that the process of autophagosome formation, maturation and digestion within lysosomes is especially efficient and rapid. A correlate of this is that LC3-II and autophagosomes are barely detectable in healthy cultured neuronal cells and in nervous system tissue. However, upon blockade of lysosomal function or of any step downstream of autophagosome formation, such as the maturation and fusion of autophagosomes with lysosomes, LC3-II rapidly accumulates (Refs 41, 42, 43, 44, 45, 46). In a sense, neurons are functioning in an 'overdrive' of macroautophagy, and that is why they are especially vulnerable to its disruption.

The conditional Atg-knockout mice have also served to reveal specific important roles of basal macroautophagy in the homeostasis of neurites. Conditional mutant mice lacking Atg7 in Purkinje neurons displayed cell-autonomous, progressive dystrophy (manifested by axonal swellings), degeneration of axonal terminals and behavioural deficits, in the absence of autophagic vacuole accumulation and in the absence of dendritic pathology (Refs 47, 48); this contrasts with the situation in pathological conditions, such as Alzheimer disease, where

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

autophagosomes accumulate in such axonal dystrophic swellings (see below). These findings underscore a specialised role of neuronal macroautophagy in the maintenance of homeostasis of axonal terminals and protection against axonal degeneration.

Another factor that should be mentioned here is ageing. It appears that the capacity for macroautophagy-mediated protein degradation declines with age, although this has not been specifically studied in the brain (Refs 49, 50, 51, 52). In invertebrate organisms, elimination or reduction of macroautophagy-related genes has consistently led to a reduced lifespan (Refs 53, 54, 55).

Concept of (macro)autophagic stress

Macroautophagic stress applies to situations in which there is perturbation of the normal flow of macroautophagic degradation. This is usually apparent as an accumulation of autophagosomes in the material studied, which can be due either to enhanced activation of the macroautophagic pathway or, apparently more often, especially in neurons, to problems further downstream that affect the late endosomal pathway, the cellular transport machinery or general lysosomal function. In the former case, the term 'productive' macroautophagy can be used to imply that the enhanced macroautophagy will eventually lead to enhanced lysosomal protein degradation, whereas in the latter case, the macroautophagy is 'nonproductive' because the autophagic flux and the rate of lysosomal degradation actually decrease (Table 1). This is an important distinction that needs to be made in situations in which autophagosomes accumulate. However, it should be stressed that the problem might also be due to a dysfunction of the macroautophagy pathway per se, such as seen with the Atg-knockout mice, where autophagosomes fail to form.

Chaperone-mediated autophagy

CMA is a selective mechanism for the degradation of specific cytosolic proteins within lysosomes, and does not involve vesicle formation. In this process, cytosolic proteins with the particular pentapeptide motif KFERQ or a biochemically related sequence are recognised by a complex of chaperones and cochaperones in the cytosol; they are then translocated one by one to the lysosomal membrane, where they bind to another complex and, through this binding, are finally threaded into the lysosomes and degraded (Refs 56, 57, 58, 59, 60). The KFERQ-like motif is present in about 30% of all cytosolic proteins, but even more proteins could become substrates if they are post-translationally modified (Refs 61, 62).

The laboratories of Fred Dice, Erwin Knecht and, more recently, Ana Maria Cuervo have been instrumental in the discovery and elucidation of the mechanism underlying this pathway of lysosomal degradation. The chaperone–cochaperone complex involved in recognition is made up of the heat shock cognate protein of 70 kDa (Hsc70), a cytosolic member of the Hsp70 chaperone family (Ref. 56) and Hsp70 cochaperones (such as Hsp40, Hsp90, Hip, Hop and Bag-1). The main element in the lysosomal membrane complex is the lysosome-associated membrane protein type 2A (LAMP-2A), an alternatively spliced form of the *Lamp2* gene, and the only one known to participate in CMA (Ref. 63). LAMP-2A is an integral lysosomal membrane protein with a single transmembrane region, a short cytosolic tail and a large, highly glycosylated luminal region. LAMP-2A can form oligomers, which are thought to form the protein translocation pore. The substrate protein is subsequently degraded after unfolding and translocation into the lysosomal lumen, with the help of lysosomal Hsc70 (a luminal form of Hsc70). Lysosomal Hsc70 and lysosomal Hsp90 are required for stabilisation, assembly and disassembly of the LAMP-2A-enriched multimeric complexes (Ref. 60). A very recent study from the Cuervo group has added a further layer of complexity to this process, because they identified glial fibrillary acidic protein (GFAP) and elongation factor 1 α (EF1α; EEF1A1) as regulators of the disassembly of the transmembrane translocation complex; through these regulatory proteins, guanosine triphosphate (GTP) mediates an inhibitory effect on CMA (Ref. 64) (Fig. 2). CMA activity is directly dependent on the levels of LAMP-2A at the lysosomal membrane and on lysosomal Hsc70 levels in the lysosomal lumen (Refs 65, 66, 67). Basal levels of CMA activity are detectable – although variable – in most cells and tissues, but CMA is often upregulated under conditions of stress or nutrient deprivation (Ref. 68). Macroautophagy and CMA are interconnected, although the molecular mechanisms that

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

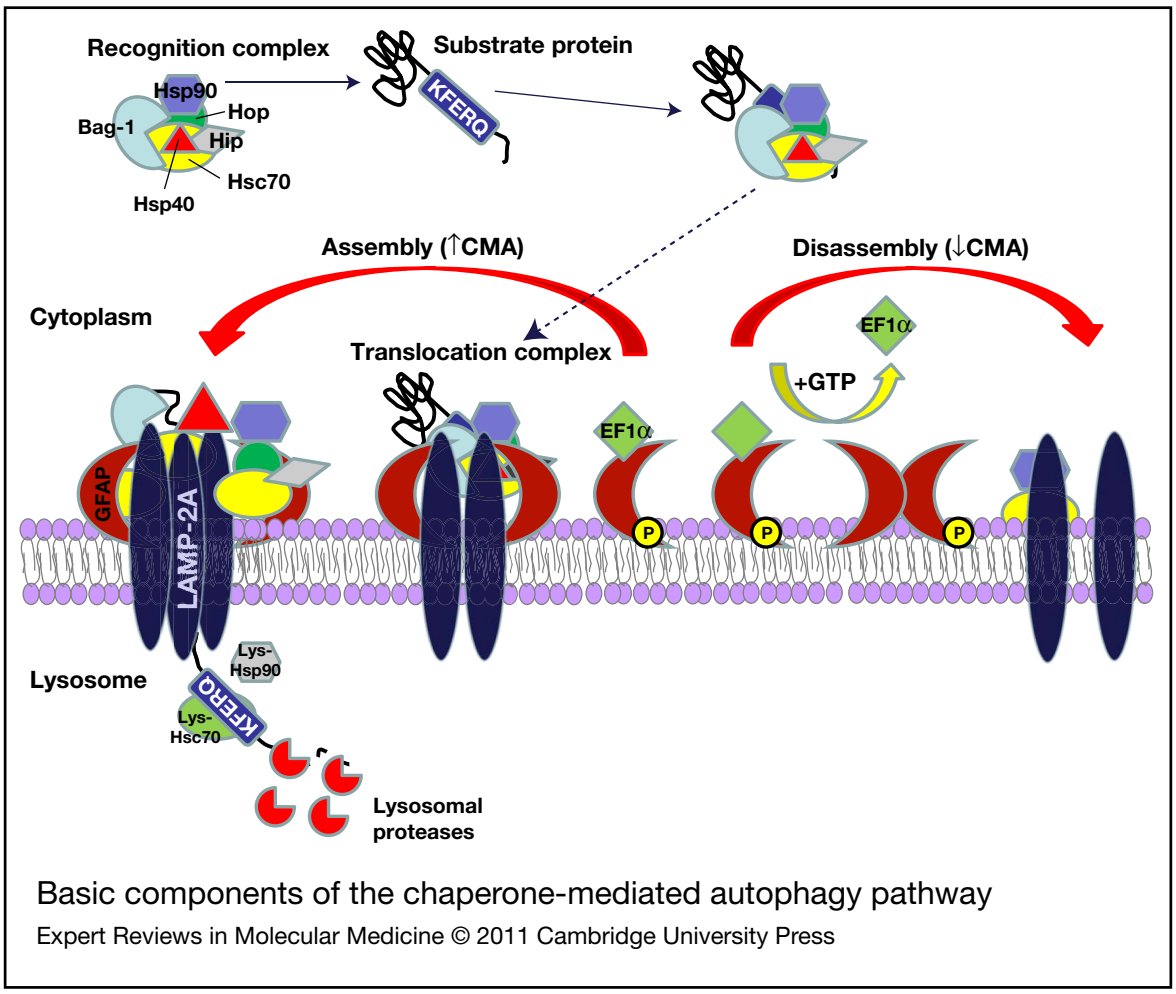

Figure 2. Basic components of the CMA pathway. CMA substrates are translocated across the lysosomal membrane by the participation of two major protein complexes: a group of cytosolic chaperones and cochaperones (cargo recognition complex) and a group of lysosomal proteins located on both sides of the lysosomal membrane (cargo translocation complex). Cytosolic Hsc70 recognises the CMA-targeting motif in the substrate protein, and in collaboration with chaperones and cochaperones delivers it to the surface of the lysosomes where it binds to LAMP-2A monomers. The stability of the CMA translocation complex is modulated by GFAP and EF1α. GFAP binds to LAMP-2A at the complex and stabilises it. However, GFAP may also form dimers with its phosphorylated form (GFAP-P), leading thus to disassembly of the translocation complex. Such dimerisation is inhibited by EF1α binding to phosphorylated GFAP. In the presence of GTP, EF1α is removed from the lysosomal membrane, thus leading to GFAP dimerisation and translocation complex disassembly (modified from Ref. 64). Lys-Hsc70 and Lys-Hsp90 are required for stabilisation, assembly and disassembly of the LAMP-2A-enriched multimeric complexes. Abbreviations: CMA, chaperone-mediated autophagy; EF1α, elongation factor 1 α; GFAP, glial fibrillary acidic protein; GTP, guanosine triphosphate; Hsc, heat shock cognate protein; Hsp, heat shock protein; LAMP-2A, lysosome-associated membrane protein type 2a.

modulate this crosstalk are not fully understood. Experimental blockage of one of them results in compensatory upregulation of the other (Refs 69, 70, 71, 72).

Importantly, CMA activity declines with age in almost all tissues analysed so far, mainly as a consequence of decreased LAMP-2A levels at the lysosomal membrane (Ref. 51). In various cell systems, overexpression of LAMP-2A is able to ameliorate CMA function, indicating that increased LAMP-2A levels are sufficient for this effect (Ref. 73). Consistent with this

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

idea is a recent in vivo study which showed that transgenic overexpression of LAMP-2A in the liver not only reversed age-associated CMA impairment, but also led to improvement of liver function (Ref. 74). This stresses the importance of LAMP-2A as a rate-limiting step in the pathway and underscores the utility of targeting this molecule in order to improve CMA function.

Not much is known about the role of CMA in the nervous system. Recent data suggest that Hsc70 and LAMP-2A are expressed in rodent and human brain (Refs 69, 75). In one study, LAMP-2A levels were developmentally induced in rat brain during the first days after birth. There was no decrease of total LAMP-2A levels with ageing in the rat brain, but lysosomal-bound LAMP-2A was not specifically assessed (Ref. 69). Furthermore, various studies in neuronal cells and cultured primary neurons, largely based on inactivation of CMA components, indicate that CMA indeed operates as a mechanism for lysosomal degradation in these cellular systems (Refs 69, 75, 76, 77, 78, 79). The particular culture conditions appear to influence the degree of participation of the CMA pathway in lysosomal degradation.

Autophagy in neurodegenerative diseases

In various neurodegenerative conditions, a common denominator is the presence of ubiquitylated inclusions, which are indicative of failure of protein degradation systems. Although this was originally construed as evidence for UPS dysfunction, conditional-knockout Atg mice (Refs 32, 33) have shown us that this is not necessarily the case, and that macroautophagy impairment can lead to similar results. There is in fact accumulating evidence of increased accumulation of autophagic vacuoles in various neurodegenerative diseases, which, as mentioned above, could be an indication of excessive induction of macroautophagy or a failure of macroautophagy completion. Autophagy imbalance has been implicated as a pathogenic mechanism in various situations of acute injury, but this will not be discussed further here. There are indications that link macroautophagic dysfunction to Huntington disease and other triple-repeat disorders, a rare form of frontotemporal dementia, prion disease, Alzheimer disease and motor neuron disease. The reader is advised to seek reviews that cover more broadly the link of autophagy to neurodegenerative diseases (Refs 68, 80, 81, 82, 83) because we focus here more on Parkinson disease (PD) and related Lewy body disorders.

A central issue in neurodegenerative diseases is whether the observed accumulation of autophagic vacuoles represents a protective effect, or at least a step in this direction, or, instead, a pathway for cell death, in which case the term 'autophagic cell death' or type II cell death, differentiating it from apoptosis or necrosis, can be applied (Refs 3, 81, 82, 84, 85, 86). A corollary to this is whether strategies targeted towards macroautophagy, which would theoretically improve clearance of aberrant protein conformations linked to such proteinopathies, could be applied as therapeutic agents. This is a continuously evolving field, and it is clear that many of the effects observed are context dependent. To give an illustrative example from outside the field of neurodegenerative disease, mice with conditional Atg7 deletion in the CNS that show severe neurodegeneration are protected from hypoxia- or ischaemia-induced neuronal death (Ref. 87). An example from the field of Alzheimer disease research comes from flies partially deficient in Atg1: although they demonstrated a reduced lifespan, they are partially protected against neurodegeneration induced by β-amyloid (APP or Aβ) because of aberrant activation of macroautophagy. $A\beta_{1–42}$ triggered a neurodegenerative cascade, accompanied by excessive accumulation of autophagic vacuoles, which was not only partially rescued by macroautophagy inhibition, but also enhanced by macroautophagy activation with rapamycin. Thus, in this system, the usual prosurvival role of neuronal macroautophagy changes to a prodeath role in the presence of $A\beta_{1–42}$ (Ref. 88).

Parkinson disease

PD represents one of the most common neurodegenerative conditions. It is classically diagnosed when the motor symptoms of tremor, bradykinesia, rigidity and postural imbalance appear (Refs 89, 90). However, it is now recognised that the disease is also characterised by a host of nonmotor symptoms, some of which might even precede the motor manifestations. A major problem is the gradual

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

emergence of cognitive decline in most patients, which can lead to dementia. In the closely related condition, dementia with Lewy bodies (DLB), cognitive decline precedes or appears concurrently with the motor defects.

At the neuropathological level, the disease was traditionally viewed as a dopamine deficiency state, with loss of dopaminergic nigral neurons and their nigrostriatal projections. However, it is now well appreciated that the neuropathological process is much more widespread, involving many neuronal populations across the peripheral and central nervous system. The neuropathogical hallmark of the disease is the appearance, in surviving neurons, of cytoplasmic inclusions, termed Lewy bodies (LBs), whereas analogous aggregates, termed Lewy neurites (LNs), accumulate in neuronal processes (Ref. 90). These aggregates stain strongly for the presynaptic protein α-synuclein (encoded by *SNCA*) and are present in DLB and a host of other neurodegenerative conditions, collectively termed synucleinopathies (Refs 91, 92). Management of PD consists of various forms of dopamine replacement therapy, which is effective in the initial disease stages. However, the emergence of motor complications and severe nonmotor symptomatology, especially dementia, complicates management, hence the need for disease-modifying therapies that attack the disease at its source.

The aetiology of PD is not known, although various theories have been proposed, including oxidative stress, mitochondrial toxin exposure and altered protein handling (Refs 93, 94, 95, 96, 97). This last theory was initially confined to the idea of UPS dysfunction, but more recent data suggest that the autophagy–lysosome system is also affected in PD. Evidence for this has accumulated in part through the association of several of the proteins linked genetically to PD with autophagic pathways. Although PD is largely sporadic, about 10–20% of patients exhibit a clear pattern of inheritance. This has led to the identification of a number of genetic defects that lead to PD. The genes involved can be broadly categorised into two groups: one leading to autosomal dominant PD, and the other to autosomal recessive PD. It is generally assumed that in the former group, a toxic gain of function is operating, whereas the latter is due to a loss of function. Although relatively rare, these genetic defects have opened new windows to the investigation of PD pathogenesis (Ref. 98).

PD and autophagic pathways

Neuropathological evidence linking autophagic pathways to the disease

The first mention of autophagy in the context of analysis of pathological specimens of PD brains came from the study of Anglade and co-workers, where ultrastructural examination of the substantia nigra pars compacta of such brains revealed some evidence of accumulation of autophagic vacuoles (Ref. 99). This was confirmed in another study (Ref. 100). However, it should be stated that many years before, Lydia Forno had observed that LBs within the stellate ganglion of PD patients displayed a rather vesicular nature, suggesting the participation of the autophagic–lysosomal pathway in the formation or dissolution of LBs (Ref. 101). A recent study has shown that LC3 accumulates within LBs and other α-synuclein-immunoreactive structures, supporting this possibility. However, whether LC3-II or LC3-I is the form that accumulates within the inclusions could not be determined. Analysis of LC3 by western blotting revealed a tendency for an increase of the LC3-II band in PD patients, but this was not statistically significant, probably because of the small number of brains analysed (Ref. 75). The accumulation of autophagic vacuoles, as well as the existence of macroautophagic components within LBs in postmortem PD brains, was also shown (Ref. 102). In this work, evidence for lysosomal disruption and release of lysosomal hydrolases was found in MPTP-treated mice, which represent a well-characterised neurotoxin model of Parkinsonism induced by mitochondrial dysfunction and oxidative stress. This led to a net loss of lysosomes in the mouse nigra. These changes were attributed to release of reactive oxygen species from the mitochondria, which damaged the lysosomal membrane. An increase of lysosomal biogenesis, which was achieved through an upregulation of the lysosomal transcription factor EB or, remarkably, the macroautophagy enhancer rapamycin, partially prevented neurodegeneration in the MPTP model (Ref. 102). A decrease in general lysosomal markers, such as cathepsin D and LAMP-1, in PD nigra was also reported in another study. This phenomenon was more

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

marked in LB-containing neurons (Ref. 103). This exciting new set of data suggests that the consistent accumulation of autophagic vacuoles in the nigra in PD is secondary to lysosomal dysfunction. The physiological neuromelanin granules in human nigra are proposed represent aborted autophagic vacuoles, containing pigments derived from catecholamine oxidation, that have not been digested by lysosomes (Ref. 104). Macroautophagic markers were also examined in brain material from patients with DLB. Interestingly, in one study, levels of Atg7 were found to be reduced, whereas those of mTOR were increased, which suggests that the net effect could be inhibition of the progression through the macroautophagy pathway. Despite this, abnormal macroautophagic structures were identified, indicating that the process was still operating but was perhaps also dysfunctional further downstream. LC3 labelling was again observed within such LB-like structures (Ref. 105). In another study, levels of LC3-II and beclin-1 were found to be increased in DLB brains (Ref. 106).

The existence of potential abnormalities in CMA components has also started to receive some attention in neuropathological studies of PD brains. In one of the above-mentioned studies (Ref. 103), a decrease in Hsc70 was observed in PD nigral neurons, but this did not appear to be entirely specific, because other lysosomal markers were also affected. mRNA encoding Hsc70 was also found to be downregulated in PD nigra in a gene-profiling study (Ref. 107). In a careful study, which examined a relatively limited number of brains, western immunoblots showed decreased levels of the two main CMA proteins, LAMP-2A and Hsc70, in both the nigra and amygdala of PD brains (Ref. 75). The authors confirmed that at least in the amygdala, the decrease in LAMP-2A was reflected in lysosomal fractions, in which they controlled for LAMP-1 levels, which were unchanged in the disease brains. These important findings suggest that there may be a specific impairment of CMA that is widespread in PD brains, and is not confined to areas of major cell loss, such as the nigra. In fact, based on our findings of the relationship of α-synuclein to CMA and macroautophagy, we have hypothesised that a triggering or at least contributing event in the generation of the PD pathogenetic cascade could be a malfunction of such degradation systems (Ref. 108). In support of this idea, two genetic defects associated with PD appear to cause direct general lysosomal dysfunction. These include loss-of-function mutations in ATP13A2, a lysosomal ATPase, which leads to a rare familial form of Parkinsonism with dementia and pyramidal tract signs (Refs 109, 110), and mutations in the lysosomal enzyme glucocerebrosidase, normally associated with the quintessential lysosomal storage disorder Gaucher disease, which leads to an increased risk of PD (Ref. 111).

α-Synuclein and autophagic pathways

α-Synuclein, which, as mentioned above, is the major constituent of LBs and LNs, is also linked genetically to the disease through point mutations or multiplications of its gene locus, *SNCA* (Refs 112, 113, 114, 115). Furthermore, polymorphisms within the *SNCA* locus confer increased risk of sporadic PD (Ref. 116). α-Synuclein is accordingly thought to be a major pathogenetic factor in both familial and sporadic PD (Refs 98, 117). A major issue has been the manner of α-synuclein degradation, because impairment of such degradation could lead to accumulation of α-synuclein, which characterises the disease. Although some studies have suggested that the UPS is the main system for α-synuclein degradation (Refs 118, 119), we and others have suggested that such degradation is mainly carried out by lysosomal pathways, and in particular by macroautophagy and CMA (Refs 77, 120, 121). Initially, wild-type α-synuclein was identified as a substrate for CMA in in vitro assays.Two of the α-synuclein mutants, A30P and A53T, bound strongly to LAMP-2A but were not internalised and degraded, and thus acted as inhibitors of CMA degradation of other substrates (Ref. 77). In subsequent studies, using siRNAs against LAMP-2A and expressing forms of α-synuclein that lack the CMA recognition motif, we were able to confirm that CMA is an important pathway for normal α-synuclein turnover, especially in primary neurons, including those derived from rat ventral midbrain (Ref. 69). Detergent-insoluble or high molecular weight oligomeric conformations of α-synuclein also increased following CMA inhibition, suggesting that CMA dysfunction could eventually lead to α-synuclein-related pathology, although discrete aggregates were not detected

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

within the time frame of our experiments (Ref. 69). We found that macroautophagy inhibition by 3-MA led to accumulation of wild-type (WT) α-synuclein (Ref. 120), suggesting that macroautophagy is also important for normal α-synuclein turnover. The results implicating CMA in degradation of WT α-synuclein in neuronal cells have recently been confirmed (Ref. 75). Furthermore, transgenic mice for α-synuclein or mice exposed to the mitochondrial toxin paraquat upregulate lysosomal LAMP-2A and are able to degrade α-synuclein more efficiently, providing indirect evidence that CMA is a mechanism for α-synuclein degradation in vivo (Ref. 122).

Based on the link of α-synuclein to PD pathogenesis, many cellular and animal models of 'synucleinopathy' have been created. In one of these cellular models, we noted that stable expression of the A53T mutant form of α-synuclein in PC12 cells induced a marked accumulation of autophagic vacuoles (Ref. 123). Labelling with Lysotracker and a form of dextran that was taken up and translocated to the lysosomes disclosed a significant decrease of lysosomal acidification in these cells, suggesting that lysosomes were dysfunctional. In fact, we found that the ability of lysosomes to degrade long-lived proteins was severely impaired in the A53T-expressing cells (Ref. 77). As discussed earlier, this could have led to the dramatic macroautophagy phenotype that was observed (Ref. 123). The increase in autophagosomes in cells and transgenic mice overexpressing mutant, or, in some cases, wild-type α-synuclein, has now been replicated in a number of studies (Refs 105, 106, 124) and mirrors the neuropathological data mentioned above.

In subsequent work, we have extended these studies to differentiated human neuroblastoma cells inducibly expressing α-synuclein and rat cortical neurons adenovirally transduced with α-synuclein. Although we saw consistent CMA dysfunction, autophagosome accumulation (as defined in this case by an increase of LC3-II immunolabelling) and neuronal toxicity, general lysosomal dysfunction was not always observed. Macroautophagic alterations and neuronal toxicity were secondary to CMA impairment, because forms of α-synuclein that were not targeted to CMA did not induce autophagosome accumulation and induced death to a lesser extent (Ref. 76).

An earlier study showed that post-translational modifications of α-synuclein differentially affect the ability of the protein to be degraded by CMA and the degradation of other CMA substrates (Ref. 78). More particularly, it was shown that only monomers and dimers of α-synuclein, but not oligomers, are degraded by CMA, whereas oxidation and nitration of the protein slightly inhibit its degradation by CMA (Ref. 78). By contrast, phosphorylation and dopamine modification of α-synuclein almost completely prevented the degradation of the protein by CMA. Only dopamine modification of α-synuclein was able to significantly inhibit the degradation of other CMA substrates. Consistent with these findings, we found, in dopaminergic cells, that even wild-type α-synuclein caused CMA dysfunction and CMA-targeting-dependent death in a dopamine-dependent fashion (Ref. 76). This is important, because it extends CMA dysfunction as a more general pathogenetic effect of α-synuclein within dopaminergic neurons beyond the rare familial cases.

Another link of pathogenic effects of α-synuclein with CMA is provided by a study which showed that both WT and A53T α-synuclein caused CMA dysfunction, and that this, in turn, led to mislocalisation of the neuronal survival factor and CMA substrate MEF2D to the cytosol, with resultant loss of its protective function. Adding to the physiological relevance of these findings, mislocalised MEF2D was increased in A53T transgenic mice and in PD patients (Ref. 79).

These results highlight the possibility of toxic effects of α-synuclein through direct interference with the CMA pathway, and also the crosstalk between the two major autophagic pathways. It would appear therefore that aberrant α-synuclein can lead to increased autophagosome accumulation either through lysosomal dysfunction or through specific CMA targeting. In the former case macroautophagy is 'nonproductive', and in the latter it is 'productive'. It is unclear at this point what determines each effect, and they could both potentially operate under certain circumstances (Fig. 3). A recent study has raised the additional possibility that α-synuclein could inhibit an early point in autophagosome formation, through interaction with Rab1a (Ref. 125). It is difficult at this point to reconcile these data with

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

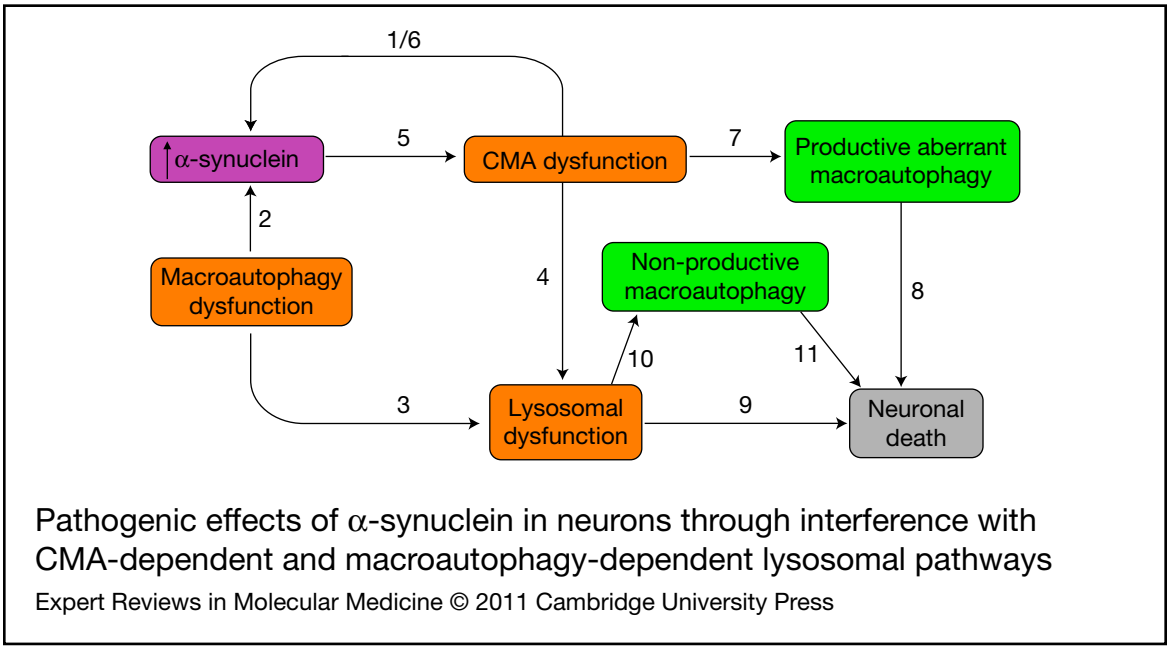

Figure 3. Pathogenic effects of α-synuclein in neurons through interference with CMA-dependent and macroautophagy-dependent lysosomal pathways. The diagram represents a hypothetical scheme of the link between α-synuclein and autophagic pathways, based on currently available data. At early stages of PD, dysfunction of CMA-dependent (arrow 1) or of macroautophagy-dependent (arrow 2) degradation pathways might lead to α-synuclein accumulation, which characterises the disease. Dysfunction of such pathways might in part be a consequence of ageing. Such dysfunction would be expected to lead in parallel to generalised lysosomal impairment (arrows 3 and 4), because the lysosome relies on these systems to efficiently degrade intracellular proteins. As aberrant α-synuclein continues to accumulate over time, it can cause specific CMA impairment (arrow 5), which can feed back into further α-synuclein accumulation (arrow 6). CMA dysfunction at this stage can also lead to aberrant activation of 'productive' macroautophagy (arrow 7), which can lead to neuronal degeneration (arrow 8). At the same time, the increasing generalised lysosomal dysfunction can lead to neuronal death either directly (arrow 9) or through aberrant accumulation of autophagosomes that cannot be degraded by the dysfunctional lysosomes ('nonproductive' macroautophagy) (arrow 10). Accumulation of such malfunctioning autophagosomes could be further detrimental to neuronal survival (arrow 11). The end result from both productive and nonproductive macroautophagic pathways at late stages of the disease would be neuronal death with evidence of accumulation of autophagosomes in dying neurons ('autophagic cell death'). Abbreviations: CMA, chaperone-mediated autophagy; PD, Parkinson disease.

our own or those that suggest substantial accumulation of autophagosomes in synucleinopathy models, as mentioned above.

An important question is whether macroautophagy in our experimental setting of cultured differentiated neuroblastoma and cortical neurons served a protective or deleterious effect. We found that pharmacological or molecular inhibition of macroautophagy was protective. This occurred even in cortical neurons, where macroautophagy was 'productive' (Ref. 76). There could be various mechanisms through which such death could occur, such as excess consumption of vital cellular constituents, leakage of lysosomal hydrolases into the cytosol or enhanced production of damaging molecules within autophagic vacuoles or autophagolysosomes.

Such results run against an accumulating body of literature suggesting that enhancement of macroautophagy is a treatment strategy against synucleinopathies or, for that matter, other neurodegenerative conditions. Induction of macroautophagy by treatment with rapamycin or overexpression of Atg7 or beclin-1 led to reversal of pathological effects induced by α-

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

synuclein in cellular and in vivo models (Refs 105, 106, 124). These apparently differential effects could be due to timing, because it is conceivable that early in the pathological process macroautophagy might be beneficial as a clearing mechanism; however, later on, when excessively activated, in cells that are already suffering and close to death, it may be deleterious (Fig. 3). Alternatively, it could be an issue of differences in the particular models used. We are currently examining our cellular systems for the effects of macroautophagy enhancers to address this possibility.

Linkage of UCH-L1 and LRRK2 to autophagic pathways

A very rare genetic cause of PD is a mutant form of ubiquitin C-terminal esterase L1 (UCH-L1), I93M, which has been identified in only a single family and has also been linked to the CMA pathway. This mutant form, but not WT UCH-L1, interacted aberrantly with the CMA components LAMP-2A and Hsc70, inhibited CMA and caused an increase in α-synuclein levels, indicating that the aberrant interaction of mutant UCH-L1 with CMA might underlie its pathogenic role (Ref. 126).

Another protein linked genetically to PD through an assumed toxic gain of function is LRRK2 (leucine-rich repeat serine/threonine protein kinase 2 or PARK8), which might also be intricately linked to the ALP. In brains and cells, LRRK2 appears to localise mainly to vesicular granular structures of the late endosomal–lysosomal pathway (Refs 127, 128, 129). Aged *Lrrk2*-null mice display an autophagy-relevant phenotype in the kidney, where LRRK2 is normally highly expressed (Ref. 130). There is induction of LC3-II and p62, and a parallel accumulation of α-synuclein and ubiquitin-positive aggregates, accompanied by extensive cellular degeneration and inflammatory responses. These results indicate a profound impairment of the macroautophagy pathway downstream of autophagosome formation. In apparent contradiction, siRNA-mediated knockdown of LRRK2 in cultured human cells increased autophagic activity and prevented starvation-induced cell death when autophagy was inhibited with bafilomycin (Refs 127, 128). It will be interesting to decipher the basis for these differences, and to further understand the physiological role of LRRK2 in the regulation of macroautophagy and broader lysosomal function.

However, the main link of LRRK2 to PD is provided through mutant forms identified in patients in families with autosomal dominant inheritance (Ref. 98). Expression of the mutant G2019S form of LRRK2 led to neuritic retraction and accumulation of autophagosomes in differentiated human neuroblastoma SH-SY5Y cells (Ref. 131). Inhibition of macroautophagy through molecular means reversed the detrimental effects of mutant G2019S LRRK2 on the length of neuronal processes (Ref. 131), a prominent feature of the degenerative phenotype associated with PD-associated LRRK2 mutations. In partial agreement with this work, expression of another PD-linked LRRK2 mutant, R1441G, induced autophagic stress characterised by the accumulation of abnormal multivesicular bodies and enlarged autophagosomes with high levels of p62 and by the appearance of skein-like inclusions (Ref. 127). In the latter study, however, no attempt was made to examine the effect on cellular homeostasis by macroautophagy modulation.

It would appear therefore that, as in our own synucleinopathy cellular models, expression of mutant forms linked to autosomal dominant PD might lead to induction of the presence of autophagosomes, and that in these settings, the macroautophagy pathway may be aberrantly activated. The data obtained with mutant LRRK2 (Ref. 131), together with the previously mentioned data illustrating selective vulnerability of neurites to genetically induced macroautophagy impairment (Ref. 47), show that macroautophagy balance is especially critical in neurites.

Proteins linked to autosomal recessive Parkinsonism provide a link to mitophagy

Apparent loss of function of Parkin (PARK2) and PINK1 constitutes the bulk of cases with autosomal recessive Parkinsonism (Ref. 98). Given the dramatic mitochondrial deficits present in fly models with deletion of the corresponding genes, it was assumed that the function of both Parkin and PINK1 was to preserve mitochondrial integrity (Refs 98, 132). This tied in well with the traditional notion that PD is related to mitochondrial dysfunction (Ref. 132). In fact, both proteins were found to

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

function in a pathway that controlled fusion–fission events in mitochondria (Ref. 132). An unexpected discovery showed that Parkin is recruited to depolarised mitochondria and enabled their autophagic degradation, in a process termed mitophagy, because damaged mitochondria are selectively targeted (Ref. 133). It has subsequently been shown that PINK1 is necessary for this action of Parkin, thus linking both these proteins to mitophagy (Refs 134, 135). In apparent contradiction, probably because depolarisation conditions were not used, loss of PINK1 enhanced autophagy and mitophagy in another study (Ref. 136). The weight of evidence suggests that inability to degrade damaged mitochondria through mitophagy might be a factor leading to autosomal recessive PD. PINK1 might have a more general role in macroautophagy because, on overexpression, it interacted with beclin-1 and enhanced basal and starvation-induced macroautophagy, which was reduced by knockdown of beclin-1 expression or by inhibition of the beclin-1 partner Vps34 (Ref. 137). Adding to the link of recessive forms of Parkinsonism with more general autophagic pathways, the orphan G-protein-coupled receptor 37 (GPR37), a potential Parkin substrate, was also recently demonstrated to induce macroautophagy (Ref. 138).

Potential therapeutic implications and future directions

Insights gained from the studies mentioned above lead to the following conclusions that: (1) alterations in autophagic pathways occur in PD, DLB and relevant models; (2) genetic defects leading to PD cause alterations of autophagic pathways; and, consequently, (3) targeting such autophagic pathways might represent a valuable therapeutic strategy.

Regarding synucleinopathies, our current view is that because of the double-edged sword action of macroautophagy (which if aberrantly activated in compromised neurons can lead to enhanced neuronal degeneration) targeting bulk macroautophagy might not be the best approach for the treatment of synucleinopathies. We suggest that targeting CMA instead may be a more fruitful approach. CMA dysfunction appears to represent a direct effect of α-synuclein-mediated toxicity and CMA might be a major pathway for α-synuclein degradation. Therefore, improving CMA function may serve to limit α-synuclein-mediated toxic lysosomal effects, while at the same time it would be expected to lead to enhanced α-synuclein clearance. It should be stressed, however, that insights regarding CMA involvement in α-synuclein clearance and neurotoxicity are largely based on cell culture data, and a note of caution is required regarding their applicability to the in vivo situation.

The most obvious strategy of enhancing CMA would be that of inducing expression of LAMP-2A. This strategy, as mentioned, has been successfully implemented in cultured cells and in mouse liver (Refs 74, 75). Given that Hsc70 represents another major component of CMA, and that lysosomes lacking Hsc70 are unable to degrade substrates in a CMA-dependent fashion, Hsc70 may also need to be induced. Apart from the obvious prospect of gene therapy to induce expression of the relevant genes, the possibility exists that pharmacological agents could act as inducers of expression of LAMP-2A and Hsc70. As the mechanism of CMA is further deciphered, more opportunities for therapeutic intervention arise, which might also include stabilisation of LAMP-2A at the level of the lysosomal membrane.

It should be noted that CMA, although selective, is still responsible for the degradation of many other cytosolic proteins, and therefore the consequences of its induction in the nervous system cannot be anticipated with certainty. Further research is clearly needed to identify CMA substrates in the nervous system and to assess the effects of CMA induction on neuronal homeostasis. However, the fact that CMA components appear to be diminished in PD brains (Ref. 76) provides a rationale for their induction and the therapeutic approach of CMA enhancement in synucleinopathies.

It is also possible that fine-tuning of macroautophagic pathways may be a valid therapeutic option, especially in earlier stages of the disease process, when it can serve to lessen the load of aberrant α-synuclein conformations. Indeed, with the exciting new information regarding selective macroautophagic pathways that are responsible for removal of aggregates, it is conceivable that targeting and enhancement of such selective pathways may prove to be a safer approach, not only for synucleinopathies but also for neurodegenerative 'proteinopathies' in general.

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

Harnessing excessive macroautophagy, which has been proved to be detrimental in some settings, including those of overexpression of α-synuclein and LRRK2 (Refs 77, 130), could also provide a therapeutic strategy. But in this case, it would be critical not to indiscriminately block macroautophagy, because this could have obvious consequences for neuronal homeostasis, especially in the setting of proteinopathies. Rather, research should be directed towards understanding why in certain settings macroautophagy induction can be detrimental, and how such effects could be curtailed.

Further research is clearly needed in the direction of microautophagy and its possible function in PD and related neurodegenerative conditions, because its role in mammalian systems remains largely obscure. Another emerging area is that of the inter-relationship between autophagic pathways and LBs. Exactly how macroautophagic and, more broadly, lysosomal components are involved in the formation and dissolution of LBs will also need to be deciphered. The discovery of the link of mitophagy to autosomal recessive forms of PD has opened up new possibilities for therepautic intervention. Enhancement of this process, as occurs when Parkin is overexpressed, and clearing damaged mitochondria may prove beneficial not only in these rare familial cases, but also in the sporadic disease where mitochondrial function may be impaired and damaged mitochondria that have lost their transmembrane potential could lead to production of oxidative stress.

Finally, autophagic systems do not act in a vacuum. They are intricately related to endosomal and intracellular trafficking systems, and these systems can have reciprocal influences. A case in point is our finding that α-synuclein can be secreted through the exosomal pathway, which is a secretion pathway for vesicles within multivesicular bodies and a late endocytic component. This process is enhanced by lysosomal inhibitors (Ref. 139). Findings in erythroleukaemic cells indicate that because an alternative pathway for multivesicular bodies is that of fusion with AVs, enhancement of macroautophagy may diminish exosomal release (Ref. 140). If indeed α-synuclein secretion by exosomes is proved to be detrimental to neuronal homeostasis, enhancement of macroautophagy might also represent a therapeutic intervention.

Acknowledgements and funding

This work was supported by an EC/People/FP7 'NEURASYN' grant to L.S. and by a PDF post-doctoral fellowship to M.X. and L.S. The authors thank the peer reviewers for their very valuable and thoughtful comments, which have led to substantial improvement of the manuscript.

References

1 De Duve, C. and Wattiaux, R. (1966) Functions of lysosomes. Annual Review of Physiology 28, 435-492
2 Muller, O. et al. (2000) Autophagic tubes: vacuolar invaginations involved in lateral membrane sorting and inverse vesicle budding. Journal of Cell Biology 151, 519-528
3 Shintani, T. and Klionsky, D.J. (2004) Autophagy in health and disease: a double-edged sword. Science 306, 990-995
4 Mizushima, N. (2005) The pleiotropic role of autophagy: from protein metabolism to bactericide. Cell Death and Differentiation 12 (Suppl 2), 1535-1541
5 Hayashi-Nishino, M. et al. (2009) A subdomain of the endoplasmic reticulum forms a cradle for autophagosome formation. Nature Cell Biology 11, 1433-1437
6 Tooze, S.A. and Yoshimori, T. (2010) The origin of the autophagosomal membrane. Nature Cell Biology 12, 831-835
7 Yang, Z. and Klionsky, D.J. (2010) Mammalian autophagy: core molecular machinery and signaling regulation. Current Opinion in Cell Biology 22, 124-131
8 Kochl, R. et al. (2006) Microtubules facilitate autophagosome formation and fusion of autophagosomes with endosomes. Traffic 7, 129-145
9 Hollenbeck, P.J. (1993) Products of endocytosis and autophagy are retrieved from axons by regulated retrograde organelle transport. Journal of Cell Biology 121, 305-315
10 Ohsumi, Y. (2001) Molecular dissection of autophagy: two ubiquitin-like systems. Nature Reviews. Molecular Cell Biology 2, 211-216
11 Klionsky, D.J. (2005) The molecular machinery of autophagy: unanswered questions. Journal of Cell Science 118, 7-18
12 Jung, C.H. et al. (2010) mTOR regulation of autophagy. FEBS Letters 584, 1287-1295
13 Ravikumar, B. et al. (2010) Regulation of mammalian autophagy in physiology and pathophysiology. Physiological Reviews 90, 1383-1435

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

14 He, C. and Klionsky, D.J. (2009) Regulation mechanisms and signaling pathways of autophagy. Annual Review of Genetics 43, 67-93
15 Hosokawa, N. et al. (2009) Atg101, a novel mammalian autophagy protein interacting with Atg13. Autophagy 5, 973-979
16 Klionsky, D.J. (2007) Autophagy: from phenomenology to molecular understanding in less than a decade. Nature Reviews. Molecular Cell Biology 8, 931-937
17 Yan, J. et al. (1998) Identification of mouse ULK1, a novel protein kinase structurally related to C. elegans UNC-51. Biochemical and Biophysical Research Communications 246, 222-227
18 Levine, B., Sinha, S. and Kroemer, G. (2008) Bcl-2 family members: dual regulators of apoptosis and autophagy. Autophagy 4, 600-606
19 Thoresen, S.B. et al. (2010) A phosphatidylinositol 3-kinase class III sub-complex containing VPS15, VPS34, Beclin 1, UVRAG and BIF-1 regulates cytokinesis and degradative endocytic traffic. Experimental Cell Research 316, 3368-3378
20 Funderburk, S.F., Wang, Q.J. and Yue, Z. (2010) The Beclin 1-VPS34 complex–at the crossroads of autophagy and beyond. Trends in Cell Biology 20, 355-362
21 Bjorkoy, G. et al. (2009) Monitoring autophagic degradation of p62/SQSTM1. Methods in Enzymology 452, 181-197
22 Bjorkoy, G., Lamark, T. and Johansen, T. (2006) p62/SQSTM1: a missing link between protein aggregates and the autophagy machinery. Autophagy 2, 138-139
23 Bjorkoy, G. et al. (2005) p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death. Journal of Cell Biology 171, 603-614
24 Klionsky, D.J. et al. (2008) Guidelines for the use and interpretation of assays for monitoring autophagy in higher eukaryotes. Autophagy 4, 151-175
25 Kawaguchi, Y. et al. (2003) The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 115, 727-738
26 Chang, C.Y. and Huang, W.P. (2007) Atg19 mediates a dual interaction cargo sorting mechanism in selective autophagy. Molecular Biology of the Cell 18, 919-929
27 Thurston, T.L. et al. (2009) The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. Nature Immunology 10, 1215-1221
28 Novak, I. et al. (2010) Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Reports 11, 45-51
29 Kanki, T. et al. (2009) Atg32 is a mitochondrial protein that confers selectivity during mitophagy. Developmental Cell 17, 98-109
30 Kirkin, V. et al. (2009) A role for NBR1 in autophagosomal degradation of ubiquitinated substrates. Molecular Cell 33, 505-516
31 Filimonenko, M. et al. (2010) The selective macroautophagic degradation of aggregated proteins requires the PI3P-binding protein Alfy. Molecular Cell 38, 265-279
32 Hara, T. et al. (2006) Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441, 885-889
33 Komatsu, M. et al. (2006) Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 441, 880-884
34 Komatsu, M. et al. (2007) Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. Cell 131, 1149-1163
35 Korolchuk, V.I. et al. (2009) Autophagy inhibition compromises degradation of ubiquitin-proteasome pathway substrates. Molecular Cell 33, 517-527
36 Zhou, X. et al. (2007) Unc-51-like kinase 1/2-mediated endocytic processes regulate filopodia extension and branching of sensory axons. Proceedings of the National Academy of Sciences of the United States of America 104, 5842-5847
37 McIntire, S.L. et al. (1992) Genes necessary for directed axonal elongation or fasciculation in *C. elegans*. Neuron 8, 307-322
38 Pickford, F. et al. (2008) The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. Journal of Clinical Investigation 118, 2190-2199
39 Fimia, G.M. et al. (2007) Ambra1 regulates autophagy and development of the nervous system. Nature 447, 1121-1125
40 Lee, J.A. et al. (2007) ESCRT-III dysfunction causes autophagosome accumulation and neurodegeneration. Current Biology 17, 1561-1567
41 Mizushima, N. (2004) Methods for monitoring autophagy. International Journal of Biochemistry and Cell Biology 36, 2491-2502
42 Mizushima, N. and Kuma, A. (2008) Autophagosomes in GFP-LC3 transgenic mice. Methods in Molecular Biology 445, 119-124
43 Mizushima, N. (2009) Methods for monitoring autophagy using GFP-LC3 transgenic mice. Methods in Enzymology 452, 13-23

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

44 Tsvetkov, A.S., Mitra, S. and Finkbeiner, S. (2009) Protein turnover differences between neurons and other cells. Autophagy 5 [Epub ahead of print]
45 Boland, B. et al. (2008) Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. Journal of Neuroscience 28, 6926-6937
46 Mitra, S., Tsvetkov, A.S. and Finkbeiner, S. (2009) Single neuron ubiquitin-proteasome dynamics accompanying inclusion body formation in huntington disease. Journal of Biological Chemistry 284, 4398-4403
47 Komatsu, M. et al. (2007) Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration. Proceedings of the National Academy of Sciences of the United States of America 104, 14489-14494
48 Yue, Z. et al. (2009) The cellular pathways of neuronal autophagy and their implication in neurodegenerative diseases. Biochimica et Biophysica Acta 1793, 1496-1507
49 Ward, W.F. (2002) Protein degradation in the aging organism. Progress in Molecular and Subcellular Biology 29, 35-42
50 Cuervo, A.M. et al. (2005) Autophagy and aging: the importance of maintaining "clean" cells. Autophagy 1, 131-140
51 Cuervo, A.M. and Dice, J.F. (2000) Age-related decline in chaperone-mediated autophagy. Journal of Biological Chemistry 275, 31505-31513
52 Vellai, T. (2009) Autophagy genes and ageing. Cell Death and Differentiation 16, 94-102
53 Simonsen, A. et al. (2008) Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila. Autophagy 4, 176-184
54 Simonsen, A., Cumming, R.C. and Finley, K.D. (2007) Linking lysosomal trafficking defects with changes in aging and stress response in Drosophila. Autophagy 3, 499-501
55 Simonsen, A. et al. (2007) Genetic modifiers of the Drosophila blue cheese gene link defects in lysosomal transport with decreased life span and altered ubiquitinated-protein profiles. Genetics 176, 1283-1297
56 Chiang, H.L. et al. (1989) A role for a 70-kilodalton heat shock protein in lysosomal degradation of intracellular proteins. Science 246, 382-385
57 Cuervo, A.M., Dice, J.F. and Knecht, E. (1997) A population of rat liver lysosomes responsible for the selective uptake and degradation of cytosolic proteins. Journal of Biological Chemistry 272, 5606-5615
58 Cuervo, A.M. and Dice, J.F. (1996) A receptor for the selective uptake and degradation of proteins by lysosomes. Science 273, 501-503
59 Agarraberes, F.A. and Dice, J.F. (2001) A molecular chaperone complex at the lysosomal membrane is required for protein translocation. Journal of Cell Science 114, 2491-2499
60 Bandyopadhyay, U. et al. (2008) The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. Molecular Cell Biol 28, 5747-5763
61 Dice, J.F. (1990) Peptide sequences that target cytosolic proteins for lysosomal proteolysis. Trends in Biochemical Sciences 15, 305-309
62 Chiang, H.L. and Dice, J.F. (1988) Peptide sequences that target proteins for enhanced degradation during serum withdrawal. Journal of Biological Chemistry 263, 6797-6805
63 Hatem, C.L., Gough, N.R. and Fambrough, D.M. (1995) Multiple mRNAs encode the avian lysosomal membrane protein LAMP-2, resulting in alternative transmembrane and cytoplasmic domains. Journal of Cell Science 108(Pt 5), 2093-2100
64 Bandyopadhyay, U. et al. (2010) Identification of regulators of chaperone-mediated autophagy. Molecular Cell 39, 535-547
65 Cuervo, A.M. and Dice, J.F. (2000) Regulation of lamp2a levels in the lysosomal membrane. Traffic 1, 570-583
66 Cuervo, A.M. et al. (1995) Activation of a selective pathway of lysosomal proteolysis in rat liver by prolonged starvation. American Journal of Physiology 269, C1200-C1208
67 Agarraberes, F.A., Terlecky, S.R. and Dice, J.F. (1997) An intralysosomal hsp70 is required for a selective pathway of lysosomal protein degradation. Journal of Cell Biology 137, 825-834
68 Martinez-Vicente, M. and Cuervo, A.M. (2007) Autophagy and neurodegeneration: when the cleaning crew goes on strike. Lancet Neurology 6, 352-361
69 Vogiatzi, T. et al. (2008) Wild type alpha-synuclein is degraded by chaperone-mediated autophagy and macroautophagy in neuronal cells. Journal of Biological Chemistry 283, 23542-23556
70 Massey, A.C. et al. (2006) Consequences of the selective blockage of chaperone-mediated autophagy. Proceedings of the National Academy of Sciences of the United States of America 103, 5805-5810

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

71 Wang, Y. et al. (2007) Loss of macroautophagy promotes or prevents fibroblast apoptosis depending on the death stimulus. Journal of Biological Chemistry 283, 4766-4777
72 Kaushik, S. et al. (2008) Constitutive activation of chaperone-mediated autophagy in cells with impaired macroautophagy. Molecular Biology of the Cell 19, 2179-2192
73 Cuervo, A.M. and Dice, J.F. (2000) Unique properties of lamp2a compared to other lamp2 isoforms. Journal of Cell Science 113(Pt 24), 4441-4450
74 Zhang, C. and Cuervo, A.M. (2008) Restoration of chaperone-mediated autophagy in aging liver improves cellular maintenance and hepatic function. Nature Medicine 14, 959-965
75 Alvarez-Erviti, L. et al. (2010) Chaperone-Mediated Autophagy Markers in Parkinson Disease Brains. Archives of Neurology 67, 1464-1472
76 Xilouri, M. et al. (2009) Abberant alpha-synuclein confers toxicity to neurons in part through inhibition of chaperone-mediated autophagy. PLoS One 4, e5515
77 Cuervo, A.M. et al. (2004) Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science 305, 1292-1295
78 Martinez-Vicente, M. et al. (2008) Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. Journal of Clinical Investigation 118, 777-788
79 Yang, Q. et al. (2009) Regulation of neuronal survival factor MEF2D by chaperone-mediated autophagy. Science 323, 124-127
80 Jaeger, P.A. and Wyss-Coray, T. (2009) All-you-can-eat: autophagy in neurodegeneration and neuroprotection. Molecular Neurodegeneration 4, 16
81 Rubinsztein, D.C. et al. (2005) Autophagy and its possible roles in nervous system diseases, damage and repair. Autophagy 1, 11-22
82 Cherra, S.J. and Chu, C.T. (2008) Autophagy in neuroprotection and neurodegeneration: a question of balance. Future Neurology 3, 309-323
83 Wong, E. and Cuervo, A.M. (2010) Autophagy gone awry in neurodegenerative diseases. Nature Neuroscience 13, 805-811
84 Kunchithapautham, K. and Rohrer, B. (2007) Autophagy is one of the multiple mechanisms active in photoreceptor degeneration. Autophagy 3, 65-66
85 Hornung, J.P., Koppel, H. and Clarke, P.G. (1989) Endocytosis and autophagy in dying neurons: an ultrastructural study in chick embryos. Journal of Comparative Neurology 283, 425-437
86 Lohr, H.R. et al. (2006) Multiple, parallel cellular suicide mechanisms participate in photoreceptor cell death. Experimental Eye Research 83, 380-389
87 Koike, M. et al. (2008) Inhibition of autophagy prevents hippocampal pyramidal neuron death after hypoxic-ischemic injury. American Journal of Pathology 172, 454-469
88 Ling, D. et al. (2009) Abeta42-induced neurodegeneration via an age-dependent autophagic-lysosomal injury in Drosophila. PLoS ONE 4, e4201
89 Forno, L.S. (1996) Neuropathology of Parkinson's disease. Journal of Neuropathology and Experimental Neurology 55, 259-272
90 Gibb, W. (1993). Parkinson's Disease and Movement Disorders (2nd edn), Williams & Wilkins.
91 Spillantini, M.G. et al. (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proceedings of the National Academy of Sciences of the United States of America 95, 6469-6473
92 Spillantini, M.G. et al. (1997) Alpha-synuclein in Lewy bodies. Nature 388, 839-840
93 Ross, C.A. and Poirier, M.A. (2004) Protein aggregation and neurodegenerative disease. Nature Medicine 10 (Suppl), S10-S17
94 Dauer, W. and Przedborski, S. (2003) Parkinson's disease: mechanisms and models. Neuron 39, 889-909
95 Abou-Sleiman, P.M., Muqit, M.M. and Wood, N.W. (2006) Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nature Reviews. Neuroscience 7, 207-219
96 Giasson, B.I. et al. (2000) Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science 290, 985-989
97 Levy, O.A., Malagelada, C. and Greene, L.A. (2009) Cell death pathways in Parkinson's disease: proximal triggers, distal effectors, and final steps. Apoptosis 14, 478-500
98 Gasser, T. (2009) Molecular pathogenesis of Parkinson disease: insights from genetic studies. Expert Reviews in Molecular Medicine 11, e22
99 Anglade, P. et al. (1997) Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease. Histology and Histopathology 12, 25-31
100 Zhu, J.H. et al. (2003) Localization of phosphorylated ERK/MAP kinases to mitochondria and autophagosomes in Lewy body diseases. Brain Pathology 13, 473-481

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

101 Forno, L.S. and Norville, R.L. (1976) Ultrastructure of Lewy bodies in the stellate ganglion. Acta Neuropathologica 34, 183197
102 Dehay, B. et al. (2010) Pathogenic lysosomal depletion in Parkinson's disease. Journal of Neuroscience 30, 12535-12544
103 Chu, Y. et al. (2009) Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions. Neurobiology of Disease 35, 385-398
104 Sulzer, D. et al. (2000) Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. Proceedings of the National Academy of Sciences of the United States of America 97, 11869-11874
105 Crews, L. et al. (2010) Selective molecular alterations in the autophagy pathway in patients with Lewy body disease and in models of alpha-synucleinopathy. PLoS One 5, e9313
106 Yu, W.H. et al. (2009) Metabolic activity determines efficacy of macroautophagic clearance of pathological oligomeric alpha-synuclein. American Journal of Pathology 175, 736-747
107 Mandel, S. et al. (2005) Gene expression profiling of sporadic Parkinson's disease substantia nigra pars compacta reveals impairment of ubiquitin-proteasome subunits, SKP1A, aldehyde dehydrogenase, and chaperone HSC-70. Annals of the New York Academy of Sciences 1053, 356-375
108 Xilouri, M. et al. (2008) Alpha-synuclein degradation by autophagic pathways: a potential key to Parkinson's disease pathogenesis. Autophagy 4, 917-919
109 Di Fonzo, A. et al. (2007) ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 68, 1557-1562
110 Ramirez, A. et al. (2006) Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nature Genetics 38, 1184-1191
111 Sidransky, E. et al. (2009) Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. New England Journal of Medicine 361, 1651-1661
112 Chartier-Harlin, M.C. et al. (2004) Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet 364, 1167-1169
113 Polymeropoulos, M.H. et al. (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045-2047
114 Kruger, R. et al. (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nature Genetics 18, 106-108
115 Singleton, A.B. et al. (2003) alpha-Synuclein locus triplication causes Parkinson's disease. Science 302, 841
116 Maraganore, D.M. et al. (2006) Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. JAMA 296, 661-670
117 Simon-Sanchez, J. et al. (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nature Genetics 41, 1308-1312
118 Bennett, M.C. et al. (1999) Degradation of alpha-synuclein by proteasome. Journal of Biological Chemistry 274, 33855-33858
119 Imai, Y., Soda, M. and Takahashi, R. (2000) Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. Journal of Biological Chemistry 275, 35661-35664
120 Webb, J.L. et al. (2003) Alpha-synuclein is degraded by both autophagy and the proteasome. Journal of Biological Chemistry 278, 25009-25013
121 Lee, H.J. et al. (2004) Clearance of alpha-synuclein oligomeric intermediates via the lysosomal degradation pathway. Journal of Neuroscience 24, 1888-1896
122 Mak, S.K. et al. (2010) Lysosomal degradation of alpha-synuclein in vivo. Journal of Biological Chemistry 285, 13621-13629
123 Stefanis, L. et al. (2001) Expression of A53T mutant but not wild-type alpha-synuclein in PC12 cells induces alterations of the ubiquitin-dependent degradation system, loss of dopamine release, and autophagic cell death. Journal of Neuroscience 21, 9549-9560
124 Spencer, B. et al. (2009) Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in alpha-synuclein models of Parkinson's and Lewy body diseases. Journal of Neuroscience 29, 13578-13588
125 Winslow, A.R. et al. (2010) alpha-Synuclein impairs macroautophagy: implications for Parkinson's disease. Journal of Cell Biology 190, 1023-1037
126 Kabuta, T. et al. (2008) Aberrant interaction between Parkinson disease-associated mutant UCH-L1 and the lysosomal receptor for chaperone-mediated autophagy. Journal of Biological Chemistry 283, 23731-23738
127 Alegre-Abarrategui, J. et al. (2009) LRRK2 regulates autophagic activity and localizes to specific membrane microdomains in a novel human

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

genomic reporter cellular model. Human Molecular Genetics 18, 4022-4034
128 Alegre-Abarrategui, J. and Wade-Martins, R. (2009) Parkinson disease, LRRK2 and the endocytic-autophagic pathway. Autophagy 5, 1208-1210
129 Higashi, S. et al. (2009) Abnormal localization of leucine-rich repeat kinase 2 to the endosomal-lysosomal compartment in lewy body disease. Journal of Neuropathology and Experimental Neurology 68, 994-1005
130 Tong, Y. et al. (2010) Loss of leucine-rich repeat kinase 2 causes impairment of protein degradation pathways, accumulation of alpha-synuclein, and apoptotic cell death in aged mice. Proceedings of the National Academy of Sciences of the United States of America 107, 9879-9884
131 Plowey, E.D. et al. (2008) Role of autophagy in G2019S-LRRK2-associated neurite shortening in differentiated SH-SY5Y cells. Journal of Neurochemistry 105, 1048-1056
132 Yao, Z. and Wood, N.W. (2009) Cell death pathways in Parkinson's disease: role of mitochondria. Antioxidants and Redox Signaling 11, 2135-2149
133 Narendra, D. et al. (2008) Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. Journal of Cell Biology 183, 795-803
134 Narendra, D.P. et al. (2010) PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biology 8, e1000298
135 Vives-Bauza, C. et al. (2010) PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. Proceedings of the National Academy of Sciences of the United States of America 107, 378-383
136 Dagda, R.K. et al. (2009) Loss of PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission. Journal of Biological Chemistry 284, 13843-13855
137 Michiorri, S. et al. (2010) The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy. Cell Death and Differentiation 17, 962-974
138 Marazziti, D. et al. (2009) Induction of macroautophagy by overexpression of the Parkinson's disease-associated GPR37 receptor. FASEB Journal 23, 1978-1987
139 Emmanouilidou, E. et al. (2010) Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. Journal of Neuroscience 30, 6838-6851
140 Fader, C.M. et al. (2008) Induction of autophagy promotes fusion of multivesicular bodies with autophagic vacuoles in k562 cells. Traffic 9, 230-250

Further reading, resources and contacts Publications

Publications

Jaeger, P.A. and Wyss-Coray, T. (2009) All-you-can-eat: autophagy in neurodegeneration and neuroprotection. Molecular Neurodegeneration 4, 16

This is a complete review of the available data regarding the function of autophagy in the central nervous system and its role in acute and chronic neurological disorders.

Mizushima, N., Yoshimori, T. and Levine, B. (2010) Methods in mammalian autophagy research. Cell 140, 313-326

This primer provides a critical overview of currently available techniques to monitor autophagy and to modulate autophagic activity in mammalian cells and the limitations in their interpretation.

Yang, Z. and Klionsky, D.J. (2010) Eaten alive: a history of macroautophagy. Nature Cell Biology 12, 814-822

This review traces the key findings that led to our current molecular understanding of the complex process of macroautophagy.

Koga, H. and Cuervo, A.M. (2010) Chaperone-mediated autophagy dysfunction in the pathogenesis of neurodegeneration. Neurobiology of Disease, doi: 10.1016/j.nbd.2010.07.006

This review summarises the recent findings on the molecular mechanisms behind CMA function, the physiological relevance of the selective lysosomal degradation through this pathway and potential links to neurodegenerative diseases.

Websites

Autophagy forum is a very informative forum that allows positing of questions (pertaining to autophagy) by researchers or posting of relevant open positions:

http://www.landesbioscience.com/journals/autophagy/forum

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011

Features associated with this article

Figures

Figure 1. Schematic representation of the macroautophagic pathway in mammalian cells.
Figure 2. Basic components of the CMA pathway.
Figure 3. Pathogenic effects of α-synuclein in neurons through interference with CMA-dependent and macroautophagy-dependent lysosomal pathways.

Table

Table 1. Alterations in the number of autophagosomes and LC3-II and p62 levels in neurons under physiological and pathological conditions.

Citation details for this article

Maria Xilouri and Leonidas Stefanis (2011) Autophagic pathways in Parkinson disease and related disorders. Expert Rev. Mol. Med. Vol. 13, e8, March 2011, doi:10.1017/S1462399411001803

Accession information: doi:10.1017/S1462399411001803; Vol. 13; e8; March 2011