Autophagy and Neuronal Cell Death in Neurological Disorders

Ralph A. Nixon^{1,2,3} and Dun-Sheng Yang^{1,2}

¹Center for Dementia Research, Nathan S. Kline Institute, Orangeburg, New York 10962

²Department of Psychiatry, New York University Langone Medical Center, New York, New York 10016

³Department of Cell Biology, New York University Langone Medical Center, New York, New York 10016

Correspondence: nixon@nki.rfmh.org

Autophagy is implicated in the pathogenesis of major neurodegenerative disorders although concepts about how it influences these diseases are still evolving. Once proposed to be mainly an alternative cell death pathway, autophagy is now widely viewed as both a vital homeostatic mechanism in healthy cells and as an important cytoprotective response mobilized in the face of aging- and disease-related metabolic challenges. In Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, and other diseases, impairment at different stages of autophagy leads to the buildup of pathogenic proteins and damaged organelles, while defeating autophagy's crucial prosurvival and antiapoptotic effects on neurons. The differences in the location of defects within the autophagy pathway and their molecular basis influence the pattern and pace of neuronal cell death in the various neurological disorders. Future therapeutic strategies for these disorders will be guided in part by understanding the manifold impact of autophagy disruption on neurodegenerative diseases.

Soon after the discovery of lysosomes by de Duve in the 1950s, electron microscopists recognized the presence of cytoplasmic organelles within membrane-limited vacuoles (Clark 1957) and observed what appeared to be the progressive breakdown of these contents (Ashford and Porter 1962). Proposing that “prelysosomes” containing sequestered cytoplasm matured to autolysosomes by fusion with primary lysosomes, de Duve and colleagues (de Duve 1963; de Duve and Wattiaux 1966) named this process “autophagy” (self-eating). Neurons, as cells particularly rich in acid phosphatase-positive lysosomes, were a preferred model in the initial investigations of autophagy. Early studies

of pathologic states such as neuronal chromatolysis (Holtzman and Novikoff 1965; Holtzman et al. 1967) linked neurodegenerative phenomena to robust proliferation of autophagic vacuoles (AVs) and lysosomes. Although de Duve appreciated the importance of lysosomes for maintaining cell homeostasis, he was especially intrigued with their potential as “suicide bags” capable of triggering cell death by releasing proteases into the cytoplasm. Despite some support for this notion (Brunk and Brun 1972), the concept was not significantly embraced until many decades later. Instead, for many years, lysosomes and autophagy were mainly considered to perform cellular housekeeping and to

Editors: Eric H. Baehrecke, Douglas R. Green, Sally Kornbluth, and Guy S. Salvesen
Additional Perspectives on Cell Survival and Cell Death available at www.cshperspectives.org

Copyright © 2012 Cold Spring Harbor Laboratory Press; all rights reserved; doi: 10.1101/cshperspect.a008839
Cite this article as *Cold Spring Harb Perspect Biol* 2012;4:a008839

R.A. Nixon and D.-S. Yang

scavenge and clean up debris during neurodegeneration in preparation for regenerative processes. The connection between autophagy and neuronal cell death reemerged in the 1970s from observations of Clarke and colleagues, who presented evidence that the developing brain deployed autophagy as a form of programmed neuronal cell death during which autophagy was massively up-regulated to eliminate cytoplasmic components, at once killing the neuron and reducing its cell mass for easy removal. Self-degradation was suggested as a more efficient elimination mechanism than apoptosis, which requires a large population of phagocytic cells and access of these cells to the dying region (Baehrecke 2005). Indeed, the best evidence for this process is in the context of massive cell death, as in metamorphosis and involutional states (Das et al. 2012).

Clarke proposed that autophagic cell death (ACD)—type 2 programmed cell death (PCD)—could be a relatively common alternative route to death distinct from apoptosis—type 1 PCD (Clarke 1990)—or caspase-independent cell death—type 3 PCD (Fig. 1). The distinguishing features of ACD are marked proliferation of AVs and progressive disappearance of organelles but relative preservation of cytoskeletal and nuclear integrity until late in the process (Schweichel and Merker 1973; Hornung et al. 1989). In this original concept of ACD or type 2 PCD, death is achieved by autophagic digestion of organelles and essential regulatory molecules and elimination of death inhibitory factors (Baehrecke 2005). With the advent of the molecular era of autophagy research in the 1990s, it became possible to verify the most important implication of ACD, namely, that the death could be prevented by inhibiting autophagy genetically or pharmacologically. Meanwhile, reports of prominent lysosomal/autophagic pathology in Alzheimer's disease (AD) (Cataldo et al. 1997; Nixon et al. 2000, 2005) and other neuropathic states (Anglade et al. 1997; Rubinsztein et al. 2005) raised important questions about whether autophagy pathology signifies a prodeath program or an attempt to maintain survival—a critical question for any potential therapy based on autophagy modulation. In this article, we will

examine evidence for the various neuroprotective roles of autophagy and review our current understanding of how specific stages of autophagy may become disrupted and influence the neurodegenerative pattern seen in major adult-onset neurological diseases. We will particularly focus on how neurons regulate the balance between prosurvival autophagy and well-established cell death mechanisms in making life or death decisions.

THE STAGES OF AUTOPHAGY

Since its initial description, autophagy has referred to the process by which unwarranted constituents of the cell are sequestered within vacuoles and degraded by lysosomes (Klionsky et al. 2010). Lysosomal digestion of the cell's own cytoplasmic material is the common cardinal feature of all forms of autophagy. Different mechanisms for delivery of substrates to the lysosomal compartment, however, distinguish among the three major subtypes of autophagy in mammalian cells (Fig. 2). The least well understood of these, microautophagy, is a constitutive and sometimes selective process by which proteins or organelles may be engulfed by invagination of the lysosomal or endosomal membrane and scission of the cargo-containing vesicle inside the lumen. Cargo selection and delivery to endosomes is facilitated by the chaperone Hsc70 and internalization relies on the same endosomal sorting complex required for transport (ESCRT) I and III complexes involved in multivesicular body (MVB) formation (Sahu et al. 2011). In chaperone-mediated autophagy (CMA), cytosolic proteins containing a KFERQ motif are delivered to a LAMP2A-containing complex on the lysosomal membrane via a complex of chaperones, including Hsc70 and HSP70, and cochaperones (EGHSP40, HSP90, HIP, HOP, and BAG1). The substrate is subsequently unfolded and degraded with the help of lysosomal Hsc70 and a complex of proteins that disassembles the transmembrane translocation complex (Bandyopadhyay et al. 2008, 2010). CMA activity is constitutive in most cells but up-regulated under conditions of stress or nutrient deprivation.

Figure 1. Neuronal cell death: three general morphological types of dying cells in the developing nervous system, as initially classified by Schweichel and Merker (1973) and later Clarke (1990). (A,B) Type 1 (“apoptotic”) cell death: (A) A neuron, from the brain of a postnatal day 6 mouse pup, in the middle of apoptotic degeneration showing cell shrinkage, cytoplasmic condensation, ruffled plasma membrane, and a highly electron-dense nucleus. Endoplasmic reticulum (ER) is still recognizable and some are dilated. A small number of autophagic vacuoles (AVs) can be seen (arrows). (B) A late-stage apoptotic neuron displaying electron-dense chromatin balls (CB), each surrounded by a small amount of highly condensed cytoplasm. (Panel from Yang et al. 2008; reprinted, with permission, from the American Association of Pathologists and Bacteriologists.) (C) Type 2 (“autophagic”) cell death: a deafferented isthmo-optic neuron in developing chick brain after uptake of horse-radish peroxidase to highlight (electron dense) endocytic and autophagic compartments. The cell death pattern features pyknosis, abundant AVs, and sometimes dilated ER and mitochondria. (Panel from Hornung et al. 1989; reproduced, with permission, from John Wiley & Sons) (D) Type 3 (“cytoplasmic, nonlysosomal”) cell death: a motoneuron displaying markedly dilated rough ER, Golgi, and nuclear envelope, late vacuolization, and increased chromatin granularity. (Panel from Chu-Wang and Oppenheim 1978; reproduced, with permission, from John Wiley & Sons) Scale bars, 1 μ m (A,B); 2 μ m (C,D).

R.A. Nixon and D.-S. Yang

Figure 2. Schematic for the three major subtypes of autophagy—macroautophagy, chaperone-mediated autophagy, and microautophagy. The mammalian target of rapamycin (mTOR) kinase, the principal regulator of macroautophagy, is activated by inhibiting the tuberous sclerosis complex (TSC1) and TSC2, thereby increasing the function of the GTP-binding protein Rheb (A). Insulin or growth factors suppress autophagy by activating the class I phosphatidylinositol 3 kinase (PI3K)—Akt/protein kinase B (PKB) pathway. Abundant intracellular stores of amino acids and ATP suppress autophagy by inhibiting AMP-activated protein kinase (AMPK), an activator of the TSC complex. Macroautophagy is orchestrated by complexes composed of autophagy gene (Atg)-related proteins, which coordinate specific steps in autophagy induction and sequestration as described in the text. The process is initiated when an “isolation” membrane is created from a preautophagosomal structure (PAS) under the direction of the class III PI3K complex and Atg proteins, including Beclin 1 (Atg6) (B). Two ubiquitin-like protein conjugation pathways (C) direct the expansion of the isolation membrane as it sequesters a region of cytoplasm and organelles into a double-membrane-limited autophagosome (AP). (See facing page for legend.)

A third form of autophagy, macroautophagy, mediates either bulk or selective degradation of cytoplasmic constituents and is arguably the mechanism with the highest degradative capacity. In this process, a double-membrane structure, termed the “phagophore,” originates from several possible sources of cellular membrane and becomes specialized as a preautophagosomal structure (PAS) (Fig. 2B). Under the coordination of two ubiquitin-like protein conjugation pathways (Fig. 2C) (Ohsumi 2001), the PAS elongates into an “isolation” membrane that envelops a region of cytoplasm ultimately forming a double-membrane-limited vesicle, the autophagosome. The outer membrane of the autophagosome fuses with a lysosome or late endosome, creating an autolysosome or an amphisome, respectively. Amphisome formation predominates in axons in which autophagosomes are actively formed and fuse rapidly with late endosomes before being delivered by retrograde transport to the lysosomes concentrated mainly at proximal axon levels and in the perikaryon (Lee et al. 2011). The digestion of sequestered material by dozens of acidic hydrolases (Gordon and Seglen 1988; Liou et al. 1997; Eskelinen 2005; Fader and Colombo 2009; Noda et al. 2009) is promoted when the autolysosome is acidified by vacuolar ATPase (vATPase), a proton pump on the lysosomal membrane, and cathepsins become fully activated (Yoshimori et al. 1991). Autophagy induction is regulated by activity of the mammalian target of rapamycin (mTOR) kinase, which is controlled by growth factor supply and signaling via the PI3 kinase-AKT pathway and by specific amino acids and ATP through AMP kinase (Fig. 2A) (He and Klionsky 2009; Ravikumar et al. 2010). Lysosomes are reformed from autolysosomes

through a process also regulated in part by mTOR (Yu et al. 2010).

NEUROPROTECTIVE ACTIONS OF AUTOPHAGY

Macroautophagy is constitutive in neurons and nonselective under nutrient deprivation conditions but can selectively target an organelle that is damaged and exposes a molecular signal that promotes sequestration (Dikic et al. 2010; Weidberg et al. 2011; Youle and Narendra 2011). Recognition of this selective form of macroautophagy has highlighted the working relationship between autophagy and the ubiquitin-proteasome system (UPS) in which a decline in UPS activity may up-regulate autophagy (Fortun et al. 2003; Korolchuk et al. 2009). Certain proteins play regulatory roles in both processes, such as p62, an adaptor protein for autophagy, VCP/P97, which acts through p62 and ubiquitin (Tresse et al. 2010), and Parkin, an E3 ubiquitin ligase implicated in Parkinson’s disease (PD) (Yoshii et al. 2011).

It is widely believed that autophagy exerts mainly prosurvival influences on normal cells and its increased activity has been linked to enhanced longevity in animal models (Cavallini et al. 2008; Morselli et al. 2010; Rubinsztein et al. 2011). Autophagy protects cells under stress from nutrient deprivation (Levine and Yuan 2005), loss of energy, or states of protein aggregation by breaking down less essential cellular constituents to recover amino acids, lipids, and other metabolites needed to maintain bioenergetics and synthesize more adaptive proteins, thereby forestalling apoptosis. Another important protective strategy in neurodegenerative disease states is the accelerated elimination by

Figure 2. (Continued) Microtubule-associated protein light chain 3-II (LC3-II), formed by phosphoethanolamine conjugation of LC3-I, translocates to the autophagosome membrane (C). Digestion of the sequestered cytoplasmic cargo is initiated when a lysosome (Ly) fuses with the outer membrane of the autophagosome to form an autophagolysosome (APL) and lysosomal hydrolases are introduced. The completion of substrate digestion within autolysosomes (AL) ultimately results in lysosome retrieval. In chaperone-mediated autophagy, cytosolic proteins containing a KFERQ motif are selectively chaperoned (Chap) and delivered to the lysosomal lumen for degradation through the binding to LAMP2 located on the lysosomal membrane. In microautophagy, small quantities of proteins or organelles directly enter lysosomes by invagination of the lysosomal or endosomal membrane.

R.A. Nixon and D.-S. Yang

autophagy of damaged and potentially toxic proteins as well as proapoptotic molecules. For example, activated caspase 3 appears in affected neurons in mouse models of AD but is mainly sequestered within autophagosomes (Yang et al. 2008). Similarly, mitophagy, the selective removal of damaged mitochondria by autophagy, is a crucial line of defense against apoptosis believed to fail in some neurodegenerative diseases. In mitophagy, the E3-ubiquitin ligase Parkin, or a related protein such as Nix (Bnip3L) (Sandoval et al. 2008), is recruited to the compromised mitochondrion by certain mitochondrial proteins exposed by the injury. The ubiquitinated protein(s) serve as a binding site for p62 and light chain 3 (LC3) to induce sequestration (Narendra et al. 2008).

AUTOPHAGY AND CELL DEATH PATHWAYS

The cross-regulation of autophagy and apoptosis provides insight into how autophagy protects against apoptotic cell death and conversely how the apoptotic program subverts autophagy to achieve its goal. Central to this cross talk is the interaction between the key apoptosis regulators, Bcl-2 and Bcl-xL, and beclin 1, a component of two separate protein complexes regulating autophagosome formation and endosome maturation, respectively. As a Bcl-2 homology (BH)–3 domain-only protein (Oberstein et al. 2007), beclin 1 may interact with Bcl-2 and Bcl-xL (Pattingre et al. 2005), which diminishes its interactions with these complexes and deprives cells of autophagy's antiapoptotic actions. Mutating the BH3 domain of beclin or the BH2 receptor domain of Bcl-2/Bcl-xL abolishes this capacity to inhibit beclin-dependent autophagy (Maiuri et al. 2007). Conversely, dissociation of beclin 1 and Bcl-2/Bcl-xL, resulting in increased autophagy and antiapoptotic effects, can be achieved in several ways. These include competitive displacement of either partner by interacting proteins (Bad, Bnip3, or Tbid), which include components of the beclin 1 complexes that support autophagy (e.g., UVRAG, Atg14L/Barkor, and Hmgb1). The interaction is also blocked by beclin phosphorylation via death-associated protein kinase (DAPK)

(Zalckvar et al. 2009), MAP kinase (ERK1 or JNK1)-mediated phosphorylation of Bcl-2 (Wei et al. 2008; Tang et al. 2010), or Traf6-mediated ubiquitination of beclin 1 (Shi and Kehrl 2010).

Pathological activation of calpains, a family of calcium-activated neutral proteases, can also inhibit autophagy by truncating Atg5, which then translocates from the cytosol to mitochondria where it associates with Bcl-xL and can trigger cytochrome *c* release (Yousefi 2006). Calpains can also inactivate caspases and potentially convert apoptotic death to necrotic death (Lankiewicz et al. 2000; Syntichaki and Tavernarakis 2002). Whether apoptosis or necrosis ensues depends on various factors, including the developmental status of the neuron, extracellular glutamate levels, cytosolic and mitochondrial calcium levels, mitochondrial membrane potential, ATP levels, and calpain activity (Pang and Geddes 1997; Nasr et al. 2003; Pang et al. 2003).

AUTOPHAGY IN NEURONS AND NEURODEGENERATION

The paucity of AVs in healthy neurons (Mizushima et al. 2004; Nixon, et al. 2005) initially led investigators to suggest that autophagy activity in neurons is relatively low unless induced by some form of stress (Holtzman et al. 1967). Recent evidence has shown, however, that neuronal autophagy is constitutive and, in fact, may be quite active, although AVs remain scarce because lysosomal clearance of these intermediates is very efficient (Boland et al. 2008). One important implication is that, although neurons seem able to accommodate high autophagy activity with minimal ill effects, they are unusually vulnerable to any impairment of autolysosomal clearance. The special reliance of neurons on autophagy has long been suspected from observations that many human primary lysosomal diseases, e.g., lysosomal storage disorders, preferentially affect the brain. This vulnerability of neurons to autophagic/lysosomal dysfunction is not surprising when it is considered that neurons must survive throughout the life of the organism and lose the capability for

mitosis, which helps mitotic cells cope with accumulating waste materials by diluting this burden through cell division. Also, neurons must maintain especially large volumes of membrane and cytoplasm associated with long axons and dendrites and must continually traffic autophagy-related compartments long distances back to the cell body where substrate clearance by lysosomes is most active (Lee et al. 2011). Even briefly inhibiting lysosomal proteolytic activity disrupts transport of AVs and causes them to selectively accumulate in dystrophic swelling (Lee et al. 2011) and in perikarya (Ivy et al. 1984; Bednarski et al. 1997).

Investigating cell death pathways in neurons and autophagy is complicated by the slow evolution of neurodegenerative diseases in which prodeath disease and prosurvival factors within a given neuron may battle over many months or years and proteolytic systems may cross talk extensively, yielding in the end a complex picture that defies classification as a distinct pattern of cell death. In AD, for example, neurons with dystrophic axons containing activated caspases, activated calpains, and massive AV accumulations may persist for months or years (Coleman 2005; Rao et al. 2008; Adalbert et al. 2009). Moreover, in most chronic neurodegenerative diseases, only a tiny percentage of the neurons may be degenerating at any given time and may be at different stages of the degenerative process when analyzed. Moreover, cell death patterns may vary across neuronal cell types even in the same disease model, whereas nonneuronal cells in brain may be mounting quite different biochemical responses. Analysis at the single cell level is, therefore, the optimal approach to cell death investigations in brain.

AUTOPHAGY OVERACTIVATION—AN UNCOMMON CELL DEATH PATHWAY IN NEURONS

Although autophagy is generally neuroprotective, can too much of a good thing at the wrong time be deleterious? ACD in the context of involution and metamorphosis during invertebrate development may be among the rare instances in which ACD, as originally defined by

Clarke, takes place, and the phenomenon in this situation seems to serve the physiological purpose of eliminating entire cell populations. In mammalian cells, however, ACD strictly defined as death executed by the autocannibalism of constituents essential for cell survival and dependent on autophagy genes is uncommon. An autophagic (type 2 PCD) pattern of death blocked by Atg-gene deletion has been observed in cells in which apoptosis is prevented by deleting Bcl-2 family members, Bax, and Bak or by inhibiting caspases (Shimizu et al. 2004; Yu et al. 2004). Even in this specialized situation, however, it is not entirely clear that autophagy is sufficient to execute death without help from proteases that mediate necrosis. In cells that have competent caspases, additional cell death pathways are invariably activated during cell death showing the type 2 PCD morphological pattern, although autophagy may serve as the upstream trigger (Pyo et al. 2005; Nixon 2006). In some cases, AV proliferation occurs in the context of cell death executed by caspases and may facilitate execution but is not essential for death (Nixon 2006).

Autophagy inhibition by 3-methyl adenine (3MA) has been used to implicate autophagy in cell death execution by showing blocked or delayed cell death after this treatment, although the interpretation of protection via autophagy inhibition should be qualified because this compound inhibits not only the class III PI3 kinase regulating autophagy but also class I PI3 kinase involved in endocytosis. Also, in most of these cases, cytoprotection is not absolute and death ultimately ensues via cytochrome *c* release and caspase 3 activation (Uchiyama 2001; Canu et al. 2005; Kaasik et al. 2005), indicating that an apoptotic pathway may be operating in parallel. Furthermore, the inhibition of a particular cathepsin (Uchiyama 2001; Canu et al. 2005; Kaasik et al. 2005) also delays or blocks cell death in many of the same models, further supporting the idea that lysosomal destabilization and cathepsin release ultimately triggers apoptosis.

Inhibiting autophagy has been reported to be beneficial in several neurodegenerative states, the clearest example being hypoxic ischemic

R.A. Nixon and D.-S. Yang

(HI) brain injury. In the most compelling of these studies, Atg deletion reduced autophagy-related pathology and nearly completely prevented severe hippocampal damage after HI brain injury in neonatal or adult mice (Koike et al. 2008). In both mouse models, however, effects of autophagy modulation were upstream of the neuronal cell death executioner pathways that were also activated in these models—both caspase 3-dependent and -independent pathways, in the case of the neonatal model, and the caspase 3-independent pathway only in the adult model. Similar observations on this injury model have been made using 3MA to assess the involvement of autophagy in neuronal death. (Wen et al. 2008; Puyal et al. 2009; Piras et al. 2011; Wang et al. 2011; Xin et al. 2011; Zhang 2012). Beneficial effects of autophagic inhibition have also been seen in several models of chronic neurodegenerative diseases. In 6-hydroxydopamine (6-OHDA) injured rat substantia nigra neurons, up-regulated autophagy (as evidenced by AV accumulation) and cell death were prevented by 3MA pretreatment (Li et al. 2011). Neuronal death induced by dysfunctional ESCRT-III, which is associated with frontotemporal dementia linked to chromosome 3, could be delayed by 3MA administration or by knocking down Atg5 and Atg7, suggesting that autophagic stress by excess accumulation of autophagosomes is detrimental to neuronal survival (Lee et al. 2007; Lee and Gao 2009).

When autophagy *inhibition* appears to be cytoprotective, the particular step in autophagy involved is not straightforward. Autophagy induction is often accompanied by increased lysosome biogenesis and up-regulated hydrolase expression (Dehay et al. 2010; Palmieri et al. 2011; Settembre et al. 2011). In situations in which lysosomal function is also compromised or lysosomes are destabilized, it is possible that autophagy inhibitors relieve autophagic stress on compromised lysosomes by slowing delivery of autophagic substrates rather than by attenuating an overaggressive autocannibalistic process. Indeed, healthy neurons in culture seem to tolerate strong autophagy induction (Lee et al. 2011) unless lysosomal function is also

impaired. In situations in which blocking autophagy is protective, fending off lysosome destabilization could be more germane to the mechanism of cytoprotection than is the blockade of authentic ACD.

NEURONAL CELL DEATH ASSOCIATED WITH FAILURE OF AUTOPHAGY

In contrast to autophagy overactivation, autophagy failure is commonly linked to a lysosome-dependent form of cell death (Boya 2011), which is relevant to the loss of neurons in various neurodegenerative diseases (Nixon et al. 2008; Settembre et al. 2008a,b; Dehay et al. 2010; Rubinsztein et al. 2011). A neuronal cell death with type 2 morphology is seen in lysosomal storage disorders owing to defects at autolysosomal stages of autophagy—loss of function of lysosomal hydrolases or structural proteins (Hartmann et al. 2000; Koike et al. 2000; Ko et al. 2005; Willenborg et al. 2005; Nixon et al. 2008; Settembre et al. 2008a; Wolfe and Nixon 2012). For example, cathepsin D is ubiquitously expressed, yet mutations that markedly lower cathepsin D activity affect the brain disproportionately causing profuse AV accumulation in neurites and progressive neuronal loss in the neocortex and hippocampus (Tyynela et al. 2000). Lysosomal dysfunction leading to the destabilization of lysosomal membranes and death of nonneuronal cells is well established (Brunk and Svensson 1999; Boya and Kroemer 2008; Boya 2011) and likely relevant to neurons in neurological disorders (Nixon et al. 2008; Dehay et al. 2010), although the evidence is mostly in vitro at present. Autophagy failure at early stages of this pathway may also induce cell death although possibly with less florid autophagic pathology. Deleting factors critical for autophagy induction or autophagosome formation such as FIP200, Atg5, or Atg7 has been shown to induce delayed neuronal cell death and cytoplasmic accumulation of ubiquitinated proteins or organelles (Hara et al. 2006; Komatsu et al. 2006, 2007; Liang et al. 2010).

Autophagy failure, depending on where the defect is along the pathway, can trigger neuronal cell death in several ways. When proteo-

lytic clearance steps are compromised, autolysosomes/lysosomes accumulate mutant and oxidized proteins, protein oligomers and aggregates, damaged organelles, and other incompletely digested products, certain of which increase the permeability of lysosomal membranes causing hydrolases to be released into the cytoplasm, in some cases even from otherwise intact lysosomes (Kroemer and Jaattela 2005). A long list of exogenous agents, including many anticancer drugs (Erdal et al. 2005), are able to disrupt lysosomal membrane integrity directly and induce rapid lysosome-dependent cell death. Similarly, the list of endogenous factors able to induce lysosomal membrane permeabilization (LMP) is growing and includes ceramide, sphingosine, oxidized lipids or lipoproteins, reactive oxygen species (ROS), calpains, certain caspases, and a few proteins/peptides implicated in AD, such as A β and ApoE (Brunk and Svensson 1999; Yuan and Yankner 2000; Boya and Kroemer 2008; Johansson et al. 2010; Repnik et al. 2012). Agents that cause cataclysmic disruption of lysosomal membranes are likely to induce rapid necrosis during which released hydrolases participate as both a trigger and as executioners along with caspases that are activated by cathepsin-mediated cleavage (Haya-shida et al. 1993; Werneburg et al. 2007). Slower release of cathepsins from lysosomes may first activate apoptotic cascades via the caspase-mediated cleavage of BID releasing of mitochondrial cytochrome *c* (Guicciardi et al. 2000), degradation of antiapoptotic Bcl-2 homologs, and activation of Bax that releases mitochondrial apoptosis-initiating factor (AIF) (Bidere et al. 2003) and can also induce LMP (Werneburg et al. 2004; Kilinc et al. 2010). In a pathological situation in which either autophagy induction, substrate recognition, or sequestration are impaired, the resultant increase in numbers of damaged mitochondria can trigger apoptosis through the intrinsic pathway and via ROS generation that oxidizes membrane lipids and destabilizes the lysosome membrane. Reduced autophagic elimination of other proapoptotic factors, such as activated caspases, may also accelerate apoptosis under these conditions (Yang et al. 2008).

AUTOPHAGY IN MAJOR NEURODEGENERATIVE DISEASES

Autophagy-related pathology has been noted in late-onset neurodegenerative diseases including AD (Cataldo et al. 1997; Nixon et al. 2005; Nixon and Cataldo 2006), PD (Anglade et al. 1997), amyotrophic lateral sclerosis (ALS) (Hart et al. 1977; Nakano et al. 1993; Sasaki 2011), Huntington's disease (HD) (Roos et al. 1985; Rudnicki et al. 2008), and several others (Liberski et al. 1995; Yue et al. 2002; Rudnicki et al. 2008). The pathology in different disease states has so far been rarely assessed quantitatively. The extent of autophagy waste "storage" in perikarya and neuronal processes and the nature of the AV subtypes that accumulate may differ significantly across these diseases, which in some cases provide useful clues to the underlying disturbance of autophagy. Combined with biochemical analyses of cell and animal models, a picture is emerging from studies of different disorders that autophagy may be altered at early stages (e.g., induction and autophagosome formation) or at late stages (e.g., proteolytic clearance of autophagosomes by lysosomes), or both, which has a different impact on the pattern of neurodegeneration.

PD

In PD, the death mainly of dopaminergic neurons in the substantia nigra is associated with accumulation of the cytosolic protein α -synuclein within inclusions called Lewy bodies. The PD cell death pattern shows features of apoptosis and necrosis as well as increased numbers of autophagosomelike structures (Fig. 3) (Stefanis 2005). Autophagy defects at early stages of autophagy as well as at later lysosomal clearance stages contribute to this complex pattern. Mutations of Parkin (Park2) and PINK1 account for the majority of autosomal recessive cases of parkinsonism (Gasser 2009). Both proteins operate in a pathway that controls mitochondrial fusion-fission events (Yao and Wood 2009) but also play roles in mitophagy that are critical to PD pathogenesis. PINK1, a serine/threonine kinase, localizes to the outer mitochondrial

R.A. Nixon and D.-S. Yang

Figure 3. Neuropathology in PD. A neuron of the substantia nigra from a case of juvenile parkinsonism. The pale central area of the perikaryon, next to a Lewy body (asterisk), shows disappearance of rough ER and mitochondria accumulation, which may imply impaired mitophagy. (Panel from Hayashida et al. 1993; reproduced, with permission, from Springer Science + Business Media.) (*Inset*) A dopaminergic neuron from a PD case, filled with neuromelanin-containing vesicles, shows a shrunken nucleus with highly condensed, marginalized chromatin (arrows). Scale bar, 1 μ m. (Panel from Hartmann et al. 2000; reproduced, with permission, from the National Academy of Sciences.)

membrane and serves as a sensor of mitochondrial membrane polarization. On normal mitochondria, PINK1 is proteolytically cleaved constitutively (Abeliovich 2010), but it becomes selectively stabilized on the outer mitochondrial membrane when mitochondrial function is compromised. This enables Parkin (a cytoplasmic E3 ubiquitin ligase) to bind and ubiquitinate certain exposed membrane proteins, which recruits p62 and LC3, that initiate mitophagy of the damaged organelle (Geisler et al. 2010; Narendra et al. 2010; Wild and Dikic 2010). It is believed that PD-causing mutations of PINK and Parkin impede mitophagy, causing damaged mitochondria to accumulate and potentially initiate apoptotic events. Additional influences of defective PINK on mitophagy and other mitochondrial dynamics, such as fission–fusion events and ROS production (Wood-Kaczmar et al. 2008; Dagda et al. 2009; Michiorri et al. 2010), may add complexity to the net role mitophagy failure plays in PD. Mutations of α -synuclein in familial PD also disrupt sub-

strate access during CMA by binding abnormally tightly to LAMP2A, thereby blocking not only its own uptake into lysosomes but that of other CMA substrates (Cuervo et al. 2004). Wild-type α -synuclein modified by dopamine, seems to cause similar CMA dysfunction suggesting that this form of α -synuclein toxicity applies to sporadic as well as familial forms of PD (Xilouri et al. 2009).

α -Synuclein is also a substrate for macroautophagy (Webb et al. 2003), which may be recruited as a compensatory mechanism when CMA is impaired. Macroautophagy stimulation by beclin 1 gene transfer, ATG overexpression, or rapamycin significantly ameliorates pathology in α -synuclein PD models (Spencer et al. 2009; Yu et al. 2009). Certain PD-related disease factors, however, may also disrupt lysosomal function and the clearance of substrates by macroautophagy. One example is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a well-characterized neurotoxin model of PD induced by mitochondrial dysfunction and oxidative stress (Yokoyama et al. 2008; Bezard and Przedborski 2011). Lysosome number drops in dopaminergic neurons very early after MPTP exposure, related in part to LMP and cytosolic release of cathepsins—events that are partially prevented by cathepsin inhibitors. Autophagosome accumulation accompanies lysosomal depletion. All of these events and neurodegeneration are attenuated by genetic or pharmacological activation of transcription factor EB (TFEB) or rapamycin, both of which increase lysosomal biogenesis (Dehay et al. 2010) in addition to inducing autophagy. Other factors contributing to general lysosomal dysfunction in some forms of PD include loss-of-function mutations of the lysosomal ATPase, ATP 13A2, a rare cause of PD (Ramirez et al. 2006; Di Fonzo et al. 2007), and mutations in the lysosomal hydrolase glucocerebrosidase that cause the lysosomal storage disorder Gaucher disease and also increase the risk of PD (Sidransky et al. 2009). The neuroprotective effects of enhancing autophagy in most PD models (Dagda et al. 2009; Dadakhujayev et al. 2010), but not all (Zhu et al. 2007), supports the pathogenic importance of autophagy defects observed in PD and PD mouse models.

Polyglutamine Expansion Diseases

Polyglutamine disorders are adult-onset progressive neurodegenerative diseases caused by expansion of a cytosine-adenine-guanine (CAG) repeat motif within the coding region of various genes. The respective proteins containing the long polyglutamine tracts typically form aggregates in the cytoplasm. Generally the age at disease onset correlates with the increased number of CAG repeats. These aggregate-prone proteins tend to be good macroautophagy substrates, and blocking autophagy leads to their increased aggregation and neurotoxicity when the protein is overexpressed (Ravikumar et al. 2004). Besides HD, the first repeat expansion disease discovered to be associated with defective autophagy as discussed below, AVs are increased in animal models of spinocerebellar ataxia 1 and 7, and spinal and bulbar muscular atrophy and neuroprotective effects of autophagic enhancement indirectly imply a role of autophagy in the disease pathogenesis (La Spada and Taylor 2010).

HD, the best known of the polyglutamine disorders, is caused by mutations of the Huntingtin (Htt) gene, encoding a 350-kDa protein that is ubiquitously expressed even though HD principally affects the brain and particularly the striatum. Although the relative neurotoxicity of aggregated versus nonaggregated Htt remains controversial, soluble forms of mutant Htt are increasingly implicated as the toxic species (Dunah et al. 2002; Arrasate et al. 2004; Cui et al. 2006). Several caspases and calpains, known to be activated in HD brain, generate toxic amino-terminal fragments of Htt most closely linked to HD pathogenesis (Ona et al. 1999; Sanchez et al. 1999; Gafni and Ellerby 2002; Graham et al. 2006). Caspase 6 cleavage of mutant Htt seems particularly important in mediating the sensitivity of HD striatal neurons to excitotoxicity (Graham et al. 2006), although polyglutamine expansion also impedes various antiapoptotic effects of Htt including inhibitory effects of caspase 3 activation (Gervais et al. 2002; Zhang et al. 2006). Although activation of apoptotic pathways is likely, the typical morphologic pattern of apoptosis is incomplete (Hickey and Chesselet 2003).

Autophagy was initially implicated in HD from the presence of abnormal endosomes and AV accumulations in HD neurons (Tellez-Nagel et al. 1974) and by the similar morphologies seen in cell models after mutant Htt is overexpressed (Kegel et al. 2000). Htt aggregates, which are poor UPS substrates (Jana et al. 2001), can be cleared by autophagy. Autophagy inducers accelerate their clearance while improving toxicity phenotypes in cell and animal models of HD, whereas inhibiting autophagosome formation or fusion with lysosomes promotes inclusion formation and cell death (Ravikumar et al. 2004). Aggregate-prone Htt seems to be a selective macroautophagy target because autophagy modulation does not affect wild-type Htt levels. Interestingly, acetylation of mutant Htt targets it to autophagosomes (Jeong et al. 2009) and selective clearance of mutant Htt can be achieved by hyperacetylation of the mutant protein with HDAC (histone deacetylase) inhibitors, which are neuroprotective in various HD models (Kazantsev and Thompson 2008).

The efficacy of autophagy inducers in clearing overexpressed mutant Htt from autophagosomes suggests that lysosomal clearance mechanisms are not the primary site of autophagy disruption in HD. Evidence from HD tissue and disease models points instead to defective recognition of cargoes during early sequestration steps. In several HD models, autophagosomes form properly and are cleared even though protein turnover by macroautophagy is paradoxically slow (Martinez-Vicente et al. 2010). The autophagosomes in these cells, however, appear relatively devoid of cargo, suggesting a possible failure of autophagosome membranes to properly engage the substrates during sequestration. In this regard, mutant Htt aggregates sequester beclin 1, which can interfere with autophagosome membrane nucleation (Shibata et al. 2006) and perhaps promote derangement of the sequestration process. Deficient autophagy would be expected to compound effects of Htt-related alterations of mitochondrial function, including loss of antiapoptotic functions of Htt when mutated in HD (Gil and Rego 2008).

R.A. Nixon and D.-S. Yang

ALS and Related Disorders

ALS, the prototypical degenerative disease of motor neurons, is sporadic in approximately 90% of cases but the remaining cases are familial, caused by mutations of at least three different genes, namely, the Cu/Zn superoxide dismutase-1 gene (SOD-1), the TAR DNA-binding protein 43 gene (TARDBP or TDP-43), and the fused in sarcoma/translation in liposarcoma gene (FUS/TLS) (Liscic and Breljak 2011). The recent finding that ALS also arises from mutations of TDP-43, a major cause of frontotemporal dementia (FTD), has highlighted the overlapping clinicopathological features of ALS, FTD-MND (FTD with motor neuron disease), or FTD-U (FTD with ubiquitin-immunoreactive inclusions). In the latter disorders, ubiquitinated inclusions appear in the cytoplasm replacing the normal nuclear staining of TDP-43 (Hirano 1996; Nakano 2000; Mackenzie 2007; Strong 2008; Strong et al. 2009; Geser et al. 2010).

A significant autophagy response occurs very early in ALS. Autophagosomes are frequently seen in otherwise normal-appearing perikarya of motor neurons in sporadic ALS patients (Sasaki 2011) and significantly are elevated by the time clinical symptoms appear (Venkatachalam et al. 2008; Pasquali et al. 2009). Autophagosomes and autolysosomes appear in close association with p62-positive inclusions and both become more frequent in degenerating neurons (Sasaki 2011). The high number of autophagosomes may imply elevated autophagy induction given the decreased mTOR phosphorylation seen in several genetic ALS models (Morimoto et al. 2007; Li et al. 2008; Hetz et al. 2009). Although damaged mitochondria increase in motor neurons in SOD1 mouse ALS models (Liu et al. 2004; Martin et al. 2007; Vande Velde et al. 2008), these are frequently in AVs, suggesting that mitophagy is competent (Wong et al. 1995). Investigations to date have not identified a significant impairment of cargo recognition, sequestration, or autophagosome formation.

Alternatively, or in addition to the possibility of increased autophagy induction, defective autophagosome clearance is also consistent with this morphological pattern and with other

data, especially given that neurons usually clear autophagosomes efficiently (Boland et al. 2008). Indeed, growing evidence points to a defect in autophagosome clearance owing to impaired fusion of endosomes, MVP, or lysosomes in some forms of ALS. Defects in the ESCRT machinery that regulates fusion of endosomes/MVB with autophagosomes to produce amphisomes (Filimonenko et al. 2007) have been implicated in frontotemporal dementia linked to chromosome 3 (FTD3) (Skibinski et al. 2005) and ALS (Momeni et al. 2006; Parkinson et al. 2006). Cell models of these diseases have shown that loss of function of various ESCRT genes disrupts autophagosome maturation by impeding autophagosome fusion with lysosomes or endosomes. For example, mutations in charged multivesicular body protein-2B (CHMP2B) in familial ALS disrupt ESCRT pathway function causing aggregates of ubiquitinated proteins and p62 to accumulate (Filimonenko et al. 2007; Lee et al. 2007). Loss-of-function mutations of dynactin, a component of the dynein complex regulating retrograde axonal transport, impair autophagy by disrupting autophagosome retrograde transport and fusion with lysosomes (Ravikumar et al. 2005; Laird et al. 2008).

AD

AD is defined by the presence of “senile or neuritic plaques” consisting of β -amyloid deposits surrounding foci of degenerating or dystrophic axons and dendrites and intraneuronal filamentous aggregates of the microtubule-associated protein tau. AD leads to widespread death of many subtypes of neurons beginning in the hippocampus and spreading progressively to the cortex in a circuit-selective pattern. Neuronal death in AD does not conform to a conventional cell death pattern and may vary in its features among neuron subtypes, showing in various proportions the features of apoptosis (e.g., activation of multiple caspases), necrosis (e.g., calpain activation and cathepsin up-regulation), and florid autophagic/lysosomal pathology.

Abnormalities of the lysosomal system in AD (Fig. 4) are a continuum that includes endosome anomalies associated with endocytic

Autophagy and Neuronal Cell Death in Neurological Disorders

Figure 4. Autophagic pathology and neurodegeneration in AD brains. (A) Cathepsin D (Cat D) immunocytochemistry of AD neocortex reveals that many amyloid plaques are cathepsin D positive (arrows). (B) A plaque of higher magnification depicts numerous Cat D-positive dystrophic neurites. (C) Electron microscopy shows that dystrophic neurites are filled mainly with autophagosomes and autolysosomes containing undigested materials. (D) A tangle-bearing neuron showing scattered bundles of paired helical filaments (arrow and *inset*) and a peripherally displaced but otherwise normal nucleus. (E) The boxed area of D is shown at higher magnification. The cytoplasm contains numerous AVs including double-membrane dense structures and multilamellar bodies (arrows) as well as many small dense bodies or lysosomes (arrowheads). (Panels C–E from Nixon et al. 2005; reproduced, with permission, from the author.) (F,G) Neurons in AD neocortex immunolabeled with Cat D antibodies depicting a later stage of degeneration with altered nuclear morphology and accumulation of hydrolase-positive lipofuscin or lipofuscin-containing autolysosomes (arrows). (F) The same neocortical pyramidal neuron showing atrophic changes by Nissl staining (F, *inset*; scale bar, 10 μ m) contains AVs and many lipofuscin granules when examined ultrastructurally. The nucleus is highly electron dense and the morphology of the whole cell suggests dark-neuron degeneration, whereas the nucleus of a neuron in (G) shows chromatin clumping and marginalization, suggesting ongoing apoptotic changes. (G, *inset*) shows hydrolase-positive aggregates of lipofuscin granules. (Panels F and G from Cataldo et al. 1994; reprinted, with permission, from Elsevier.)

R.A. Nixon and D.-S. Yang

pathway up-regulation and increased lysosome biogenesis—the earliest appearing disease-specific cellular pathologies in the disease (Nixon et al. 2006). AVs progressively accumulate profusely in affected neurons and become the predominant organelles within enormously swollen dystrophic neurites, a hallmark of AD neuropathology. The selective accumulation of AVs of all types within the dystrophic swellings likely reflects selective and specific impairment of the axonal transport of autophagy/lysosomal-related compartments (Lee et al. 2011). Neuritic dystrophy in AD is much more extensive than that seen in other aging-related neurodegenerative diseases, and the huge mass of accumulated waste protein within AVs is reminiscent of that seen in some primary lysosomal storage disorders (Nixon et al. 2008).

Current evidence indicates that autophagy is principally defective at the stage of autolysosomal proteolysis in AD. The presence of abundant mature autophagosomes containing partially digested substrates and cathepsins (Nixon et al. 2005) contrasts with the exceptional efficiency of AV clearance in normal neurons (Boland et al. 2008). Neuritic dystrophy and selective AV accumulation can be reproduced by blocking lysosomal proteolysis pharmacologically or genetically in *in vitro* and *in vivo* models (reviewed in Nixon and Yang 2011), whereas they are not seen when autophagy is strongly induced in otherwise healthy neurons (Boland et al. 2008; Lee et al. 2011). Lysosomal proteolysis failure is further supported by the recently identified role of presenilin 1 (PS1) as a chaperone essential for the delivery of the proton pump, vacuolar vATPase, to lysosomes, which is essential for lysosome acidification and protease activation. Mutations of PS1, the most common cause of early-onset familial AD (Sherrington et al. 1995), lead to markedly defective lysosomal acidification and autolysosomal maturation (Lee et al. 2010), explaining why PS1 mutations potentiate autophagic/lysosomal, amyloid, and tau pathologies as well as accelerate neuronal cell death in patients with PS-FAD or mouse models (Cataldo et al. 2004).

Inheritance of the $\epsilon 4$ allele of the apolipoprotein E gene (ApoE4) is the strongest genetic

risk factor for late-onset AD. ApoE4 has numerous biological activities but prominent among them are allele-specific effects on cholesterol regulation that promote the specific endocytic dysfunction arising in early AD (Cataldo et al. 1996, 2000). Moreover, a unique proteolytically processing pattern of ApoE4 in lysosomes yields a “molten globule” structure that induces reactive intermediates, which destabilize lysosomal membranes leading to lysosomal leakage and apoptosis (Ji et al. 2002, 2006; Mahley and Huang 2006). The expression of ApoE4, but not the ApoE3 allele, increases levels of intracellular A β peptide (A β), enlarges lysosomes and alters their morphology in a mouse AD model, and causes neurodegeneration of neurons typically vulnerable in AD (Belinson et al. 2008). Similarly, overexpression of human A β 42, but not A β 40, in *Drosophila* neurons induces age-related autophagic/lysosomal dysfunction and neurotoxicity (Ling et al. 2009) believed to arise from lysosomal membrane destabilization mediated directly by A β (Yang et al. 1998; Glabe 2001) or by oxidized, incompletely degraded autophagic substrates (Terman and Brunk 2006; Kurz et al. 2008).

The prominent defects in clearance of autophagic substrates by lysosomes may be compounded by an increased induction of autophagy in AD, which is known to accelerate autophagy pathology (Boland et al. 2008) and increase neurotoxicity. Lysosome biogenesis in AD brain and AD mouse models (Cataldo et al. 1995, 1996, 2004; Ginsberg et al. 2010) is up-regulated as is the transcription of a wide range of autophagy-related genes in the AD cortex (Lipinski et al. 2010) and in CA1 hippocampal neurons specifically (S Ginsberg and R Nixon, unpubl.). Some analyses of mTOR signaling, although not all, are consistent with increased autophagy induction (Bhaskar et al. 2009; Caccamo et al. 2010; Nixon and Yang 2011). Although an initial report of lowered beclin 1 levels in brain suggested that early steps of autophagy may be impaired (Pickford et al. 2008; Jaeger et al. 2010), this finding has not been confirmed in a later more detailed analysis (R Nixon, P Mohan, and E Masliah, unpubl.).

The significance of autophagy failure to the pathogenesis of AD is underscored by the

efficacy of autophagy enhancement in ameliorating AD-related pathologies (e.g., A β deposition and tau pathology) and synaptic and cognitive deficits in AD models (Karuppagounder et al. 2009; Ahmed et al. 2010; Greco et al. 2010; Spilman et al. 2010; Majumder et al. 2011; Tian et al. 2011; Yang et al. 2011). Interestingly, in one recent study, rapamycin administration before development of AD pathology and presumably before lysosomal failure delayed the onset and diminished the severity of the AD phenotype, whereas administration after the appearance of pathology had little beneficial effect, highlighting the importance of lysosomal failure (Majumder et al. 2011). The therapeutic efficacy of genetic manipulations selectively targeting the lysosome to increase its proteolytic efficiency (Sun et al. 2008; Yang et al. 2011) has established the particular importance of lysosomal proteolysis defects in promoting disease progression.

CONCLUDING REMARKS

Investigations of autophagy in neurodegenerative disease have greatly intensified since the first reviews appeared on this subject a decade ago (Nixon et al. 1995). Autophagy is now firmly

established as a vital homeostatic and quality control mechanism in healthy neurons and as a cytoprotective response when further induced in chronic neurodegenerative diseases. Autophagy protects neurons against metabolic challenges by generating supplies for energy production and cell repair, eliminating toxic damaged proteins and organelles, and suppressing apoptotic signaling. With increasing cellular age, autophagy becomes less efficient despite a greater need to eliminate mounting levels of damaged proteins, organelles, and other apoptosis-inducing stimuli. In AD, PD, and likely other disorders, progressive autophagy dysfunction, including impairment driven by causative gene mutations or other disease risk factors, compounds the adverse effects of aging on autophagy in promoting neuronal cell death. Defects in autophagy that impair the early stages of this process—induction or cargo recognition and sequestration—cause autophagic substrates, including mitochondria, to accumulate in the cytoplasm and trigger apoptosis, as in PD. Failure at later stages of autophagy related to the efficient digestion of sequestered substrates leads to the buildup of partially digested toxic products in autolysosomes and lysosomes, as seen in AD. In this

Figure 5. Possible states of impairment in the autophagy pathway in different neurodegenerative diseases and possible links to neuronal cell death. The autophagy defect may conceivably promote neuronal cell death via two possible mechanisms: (1) impaired mitophagy resulting in accumulation of damaged mitochondria and mitochondrial membrane permeability (MMP) leading to cytochrome *c* release and apoptotic cell death; and (2) impaired lysosomal clearance of autophagy substrate leading to lysosomal membrane permeabilization (LMP) and cathepsin release into cytosol, thereby inducing either apoptotic or necrotic cell death. Increased autophagy induction in the face of a downstream block in the pathway may be a counterproductive response. AP, autophagosome; CMA, chaperone-mediated autophagy; Cyto *c*, cytochrome *c*; Ly, lysosome; MA, macroautophagy.

R.A. Nixon and D.-S. Yang

situation, consequent injury and destabilization of lysosomal membranes and leakage of cathepsins can trigger either apoptotic or necrotic cascades (Fig. 5). Extensive cross talk between regulators of autophagy and apoptosis has provided insight into how autophagy protects against apoptosis and how the balance between these opposing forces contributes to the complex patterns of neuronal cell death seen in nervous system diseases. Although much more work is needed to clarify these mechanisms, recent preclinical investigations in neurodegenerative disease models have provided glimpses that autophagy modulation may be a fruitful therapeutic strategy.

ACKNOWLEDGMENTS

We are grateful to Nicole Piorkowski for assistance with manuscript preparation, and to Corrinne Peterhoff for assistance with figure preparation and artwork. Studies from our laboratories are supported by the National Institute on Aging and the Alzheimer's Association.

REFERENCES

*Reference is also in this collection.

Abeliovich A. 2010. Parkinson's disease: Mitochondrial damage control. *Nature* **463**: 744–745.

Adalbert R, Nogradi A, Babetto E, Janeckova L, Walker SA, Kerschensteiner M, Miggelid T, Coleman MP. 2009. Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies. *Brain* **132**: 402–416.

Ahmed T, Enam SA, Gilani AH. 2010. Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease. *Neuroscience* **169**: 1296–1306.

Anglade P, Vyas S, Javoy-Agid F, Herrero MT, Michel PP, Marquez J, Mouatt-Prigent A, Ruberg M, Hirsch EC, Agid Y. 1997. Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease. *Histol Histopathol* **12**: 25–31.

Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. 2004. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* **431**: 805–810.

Ashford TP, Porter KR. 1962. Cytoplasmic components in hepatic cell lysosomes. *J Cell Biol* **12**: 198–202.

Baehrecke EH. 2005. Autophagy: Dual roles in life and death? *Nat Rev Mol Cell Biol* **6**: 505–510.

Bandyopadhyay U, Kaushik S, Varticovski L, Cuervo AM. 2008. The chaperone-mediated autophagy receptor or-

ganizes in dynamic protein complexes at the lysosomal membrane. *Mol Cell Biol* **28**: 5747–5763.

Bandyopadhyay U, Sridhar S, Kaushik S, Kiffin R, Cuervo AM. 2010. Identification of regulators of chaperone-mediated autophagy. *Mol Cell* **39**: 535–547.

Bednarski E, Ribak CE, Lynch G. 1997. Suppression of cathepsins B and L causes a proliferation of lysosomes and the formation of meganeurites in hippocampus. *J Neurosci* **17**: 4006–4021.

Belinson H, Lev D, Masliah E, Michaelson DM. 2008. Activation of the amyloid cascade in apolipoprotein E4 transgenic mice induces lysosomal activation and neurodegeneration resulting in marked cognitive deficits. *J Neurosci* **28**: 4690–4701.

Bezard E, Przedborski S. 2011. A tale on animal models of Parkinson's disease. *Mov Disord* **26**: 993–1002.

Bhaskar K, Miller M, Chludzinski A, Herrup K, Zagorski M, Lamb BT. 2009. The PI3K-Akt-mTOR pathway regulates A β oligomer induced neuronal cell cycle events. *Mol Neurodegener* **4**: 14.

Bidere N, Lorenzo HK, Carmona S, Laforge M, Harper F, Dumont C, Senik A. 2003. Cathepsin D triggers Bax activation, resulting in selective apoptosis-inducing factor (AIF) relocation in T lymphocytes entering the early commitment phase to apoptosis. *J Biol Chem* **278**: 31401–31411.

Boland B, Kumar A, Lee S, Platt FM, Wegiel J, Yu WH, Nixon RA. 2008. Autophagy induction and autophagosome clearance in neurons: Relationship to autophagic pathology in Alzheimer's disease. *J Neurosci* **28**: 6926–6937.

Boya P. 2011. Lysosomal function and dysfunction: Mechanism and disease. *Antioxid Redox Signal* **17**: 766–774.

Boya P, Kroemer G. 2008. Lysosomal membrane permeabilization in cell death. *Oncogene* **27**: 6434–6451.

Brunk U, Brun A. 1972. The effect of aging on lysosomal permeability in nerve cells of the central nervous system. An enzyme histochemical study in rat. *Histochemie* **30**: 315–324.

Brunk UT, Svensson I. 1999. Oxidative stress, growth factor starvation and Fas activation may all cause apoptosis through lysosomal leak. *Redox Rep* **4**: 3–11.

Caccamo A, Majumder S, Richardson A, Strong R, Oddo S. 2010. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid- β , and Tau: Effects on cognitive impairments. *J Biol Chem* **285**: 13107–13120.

Canu N, Tufi R, Serafino AL, Amadoro G, Ciotti MT, Calissano P. 2005. Role of the autophagic-lysosomal system on low potassium-induced apoptosis in cultured cerebellar granule cells. *J Neurochem* **92**: 1228–1242.

Cataldo AM, Hamilton DJ, Nixon RA. 1994. Lysosomal abnormalities in degenerating neurons link neuronal compromise to senile plaque development in Alzheimer disease. *Brain Res* **640**: 68–80.

Cataldo AM, Barnett JL, Berman SA, Li J, Quarless S, Bursztajn S, Lippa C, Nixon RA. 1995. Gene expression and cellular content of cathepsin D in Alzheimer's disease brain: Evidence for early up-regulation of the endosomal-lysosomal system. *Neuron* **14**: 671–680.

Cataldo AM, Hamilton DJ, Barnett JL, Paskevich PA, Nixon RA. 1996. Properties of the endosomal-lysosomal

Autophagy and Neuronal Cell Death in Neurological Disorders

- system in the human central nervous system: Disturbances mark most neurons in populations at risk to degenerate in Alzheimer's disease. *J Neurosci* **16**: 186–199.
- Cataldo AM, Barnett JL, Pieroni C, Nixon RA. 1997. Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer's disease: Neuro-pathologic evidence for a mechanism of increased β -amyloidogenesis. *J Neurosci* **17**: 6142–6151.
- Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. 2000. Endocytic pathway abnormalities precede amyloid β deposition in sporadic Alzheimer's disease and Down syndrome: Differential effects of APOE genotype and presenilin mutations. *Am J Pathol* **157**: 277–286.
- Cataldo AM, Peterhoff CM, Schmidt SD, Terio NB, Duff K, Beard M, Mathews PM, Nixon RA. 2004. Presenilin mutations in familial Alzheimer disease and transgenic mouse models accelerate neuronal lysosomal pathology. *J Neuropathol Exp Neurol* **63**: 821–830.
- Cavallini G, Donati A, Gori Z, Bergamini E. 2008. Towards an understanding of the anti-aging mechanism of caloric restriction. *Curr Aging Sci* **1**: 4–9.
- Chu-Wang IW, Oppenheim RW. 1978. Cell death of motoneurons in the chick embryo spinal cord. I. A light and electron microscopic study of naturally occurring and induced cell loss during development. *J Comp Neurol* **177**: 33–57.
- Clark SL Jr. 1957. Cellular differentiation in the kidneys of newborn mice studies with the electron microscope. *J Biophys Biochem Cytol* **3**: 349–362.
- Clarke PG. 1990. Developmental cell death: Morphological diversity and multiple mechanisms. *Anat Embryol* **181**: 195–213.
- Coleman M. 2005. Axon degeneration mechanisms: Commonality amid diversity. *Nat Rev Neurosci* **6**: 889–898.
- Cuervo AM, Stefanis L, Fredenburg R, Lansbury PT, Sulzer D. 2004. Impaired degradation of mutant α -synuclein by chaperone-mediated autophagy. *Science* **305**: 1292–1295.
- Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D. 2006. Transcriptional repression of PGC-1 α by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell* **127**: 59–69.
- Dadakhujiev S, Noh HS, Jung EJ, Cha JY, Baek SM, Ha JH, Kim DR. 2010. Autophagy protects the rotenone-induced cell death in α -synuclein overexpressing SH-SY5Y cells. *Neurosci Lett* **472**: 47–52.
- Dagda RK, Cherra SJ 3rd, Kulich SM, Tandon A, Park D, Chu CT. 2009. Loss of PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission. *J Biol Chem* **284**: 13843–13855.
- * Das G, Shrivastava BV, Baehrecke EH. 2012. Regulation and function of autophagy during cell survival and cell death. *Cold Spring Harb Perspect Biol* doi: 10.1101/cshperspect.a008813.
- de Duve C. 1963. The lysosome. *Sci Am* **208**: 64–72.
- de Duve C, Wattiaux R. 1966. Functions of lysosomes. *Annu Rev Physiol* **28**: 435–492.
- Dehay B, Bove J, Rodriguez-Muela N, Perier C, Recasens A, Boya P, Vila M. 2010. Pathogenic lysosomal depletion in Parkinson's disease. *J Neurosci* **30**: 12535–12544.
- Di Fonzo A, Chien HF, Socal M, Giraudo S, Tassorelli C, Iliceto G, Fabbrini G, Marconi R, Fincati E, Abbruzzese G, et al. 2007. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. *Neurology* **68**: 1557–1562.
- Dikic I, Johansen T, Kirkin V. 2010. Selective autophagy in cancer development and therapy. *Cancer Res* **70**: 3431–3434.
- Dunah AW, Jeong H, Griffin A, Kim YM, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N, Krainc D. 2002. Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. *Science* **296**: 2238–2243.
- Erdal H, Berndtsson M, Castro J, Brunk U, Shoshan MC, Linder S. 2005. Induction of lysosomal membrane permeabilization by compounds that activate p53-independent apoptosis. *Proc Natl Acad Sci* **102**: 192–197.
- Eskelinen EL. 2005. Maturation of autophagic vacuoles in Mammalian cells. *Autophagy* **1**: 1–10.
- Eskelinen EL, Saftig P. 2009. Autophagy: A lysosomal degradation pathway with a central role in health and disease. *Biochim Biophys Acta* **1793**: 664–673.
- Fader CM, Colombo MI. 2009. Autophagy and multivesicular bodies: Two closely related partners. *Cell Death Differ* **16**: 70–78.
- Filimonenko M, Stuffers S, Raiborg C, Yamamoto A, Malerod L, Fisher EMC, Isaacs A, Brech A, Stenmark H, Simonsen A. 2007. Functional multivesicular bodies are required for autophagic clearance of protein aggregates associated with neurodegenerative disease. *J Cell Biol* **179**: 485–500.
- Fortun J, Dunn WA Jr, Joy S, Li J, Notterpek L. 2003. Emerging role for autophagy in the removal of aggregates in Schwann cells. *J Neurosci* **23**: 10672–10680.
- Gafni J, Ellerby LM. 2002. Calpain activation in Huntington's disease. *J Neurosci* **22**: 4842–4849.
- Gasser T. 2009. Molecular pathogenesis of Parkinson disease: Insights from genetic studies. *Expert Rev Mol Med* **11**: e22.
- Geisler S, Holmstrom KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ, Springer W. 2010. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol* **12**: 119–131.
- Gervais FG, Singaraja R, Xanthoudakis S, Gutekunst CA, Leavitt BR, Metzler M, Hackam AS, Tam J, Vaillancourt JP, Houtzager V, et al. 2002. Recruitment and activation of caspase-8 by the Huntingtin-interacting protein Hip-1 and a novel partner Hip1. *Nat Cell Biol* **4**: 95–105.
- Geser F, Lee VM, Trojanowski JQ. 2010. Amyotrophic lateral sclerosis and frontotemporal lobar degeneration: A spectrum of TDP-43 proteinopathies. *Neuropathology* **30**: 103–112.
- Gil JM, Rego AC. 2008. Mechanisms of neurodegeneration in Huntington's disease. *Eur J Neurosci* **27**: 2803–2820.
- Ginsberg SD, Alldred MJ, Counts SE, Cataldo AM, Neve RL, Jiang Y, Wu J, Chao MV, Mufson EJ, Nixon RA, et al. 2010. Microarray analysis of hippocampal CA1 neurons implicates early endosomal dysfunction during Alzheimer's disease progression. *Biol Psychiatry* **68**: 885–893.

R.A. Nixon and D.-S. Yang

- Glabe C. 2001. Intracellular mechanisms of amyloid accumulation and pathogenesis in Alzheimer's disease. *J Mol Neurosci* **17**: 137–145.
- Gordon PB, Seglen PO. 1988. Prelysosomal convergence of autophagic and endocytic pathways. *Biochem Biophys Res Commun* **151**: 40–47.
- Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, Pearson J, Shehadeh J, Bertram L, Murphy Z, et al. 2006. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. *Cell* **125**: 1179–1191.
- Greco SJ, Bryan KJ, Sarkar S, Zhu X, Smith MA, Ashford JW, Johnston JM, Tezapsidis N, Casadesus G. 2010. Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease. *J Alzheimers Dis* **19**: 1155–1167.
- Guicciardi ME, Deussing J, Miyoshi H, Bronk SF, Svingen PA, Peters C, Kaufmann SH, Gores GJ. 2000. Cathepsin B contributes to TNF- α -mediated hepatocyte apoptosis by promoting mitochondrial release of cytochrome c. *J Clin Invest* **106**: 1127–1137.
- Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, et al. 2006. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* **441**: 885–889.
- Hart MN, Cancilla PA, Frommes S, Hirano A. 1977. Anterior horn cell degeneration and Bunina-type inclusions associated with dementia. *Acta Neuropathol* **38**: 225–228.
- Hartmann A, Hunot S, Michel PP, Muriel MP, Vyas S, Faucheux BA, Mouatt-Prigent A, Turmel H, Srinivasan A, Ruberg M, et al. 2000. Caspase-3: A vulnerability factor and final effector in apoptotic death of dopaminergic neurons in Parkinson's disease. *Proc Natl Acad Sci* **97**: 2875–2880.
- Hayashida K, Oyanagi S, Mizutani Y, Yokochi M. 1993. An early cytoplasmic change before Lewy body maturation: An ultrastructural study of the substantia nigra from an autopsy case of juvenile parkinsonism. *Acta Neuropathol* **85**: 445–448.
- He C, Klionsky DJ. 2009. Regulation mechanisms and signaling pathways of autophagy. *Annu Rev Genet* **43**: 67–93.
- Hetz C, Thielen P, Matus S, Nassif M, Court F, Kiffin R, Martinez G, Cuervo AM, Brown RH, Glimcher LH. 2009. XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. *Genes Dev* **23**: 2294–2306.
- Hickey MA, Chesselet MF. 2003. Apoptosis in Huntington's disease. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 255–265.
- Hirano A. 1996. Neuropathology of ALS: An overview. *Neurology* **47**: S63–S66.
- Holtzman E, Novikoff AB. 1965. Lysosomes in the rat sciatic nerve following crush. *J Cell Biol* **27**: 651–669.
- Holtzman E, Novikoff AB, Villaverde H. 1967. Lysosomes and GERL in normal and chromatolytic neurons of the rat ganglion nodosum. *J Cell Biol* **33**: 419–435.
- Hornung JP, Koppel H, Clarke PG. 1989. Endocytosis and autophagy in dying neurons: An ultrastructural study in chick embryos. *J Comp Neurol* **283**: 425–437.
- Ivy GO, Schottler F, Wenzel J, Baudry M, Lynch G. 1984. Inhibitors of lysosomal enzymes: Accumulation of lipofuscin-like dense bodies in the brain. *Science* **226**: 985–987.
- Jaeger PA, Pickford F, Sun CH, Lucin KM, Masliah E, Wyss-Coray T. 2010. Regulation of amyloid precursor protein processing by the Beclin 1 complex. *PLoS ONE* **5**: e11102.
- Jana NR, Zemskov EA, Wang G, Nukina N. 2001. Altered proteasomal function due to the expression of polyglutamine-expanded truncated N-terminal huntingtin induces apoptosis by caspase activation through mitochondrial cytochrome c release. *Hum Mol Genet* **10**: 1049–1059.
- Jeong H, Then F, Melia TJ Jr, Mazzulli JR, Cui L, Savas JN, Voisine C, Paganetti P, Tanese N, Hart AC, et al. 2009. Acetylation targets mutant huntingtin to autophagosomes for degradation. *Cell* **137**: 60–72.
- Ji ZS, Miranda RD, Newhouse YM, Weisgraber KH, Huang Y, Mahley RW. 2002. Apolipoprotein E4 potentiates amyloid β peptide-induced lysosomal leakage and apoptosis in neuronal cells. *J Biol Chem* **277**: 21821–21828.
- Ji ZS, Mullendorff K, Cheng IH, Miranda RD, Huang Y, Mahley RW. 2006. Reactivity of apolipoprotein E4 and amyloid β peptide: Lysosomal stability and neurodegeneration. *J Biol Chem* **281**: 2683–2692.
- Johansson AC, Appelqvist H, Nilsson C, Kagedal K, Roberg K, Ollinger K. 2010. Regulation of apoptosis-associated lysosomal membrane permeabilization. *Apoptosis* **15**: 527–540.
- Kaasik A, Rikk T, Piirsoo A, Zharkovsky T, Zharkovsky A. 2005. Up-regulation of lysosomal cathepsin L and autophagy during neuronal death induced by reduced serum and potassium. *Eur J Neurosci* **22**: 1023–1031.
- Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF, Gibson GE. 2009. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. *Neurochem Int* **54**: 111–118.
- Kazantsev AG, Thompson LM. 2008. Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. *Nat Rev Drug Discov* **7**: 854–868.
- Kegel KB, Kim M, Sapp E, McIntyre C, Castano JG, Aronin N, DiFiglia M. 2000. Huntingtin expression stimulates endosomal-lysosomal activity, endosome tubulation, and autophagy. *J Neurosci* **20**: 7268–7278.
- Kilinc M, Gursay-Ozdemir Y, Gurer G, Erdener SE, Erdemli E, Can A, Dalkara T. 2010. Lysosomal rupture, necroapoptotic interactions and potential crosstalk between cysteine proteases in neurons shortly after focal ischemia. *Neurobiol Dis* **40**: 293–302.
- Klionsky DJ, Codogno P, Cuervo AM, Deretic V, Elazar Z, Fuyo-Margaretto J, Gewirtz DA, Kroemer G, Levine B, Mizushima N, et al. 2010. A comprehensive glossary of autophagy-related molecules and processes. *Autophagy* **6**: 438–448.
- Ko DC, Milenkovic L, Beier SM, Manuel H, Buchanan J, Scott MP. 2005. Cell-autonomous death of cerebellar purkinje neurons with autophagy in Niemann-Pick type C disease. *PLoS Genet* **1**: 81–95.
- Koike M, Nakanishi H, Saftig P, Ezaki J, Isahara K, Ohsawa Y, Schulz-Schaeffer W, Watanabe T, Waguri S, Kametaka S, et al. 2000. Cathepsin D deficiency induces lysosomal

Autophagy and Neuronal Cell Death in Neurological Disorders

- storage with ceroid lipofuscin in mouse CNS neurons. *J Neurosci* **20**: 6898–6906.
- Koike M, Shibata M, Tadakoshi M, Gotoh K, Komatsu M, Waguri S, Kawahara N, Kuida K, Nagata S, Kominami E, et al. 2008. Inhibition of autophagy prevents hippocampal pyramidal neuron death after hypoxic-ischemic injury. *Am J Pathol* **172**: 454–469.
- Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, et al. 2006. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* **441**: 880–884.
- Komatsu M, Wang QJ, Holstein GR, Friedrich VL Jr, Iwata J, Kominami E, Chait BT, Tanaka K, Yue Z. 2007. Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration. *Proc Natl Acad Sci* **104**: 14489–14494.
- Korolchuk VI, Mansilla A, Menzies FM, Rubinsztein DC. 2009. Autophagy inhibition compromises degradation of ubiquitin-proteasome pathway substrates. *Mol Cell* **33**: 517–527.
- Kroemer G, Jaattela M. 2005. Lysosomes and autophagy in cell death control. *Nat Rev Cancer* **5**: 886–897.
- Kurz T, Terman A, Gustafsson B, Brunk UT. 2008. Lysosomes and oxidative stress in aging and apoptosis. *Biochim Biophys Acta* **1780**: 1291–1303.
- Laird FM, Farah MH, Ackerley S, Hoke A, Maragakis N, Rothstein JD, Griffin J, Price DL, Martin LJ, Wong PC. 2008. Motor neuron disease occurring in a mutant dynactin mouse model is characterized by defects in vesicular trafficking. *J Neurosci* **28**: 1997–2005.
- Lankiewicz S, Marc Luetjens C, Truc Bui N, Krohn AJ, Poppe M, Cole GM, Saido TC, Prehn JH. 2000. Activation of calpain I converts excitotoxic neuron death into a caspase-independent cell death. *J Biol Chem* **275**: 17064–17071.
- La Spada AR, Taylor JP. 2010. Repeat expansion disease: Progress and puzzles in disease pathogenesis. *Nat Rev Genet* **11**: 247–258.
- Lee JA, Gao FB. 2009. Inhibition of autophagy induction delays neuronal cell loss caused by dysfunctional ESCRT-III in frontotemporal dementia. *J Neurosci* **29**: 8506–8511.
- Lee JA, Beigneux A, Ahmad ST, Young SG, Gao FB. 2007. ESCRT-III dysfunction causes autophagosome accumulation and neurodegeneration. *Curr Biol* **17**: 1561–1567.
- Lee JH, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM, Martinez-Vicente M, Massey AG, Sovak G, Uchiyama Y, et al. 2010. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* **141**: 1146–1158.
- Lee S, Sato Y, Nixon RA. 2011. Lysosomal proteolysis inhibition selectively disrupts axonal transport of degradative organelles and causes an Alzheimer's-like axonal dystrophy. *J Neurosci* **31**: 7817–7830.
- Levine B, Yuan J. 2005. Autophagy in cell death: An innocent convict? *J Clin Invest* **115**: 2679–2688.
- Li L, Zhang X, Le W. 2008. Altered macroautophagy in the spinal cord of SOD1 mutant mice. *Autophagy* **4**: 290–293.
- Li L, Wang X, Fei X, Xia L, Qin Z, Liang Z. 2011. Parkinson's disease involves autophagy and abnormal distribution of cathepsin L. *Neurosci Lett* **489**: 62–67.
- Liang CC, Wang C, Peng X, Gan B, Guan JL. 2010. Neural-specific deletion of FIP200 leads to cerebellar degeneration caused by increased neuronal death and axon degeneration. *J Biol Chem* **285**: 3499–3509.
- Liberski PP, Budka H, Yanagihara R, Gajdusek DC. 1995. Neuroaxonal dystrophy in experimental Creutzfeldt-Jakob disease: Electron microscopical and immunohistochemical demonstration of neurofilament accumulations within affected neurites. *J Comp Pathol* **112**: 243–255.
- Ling D, Song HJ, Garza D, Neufeld TP, Salvaterra PM. 2009. Aβ42-induced neurodegeneration via an age-dependent autophagic-lysosomal injury in *Drosophila*. *PLoS ONE* **4**: e4201.
- Liou W, Geuze HJ, Geelen MJ, Slot JW. 1997. The autophagic and endocytic pathways converge at the nascent autophagic vacuoles. *J Cell Biol* **136**: 61–70.
- Lipinski MM, Zheng B, Lu T, Yan Z, Py BF, Ng A, Xavier RJ, Li C, Yankner BA, Scherzer CR, et al. 2010. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. *Proc Natl Acad Sci* **107**: 14164–14169.
- Liscic RM, Breljak D. 2011. Molecular basis of amyotrophic lateral sclerosis. *Prog Neuropsychopharmacol Biol Psychiatry* **35**: 370–372.
- Liu J, Lillo C, Jonsson PA, Vande Velde C, Ward CM, Miller TM, Subramaniam JR, Rothstein JD, Marklund S, Andersen PM, et al. 2004. Toxicity of familial ALS-linked SOD1 mutants from selective recruitment to spinal mitochondria. *Neuron* **43**: 5–17.
- Mackenzie IR. 2007. The neuropathology of FTD associated with ALS. *Alzheimer Dis Assoc Disord* **21**: S44–S49.
- Mahley RW, Huang Y. 2006. Apolipoprotein (apo) E4 and Alzheimer's disease: Unique conformational and biophysical properties of apoE4 can modulate neuropathology. *Acta Neurol Scand Suppl* **185**: 8–14.
- Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. 2007. Self-eating and self-killing: Crosstalk between autophagy and apoptosis. *Nat Rev Mol Cell Biol* **8**: 741–752.
- Majumder S, Richardson A, Strong R, Oddo S. 2011. Inducing autophagy by rapamycin before, but not after, the formation of plaques and tangles ameliorates cognitive deficits. *PLoS ONE* **6**: e25416.
- Martin DN, Balgley B, Dutta S, Chen J, Rudnick P, Cranford J, Kantartzis S, DeVoe DL, Lee C, Baehrecke EH. 2007. Proteomic analysis of steroid-triggered autophagic programmed cell death during *Drosophila* development. *Cell Death Differ* **14**: 916–923.
- Martinez-Vicente M, Tallozy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D, et al. 2010. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat Neurosci* **13**: 567–576.
- Michiorri S, Gelmetti V, Giarda E, Lombardi F, Romano F, Marongiu R, Nerini-Molteni S, Sale P, Vago R, Arena G, et al. 2010. The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy. *Cell Death Differ* **17**: 962–974.

R.A. Nixon and D.-S. Yang

- Mizushima N, Yamamoto A, Matsui M, Yoshimori T, Ohsumi Y. 2004. In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker. *Mol Biol Cell* **15**: 1101–1111.
- Momeni P, Schymick J, Jain S, Cookson MR, Cairns NJ, Greggio E, Greenway MJ, Berger S, Pickering-Brown S, Chio A, et al. 2006. Analysis of IFT74 as a candidate gene for chromosome 9p-linked ALS-FTD. *BMC Neurol* **6**: 44.
- Morimoto N, Nagai M, Ohta Y, Miyazaki K, Kurata T, Morimoto M, Murakami T, Takehisa Y, Ikeda Y, Kamiya T, et al. 2007. Increased autophagy in transgenic mice with a G93A mutant SOD1 gene. *Brain Res* **1167**: 112–117.
- Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, Criollo A, Galluzzi L, Malik SA, Vitale I, et al. 2010. Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. *Cell Death Dis* **1**: e10.
- Nakano I. 2000. Frontotemporal dementia with motor neuron disease (amyotrophic lateral sclerosis with dementia). *Neuropathology* **20**: 68–75.
- Nakano I, Shibata T, Uesaka Y. 1993. On the possibility of autolysosomal processing of skein-like inclusions. Electron microscopic observation in a case of amyotrophic lateral sclerosis. *J Neurol Sci* **120**: 54–59.
- Narendra D, Tanaka A, Suen DF, Youle RJ. 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol* **183**: 795–803.
- Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, Cookson MR, Youle RJ. 2010. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol* **8**: e1000298.
- Nasr P, Gursahani HI, Pang Z, Bondada V, Lee J, Hadley RW, Geddes JW. 2003. Influence of cytosolic and mitochondrial Ca^{2+} , ATP, mitochondrial membrane potential, and calpain activity on the mechanism of neuron death induced by 3-nitropropionic acid. *Neurochem Int* **43**: 89–99.
- Nixon RA. 2006. Autophagy in neurodegenerative disease: Friend, foe or turncoat? *Trends Neurosci* **29**: 528–535.
- Nixon RA, Cataldo AM. 1995. The endosomal-lysosomal system of neurons: New roles. *Trends Neurosci* **18**: 489–496.
- Nixon RA, Cataldo AM. 2006. Lysosomal system pathways: Genes to neurodegeneration in Alzheimer's disease. *J Alzheimers Dis* **9**: 277–289.
- Nixon RA, Yang DS. 2011. Autophagy failure in Alzheimer's disease—Locating the primary defect. *Neurobiol Dis* **43**: 38–45.
- Nixon RA, Cataldo AM, Mathews PM. 2000. The endosomal-lysosomal system of neurons in Alzheimer's disease pathogenesis: A review. *Neurochem Res* **25**: 1161–1172.
- Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, Cataldo A, Cuervo AM. 2005. Extensive involvement of autophagy in Alzheimer disease: An immuno-electron microscopy study. *J Neuropathol Exp Neurol* **64**: 113–122.
- Nixon RA, Yang DS, Lee JH. 2008. Neurodegenerative lysosomal disorders: A continuum from development to late age. *Autophagy* **4**: 590–599.
- Noda T, Fujita N, Yoshimori T. 2009. The late stages of autophagy: How does the end begin? *Cell Death Differ* **16**: 984–990.
- Oberstein A, Jeffrey PD, Shi Y. 2007. Crystal structure of the Bcl-XL-Becn1 peptide complex: Becn1 is a novel BH3-only protein. *J Biol Chem* **282**: 13123–13132.
- Ohsumi Y. 2001. Molecular dissection of autophagy: Two ubiquitin-like systems. *Nat Rev Mol Cell Biol* **2**: 211–216.
- Ona VO, Li M, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, Frey AS, Menon AS, Li XJ, Stieg PE, et al. 1999. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. *Nature* **399**: 263–267.
- Palmieri M, Impey S, Kang H, di Ronza A, Pelz C, Sardiello M, Ballabio A. 2011. Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. *Hum Mol Genet* **20**: 3852–3866.
- Pang Z, Geddes JW. 1997. Mechanisms of cell death induced by the mitochondrial toxin 3-nitropropionic acid: Acute excitotoxic necrosis and delayed apoptosis. *J Neurosci* **17**: 3064–3073.
- Pang Z, Bondada V, Sengoku T, Siman R, Geddes JW. 2003. Calpain facilitates the neuron death induced by 3-nitropropionic acid and contributes to the necrotic morphology. *J Neuropathol Exp Neurol* **62**: 633–643.
- Parkinson N, Ince PG, Smith MO, Highley R, Skibinski G, Andersen PM, Morrison KE, Pall HS, Hardiman O, Collinge J, et al. 2006. ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). *Neurology* **67**: 1074–1077.
- Pasquali L, Longone P, Isidoro C, Ruggieri S, Paparelli A, Fornai F. 2009. Autophagy, lithium, and amyotrophic lateral sclerosis. *Muscle Nerve* **40**: 173–194.
- Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, Mizushima N, Packer M, Schneider MD, Levine B. 2005. Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. *Cell* **122**: 927–939.
- Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, et al. 2008. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice. *J Clin Invest* **118**: 2190–2199.
- Piras A, Gianetto D, Conte D, Bosone A, Vercelli A. 2011. Activation of autophagy in a rat model of retinal ischemia following high intraocular pressure. *PLoS ONE* **6**: e22514.
- Puyal J, Vaslin A, Mottier V, Clarke PG. 2009. Postischemic treatment of neonatal cerebral ischemia should target autophagy. *Ann Neurol* **66**: 378–389.
- Pyo JO, Jang MH, Kwon YK, Lee HJ, Jun JJ, Woo HN, Cho DH, Choi B, Lee H, Kim JH, et al. 2005. Essential roles of Atg5 and FADD in autophagic cell death: Dissection of autophagic cell death into vacuole formation and cell death. *J Biol Chem* **280**: 20722–20729.
- Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, et al. 2006. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat Genet* **38**: 1184–1191.

Autophagy and Neuronal Cell Death in Neurological Disorders

- Rao MV, Mohan PS, Peterhoff CM, Yang DS, Schmidt SD, Stavrides PH, Campbell J, Chen Y, Jiang Y, Paskevich PA, et al. 2008. Marked calpastatin (CAST) depletion in Alzheimer's disease accelerates cytoskeleton disruption and neurodegeneration: Neuroprotection by CAST overexpression. *J Neurosci* **28**: 12241–12254.
- Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, et al. 2004. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet* **36**: 585–595.
- Ravikumar B, Acevedo-Arozena A, Imarisio S, Berger Z, Vacher C, O'Kane CJ, Brown SD, Rubinshtein DC. 2005. Dynein mutations impair autophagic clearance of aggregate-prone proteins. *Nat Genet* **37**: 771–776.
- Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, Jimenez-Sanchez M, Korolchuk VI, Lichtenberg M, Luo S, et al. 2010. Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol Rev* **90**: 1383–1435.
- Repnik U, Stoka V, Turk V, Turk B. 2012. Lysosomes and lysosomal cathepsins in cell death. *Biochim Biophys Acta* **1824**: 22–33.
- Roos RA, Bots GT, Hermans J. 1985. Neuronal nuclear membrane indentation and astrocyte/neuron ratio in Huntington's disease. A quantitative electron microscopic study. *J Hirnforsch* **26**: 689–693.
- Rubinshtein DC, DiFiglia M, Heintz N, Nixon RA, Qin ZH, Ravikumar B, Stefanis L, Tolkovsky AM. 2005. Autophagy and its possible roles in nervous system diseases, damage and repair. *Autophagy* **1**: 11–22.
- Rubinshtein DC, Marino G, Kroemer G. 2011. Autophagy and aging. *Cell* **146**: 682–695.
- Rudnicki DD, Pletnikova O, Vonsattel JP, Ross CA, Margolis RL. 2008. A comparison of huntington disease and huntington disease-like 2 neuropathology. *J Neuropathol Exp Neurol* **67**: 366–374.
- Sahu R, Kaushik S, Clement CC, Cannizzo ES, Scharf B, Follenzi A, Potolicchio I, Nieves E, Cuervo AM, Santambrogio L. 2011. Microautophagy of cytosolic proteins by late endosomes. *Dev Cell* **20**: 131–139.
- Sanchez I, Xu CJ, Juo P, Kakizaka A, Blenis J, Yuan J. 1999. Caspase-8 is required for cell death induced by expanded polyglutamine repeats. *Neuron* **22**: 623–633.
- Sandoval H, Thiagarajan P, Dasgupta SK, Schumacher A, Prchal JT, Chen M, Wang J. 2008. Essential role for Nix in autophagic maturation of erythroid cells. *Nature* **454**: 232–235.
- Sasaki S. 2011. Autophagy in spinal cord motor neurons in sporadic amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol* **70**: 349–359.
- Schweichel JU, Merker HJ. 1973. The morphology of various types of cell death in prenatal tissues. *Teratology* **7**: 253–266.
- Settembre C, Fraldi A, Jahreiss L, Spanpanato C, Venturi C, Medina D, de Pablo R, Tacchetti C, Rubinshtein DC, Ballabio A. 2008a. A block of autophagy in lysosomal storage disorders. *Hum Mol Genet* **17**: 119–129.
- Settembre C, Fraldi A, Rubinshtein DC, Ballabio A. 2008b. Lysosomal storage diseases as disorders of autophagy. *Autophagy* **4**: 113–114.
- Settembre C, Di Malta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, et al. 2011. TFEB links autophagy to lysosomal biogenesis. *Science* **332**: 1429–1433.
- Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, et al. 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* **375**: 754–760.
- Shi CS, Kehrl JH. 2010. TRAF6 and A20 regulate lysine 63-linked ubiquitination of Beclin-1 to control TLR4-induced autophagy. *Sci Signal* **3**: ra42.
- Shibata M, Lu T, Furuya T, Degterev A, Mizushima N, Yoshimori T, MacDonald M, Yankner B, Yuan J. 2006. Regulation of intracellular accumulation of mutant Huntingtin by Beclin 1. *J Biol Chem* **281**: 14474–14485.
- Shimizu S, Kanaseki T, Mizushima N, Mizuta T, Arakawa-Kobayashi S, Thompson CB, Tsujimoto Y. 2004. Role of Bcl-2 family proteins in a non-apoptotic programmed cell death dependent on autophagy genes. *Nat Cell Biol* **6**: 1221–1228.
- Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, et al. 2009. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* **361**: 1651–1661.
- Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, Nielsen JE, Hodges JR, Spillantini MG, Thusgaard T, et al. 2005. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat Genet* **37**: 806–808.
- Spencer B, Potkar R, Trejo M, Rockenstein E, Patrick C, Gindi R, Adame A, Wyss-Coray T, Masliah E. 2009. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in α -synuclein models of Parkinson's and Lewy body diseases. *J Neurosci* **29**: 13578–13588.
- Spilman P, Podlutska N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, Richardson A, Strong R, Galvan V. 2010. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid- β levels in a mouse model of Alzheimer's disease. *PLoS ONE* **5**: e9979.
- Stefanis L. 2005. Caspase-dependent and -independent neuronal death: Two distinct pathways to neuronal injury. *Neuroscientist* **11**: 50–62.
- Strong MJ. 2008. The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* **9**: 323–338.
- Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, Murphy J, Shoesmith C, Rosenfeld J, Leigh PN, et al. 2009. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* **10**: 131–146.
- Sun B, Zhou Y, Halabisky B, Lo I, Cho SH, Mueller-Stieber S, Davidze N, Wang X, Grubb A, Gan L. 2008. Cystatin C-cathepsin B axis regulates amyloid β levels and associated neuronal deficits in an animal model of Alzheimer's disease. *Neuron* **60**: 247–257.
- Syntichaki P, Tavernarakis N. 2002. Death by necrosis. Uncontrollable catastrophe, or is there order behind the chaos? *EMBO Rep* **3**: 604–609.

R.A. Nixon and D.-S. Yang

- Tang D, Kang R, Livesey KM, Cheh CW, Farkas A, Loughran P, Hoppe G, Bianchi ME, Tracey KJ, Zeh HJ 3rd, et al. 2010. Endogenous HMGB1 regulates autophagy. *J Cell Biol* **190**: 881–892.
- Tellez-Nagel I, Johnson AB, Terry RD. 1974. Studies on brain biopsies of patients with Huntington's chorea. *J Neuropathol Exp Neurol* **33**: 308–332.
- Terman A, Brunk UT. 2006. Oxidative stress, accumulation of biological “garbage,” and aging. *Antioxid Redox Signal* **8**: 197–204.
- Tian Y, Bustos V, Flajolet M, Greengard P. 2011. A small-molecule enhancer of autophagy decreases levels of A β and APP-CTF via Atg5-dependent autophagy pathway. *FASEB J* **25**: 1934–1942.
- Tresse E, Salomons FA, Vesa J, Bott LC, Kimonis V, Yao TP, Dantuma NP, Taylor JP. 2010. VCP/p97 is essential for maturation of ubiquitin-containing autophagosomes and this function is impaired by mutations that cause IBMPFD. *Autophagy* **6**: 217–227.
- Tynnela J, Sohar I, Sleat DE, Gin RM, Donnelly RJ, Baumann M, Haltia M, Lobel P. 2000. A mutation in the ovine cathepsin D gene causes a congenital lysosomal storage disease with profound neurodegeneration. *Embo J* **19**: 2786–2792.
- Uchiyama Y. 2001. Autophagic cell death and its execution by lysosomal cathepsins. *Arch Histol Cytol* **64**: 233–246.
- Vande Velde C, Miller TM, Cashman NR, Cleveland DW. 2008. Selective association of misfolded ALS-linked mutant SOD1 with the cytoplasmic face of mitochondria. *Proc Natl Acad Sci* **105**: 4022–4027.
- Venkatachalam K, Long AA, Elsaesser R, Nikolaeva D, Broadie K, Montell C. 2008. Motor deficit in a *Drosophila* model of mucopolidosis type IV due to defective clearance of apoptotic cells. *Cell* **135**: 838–851.
- Wang JY, Xia Q, Chu KT, Pan J, Sun LN, Zeng B, Zhu YJ, Wang Q, Wang K, Luo BY. 2011. Severe global cerebral ischemia-induced programmed necrosis of hippocampal CA1 neurons in rat is prevented by 3-methyladenine: A widely used inhibitor of autophagy. *J Neuropathol Exp Neurol* **70**: 314–322.
- Webb JL, Ravikumar B, Atkins J, Skepper JN, Rubinstein DC. 2003. α -Synuclein is degraded by both autophagy and the proteasome. *J Biol Chem* **278**: 25009–25013.
- Wei Y, Pattingre S, Sinha S, Bassik M, Levine B. 2008. JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy. *Mol Cell* **30**: 678–688.
- Weidberg H, Shvets E, Elazar Z. 2011. Biogenesis and cargo selectivity of autophagosomes. *Annu Rev Biochem* **80**: 125–156.
- Wen YD, Sheng R, Zhang LS, Han R, Zhang X, Zhang XD, Han F, Fukunaga K, Qin ZH. 2008. Neuronal injury in rat model of permanent focal cerebral ischemia is associated with activation of autophagic and lysosomal pathways. *Autophagy* **4**: 762–769.
- Werneburg N, Guicciardi ME, Yin XM, Gores GJ. 2004. TNF- α -mediated lysosomal permeabilization is FAN and caspase 8/Bid dependent. *Am J Physiol Gastrointest Liver Physiol* **287**: G436–G443.
- Werneburg NW, Guicciardi ME, Bronk SF, Kaufmann SH, Gores GJ. 2007. Tumor necrosis factor-related apoptosis-inducing ligand activates a lysosomal pathway of apoptosis that is regulated by Bcl-2 proteins. *J Biol Chem* **282**: 28960–28970.
- Wild P, Dikic I. 2010. Mitochondria get a Parkin' ticket. *Nat Cell Biol* **12**: 104–106.
- Willenborg M, Schmidt CK, Braun P, Landgrebe J, von Figura K, Saftig P, Eskelinen EL. 2005. Mannose 6-phosphate receptors, Niemann-Pick C2 protein, and lysosomal cholesterol accumulation. *J Lipid Res* **46**: 2559–2569.
- Wolfe DM, Nixon RA. 2012. Autophagy failure in Alzheimer's disease and lysosomal storage disorders: A common pathway to neurodegeneration. In *Autophagy of the nervous system: Cellular self-digestion in neurons and neurological diseases* (ed. Yue Z, Chu CT). World Scientific, Hackensack, NJ.
- Wong PC, Pardo CA, Borchelt DR, Lee MK, Copeland NG, Jenkins NA, Sisodia SS, Cleveland DW, Price DL. 1995. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. *Neuron* **14**: 1105–1116.
- Wood-Kaczmar A, Gandhi S, Yao Z, Abramov AY, Miljan EA, Keen G, Stanyer L, Hargreaves I, Klupsch K, Deas E, et al. 2008. PINK1 is necessary for long term survival and mitochondrial function in human dopaminergic neurons. *PLoS ONE* **3**: e2455.
- Xilouri M, Vogiatzi T, Vekrellis K, Park D, Stefanis L. 2009. Aberrant α -synuclein confers toxicity to neurons in part through inhibition of chaperone-mediated autophagy. *PLoS ONE* **4**: e5515.
- Xin XY, Pan J, Wang XQ, Ma JF, Ding JQ, Yang GY, Chen SD. 2011. 2-Methoxyestradiol attenuates autophagy activation after global ischemia. *Can J Neurol Sci* **38**: 631–638.
- Yamashima T, Oikawa S. 2009. The role of lysosomal rupture in neuronal death. *Prog Neurobiol* **89**: 343–358.
- Yang AJ, Chandswangbhuvana D, Margol L, Glabe CG. 1998. Loss of endosomal/lysosomal membrane impermeability is an early event in amyloid A β 1–42 pathogenesis. *J Neurosci Res* **52**: 691–698.
- Yang DS, Kumar A, Stavrides P, Peterson J, Peterhoff CM, Pawlik M, Levy E, Cataldo AM, Nixon RA. 2008. Neuronal apoptosis and autophagy cross talk in aging PS/APP mice, a model of Alzheimer's disease. *Am J Pathol* **173**: 665–681.
- Yang DS, Stavrides P, Mohan PS, Kaushik S, Kumar A, Ohno M, Schmidt SD, Wesson D, Bandyopadhyay U, Jiang Y, et al. 2011. Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. *Brain* **134**: 258–277.
- Yao Z, Wood NW. 2009. Cell death pathways in Parkinson's disease: Role of mitochondria. *Antioxid Redox Signal* **11**: 2135–2149.
- Yokoyama H, Kuroiwa H, Yano R, Araki T. 2008. Targeting reactive oxygen species, reactive nitrogen species and inflammation in MPTP neurotoxicity and Parkinson's disease. *Neurol Sci* **29**: 293–301.
- Yoshii SR, Kishi C, Ishihara N, Mizushima N. 2011. Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane. *J Biol Chem* **286**: 19630–19640.

Autophagy and Neuronal Cell Death in Neurological Disorders

- Yoshimori T, Yamamoto A, Moriyama Y, Futai M, Tashiro Y. 1991. Bafilomycin A1, a specific inhibitor of vacuolar-type H^+ -ATPase, inhibits acidification and protein degradation in lysosomes of cultured cells. *J Biol Chem* **266**: 17707–17712.
- Youle RJ, Narendra DP. 2011. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol* **12**: 9–14.
- Yousefi S. 2006. Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis. *Nat Cell Biol* **8**: 1124–1132.
- Yu L, Alva A, Su H, Dutt P, Freundt E, Welsh S, Baehr-ecke EH, Lenardo MJ. 2004. Regulation of an ATG7-beclin 1 program of autophagic cell death by caspase-8. *Science* **304**: 1500–1502.
- Yu WH, Dorado B, Figueroa HY, Wang L, Planel E, Cookson MR, Clark LN, Duff KE. 2009. Metabolic activity determines efficacy of macroautophagic clearance of pathological oligomeric α -synuclein. *Am J Pathol* **175**: 736–747.
- Yu L, McPhee CK, Zheng L, Mardones GA, Rong Y, Peng J, Mi N, Zhao Y, Liu Z, Wan F, et al. 2010. Termination of autophagy and reformation of lysosomes regulated by mTOR. *Nature* **465**: 942–946.
- Yuan J, Yankner BA. 2000. Apoptosis in the nervous system. *Nature* **407**: 802–809.
- Yue Z, Horton A, Bravin M, DeJager PL, Selimi F, Heintz N. 2002. A novel protein complex linking the $\delta 2$ glutamate receptor and autophagy: Implications for neurodegeneration in lurcher mice. *Neuron* **35**: 921–933.
- Zalckvar E, Berissi H, Mizrahy L, Idelchuk Y, Koren I, Eisenstein M, Sabanay H, Pinkas-Kramarski R, Kimchi A. 2009. DAP-kinase-mediated phosphorylation on the BH3 domain of beclin 1 promotes dissociation of beclin 1 from Bcl-XL and induction of autophagy. *EMBO Rep* **10**: 285–292.
- Zhang Y, Leavitt BR, van Raamsdonk JM, Dragatsis I, Goldowitz D, MacDonald ME, Hayden MR, Friedlander RM. 2006. Huntingtin inhibits caspase-3 activation. *EMBO J* **25**: 5896–5906.
- Zhang J, Zhang Y, Li J, Xing S, Li C, Li Y, Dang C, Fan Y, Yu J, Pei Z, et al. 2012. Autophagosomes accumulation is associated with β -amyloid deposits and secondary damage in the thalamus after focal cortical infarction in hypertensive rats. *J Neurochem* **120**: 564–573.
- Zhu JH, Horbinski C, Guo F, Watkins S, Uchiyama Y, Chu CT. 2007. Regulation of autophagy by extracellular signal-regulated protein kinases during 1-methyl-4-phenylpyridinium-induced cell death. *Am J Pathol* **170**: 75–86.

Cold Spring Harbor Perspectives in Biology

Autophagy and Neuronal Cell Death in Neurological Disorders

Ralph A. Nixon and Dun-Sheng Yang

Cold Spring Harb Perspect Biol 2012; doi: 10.1101/cshperspect.a008839 originally published online September 13, 2012

Subject Collection [Cell Survival and Cell Death](#)

Programmed Cell Death in the Evolutionary Race against Bacterial Virulence Factors

Carolyn A. Lacey and Edward A. Miao

The Evolutionary Origins of Programmed Cell Death Signaling

Kay Hofmann

Regulation of Cell Death and Immunity by XIAP

Philipp J. Jost and Domagoj Vucic

Dysregulation of Cell Death in Human Chronic Inflammation

Yue Li, Christoph Klein and Daniel Kotlarz

Cell Death in Plant Immunity

Eugenia Pitsili, Ujjal J. Phukan and Nuria S. Coll

Recent Insights on Inflammasomes, Gasdermin Pores, and Pyroptosis

Nathalia M. de Vasconcelos and Mohamed Lamkanfi

Phagocyte Responses to Cell Death in Flies

Andrew J. Davidson and Will Wood

Mechanism and Regulation of Gasdermin-Mediated Cell Death

Shiyu Xia, Louis Robert Hollingsworth IV and Hao Wu

Cell Death and Neurodegeneration

Benjamin J. Andreone, Martin Larhammar and Joseph W. Lewcock

Death Receptors and Their Ligands in Inflammatory Disease and Cancer

Alessandro Annibaldi and Henning Walczak

The Killer Pseudokinase Mixed Lineage Kinase Domain-Like Protein (MLKL)

James M. Murphy

Neutrophil Extracellular Traps in Host Defense

Sabrina Sofia Burgener and Kate Schroder

Cell-Cycle Cross Talk with Caspases and Their Substrates

Patrick Connolly, Irmina Garcia-Carpio and Andreas Villunger

Cracking the Cell Death Code

Carla V. Rothlin and Sourav Ghosh

BAX, BAK, and BOK: A Coming of Age for the BCL-2 Family Effector Proteins

Tudor Moldoveanu and Peter E. Czabotar

Multitasking Kinase RIPK1 Regulates Cell Death and Inflammation

Kim Newton

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**

Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense

Oligo Modifications?
Your wish is our command.

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**

Oligo Modifications?
Your wish is our command.

Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense