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Cell death pathways and autophagy in the central nervous system and its involvement in neurodegeneration, immunity and central nervous system infection: to die or not to die – that is the question

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Summary

Death rules our lives. In this short paper, we summarize new insights into molecular mechanisms of neurodegeneration. Here we review the most important processes of cell death: apoptosis and oncosis. We focus on autophagy, which is pivotal for neuronal homeostasis, in the context of neurodegeneration, infection and immunity. Its dysfunction has been linked to several neurodegenerative diseases such as Parkinson's, Huntington's and Alzheimer's diseases. Our understanding is still incomplete, but may highlight attractive new avenues for the development of treatment strategies to combat neurodegenerative diseases.

Keywords: Alzheimer's disease, DNA viruses, immune regulation, infections, inflammation/inflammatory mediators including eicosanoids

Introduction

Autophagy is an important homeostatic process that enables cells to flourish after controlled clearance of their own malfunctioning cytoplasmic constituents and/or organelles. Knowledge of its roles in the central nervous system (CNS) is still patchy [1]. It is known that autophagosomes accumulate in several brain disorders [2,3]. Furthermore, autophagy is proving to be essential for neuronal homeostasis, plasticity and protein quality control in neurones [4–6]. Finally, neurodegeneration and protein inclusions have been described in mouse models. Indeed, mice deficient in autophagy-1-related genes (Atgs), Atg-5 and Atg-7, spontaneously show signs of neurodegeneration due to the accumulation of ubiquitin-tagged cargo [7,8]. The same autophagic machinery that is used for the selective disposal of pathogens also influences both innate and adaptive immune responses [6].

Here we present a short overview of autophagy in the context of immunity, CNS infection and its dysregulation in neurodegenerative diseases.

Autophagy: a role in cell survival

Derived from the Greek roots 'auto' (self) and 'phagy' (eat), autophagy was a term coined by de Duve in 1963 [9]. Even though it was described more than 40 years ago, much about this process is as yet unknown. Autophagy was described initially as a cell death mechanism, but evidence is increasing that autophagy accompanies cell death and is, in fact, cryoprotective. Autophagy describes an intracellular bulk degradation system that channels malfunctioning components into the lysosomal machinery of the cell. Components degraded via autophagy may range from proteins to entire organelles (e.g. mitochondria) to invading microbes, and may be targeted specifically or non-specifically. Three types of autophagy have been characterized: macro-, micro- and chaperone-mediated autophagy [10] (Fig. 1).

In macroautophagy, a double membrane forms around the cytosolic components to be degraded, forming an autophagosome. That then fuses with a nearby lysosome, giving rise to an autolysosome, where the intracellular components are degraded by acid hydrolases. Microautophagy does not involve the formation of autophagosomes, but describes the direct engulfment of the intracellular components by the lysosome itself. In chaperone-mediated autophagy, only soluble proteins are degraded. The soluble unfolded substrate proteins are transferred across the lysosomal membrane via the lysosomal-associated membrane protein 2 (LAMP-2A) integral membrane receptor and an accessory chaperone, the heat shock cognate protein Hsc70 [6,11].

When cells are under environmentally difficult conditions, autophagy helps survival of both the cell and the organism, notably in nutrient and growth factor deprivation, development, endoplasmic reticulum stress, microbial infection and diseases in which protein aggregates accumulate [6]. Autophagy is usually triggered under stress conditions, its main function being to help cell survival both by

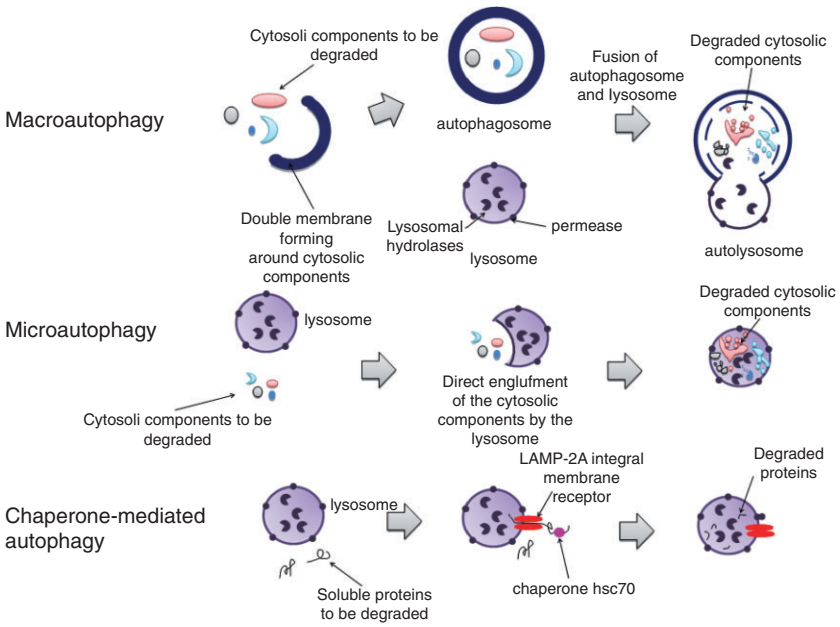

Fig. 1. Schematic diagram of the autophagic machinery.

supplying emergency amino acids and adenosine triphosphate (ATP) and by removing malfunctioning proteins and organelles. It may play a similar role to apoptosis and oncosis in minimizing not only the accumulation of damaged/senescent organelles and cells but also the spread of pathogens [12,13].

Classical apoptosis

Apoptosis (Greek for 'falling of leaves') defines a slow and active (ATP-dependent) process apparently designed for harmless/controlled disposal of cells/their débris via a fixed programmed death pathway, which involves activation of the 'caspase cascade'. Three mechanisms are known to trigger its activation: (1) a death receptor↔ligand-mediated 'extrinsic pathway'; (2) a mitochondrial or intrinsic pathway ultimately involving the production of active caspases and apoptosis-inducing factor (AIF); and (3) an endoplasmic reticulum-mediated mechanism [14]. In apoptosis, cells shrink; the chromatin is condensed, marginated and fragmented; the cytosol becomes denser. Eventually, the cytosol, the nucleus and its DNA all fragment; there is blebbing of the plasma membrane and the cell disintegrates into apoptotic bodies (cell organelles and/or nuclear material surrounded by an intact plasma membrane), which are phagocytosed and destroyed rapidly without risk of autoimmunization. Apoptosis, in particular, plays important roles in shaping organs during development, in the homeostasis and integrity of tissues, as well as in protection against cancers, autoimmune disorders and mitochondrial diseases [15].

Oncosis

Oncosis (Greek for swelling), 'cell murder', is a much faster process than apoptosis, only one minor variant of which is caspase-dependent. A catabolic degenerative process, it is triggered by severe pathological injury (e.g. by oxidative stress, inhibitors of ATP synthesis, detergents, heat shock) and does not require ATP. Oncosis usually instigates a local immune/inflammatory response [16], and rapidly destroys damaged cells. Thus it is very useful in stopping the spread of pathogens and preventing damaged cells from lingering.

In the past, the term 'necrosis' has been incorrectly used to also include oncosis [14,17]. Necrosis should be used to describe dead cells and does not encompass the route through which cell death occurred.

Autophagy and immunity

Autophagy is important in the elimination of pathogens – mainly by their direct engulfment, although more sophisticated mechanisms have also been described.

Autophagy has been linked to the initiation of innate immune responses. These are our first line of defence against pathogens and tissue injury. They comprise several reactions that isolate and destroy pathogens and restore tissue homeostasis. Pathogen-associated molecular patterns (PAMPs) can be detected by pattern-recognition receptors (PRR) expressed mainly on antigen-presenting cells, as proposed by Janeway in 1989 [18]. The PRRs thus identified include Toll-like receptors (TLRs), retinoic acid inducible gene I (RIG-I)-like and nucleotide oligomerization domain (NOD)-like receptors. TLR-3, -7 and -9 recognize microbial patterns inside endosomes [double- or single-stranded RNAs or cytosine-guanine-dinucleotide (CpG) DNA], whereas TLR-2, -4 and -5 recognize bacterial peptidoglycans, lipopolysaccharides and flagellins on cell surfaces [19]. Once stimulated, these receptors activate signalling pathways and initiate anti-pathogen responses. However, innate immune responses can also be alerted by exposure to endogenous

danger stimuli or danger-associated molecular patterns (DAMPs), as proposed by Matzinger in 1994 [20]. These DAMPs include intracellular proteins released from necrotic cells during tissue injury and other molecules such as ATP and DNA.

The first evidence came from studies with vesicular stomatitis virus; they showed that the autophagic machinery can deliver viral material to the endosomes of plasmacytoid dendritic cells via membrane fusion. These viral nucleic acids then bind to endosomal TLR-7 [13], and thus stimulate innate immune activation and especially type I interferon production [21,22].

Recent evidence suggests overlap between autophagy and inflammasome pathways, two important players in the innate immune system. The inflammasome is a stranger- and danger-sensing multi-protein complex, which can activate an inflammatory cascade [23] via interleukin (IL)-1 secretion. The mechanisms underlying the regulation of inflammation by autophagy are poorly understood. A recent study found that autophagic proteins control the inflammation induced by NOD-like receptor protein-3 (NALP-3) [24]; genetic depletion of two autophagy proteins, beclin-1 and light chain 3B (LC3B), enhanced the accumulation of dysfunctional mitochondria. It was proposed that autophagic proteins regulate NALP-3-dependent inflammation by maintaining mitochondrial integrity [24,25]. Another autophagic protein, Atg16L1, which is implicated in Crohn's disease, was found to regulate endotoxin-induced activation of inflammasomes [26]. These findings highlight the potential contribution of the autophagic machinery to the regulation of inflammation.

Autophagy has also been implicated in adaptive immune responses [27–33]. These are antigen-specific and involve human leucocyte antigen (HLA) class I-restricted CD8 and HLA class II-restricted CD4 T cells. Endogenously synthesized antigens are processed by proteasomes; the resulting fragments are loaded onto HLA-class I molecules within the endoplasmic reticulum before presentation on the cell surface and recognition by CD8 T cells. HLA class II molecules, by contrast, were thought to present epitopes only from exogenous antigens to CD4 T cells. However, autophagy seems to provide an intriguing alternative route for endogenous antigens to access HLA class II molecules. For example, viral antigens in autophagosomes fuse with late endosomes and then load onto their class II molecules for presentation to CD4 T cells. The first genetic evidence for this came from a study where inhibition of autophagy decreased efficient class II presentation of peptides derived from endogenously synthesized viral Epstein–Barr virus-encoded nuclear antigen (EBNA-1) [32].

Autophagy in defence against pathogens

Viral and bacterial peptides are targeted to autophagosomes via a process called xenophagy ('to eat what is foreign') [34]. This process is mediated mainly by a set of adaptor molecules that target ubiquitin-tagged cargo to the autophagic machinery. The mechanisms are not understood fully, but the process seems highly selective and also capable of orchestrating powerful adaptive immune responses [22].

Ubiquitination of bacteria is mediated by autophagy (Atg) and adaptor proteins [35]. Adaptors such as p62 contain binding sites for both ubiquitinated cargo and LC-3, a protein localized in the autophagosome membrane [36]. Degradation of intracellular bacteria, e.g. group A *Streptococci*, depends on Atg-5 [37]. Atg genes also protect mice against infection by *Toxoplasma gondii* [38], *Listeria monocytogenes* and *Salmonella enteritidis* [39,40]. However, some bacteria use devious strategies to escape autophagic degradation, for example by mimicking host cell organelles [41].

Our knowledge of viral targeting is even less complete. The best-studied infection in this context is with Sindbis virus, a member of the alphavirus genus with a positive-stranded RNA genome. Interestingly, it is used in mouse models of human viral encephalitis. Alphavirus infection of the CNS is controlled by neuronal over-expression of Beclin-1, the first identified human autophagy protein, an analogue of yeast Atg6 [42].

Another neurotropic virus is *Herpes simplex* virus (HSV-1), a double-stranded DNA α-herpes virus, one cause of sporadic viral encephalitis. Interestingly, in mice and humans, that depends critically upon its neurovirulence factor infected cell protein 34·5 (ICP34·5) [43], which inhibits host autophagy [44]. Infection of mice with ICP34·5-deficient virus led to increased neuronal survival and lower viral load in the CNS [44]. Other viruses interfering with the autophagy machinery include the neurotropic β-herpes virus cytomegalovirus (CMV) and human herpes virus-8 (HHV-8) viruses [Kaposi's sarcoma-associated herpesvirus (KSHV)] and the γHV68 virus [25,29,45–47]. HCMV-infected cells are rendered resistant to rampamycin-induced autophagy by the activation of the mammalian target of rampamycin (mTOR) signalling pathway, which regulates cell homeostasis [46]. In contrast, HHV-8 enhances the autophagic process [48]. It encodes the protein RTA (replication and transcription factor), which is pivotal for lytic replication of the virus. The murine γHV68 mediates evasion from autophagy. The virus encodes a Bcl2 homologue, which counteracts autophagy [47].

Viruses may not only contribute directly but also indirectly to neurodegeneration; for example, by interfering with housekeeping functions such as basal autophagy within the CNS. That may lead to the accumulation of protein aggregates, and thus contribute to neurodegeneration [7,8]. It was proposed that Alzheimer's disease progression may be accelerated by HSV-1-mediated inhibition of autophagy, resulting in reduced degradation of components of amyloid plaques [49]. Clearly, decoding mechanisms employed in persistent virus infections that hamper autophagy also highlights the need for effective treatments against

neurodegenerative disorders, either targeting the virus or the autophagy machinery.

Impaired autophagy in neurodegenerative diseases

Many neurodegenerative diseases are either inherited/manifest early in life or else develop sporadically with age. For example, in Parkinson's, Alzheimer's and motor neurone diseases, there is progressive loss of structure and function of neurones, often with characteristic intracellular protein aggregates. Being so large and long-lived, neurones rely heavily on clearance of damaged organelles and faulty proteins to prevent cumulative neurotoxicity [3]. Typical findings are of aggregated α-synuclein in the Lewy bodies in Parkinson's, tau-containing neurofibrillary tangles in Alzheimer's and intracellular inclusions of mutant huntingtin in Huntington's disease brains. The role of autophagy in the removal of apparently toxic aggregates is of great interest, as it is becoming clear that distinct anomalies in autophagy occur in each disorder, as summarized in Table 1. Neurodegeneration can also occur in head trauma, multiple sclerosis, schizophrenia, epilepsy and stroke, so any novel therapeutics might have even wider applications.

Alzheimer's disease is characterized by senile plaques, which contain β-amyloid aggregates, and intracellular neurofibrillary tangles containing tau. It has been linked to deregulation of autophagy; electron microscopy showed extensive accumulation of immature autophagic vacuoles within neuritic processes, including synaptic terminals [50]. Beclin-1, which is needed for the initiation of autophagosome formation, is reduced in patients with Alzheimer's disease [51], which might hold the key to the defective autophagy there.

Huntington's disease is an autosomal dominant neurodegenerative disorder. Inefficient cargo removal has been described in its animal models, together with empty autophagosomes [52]. Disposal of protein aggregates, faulty organelles and even pathogens by macroautophagy is a more delicate process than appreciated previously, and shows selectivity in the sequestration of different autophagic cargoes [53]. This selectivity is achieved by post-translational modifications such as polyubiquitination, which is recognized by adaptors. The sequestered cargo is then degraded in lytic compartments (e.g. lysosomes, endosomes). This process seems to be affected in Huntington's disease, but further studies are needed for a more comprehensive picture.

Parkinson's disease is the most common neurodegenerative movement disorder, and one of the first to be linked to autophagy. It is characterized by selective loss of neurones in the substantia nigra and the presence of Lewy bodies, abnormal aggregates containing α-synuclein inside nerve cells, whose formation would normally be prevented by autophagy [54]. Here, too, autophagosomes accumulate, as in Alzheimer's disease, again implying impaired lysosomal degradation.

Pharmacological modulation of autophagy

Autophagy inhibitors are an active area of research in the cancer field and autophagy is a drug target for cardioprotection [55,56]. Statins [or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors] are used in the prevention of cardiovascular disease. They lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Interestingly, prophylactic treatment with simvastatin increased autophagy in neuronal cells after neonatal hypoxia–ischaemia, and suggests a potential protective mechanism in the early stage of brain injury [57]. Lithium, used medically as a mood-stabilizing drug in the treatment for bipolar disorder, also impacts upon the autophagy machinery. It shows neuroprotective action and a beneficial effect on motor neurone survival, which is attributed partially to its activation of autophagy, in addition to its anti-apoptotic and anti-oxidant properties [58,59].

Conclusion

Safe cell death/disposal of débris is crucial to keep us alive and healthy. Our body uses autophagy and apoptosis as clearing mechanisms to eliminate malfunctioning, damaged, excess and/or pathogen-infected cells/débris that might otherwise be harmful/autoimmunogenic. However, if uncontrolled cell death can, instead, be deleterious. Much remains to be uncovered about how autophagy operates in the context of neurodegeneration and neuroinflammation.

Table 1. Autophagy dysregulation in neurodegenerative disorders.

Disease	Observation	Impaired autophagy	Reference
Alzheimer's disease	Accumulation and impaired clearance of autophagic vacuoles	Yes	**50** Nixon RA *et al.*, J Neuropathol Exp Neurol 2005; **64:** 113–22 **51** Jaeger PA and Wyss-Coray T, Arch Neurol 2010; **67:** 1181–84.
Huntington's disease	Failed cargo-recognition	Yes	**52** Martinez-Vicente M *et al.*, Nat Neurosci 2010; **13:** 567–76.
Parkinson's disease	Defects in activation of autophagy and in lysosomal clearance	Yes	**6** Mizushima N *et al.* Nature 2008; 451: 1069–1075. **54** Webb JL *et al.*, J Biol Chem 2003; **278:** 25009–13.

Autophagy may accompany cell death but may also involve engulfment and degradation of organelles and proteins, which helps the cell to survive. Its modulation may be important in preventing or treating neurodegenerative conditions such as Alzheimer's, Parkinson's, motor neurone and Huntington's diseases and others with neurodegenerative components. This area warrants further study as it holds new therapeutic potential.

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Disclosure

The authors have nothing to disclose.

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