Neurobiology of Disease 43 (2011) 38–45

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Autophagy failure in Alzheimer's disease—locating the primary defect

Ralph A. Nixon [a,b,c,*], Dun-Sheng Yang [a,b]

[a] Center for Dementia Research, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA
[b] Department of Psychiatry, New York University Langone Medical Center, New York, NY, USA
[c] Department of Cell Biology, New York University Langone Medical Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 9 November 2010
Revised 31 December 2010
Accepted 27 January 2011
Available online 3 February 2011

Keywords:
Alzheimer's disease
Autophagy
Lysosome
Autolysosome
Dystrophic neurite
Proteolysis
Presenilin 1
Mouse model
Lysosomal storage disorders

ABSTRACT

Autophagy, the major degradative pathway for organelles and long-lived proteins, is essential for the survival of neurons. Mounting evidence has implicated defective autophagy in the pathogenesis of several major neurodegenerative diseases, particularly Alzheimer's disease (AD). A continuum of abnormalities of the lysosomal system has been identified in neurons of the AD brain, including pathological endocytic pathway responses at the very earliest disease stage and a progressive disruption of autophagy leading to the massive buildup of incompletely digested substrates within dystrophic axons and dendrites. In this review, we examine research on autophagy in AD and evaluate evidence addressing the specific step or steps along the autophagy pathway that may be defective. Current evidence strongly points to disruption of substrate proteolysis within autolysosomes for the principal mechanism underlying autophagy failure in AD. In the most common form of familial early onset AD, mutant presenilin 1 disrupts autophagy directly by impeding lysosomal proteolysis while, in other forms of AD, autophagy impairments may involve different genetic or environmental factors. Attempts to restore more normal lysosomal proteolysis and autophagy efficiency in mouse models of AD pathology have yielded promising therapeutic effects on neuronal function and cognitive performance, demonstrating the relevance of autophagy failure to the pathogenesis of AD and the potential of autophagy modulation as a therapeutic strategy. This article is part of a Special Issue entitled "Autophagy and protein degradation in neurological diseases."

Contents

Introduction

Alois Alzheimer's discovery of neurofibrillary tangles, and their presence together with senile plaques in the brain of a patient with progressive dementia, established the two neuropathologic features that still define Alzheimer's disease (AD). Coinciding with these seminal studies were more detailed descriptions of senile plaques by Marinesco, Fischer, and even Ramon y Cajal (Garcia-Marin et al., 2007; Goedert, 2009), which emphasized the widespread incidence of gross focal swellings of axons and possibly dendrites, termed dystrophic neurites, that were particularly profuse within senile plaques but were also seen throughout affected regions of the parenchyma. Although dystrophic neurites were originally detected

* Corresponding author at: Nathan Kline Institute, 140 Old Orangeburg Rd, Orangeburg, NY 10962, USA.
E-mail address: nixon@nki.rfmh.org (R.A. Nixon).
Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2011.01.021

by Alzheimer from their argyrophilia, reflecting pathologically hyperphosphorylated cytoskeletal proteins, dystrophic swellings in the AD brain were subsequently shown to be filled mainly with autophagic vacuoles—vesicular compartments of the autophagic-lysosomal pathway (Nixon et al., 2005). In well-preserved biopsied AD neocortex, ultrastructural and immunogold labeling studies have distinguished not only dense lysosomes (Terry et al., 1964) but also various types of autophagic vacuoles (AVs) including autophagosomes, amphisomes, multilamellar bodies, and autolysosomes, representing "intermediate" stages in the progression of autophagy (Nixon et al., 2005). These observations suggested that the normally efficient autophagic process in neurons is stalled in AD. In recent studies, investigators have begun to pinpoint the site or sites at which autophagy may be disrupted and explore the possibility that modulating specific steps in this process could have a therapeutic impact on pathology and function in AD mouse models. In this review, we consider evidence indicating that neuronal autophagy is defective in AD and evaluate data addressing mechanisms underlying this defect and possible implications for the pathogenesis and therapy of AD.

The stages of autophagy

The term autophagy refers to all processes in which components of the cell are degraded in lysosomes/vacuoles and recycled (Klionsky et al., 2010). Based on how substrates are delivered to the lysosomal compartment, autophagy is classified into three general subtypes in most mammalian cells: chaperone-mediated autophagy (CMA), microautophagy and macroautophagy (Cuervo, 2004; Mizushima et al., 2008). In CMA (Cuervo, 2010), cytosolic proteins containing a KFERQ motif are selectively targeted to the lysosomal lumen for degradation. In a second process called microautophagy, small quantities of cytoplasm are non-selectively introduced into lysosomes when the lysosomal membrane invaginates and pinches off small vesicles for digestion within the lumen. Finally, a third pathway, macroautophagy, conserved from yeast to mammals, mediates large-scale degradation of cytoplasmic constituents including organelles (He and Klionsky, 2009). Macroautophagy, referred to by the general term autophagy in this review, is considered the greatest contributor to the overall autophagy rate under most conditions. This process is regulated by signaling cascades mediated through the liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) or the class I phosphatidylinositol 3-kinase (PI3K)/Akt pathways which converge on the mammalian target of rapamycin (mTOR) kinase through TSC/Rheb (tuberous sclerosis complex/Ras homolog enriched in brain) (Hay and Sonenberg, 2004; He and Klionsky, 2009). The inhibition of mTOR sets in motion a sequence of events coordinated by complexes of autophagy-related (Atg) proteins that initiate the formation of the autophagosome (Diaz-Troya et al., 2008; Levine and Kroemer, 2008).

Autophagy begins when an "isolation membrane" is created from a pre-autophagosomal structure (PAS) or phagophore, such as the ER-derived cup-shaped omegasome, and sequesters a region of cytoplasm to form a double-membrane-limited autophagosome (Axe et al., 2008; Geng et al., 2010; Hailey et al., 2010; Hayashi-Nishino et al., 2009; Itakura and Mizushima, 2010; Ravikumar et al., 2010; Tian et al., 2010; Xie and Klionsky, 2007). The outer membrane of the autophagosome then fuses with a lysosome or a late endosome to form either an autolysosome or an amphisome, respectively, thereby initiating the digestion of sequestered material by a range of acidic hydrolases (Eskelinen, 2005; Fader and Colombo, 2009; Gordon and Seglen, 1988; Liou et al., 1997; Noda et al., 2009). Acidification of autolysosomes by vacuolar [H+] ATPase (v-ATPase), a proton pump assembled on the lysosome membrane, is crucial for activating cathepsins and effecting proteolysis of substrates (Yoshimori et al., 1991). The completion of substrate digestion within autolysosomes ultimately yields lysosomes, which are smaller, less dense vesicles containing mainly lysosomal hydrolases (Fig. 1) (Nixon, 2007; Yu et al., 2010). While the term "maturation" is often used to describe the fusion between autophagosomes and lysosomes/late endosomes (Noda et al., 2009), maturation is a continuous process that includes completion of substrate degradation within autolysosomes and the restoration of lysosomes. The functional relationship among different stages of autophagy is underscored by the recent finding that the beginning of this process (i.e., autophagosome formation) and its end (the reformation of lysosomes) are both regulated by mTOR (Yu et al., 2010). In addition to referring to the specific subtypes of autophagy-related vesicular structures, we will also use the term autophagic vacuoles (AVs) as the general term for autophagy-related vesicular structures that include autophagosomes, amphisomes, multilamellar bodies, and autolysosomes.

Since its very early descriptions, autophagy has been defined as the lysosomal *digestion* of a cell's own cytoplasmic material, and not simply as the sequestration of these components. Appreciation of this notion has become particularly critical to understanding how autophagy may be involved in disease states because impairments of any of the steps in autophagy may result in a diminished turnover of specific autophagy substrates. Identifying which step along the autophagy pathway may be defective in a given neurodegenerative disease, therefore, requires an evaluation of autophagosome formation, autophagosome clearance by lysosomes, and autophagic flux—the rate at which a given substrate cycles through the entire autophagy process. Autophagic flux reflects a dynamic balance between the rates of substrate sequestration and degradation (Fig. 2) (Chu, 2006; Wong and Cuervo, 2010).

Autophagy pathology in the AD brain is extensive

Abnormalities of lysosomal system function in the AD brain range from the earliest known disease-specific pathology in the disease, which involves the endocytic pathway (Nixon and Cataldo, 2006), to the most abundant pathology in the AD brain involving the autophagic pathway, which is the main focus of this review. The autophagy pathology of AD, including accumulated AVs of all types and the numbers of dystrophic neurites containing these AVs, is uniquely extensive when compared to that in other aging-related neurodegenerative diseases (Nixon and Cataldo, 2006; Nixon et al., 2005). The near complete replacement of normal cytoplasmic contents by AVs in dystrophic neurites and the increased frequency of AVs in less extensively affected neurites (Fig. 3), together with the uniquely high number of dystrophic neurites in senile plaques and elsewhere throughout the AD brain, represents an enormous "burden" of undigested or partially digested proteins. This burden of waste proteins is comparable to that seen in certain primary lysosome storage disorders (LSDs), which are associated with severe neurodegeneration in early life (Nixon et al., 2008). Interestingly, neurofibrillary tangles and increased amyloidogenic processing of amyloid precursor protein (APP) as well as neuritic dystrophy, have been identified in certain primary LSDs as well as AD and potentially represent clues about common pathogenic mechanisms (see below). Autophagy-related pathology, including lesser degrees of AV "storage" in neurons, has also been increasingly recognized in other late-onset neurodegenerative diseases (Anglade et al., 1997; Liberski et al., 1995; Rudnicki et al., 2008; Yue et al., 2002; Zhou et al., 1998), although the severity and extent of the neuritic dystrophy in AD (Fig. 3) (Masliah et al., 1993; Nixon et al., 2005; Schmidt et al., 1994; Suzuki and Terry, 1967) distinguish it from these other aging-related neurodegenerative diseases (Benzing et al., 1993).

It is noteworthy that the composition of organelles within dystrophic swellings in the AD brain also differs from that seen in the many other disorders characterized by neuroaxonal dystrophy. In