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Review

The elimination of accumulated and aggregated proteins: A role for aggrephagy in neurodegeneration

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ABSTRACT

The presence of ubiquitinated protein inclusions is a hallmark of most adult onset neurodegenerative disorders. Although the toxicity of these structures remains controversial, their prolonged presence in neurons is indicative of some failure in fundamental cellular processes. It therefore may be possible that driving the elimination of inclusions can help re-establish normal cellular function. There is growing evidence that macroautophagy has two roles; first, as a non-selective degradative response to cellular stress such as starvation, and the other as a highly selective quality control mechanism whose basal levels are important to maintain cellular health. One particular form of macroautophagy, aggrephagy, may have particular relevance in neurodegeneration, as it is responsible for the selective elimination of accumulated and aggregated ubiquitinated proteins. In this review, we will discuss the molecular mechanisms and role of protein aggregation in neurodegeneration, as well as the molecular mechanism of aggrephagy and how it may impact disease. This article is part of a Special Issue entitled "Autophagy and protein degradation in neurological diseases."

Contents

Introduction . . . 17
Protein aggregation in neurodegeneration . . . 18
The formation of protein inclusions in neurons . . . 18
The toxicity of protein aggregates . . . 19
The accumulation of ubiquitinated proteins . . . 20
Mammalian macroautophagy . . . 20
Nucleation and expansion . . . 21
Maturation . . . 22
Aggrephagy — the mammalian counterpart to Cvt? . . . 22
The yeast Cvt pathway . . . 22
Aggrephagy . . . 23
Regulation of aggrephagy . . . 24
Concluding remarks . . . 24
References . . . 24

Introduction

Intracellular protein aggregation is a hallmark of a wide array of neurological disorders, including tauopathies, synucleinopathies, TDP-43 proteinopathies and polyglutamine disorders. Although the

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relationship between protein aggregation with disease pathogenesis is unclear (Caughey and Lansbury, 2003; Jellinger, 2009; Ross and Poirier, 2005; Spires-Jones et al., 2009; Williams and Paulson, 2008), several studies using mouse genetics, lentiviral technologies and RNA interference have shown that elimination of the accumulation-prone proteins permits symptomatic reversal in different neurodegenerative models (Harper, 1996; Lin et al., 2009; Regulier et al., 2003; Xia et al., 2004; Yamamoto et al., 2000; Zu et al., 2004). Often correlating with the regression of symptoms is the disappearance of aggregated protein, indicating that neurons can eliminate these proteins, despite their heterogeneous structure and cellular distribution. Moreover, while these studies do not establish a causative link between protein aggregation and neurodegeneration, they clearly suggest that elimination of accumulated proteins may alleviate underlying cellular dysfunction, and potentiate recovery across different disorders.

So, how are aggregation-prone proteins disposed of by neurons? Unlike many cells used to study protein aggregation, neurons are post-mitotic and cannot dilute their cytosol by cell division or asymmetrically distribute inclusions (Rujano et al., 2006). Instead, neurons must rely upon two distinct cellular mechanisms of protein degradation: the ubiquitin–proteasome system (UPS) and autophagy-mediated lysosomal degradation. The UPS is a highly conserved system by which proteins are targeted to the proteasome upon covalent modification by ubiquitin (Glickman and Ciechanover, 2002). Studies examining the role of the UPS in neurodegeneration are extensive, and are covered elsewhere in this issue. In this review, we will discuss the emerging importance of lysosome-mediated degradation of aggregated cytosolic proteins by macroautophagy. Predominantly known as a non-selective degradative response to starvation, macroautophagy also is required for the selective elimination of organelles, infective agents, and more recently, protein aggregates. In this review, we will examine how aggrephagy, the selective elimination of aggregates by macroautophagy, can play a role in eliminating protein aggregates that have been implicated in neurodegenerative disease.

Protein aggregation in neurodegeneration

The ability of proteins to aggregate or come together as a larger complex is a fundamental process through which proteins exert their normal function. In the context of neurodegeneration, protein aggregates generally refer to oligomeric complexes of misfolded or unfolded proteins that can be structured or amorphous, which are insoluble and metabolically stable under physiologic conditions (Kopito, 2000). Together with the pattern of neuronal dysfunction and degeneration, the presence of these structures, termed histologically as intracellular inclusions, bodies, tangles or threads, is often part of the diagnostic repertoire of a pathogenic process (Table 1). Their abnormal presence and prevalence across numerous disorders have led to models implicating their role in pathogenesis, and have begun to influence how disorders are classified. For example, the discovery of TDP-43 as the major component of the ubiquitinated inclusions in amyotrophic lateral sclerosis (ALS) (Arai et al., 2006; Tan et al., 2007; Zhang et al., 2008) and forms of frontotemporal lobar degeneration (FTLD-TDP) (Liscic et al., 2008; Mackenzie et al., 2010) has strengthened the link between these diseases.

Most of our fundamental understanding of protein aggregation has been derived from animal models, cell lines and in vitro studies. From these studies, protein aggregation has emerged as a complex multistep process reflected in the variability of protein aggregate structure, size and intracellular localization (Woulfe, 2008). Since all of these variables can be observed within a single pathologic sample (DiFiglia et al., 1997; Galvin et al., 2001; Gray et al., 1987; Jellinger, 2009; Katsuse et al., 2003; Liscic et al., 2008), it is critical to keep in mind which structure we are examining when studying pathogenesis.

The formation of protein inclusions in neurons

The maturation of misfolded or unfolded protein into protein aggregates can vary across different disorders, but generally protein aggregation results from proteins that fold into an abnormal conformation, leading to the formation of oligomeric intermediates (Merlini et al., 2001). These intermediates can aggregate and further mature into small protein aggregates. These small protein aggregates can form into a wide variety of structures (Dobson, 2003). Due to their structural stability, amyloid fibrils are the most commonly studied structure, although they may not be the most prevelant (Dobson, 2003). These smaller aggregates, both structured and unstructured, continue to grow and multimerize into larger aggregates or inclusions (Grune et al., 2004; Kopito, 2000). Different kinds of aggregates can be found in the neuropil, soma and nuclei, depending upon the protein and disorder examined (Table 1) (DiFiglia et al., 1997; Geschwind, 2003; Gray et al., 1987; Gutekunst et al., 1995; Jellinger, 2009; van der Zee et al., 2007; Wakabayashi and Takahashi, 2006).

Larger cytoplasmic inclusions can evolve further and coalesce into an aggresome, a pericentriolar, membrane-free cytoplasmic inclusion formed specifically at the microtubule organizing center (MTOC) containing misfolded, ubiquitinated proteins caged within intermediate filaments such as vimentin or keratin (Johnston et al., 1998; Kopito, 2000). It has been proposed that the aggresome is a protective structure, formed to sequester proteins that cannot be degraded by the proteasome and packaged for degradation by autophagy (Johnston et al., 1998; Kopito, 2000). Although studies in heterologous systems clearly demonstrate that disease-causing proteins become packaged in this manner (Iwata et al., 2005; Johnston and Madura, 2004; Waelter et al., 2001; Wong et al., 2008), this may not be the case for neurons. For instance, neuronal cytoplasmic inclusions (NCIs) are ubiquitinated but rarely vimentin-positive, possibly because vimentin is expressed predominantly in immature neurons and become replaced by neurofilaments (NFs) as neurons mature (Bennett et al., 1981; Cochard and Paulin, 1984). Nonetheless, in multiple systems atrophy, glial cytoplasmic inclusions are also vimentin-negative (Wakabayashi and Takahashi, 2006) (Table 1). Further, abnormal accumulation of NFs is found across several neurodegenerative diseases and mutations within the NF light chains have been implicated in their accumulation in Charcot Marie Tooth Type 2 (CMT2) neuropathies; however, NFs are the major constituent of the inclusion and do not form a 'cage' as described for an aggresome (Perrot and Eyer, 2009; Roy et al., 2005). Moreover, although the readily dividing, stable cell lines used to study protein aggregation possess MTOCs, studies indicate that after neurogenesis (Doxsey et al., 2005; Wang et al., 2009), neuronal centrosomes no longer function as MTOCs, and no longer extend microtubules or recruit γ-tubulin (Stiess et al., 2010). Despite the lack of MTOCs, however, microtubule nucleation is still required for proper neuronal function and maintenance (Ahmad et al., 1994; Yu et al., 1994), but rather than at a central perinuclear point, microtubules nucleate across multiple sites throughout the cell (Stiess et al., 2010). Larger inclusions therefore still may form in a microtubule-dependent manner (McNaught et al., 2002), but may not fulfill the strict definition of an aggresome. Moreover, the lack of a single MTOC also may explain why aggregates are not limited to the soma.

One indication that neurons create aggresome-like structures is found in studies with histone deacetylase 6 (HDAC6). HDAC6 is a ubiquitin-binding microtubule deacetylase, that is required to recruit ubiquitinated, misfolded proteins to the aggresome (Iwata et al., 2005; Kawaguchi et al., 2003). HDAC6 may not be a structural element, however, since depletion of HDAC6 did not disrupt preformed inclusions (Iwata et al., 2005). Unfortunately, reports on HDAC6 immunoreactivity of NCIs in disease have been limited — although HDAC6-positive Lewy Bodies from neocortical and brain stem samples from Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB) brains, respectively, were reported (Kawaguchi et al.,