

Could a Common Mechanism of Protein Degradation Impairment Underlie Many Neurodegenerative Diseases?

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ABSTRACT: At the cellular level, many neurodegenerative diseases (NDs), often considered proteinopathies, are characterized by the accumulation of misfolded and damaged proteins into large insoluble aggregates. Prominent species that accumulate early and play fundamental roles in disease pathogenesis are amyloid β ($A\beta$) and tau in Alzheimer disease, α -synuclein (α -syn) in Parkinson disease, and polyQ-expanded huntingtin (Htt) in Huntington disease. Although significant efforts have focused on how the cell deals with these protein aggregates, why is it that these misfolded proteins are not degraded normally in the first place? A vast body of literature supports the notion that the cell's protein degradation system for individual proteins—the ubiquitin proteasome system (UPS)—does not function sufficiently in many NDs. The proteasome itself has received significant focus for years due to its obvious failure to degrade misfolded proteins in ND, but no general mechanism has been uncovered. We have recently found that specific pathologically relevant oligomers can potently and directly inhibit the proteasome. What is most interesting is that the misfolded protein's primary amino acid sequence was irrelevant to its ability to inhibit. Instead, the culprit is the 3-dimensional shape of the misfolded oligomers. It turns out that many misfolded proteins in ND can take on this proteasome-impairing shape suggesting that there could be a common mechanism for UPS impairment in many NDs. The proteasome is already an important target for treating cancer, could it also be targeted to broadly treat ND?

KEYWORDS: Neurodegeneration, oligomers, protein degradation, proteasome, ubiquitin proteasome pathway

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Ubiquitin Proteasome System Impairment in Neurodegenerative Diseases and Aging

The proteasome in neurodegenerative diseases

A vast number of human, animal model, and cell model studies have indicated that the ubiquitin proteasome system (UPS) is impaired in various neurodegenerative diseases (NDs)—Alzheimer, Parkinson, Huntington, prion, and others. It is not understood why the proteasome fails to rid the cell of such misfolded proteins before they oligomerize, eventually forming large aggregates. One explanation is, as proteasome activity decreases with age, the cell is more susceptible to protein accumulation and aggregation later in life, which is when NDs primarily occur, and a wide range of literature supports this hypothesis.^{1–5} In fact, impairment of the proteasome by mutagenesis or pharmacologic inhibition in mice, by itself, can cause pathologies and symptoms associated with ND.⁶ In addition, several well-known genetic causes of Alzheimer disease (AD), Parkinson disease (PD), and Amyotrophic Lateral Sclerosis (ALS) are due to disruptions of the UPS pathway. Currently, we do not understand the age-related decline of UPS function but it does correlate with the late onset of many NDs. Proteasome function has been shown to be impaired in most NDs,^{7–12} and a recent genome-wide association study has identified the UPS as a risk pathway for AD.^{13,14} However, it has been difficult to elucidate the mechanism of inhibition that has been observed and though not all studies find UPS impairment the majority do.

In AD, the earliest pathologic hallmarks correlating with cognitive impairment is synaptic loss in the neocortex

and hippocampus, which play important roles in learning and memory. Interestingly, there is weak correlation between insoluble protein deposit pathology and disease severity, suggesting that other elements are responsible for neurotoxicity. The AD pathogenesis is characterized by the general accumulation of proteins, including misfolded metastable proteins such as amyloid β ($A\beta$) and tau. Even α -synuclein (α -syn), the primary misfolded protein found in PD, accumulates in subsets of AD. Huntingtin (htt) protein itself causes Huntington disease, when its poly-glutamine (polyQ) track gets expanded (ie, CAG repeat expansion), which slows its rapid degradation by the proteasome and it accumulates into aggregates. These misfolded proteins are normally degraded by the UPS (in their monomeric forms), which demonstrates that the UPS obviously does not function sufficiently to prevent their cellular accumulation in these diseases. It is now widely understood that small soluble oligomers play a key role in AD pathogenesis, which is based on their measurable toxicities and correlation with the severity of the disease.^{15–18} The most recent evidence indicates that specific small soluble $A\beta$ oligomers are likely to be the initiating neurotoxic species in AD.^{19–21} In a similar fashion, small soluble oligomers of tau are also found to be the earliest and most toxic misfolded forms of tau^{18,22–24} that contribute to disease severity. Although these 2 proteins spend most of their time isolated from each other, with $A\beta$ outside the cell and tau inside (especially in axons), they can also be found together. In fact, $A\beta$ is found in the cytosol with tau.²⁵ Recent evidence showing that toxic oligomers can travel along neuronal pathways from cell to



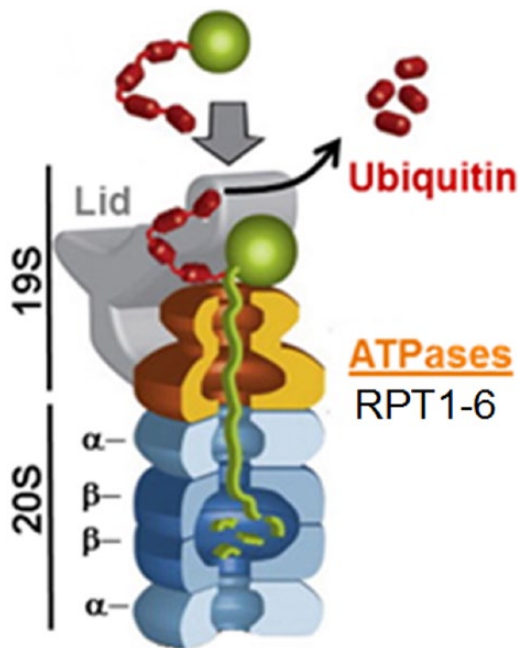


Figure 1. The 26S proteasome. Ubiquitinated proteins bound to the 19S are unfolded by the ATPases, which are injected through the opened gate and into the 20S for degradation. The 19S can bind to one or both ends of the 20S.

cell, in a transmissible-like fashion, also points to a small soluble oligomers as pathogenic agents.^{26–28} Consistent with this model, evidence also suggests that the incorporation of toxic oligomers into large aggregates is actually protective for the cell,^{29–31} as some large aggregates are inert. Of course, when aggregates become large enough they can have other toxicities due to their sheer size (eg, by disrupting membranes or sequestering proteostasis mechanisms such as protein chaperones or ubiquitin).³² Likewise, this narrative is also shared by oligomers of α -syn^{33,34} and htt,^{35,36} as evidence indicates that they too are likely the most neurotoxic species; however, this hypothesis has not been fully vetted especially regarding its generality. For instance, poly(GA)-containing aggregates can sequester and impair proteasomes,³⁷ whereas polyQ-containing aggregates do not.³⁸ Taken together, recent evidence supports a model whereby soluble oligomers, perhaps even in cooperation with one another, are the primary pathogenic drivers of ND.

At the risk of oversimplifying, AD is, to the best of our current knowledge, caused by the generation and accumulation of particular misfolded proteins that can form pathologic (or toxic) oligomers that impair synaptic function with associated mitochondrial dysfunction and ultimately neuronal cell death. Remarkably, the proteasome plays an essential role in maintaining all 3 of these critical cellular processes that go awry in AD—misfolded protein degradation, synaptic function (LTP/LTD),^{39,40} and mitochondrial function.^{41–43} Proteasome impairment has been pointed to as a major contributor to AD pathogenesis for years,^{23,44–48} as it has for many other NDs as well,^{7–12,49} but the evidence has only been correlative and no molecular mechanisms have been elucidated. Is it possible that

a common mechanism for UPS impairment could be shared by all of these diseases?

Normal Proteasome Function

The principle degradative machinery of the UPS is the 26S proteasome which is a 2.5MDa molecular machine that destroys the vast majority of proteins in the cell and its function is critical as it regulates essentially every cellular process.⁵⁰ It is composed of an adenosine triphosphatase (ATPase) regulatory complex (19S) that binds to one or both ends of the 20S core proteasome⁵¹ where proteolysis occurs (Figure 1). The 20S is a cylindrical complex with a hollow center. The 19S and its ATPases (orange) are required for ubiquitin-dependent degradation of folded substrates. As tightly folded proteins are too large to enter the 20S, the ATPases must use ATP to unfold proteins and inject them into the 20S for degradation. The outer rings of the 20S contain 7 α -subunits (α 1–7; light blue) with a central pore. Proteins must translocate through this pore to enter the degradation chamber of 20S (β -subunits; dark blue). The translocation of proteins through this channel constitutes a critical regulatory step in protein degradation as their passage is restricted by the N-termini of the α -subunits, which function as a substrate gate (Figure 1). The ATPase ring complex opens this gate, allowing substrate entry during protein degradation, thus regulating proteolysis.^{52–55} The C-termini of these ATPases have a 3-residue motif called the HbYX motif that inserts into pockets on the outer α -ring of 20S that allows the 19S to bind to the 20S and induce gate-opening.

A Common Mechanism of Proteasome Impairment

Considering that protein degradation by the proteasome requires a complex multistep process, we reasoned that perhaps pathologic oligomers impair one of the steps in protein degradation. Based on this, we investigated the hypothesis that there exists a universal mechanism of proteasomal impairment in NDs. We found that specific small soluble oligomers of 3 disease-related proteins (amyloid β , α -synuclein, and polyQ-expanded Huntingtin) potently inhibit proteasome function,⁵⁶ which as we have discussed is not a particularly novel concept. The novel finding was that the amino acid sequence of the protein is unimportant for its ability to inhibit the proteasome. Instead, it is the misfolded tertiary structure of the protein that is critical for proteasome inhibition. We found that small soluble oligomers of these 3 different proteins, when misfolded in a similar conformation, bind to and inhibit the proteasome with high affinity. These inhibitory oligomers are recognized by the A11 antibody, are known to be neurotoxic, and have been found in the brains of patients with different NDs. Our results thus introduce a general mechanism of proteasome impairment across the spectrum of NDs. We further demonstrated that these oligomers inhibit ubiquitin-dependent protein degradation by allosterically stabilizing the closed state of the 20S gate, thus inhibiting substrate entry.⁵⁶ In short, A11+ oligomers regardless of their primary sequence can prevent the 19S from

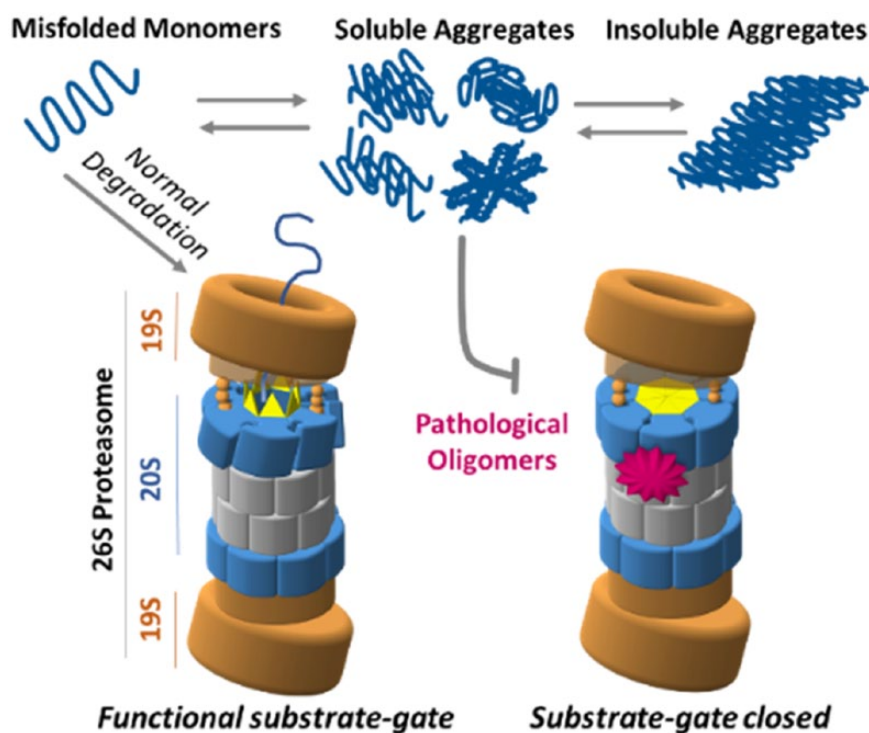


Figure 2. Pathologic oligomers from neurodegenerative diseases (NDs) inhibit the proteasome stabilizing its closed gate conformation. Misfolded proteins that oligomerize and are A11+ are potent allosteric inhibitors of the 20S and 26S proteasome, providing a general mechanism for proteasome impairment in protein misfolding disorders. Gate-opening by the HbYX mechanism directly opposes the allosteric inhibition by oligomers.

inducing gate-opening in the 20S, which is required for substrate injection and degradation. Because these inhibitory oligomers have been found in many different NDs, we posit that this mechanism of proteasome impairment constitutes a general and shared mechanism in these diseases. Moreover, as the inhibitory species of these ND-related proteins turns out to be a very specific oligomer with a specific conformation (only A11+ oligomers can inhibit), it is no surprise that some studies failed to find proteasome impairment because the A11+ oligomers only form under the proper conditions and may not be present in all model systems. Studies investigating proteasome impairment in NDs typically use heterogeneous oligomer preparation without accounting for the different conformational states of the oligomers. Further efforts will be required to determine the extent to which this impairment mechanism elicits a physiological response in model organisms and in humans, but this initial discovery provides a tangible and direct mechanism of proteasome impairment that can be investigated in ND with currently available approaches. These findings thus bolster therapeutic efforts that are already ongoing, to find activators of proteasome function, and this study provides a mechanistic framework to do so as the general structure of the 26S proteasome is known (Figure 2).

Restoring and Enhancing Proteasome function in NDs

Because the mechanism of inhibition by oligomers is due to an allosteric effect on the 20S proteasome, it is possible that small

molecules may reverse inhibition by oligomers. In fact, we have found that small peptides corresponding to the HbYX motif are able to reverse inhibition by these A11+ oligomers. However, the mechanism by which HbYX peptides induce gate-opening in the 26S core particle is not well-understood. Recent structural studies of the 26S proteasome indicate that understanding how the 19S ATPases induce gate-opening is not trivial, and future studies are required to clarify the mechanism. Nevertheless, the cryo-EM structure of the homologous archaeal 20S proteasome with the bound HbYX peptides has been generated.⁵⁵ In this structure, HbYX binding to intersubunit pockets on top of the α -ring induces a rotation in the α -subunits, repositioning the base of the gating residues from a closed to an open gate conformation. Understanding exactly where the A11+ oligomers bind to the 20S and elucidating the conformational changes that induce allosteric inhibition will be key to future efforts aimed at developing small molecules to reverse the inhibition. In the meantime, mutations to the 20S gating residues are also capable of inducing gate-opening and we showed that these mutations prevent allosteric inhibition by A11+ oligomers. Interestingly, a study by Choi et al showed that a similar gate-opening mutation enhances ubiquitin-dependent protein degradation in a human cell line. Future efforts are required to determine whether such mutations can alleviate proteasomal impairment in models of ND. A common mechanism of proteasome impairment in ND fits into the framework of what we have learned about protein degradation in ND in recent decades. If this mechanism is ubiquitous in ND and plays a substantial pathologic role, then

therapeutics that counteract this mechanism would be very exciting, as they could provide a method for treating a fundamental component of ND. Regardless of this specific impairment mechanism, finding ways to activate proteasome function would be expected to be beneficial to treat a root issue of these devastating proteinopathies.

Author Contributions

This article commentary is written and prepared by DMS.

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