

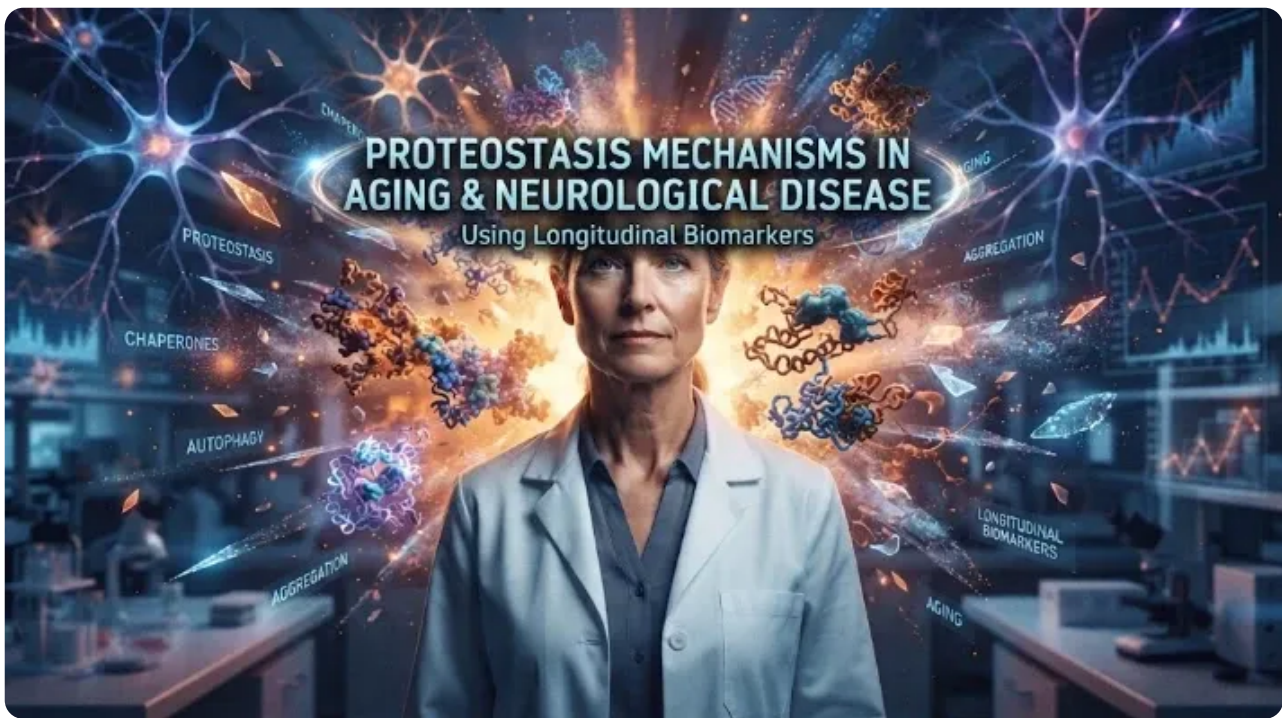
Proteostasis Mechanisms through Aging Biology in Neurological Disease Using Longitudinal Biomarkers

Sadia Tasneem

Aug 3, 2025

Abstract

The article examines proteostasis as a declining biological reserve that links aging with neurological disease. Neurons depend on chaperones, the ubiquitin–proteasome system, autophagy, lysosomes, translation control, and mitochondrial quality maintenance over decades. Age-related slowing of protein turnover can reduce the margin for handling misfolded or aggregation-prone proteins such as amyloid beta, tau, alpha-synuclein, TDP-43, and polyglutamine proteins. The article emphasizes selective cellular vulnerability, arguing that different neuronal populations tolerate proteostatic stress differently. Single-nucleus multiomics, spatial proteomics, longitudinal fluid biomarkers, imaging, and induced neural models are proposed to identify the transition from compensatory stress response to irreversible damage. Biomarkers such as neurofilament light, GFAP, and phosphorylated tau require temporal and systemic context. Experimental challenge and rescue assays can assess reserve directly. The article concludes that neurodegeneration reflects not only protein accumulation but progressive loss of the capacity to maintain molecular quality control.



Protein, which is continually synthesized, folded, transported, modified, and removed, is vital to maintain the life of neurons for decades. That long life time poses a special proteostasis problem. Damage to a short-lived cell can be eliminated upon replacement, but repair or removal of molecular damage, and maintenance of synapses and circuitry, often demands special care for neurons. Growing with age, this margin of safety is reduced, which may account for the ubiquity of disturbed protein homeostasis in neurodegenerative disease.

There are several coordinated systems involved in proteostasis. Proteins' molecular chaperones assist in folding and inhibit aggregation. Ubiquitin proteasome system degrades a lot of damaged or short-lived proteins. Larger protein assemblies and organelles are eliminated by autophagy and lysosomal pathways.

Translation control prevents new protein synthesis when stress is applied. If one arm fails, the other arms may be overloaded, which leads to local stress to impact the entire network.

This balance alters with age before the onset of disease. Studies on protein turnover in older brain tissue have revealed that protein half-lives are longer, on average, and that protein metabolism pathways are selectively altered in the brain of ageing animals. Whilst not always a bad thing, slower turnover will conserve energy, but can also let damaged molecules hang around for a longer period of time. The question is whether turnover stays in balance with the quality of proteins and cell needs.

The decline in Proteostasis is particularly relevant for proteins that have aggregation potential. Amyloid beta, tau, alpha synuclein, TDP 43 and polyglutamine expanded proteins are structurally and pathophysiologically distinct types of proteins, but all are capable of disrupting clearance and quality control. Other proteins can bind to aggregation, disrupt membranes, impair transport and trigger stress responses. Pathology is the pattern that emerges is the result of the offending protein and the cell's ability to handle it.

The process of selecting vulnerabilities increases the difficulty of interpretation. The same disease-associated protein can be found in two neuronal populations, but have very different outcomes. Stress burden can change due to axonal length, firing rate, calcium handling, mitochondrial demand, local chaperone expression and connectivity. Thus, cell type-resolution is needed in the study of aging biology, and cannot be done under the assumption that the brain is uniformly impacted by a one proteostasis defect.

Single nucleus multiomics can provide that resolution. Transcriptomic analysis can be used to characterize cell states and stress programs, and chromatin accessibility analysis can pinpoint changes in regulation that may occur before changes in gene expression. Proteomic measurements bring the true amounts and state of modification of proteins. If these layers are all at the same stage of the disease, researchers can ask themselves whether there is a loss of quality control capacity in vulnerable neurons before there is any visible degeneration, or whether it is only after damage has accumulated.

Longitudinal biomarkers are required as cross sectional tissue represents different people at different times. Neurofilament light can be an index of axonal injury, the levels of GFAP can be an index of astrocytic activation, and the level of phosphorylated tau markers can reflect Alzheimer related pathology. Multiple measurements can determine the time of onset when each of these signals start to shift in relation to cognition, imaging, and other molecular markers. Temporal sequence is key to understanding early cause from late effect.

Abnormalities of the biomarkers can occur many years before Alzheimer disease is clinically diagnosed from long studies of Alzheimer disease. Amyloid changes may precede tau changes and neurodegeneration and cognitive decline. The trajectories are not a single protein cascade that can be reduced to an Alzheimer disease but they illustrate that molecular disease is occurring long before the symptoms. The same logic can be applied to proteostasis research in order to find the transition point from a compensatory stress response to irreversible damage.

The additional dimension of spatial proteomics is that there are regional variations in aggregate burden and response to stress. A protein may be normal in one part of the organism but in another part abnormal. Local failure points can be identified via mapping of chaperones, degradation machinery, mitochondrial proteins and inflammatory signals around vulnerable circuits. Another advantage of tissue context is that it reveals interactions between neurons, astrocytes, microglia, and vascular cells, that are absent in isolated cultures.

Human data can then be used to suggest mechanisms which can be tested in induced neural cell models. Disease variants can be carried by patient derived cells which can be differentiated to relevant neuronal or glial types. Gene correction leads to an "isogenic" control whereas manipulation of chaperone, autophagy genes, or stress pathway can be used to assess causality. These models are unable to mimic decades of human ageing itself, but stress and maturation methods can reveal weaknesses in proteostasis that are genotype dependent.

Age must not be considered as a single variable. Biological age is related to inflammation, metabolic state, mitochondrial function, vascular health, endocrine signaling and cellular senescence. People who are the same age may have a different proteostatic reserve. The advantage of a longitudinal study is that it allows the measurement of several domains of aging and the interpretation of an increase in the neurodegeneration biomarkers in terms of systemic physiology rather than just age.

This is the basis for therapeutic timing. The restoration of circuits after neuronal loss is too large will not be possible by increasing autophagy. Protein quality control interventions are more likely to be feasible before irreversible degeneration takes over. It may therefore be more useful to have biomarkers that can document loss of proteostatic reserve than those that only confirm the established injury. The difficulty is, how to get them to be specific enough that they can be used to take some action but not to consider normal ageing as illness.

Independent cohorts and repeated assays are required for validation. Protein biomarkers can change depending on kidney function, acute illness, assay platform and collection of samples. A longitudinal signal needs to be consistent between populations and should be related to biologically meaningful changes. Blood markers, combined with CSF, imaging, and functional outcome, can determine whether it is actually a peripheral measurement that reflects the biology of the central nervous system.

The heat shock response is an example of a method by which reserve can be

experimentally measured. Cells subjected to a targeted proteotoxic stress upregulate chaperones and other protective proteins. Delayed, blunted or poorly resolved responses may be observed in aged or disease vulnerable cells. Comparing protein levels in the presence of a challenge with baseline conditions can uncover an undetected deficiency.

Measurements of the proteasomes and lysosomes should be done separately since each will degrade different substrates. The activity of the proteasomes may decrease and autophagic flux may increase as compensation, or the activity of the lysosomes may lead to accumulation even if the autophagosomes are formed normally. Thus, flux assays are more informative than counting autophagy-related structures at a specific time point. An abundance of autophagosomes may indicate a clearance process that is either active or stalled.

Mitochondrial quality control is part of proteostasis as it produces reactive oxygen species and disrupts ATP production to support protein folding and degradation. Mitophagy, mitochondrial unfolded protein responses and cytosolic proteostasis can be mutually reinforcing. Energy failure can accompany the decline in protein quality control, and can be identified by longitudinal markers that represent a combination of neuronal injury and mitochondrial stress.

These pathways can be modified by sex and genetic background. APOE genotype, variants of lysosomal genes, and variations in endocrine signalling can impact aging trajectories. Subgroup analysis can be performed to see if the same proteostasis marker has different risk within subgroups. These results should be reproduced prior to the use of a biomarker for individual prediction.

Another experimental test is aging interventions. Model organisms can be manipulated for proteostasis and metabolic stress by caloric restriction, exercise, or pharmacologic means. A biomarker that reflects the beneficial effect of higher protein quality control before there is a functional benefit, makes it a useful early response biomarker, not a late injury marker.

Observational biomarkers can be complemented with cellular challenge assays which measure reserve directly. One of the markers associated with poor recovery from proteotoxic stress is able to identify a loss of function prior to visible brain injury.

Richard I. Morimoto's work on proteostasis, aging and neurodegenerative disease does adhere to a model of molecular quality control as a dynamic reserve, rather than a binary pathway. Longitudinal biomarkers can unveil the changes in that reserve before

symptoms occur, whereas single cell and spatial approaches can identify which cells fail first. The best mechanistic overview will bridge the biology of aging, protein turnover, stress response, and tissue injury with time. Neurodegeneration consequently is not only a problem of accumulation, but a loss of the ability to maintain a molecularly organized long-lived nervous system.