

Aging Biology Trajectories Linking Proteostasis to Neurological Disease Using Longitudinal Biomarkers

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Abstract

The article examines aging and neurological disease through longitudinal trajectories of proteostasis rather than cross-sectional comparisons. Chaperones, autophagy, proteasomal degradation, translation control, mitochondrial quality, and stress signaling all change with age, but a single measurement cannot determine whether the change is protective compensation or emerging failure. Repeated biomarkers can reveal rate, acceleration, and transition points before diagnostic thresholds are crossed. Alzheimer-related longitudinal data illustrate how molecular abnormalities can precede clinical symptoms by years. The article proposes combining fluid biomarkers, imaging, genetic risk, single-cell tissue states, and multidomain aging measures in non-linear trajectory models. Independent cohort replication and assay harmonization are essential for long studies. Intervention responses can test whether a marker tracks a modifiable mechanism rather than merely injury. The discussion also distinguishes resistance to pathology from cognitive resilience. Overall, the framework seeks to identify when normal aging diverges into accelerated loss of proteostatic reserve and progressive neurological disease.



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Snapshots are generally used to compare aging and neurodegeneration; e.g., younger adults vs. older adults, cognitively normal groups vs. patients, low pathology vs. high pathology. Those comparisons show differences, but don't show the path from state to state. A trajectory perspective poses a more challenging question: which of the changes in proteostasis are the primary ones, which are compensatory, and which are indicative of the nervous system having entered the progressive disease phase of aging? Longitudinal biomarkers can give the time structure that is required to answer that question.

The changes in protein homeostasis are not only observed in the brains of patients with diagnosed neurodegeneration, but are also age-related in the normal brain. The activity of chaperones, autophagy, degradation of proteins by the proteasome, regulation of translation, mitochondrial quality and signaling of stress change over the lifespan. Some changes may be protective adaptations, due to reduced energy availability, or to damage accumulation. Others hinder the ability to expel misfolded proteins and damaged organelles. One measurement is not sufficient to reliably identify adaptation or potential failure.

Direction and rate can be determined by repeated sampling of the biomarker. A steady concentration for a number of years does not necessarily indicate a concentration that is increasing rapidly, even if both values are within the population range. The rate of change can be used to detect an accelerating process before a diagnostic threshold is reached. This is especially important for slowly progressive neurological disease in which there can be a slight delay between the onset of the molecule and functional impairment, which can

span years.

Alzheimer disease is a good illustration of temporal staging. longitudinal cohort studies have demonstrated that amyloid related abnormalities progress many years before diagnosis, with tau related abnormalities reported before imaging abnormalities of neurodegeneration, and measurable cognitive decline reported in turn. The overall message of the disease biology — though not the order of the individual phases — is strong: that disease biology progresses in a partially ordered sequence rather than emerging at the onset of symptoms.

Interpretation of proteostasis markers must be done in the framework of that phased model. Compensatory chaperones, autophagy and stress responses can be activated by increases in misfolded protein load. In an early phase a more robust quality control would have gone hand-in-hand with pathology. Subsequently, these roads can be depleted or distorted. An increased level of QC protein may be interpreted as protection or failure if not repeated.

Traditional averages may not capture patterns in data, but latent trajectory modelling can. Instead of requiring all participants to be on one curve, statistical models can detect sub-groups with delayed, slow or fast change, or nonlinear change. As modifiers, genetic risk, vascular disease, sleep, metabolic health, and inflammatory state can then be tested. It doesn't ignore the differences among brains; it doesn't try to fit them into the same universal timeline.

Imaging enhances the trajectory inference as molecular signals can be correlated with structural and functional change. Regional atrophy and connectivity can be monitored via MRI and selected protein pathologies via PET. If imaging and fluid biomarkers are taken multiple times, scientists can determine if the disruption of proteostasis comes before or after tissue loss, or if different areas of the body experience proteostasis disruption simultaneously.

Another anchor is genetic information. Mutations in genes such as APOE, lysosomal biology, endosomal trafficking, protein processing, mitochondrial function and immune signaling may modify disease risk. The interpretation of the causal direction of the variant associated with the given longitudinal pattern is fixed at conception. The risk allele is associated with earlier biomarker acceleration, while the clinical resilience allele is only associated with later clinical resilience.

The specificity of cell type is still necessary. Bulk blood or cerebrospinal fluid represents

the sum of the signals generated by many tissues and cell populations. Studies with single nuclei from post mortem tissue can distinguish different states of the neuronal and glial cells in various pathological stages. Linking these cell states to antemortem biomarker trajectories will help determine which cellular programmes were probably involved in the signals observed while alive.

Overfitting is avoided by external disease stage replication. A trajectory that has been identified in one elderly group may be a function of who enrolled in the program, what type of assays was used or what were the demographics. The same model tested in an independent cohort that has different recruitment and measurement conditions can indicate if the pattern generalises. When a proposed biomarker will be used to identify an early stage that is not apparent clinically, replication is particularly important.

Brain specific markers are not the only markers of biological aging. Circulating proteins are affected by inflammation, vascular dysfunction, kidney function, metabolic regulation, and cellular senescence, which all impact neurological risk. An example of this is that a change in NF-L should not be interpreted alone but taking into account factors that influence concentration or clearance. Multidomain aging panels can be used to differentiate systemic changes from CNS injury.

Useful trajectory model should facilitate prediction, not just description. Ability to predict ability to predict cognitive decline, imaging progression or transition to a clinical syndrome can be tested for baseline and rates of change. Not just statistical significance, but a measure of predictive performance should be used to assess held out data. A measure of predictive performance should be used to assess held out data, not just one of statistical significance. Well, a model that does not separate groups well in the future but does well in the past is a useless model.

Trajectories can be tested in an intervention study. Where treatment alters a proteostasis marker, the critical question will be whether downstream injury and function also changes in the predicted direction. As long as there is no clinical or mechanistic logic, there is the risk of a wrong movement of the biomarkers. Molecular response can be detected by serial sampling during intervention to determine whether it is adequate to be a treatment monitoring signal.

Trajectory analysis can also differentiate between resistance to disease and resilience. In one individual, the molecular pathology may build up slowly, and in the other, the same pathology process may accumulate and cognition may be retained. Such patterns suggest different mechanisms. The conceptually different proteostasis markers for slower

pathological accumulation are not the same as those associated with maintained function despite pathology.

Point models can determine the time of acceleration in a set of individual curves. Rather than the assumption of a smooth linear rise, algorithms can detect a time of relative stability followed by a time of rapid change. The estimated transition can then be correlated with genetics, sleep, vascular events, or inflammatory events. These models require sufficient repeated measurements to ensure that they are not fitting random fluctuation.

Technology like that changes over time, which makes it necessary to harmonize your assays over long studies. A cohort can be followed over 10 years and can change reagent lots, instruments, and biomarker platforms. Methods can be linked together by reference samples or by calibration equations. If not harmonised, a biological trend can be partially attributed to laboratory sensitivity changes.

When interpreting the clinical picture, it will be important to maintain doubt. A biomarker trajectory may provide an indication of risk, but not of destiny. It is more appropriate to report probability and confidence intervals than to fix the future of a disease. This is especially important at the early stages, when false certainty can induce unnecessary fear accompanied by a limited treatment option.

Comparisons of trajectory should contain individuals who are not ill despite their high age or substantial illness. These hardy individuals can show protective programs for proteostasis that are not detected by case-control studies. While reducing pathology is the focus of targeting, targets can be nominated for extending reserve based on molecular differences that preserve the function.

Additionally, competing risk can be an issue in older age groups. Observed trajectories may be biased and interrupted by death, stroke, cancer, and other disease processes that affect the nervous system. These events should be accounted for in statistical models otherwise slow progression of biomarkers may be misinterpreted.

This comparison can reveal protective programs that slow down functional decline while maintaining a similar chronological age and molecular burden.

To some, Richard I. Morimoto's studies of the biology of proteostasis and aging emphasize the need of a time axis in neurodegenerative biology. Compensation, vulnerability and accelerated degradation may be co-occurring in the same protein quality control network. Longitudinal markers, genetic factors, and imaging can distinguish those phases and

pinpoint areas where the disease diverges from the normal aging process. The outcome is a more nuanced understanding of the risk of neurologic disease: not a binary one based on age, but one based on molecular reserve coupled to inherited susceptibility, tissue context, and the rate of proteostasis failure.