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Short Communication

A Need for Proteomics: Untangling the Relationship between Protein Turnover, Aging, and Longevity

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ABSTRACT

Mass Spectrometry-based protein turnover studies have shed light on the remarkable relationship between protein turnover and longevity. Here, we discuss the potential implications of the strong correlation between protein longevity (longer soluble protein half-lives) and longer mammalian lifespan, and conversely, the accumulation old insoluble proteins with age. We propose several strategies that can be employed in future studies to address the interesting questions raised by these observations-which protein half-life best correlate with longevity? Is protein half-live a biomarker for interventions that extend lifespan? How do post-translational modifications affect protein turnover?

Keywords: Protein turnover; Proteostasis; Mass spectrometry; Proteomics; Stable isotope labeling; Metabolic labeling; Aging; Longevity; Post-translational modifications

DESCRIPTION

We provide a short communication on our previously published article titled "Accumulation of "Old Proteins" and the Critical Need for MS-based Protein Turnover Measurements in Aging and Longevity" which highlighted the need to measuring protein turnover and protein half-lives in the context of aging and longevity. We specifically focused on Long-Lived Proteins (LLP), such as the nuclear pore complexes, extracellular matrix proteins, and protein aggregates. We discussed the role of these LLPs during aging and disease and presented relevant mass spectrometric workflows how to measure protein turnover and gain insights into the systems biology of proteostasis and aging [1].

LONGEVITY IS CORRELATED WITH LONGER PROTEIN HALF-LIVES IN MAMMALS

Dysfunctional proteostasis is a hallmark of aging and age-related diseases, such as Alzheimer's disease, cardiac dysfunction, type 2 diabetes, among others. The rise of mass spectrometry-based workflows that enable the direct measurement of *in vivo* protein turnover rates across hundreds of proteins in a single experiment have resulted in remarkable discoveries about the potential role of protein turnover in mammalian longevity. In nearly all studies estimating protein turnover rates in mouse models of longevity, whether conferred by dietary interventions [2-4], pharmacological interventions [2-4], or genetic interventions [4,5], increased maximal lifespan is correlated with longer proteome half-lives across multiple tissues [6]. Comparative studies between laboratory mice and the long-lived naked mole rat have confirmed this phenomenon across rodents [7,8]. A recent study from the Ghaemmaghami group surveyed protein half-lives across species with diverse lifespans, including humans and the longest living mammal–the bowhead whale-and they have shown a stunning correlation of maximal lifespan and protein half-lives across many species [9].

These observations raised interesting possibilities with regard to the relationship between the turnover of the proteome and longevity of mammalian species. First, these findings suggest slower global protein turnover may be an indicator of a healthy proteome and a requirement for longevity. Second, these observations suggest that slower rates of global protein turnover may be biomarkers for longevity. Going forward, it will be important to utilize Mass Spectrometry (MS)-based strategies to test these possibilities in an experimental setting. For example, it will be of high interest to assess whether longer proteome half-lives can be used to screen for interventions that will extend lifespan in mammalian models. Critically, MS-based approaches provide the granularity to determine the half-lives of individual

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proteins for hundreds of proteins across the proteome, and it will be important to determine whether specific subsets of proteins are the best predictors of whether an intervention will extend lifespan. Given the wide range of protein half-lives measured in a single experiment (ranging from hours to months) and the range of responses of individual proteins to treatments, it will be crucial to identify a set of specific proteins with responses to treatment that most closely correlates to increases in lifespan. Ideally, this biomarker panel may consist of relatively abundant proteins with shorter half-lives, which can be more easily measured in a short stable isotope labeling experiment.

A BETTER STRATEGY FOR PROTEOME MAINTENANCE

The critical question still remains-why does longevity require longer protein half-lives? The reason remains unclear, but there are several hypotheses that may explain these observations. Swovick et al. proposed that long-lived species have developed more selective and energy efficient mechanisms to select and degrade damaged proteins, thus on the bulk level, protein turnover is reduced [9]. Another explanation is that long-lived animals synthesize proteins with less 'errors' and better maintain proteins-thus requiring fewer turnovers. Indeed, longer-lived animals tend to produce less reactive oxygen species [2,9] and have improved translational fidelity [10]. Improving translational fidelity and maintenance of proteins may be a better strategy to maintain proteins that are difficult to degrade and replace, such as highly insoluble protein aggregates and Extracellular Matrix (ECM).

UNDERSTANDING THE ACCUMULATION OF OLD AND INSOLUBLE PROTEINS WITH AGE

Yet another hallmark of aging and indicator of dysfunctional proteostasis is the accumulation of old and damaged insoluble proteins, such as highly modified ECM proteins and protein aggregates [1,11]. Unlike the long-lived soluble proteins traditionally measured by protein turnover studies discussed above, these long lived insoluble, aggregated, or otherwise sequestered proteins indicate a deficiency in the cells ability to turn them over. By nature of 'existing' longer, long-lived proteins have more opportunity to accumulate Post-Translational Modifications (PTMs) that may alter their structure and function. Interestingly, we have previously observed the accumulation of "old" ubiquitinated proteins in aged mice [12], suggesting a failure of a subset of highly modified proteins to turn over. Conversely, it is possible that the accumulation of specific PTMs sequesters proteins from being turned over by increasing insolubility or aggregation propensity. In future studies, it will be worthwhile to better examine the relationship between the PTMs, protein solubility, and protein turnover in a more systematic and comprehensive way using MS-based approaches. Methodological advancements in the identifying and quantification of PTMs [13] have enabled the comprehensive assessment of multiple PTMs across the proteome, even with limited protein quantities. The application of these methods in combination with stable-isotope labeling may shed light on the relationship between protein modification and turnover.

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