CLINICAL IMPLICATIONS OF BASIC RESEARCH

Stress, Aging, and Neurodegenerative Disease

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Aging and stress, stress and aging — these two human conditions, when paired, can profoundly affect the quality of life. When events go awry, molecular processes take place that, over time, can lead to neurodegenerative disease. At the root of the problem is a fundamental process: protein folding. Since proteins are the predominant products of gene expression and provide much of the shape and functionality of the cell, their proper synthesis, folding, assembly, translocation, and clearance are essential for the health of the cell and the organism. When proteins misfold, they can acquire alternative proteotoxic states that seed a cascade of deleterious molecular events resulting in cellular dysfunction. When these events occur in neurons, the consequences can be devastating.

Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and other neuropathies involve the cytopathological appearance of intracellular and extracellular protein aggregates in the brains of affected persons. It is increasingly clear that the relevant event in these neurodegenerative diseases is a toxic gain-of-function mutation associated with the appearance of oligomers and other toxic aggregates consisting of the β-amyloid peptide, α-synuclein, superoxide dismutase, and huntingtin, respectively. The way in which these toxic species form, the processes that determine their persistence or clearance, and the molecular basis of their toxicity are critical to the mechanisms of these diseases.

Because the necessity of correct protein folding is common to all forms of life, many insights have been provided by studies of organisms such as the yeast *Saccharomyces cerevisiae* and the invertebrates *Caenorhabditis elegans* and *Drosophila melanogaster*. One such study was recently reported by Cohen and colleagues.[1] It builds on a previous study showing that two factors determine the cellular toxicity of mutant huntingtin in a worm model of disease: the length of the mutant polyglutamine repeat (the substantive expansion of which causes disease in humans) and the expression of proteins in the insulin-signaling pathway that regulate the life span.[2] The idea that the molecular determinants of longevity might influence polyglutamine-mediated toxicity is supported by observations that the length of time until disease develops — days in *C. elegans*, weeks in *D. melanogaster*, months in mice, and years in humans — correlates approximately with the life span of the organism. The association between the life span and the cellular stress response is suggested by the insulin-signaling pathway's requirement for heat-shock factor 1 (HSF-1), the activator of the heat-shock response that induces the expression of molecular chaperones (a large class of proteins that assist in protein folding and thus guard against misfolding) during stress.[3,4] Consequently, the inhibition of HSF-1 function also increases polyglutamine aggregation, resulting in toxic effects that decrease the life span of *C. elegans*. Conversely, overexpression of HSF-1 suppresses polyglutamine-mediated toxicity and extends the life span. Collectively, these observations provide support for the hypothesis that graceful aging depends on the cell's ability to counter the effects of stress by maintaining protein folding, which in turn permits appropriate protein function.

Cohen et al. showed that activation of the insulin-signaling pathway suppresses the toxicity of aggregates of amyloid β_{42}, the peptide found in lesions in the brains of patients with Alzheimer's disease. With the use of a *C. elegans* model that expresses amyloid β_{42}, these investigators showed that in suppressing the toxicity of aggregates, the insulin-signaling pathway activates two downstream pathways, both of which affect the fate of an aggregation-prone protein. Each pathway is triggered by a transcription factor: HSF-1 or abnormal dauer formation 16 (DAF-16). The authors showed that HSF-1 promotes disaggregation by elevating the levels of protective molecular chaperones, whereas DAF-16 enhances the formation of large, inert aggregates from toxic oligomers (Fig. 1).

Although these activities might appear to op-

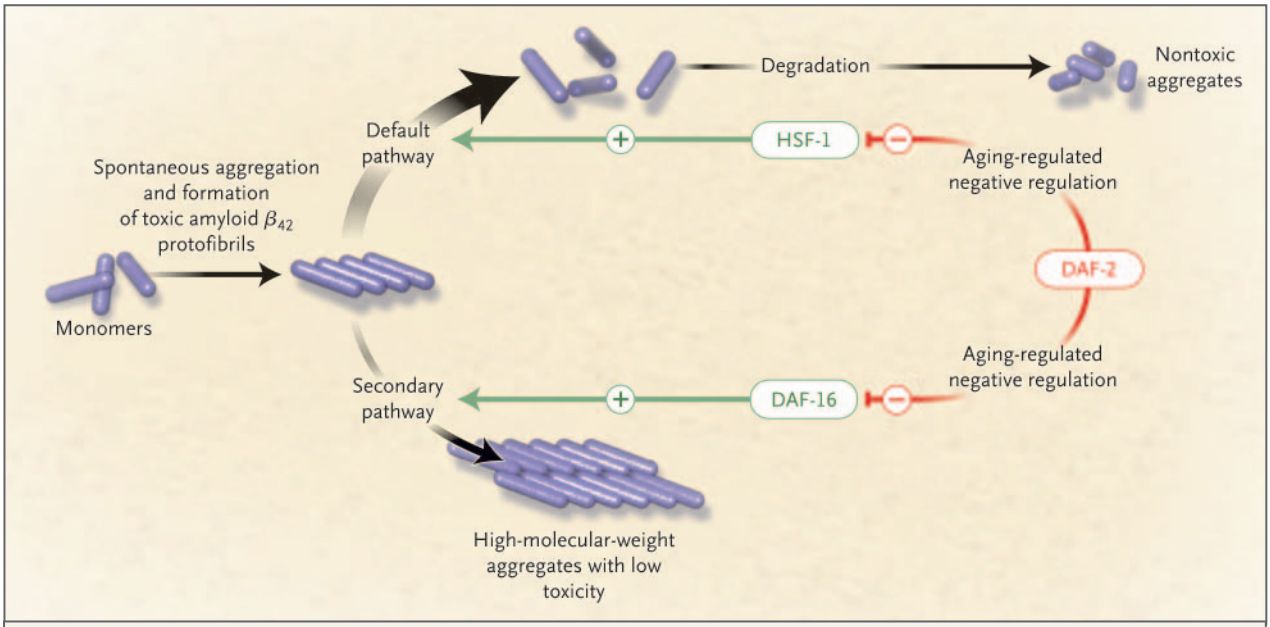

Figure 1. A Model of Age-Related Protection against Proteotoxicity.

The insulin-signaling pathway is triggered in *C. elegans* by a receptor called DAF-2. It has a profound effect on aging — a mutation of *daf2* can result in a doubling of the life span of this organism, and similar results have been observed in mice. DAF-2 represses two downstream pathways: one is commandeered by the transcription factor HSF-1 and the other by the transcription factor DAF-16. (Transcription factors are proteins that "turn on" specific genes.) A recent study by Cohen et al.[1] shows that both HSF-1 and DAF-16 provide protection against proteotoxicity of the amyloid β_{42} peptide, an aggregation-prone peptide that can spontaneously form small toxic aggregates. The default pathway, regulated by HSF-1, identifies and breaks apart toxic aggregates. When the HSF-1 machinery is overloaded, however, a molecular apparatus regulated by DAF-16 grinds into gear, resulting in the formation of less toxic high-molecular-weight aggregates.

pose one another, Cohen and colleagues proposed an intriguing hierarchy of cellular protection mechanisms. They suggested that HSF-1 is the first line of defense against damaged proteins, initiating the expression of molecules that recognize and disaggregate the nascent oligomeric and aggregate species. DAF-16 may provide a secondary line of defense against the toxic oligomers that escape from HSF-1–mediated clearance by converting them into large, inert aggregates. HSF-1 and DAF-16 have many downstream gene targets, so it will be important to identify those genes that are key to disaggregation or aggregation.

Cohen et al. also observed that the amyloid β_{42} peptide expressed in their *C. elegans* model appears to exert its toxic effects in the cytoplasm of the cell. This finding challenges the notion that extracellular plaques in Alzheimer's disease are the sole basis of toxic effects.

The study reported by Cohen et al. shows that cellular degeneration in diseases of protein conformation is unlikely to be caused by a single defect; instead, it is likely to be the net consequence of cumulative insults to the quality control of protein folding, resulting in deleterious effects on multiple cellular processes. Although the authors do not explicitly say as much, this study suggests the promise of new therapeutic strategies that harness existing cellular mechanisms to prevent the widespread disruption of protein homeostasis.

No potential conflict of interest relevant to this article was reported.

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