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Title: NEUROENDOCRINE CONTROL OF THE PROTEOSTATIC NETWORK BY HPK-1 DELAYS AGING

Abstract:
The progressive decline of cellular proteostasis is a hallmark of normal organismal aging, and is the basis for the onset and progression of a growing number of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's disease. Here, we show the transcriptional cofactor HPK-1 (homeodomain-interacting protein kinase) functions as a key regulator of the proteostatic response that originates in the nervous system of Caenorhabditis elegans. HPK-1 acts in the nervous system to stimulate the release of both paracrine and endocrine signals that cell non-autonomously trigger protective peripheral responses. An unexpected discovery is that these responses can qualitatively differ depending on the neuronal type from which they arise. We find an HPK-1-dependent signal from serotonergic neurons that functions as a component of the thermosensory circuit, which acts in conjunction with the heat shock transcription factor 1 (HSF-1) to restore proteostasis in response to acute damage within the proteome. In contrast, HPK-1 dependent signaling from GABAergic neurons regulates autophagy, likely in response to metabolic control of Target of Rapamycin Complex 1 (TORC1) activity. Each of these distinct adaptive responses improves proteostasis in a cell non-autonomous manner. The role of hpk-1 homologs as metabolic or genotoxic stressors has been observed from yeast to mammals, suggesting this family of transcriptional cofactors arose early in evolution to couple metabolic and stress signaling. Our findings are also the first to provide a unified in vivo model for HPK-1 action, and suggest these findings represent significant new insights into how the nervous system coordinates adaptive metabolic and stress response pathways across tissues to delay aging throughout an animal.