Transcellular stress signalling: How proteotoxic stress is communicated between different tissues in *C.elegans*

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Introduction

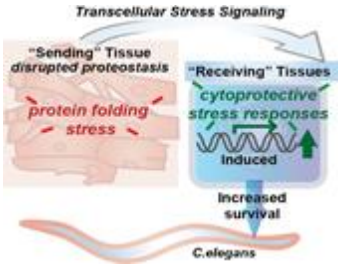

Figure 1: Model explaining Transcellular Stress Signalling in C. elegans.

In all biological systems, cells throughout their lifetime are exposed to different physiological and environmental stress conditions that lead to protein damage and cellular dysfunction – and ultimately disease. Cumulative protein misfolding and aggregation is one of the hallmarks implicated in the pathologies of misfolding diseases associated with neurodegeneration, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease, as well as cancer, diabetes and several myopathies. Maintaining a healthy cellular proteome is crucial to cellular viability. This is achieved by the proteostasis network, which integrates protein biogenesis, protein folding by molecular chaperones, as well as clearance mechanisms and stress response pathways. However, in an entire organism, cellular damage associated with misfolded proteins are rarely confined to a single tissue, but often involve peripheral tissues in ways we are only beginning to understand. Because the regulation of stress response mechanisms that maintain cellular proteostasis have been historically investigated in isolated tissue culture cells and unicellular organisms, regulation of proteostasis is understood in a strict cell-autonomous manner, regardless of the health state of neighbouring cells. Recent evidence in different multicellular model systems, such as fruit fly *D. melanogaster* and nematode *C. elegans* as well as mammalian tissue culture now show that cellular stress responses are organized coordinately between and across tissues by transcellular stress signalling in metazoans. For example an imbalance of proteostasis within one tissue is sensed and signalled to other tissues within the organism to adjust chaperone levels, minimize the risk of proteotoxic damage and increase survival (Figure 1).

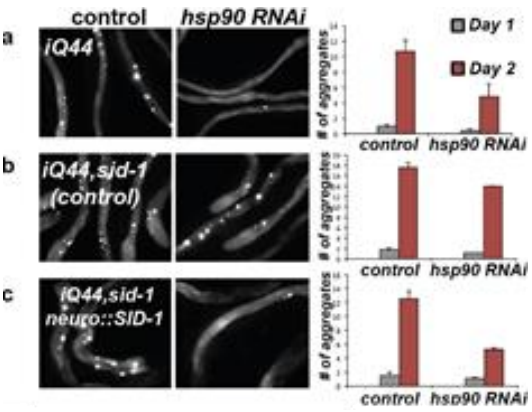

Figure 2:Transcellular stress delays polyQ aggregation of an intestinal iQ44::YFP disease model. (a) Systemic RNAi-mediated knockdown of hsp90 reduces age-dependent Q44 aggregation. (b) iQ44::YFP animals in the background of the RNAi-insensitive sid-1 mutant are unaffected by RNAi. (c) Neuron-specific hsp90 RNAi reduces intestinal iQ44::YFP aggregation by almost 50%, when compared to RNAi insensitive iQ44,sid-1 control animals in (b).

Results

This project aims to determine how the transcellular stress signalling response between tissues can be utilized to enhance cytoprotective stress responses to restore the health of tissues affected by protein folding disease. To address these questions, we use *C. elegans*, a well-established metazoan model organism for protein misfolding diseases and proteostasis. First results using a *C. elegans* Huntington's (PolyQ) disease model, where Q44 fused to YFP is expressed the intestine shows that transcellular stress signalling may indeed alleviate age-dependent aggregation. For example, by tissue-specific genetic manipulation of *hsp90* levels in neurons, which induces the heat shock response and cytoprotective chaperones in multiple tissues, aggregation of intestinal polyQ (*iQ44::YFP*) is reduced by almost 50% (Figure 2). Current studies are aimed at identifying transcellular signalling molecules mediating this response and extending to other *C. elegans* neurodegenerative disease models.

Publications

Van Oosten-Hawle, P. & Morimoto, R. (2014) Transcellular chaperone signaling: An organismal strategy for integrated cell stress responses. *J. Exp. Biol.* **217**:129-136.

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