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The Plasticity of Aging and Survival: a Role for the Thioredoxin System in *Caenorhabditis elegans*

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ABSTRACT

Thioredoxin and related systems regulate many biological processes in diverse species. In mammals, in addition to protecting against oxidative damage, they also play key roles as regulators of transcription factors, signaling cascades and immune responses. Many discoveries made in mammalian models have contributed to the description of numerous functions for the thioredoxin and related systems. However, studies performed in mammalian models offer limited information and versatility with respect to how the thioredoxin system dynamically interacts with the surrounding environment in living animals. For instance, *in vivo* examination of mammalian mutants is severely restricted since systemic mutations for thioredoxin and thioredoxin reductase result in embryonic lethality. In the invertebrate animal model *Caenorhabditis elegans*, survival programs during post-embryonic development and aging are plastic, and modifiable by the environment. Hence, *C. elegans* provides a framework for the use of effective cell-biological and genetic tools to investigate *in vivo* the biology of thioredoxins and related proteins in the context of a changing environment.

Here, we show that the *C. elegans* genome contains many putative homologs of the mammalian thioredoxin system and related molecules. Moreover, we report for the first time in any metazoan that a thioredoxin gene (*trx-1*) is expressed only in the nervous system and is involved in the regulation of aging (Paper I). In addition, we show that the selenoprotein, thioredoxin reductase (TRXR-1), instead of protecting against oxidative stress, is responsible, together with glutathione reductase (GSR-1), for the removal of old cuticle during molting in *C. elegans*. Our findings suggest that TRXR-1 and GSR-1 regulate molting likely by activating glutathione (GSH) function in the cuticle (Paper II). Next, we demonstrate that the thioredoxin TRX-1 is involved in ASJ neuron-dependent signaling pathways that regulate dauer formation in *C. elegans*. Our data suggest that redox-independent functions of TRX-1 in ASJ neurons are necessary to modulate neuropeptide expression, including that of the insulin-like neuropeptide gene *daf-28*, during dauer formation (Paper III). Lastly, we show for the first time in an *in vivo* animal model that a thioredoxin (TRX-1) is necessary for the metabolic changes triggered by dietary restriction (DR) to extend adult lifespan. We are also the first to show that DR upregulates thioredoxin (*trx-1*) expression in the nervous system. We propose that DR activates TRX-1 in ASJ neurons of aging adults to then stimulate the metabolic changes necessary to extend adult lifespan (Paper IV).

In conclusion, we show evidence for the crucial role of conserved members of the thioredoxin system in controlling aging and survival in *C. elegans*. Furthermore, the data presented suggest the plastic nature of molting, dauer formation and aging in *C. elegans* and how the thioredoxin system and related molecules assist to maintain such environmental sensitivity. Basic cell-biological processes and the thioredoxin and related systems possess a substantial degree of functional conservation between mammals and invertebrates. Hence, the novel roles discovered for thioredoxins and related molecules to regulate aging and survival in *C. elegans*, might lead the way in disclosing similar mechanisms in mammals.

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