**ABSTRACT**

Genetic screens for longevity genes in Caenorhabditis elegans led to the discovery that lifespan is extended when global protein translation is reduced. However, how reduced protein translation causes this extension in lifespan is unknown. In this study, we searched for transcription factors that are preferentially translated when global protein translation is inhibited. We identified ATF-5, which is a stress response transcription factor that is similar to the mammalian homolog ATF4. We found that ATF-5 is preferentially translated under stress conditions that lead to a reduction in global protein translation. Under normal conditions, ATF-5 translation does not occur even though atf-5 mRNA is highly expressed. By contrast, induction of endoplasmic reticulum stress by compounds such as tunicamycin, dithiothreitol, tricaine, and thapsigargin, actively promotes translation of ATF-5. Surprisingly, animals that lack atf-5 look superficially wild type and are not stress sensitive to endoplasmic reticulum or oxidative stress. To test whether atf-5 is important for reduced translation mediated longevity, we pharmacologically inhibited translation in adult C. elegans by using cycloheximide and measured their lifespan. While the lifespan of wild type animals is extended by cycloheximide in a dose-dependent manner, animals lacking atf-5 show no lifespan extension. Taken together, our results suggest that lifespan extension via reduced translation requires ATF-5. This work will allow for the dissection of mechanisms responsible for down regulation of protein synthesis and how this protects the organism.

**BACKGROUND**

Lifespan extension in C. elegans comes as a result of conditions that shift cells from states of nutrient utilization and growth to states of cell maintenance and stress resistance. Reducing translation, or inhibiting protein synthesis, has also been shown to increase lifespan in organisms including fruit flies, single-celled yeast and nematodes. Lifespan extension in mammals has been shown to occur as a result of conditions that lead to a reduction in global protein translation. Under normal conditions, the mammalian homolog ATF4. We found that ATF-5 is preferentially translated under stress conditions is of much importance. This relationship will provide insight into the balance between protein synthesis and inhibition. More investigations into the role of ATF-5 in lifespan extension will allow for a better understanding of normal aging as well as disease seeing as though the increased accumulation of unfolded proteins in the ER comes as a result of aging and age-dependent diseases. ATF-5 homologues such as the yeast GCN-4 and the mammalian ATF-4 may serve similar roles in the given organism. If the mammalian homologue has a similar function to that of ATF-5, there is a possibility that lifespan extension is possible in higher organisms such as mammals.

**REFERENCES**


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