# NHR-49 Helps Germline-Less Worms Chew the Fat

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Numerous studies have demonstrated a tradeoff between reproduction and aging, as decreased fertility is associated with increased longevity in many species, from the nematode C. elegans to humans. Despite this, reproductive fitness confers physiological benefits, highlighting a complex relationship between reproduction and aging. One point of connection between reproduction and aging is fat metabolism, particularly lipid homeostasis. For instance, obesity on one hand and low body weight on the other account for approximately 12% of female infertility, and reproductive senescence in mammals is associated with altered patterns of fat storage and weight gain. In terms of aging, obesity is associated with increased risk of several age-associated diseases, including diabetes, cardiovascular disease, and cancer. While lifespan and fertility are generally at odds, recent work has suggested that lipid metabolism is a point of contact between these two processes. To better understand the effect of germline removal on lipid metabolism, research technician Shaw-Wen Chen in the lab of Dr. Carissa Olsen (Basic Sciences Division) and collaborators at the Universities of Pittsburgh, Pennsylvania, and California-San Francisco investigated the roles of nuclear hormone receptors (NHRs), transcriptional regulators that often bind lipids, in regulation of lifespan of *C. elegans* in which the germline has been removed. "In order to begin to understand how reproduction influences lifespan, we used a combination of gene expression analysis and lipid biochemistry to identify a key transcription factor, nhr-49, involved in this regulation and explore its impact on fat metabolism," said Dr. Olsen.

To identify NHRs involved in lifespan extension after germline loss, the authors performed a targeted RNAi screen of NHRs in *C. elegans*. They identified 19 NHRs that, when knocked down, both shortened the lifespan of germline-less worms and prevented upregulation of a reporter gene whose expression is increased by germline ablation. Strikingly, RNAi depletion of NHR-49 was associated with complete loss of this extended lifespan, a phenotype confirmed by lifespan analysis of *nhr-49* mutants. Consistent with a role for NHR-49 in lifespan extension, the authors detected a robust increase in NHR-49 protein levels following germline loss. Notably, it was also found that overexpression of NHR-49 in non-germline tissues also extended the lifespan of fertile worms to a modest extent.

Using high-throughput RNA sequencing (RNA-seq) to identify NHR-49-regulated genes, the authors found that many genes involved in fatty acid oxidation and desaturation were increased. RNAi knockdown of several of these NHR-49 targets reduced lifespan in germline-ablated worms, suggesting a key role for NHR-49 in mediating extended lifespan by controlling specific lipid metabolic pathways. Consistent with this idea, loss of NHR-49 was associated with decreased fat storage and *de novo* lipid synthesis in germline-ablated worms, and *nhr-49* mutants displayed age-related depletion of fat stores. Further experiments revealed a role for NHR-49 in desaturation of multiple fatty acids.

This study delineates a molecular mechanism by which reduced fertility promotes extended longevity, wherein germline ablation reprograms lipid metabolism. "Interestingly, we observed a role for nhr-49 in both fat synthesis and fat breakdown, and understanding how these two contradicting processes impact metabolism in a meaningful way will be the focus of future work," said Dr. Olsen.

Ratnappan R, Amrit FR, Chen SW, Gill H, Holden K, Ward J, Yamamoto KR, Olsen CP, Ghazi A. 2014. Germline signals deploy NHR-49 to modulate fatty-acid ß-oxidation and desaturation in somatic tissues of *C. elegans*. *PLOS Genet* 10(12):e1004829.

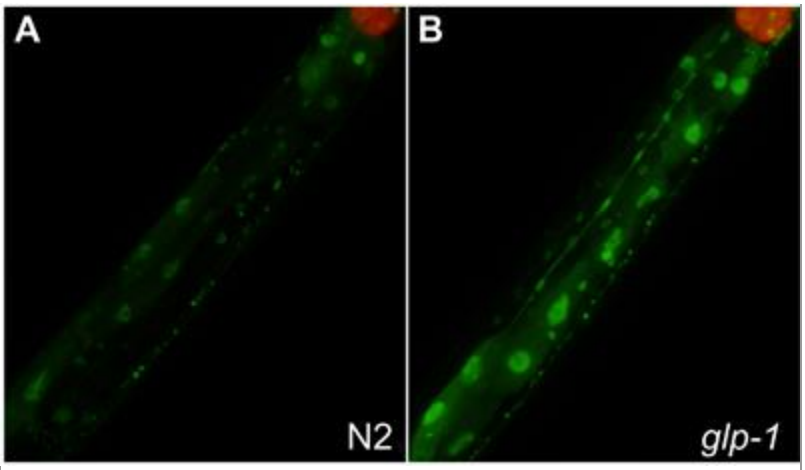


*Image from the publication*

(A) Expression of NHR-49 in wild-type N2 and (B) germline-null glp-1 worms as assayed with a fluorescent reporter fusion.