Study links developmental and lipid handling pathways in C. elegans

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Caenorhabditis elegans. Credit: Wikipedia

A Massachusetts General Hospital (MGH) research team reports finding that a previously unknown interaction between metabolic pathways in two different tissues within the C.elegans roundworm triggers a key step

in maturation. In their report published in *Genes & Development*, the investigators describe finding how microRNAs in the skin of the roundworm, which are known to control the animals' transition through key developmental stages, link to a signaling pathway that directs the transport of lipids from storage in the intestine to reproductive cells for support of embryonic growth.

"This intertissue dialogue between two specialized tissues is a remarkable strategy to precisely choreograph the transition to adulthood," says Robert Dowen, PhD, formerly of the MGH Department of Molecular Biology and lead author of the report. "It's quite surprising that *C. elegans* has evolved a very elegant mechanism to integrate developmental, metabolic and reproductive information for three distinct tissues at a very specific point in the growth of the animal."

Corresponding author Gary Ruvkun, PhD, MGH Department of Molecular Biology, says, "The microRNAs in the skin of *C. elegans* act like a clock. They control the developmental steps of the roundworm, culminating in a massive shift in fat metabolism towards production of eggs at the point of adulthood." Dowen was a research fellow in Ruvkun's laboratory prior to joining the Integrative Program for Biological and Genome Studies at the University of North Carolina at Chapel Hill

Ruvkun's studies in *C. elegans* have led to many fundamental discoveries about the molecular control of development. In collaboration with Victor Ambros, PhD, now at the University of Massachusetts Medical School, Ruvkun discovered, via genetic analyses in *C. elegans*, the first microRNA and its mechanism of repressing the translation of messenger RNAs into protein. Ruvkun subsequently discovered that microRNAs are used in diverse organisms, including humans.

Once *C. elegans* larvae have hatched, they begin feeding on bacteria and

grow rapidly, enlarging more than 100 times before reaching adulthood. Key steps in the transition from larva to adult are regulated by lin-4 and let-7, the first microRNAs discovered by Ruvkun and Ambros. When the roundworm reaches adulthood, nutrients that previously drove growth accumulate as fat in the intestine. But in order to reproduce, those fat stores need to be moved to reproductive cells in a process called vitellogenesis, which is accomplished through particles similar to the LDL molecules that carry lipids in humans and other mammals.

While insulin signaling is known to be essential to vitellogenesis, the research team suspected that additional pathways were likely to play a role in regulating the process. Their investigation revealed that regulation of vitellogenesis by means of expression in the hypodermis - tissue corresponding to the animals' skin - of lin-4, let-7 and the transcription factor lin-29 is mediated by the TORC2 signaling pathway in the intestine, which is involved with energy metabolism.

While several metabolic activities originally identified in *C. elegans* also apply to other animals, including humans, Dowen notes that whether mammalian lipid-transport molecules are controlled by the same proteins that regulate fat metabolism in *C. elegans* remains to be seen. "One of the questions we need to investigate next is what are the signaling molecules that couple hypodermal development to intestinal fat metabolism, including regulators of the TORC2 protein complex, which is a key mediator of cell growth and metabolism."

More information: Robert H. Dowen et al, A microRNA program in thehypodermis couples to intestinal mTORC2/PQM-1 signaling to modulate fat transport, *Genes & Development* (2016). DOI: 10.1101/gad.283895.116

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