

Review

Investigating Connections between Metabolism, Longevity, and Behavior in *Caenorhabditis elegans*George A. Lemieux¹ and Kaveh Ashrafi^{1,*}

An overview of *Caenorhabditis elegans* as an experimental organism for studying energy balance is presented. Some of the unresolved questions that complicate the interpretation of lipid measurements from *C. elegans* are highlighted. We review studies that show that both lipid synthesis and lipid breakdown pathways are activated and needed for the longevity of hermaphrodites that lack their germlines. These findings illustrate the heterogeneity of triglyceride-rich lipid particles in *C. elegans* and reveal specific lipid signals that promote longevity. Finally, we provide a brief overview of feeding behavioral responses of *C. elegans* to varying nutritional conditions and highlight an unanticipated metabolic pathway that allows the incorporation of experience in feeding behavior.

Advantages of an Invertebrate Experimental System for Understanding Energy Balance

Having diverged from a common ancestor with mammals approximately 1 billion years ago, *C. elegans* has evolved distinct behaviors and organismal survival strategies and lacks certain easily identifiable orthologous molecules (e.g., leptin, PGC-1 α) and specialized tissues (e.g., white or brown adipose tissues, macrophages) that are dominant themes in the mammalian metabolic biology literature. Thus, *C. elegans* might seem to be a peculiar experimental model for studying metabolism, its regulators, and its consequences on physiology and behavior. A proposal to identify genes that regulate entry of *C. elegans* into an organism-specific, alternative developmental state induced by various nutrient and environmental stresses could easily be dismissed as unlikely to yield anything of relevance to human disease. However, it was genetic studies of just such a state that identified components of TGF- β -like and insulin-like signaling pathways and revealed that antagonism of a program under control of a FOXO-family transcription factor is a major consequence of insulin signaling [1]. At the time of this discovery, insulin was one of the most intensively studied signal transduction pathways in history, yet investigations in other systems had failed to identify aspects of its signaling related to transcriptional control, a now well-established and critical aspect of insulin signaling in mammals [2].

Among the reasons that fundamental discoveries related to insulin signaling pathways were possible in *C. elegans*, despite it lacking an obvious equivalent of the pancreas and blood in which sugar levels need to be regulated, are the experimental advantages of this organism. These include investigation of heritable phenotypes through genetic screening, the efficiency of determining the molecular bases of such phenotypes, and the experimental ease with which the phenotypic effects of multiple mutations can be investigated relative to each other. While the

Trends

Caenorhabditis elegans allows the investigation of numerous evolutionarily conserved fat and feeding regulatory mechanisms.

C. elegans studies have led to the deciphering of regulatory connections that were subsequently shown to function similarly in mammals, but also to findings that challenge certain paradigms of mammalian fat biology.

One difficulty in studying lipids in *C. elegans* is that there are currently no easy methods to unambiguously distinguish lipids in storage depots from those that are in lipoprotein-like yolk particles.

Both lipid synthesis and lipid breakdown pathways are activated in long-lived animals that lack their germlines and specific signaling lipids that promote activity of prolongevity pathways have been identified.

Levels of a specific tryptophan-derived metabolite underlie the incorporation of experience in feeding behavior.

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relative simplicity of *C. elegans* is often viewed as a weakness, it is precisely this feature that helps illuminate conserved principles of energy balance and deconvolutes connections between processes previously considered disparate. Even at a time that technological advances make comparable approaches increasing feasible in other experimental systems, these decisive experimental advantages remain for *C. elegans*.

Here we highlight several recent advances in linking metabolism to aging and behavior in *C. elegans*, but also emphasize challenges in interpreting lipid phenotypes in this organism. Additional information pertaining to *C. elegans* fat and feeding regulatory pathways have appeared in several recent reviews [3–5].

Overview of *C. elegans* Energy Balance Pathways

In the hermaphroditic *C. elegans*, significant amounts of neutral lipids are seen in the intestinal and skin-like epidermal cells as well as oocytes and embryos within the germline. *C. elegans* do not have a specialized adipose tissue or even a liver; nevertheless, many functions of these organs and associated molecular mechanisms are found in *C. elegans*. Its intestine, in addition to performing enterocytic functions, expresses many genes that perform liver-like functions, including lipid synthesis and lipoprotein secretion [6]. The germline receives nutrients in the form of lipid-rich lipoprotein particles, namely yolk, that are synthesized in the intestine, secreted into the body cavity, and taken up by the developing oocytes through receptor-mediated endocytosis [7,8]. Although the *C. elegans* intestine has received most of the attention when visualizing lipids in intact animals, the triglyceride depots in the skin-like epidermal cells may be more akin in function to those stored in mammalian adipocytes.

Despite significant differences, many known metabolism genes are conserved between *C. elegans* and humans, including lipid, sugar, and amino acid synthesis and catabolism genes, lipogenesis regulators such as SREBP, and nutrient-sensing kinase complexes such as TOR and AMPK [3]. Additional similarities include neuroendocrine pathways such as insulin and steroid hormone signaling as well as neuromodulators such as serotonin and dopamine and feeding regulatory neuropeptides such as oxytocin and opioid-like peptides [4,5,9]. As in mammals, the nervous system of *C. elegans* integrates both external and internal cues to modulate behavior but also peripheral physiology via hormone secretion [5,10,11]. In turn, inputs from the periphery modulate feeding behavior in *C. elegans* [12,13].

Investigation of *C. elegans* lipid metabolic pathways has identified molecular mechanisms that have proven to be conserved in mammals; for example, the relationship between the SREBP transcription factor and the mediator complex [14] as well as the role of SREBP in controlling aspects of 1-carbon metabolism [15]. Investigation of other conserved regulators of organismal energy balance – for instance, that of serotonin signaling and the *C. elegans* counterparts of the genes that underlie the obesity-associated Bardet-Biedl syndrome (BBS) – have led to conclusions that differ from those coming from mammalian studies (Box 1). Whether these discrepancies highlight species differences or suggest a need for reevaluation of the mammalian paradigms remains to be determined. Finally, some of the pharmacological tools that affect fat in mammals are similarly effective in changing the lipid content of *C. elegans* and this organism has been used to identify novel small molecules that alter fat through mechanism that are conserved in mammals [16].

Methods and Considerations When Interpreting Lipid Phenotypes in *C. elegans*

The transparency and small size of *C. elegans* allows visualization of lipid depots in all tissues of intact animals. Vital dyes, fixed staining methods, and label-free Raman microscopy techniques have been employed to examine lipid depots in *C. elegans* [17–24]. Biochemical techniques

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