Time to move the fat

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In this issue of *Genes & Development*, Dowen and colleagues (pp. 1515–1528) elegantly unify two previously unconnected aspects of physiology. The investigators provide significant genetic evidence to support a critical link between developmental timing decisions and the regulation of lipid mobilization at the transition to adulthood in *Caenorhabditis elegans*. This novel connection involves cross-tissue signaling from the hypodermis (epidermis) to the intestine to promote reproductive success in the germline.

Regulation of animal development involves more than cell division, fate specification, differentiation, and pattern formation; it also requires changes in metabolic status. Metabolism (status and biomolecule availability) not only profoundly impacts various developmental events but also is affected in turn by key developmental decisions to support various cellular functions. For example, the unique ability of a specific cell type to store and consume energy is the consequence of particular developmental events. The interplay of development and metabolism has been a relatively underexplored research area partly due to the immense complexity of the underlying mechanisms not only within cells but also between tissues. For example, the overall production and consumption of certain biomaterials, such as lipids, must somehow be coordinated with temporal developmental stages. However, the temporal developmental regulation could be initiated in a tissue separate from the site of the major fat metabolic events. The study of such cross-talk, requiring the use of genetic model organisms, is highly desirable.

Fat storage and mobilization have an intimate relationship with animal reproductive development, as the lipids provide needed resources during oogenesis and early embryogenesis (Fig. 1; Della Torre et al. 2014). Lipid storage has long been considered to be a reproductive adaption and may serve as the connection between development of somatic tissues and the germline. Mobilization of fat from somatic tissues to germ cells is a critical step in this interaction and must be carefully coordinated with overall development. In the nematode *Caenorhabditis elegans*, larvae (juveniles) consume food to fuel their own growth and development. By adulthood, lipids accumulate as droplets in the intestinal cells, and the transition to full reproductive capacity includes the mobilization of these lipids (Lemieux and Ashrafi 2015). Mobilization of large fat stores (vitellogenesis) requires assembly of low-density protein lipid (LDL) particles with key proteins termed vitellogenins (similar to ApoB genes in humans) (Fig. 1) that are expressed at the onset of adulthood. Vitellogenins shuttle the lipids from somatic tissue to oocytes and embryos to support reproduction. Several other recent studies have revealed diverse roles for and regulation of vitellogenins (Goszczynski et al. 2016; Seah et al. 2016; Wang et al. 2016). Previous work has also indicated a critical regulation of this process by the insulin/IGF-like signaling (IIS) pathway to coordinate nutrient availability and animal growth/development (DePina et al. 2011). Additional regulation, especially the connection with developmental timing that controls the larval-to-adult transition, was unknown.

Developmental timing has been extensively studied in *C. elegans*, focusing mainly on the heterochronic genetic pathway that controls the temporal transition between different developmental stages (Ambros 2000). MicroRNAs (miRNAs), including the first two miRNAs (LIN-4 and LET-7) ever discovered, have been shown to play critical roles in maintaining the precise gene expression dynamics needed for the temporal switch (Ambros 2011). However, much of the timing regulation focuses on activities in hypodermal seam cells that have particular cell division and differentiation patterns to mark the different stages. How the activities of the heterochronic pathway impact development in other tissues, particularly fat metabolism in the intestine, remains largely unknown. Dowen et al. (2016) have made a major advance toward answering this important question.

Dowen et al. (2016) used a powerful tandem genetic screen approach to identify genes impacting the expression of vitellogenin genes in order to uncover the
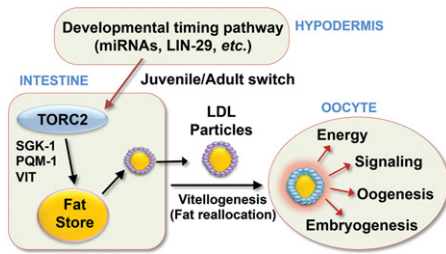
Figure 1. Developmental timing control of fat mobilization. Signaling from the hypodermis (epidermis) initiates fat mobilization from the intestinal reserve. Lipids are transported by LDL-type particles complexed with proteins (VIT) to developing oocytes.

regulatory mechanism of this metabolic switch. The first screen used a transgene reporter and RNAi to identify 16 genes required for expression of a vitellogenin gene (*vit-3*). Identification of miRNA-specific argonautes (*alg-1/2*) and *elt* GATA factor genes (*elt-1/2*) provided strong clues that developmental timing pathways must somehow signal from the hypodermis to the intestine. Less well known in developmental timing, the GATA factor ELT-1 was recently shown to exert developmental timing control by promoting expression of *let-7* miRNA (Cohen et al. 2015). Pursuing this possibility, the investigators found that developmental timing regulators, including specific miRNAs LIN-4 and LET-7 and transcription factor LIN-29, promote hypodermal signaling to the intestine to cue a metabolic shift from intestinal lipid storage to germline lipid utilization. The investigators further provide evidence that the hypodermal LIN-29-initiated signal to the intestine is mediated by the TORC2 complex (*let-363*/tor and *rict-1*/rictor) and not TORC1 (*daf-15*/raptor). They also demonstrated that SGK-1, a known kinase downstream from TORC2, critically mediates the regulation of vitellogenesis by LIN-29, consistent with previous work showing that TORC2 signaling through SGK-1 regulates *C. elegans* lipid storage (Jones et al. 2009). The investigators then carried out a genetic suppressor screen to identify genes acting downstream from SGK-1 to regulate *vit-3* expression. They identified *pqm-1* that encodes a C2H2 zinc finger transcription factor, suggesting that this transcription factor is negatively regulated by SGK-1 and subsequently inhibits the transcription of the vitellogenins.

The finding that the developmental timing regulatory mechanism in the hypodermis potentially regulates lipid mobilization, as suggested by vitellogenin gene expression, provides an exciting insight regarding the regulation of specific developmental decisions on metabolism. Since LIN-29 functions to specify the larval-to-adult transition (Ambros 2000), when the reproductive system will advance to oogenesis, this newly identified role of LIN-29 in mediating the timing of a signal to mobilize lipids makes perfect sense. Moreover, the novel roles revealed

for TORC2, SGK-1, and PQM-1 provide valuable mechanistic insights about this signaling event, creating a useful genetic scaffold for future studies. Truly, use of the many genetic tools available in *C. elegans* has revealed an unexpected, dual-tissue genetic connection. It will be very interesting in future studies to determine the physiological impact of these genetic changes that occur in distinct tissues but act on oocyte maturation, as others have questioned the impact of yolk protein production on reproductive success (Van Rompay et al. 2015). Further analysis at the protein level, coupled with functional assays, will make significant contributions to our understanding.

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