OUTLOOK

Feeding the germline

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Nucleotides are required in order to replicate DNA in the developing germline. Here, Chi and colleagues (pp. 307–320) have used *Caernohabditis elegans* to identify a GLP-1-dependent checkpoint that senses food (bacterially)-supplied nucleotide levels, arresting reproductive development in the absence of sufficient nucleotide supplies.

Everygrowing body needs nutrients. In fact, the need to regulate development and growth in concert with appropriate nutrient levels is so important that multiple genetic pathways—including the insulin/IGF-1, TOR, AMPK, and TGF-β signaling pathways—function primarily to report on the status of these nutrients and enforce checkpoints that prevent excessive growth in their absence.

Caenorhabditis elegans is a master of survival in part because of its ability to arrest growth at multiple points in the absence of sufficient resources; the alternative third larval dauer stage is the most famous of these arrests, but L1 diapause and adult reproductive diapause (ARD) can also be induced when the animals sense that nutrient levels are too low to successfully proceed to reproduction (Cassada and Russel 1975; Johnson et al. 1984; Angelo and Van Gilst 2009). Germline proliferation is also subject to several of these regulatory checks in GLP-1/Notch-independent pathways: The insulin-like peptides INS-3 and INS-33 act nonautonomously upstream of IIS to regulate DAF-16-dependent germline proliferation (Michaelson et al. 2010); TOR (*let-363*), RAPTOR (*daf-15*), and ribosomal protein S6 kinase (*rsks-1*) are required in the germline autonomously to promote germline proliferation (Korta et al. 2012); and the TGF-β ligand DAF-7 relays nutrient status information from ASI sensory neurons to the TGF-β receptor (DAF-1) and co-SMAD (DAF-5) in the DTCs (distal tip cells), ultimately affecting germline proliferation (Dalfo et al. 2012).

We normally think of amino acids, carbohydrates, and fats as major nutrients, and the mechanisms that regulate their sensing and intake have been well studied. However, organisms also need a source of nucleotides in order to replicate their DNA in proliferating cells. The germline of the adult animal is the most intensive user of nucleotides, so it would be logical for it to adjust cell proliferation rates accordingly with the nucleotide supply. Here, Chi et al. (2016) report finding exactly such a system: Nucleotide levels provided in the worms' food source, bacteria, affect fertility through the regulation of germline proliferation via the GLP-1/NOTCH and MAPK pathways.

The investigators first found that cytidine deaminase mutants, which cannot use the pyrimidine salvage pathway to generate nucleotides, have a fertility defect that is, surprisingly, rescued by feeding with the RNAi library *Escherichia coli* strain HT115 rather than the standard laboratory *E. coli* strain (OP50). This rescue is not due to RNase III loss but rather an insertion in the cytR gene, which normally represses nucleoside uptake and metabolism, thus increasing uridine levels in the HT115 bacteria. Supplementation of OP50 with uridine, cytidine, or thymidine also rescued fertility of the cytidine deaminase mutants, strengthening the connection between uridine/thymidine (U/T) uptake and fertility. Thus, low U/T levels in bacteria leads to sterility in mutants deficient in the pyrimidine salvage pathway.

Examination of the gonads during development revealed that mitotic proliferation arrest was responsible for the decrease in germ cell number, leading to sterility. This arrest could be due to a checkpoint or a simple lack of components; the former would most likely involve a signaling pathway that could be overridden. While the usual suspects, insulin/IGF-1 signaling and TORC1 pathways, were not involved, activation of the Notch signaling pathway at least partially recovered germline signaling. This result suggests that both a checkpoint and the U/T levels themselves affect germline proliferation. While the identity and location of the sensor that communicates the status of U/T levels to the Notch pathway were not identified, post-transcriptional regulation of GLP-1 levels

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and MAPK activation appear to regulate germline proliferation under low-U/T conditions in the absence of the pyrimidine salvage pathway.

The addition of a nucleotide nutrient-sensing mechanism of growth and reproduction regulation to the list of nutrient-sensing pathways provides a complement to the TORC1 pathway's sensing of amino acids and the insulin pathway's sensing of sufficient carbohydrate levels. Interestingly, the diversity of nutrient-sensing signaling pathways indicates that *C. elegans* tailors mechanisms to sense the need for specific nutrients at specific times in development. Considering that these pathways are evolutionarily conserved and that all organisms need to tune the demands of their tissues and cells to the available food, what we learn from worms will also provide insight into our knowledge in nutrient sensing in higher animals.

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