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A PBX/MEIS Complex Balances Reproduction and Somatic Resilience

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Abstract

Resource reallocation to metabolic processes promoting reproduction is critical for the survival of a species and therefore is tightly regulated. In this issue of *Developmental Cell*, Dowen (2019) finds that a PBX/MEIS homeodomain transcription factor complex controls a transcriptional network that balances reproduction versus longevity and somatic maintenance.

In their natural environments, animals are constantly challenged by fluctuating environmental conditions and changes in resource availability. Reproduction is metabolically costly and thus requires tightly regulated resource reallocation. During times of plenty, metabolic pathways shift reserves from the soma to the germline to support reproduction, but under adverse environmental conditions, such as starvation or stress, somatic resilience mechanisms are activated, often at the cost of germline functions. The underlying genetic and metabolic networks integrating developmental and environmental signals to balance soma-to-germ-line resource reallocation are poorly understood. In this issue of *Developmental Cell*, Robert Dowen identifies a transcriptional complex of two conserved homeodomain transcription factors, CEH-60/PBX and UNC-62/MEIS, as critical regulators that promote reproduction while suppressing somatic resilience and longevity.

In *Caenorhabditis elegans*, somatic lipid resources are transported from the intestine to the germline by vitellogenin lipoproteins (Kimble and Sharrock, 1983). Vitellogenins pack intestinal lipids into LDL-like particles to mobilize fat stores in a process termed vitellogenesis. The CEH-60 homeodomain transcription factor was identified in a genetic screen as a potent activator of vitellogenin transcription (Dowen et al., 2016). CEH-60 functions at the critical transition from late larval development to adulthood. At this developmental stage, lipids relocate from the intestine to the germline, where they are taken up by developing oocytes through receptor-mediated endocytosis (Grant and Hirsh, 1999). Vitellogenin expression has been implicated in a trade-off between reproductive fitness and longevity: while loss of vitellogenin gene expression increases lifespan (Murphy et al.,

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2003), the forced expression of vitellogenins is sufficient to deplete intestinal fat stores and decreases the lifespan of long-lived mutants (Seah et al., 2016).

The disposable soma theory of aging postulates that an organism has a limited amount of available resources, resulting in a metabolic trade-off between growth and reproduction versus somatic resistance (Kirkwood, 1977). Thus, a greater investment in reproduction should decrease somatic resilience. Surprisingly, Dowen shows here that inactivation of *ceh-60* or *unc-62* significantly extends lifespan but seems to have no effect on brood size (Dowen, 2019; Van Nostrand et al., 2013; Van Rompay et al., 2015). The fact that progeny number does not decrease while lifespan increases contradicts the trade-off mechanism proposed in the disposable soma hypothesis. However, maternal vitellogenesis defects in *ceh-60* mutants compromise progeny survival during early-stage larval starvation, which would result in a clear evolutionary fitness disadvantage in their natural habitat (Van Rompay et al., 2015). Here, Dowen demonstrates that the increased lifespan of *ceh-60* loss-of-function mutants correlates with an upregulation of genes controlling somatic resistance, uncoupled from the downregulation of vitellogenesis. The transcriptional data suggested that the CEH-60/UNC-62 heterodimer acts as a potent repressor of pathogen response gene expression. Indeed, inactivation of *ceh-60* increased survival of worms exposed to the bacterial pathogen *Pseudomonas aeruginosa*. Thus, *ceh-60* controls two separate processes, promoting reproduction by activating vitellogenin expression, while simultaneously repressing genes critical for survival in the presence of pathogens.

If CEH-60/PBX and its binding partner UNC-62/MEIS are crucial repressors of longevity and pathogen response, how do they interact with known longevity pathways, such as Insulin/IGF-1-like signaling, and what are the critical tissues for such an interaction? Dowen elegantly utilizes powerful *C. elegans* genetic approaches to dissect the role of CEH-60 in longevity regulation, finding that lifespan extension in the absence of CEH-60 depends on the intestine and the function of two key lifespan regulators, the FOXO transcription factor DAF-16 and mammalian Nrf2 ortholog SKN-1. Using ChIP-seq and mRNA-seq approaches, Dowen determined that CEH-60 and an intestinally enriched isoform of UNC-62 (Van Nostrand et al., 2013) act as potent transcriptional repressors. Both factors bind to similar promotor regions and physically form a complex. Although CEH-60 and UNC-62 mainly repress their targets, they also strongly activate a small subset of genes, including several vitellogenins. As DAF-16 and SKN-1 act largely as direct transcriptional activators, it is intriguing to identify transcription factors that predominantly mediate repressive gene regulatory function, potentially opposing such known activators. Thus, the promoter context, including additional transcriptional regulators and potentially co-activators and co-repressors, appears to be critical for CEH-60/UNC-62 transcriptional readouts.

The CEH-60/UNC-62 heterodimer does not act alone, and its transcriptional output—gene activation versus repression—is dependent on its promoter context. CEH-60/UNC-62 associates with the C2H2 zinc finger transcription factor PQM-1 (Tepper et al., 2013) at the GATA-like DAE motif (DAF-16-associated element) (Murphy et al., 2003) to mediate its function, largely at repressed CEH-60 targets. PQM-1 physically interacts with CEH-60 and the two factors bind to the same genomic regions, cooperating with UNC-62 in repression of gene expression. *pqm-1* is also required for *ceh-60* mutant lifespan extension, further

supporting the model that PQM-1 cooperates with the CEH-60 complex. Interestingly, phosphorylation on PQM-1 at a putative AKT/SGK-1 phosphorylation site may be required for its repressive activity, suggesting that upstream nutrient-sensing pathways, including Insulin/IGF-1-like signaling and TORC2 signaling, might tightly control PQM-1's function and association with the CEH-60/UNC-62 transcriptional complex. Thus, this dynamically regulated complex could act as a governor of cellular resources, integrating signals from nutrient-sensing pathways into developmentally timed somatic resistance and reproductive readouts.

Dowen describes pathogen resistance and defense response as examples of ''somatic resilience'' in a soma-to-germline resource reallocation model, proposing that elevated pathogen resistance is important during larval development, but enhanced pathogen defense is replaced by an increased investment in reproduction through mobilization of fat stores (vitellogenesis) to promote embryo development during the transition from late larvae to early adulthood. CEH-60 is expressed at this developmental transition state and appears to act as a major metabolic gatekeeper, repressing somatic resilience while simultaneously boosting the fat mobilization that is essential for reproduction.

This work on the PBX/MEIS complex and its interactions with other transcription factors, particularly PQM-1, highlights the need for organisms to regulate competing processes. Even relatively simple organisms with simple tissues, such as *C. elegans*, need to coordinate gene expression to optimize responses to their environmental conditions. It is expensive to express genes that are unnecessary under particular conditions, so the ability to repress longevity and innate immunity genes when reproduction is the primary demand, and vice versa, is important in tuning these responses. Regulating the network of gene interactions that control shifts in metabolism to meet the needs of the organism is necessary in more complex organisms as well. Since the mammalian PBX/MEIS transcription factors are conserved orthologs of the CEH-60/UNC-62 heterodimer, the complex gene network regulation elegantly dissected here is unlikely to be simply a *C. elegans* phenomenon. Therefore, it will be crucial to investigate the functions of PBX/MEIS in human lipid metabolism and pathogen response in the future.

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