

Heterochronic Genes and the Control of Larval Stages

Heterochronic genes are those genes that govern the normal progression of life history stages in an organism. In organisms such as ecdysozoan insects or nematodes, there are specific larval molts, and these molts are regulated by a combination of environmental and genetic factors. The factors involved in regulating the larval and metamorphic molts of some insects will be discussed in the chapter on metamorphosis (see Chapter 18). Here, we will briefly outline the heterochronic network of the nematode *C. elegans* (Resnick et al. 2010). This network involves the heterochronic genes encoding certain transcription factors and the microRNAs that regulate the timing of their expression. Moreover, under adverse environmental conditions, a “dauer” larva is formed, and this arrested stage of development is characterized by the freezing of development at a stage equivalent to the end of the second larval stage.

Upon completing embryogenesis, the worms hatch and develop through four larval stages (L1–L4), each terminating with a molt. After the fourth larval stage, the larvae molts into an adult. Here, the hypodermal seam cells that lay down the cuticle fuse and a new type of cuticle is produced.

The L1 stage is initiated by the appearance of the Lin-14 transcription factor. Lin-14 reciprocally induces Lin-28. If Lin-14 is mutated, the L2 state is brought about (possibly by Lin-28's activation of Hbl-1.)

Timely down-regulation of Lin-14 and Lin-28 is brought about by the appearance of the Lin-4 microRNA, which is discussed in Chapter 2. Lin-4 binds to the 3'UTR of these messages, preventing their translation.

The L2 stage is characterized by the Hbl-1 protein, an RNA-binding protein that is a homologue to the *Drosophila* hunchback protein. Hbl-1 stimulates those activities producing the second larval state and cuticle, and it inhibits those of the L3 state.

The L2 stage is superseded by L3, as three critical microRNAs inhibit the mRNA for Hbl-1. These microRNAs are mir-48, mir-241, and mir-84.

During the L3 stage, Let-7 levels begin to increase. Let-7 is a microRNA with numerous targets, and it regulates the transition from larval stage to adult stage. Let-7 down-regulates Lin-41, which would normally suppress the expression of the Lin-29 transcription factor. Now, the Lin-29 factor is active, and it inhibits the larval state and promotes those genes producing the adult phenotype.

But as mentioned earlier, adverse conditions such as poor food resources produce a dauer larva that will not progress to the L3 stage. Here, the larva can persist for months. This dauer larval state appears to be initiated by the DAF genes that sense environmental cues. In favorable conditions, DAF-9 produces steroid acids that bind to DAF-12, allowing it to act as a positive transcription factor for production of the mir-241, mir-84, and mir-48 microRNAs. This allows the transition from L2 to L3. However, in unfavorable environments, the steroid acids are not produced, and when the DAF-12 protein binds to the DNA, it binds an inhibitor of mir-241, mir-48, and mir-84 transcription. The larva is arrested at this state. The dauer (“permanent”) larva is able to survive harsh conditions for long periods of time. Getting out of the dauer stage involves some complicated maneuvering of the developmental pathways involving the regulation of Hbl-1 (Karp and Ambros 2012.)

A more complicated version of the regulatory pathway (still somewhat simplified) is shown in Figure 1.

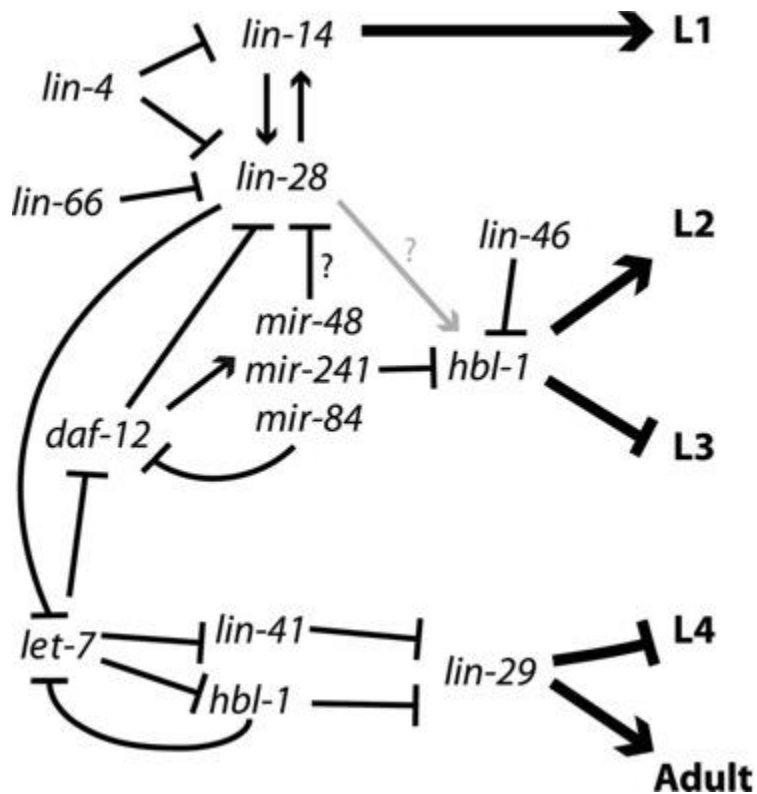


Figure 1 A model for the *C. elegans* heterochronic gene pathway. Arrows show activation; bars indicate repressions. These interactions allow the succession of larval stages and also the formation of the “dauer” larva, when Daf12 represses, rather than activates, a family of microRNAs. (From Resnick et al. 2010.)

Literature Cited

- Karp, X. and V. Ambros. 2012. Dauer larva quiescence alters the circuitry of microRNA pathways regulating cell fate progression in *C. elegans*. *Development* 139: 2177–2186.
- Resnick, T. D., K. A. McCulloch and A. E. Rougvié. 2010. miRNAs give worms the time of their lives: small RNAs and temporal control in *Caenorhabditis elegans*. *Dev. Dyn.* 239: 1477–1489.

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