A developmental clock with a checkpoint function

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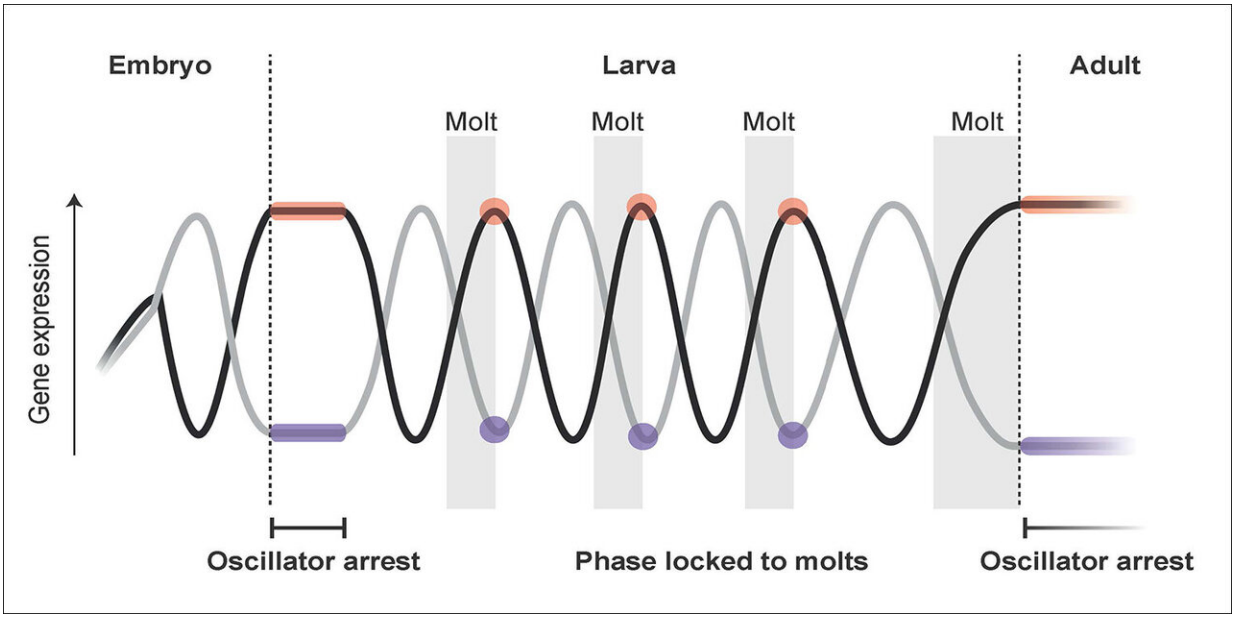

The genes of the C. elegans oscillator are expressed in a rhythmic pattern, are coupled to larval development, and can arrest in a specific recurring state, consistent with a developmental checkpoint function. Credit: Friedrich Miescher Institute for Biomedical Research

The group of Helge Grosshans characterized the "C. elegans oscillator", over 3,700 genes that are rhythmically expressed during the larval development of C. elegans. They demonstrated the coupling of the oscillator with molting and got insights into how it is wired. Their findings suggest that the oscillator functions as a developmental clock

with a developmental checkpoint function.

Gene expression oscillations—meaning the rhythmic expression of genes—occur in many biological systems. They are well-suited for time-keeping, acting as 'molecular clocks' that control repetitive processes. For example, gene expression oscillations underlie the circadian clocks that regulate the daily sleep-wake cycle of animals.

'Developmental clocks' similarly utilize gene expression oscillations to synchronize processes in tissue and organ development. Helge Grosshans and his research group have extensively studied developmental time-keeping in the roundworm C. elegans. In 2014, the group showed that the transcription of thousands of genes is subject to oscillations during larval development of this roundworm and that the oscillation period coincided roughly with the duration of a larval stage.

Milou Meeuse and Yannick Hauser, two Ph.D. students in the Grosshans group, investigated this phenomenon in more detail to gain insight into the architecture and function of the "C. elegans oscillator". Their study, supported by and ERC Advanced Grant, has recently been published in *Molecular Systems Biology*.

They performed extensive experiments to monitor gene expression over the entire period of C. elegans post-embryonic development and into adulthood. This allowed them to identify over 3,700 rhythmically expressed genes—about a quarter of all expressed genes. They identified four cycles of gene expression for the oscillating genes, reflecting progression through the four larval stages. Indeed, they found that oscillations occur in close synchrony with the molting cycle, i.e. the process of new cuticle synthesis and old cuticle shedding that occurs at the end of each larval stage. The researchers further observed that oscillations initiate in embryos, arrest transiently after hatching and in response to perturbation (for example, when the larva does not get food

anymore) and cease in adults. See image at the bottom.

"With our experiments, we clearly demonstrated the coupling of the oscillator with molting," says Milou Meuse, one of the first authors of the study. "We also showed that the oscillator can be halted, but only at specific times. These are the times when the worm "checks" whether the conditions are suitable to continue development for another full oscillation, or whether it had better arrest and wait, for example until food is available again. In other words, the oscillator has a developmental checkpoint function."

Co-first author Yannick Hauser adds: "It was really amazing to realize that we can explain how this checkpoint function arises from a specific oscillator architecture by drawing from nonlinear dynamics theory. This will now allow us to develop mathematical models to represent and further study the oscillator."

It is clear from this that the C. elegans oscillator is a developmental clock that helps the worm to take the right decisions regarding the timing of its development.

More information: Milou WM Meeuse et al. Developmental function and state transitions of a gene expression oscillator in Caenorhabditis elegans, *Molecular Systems Biology* (2020). DOI: 10.15252/msb.20209498

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