JCB Journal of Cell Biology

SPOTLIGHT

Hatched and starved: Two chromatin compaction mechanisms join forces to silence germ cell genome

Ana Karina Morao and Sevinc Ercan

Animals evolved in environments with variable nutrient availability and one form of adaptation is the delay of reproduction in food shortage conditions. Belew et al. (2021. *J. Cell Biol.* https://doi.org/10.1083/jcb.202009197) report that in the nematode *C. elegans*, starvation-induced transcriptional quiescence in germ cells is achieved through a pathway that combines two well-known chromatin compaction mechanisms.

Food availability is one of the biggest environmental challenges that animals commonly face. To ensure fitness, animals have evolved strategies to coordinate growth with food availability. The development of the nematode *Caenorhabditis elegans* illustrates clear examples of such strategies. During larval development, there are multiple stages at which worms can suspend growth if food becomes scarce. For example, if larvae face starvation upon hatching, they interrupt postembryonic development. This process, known as first larval stage (L1) arrest, allows them to survive for extended periods of time and resume development when food is present (1).

At the cellular level, quiescence has been associated with genome compaction and low transcriptional output in different species (2). In the case of *C. elegans*, embryonic divisions produce two primordial germ cells named Z2 and Z3 that arrest at a G2-like stage (3). When larvae hatch in the presence of food, the germ cells decompact their genome, activate transcription, and go through several divisions to proliferate. When hatched larvae face nutrient scarcity, germ cells enter a quiescent state characterized by further genome compaction. What are the mechanisms employed by cells to shut down transcription in response to environmental cues? In this issue of *JCB*, Belew et al. identify a new pathway, active through late embryogenesis and L1, that senses food shortage and mediates whole genome compaction, leading to transcriptional repression in germ cells (4).

In starved L1 larvae, the chromatin of Z2/Z3 cells is highly compacted and preferentially positioned at the nuclear periphery. To determine at which stage compaction is established, Belew and colleagues visualized this compaction throughout development and in starvation conditions by imaging mCherry-tagged histone H2B in living cells. The authors quantified chromatin compaction by simply partitioning the nuclei into two compartments: an outer compartment corresponding to the nuclear periphery and an inner compartment corresponding to the nuclear center. The degree of chromatin compaction was then expressed as a percentage of chromatin found within the inner compartment. This analysis showed that the genome of Z2/Z3 cells starts to get compacted at the gastrulation stage (Fig. 1). Importantly, if hatched worms are kept in nutrient-free media overnight, the genome gets further compacted and pushed to the nuclear periphery (Fig. 1). Thus, germ cells can go through two stages of genome compaction, one during late embryonic development that happens independent of food availability and another that happens upon starvation.

This observation motivated the authors to identify the molecular players underlying the starvation-induced genome compaction. Through a candidate RNAi screen, they found several genes involved in the two distinct chromatin compaction mechanisms. The authors report that condensin II and topoisomerase II (TOP-2), which compact chromosomes in preparation for cell division during mitosis, are required for the first stage of compaction during late embryogenesis (Fig. 1; 5). The second level of compaction that occurs upon starvation involves heterochromatin and requires CEC-4, which binds to H3K9me2/3 and promotes chromatin association to the nuclear periphery, and HPL-2 (homologue of HP-1; Fig. 1; 6).

The compaction mediated by condensin II/TOP-2 and heterochromatin, although viewed as two independent processes, were proposed to be interconnected (7, 8). Yet, how the two processes work together is unclear. Importantly, the authors showed that condensin II and TOP-2 are required for the high levels of H3K9me2/3 and HPL-2 observed in the Z2/Z3 cells during starvation-induced genome compaction (4). Furthermore, the authors report that depletion of both condensin/TOP-2 and heterochromatin pathways lead to activation of transcription, connecting genome compaction to transcriptional repression. Thus,

Department of Biology, Center for Genomics and System Biology, New York University, New York, NY.

Correspondence to Sevinc Ercan: se71@nyu.edu.

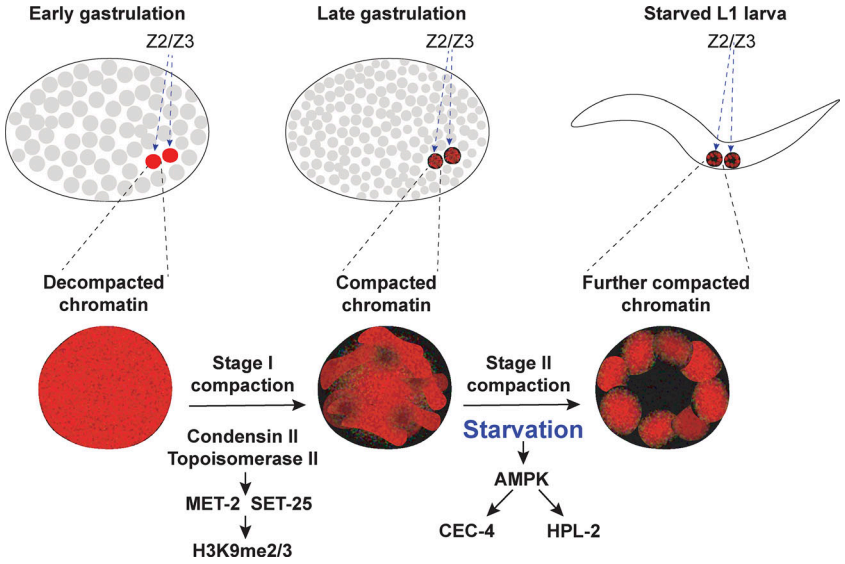

Figure 1. **Genome compaction in primordial germ cells (Z2/Z3) during *C. elegans* embryonic development and in starvation conditions.** Upon birth, the chromatin of Z2/Z3 cells is in a decompacted configuration. During late gastrulation, condensin II and TOP-2 perform a first round of chromatin compaction and mediate the deposition of H3K9me2/3 by MET-2 and SET-25 methyltransferases. If hatched larvae are kept in no-food conditions, AMPK is activated and mediates a second round of compaction that additionally requires CEC-4 and HPL-2.

condensin II and TOP-2 act upstream of H3K9me2/3 deposition in a pathway that compacts chromatin and represses germ cell transcription in the absence of food.

How does the absence of food control the two chromatin compaction processes? The authors found that the AMP-activated kinase (AMPK), which regulates the cellular response to starvation across different species, is required for the starvation-induced genome compaction. Since AMPK operates via phosphorylation, it is possible that some proteins acting within the global genome compaction pathway identified by Belew et al. are targets of AMPK (9).

Interestingly, Belew et al. showed that somatic cells did not respond to lack of food by compacting their genome; therefore, transcriptional shutdown in response to starvation may be specific to germ cells. Global transcriptional repression is a property of germ cells in *Drosophila*, mice, and *C. elegans* (10). It is possible that transcriptional silencing is a mechanism employed by germ cells to safeguard their genome integrity. Whether these germline silencing mechanisms leave "traces" in the form of histone modification patterns is an intriguing possibility. This information could then be transmitted and thus affect the response of future generations to environmental stresses. Examples of intergenerational and transgenerational effects due to starvation exist in *C. elegans*. For instance, F3 progeny of worms that were starved at the L1 stage have increased starvation resistance (11). Future work should address how epigenetic changes leading to transcriptional silencing could mediate adaptive response to starvation.

While transcriptional regulation of individual genes requires specific transcription factors, the global genome compaction pathway identified by Belew et al. utilizes two processes involved in chromosome condensation and domain-scale gene silencing to shut down transcription (4). Condensin II and TOP-2 are key components of compact and transcriptionally silent mitotic chromosomes. Notably, condensin participates in chromosome-wide transcriptional repression in the context of *C. elegans* X chromosome dosage compensation and quiescence in budding yeast (2, 12). Similarly, heterochromatin formation is a mechanism that compacts and silences multiple genes and regions of chromosomes in several different developmental contexts. This study shows how the two processes can work together and respond to environmental cues. Several new questions are raised by these observations. For instance, how do condensin II and TOP-2 mediate heterochromatin assembly? How does this compaction mechanism specifically act in the germ cells? How does AMPK control compaction, and are there other developmental cues or processes in other organisms controlled in a similar way? Insights into the control of genome structure and transcription at a global level across processes and species should begin to answer these questions.

Acknowledgments

S. Ercan and A.K. Morao were supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number R35 GM130311.

The authors declare no competing financial interests.

References

1. Baugh, L.R., and P.J. Hu. 2020. *Genetics.* https://doi.org/10.1534/genetics.120.303565
2. Swygert, S.G., et al. 2019. *Mol. Cell.* https://doi.org/10.1016/j.molcel.2018.11.020
3. Fukuyama, M., et al. 2006. *Curr. Biol.* https://doi.org/10.1016/j.cub.2006.02.073
4. Belew, M.D., et al. 2021. *J. Cell Biol.* https://doi.org/10.1083/jcb.202009197
5. Shintomi, K., et al. 2015. *Nat. Cell Biol.* https://doi.org/10.1038/ncb3187
6. Ahringer, J., and S.M. Gasser. 2018. *Genetics.* https://doi.org/10.1534/genetics.117.300386
7. Llères, D., et al. 2017. *Cell Rep.* https://doi.org/10.1016/j.celrep.2017.01.043
8. Wang, J., et al. 2017. *Genes Dev.* https://doi.org/10.1101/gad.301499.117
9. Hardie, D.G., et al. 2012. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/nrm3311
10. Nakamura, A., and G. Seydoux. 2008. *Development.* https://doi.org/10.1242/dev.022434
11. Jobson, M.A., et al. 2015. *Genetics.* https://doi.org/10.1534/genetics.115.178699
12. Albritton, S.E., and S. Ercan. 2018. *Trends Genet.* https://doi.org/10.1016/j.tig.2017.09.010