JCB Journal of Cell Biology

SPOTLIGHT

When one nucleus is not enough: Intestinal polyploidy fuels healthier progeny in *C. elegans*

Priya Sivaramakrishnan[1]

In this issue, Lessenger and colleagues (https://doi.org/10.1083/jcb.202403154) investigate why certain differentiated tissues require extremely high DNA content. Using the nematode worm *Caenorhabditis elegans*, they show that restricting genome copies in intestinal cells triggers compensatory gene expression adaptations, which maintain organismal fitness at the expense of offspring vitality.

Biology's remarkable diversity extends to cell size, with dramatic differences across and within organisms. In humans, red blood cells measure just 7–8 µm, while oocytes exceed 100 µm, and neurons can stretch over a meter. How do cells meet the molecular requisites to produce components essential for their structure and function at such vastly different scales? One strategy is polyploidization or increasing genome copy number. Since DNA serves as the template for RNA, and RNA encodes proteins, additional genome copies can, in principle, amplify transcriptional capacity and align gene expression with the needs of a cell.

Polyploidy is a common adaptation across many different organisms. It enhances yields in crop plants like potatoes and coffee. It is also associated with cell types that have high physiological output, such as *Drosophila* nurse cells that supply RNA and protein to the developing oocyte, and massive mammalian megakaryocytes that bud off platelets (1, 2). However, whether polyploidy is causally required to boost gene expression remains an open question. Total mRNA and protein levels often do scale with genome copy number under normal conditions, helping maintain average concentration homeostasis (3, 4, 5). Some plant cells show near-linear scaling between ploidy and gene expression, whereas in yeast and mammalian systems, many individual mRNAs and proteins exhibit sub- or super-scaling behavior, departing from a simple one-to-one correlation with DNA content (6, 7, 8). This scattered picture leaves an important question: when and why does extra DNA become indispensable?

Evidence from unicellular yeast and cultured mammalian cells suggests that diluting DNA relative to cytoplasm can slow growth and create starvation-like states associated with senescence and aging (9, 10). This underscores that a critical DNA-to-cytoplasm ratio likely coordinates optimal biosynthesis. Yet, it remains unclear whether ploidy determines cell size or if larger cells inherently require increased ploidy. Proliferating cells can time their divisions to restore DNA-to-cytoplasmic ratios, but terminally differentiated cells, like those in tissues, lack that escape hatch. This prompts speculation about whether an organ could simply generate many smaller diploid cells instead of fewer giant polyploid cells or if fundamental, tissue-level constraints drive polyploidization to meet intense metabolic obligations.

A new study by Lessenger et al. (11) tackles these issues using the *Caenorhabditis elegans* intestine, which provides an ideal system to test whether high ploidy is essential for robust molecular output. The adult intestine, derived from a single embryonic progenitor, contains 20 binucleate cells that each ramp up from 2C (diploid) to 32C, yielding ~1,024 genome copies across the organ. This tissue is central for biomass production, generating enormous quantities of yolk proteins essential for reproduction. To determine whether polyploidy directly influences biosynthetic capacity, the authors employed a tissue- and time-specific genetic approach to degrade CDK-2, a key cell cycle kinase, during the normal rounds of genome amplification in intestinal cells. This effectively limited the rise in DNA content, allowing them to probe how diminished ploidy affects cell size, biomolecule abundance, and, ultimately, the worm's fitness and progeny development (Fig. 1).

As expected, animals with fewer genome equivalents in the intestine had smaller gut cells and a reduced intestinal size. Yet strikingly, the worms themselves grew to near-normal overall size. The authors propose that although the DNA-dilute intestine still fulfills basic nutritional needs, the organ sacrifices certain high-demand functions. Chief among them is yolk production to better sustain the next generation.

One might predict that drastically reducing DNA would cripple mRNA production. Indeed, total mRNA concentration declined, but not in proportion to the steep drop in genome copies. Employing another neat trick, by spiking in dissected intestines from the related nematode *Pristionchus pacificus*, the authors could measure absolute transcript levels per genome. They found that the remaining DNA compensates by ramping up transcription, yet this offset was uneven. Highly expressed genes suffered

[1]Department of Pathology and Laboratory Medicine, Center for Computational and Genomic Medicine, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA.

Correspondence to Priya Sivaramakrishnan: psiv@pennmedicine.upenn.edu.

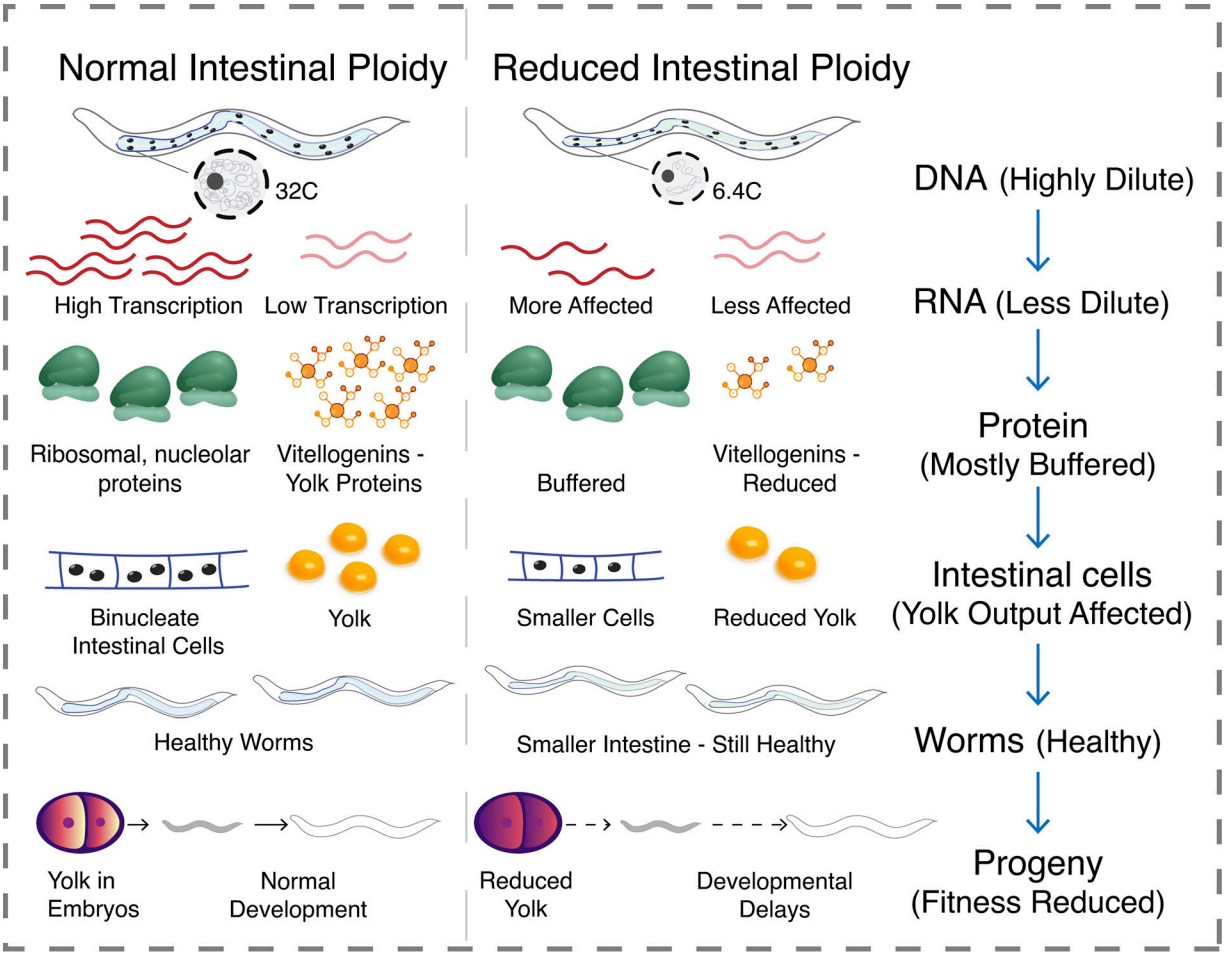

Figure 1. **Multiscale consequences of reduced ploidy in the *C. elegans* intestine.** Model contrasts wild-type/normal ploidy with reduced ploidy. Lowering genomic content per nucleus leads to diluted DNA, but transcriptional output is increased such that RNA is less dilute than DNA, but highly expressed genes are more affected. Protein levels are mostly buffered, with the exception of yolk. Maintenance of protein abundance sustains organismal health but leads to embryos with lower yolk levels that cause developmental delays in the offspring.

disproportionately. The authors suggest that the promoters of these genes, which are already near saturation with RNA polymerase II cannot boost transcript output further. This partial compensation challenges a simple one-size-fits-all model of transcription scaling.

Despite reduced mRNA, the total protein concentration in the intestine was maintained, partly through an upregulation of ribosomal and translational machinery. Even so, this was insufficient to rescue the production of yolk proteins (vitellogenins). Thus, the worms made do with less DNA but paid a reproductive cost—limited yolk decreased embryonic provisioning, slowing offspring development. Similar effects have been reported when intestinal cells fail to undergo binucleation, which also reduces vitellogenin production and delays progeny growth (12). This shared phenotype underscores the crucial role of high ploidy in meeting the intestine's specialized demands.

Lessenger et al. compellingly argue that polyploidy is no developmental quirk but a requirement critical to sustaining robust gene expression in tissues where continuous cell division could disrupt structure or function. Moving forward, tools from this study can be combined with refined labeling strategies to dissect the interplay between rates of mRNA/protein synthesis versus decay under DNA-dilute conditions. Pinpointing the sensors or limiting factors that allow cells to "know" when DNA content is too low remains a key challenge. The general concept of a cell being "aware" of its ploidy or cell size is intriguing. One striking illustration is the heterokaryon experiment in which fusing a small melanoma cell to a large fibroblast triggered an upscaling of transcription from the smaller nucleus (13). While one might intuitively assume that RNA polymerase II and general transcription machinery alone can drive scaling, there appears to be more complex feedback between transcript and protein production and their relative stabilities that needs further exploration.

Polyploidy supports diverse functions in tissues, from maintaining tissue integrity and architecture, as suggested by the authors of this study, to enabling regeneration in the liver or buffering against genotoxic stress during aging. While the intestine demands substantial yolk production, these findings hint that other high-output tissues might similarly rely on polyploidy to prioritize certain gene products. Understanding how and why certain transcripts are more or less buffered could uncover universal principles of gene regulation in large, polyploid cells.

As we continue to unravel these mysteries, the humble worm's gut stands as a powerful model, illustrating how fundamental processes such as gene expression, cell size, and DNA content converge to orchestrate the well-being of organisms and their future offspring. Lessenger et al. provide foundational insights, giving us a deeper appreciation for why, sometimes, one nucleus simply is not enough.

Acknowledgments

Author contributions: P. Sivaramakrishnan: Funding acquisition, Writing - original draft, Writing - review & editing.

Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

References

1. Balachandra, S., et al. 2022. *Annu. Rev. Genet.* https://doi.org/10.1146/annurev-genet-080320-030537
2. Lee, H.O., et al. 2009. *Genes Dev.* https://doi.org/10.1101/gad.1829209
3. Basier, C., and P. Nurse. 2023. *EMBO J.* https://doi.org/10.15252/embj.2022113333
4. Zhurinsky, J., et al. 2010. *Curr. Biol.* https://doi.org/10.1016/j.cub.2010.10.002
5. Xie, S., et al. 2022. *Annu. Rev. Cell Dev. Biol.* https://doi.org/10.1146/annurev-cellbio-120219-040142
6. Song, Q., et al. 2020. *Genome Biol.* https://doi.org/10.1186/s13059-020-02094-0
7. Swaffer, M.P., et al. 2023. *Cell.* https://doi.org/10.1016/j.cell.2023.10.012
8. Yahya, G., et al. 2022. *Nat. Commun.* https://doi.org/10.1038/s41467-022-33904-7
9. Neurohr, G.E., et al. 2019. *Cell.* https://doi.org/10.1016/j.cell.2019.01.018
10. Lanz, M.C., et al. 2024. *Nat. Struct. Mol. Biol.* https://doi.org/10.1038/s41594-024-01353-z
11. Lessenger, A.T., et al. 2025. *J. Cell Biol.* https://doi.org/10.1083/jcb.202403154
12. van Rijnberk, L.M., et al. 2022. *PLoS Biol.* https://doi.org/10.1371/journal.pbio.3001597
13. Padovan-Merhar, O., et al. 2015. *Mol. Cell.* https://doi.org/10.1016/j.molcel.2015.03.005