Nuclear sizER in Early Development

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In this issue of Developmental Cell, Mukherjee et al. (2020) investigate control of nuclear growth by live imaging of early embryogenesis, perturbations of blastomere dimensions, and reconstitution in vitro. The authors uncover new mechanisms of nuclear size scaling by the amount of inherited perinuclear ER and duration of interphase.

A central requirement in biology is the coupling of organelle and cell size to coordinate cell growth and division during proliferation and to ensure proper scaling of components during the reductive divisions of early embryogenesis. Nucleus size control is particularly important because dysregulation of nucleus size or of nucleocytoplasmic volume ratio (N:C) is associated with cellular transformation and tumor growth (Zink et al., 2004). Additionally, perturbations to nuclear size, cell size, or N:C ratio can affect the timing of zygotic gene transcription in early development (Chen et al., 2019; Jevtić and Levy, 2015). During the cell cycle, nuclei disassemble in mitosis, and their re-assembly requires condensation of the endoplasmic reticulum (ER) around chromatinids to form the nascent lamina and nuclear envelope (Anderson and Hetzer, 2007). In recent years, the mechanisms controlling subsequent growth of the nucleus during interphase and the overall nucleus size set point have received intense scrutiny. Multiple distinct pathways appear to regulate nucleus growth, including nuclear import, DNA ploidy, and availability of membrane and its association with or transport on microtubules (Hara and Merten, 2015; Levy and Heald, 2010). Additionally, in the rapid cleavage stages of early embryogenesis, nuclei might not achieve a steady-state size due to the short duration of interphase. A number of challenges have hampered our understanding of nucleus growth control, including difficulty in live imaging of whole-mount embryos, trouble in decoupling cell size and nucleus size, and imperfect reconstruction of cell and organelle volumes.

In work published in this issue of Developmental Cell, Mukherjee et al. (2020) overcome key experimental hurdles in one shot by measuring nucleus growth in real time and decoupling nucleus volume from cell volume. Using live imaging of nuclear growth and immunostaining followed by imaging of ER in fixed embryos, they identify perinuclear ER (pER) as a key limiting component to nucleus growth in blastomere divisions of sea urchin early embryos (Figure 1) (Mukherjee et al., 2020). First, the authors establish that during these rapid early divisions, from 1- to 32-cell stages, nuclei do not reach steady-state sizes. Next, a number of clever approaches allow the authors to distinguish between the contribution of cell size versus a pool of pER to nucleus size. Sea urchin embryos contain a gradient of cell sizes, including small micromeres and large macromeres, enabling the authors to show that nucleus size is not directly coupled to cell volume. Additionally, using magnetic beads that interface with asters (Salé et al., 2019), they generate highly asymmetric cell divisions that decouple cell size and nucleus size. Further, they produce volume-reduced embryos via cutting to show that nuclear growth is not limited by cytoplasmic volume in 1-cell embryos. These results clearly demonstrate that an inherited component, but not the absolute cytoplasmic volume, sets nuclear growth and maximum nucleus size.

To corroborate their findings, Mukherjee et al. (2020) demonstrate that a simple mathematical model based on bipartite segregation of pER predicts the scaling of nucleus volume. In short, the limited available pool of pER decreases ~2.2-fold at each cell division, and the amount of pER fuels the proportionate growth of newly formed nuclei. The authors further validate their findings using vertebrate embryos and an in vitro model system. They find that pER volume is correlated with nuclear surface area, particularly in blastomeres isolated from late blastula and early gastrula stages of developing Xenopus. Additionally, they find that the amount of pER accumulated around newly assembled nuclei is proportional to cytoplasmic volume in cell-like compartments containing Xenopus egg extracts. By supplementing the system with additional membrane fraction, including ER, they further demonstrate that available membrane fuels nuclear growth.

In limiting component models for organelle growth, key factors might be well mixed in the cytosol and/or anchored to subcellular structures that are inherited during cell division. In the former case, organelle size scaling would be strongly correlated to cell size (Good et al., 2013), whereas with anchored limiting components, the organelle size set point could be decoupled from cytoplasmic volume. Experiments in mouse have shown spindle assembly checkpoint activity scales with the amount of a limiting component localized to the nuclear membrane rather than simply overall cell size (Kyogoku and Kitajima, 2017). As in the work highlighted here, subcellular activity scales directly with a pool of localized material rather than strictly with absolute cytoplasmic volume. Of course, cell volume might play a key role in nucleus growth control during other stages of embryogenesis, for example, by dictating the amount of pER in an egg or 1-cell embryo. Additionally, cytoplasmic volume might have a more direct role in controlling nucleus size at later stages of sea urchin development if the rate limiting step for growth shifts to the cytosolic availability of nuclear import factors.
The findings of this study represent significant progress in our understanding of nucleus growth regulation and size homeostasis during the cleavage stage of embryo development. Additionally, the work from Mukherjee et al. (2020) raises a number of questions. For example, why is localized pER the predominant source of material for nucleus growth? Is this mechanism inherently due to pER anchoring to the centrosome, in contrast to Golgi membranes or endomembranes, which might be more distributed throughout the cytosol? Additionally, what role might pER play in the dysregulation of nucleus size observed in cancer cells? Quantitation of pER in disease models might reveal that it contributes to increased nucleus growth and an inappropriate large N:C ratio. Importantly, does the local pool of pER broadly control nucleus size during early embryogenesis of model vertebrate systems or in mammalian embryo development? Future studies are needed to determine whether pER limits nucleus growth in early cleavages of Xenopus or zebrafish whose blastomere volumes are more than 1000-fold larger than those from sea urchins. For example, in the giant blastomeres of large vertebrate embryos, nuclei and mitotic spindles reach plateau sizes (Good et al., 2013; Levy and Heald, 2010). It will be important in future work to determine the extent to which the scaling rules uncovered in the sea urchin embryo can be applied to proliferative cells and the development of other model organisms.

REFERENCES


