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How chromosomes shrink to fit

Chromosome length in early embryo reflects the dimensions of the cell and nucleus.

Cells in an early embryo need to downsize their DNA. Ladouceur et al. show that a cell's size and the size of its nucleus determine how small its chromosomes become (1).

Like someone who's moved from a house to an apartment, cells in an early embryo run into space limitations. The embryo remains the same size for its first few divisions, so the cells have to become much smaller, shrinking by as much as 99%. Some components, such as individual mitochondria and clathrin-coated vesicles, seemingly remain the same size as cells miniaturize. But the centrosome, mitotic spindle, and nucleus contract. For more than a century researchers have known that cells in early embryos also compact their chromosomes. To prevent tangling during mitosis, the biggest chromosomes can't exceed half the length of the mitotic spindle (2). However, researchers didn't know which cues cells rely on to determine chromosome size. One research group addressed the question by allowing small nuclei to stew in extracts from large cells for an entire cell cycle (3). The nuclei expanded, suggesting that chromosome size tracks cell size. Another group concluded that chromosome size tracks nuclear size after artificially shrinking nematode nuclei and finding that the chromosomes also got smaller (4).

Ladouceur et al. set out to resolve this contradiction by following *C. elegans* embryos through the 16-cell stage. The researchers noticed that chromosomes didn't begin shrinking until after the 4-cell stage. Once they did begin to contract, the chromosomes shortened at a regular rate of about 52 nm for every µm reduction in cell diameter.

To test the effect of cell size on chromosome shrinkage, the researchers forced embryos and cells to become smaller by depleting the protein IMA-3, a component of the nuclear pore complex. Chromosomes in the tiny embryos started compacting after the 2-cell stage instead of after the 4-cell stage, a sign that cell size influences the process. Moreover, if chromosome size doesn't track cell size, the team's manipulation should change the rate of chromosome shrinkage. Instead, the chromosomes shortened at the same pace as in controls.

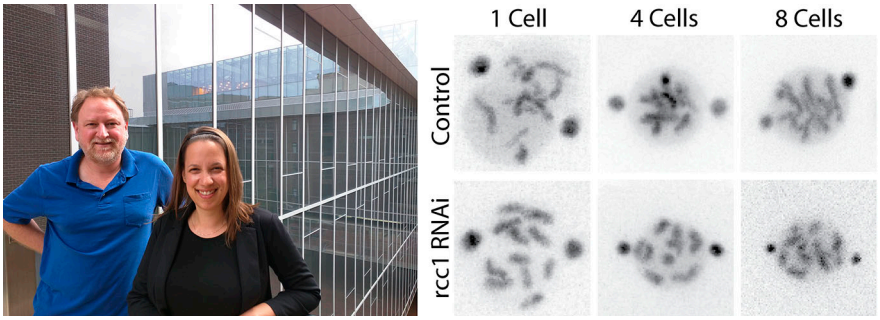
Although those findings supported the contention that chromosome length depends on cell size, they didn't rule out a role for nuclear size. Proteins that control import of material into the nucleus affect its dimensions as well as the dimensions of the cell. The researchers found that depleting one of these proteins, RCC1, resulted in cells with disproportionately small nuclei. Cells lacking RCC1 also had chromosomes that were disproportionately small, bolstering the notion that nucleus size also helps determine chromosome size.

> "Chromosomes respond to cell size, and they also respond to nuclear size."

Chromosomes in embryos lacking RCC1 were extra compact. Since RCC1 binds to chromatin, it could be directly controlling chromosome size. But it could also exert an indirect effect because it helps set up the Ran GTP gradient that powers import and export of cargoes through nuclear pores. To test these possibilities, the scientists depleted other proteins that help establish this gradient. Eliminating one of them, RAN-4 (NTF2), produced abnormally short chromosomes.

"What we've done is to show experimentally that chromosomes respond to cell size, and they also respond to nuclear size," says senior author Paul Maddox. Researchers still need to determine how both variables influence chromosome length, but the mechanism requires movement of material through the nuclear pores. One possible explanation, the authors suggest, is that the embryo starts out with a large amount of a protein that inhibits compaction of chromosomes. With every division, each cell in the embryo carries less and less of the inhibitor, allowing its chromosomes to scrunch tighter and tighter. This hypothesis also explains why disturbing the Ran GTP gradient leads to shorter chromosomes, because less of the inhibitor would be able to enter the nucleus.

Focal Point



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Paul Maddox (left), Anne-Marie Ladouceur (right), and Jonas Dorn determined what factors dictate the size of chromosomes in early *C. elegans* embryos. They found that the length of chromsomes depends on nuclear and cell size. The Ran GTP gradient across the nuclear membrane also affects chromosome compaction. In a control embryo, the chromosomes get smaller from division to division (top row). But in an embryo lacking RCC1, which helps establish the Ran GTP gradient, the chromosomes shrink faster (bottom row).

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4. Hara, Y., et al. 2013. *Mol. Biol. Cell*. 24:2442–2453.