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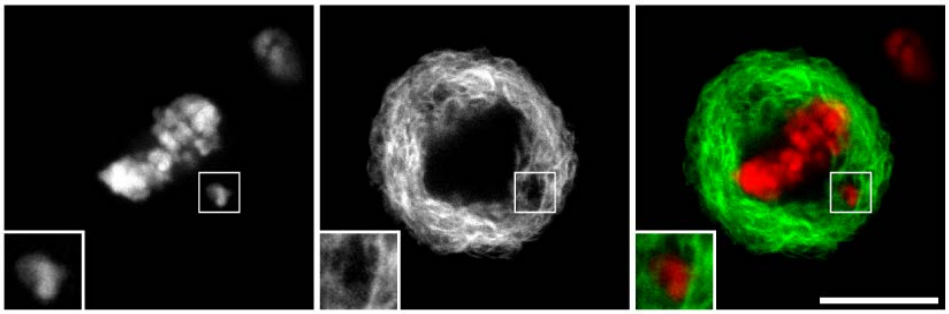
ENDOMEMBRANES PROMOTE CHROMOSOME MISSEGREGATION

Misaligned chromosomes can become ensheathed by intracellular membranes during mitosis, leading to missegregation and micronucleus formation.

In order to segregate correctly during mitosis, chromosomes must attach to the mitotic spindle and align themselves at the metaphase plate. Errors or delays in this process can lead to cells with micronuclei and/or abnormal numbers of chromosomes, features that are frequently seen in cancer cells and are thought to contribute to tumor progression.



During mitosis, chromosomes (red) that lie outside of the central exclusion zone become ensheathed by endomembranes (green), impairing their alignment at the metaphase plate. © 2022 Ferrandiz et al.

At the onset of mitosis, the nuclear envelope breaks down and the endoplasmic reticulum and Golgi apparatus disperse to the periphery of the cell, while the mitotic spindle assembles in a central "exclusion zone" that is largely devoid of membranes and organelles. "We wanted to know what happens to misaligned chromosomes that find themselves among the organelle remnants, or endomembranes, beyond the exclusion zone," explains Stephen Royle of Warwick Medical School.

Using light and electron microscopy, Royle and colleagues observed that misaligned chromosomes beyond the exclusion zone become ensheathed by 3–4 layers of endomembranes. "That immediately raised questions about the fate of these chromosomes and whether ensheathing leads to aberrant mitosis," says first author Nuria Ferrandiz.

The researchers found that ensheathed chromosomes fail to form stable attachments to spindle microtubules, preventing their movement to the metaphase plate. As a result, cells containing ensheathed chromosomes activate the spindle assembly checkpoint, delaying their progression through mitosis. Eventually, however, the checkpoint is exhausted, and the cells divide without aligning the ensheathed chromosome correctly, increasing the frequency of chromosome missegregation and micronucleus formation. Notably, the nuclear envelope surrounding these micronuclei was disrupted, exposing the missegregated chromosomes to the cytosol and leaving them potentially vulnerable to DNA damage.

To confirm that ensheathing causes chromosome missegregation, Royle and colleagues developed a method to clear endomembranes away from misaligned chromosomes positioned outside of the exclusion zone. In cells expressing an FKBP-tagged ER-resident membrane protein and an FRB-tagged plasma membrane protein, the researchers were able to induce the relocalization of most endomembranes to the cell boundary by adding rapamycin, a drug that promotes FKBP-FRB dimerization. Removing endomembranes in this way allowed formerly ensheathed chromosomes to move to the metaphase plate and segregate correctly.

"Taken together, our findings indicate that endomembranes are a risk factor for chromosome missegregation if misaligned chromosomes go beyond the exclusion zone boundary during mitosis," Royle says.

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