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CHROMOSOME BIOLOGY

Keeping chromosomes apart

The mechanisms ensuring the proper separation of mitotic chromosomes (a process referred to as 'chromosome individualization') are not fully clear. Ki67 is a cell proliferation marker that associates with the chromosome surface, although its role there is not fully characterized. Cuylen and colleagues now show that, following disassembly of the nuclear envelope at the transition between prophase and prometaphase, Ki67 prevents chromosomes from clustering in the cytoplasm.

The authors performed an siRNA screen in HeLa cells to identify proteins, the depletion of which prevented chromosome individualization. Live-cell imaging revealed that only siRNAs against *MKI67*, the gene encoding Ki67, caused chromosome clustering. Further experiments showed that, although Ki67 is not required to initiate chromosome individualization, it maintains it following the breakdown of the nuclear envelope by decreasing adhesion between chromosomes. Mapping studies revealed that the carboxy-terminal domain of Ki67, which binds to chromosomes, is required for chromosome individualization but that this function of Ki67 does not localize in any other specific portion of the protein.

So, how does Ki67 reduce adhesion between chromosomes to ensure their separation? As it is a large amphiphilic protein with a high positive charge — properties reminiscent of surfactants, which can prevent particles or droplets from aggregating using steric hinderance and/or electrostatic repulsion — the authors asked whether Ki67 separated chromosomes by a similar mechanism. Indeed, Ki67 proteins with a reduced size and charge were less efficient at restoring chromosome separation in Ki67-depleted cells, and rescue efficiency correlated with protein size and predicted charge. In addition, overexpressing high levels of core histones, which, like Ki67, are highly charged DNA-binding proteins, also rescued chromosome clustering in Ki67-depleted cells; this adds weight to the idea that electrical charge helps to separate mitotic chromosomes.

Finally, the authors showed that ~270,000 Ki67 molecules bind to the entire set of mitotic chromosomes, suggesting that there is enough Ki67 present for nearby chromosomes to repel each other. Confocal microscopy also revealed that Ki67 takes on a 'brush-like' molecular organization that is typical of surfactants: it binds to the chromosome through its C-terminal end and sticks out into the cytoplasm perpendicular to it.

In short, this study demonstrates that Ki67 acts like a biological surfactant in prometaphase to keep mitotic chromosomes separate in the cytoplasm following their release from the nuclear envelope.

Katharine H. Wrighton

ORIGINAL ARTICLE Cuylen, S. *et al.* Ki-67 acts as a biological surfactant to disperse mitotic chromosomes. *Nature* http://dx.doi.org/10.1038/nature18610 (2016)
FURTHER READING Ramkumar, N. & Baum, B. Coupling changes in cell shape to chromosome segregation. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2016.75 (2016)