

Organization and maintenance of centromere

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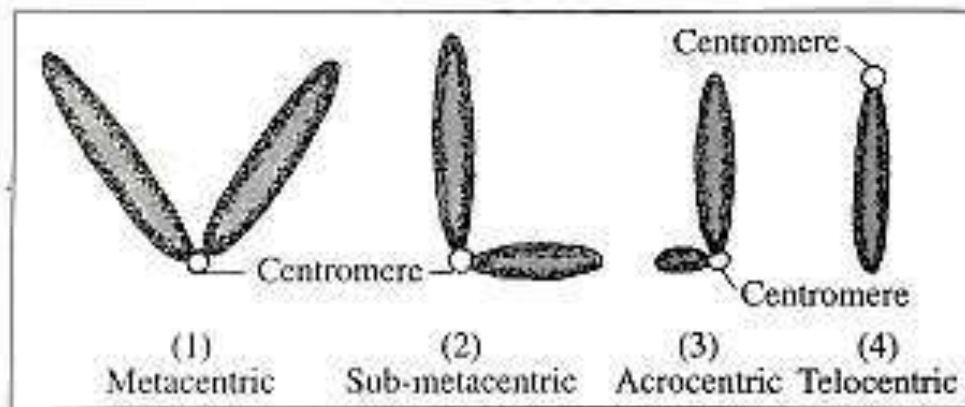
Introduction

- ❑ It is the site on chromosome where a chromosome is attached to the kinetochore and microtubule.
- ❑ It is the specialized DNA of a chromosome that links a pair of sister chromatids (a dyad).
- ❑ It is a large complex structure where the kinetochore is embedded in silent heterochromatin.
- ❑ It is the most fundamental region of the chromosome that maintain accurate genome segregation and stability.
- ❑ It is the most condensed and constricted region of a chromosome.
- ❑ It also serves as the point of attachment for spindle fibers.
- ❑ It is extremely important for cell division in eukaryotes; its deregulation in the cell cycle can lead to several checkpoint disorders and pathogenicity.
- ❑ While, kinetochores are two discs of proteins, located at the centromere, on opposite sides of the chromosome.
- ❑ The microtubules that attach to the chromosomes actually attach to the kinetochores (which is why those microtubules are called kinetochore microtubules).

Location of centromere

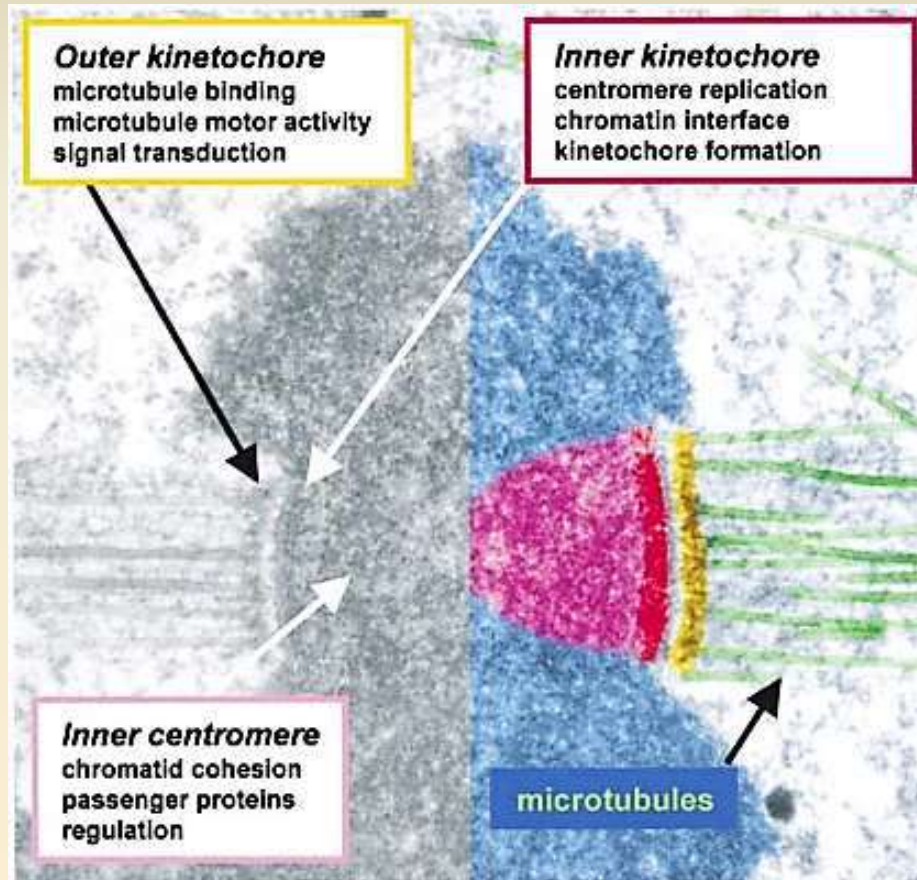
Generally, centromeres are located on the central area of the chromosome. However, it does not occur always. It is because of short arm and long arm of chromosomes. Thus, a centromere may be of following types;

- ❑ **Metacentric:** Centromeres are located near the chromosome center.
- ❑ **Submetacentric:** Centromeres are non-centrally located so that one arm is longer than the other.
- ❑ **Acrocentric:** Centromeres are located near the end of a chromosome.
- ❑ **Telocentric** :Centromeres are found at the end or telomere region of a chromosome.



Types of Chromosomes

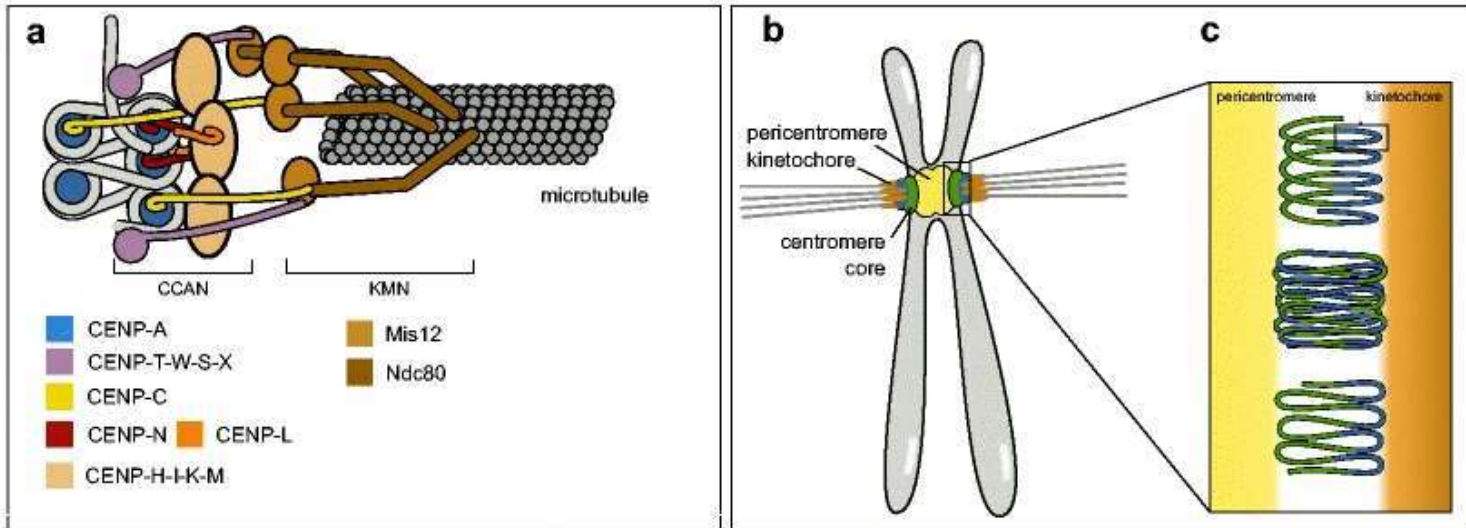
Structure of centromere



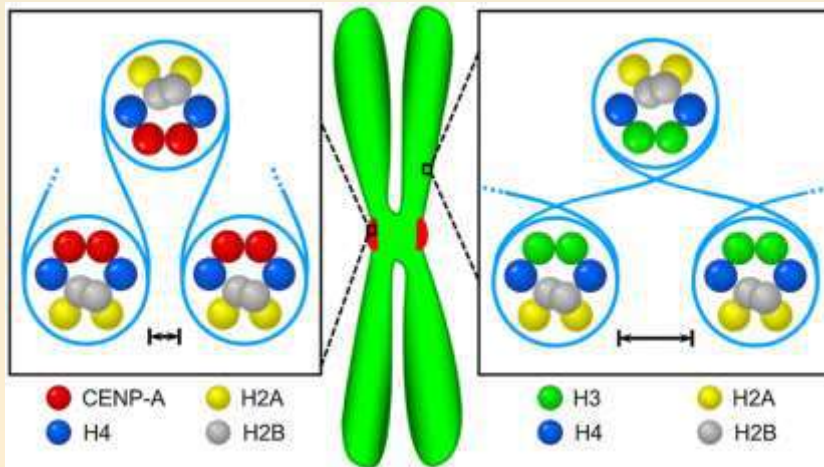
Inner centromere
↓
Cohesins and
regulatory proteins
such as Aurora B
and Kin I.

Organization of centromere.
Cell, Vol. 112, 407–421, February 21, 2003

Structural organization of a centromere



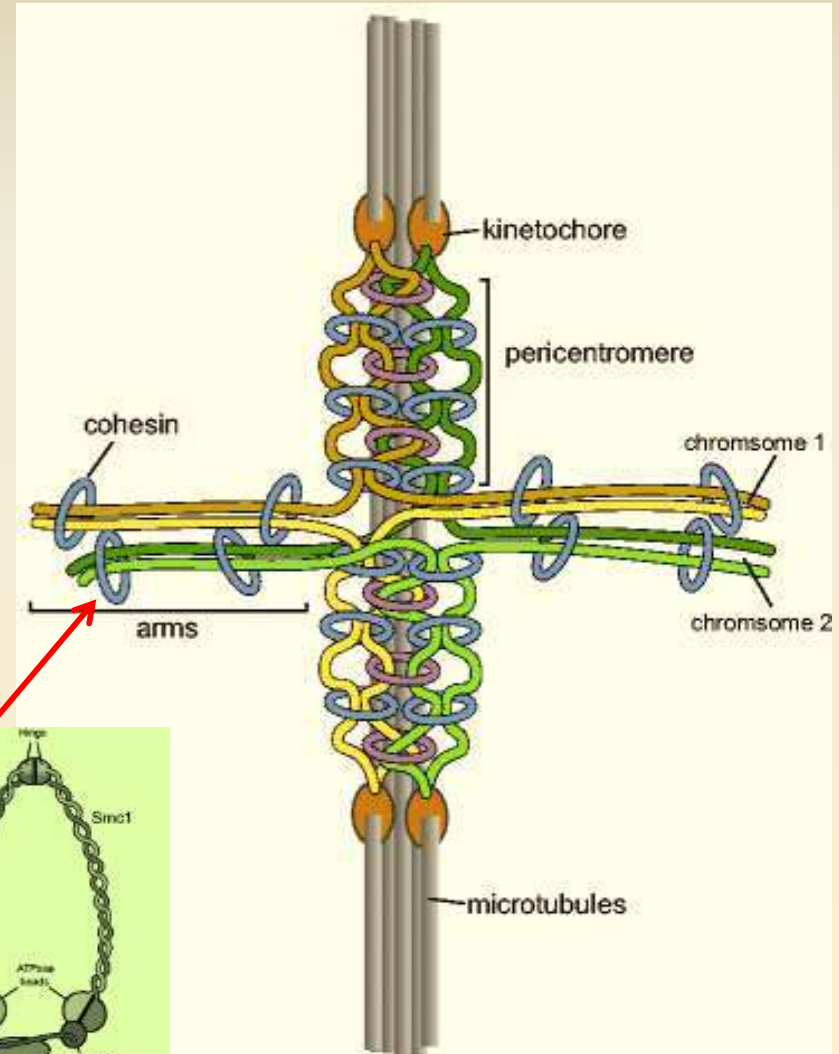
Bloom & Costanzo 2017; DOI https://doi.org/10.1007/978-3-319-58592-5_21



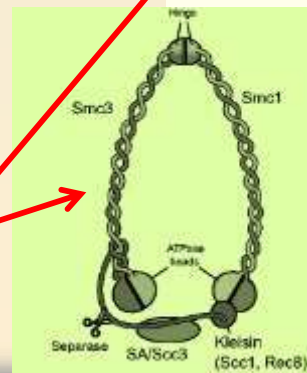
CENP-A-H3 nucleosome

Structural organization of a centromere

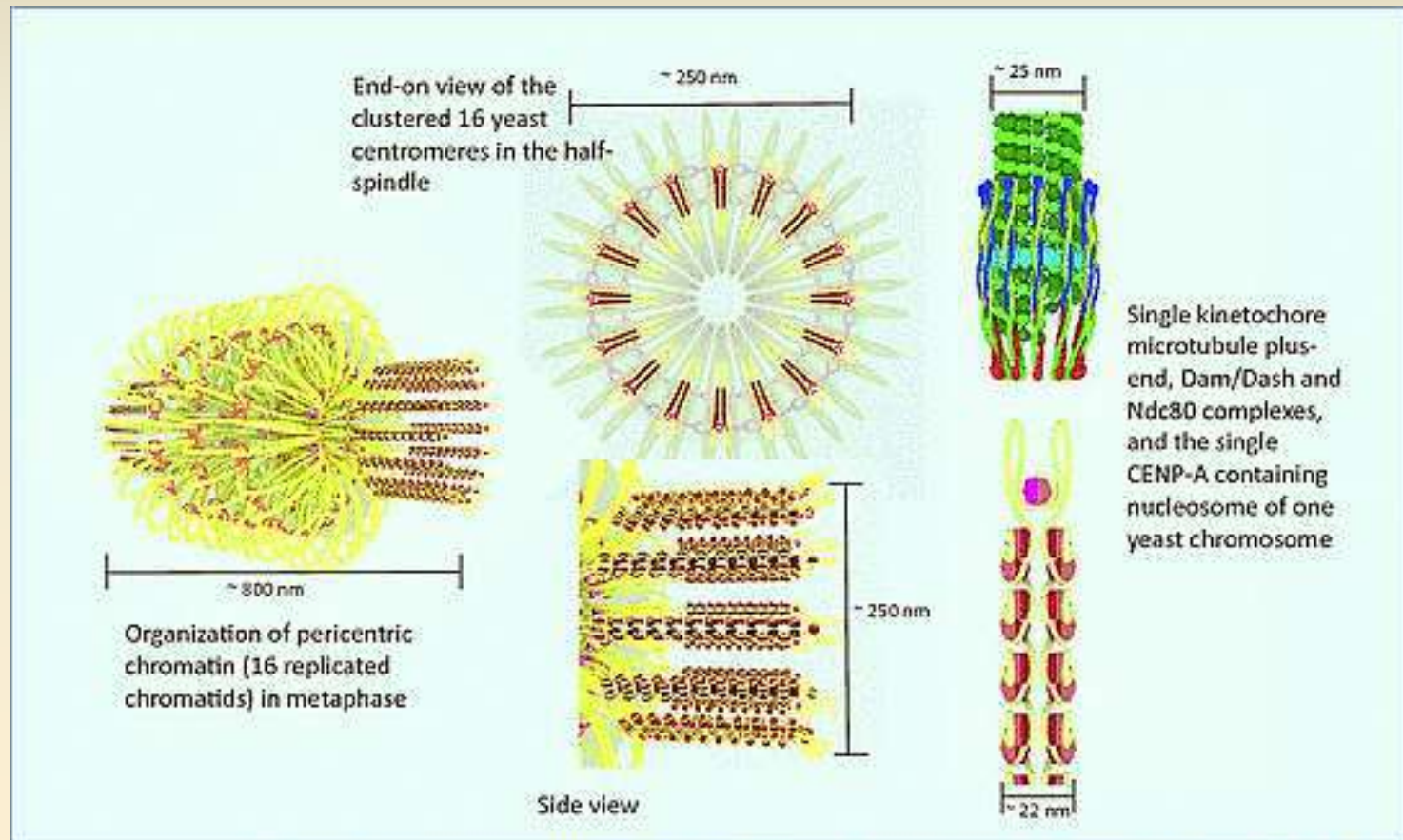
- ❑ Schematic representation of two sister chromosomes of *S. cerevisiae* attached to the mitotic spindle showing how cohesin shapes the centromeres in yeast mitosis.
- ❑ Here, Cohesin connects sister chromatids at chromosome arms but also links together centromeric chromatin, both by intrachromosome (*blue*) and interchromosome (*purple*) strand trapping, thereby forming a barrel-shaped structure underneath the kinetochore.



Structure of cohesin molecule

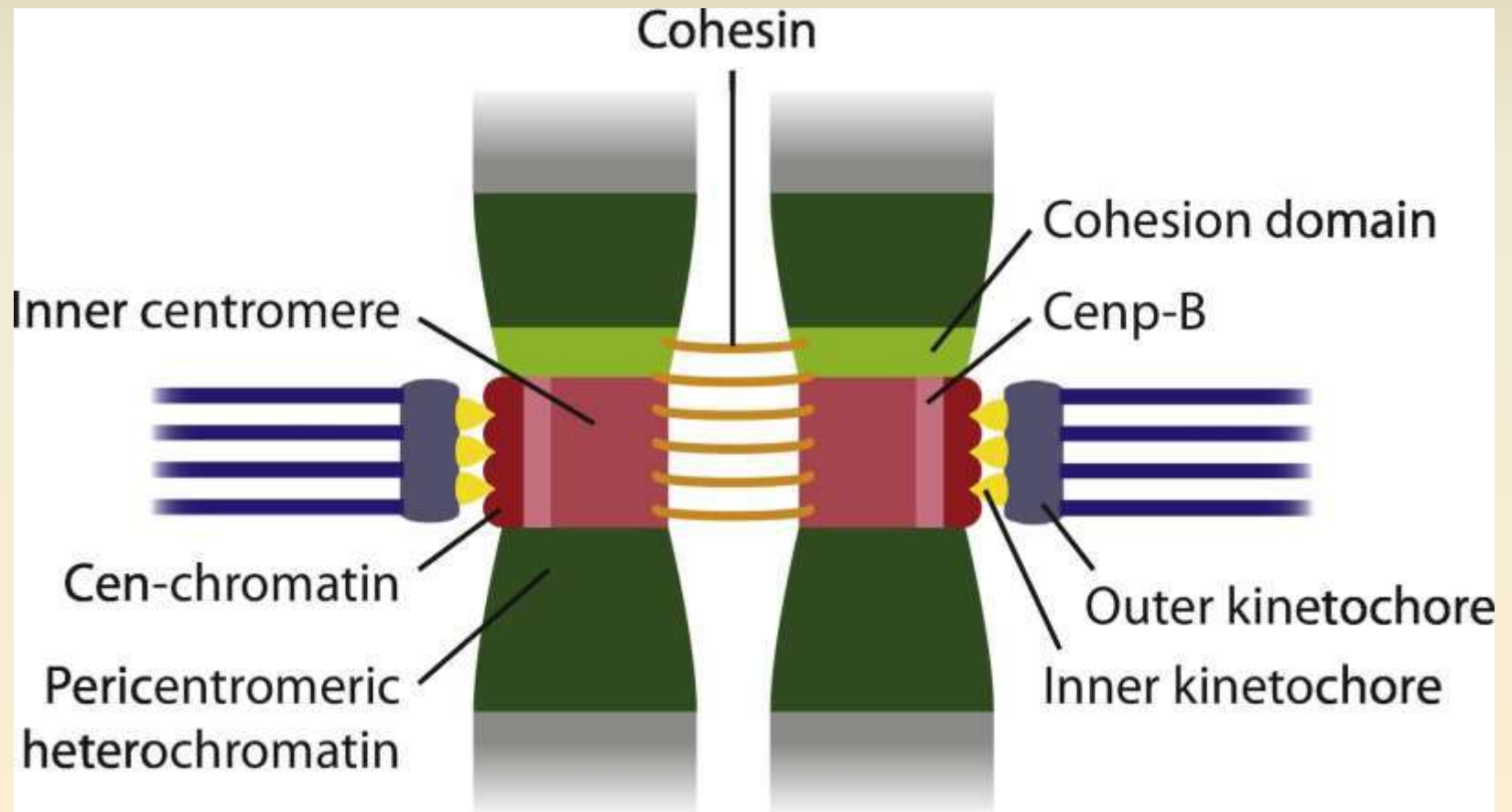


Structural organization of a centromere



Bloom & Costanzo 2017; DOI https://doi.org/10.1007/978-3-319-58592-5_21

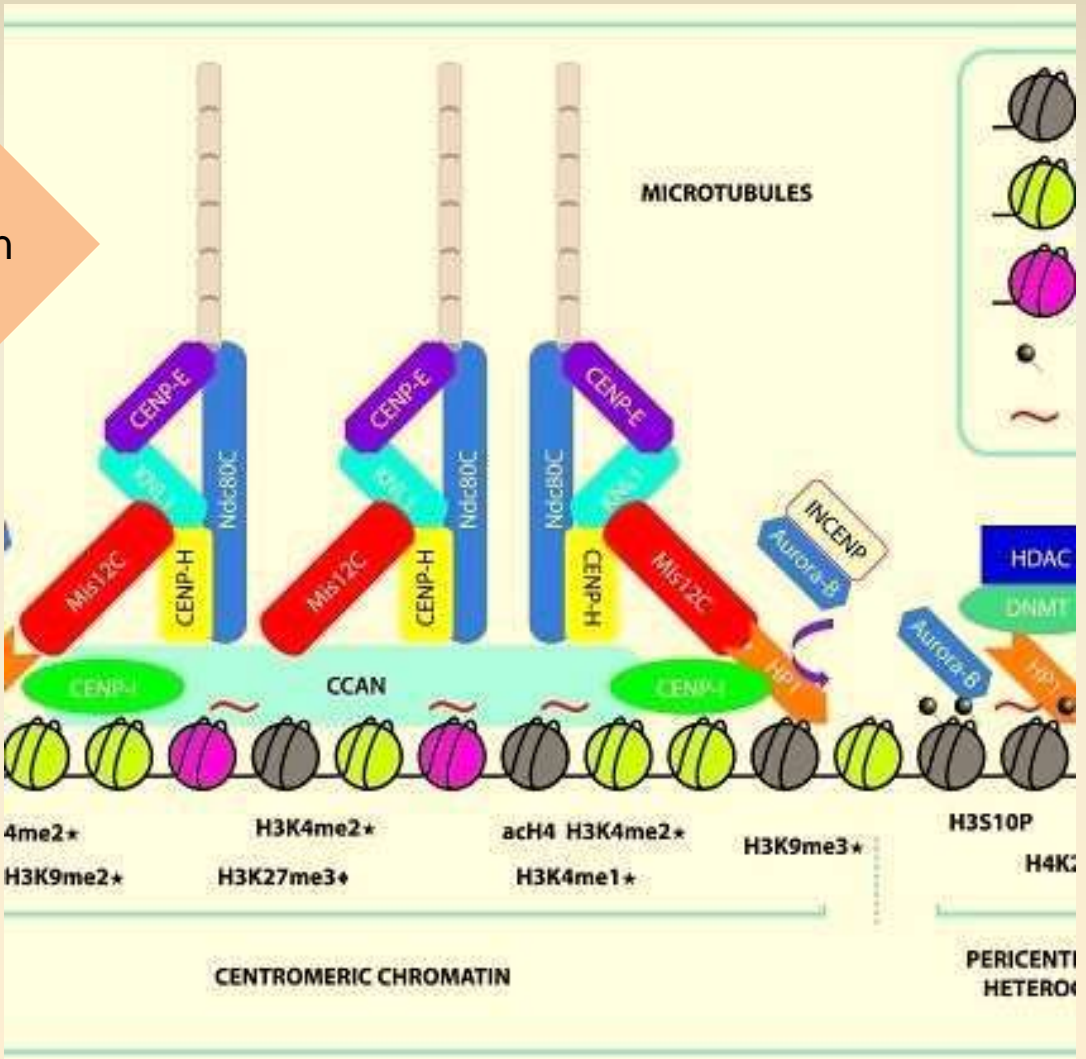
Structural organization of a centromere



Chromatin domain organization of eukaryotic centromeres.
Journal of Molecular Biology 2020; 432(15): 4257-4269 .

Structural organization of a centromere

Schematic representation of centromeric and pericentromeric chromatin and the formation of an epigenetic complex that further shapes the kinetochore.



Epigenetics : Official journal of the DNA Methylation Society. 2012, 7. 3-13. DOI: 10.4161/epi.7.1.18504.

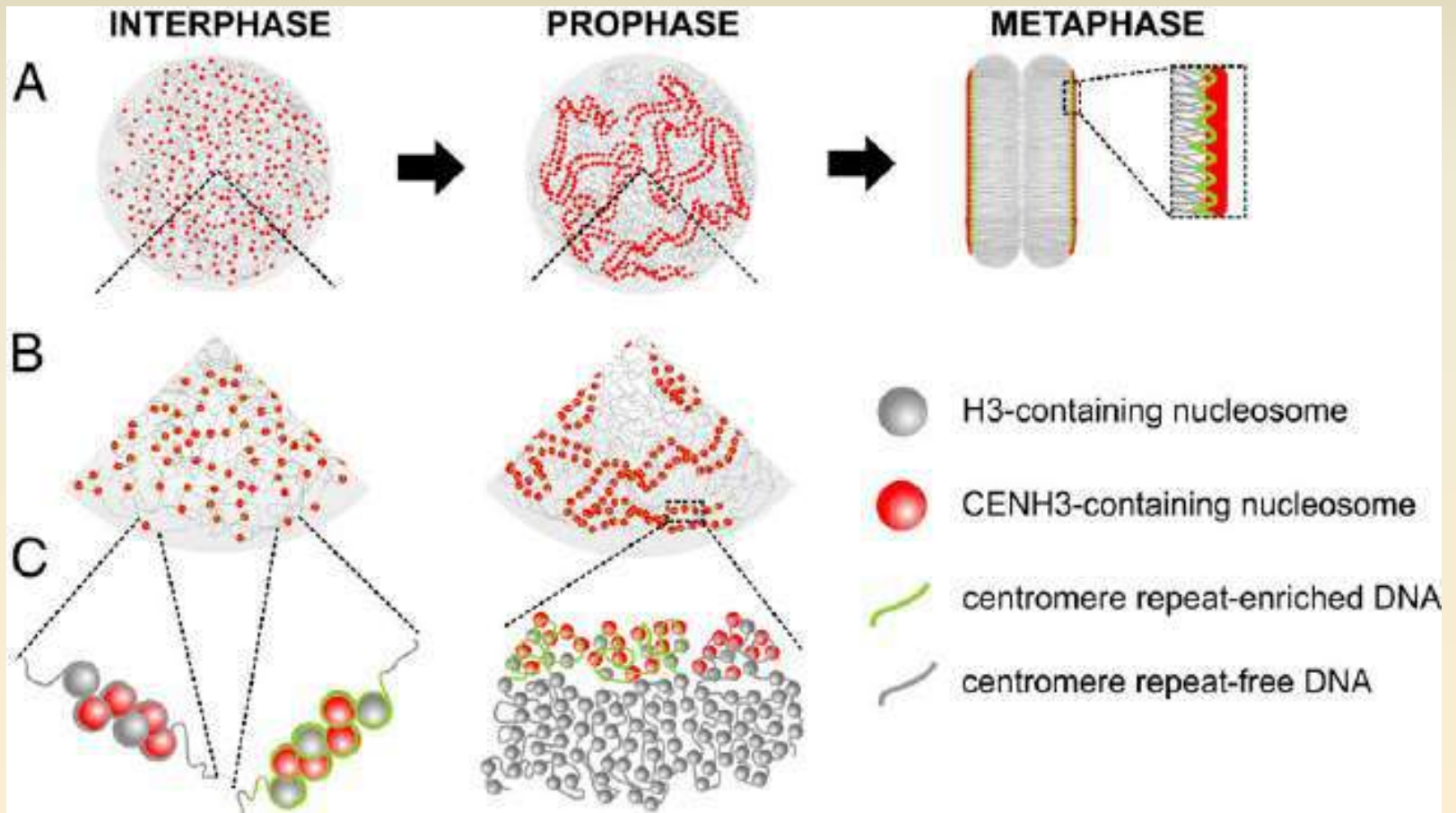
Centromere localization and dynamics

- ❑ Centromeres are maintained epigenetically, not genetically.
- ❑ Centromeric nucleosome contain an atypical histone H3, known as CENP-A, that can acquire a variety of conformations from tetramers, hemisome octamers, hexamers, etc.
- ❑ The incorporation of CENP-A or Cse-4 results in unique molecular determinants including histone fold domain (HFD), essential N-terminus domain (END), CENP-A targeting domain (CATD) within HFD, etc. that interact with DNA.
- ❑ The histone chaperones induces the CENP-H3 deposition at heterochromatic DNA with extinct centromere.
- ❑ This non-canonical histone directs kinetochore assembly.
- ❑ The separation of separation is dependent on other proteins named as condensin I & Condensin II.
- ❑ Depeletion of condensin I increases asynchrony in separation, while depletion in condensin II abolishes metaphase oscillations and impairs centromere speed in anaphase.

Centromere localization and dynamics

- ❑ After deposition of CENP-A-H3 complex (varied conformations) a centromere is formed.
- ❑ During interphase, holocentromeres dissociate into individual CENP-A-H3/centromere repeat-containing units.
- ❑ In prophase, they reassociate and form holocentromeres along the sister chromatids
- ❑ In metaphase, most of the CENP-A-H3-containing nucleosomes associate with centromere repeat enriched sequences and aligned on the spindle with sister kinetochores.
- ❑ Centromere at metaphase was positioned in a bioriented manner towards the poles.
- ❑ CENP-A proteins are highly flexible proteins which dissociated in sister centromere in anaphase.
- ❑ Upon microtubular contraction (a polymerization and depolymerization event of the tubulin proteins), sister chromatid with sister centromere containing sister kinetochore move apart.

Centromere localization and dynamics

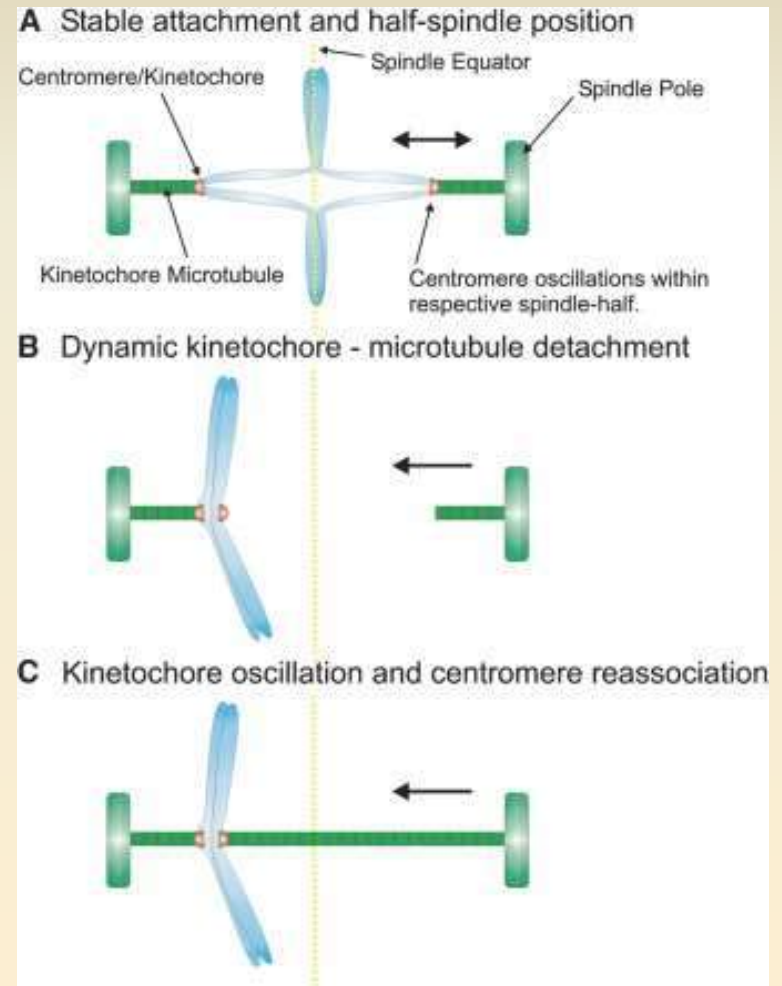


Proceedings of the National Academy of Sciences 2015, 112(44)

Centromere localization and dynamics

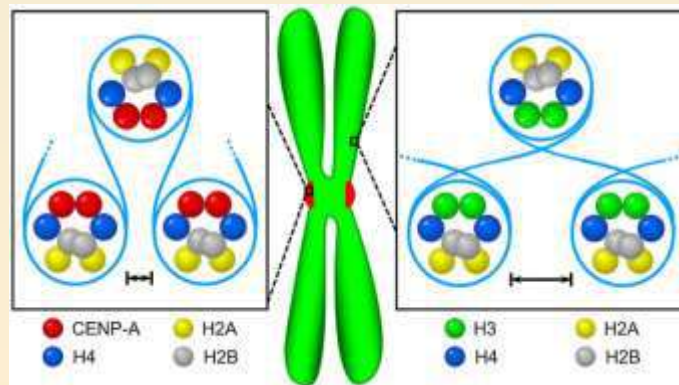
- (A) At metaphase, kinetochores remain attached to their respective spindle poles and are dynamically positioned within their proximally attached spindle halves.
- (B) Dynamic kinetochore-microtubule attachment leading to centromere movements across the spindle equator into the opposite spindle half. Loss in kinetochore attachment to single microtubules results in centromere reassociation with a sister centromere crossing into the opposite spindle half.
- (C) Kinetochore oscillations from one spindle half to the opposite.

Pearson et al. 2004, Current Biology.
DOI:<https://doi.org/10.1016/j.cub.2004.09.086>



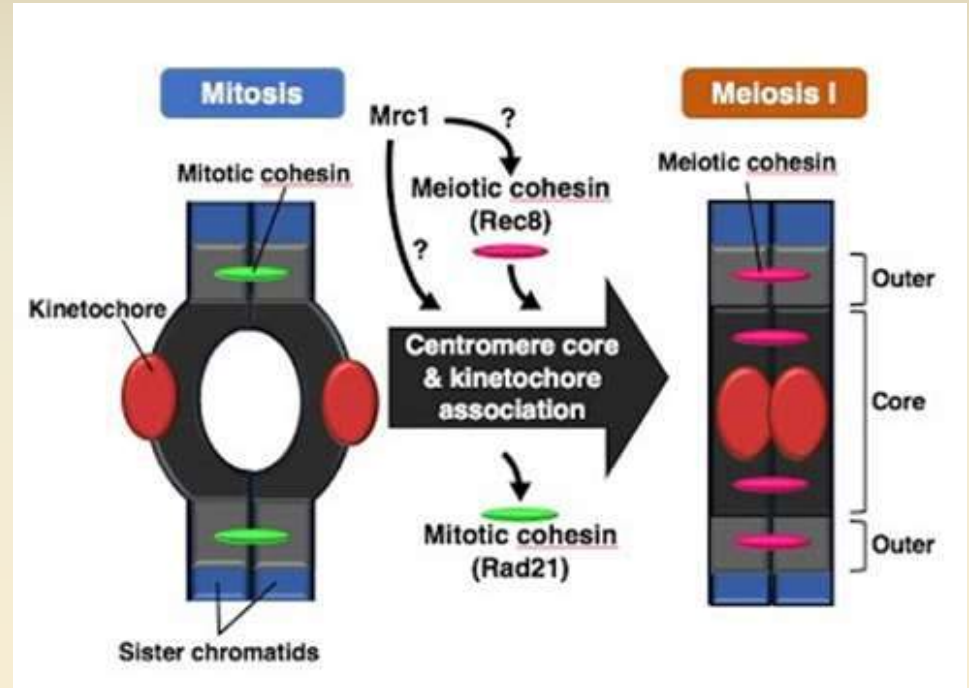
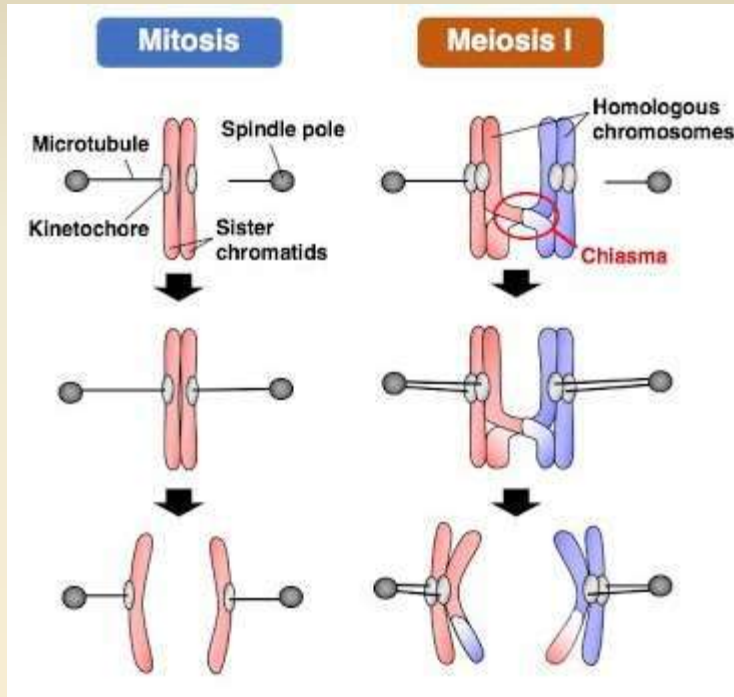
Maintenance of centromere

- ❑ Centromeres are maintained by centromere protein (CENP), which forms CENP-nucleosome with DNA.
- ❑ There are three variants of CENP which have distinct role in the centromere maintenance – CENP-A, CENP-N, CENP-C.
- ❑ CENP-C is most conserved protein, however it is dispensable.
- ❑ Upon crossbridging of CENP-A with central domain of CENP-C and folded N-terminal domain of CENP-N, both the proteins are rigidified 1000-fold.
- ❑ Thus, CENP-nucleosome is formed where CENP-C clamps down a stable nucleosome conformation and CENP-N fastens CENP-A to the DNA.
- ❑ This fastening of CENP-A with DNA involves arginine anchor.



CENP-A-H3 nucleosome

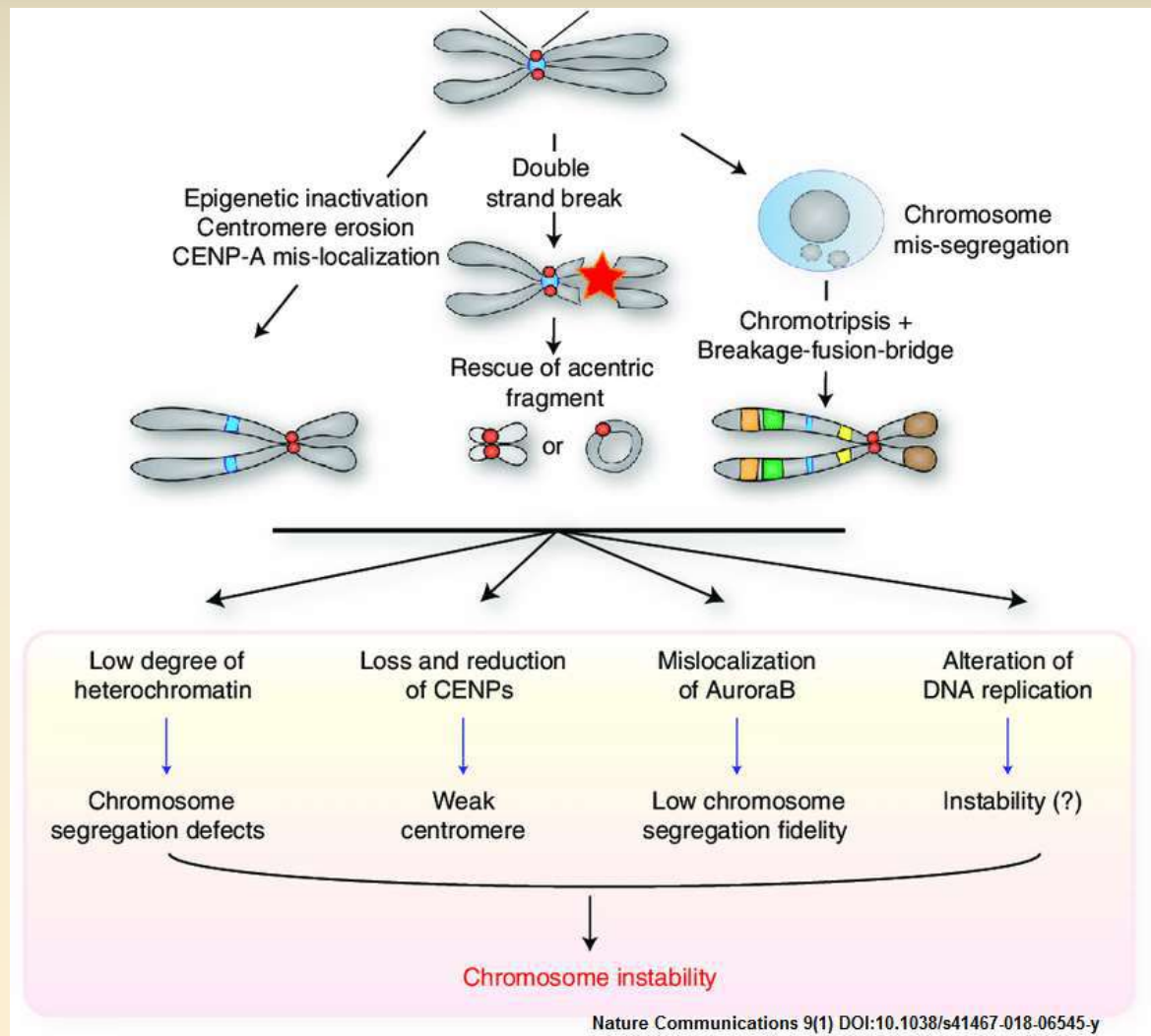
Centromere regulation during cell division



Centromere regulation during mitosis and meiosis.
Yamamoto et al., 2008., *JCB*

Neocentromere

- ❑ Neocentromere is a new centromere that forms on a chromosome at a location that is normally not centromeric – usually as a result of disruption of the natural centromere.
- ❑ Most natural centromeres contain highly repetitive sequences, whereas neocentromeres usually possess unique sequences.
- ❑ These neocentromeres should not be confused with “knobs”, which were also described as “**neocentromeres**” in maize in the 1950s.



Division of nucleoid in prokaryotic chromosome

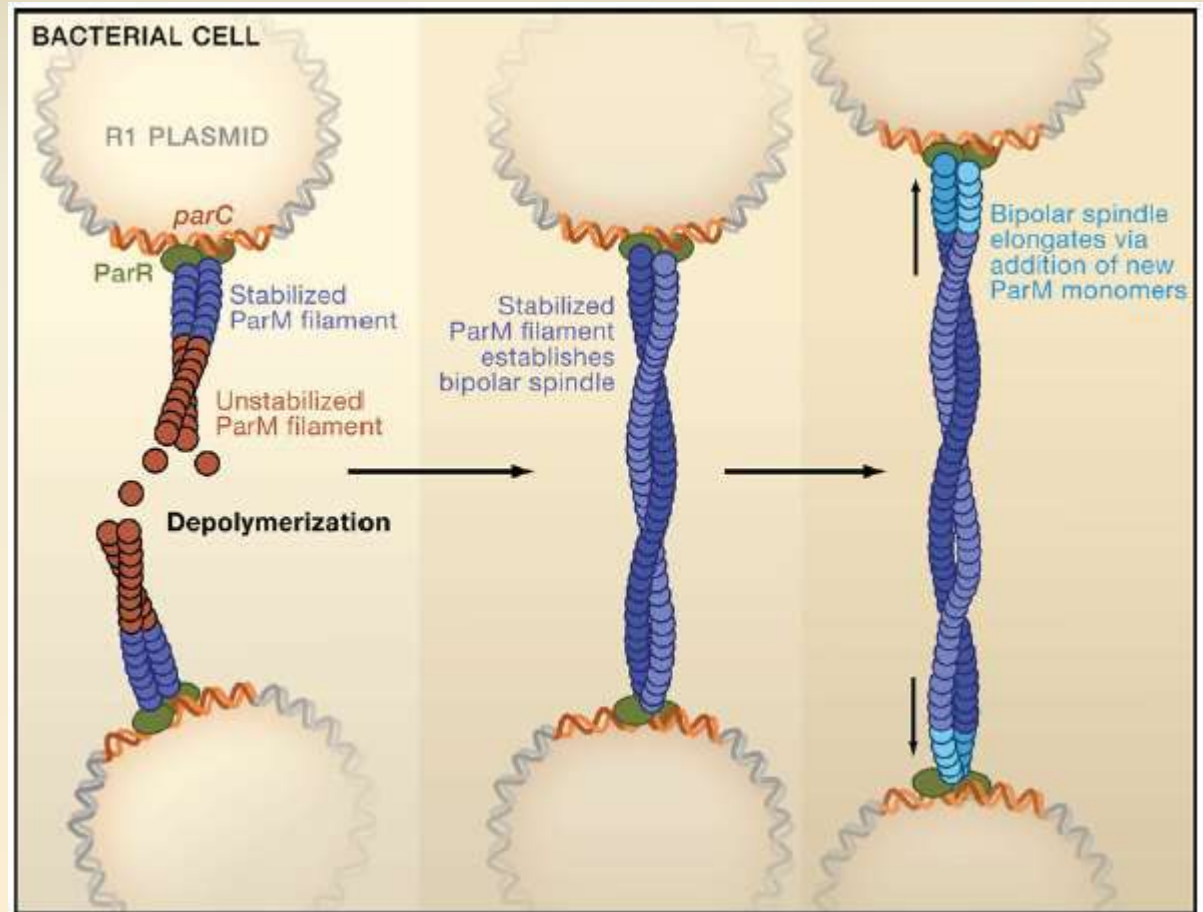


Figure 1. Plasmid Segregation in Bacteria
Cell 138, September 18, 2009.

Further reading

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- Alberts B., Johnson A., Lewis J., Raff M., Roberts K., Walter P. 2002. Molecular Biology of the Cells. Garland Science, New York, USA.
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- Krebs J.E., Goldstein E.S., Kilpatrick S.T. 2017. Lewin's Genes XII. Jones and Bartlett Publishers, Inc., Burlington, MA, USA.
- <https://sites.google.com/site/ayuyamamuenglish/home/yan-jiutema>

