

4. Chromosomal Instability

1 unit, John Maciejowski, September 17, 2026

Chromosome segregation and its errors

- The mitotic spindle and kinetochore-microtubule attachment
- Merotelic attachment and lagging chromosomes
- The spindle assembly checkpoint and why it fails
- Cohesion defects and premature sister chromatid separation

Numerical and structural chromosomal instability

- Whole-chromosome missegregation and aneuploidy
- Structural instability from replication stress and fragile sites
- Measuring instability in cells and in tumors

Micronuclei

- Defective nuclear envelope assembly on missegregated chromosomes
- Nuclear envelope rupture and loss of compartmentalization
- Impaired replication and repair inside micronuclei
- Chromosome pulverization

Dicentric chromosomes and chromosome bridges

- Telomere loss and end-to-end fusion
- Bridge stretching, actomyosin forces, and breakage
- Breakage-fusion-bridge cycles

Chromothripsis

- Reassembly of shattered fragments
- Mitotic tethering and inheritance of fragments
- Signatures left in the genome sequence

Coupling chromosome breakage to point mutation

- Exposed single-stranded DNA as a substrate
- Cytosolic nucleases and deaminases
- Kataegis

Fates of cytoplasmic DNA

Punctuated and gradual models of genome evolution

Discussion Paper:

Maurais EG, Mazzagatti A, Lin YF, Narozna M, Hu Q, Dahiya R, Santiago-Ferrer D, Herlihy CP, Krebs M, Pateraki N, Parcharidou E, Papathanasiou S, Beliveau BJ, Gorbsky GJ, Cortes-Ciriano I, Ly P. Genome instability triggers intercellular DNA transfer between human cells. *Cell*. 2026 Jul 23;189(15):4548-4561.e14. doi: 10.1016/j.cell.2026.04.041. Epub 2026 May 19. PMID: 42161273.

Background Paper:

Hatch EM, Fischer AH, Deerinck TJ, Hetzer MW. Catastrophic nuclear envelope collapse in cancer cell micronuclei. *Cell*. 2013 Jul 3;154(1):47-60. doi: 10.1016/j.cell.2013.06.007. PMID: 23827674; PMCID: PMC3749778.

Review Paper:

Levine MS, Holland AJ. The impact of mitotic errors on cell proliferation and tumorigenesis. *Genes Dev*. 2018 May 1;32(9-10):620-638. doi: 10.1101/gad.314351.118. PMID: 29802124; PMCID: PMC6004076.