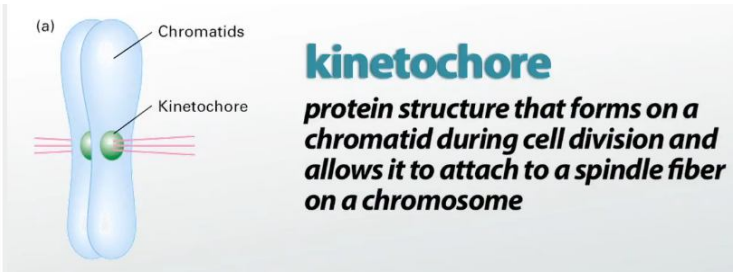
CC4: Cell Biology
Unit 3: Cytoplasmic organelles II
Kinetochore

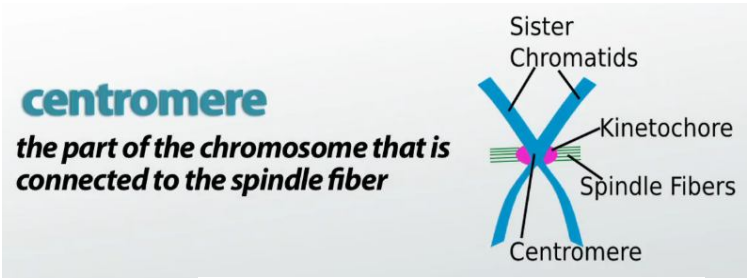
Ruksa Nur
Assistant Professor
Department of Zoology
Dinabandhu Andrews College
Kolkata-700 084

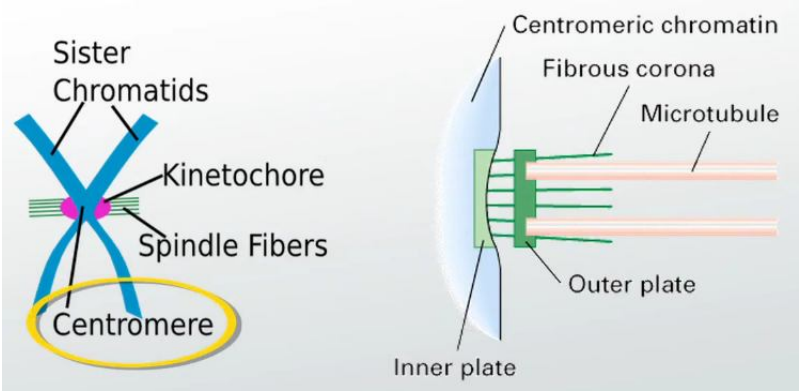
Kinetochore Structure

Kinetochores consist of three regions: an inner and outer region, as well as a fibrous corona. Each region works in its own particular way to aid in the separation of the sister chromatids. Each chromatid receives its own kinetochore.



The inner plate of the kinetochore is connected with the centromere, where it works closely with centromeric DNA. The centromere is where the sister chromatids connect and form a **chromosome**. The outer plate of the kinetochore is attached to, and works in conjunction with, the microtubules, which are connected to the spindles at either end of the cell poles. The fibrous corona is created from a network of permanent and temporary proteins and helps regulate the attachment of the microtubules to the outer plate.





Due to their location and organization, all three regions of the kinetochore share an equal role in its function. Their activities and relationships only occur during cell division and are essential in that they help to pull the chromatids apart.

Key Points

- The kinetochore is a large proteinaceous structure that mediates interactions between chromosomal DNA and spindle-microtubule polymers.

- More than 80 kinetochore proteins have been identified using various genetic, functional, cell biology and proteomics approaches.

- Specialized nucleosomes that contain the histone H3 variant CENP-A form the structural foundation for the kinetochore. A combination of sequence-independent epigenetic mechanisms ensure that CENP-A nucleosomes are directed to centromeres.

- A combination of proteins form the interface with microtubules and provide distinct functions, including generating a core attachment site, coupling kinetochore movement to disassembling microtubules, affecting the polymerization dynamics of kinetochore-bound microtubules and driving translocation along spindle microtubules.

- Multiple signalling pathways regulate the fidelity and timing of chromosome segregation and kinetochore function, including the mitotic checkpoint and several mitotic kinases.

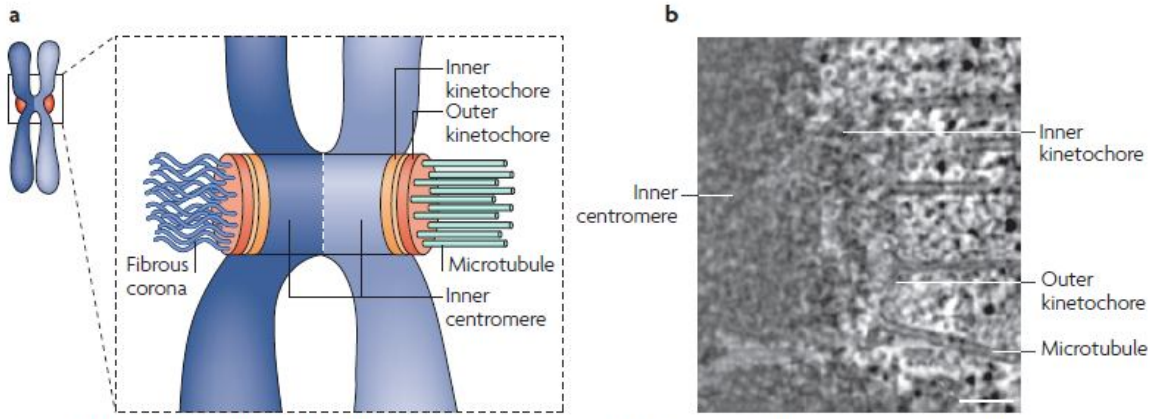


Figure 2 | **Vertebrate kinetochore ultrastructure. a** | A schematic of a mitotic chromosome with paired sister chromatids — the chromatid on the right is attached to microtubules and the chromatid on the left is unattached. The inner kinetochore, the outer kinetochore, the inner centromere and the fibrous corona, which is detectable on the unattached kinetochore, are highlighted. **b** | Electron micrograph of a human kinetochore (image courtesy of Y. Dong and B. McEwen, State University of New York at Albany, USA). The micrograph represents a single slice from a tomographic volume of a high-pressure frozen mitotic cell and has been labelled as in **a** to highlight the key structural features of the kinetochore. Scale bar, 100 nm.

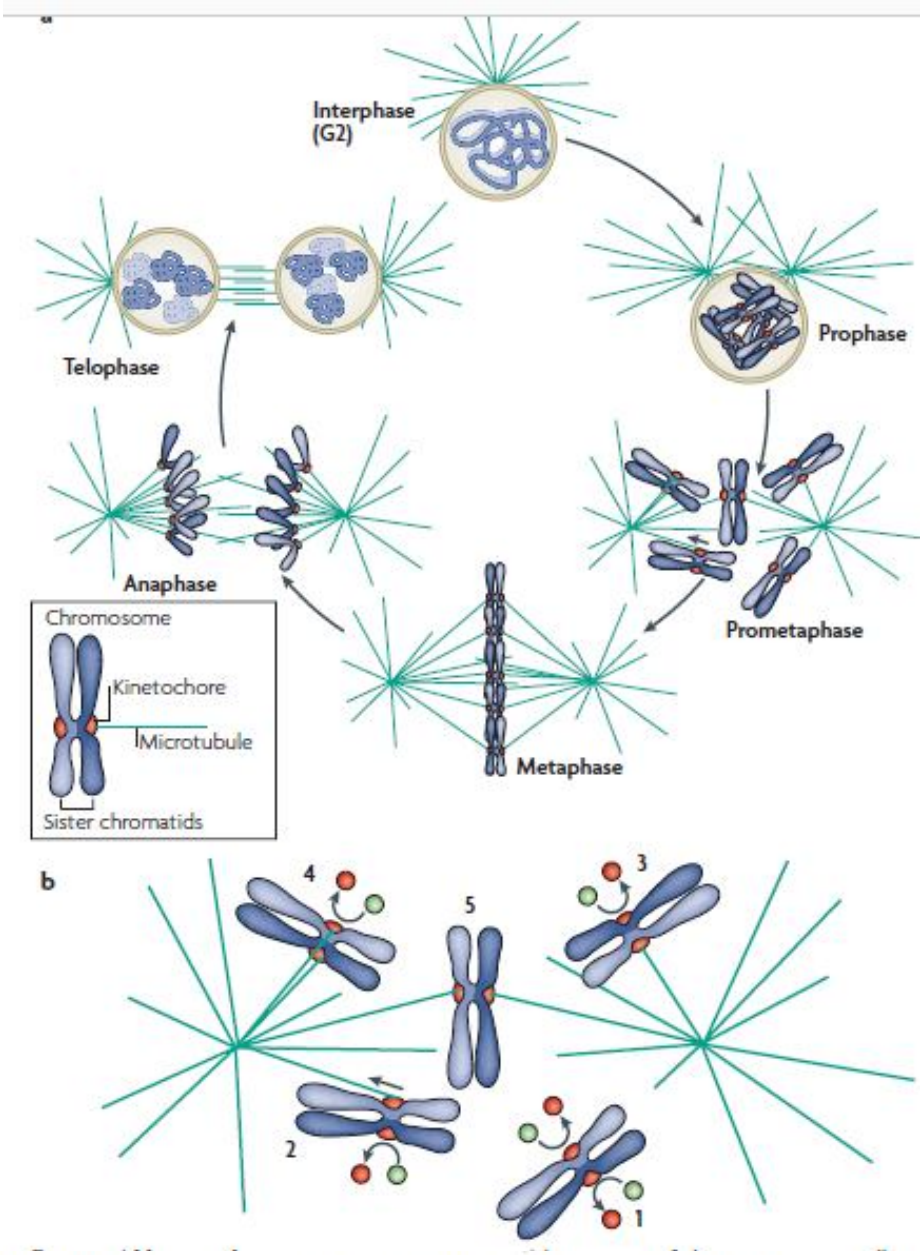


Figure 1 | **Mitotic chromosome segregation. a** | A summary of chromosome–spindle interactions during the M phase of the cell cycle. Replicated interphase chromatin is condensed during prophase; concomitantly, kinetochores assemble on the centromere regions of chromosomes. After nuclear envelope breakdown, during prometaphase, kinetochores interact with spindle microtubules. By metaphase, all chromosomes are bi-oriented and aligned in the middle of the spindle. During anaphase, separated sister chromatids move away from each other to opposite spindle poles. Subsequently, during telophase, the chromatid masses decondense and the nuclear envelope reforms to generate the daughter nuclei. **b** | A detailed view of the prometaphase stage, highlighting key activities of the kinetochore in chromosome segregation. Various intermediates (**1**–**5**) can be detected along the path from unattached (**1**) to bi-oriented (**5**) chromosomes. Lateral associations between kinetochores and spindle microtubules (**2**), which result in poleward chromosome movement, are frequently observed after nuclear envelope breakdown. Lateral attachments mature to end-on attachments, first with one kinetochore (**3**) and subsequently with both (**5**). Unattached kinetochores (as in **1**, **2** and **3**) catalyse the formation of an inhibitor (red circles) that prevents anaphase onset. Attachment errors, such as the one depicted in **4**, are also common and are detected and eliminated to prevent chromosome loss.

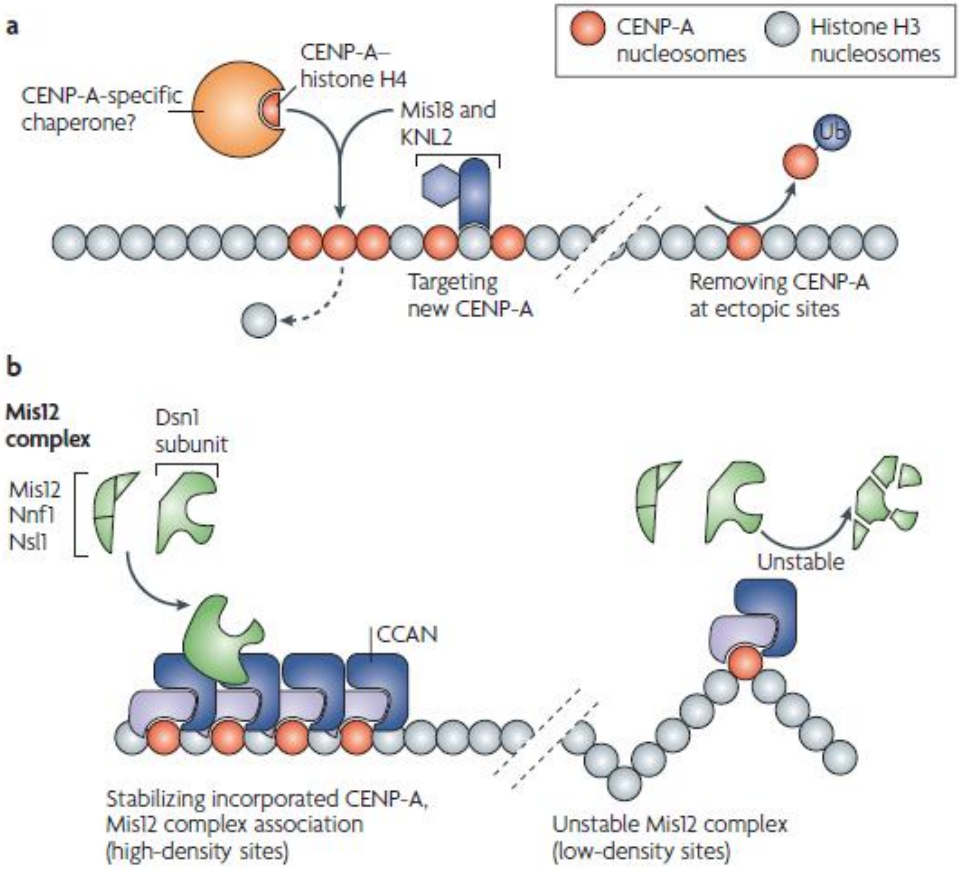


Figure 3 | **Kinetochore specification.** A model showing the proteins and complexes that are implicated in kinetochore specification. Centromeric chromatin is characterized by the presence of specialized nucleosomes that contain the histone H3 variant CENP-A. **a** | Factors that restrict CENP-A to centromeres. CENP-A (which forms a dimer with histone H4) is epigenetically maintained at centromeres by a combination of activities, including targeted deposition and removal at ectopic sites, possibly through ubiquitylation and degradation. The two proteins specifically implicated in CENP-A loading, Mis18 and KNL2 (also known as M18BP1), which form a complex in vertebrates, are depicted as guiding specific CENP-A loading. The mechanism of action of these proteins is currently not known. **b** | Kinetochore proteins downstream of CENP-A that are involved in kinetochore specification. The constitutive centromere-associated network (CCAN), which is closely associated with CENP-A nucleosomes throughout the cell cycle, is shown as stabilizing newly incorporated CENP-A. We suggest that the Mis12 complex (which consists of Dsn1 (known as KNL-3 in *Caenorhabditis elegans*), Mis12, Nnf1 and Nsl1) provides a second layer of specificity by acting as a molecular 'keystone' that licenses kinetochore assembly. This proposal is based on the inherent instability of the Dsn1 subunit of the Mis12 complex from *C. elegans* and humans. We speculate that interactions between an array of centromeric chromatin and multiple Mis12 complexes lead to the local stabilization of Dsn1 and restrict kinetochore assembly to that region of the chromosome.