Medical & healthcare, Drug design

Structural analysis on the protein complexes required for chromosome segregation

Graduate School of Frontier Biosciences
Professor Tatsuo Fukagawa

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Abstract

To maintain life all genome information must be transmitted accurately into next generation-cells. Inaccurate transmission of chromosomes including genome information causes genome instabilities, which lead to cancer formation. Therefore, it is essential to study mechanisms how chromosomes are accurately segregated. Chromosome segregation is performed through attachment of spindle microtubules to a special structure on chromosome called "kinetochore". We are extensively studying kinetochore architecture and function to understand molecular mechanisms for chromosome segregation. Recently, we have shown a key structural change for kinetochore proteins.

Background & Results

The centromere is an essential genomic region for accurate chromosome segregation. In most organisms, the centromere is specified at a particular locus on each chromosome by sequence independent epigenetic mechanisms, and histone H3 variant CENP-A is a key epigenetic marker for centromere formation. Once the CENP-A nucleosome is established in the centromere, additional proteins recognize the CENP-A nucleosome to form a kinetochore. CENP-C and CENP-N are known as CENP-A binding proteins. We have previously demonstrated that CENP-C binding to the CENP-A nucleosome is regulated by CENP-C phosphorylation. However, it is still unknown how CENP-C phosphorylation regulates its binding to CENP-A. Further, it is not completely understood how and whether CNPE-C and CENP-N act on the CENP-A nucleosome together. In our recent study, we reveal a stable CENP-A nucleosome binding mode of CENP-C through the unique structured region, using cryo-EM in combination with a biochemical approach. We found that the CENP-C structure bound to the CENP-A nucleosome was stabilized by an intramolecular link through the phosphorylated residue. Furthermore, the stable CENP-A-CENP-C complex excluded CENP-N from the CENP-A nucleosome. These structural outcomes provide a mechanistic insight into the dynamic kinetochore assembly regulated by CDK1 mediated CENP-C phosphorylation.

Significance of the research and Future perspective

Because defects in chromosome segregation cause various diseases including cancer, it is significant to examine structures of kinetochore complexes with high resolution. In addition, mutations or overexpression of kinetochore proteins are known to induce cancer formation, and the kinetochore proteins are good target for design of anti-cancer drug. Our structural study would contribute such a drug design.

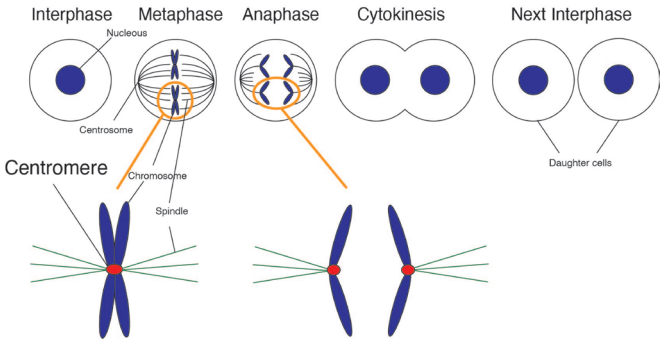

Fig. 1 Chromosome segregation during mitosis. Spindles bind to a centromere region, and chromosomes are divided into daughter cells.

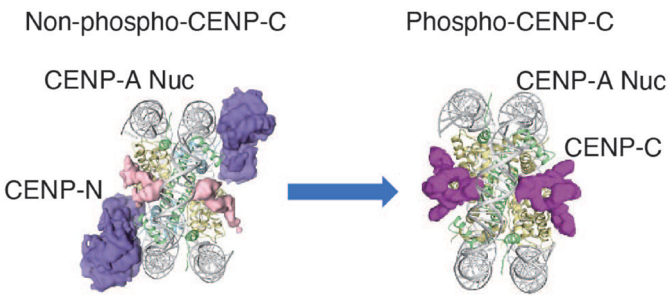

Fig. 2 Cryo-EM analysis of the CENP-A nucleosome complexed with CENP-C or CENP-N. Phosporylated CENP-C dominatly binds to the CENP-A nucleosome.

Patent	Japanese Patent No. 4820995, No. 4787960
Treatise	Ariyoshi, Mariko; Fukagawa, Tatsuo et al. Cryo-EM structure of the CENP-A nucleosome in complex with phosphorylated CENP-C, EMBO Journal. 2021; 40(5): e105671. doi: 10.15252/embj.2020105671 Hori, Tetsuya; Fukagawa, Tatsuo et al. Essentiality of CENP-A depends on its binding mode to HJURP, Cell Reports, 2020; 33(7): 108388. doi: 10.1016/j.celrep.2020.108388
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