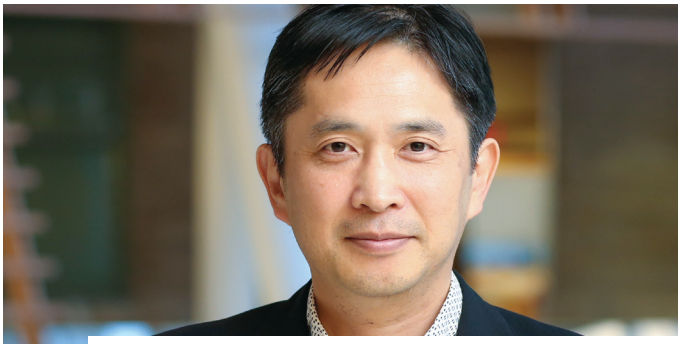

Hironori Funabiki, Ph.D.

TRI-INSTITUTIONAL PROFESSOR • PROFESSOR, LABORATORY OF CHROMOSOME AND CELL BIOLOGY

Chromosomes carry core operating programs for life. During mitosis, a full set of chromosomes must be equally transmitted to the offspring of each dividing cell. Failures in this process can result in numerous disorders, such as cancers. Funabiki studies the molecular signatures and mechanisms of chromosome identity and inheritance.

The human body is composed of trillions of cells, which are produced and maintained by massive numbers of cell divisions. Human cells typically have 46 chromosomes, but this number often deviates in cancer cells. Cellular DNA content can be also altered by the invasion of pathogens. The Funabiki lab studies the mechanisms by which cells ensure accurate chromosome numbers, detect abnormal chromosomes and foreign DNA, and adapt to these aberrations or eliminate them. Through this work, the Funabiki lab aims to understand the molecular basis for cancers and other diseases.

The structural and signaling roles of the nucleosome during mitosis. For successful cell divisions, meter-long strands of genomic DNA must be compacted 10,000-fold into mitotic chromosomes with distinct shapes and sizes. Mitotic chromosomes also promote assembly of functional architectures, such as spindles and kinetochores, which mediate chromosome segregation. The primary folding unit of genomic DNA is the nucleosome, which is comprised of 150 base pairs of DNA wrapped around histone proteins. The Funabiki lab studies how this nanometer-scale nucleosome shapes the structure and function of mitotic chromosomes. The lab developed a strategy to reconstitute the nucleosome using recombinant histones in the physiological cell-free system, which allowed them to reveal the mechanism by which nucleosomes act as a signaling platform to drive the assembly of machineries that control mitosis. The Funabiki lab now combines proteomics, innovative imaging techniques, and cryo-electron microscopy to define how architectural organizations and functions of chromosomes are regulated to ensure accurate chromosome inheritance during mitosis.

Centromere integrity and DNA methylation. Specialized chromosome segments called centromeres control chromosome segregation. Human centromeres are composed of long arrays of repetitive sequences, called satellite DNAs. Why and how centromeres maintain this repeat organization remains enigmatic. The Funabiki lab demonstrated that HELLS and CDCA7, whose mutations cause immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome, form a novel nucleosome remodeling complex to maintain DNA methylation at centromere-associated satellite DNAs. Dysregulation of HELLS and CDCA7 is also implicated in cancers. Funabiki aims to understand the key mechanisms that help maintain the repeat sequences and DNA methylation, and their relevance to ICF syndrome and cancers.

Chromosome identity, mitotic failures, and cancers. To defend against foreign DNA, a cellular sensor called cGAS recognizes cytoplasmic DNA and induces inflammation. The Funabiki lab found that host chromosomal DNA does not have this effect because its nucleosomes act as a chromosomal signature that prevents cGAS activation. As cGAS is activated upon mitotic failures, which are commonly coupled to cancers and chemotherapies, Funabiki studies the mechanism by which cGAS is regulated during mitosis.

EDUCATION

B.S., 1990
M.S., 1992
Ph.D., 1995
Kyoto University

POSTDOC

Kyoto University, 1995–1996

University of California, San Francisco, 1996–2000

Harvard University, 2000–2002

POSITIONS

Assistant Professor, 2002–2007
Associate Professor, 2007–2014
Professor, 2014–
The Rockefeller University

AWARDS

Searle Scholar, 2002

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SELECTED PUBLICATIONS

Arimura, Y. et al. Structural features of nucleosomes in interphase and metaphase chromosomes. *Mol. Cell* 81, 4377–4397 (2021).

Choppakatla, P. et al. Linker histone H1.8 inhibits chromatin binding of condensins and DNA topoisomerase II to tune chromosome length and individualization. *ELife* 10, e68918 (2021).

Kujirai, Y. et al. Structural basis for the inhibition of cGAS by nucleosomes. *Science* 370, 455–458 (2020).

Zierhut, C. et al. The cytoplasmic DNA sensor cGAS promotes mitotic cell death. *Cell* 178, 302–315 (2019).

Jenness, C. et al. HELLS and CDCA7 comprise a bipartite nucleosome remodeling complex defective in ICF syndrome. *Proc. Natl. Acad. Sci. U.S.A.* 115, E876–E885 (2018).