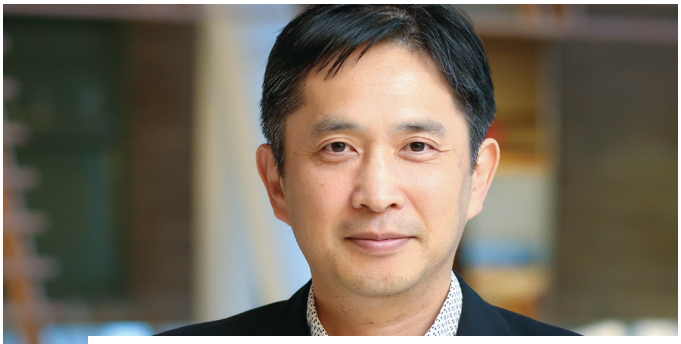

Hironori Funabiki, Ph.D.

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

Chromosomes carry core operating programs for life. Genetic and epigenetic information encoded in chromosomes must be accurately copied and transmitted to the offspring of each dividing cell. Failures in maintaining chromosome integrity can result in numerous disorders, such as birth defects, cancers, and immunodeficiencies. Funabiki studies the molecular signatures of chromosome integrity, identity and mechanisms of chromosome inheritance.

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

The structural and signaling roles of the nucleosome during mitosis. To enable the accurate distribution of genetic information during cell division, genomic DNA is compacted 10,000-fold into mitotic chromosomes. The primary folding unit of genomic DNA is the nucleosome, which is comprised of 150 base pairs of DNA wrapped around histone proteins. Research in the Funabiki lab revealed that mitotic nucleosomes act as a signaling platform by activating the protein kinase Aurora B to regulate mitotic apparatuses required for chromosome segregation, such as the spindle and the kinetochore. Combining the unique frog egg extract system and diverse biochemical, imaging, and innovative cryo-electron microscopy methods, the Funabiki lab studies how architectural and signaling functions of nucleosomes and other mitotic regulators are coordinated to ensure accurate chromosome inheritance.

Centromere integrity, DNA methylation, and ICF syndrome. The centromere is a specialized chromosome region upon which the kinetochore is assembled to support 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. The Funabiki lab found that CDCA7 is a sensor of hemimethylated DNA, in which only one strand of the double-stranded DNA molecule is methylated. Further research is now aimed at understanding how defective hemimethylation-sensing by CDCA7 causes centromere instability, ICF syndrome, and cancer.

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 signature that prevents cGAS activation. However, cGAS becomes activated upon mitotic failures, which are commonly observed in cancers and chemotherapies. The Funabiki lab studies how mitotic failures induce cGAS activation.

EDUCATION

B.S., 1990
M.S., 1992
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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

Sinsheimer Fund Scholar, 2003

SELECTED PUBLICATIONS

Wassing, I. et al. CDCA7 is an evolutionarily conserved hemimethylated DNA sensor in eukaryotes. *Sci .Adv.* 10, eadp5753 (2024).

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

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

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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).