【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : Conserved molecular mechanisms controlling chromosome segregation

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Research Area : Biology
Keyword : Genetics, Genome

【Purpose and Background of the Research】

During the mitotic cell cycle, chromosomes are replicated and segregated equally to daughter cells. Chromosome mis-segregation in mitosis may contribute to tumorigenesis. To generate progeny, the number of chromosomes is reduced once by half to produce haploid gametes, a process called meiosis. Meiotic chromosome segregation is also important clinically, as failures in this process cause miscarriage and birth defects such as Down syndrome in humans. Thus, it is very important for biological and medical science to understand the regulatory mechanisms of chromosome segregation.

Our studies in fission yeast have revealed that mono-orientation of kinetochores is established by cohesion at the centromeric core region, advocating the 'cohesion-mediated mono-orientation model'. In this research project we will study the novel meiotic kinetochore protein in mice and address the question of whether the fundamental molecular mechanism of mono-orientation is conserved between yeast and mammals. Recently we discovered the Inner Centromere Shugoshin (ICS) network, by which the Aurora B kinase-shugoshin complex is localized to the inner centromeres (Fig. 1). Here we will examine the possibility that impairment of the ICS network may be a major reason for chromosome instability (CIN), a defect widely observed in cancer cells. These studies will uncover the crucial mechanism of CIN generation in human cells.

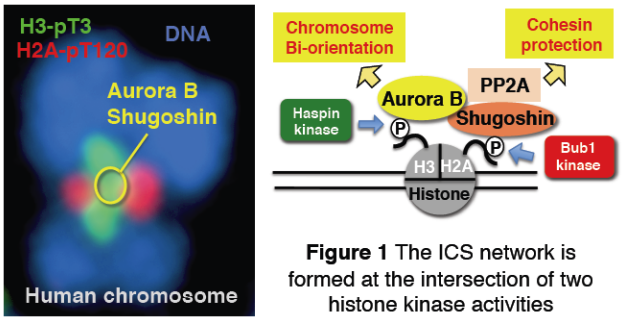

Figure 1 The ICS network is formed at the intersection of two histone kinase activities

【Research Methods】

We will conduct an extensive study of the molecular function of the mono-orientation factor in fission yeast. Further, we will analyze the novel meiotic kinetochore factor in mice by making and analyzing KO mice. We will compare the mechanism of meiotic kinetochore regulation (mono-orientation) between yeast and mouse.

We will examine the importance of kinetochore plasticity for chromosome bi-orientation during mitosis by examining several mutants defective in kinetochore structure. Moreover, we will study cancer-specific defects in the ICS network and explore their molecular details.

【Expected Research Achievements and Scientific Significance】

Our study will advance the understanding of chromosome cohesion and orientation at the molecular level and will reveal a major mechanism of aneuploidy. Moreover, our results will reveal the precise mechanism of chromosome bi-orientation in mitosis, which largely depends on shugoshin in human cells. The linkage of the ICS network with CIN will be revealed at the molecular level, thus advancing our understanding of tumorigenesis.

【Publications Relevant to the Project】

1) Sakuno, T., Tada, K., and Watanabe, Y. Kinetochore geometry defined by cohesion within the centromere. ***Nature*** 458, 852-858 (2009).
2) Yamagishi, Y., Honda, T., Tanno Y., and Watanabe, Y. Two histone marks establish the inner centromere and chromosome bi-orientation. ***Science*** 330, 239-243 (2010).

【Term of Project】 FY2013-2017

【Budget Allocation】 416,400 Thousand Yen

【Homepage Address and Other Contact Information】

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