【Grant-in-Aid for Scientific Research(S)】

Integrated Science and Innovative Science (Comprehensive fields)

Title of Project：Telomere Functions in Cancer Development

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Research Area：Cancer Biology

Keyword：Genetic Instability, Telomere, Next-generation Sequencer

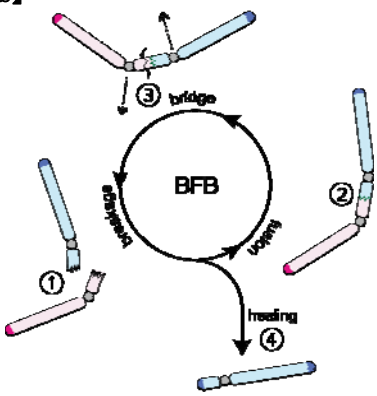
【Purpose and Background of the Research】

In Japan, cancer is the leading cause of death. However, the current measures for cancer treatment is not satisfying.

Genetic instability is uniquely possessed by cancer cells, but not by normal cells. Cancer cells acquire a broad range of random genetic abnormalities. Recently, it is recognized that variable numbers and composition of chromosomes contribute to the progression of cancer. However, the molecular details of how aberrant chromosomes are formed in cancer cells are not well understood.

It has been proposed that the insufficient functions of telomeres, the end of chromosomes, play a key role in chromosome aberration. However, this hypothesis has not been examined experimentally. The aim of this study is to elucidate whether telomere dysfunctions lead to genetic instability in cancer cells, and how this pathway is important for the progression of cancer.

【Research Methods】



Telomeres cap the end of chromosomes, thereby preventing the fusion of two chromosomes. Dysfunctional telomeres promote the formation of fusion chromosomes (step one to two in the figure), which possess two kinetochores and thus called dicentric chromosomes (step three). In M phase, two spindles emanating from the opposite poles can simultaneously attach and pull the two kinetochores on the dicentric chromosomes, which eventually lead to a break between the two kinetochores. Thus formed broken chromosomes lack the telomere and again follow the steps one to three. However, when telomerase is active, it can heal the broken end by adding telomeric DNA sequence and the healed abnormal chromosomes may be stabilized (step four). This hypothesis was proposed more than fifty years ago to explain how chromosomes dysfunctional for telomeres produce abnormal chromosomes, but experimental tests of the scenario have never conducted before.

We will first identify the presence of fusion chromosomes in cells and organisms defective in telomere functions. Toward this goal, we will exploit the next-generation sequencer and sequence the fusion points by massive sequencing.

Once it has been proved that fused chromosomes play a role in chromosomal instability in cancer cells, we will test the role of telomerase using telomerase-knockout mice.

【Expected Research Achievements and Scientific Significance】

Molecular elucidation of how telomeres and telomerase facilitate chromosomal instability will help us to prevent the progression of cancer cells by targeting key molecules in telomeres.

【Publications Relevant to the Project】

Ishikawa, F. Telomere crisis, the driving force in cancer cell evolution. Biochem. Biophys. Res. Commun., 230, 1-6 (1997)

Miyoshi, T., Kanoh, J., Saito, M., and Ishikawa, F. Fission yeast Pot1-Tpp1 protects telomeres and regulates telomere length. Science, 320, 1341-1344 (2008)

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.lif.kyoto-u.ac.jp/labs/fish