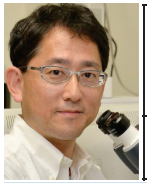
【Grant-in-Aid for Scientific Research (S)】

Plastic regulation of chromosome dynamics in cancer



Principal Investigator	Japanese Foundation For Cancer Research, Cancer Institute, Experimental Pathology, Chief HIROTA Toru Researcher Number:50421368
Project Information	Project Number : 22H04996 Project Period (FY) : 2022-2026 Keywords : Chromosomal instability, Chromatin, Aurora B, Cancer stem cells

Purpose and Background of the Research

●Outline of the Research

Aneuploidy is a widespread feature of malignancies which is caused by persistent chromosome segregation defects in mitosis through a mechanism called chromosomal instability, or CIN. Acquisition of CIN renders tumors cellular diversity, i.e., intra-tumor heterogeneity, which is thought to causally relate to malignant properties of advanced disease.

CIN has both positive and negative effects on cell proliferation. In clinical cancers, chromosomal instability positively correlates with malignant features including drug resistance, relapse and poor prognosis. However, increase or decrease of chromosome number by experimental induction of CIN limits cellular fitness and often inhibits cell proliferation. This seemingly contradictory observations are called “aneuploid paradox”, which as long been an outstanding question in cancer biology field.

To approach this question, we will study cancer stem cells that were found to be chromosomally unstable and generates aneuploid populations as they proliferate. We will isolate clones with different levels of CIN and karyotype distributions, and address chromosomal and chromatin structures relating malignant characteristics. Specifically, we will combine state-of-the-art super-resolution microscopy analysis and integrated genomic analyses, to characterize chromosome structures causally related to phenotypes. Moreover, given the plastic nature of the level of CIN, we will address the possible role of this plasticity in the acquisition of malignant phenotypes. Through these approaches, we will try to introduce a conceptual advance in our understanding the pathological relevance of chromosomal instability in cancer biology.

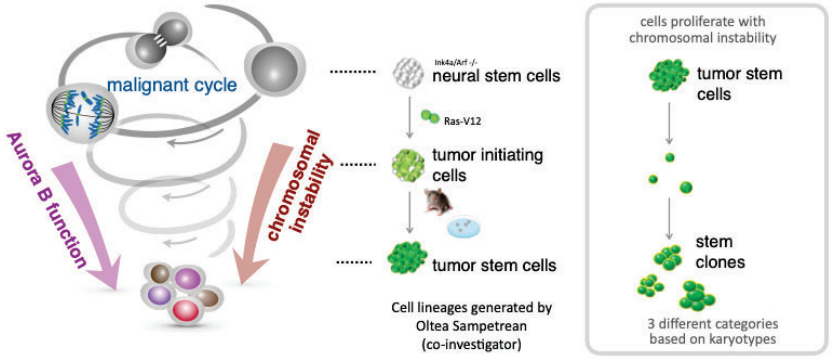


Figure 1. Experimental settings using engineered tumor stem cells and its isolated clones

● Previously we found that an insufficiency of Aurora B function underlies CIN in many cancers (Dev Cell 2016). With the support of Grant-in-Aid for Scientific Research (A) (FY2018-2021), we have then identified mechanism for the system level regulation of Aurora , and thus the level of CIN can be reversibly altered (in preparation).

● Working hypothesis

Having known the plastic nature of CIN, an intriguing possibility we thought was that cancer takes advantage of this plasticity to be able to cope with a negative effect of aneuploidy. Along with this hypothesis, we will investigate how we can control the level of CIN by manipulating Aurora B function, and verify the capacity of tumor stem cells when CIN level is irreversibly fixed.

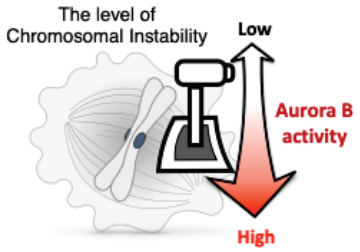


Figure 2. The plastic regulation of Aurora B provides means to control CIN.

● Prospective impact

Understanding the pathological relevance of CIN, we shall be able to develop a novel diagnostic means to assess what we collectively call “advanced disease”. It will also open an avenue to targeting chromosomal instability of cancer cells, namely to intervention of its plastic regulation. These attempts must facilitate our ultimate goal to conquer progressive statuses of cancers.

Expected Research Achievements

● Chromosome profiles relating proliferative characteristics

A solution for the aneuploidy paradox must be obtained through exploration of how chromosome-level alterations causally relate to proliferative capacities as follows:

・ Chromosome structure, higher order structure of chromatin, gene expression profiles are all combined to investigate chromosome profiles responsible for progressive cell growth.

・ We will develop a novel microscopic method that integrates the detection of chromatin structure alteration on single cell basis, which allows for studying heterogenous population of tumors.

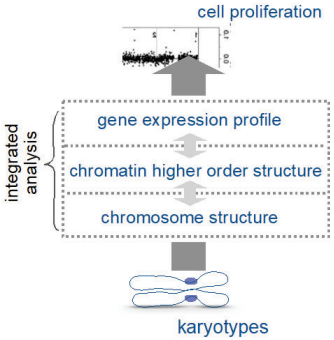


Figure 3. Integrated analysis of chromosomes and chromatin

● Plastic nature of chromosome dynamics in cell growth

・ We will investigate the molecular mechanisms how Aurora B system is maintained and can shift its level upward/downward, by studying the reaction to perturbations.

・ Along with our working hypothesis, we will then engineer tumor stem cells that have impaired Aurora B system and examine how plastic regulation of chromosome dynamics contributes to the malignant phenotypes of tumors.

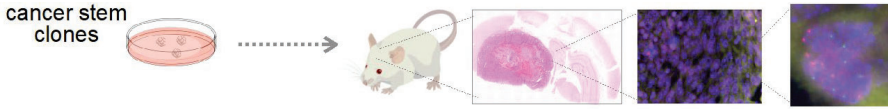


Figure 4. Testing the significance of chromosomal instability in living environment.

● Pathological significance of plastic regulation of chromosome dynamics

We will characterize chromosome structures, that surpass the negative effects on cellular fitness, and will understand the advantage of plastic regulation of chromosome dynamics. These understandings will revise our view of cancer’s chromosomal instability, i.e., tipping the balance between the double-edged sword.

Homepage Address, etc.	Hirota laboratory original HP: https://www.jfcr.or.jp/tci/exppathol/index.html Japanese Foundation for Cancer Research HP: https://www.jfcr.or.jp/laboratory/department/experiment/index.html