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

Broad Section H

Title of Project： Comprehensive analysis of molecular machineries for mitotic spindle formation in human cells and its application to development of next generation anti-cancer drug.

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Research Project Number：19H05651　Researcher Number：80605725
Keyword：cell division, centrosome, centriole, mitotic spindle, mitotic inhibitor

【Purpose and Background of the Research】

The centrosome is an evolutionarily conserved organelle in eukaryotes, and is important for formation of mitotic spindles, and thus is deeply involved in proper chromosome segregation and maintenance of genome stability. On the other hand, in human cancer cells, it has been reported that cell division proceeds by a centrosome-independent spindle formation mechanism even if the centrosome is physically removed. Recently, we found that in different cancer cell types, the contribution of centrosomes in spindle formation is significantly different. Therefore, in this study, we will identify various spindle formation machineries by performing comparative analysis using many types of human cancer cells as a model. Furthermore, we analyze the molecular basis that controls mitotic spindle formation in an integrated manner, and elucidate the mechanisms of centrosome-dependent and independent mitotic spindle formation in various types of human cancer cells. In addition, by combining the latest cytogenetics, cell biology and chemical biology, it is possible to develop mitotic-phase specific anti-cancer drug.

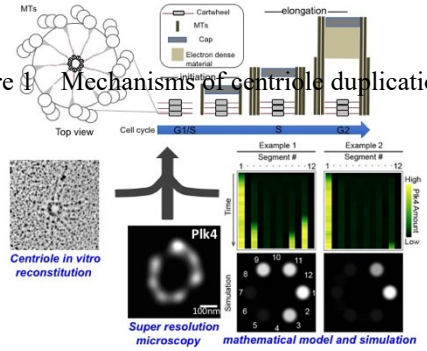

Figure 1　Mechanisms of centriole duplication

【Research Methods】

1) Elucidation of centrosome duplication mechanisms by a combination of super resolution microscopy and *in vitro* reconstruction system. 2) Comprehensive identification and functional analysis of centrosome-independent spindle formation machineries using cytogenetic methods in various human cancer cell types. 3) Develop small molecule compounds that specifically inhibit mitotic spindle formation. 4) Elucidation of the spindle formation mechanism in blood cancer cells.

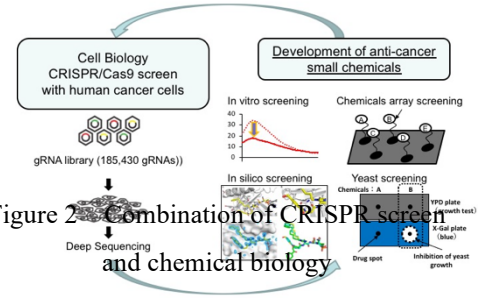

Figure 2　Combination of CRISPR screen and chemical biology

【Expected Research Achievements and Scientific Significance】

In this research, we use super resolution microscopy technology, simulation, structural biological analysis, etc., and clarify the basic principles that mediate centriole duplication and mitotic spindle formation. Also, we will establish an accurate duplication model of centrosomes using mathematical models and simulations based on raw data. Furthermore, the findings obtained from this study are expected to lead not only to a better understanding of the cell division processes of various cancer cell types but also to the development of new anti-cancer strategies.

【Publications Relevant to the Project】

・Ohta M., Watanabe K., Ashikawa T., Nozaki Y., Yoshiba S., Kimura A. and Kitagawa D. (2018) Bimodal Binding of STIL to Plk4 Controls Proper Centriole Copy Number. *Cell Reports*, 23, 3160-3169, doi: 10.1016/j.celrep.2018.05.030.
・Tsuchiya Y., Yoshiba S., Gupta A., Watanabe K. and Kitagawa D. (2016) Cep295 is a conserved scaffold protein required for generation of a bona fide mother centriole. *Nature Communications*, doi: 10.1038/ncomms12567.

【Term of Project】 FY2019-2023

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~seiri/index.html