【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project： Comprehensive understanding of mechanisms underlying the piRNA pathway

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【Purpose and Background of the Research】

piRNAs are small RNAs enriched in animal gonads where they arms race with transposons to maintain germline genome integrity. Although transposons are powerful agents contributing to evolution, they are also regarded as selfish DNA parasites. Indeed, loss of piRNAs causes derepression of transposons, leading to DNA damage and failure in gonadal development and fertility. Thus, piRNA-mediated transposon silencing is indispensable for animals that undergo obligate sexual production. The piRNA studies have intensively been conducted worldwide from which fundamental scheme of the pathway have emerged. However, the molecular mechanism is not yet fully understood. In this proposal, we aim to gain insights into the molecular mechanisms underlying the piRNA-mediated transposon silencing pathway to reach our goal: Comprehensive understanding of the pathway.

【Research Methods】

To reach our final goal, we will pursue five research plans, RP-1 to RP-5, which are indicated below.

[RP-1] Understanding of the mechanism underlying piRNA biogenesis in OSCs
[RP-2] Understanding the molecular mechanism underlying piRNA biogenesis in germ cells
[RP-3] Understanding the mechanism underlying piRNA-driven transcriptional silencing in OSCs
[RP-4] Solving the 3D structures of piRNA factors
[RP-5] Understanding the mechanism underlying dynamics of local heterochromatin in mouse gonocytes

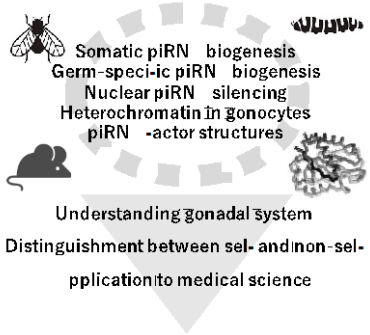

Figure 1. Comprehensive understanding of the piRNA pathway

【Expected Research Achievements and Scientific Significance】

Genetic studies identified maternal effect genes with an involvement in the piRNA pathway. Our expertise and use of cultured OSCs allow us to biochemically analyze their functions, and gain new insights into the molecular functions in piRNA biogenesis and piRNA-mediated silencing mechanism. Our continued studies will further contribute to understanding of the natural biological functions of the germline. This is unique, important and necessary, as the *in vivo* engineering of the piRNA-mediated gene silencing or related pathways may result in biotechnological and biomedical applications such as the development of antiviral and cancer therapies, and methods to treat diseases related to functional defects in the ovaries and testes, including infertility.

【Publications Relevant to the Project】

・Ishizu H, Kinoshita T, Hirakata S, Komatsuzaki C and *Siomi MC. Distinct and collaborative functions of Yb and Armitage in transposon-targeting piRNA biogenesis. ***Cell Reports*** 27:1-14. 2019
・Nishida KM, Sakakibara K, Iwasaki Y, Yamada H, heteroMurakami R, Murota Y, Kawamura T, Kodama T, Siomi H and *Siomi MC. Hierarchical roles of mitochondrial PAPI and Zucchini in *Bombyx* germline piRNA biogenesis. ***Nature*** 555:260-264. 2018
・Matsumoto N, Nishimasu H, Sakakibara K, Nishida KM, Hirano T, Ishitani R, Siomi H, *Siomi MC and *Nureki O. Crystal structure of silkworm PIWI-clade Argonaute Siwi bound to piRNA. ***Cell*** 167:484-497. 2016
・Sumiyoshi T, Sato K, Yamamoto H, Iwasaki YW, Siomi H and *Siomi MC. Loss of l(3)mbt leads to acquisition of the ping-pong cycle in *Drosophila* ovarian somatic cells. ***Genes & Development*** 30:1617-1622. 2016

【Term of Project】 FY2019-2023

【Budget Allocation】 417,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-siomilab.biochem.s.u-tokyo.ac.jp/publications.html