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

Broad Section F

Title of Project： **Genome immunity: elucidation of the antiviral activity of endogenous bornaviruses and their utilization as functional resources**

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Keyword：Endogenous viruses, Bornavirus, RNA, Antiviral activity

【Purpose and Background of the Research】

The genomes of our organisms contain many genetic sequences derived from viruses. In 2010, we discovered endogenous elements derived from ancient bornavirus infection (endogenous bornaviruses) in the genomes of many mammals, including humans, and suggested that our genomes have more viral-derived sequences than previously thought. On the other hand, we also demonstrated in previous studies that transcripts derived from endogenous bornavirus elements suppress exogenous bornaviral infection as RNAs or proteins. These observations suggest that our genomes possess the inherited systems of antiviral (genomic immunity) similar to the CRISPR/Cas system.

The aim of this study is to investigate in detail the molecular mechanisms of the antiviral activity of endogenous bornaviruses, and to elucidate the biological principle of genomic immunity. We also aim to create scientific and technological innovations by applying the findings from this study (Fig. 1).

【Research Methods】

We will conduct the following analyses.

(1) Elucidation of the mechanism of the antiviral activity of endogenous bornaviruses: We will perform an in-depth analysis to understand the expression profiles of endogenous bornaviruses and elucidate the mechanisms of the antiviral activity of their transcripts.

(2) Elucidation of the sequence characteristics and expression mechanism of endogenous bornavirus RNAs: To elucidate the features of endogenous bornavirus RNAs important for antiviral activity, we will investigate their structure, modification and expression in detail.

(3) Regulation of antiviral activity by modifying the RNA sequences: To manipulate the antiviral function, we will modify the RNAs produced from endogenous bornaviruses and regulate their activities in vitro.

(4) Sequence design for the regulation of antiviral activity: We will generate cell lines with various mutations in the sequences of endogenous bornavirus elements and investigate their antiviral defense characteristics.

(5) Establishment of cell lines expressing antiviral RNAs to specific viruses: To establish cell lines resistant to specific viruses, cassette constructs expressing synthesized antiviral RNAs are transduced into the cells.

【Expected Research Achievements and Scientific Significance】

This study will elucidate the biological principle of "genomic immunity" by endogenous viruses and lead to the discovery of CRISPR-Cas-like mechanism of mammals. Our research achievements will also develop antiviral drugs and vaccines based on a new principle of action, as well as establish safe transplanted cells and vaccine production cells to prevent viral contamination.

【Publications Relevant to the Project】

- Horie M, Honda T, Suzuki Y, Kobayashi Y, Daito T, Oshida T, Ikuta K, Jern P, Gojobori T, Coffin JM and **Tomonaga K**. Endogenous non-retroviral RNA virus elements in mammalian genomes. Nature 463:84-87 (2010)
- Parrish NF, Fujino K, Shiromoto Y, Iwasaki YW, Ha H, Xing J, Makino A, Kuramochi-Miyagawa S, Nakano T, Siomi H, Honda T and **Tomonaga K**. piRNA derived from ancient viral processed pseudogenes as transgenerational sequence-specific immune memory in mammals. RNA 21:1691-1703 (2015)

【Term of Project】FY2020- 2024

【Budget Allocation】147,200 Thousand Yen

【Homepage Address and Other Contact Information】

https://t.rnavirus.virus.kyoto-u.ac.jp

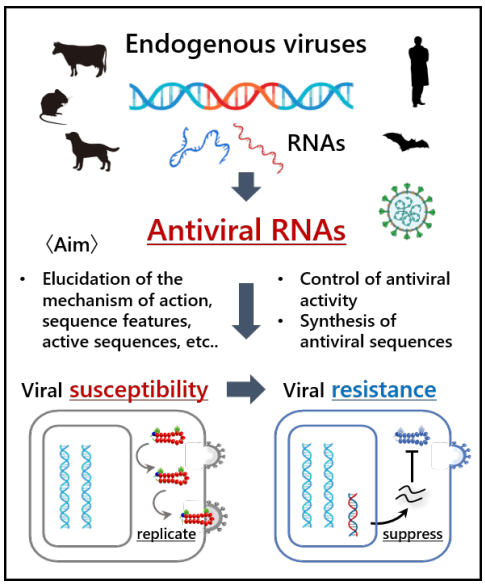

Fig.1 Genome immunity and its application