【Grant-in-Aid for Transformative Research Areas（A）】

Integrated understanding of RNA-induced perturbations in living systems and their adaptive mechanisms

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Purpose and Background of the Research

●Outline of the Research

Organisms have adapted to invasive RNAs or the expression of RNAs that perturb their own systems over a long period of time by developing mechanisms to eliminate or suppress, and sometimes by co-opting them. However, with the frequent emerging viral infections in recent years, the opportunities to accept exogenous RNAs are rapidly increasing. In addition, the majority of genomes are composed of sequences originated from exogenous RNAs. Retrotransposons, a prime example, have given rise to the expression of endogenous RNAs, are being elucidated to have various functions other than transposition. Therefore, in this research area, we define perturbing RNAs (perRNAs) as a group of RNAs that perturb living systems, whether exogenous or endogenous, and aim to characterize them to comprehensively understand the regulatory mechanisms of perRNAs and their roles in disease and adaptation to environmental changes. The results of this research area will be widely disseminated as a “perRNA database” to share the novel concept of perRNA with researchers in Japan and overseas. This will make it possible to elucidate perRNAs associated with a wide range of species, diseases, and environmental changes, and to predict their physiological effects with a high degree of accuracy. As a result, physiological phenomena, causes of diseases, and adaptation mechanisms to environmental changes will be clarified, leading to the development of new disease treatments and RNA medicines with fewer adverse reactions.

Class of RNAs that perturb living systems = perturbing RNAs (perRNA)

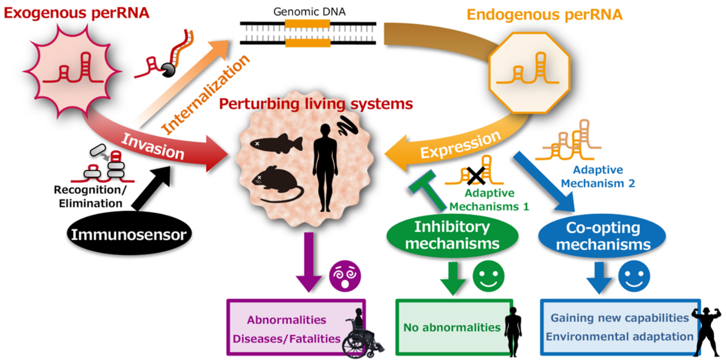
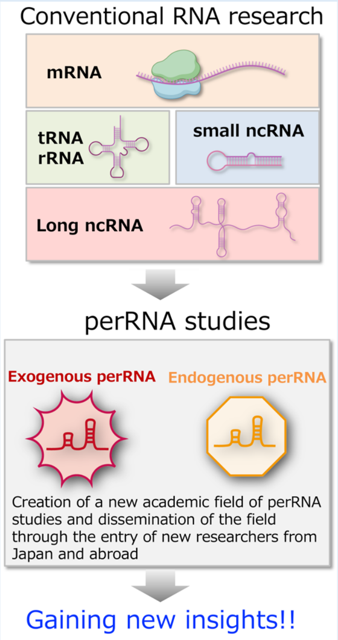


Figure 1. Conceptual Diagram of the perRNA Research

●Background

In recent years, emerging RNA viral infections such as COVID-19 have increased in the human population, and these viral RNAs perturb the host's biological systems, sometimes causing cellular and individual death (**Figure 1: Exogenous perRNA**). In addition, artificial RNAs, as represented by mRNA vaccines, are expected to be used with increasing frequency. On the other hand, the majority of biological genomes are composed of sequences derived from foreign RNAs. Retrotransposons, a prime example, have given rise to the expression of endogenous RNAs, are being elucidated to have various functions other than transposition (**Figure 1: Endogenous perRNA**). Furthermore, the risk of double-stranded RNA formation between inactive repeat sequences has increased, and it has become essential to distinguish them from exogenous double-stranded RNAs such as viral RNAs. It is assumed that the organism has multiple layers of inhibitory mechanisms as adaptive measures against such endogenous perRNAs (**Figure 1: Adaptive mechanism 1**). In addition, it is becoming aware of some cases in which organisms co-opt RNAs that are derived from retrotransposon (**Figure 1: Adaptation mechanism 2**), but much of these mechanisms remain unresolved.

The goal of this research area is to understand the adaptive mechanisms that enable coexistence with perRNAs. This ambitious project aims to comprehensively reconsider RNAs from the viewpoint of negative functions, bringing about a paradigm shift from preconceived notions about RNA (**Figure 2**).



Conventional RNA research

mRNA

tRNA
rRNA

small ncRNA

Long ncRNA

perRNA studies

Exogenous perRNA

Endogenous perRNA

Creation of a new academic field of perRNA studies and dissemination of the field through the entry of new researchers from Japan and abroad

Gaining new insights!!

Figure 2. Reconsidering RNA from the perspective of negative function

Expected Research Achievements

●Research contents

Group A01: Identification and characterization of perRNAs

From public databases and transcriptome data obtained by each group's research, perRNA candidates with specific functions will be extracted and characterized in terms of sequence, structure, and dynamics.

Group A02: Elucidation of molecular mechanisms that manipulate perRNAs

To understand perRNA adaptation mechanisms, we will elucidate the mechanisms that manipulate perRNA functions. Essentially, perRNAs that disturb cellular and individual homeostasis are suppressed so that their functions are not exerted. To this end, it is essential to understand the recognition mechanisms that sense perRNAs, induce their degradation, and suppress their expression and function. We will also investigate the mechanisms underlying co-opted perRNAs.

●Ripple effects

The outcomes of each research group will be registered in the “perRNA database”, which will enable the prediction of physiological effects of perRNAs in a wide range of species, diseases, and environmental changes with assistance of AI. The accumulation of such knowledge will provide an opportunity to reconsider RNAs from the viewpoint of negative functions, bringing about a paradigm shift from preconceived notions about RNA (**Figure 2**). As a result, it is expected to be applied to the development of new disease therapies and RNA medicines with fewer adverse reactions.

Homepage Address, etc.	https://perturb-rna.m.chiba-u.ac.jp/