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

Elucidation of the mechanism for dimensional response genome across species regulated by nucleic acid structures

Area Leader
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Greetings

Until now, nucleic acids comprised in the genome have been considered molecular units that contain all genetic information. In contrast, proteins are believed to be to regulators of gene expression. However, in recent years, several reports have described non-canonical structures of nucleic acids (triplex, G-quadruplex, cruciform structures, and among others) that can regulate gene expression in human cells, which may overturn this preconceived notion. For example, the formation of G-quadruplexes in oncogenes can suppress its expression. The roles of nucleic acid structures as promoters of cancer is now attracting attention, and novel drugs targeting nucleic acid complex structures are being explored worldwide.

It is known that the structure of nucleic acids changes dynamically under the influence of the surrounding environment. We have considered that, in all living organisms, nucleic acids sense the surrounding environment, change their structure multidimensionally, and proactively regulate their expression. In previous research, the structure and function of nucleic acids have been analyzed for each species; however, from a physicochemical perspective, the mechanism of nucleic acid structure formation is considered to be species-independent. Nevertheless, to the best of our knowledge, no study to date has analyzed similarities and differences in gene expression mechanisms by non-canonical structures beyond the framework of biological species.

In this research area, we will conduct new investigations aiming at the following two points:

1) Elucidation of the "dimensional response genome”

We will focus on nucleic acid structures that fluctuate in a multidimensional manner in response to the environment and elucidate the molecular mechanisms that regulate gene expression from a physicochemical point of view, regardless of the biological species framework, which we call "dimensional response.” To this end, we aim to propose the existence and significance of a new genomic function based on nucleic acid structures, called “dimensional response genome," that are transversal to all disciplines that deal with life.

2) Development of a genome bank (DiR-GB) that can predict and use the dimensional response genome

We will explain the unified expression regulation mechanisms independent of species and construct a genome bank (Dimension Responsive Genome Bank [DiR-GB]) that will gather all the information.

The DiR-GB will deepen our understanding of the roles of nucleic acid structures in human cells and is expected to

be used to predict multidimensional responses of targeted organisms (not only humans, but also viruses and plants) for development of technologies to control biological phenomena. The DiR-GB will be made public so it can be freely used by researchers worldwide in a wide range of fields, including medical engineering, agriculture, and materials chemistry.

In this research project, we will integrate research approaches from other fields and promote the following research in a stepwise manner (Figure 1).

[1] Using analytical chemistry and information science approaches, we will analyze the information from various organisms whose whole genome sequences have been deciphered and which can form the non-canonical structure of nucleic acids. The "structural information" of nucleic acids that show multiple responses will be determined.

[2] Using physical chemistry, biochemistry, and inorganic materials science approaches, we will understand the "molecular mechanism" of nucleic acid structure-dependent dimensional responses based on direct observation of non-canonical structures in living cells and physicochemical parameters of nucleic acid structure changes in response to environmental changes in cellular model systems.

[3] Using molecular biology and phytochemistry approaches, we will analyze gene expression changes in response to non-canonical structures and correlate them with phenotypic changes in cells and individuals to understand the "regulatory function" of biological phenomena by multiple responses.

The findings will be integrated to create the Dimension Responsive Genome Bank (DiR-GB) — the first data bank of nucleic acid structures that show dimensional responses in various species.

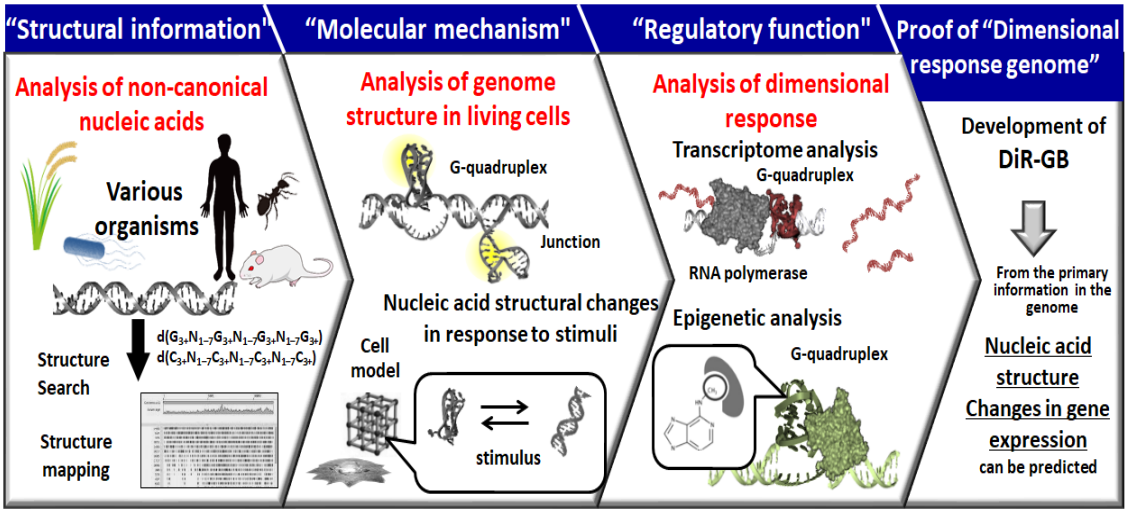

Figure 1. Research plan for elucidating the mechanism of "dimensional responsive genomics," in which nucleic acid structures regulate cellular functions in dimensional response.

Introduction of each group's research

A01 Group

Comprehensive analysis of nucleic acid structures involved in modulation of gene expression across species

Thanks to recent advances in sequencing technologies, genomics and transcriptomics information from diverse species have been analyzed and became publicly available. In addition, approaches to assess large-scale sequence information has also been greatly improved, allowing us to track the evolutionary process from the genetic standpoint. While most research in the field is based on the primary DNA and RNA structures, it is becoming clearer that these molecules can have various higher-order structures that are profoundly implicated on gene expression regulation. Thus, it is important to consider the structural information of nucleic acids, which shows dimensional responses to the overall cellular environment, to accurately determine the overall mechanistic landscape of gene expression regulation.

In our group, A01, we aim to demonstrate that nucleic acid structures, which are responsible for modulating gene expression, are present in various species and are optimized to function in each living condition by conducting genome-wide and transcriptome-wide analyses of their gene expression. In particular, we will discuss functional similarities and differences within nucleic acid structures among species using bioinformatic approaches, which will represent the foundations for further physicochemical and biochemical analyses to be conducted by other groups.

Principal Investigator

Name: Tamaki Endoh

Affiliation: Frontier Institute for Biomolecular Engineering Research (FIBER), Konan University

Title: Associate Professor

Research Interest: Cellular Engineering、Biomolecular Engineering

Roles in this research area: Genome-wide and transcriptome-wide analyses of gene expression influenced by nucleic acid structures

Address of the research map: https://researchmap.jp/t-endoh90550236

Co-Investigator

Name: Yiwei Ling

Affiliation: Medical AI center, Niigata University School of Medicine

Title: Assistant Professor

Research Interest: Bioinformatics

Bioinformatic analyses of nucleic acid structures involved in gene regulation

Address of the research map: https://researchmap.jp/yiwei-LING

Research Collaborator

Name: Shujiro Okuda

Affiliation: Medical AI center, Niigata University School of Medicine

Title: Professor

Research Interest: Bioinformatics

Bioinformatic analyses of nucleic acid structures involved in gene regulation

Address of the research map: https://researchmap.jp/read0145560

A02 Group

Elucidation of the mechanism for dimensional response genome using intracellular environmental evaluation systems

The aim of this study is to comprehensively analyze the non-canonical structures of nucleic acids in diverse species and to elucidate the dimensional response genomes regulated by these non-canonical structures. Therefore, in group A02, we will accurately predict the structure and function of nucleic acids *in vitro* by constructing evaluation systems for the intracellular environment using living cells and metal-organic structures. In addition, we will examine nucleic acid structures in these evaluation systems and construct a databank that will gather information on gene sequences and the "structures" of nucleic acids in cells of various species. Collected findings will be integrated with those of transcriptome and epigenome analyses obtained by Groups A01 and A03 to create the Dimension Responsive Genome Bank (DiR-GB)—the first data bank of nucleic acid structures that show dimensional responses in various species. Furthermore, by utilizing the information of DiR-GB, we can control the biological phenomena of targeted genes in humans, viruses, and plants using chemical approaches. Our research results can be expected to prove valuable in a wide range of fields, including medical engineering, agriculture, and materials chemistry.

Principal Investigator

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Title: Associate Professor

Research Interest: Functional Nucleic Acid Chemistry

Roles in this research area: Elucidation of the underlying mechanism of the dimensional response genome using intracellular environmental evaluation systems

Address of the research map: https://researchmap.jp/tateishi20593495

Co-Investigator

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Research Interest: Inorganic materials science

Roles in this research area: Evaluation of the behavior of nucleic acids in MOF microspace

Address of the research map: https://researchmap.jp/read0148803

Research Collaborator

Name: Saki Matsumoto

Affiliation: Frontier Institute for Biomolecular Engineering Research (FIBER), Konan University

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Research Interest: Nucleic Acid Chemistry, Organic Chemistry

Address of the research map: https://researchmap.jp/matsumoto-s

A03 Group
Elucidation of multidimensional physiological functions of nucleic acid structures

Genomic DNA and RNA contain multidimensional information beyond their sequences, such as higher-order structures and chemical modifications. The nucleic acid structure and epigenetic modification in response to various intracellular environments, including temperature, ion concentration, and hydration state, are believed to play a key role in maintaining biological activities under various environmental conditions. In group A03, we aim to analyze physiological functions of higher-order nucleic acid information, such as structures of DNA and RNA, as well as nucleic acid modifications, to clarify multidimensional response mechanisms that go beyond the primary sequence of macromolecules. In particular, we will study the relationship between RNA modifications and RNA G-quadruplex (G4) structures in animal cells, and their effects on gene expression. We will also investigate how the G4 structure and epigenetic profile of *Arabidopsis* change in response to developmental stages and environmental signals, and their effects on physiological functions of the plants. By collaborating with other members, we expect to provide valuable information to shed light into multidimensional physiological functions of nucleic acid structures in cells and individual plants at the molecular level.

Principal Investigator

Name: Miki Imanishi

Affiliation: Institute for Chemical Research, Kyoto University

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Research Interest: Epigenetic and epitranscriptomic regulation, Nucleic acid binding proteins

Roles in this research area: Elucidation of the intracellular functions of the non-canonical structures of nucleic acids

The address of the research map is https://researchmap.jp/mikiimanishi

Co-Investigator

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