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

Quantitative prediction of nucleic acid structures and functions affected by spaciotemporal environmental factors in cells

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Project Information	Project Number : 22H04975 Project Period (FY) : 2022-2026 Keywords : Nucleic Acid Structures, Intracellular Environments, Energy Database, Stability Prediction, Gene Expression

Purpose and Background of the Research

●Outline of the Research

Genetic information of all living organisms is in nucleic acids, DNA and RNA. The canonical structure of nucleic acids is the double helix based on Watson-Crick base pairing. This structure is fundamental to proceed replication, transcription, and translation, which are the key reactions in central dogma. In contrast, nucleic acids can form non-canonical (or non-double helical) structures such as triplex, quadruplex, junction, and so on. The principal investigator of this research project, Naoki Sugimoto, has demonstrated that the non-double helical nucleic acid structures potentially modulate the efficiency and rate of reactions in replication, transcription, and translation (N. Sugimoto et al., *Proc. Natl. Acad. Sci. U. S. A.*, 114, 9605 (2017), *J. Am. Chem. Soc.*, 140, 642 (2018), *Nat. Struct. Mol. Biol.*, 25, 279 (2018), *J. Am. Chem. Soc.*, 143, 16458 (2021), etc.). These results were obtained based on the research grants from JSPS KAKENHI (Grant number: 24245033, 16H02283, 19H00928, etc.). In addition, from other KAKENHI projects focusing on environmental effects on nucleic acid structures (Grant number: 17H06347, etc.), it was clarified that intracellular multimolecular crowding alters physicochemical properties of nucleic acids (N. Sugimoto et al., *Angew. Chem. Int. Ed.*, 57, 6868 (2018), *Sci. Rep.*, 10, 2504 (2020), *Proc. Natl. Acad. Sci. U. S. A.*, 117, 14194 (2020), etc.). Thus, it is considered that the canonical double helical nucleic acid structures are code for maintaining the genetic information and non-double helical nucleic acid structures are that for modulating expression of the genetic information.

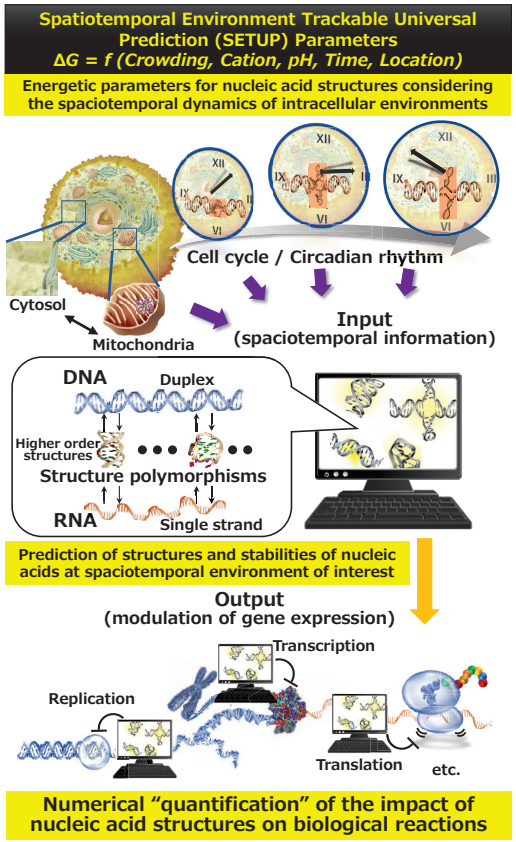

Figure 1. Research concept to quantify the stabilities of nucleic acid structures with their biological significance

Based on the research background, there is a growing need for energy parameters that accurately predict the intracellular stability of nucleic acid structures including double helical and non-double helical structures that enable to quantify the effects of nucleic acid structures on gene expression processes with their molecular mechanisms.

This research aims to predict "when, where, and how" double helical and non-double helical structures, which are involved in "retention of genetic information" and "regulation of gene expression", respectively, form and function in the cell. We will obtain Spatiotemporal Environment Trackable Universal Prediction (SETUP) Parameters that enable prediction of the stabilities of nucleic acid structures by taking into account the spatiotemporal environment inside cells. **From the viewpoint of energetic parameters, we will predict the impact of nucleic acid structures on biological reactions with the goal of a paradigm shift from "visualization" to "quantification" of life phenomena that can clarify the functions of nucleic acid structures (Figure 1).**

Expected Research Achievements

According to the research steps shown in Figure 2, we first evaluate dynamic behaviors of intracellular molecular environments. Then, we quantitatively analyze the nucleic acid structures, in which stabilities are affected by the dynamics of the physicochemical factors in cells, to obtain energy parameters that accurately predict the intracellular stability of any nucleic acid structures including double helical and non-double helical structures. Finally, based on the parameters, we construct a database that can quantify the effects of nucleic acid structures on biological reactions and their molecular mechanisms.

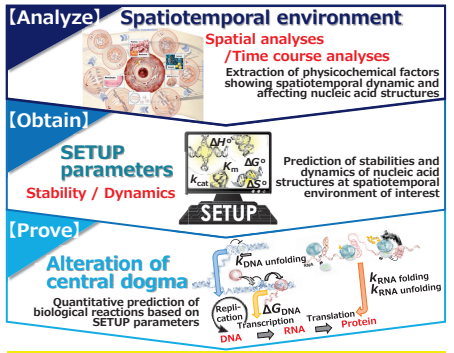

Figure 2. Research flow in this project.

Recent developments in the fields of chemical biology and analytical chemistry have enabled "visualization" of nuclei acid structures and their dynamic behaviors inside cells. This research project would provide important knowledge beyond the "visualization" that enables numerical "quantification" of the nucleic acid structures. Quantitative treatment of nucleic acid structures inside cells is expected to make a significant contribution to various technological applications (Figure 3).

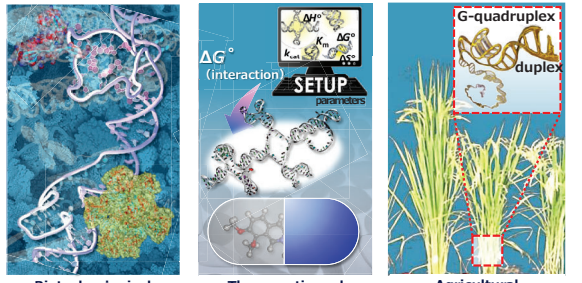

Figure 3. Research fields to which achievements of this research project are expected to be applicable.

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