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

Creation of Aptameric Biology

Head Investigator	Tokyo University of Agriculture and Technology, Graduate School of Engineering, Assistant Professor TSUKAKOSHI Kaori　　Researcher Number:20708474
Research Area Information	Number of Research Area : 22B205　Project Period (FY) : 2022-2024 Keywords : DNA aptamer, Protein function, Homeostasis, Brain

Purpose and Background of the Research

●Outline of the Research

The role of the homeostasis mechanism is to regulate the environment of tissues and cells against dangerous stimulation. Multiple protein molecules function in a concerted manner to perform everything from sensing to elimination of stimulations. Since the brain is an organ whose function is mainly controlled by neurons with extremely low cell proliferative activity, the homeostatic mechanism plays an important role in maintaining the function of the brain. In fact, strong stimulation, such as inflammation and misfolding of proteins, can lead to the onset of dementia and other diseases. Therefore, understanding the "defense mechanisms against stimulation" in the brain is of critical importance from both academic and disease prevention perspectives.

This research area aims to create a novel biological research field, "aptamer biology." This challenging research aims to revolutionize life science research by applying aptamer-based protein activity enhancing methods. By introducing aptamers that enhance the function of proteins involved in brain homeostasis into the mouse brain, we will conduct pathway-specific research to elucidate the life system that controls the homeostasis mechanism in the brain (Figure 1). We have named this type of biological research based on protein manipulation by aptamers "aptamer biology."

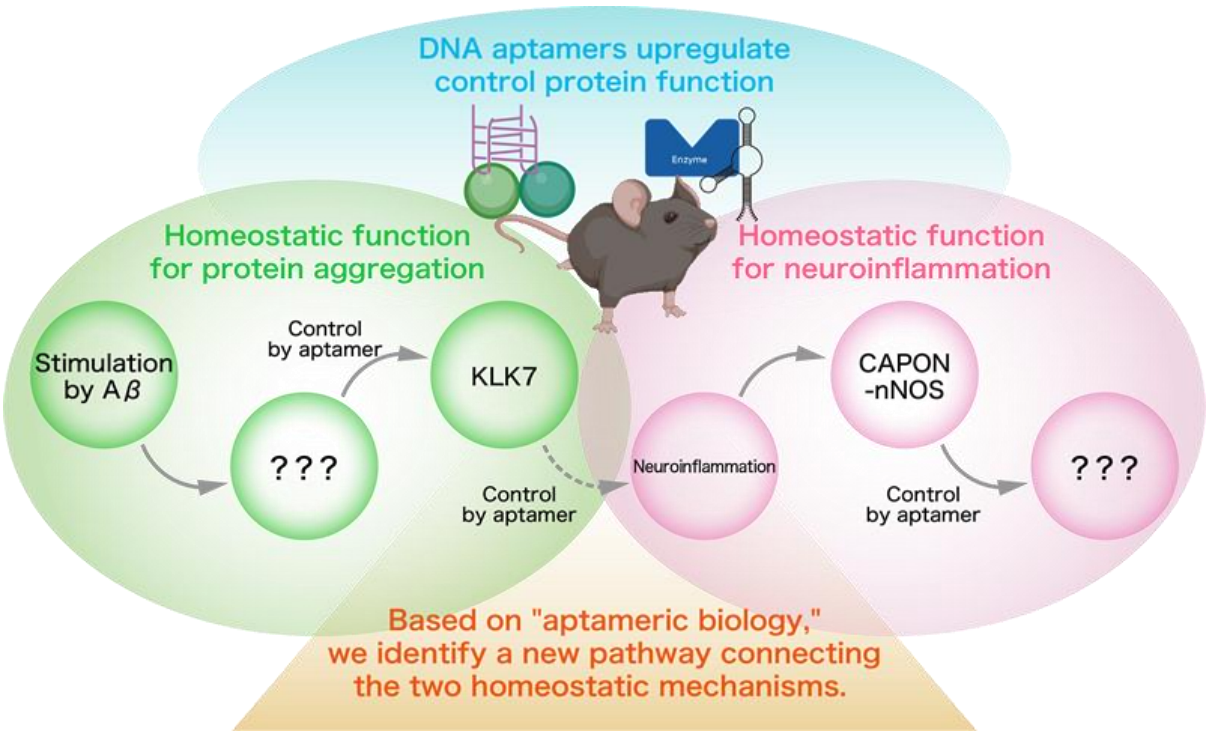

Figure 1. Schematic diagram of the research to be conducted in the "Creation of Aptamer Biology."

●What is DNA aptamer?

DNA aptamers are DNA molecules that recognize and bind to specific molecules. Aptamers can be prepared by complete chemical synthesis, and DNA aptamers can be synthesized in a single day. A large number of aptamers have been developed, especially for proteins, for use in disease diagnosis and as seeds for pharmaceuticals (see Figure 2; DNA aptamers that bind to proteins shown in red shown in purple and blue).

In this research area, we aim to develop DNA aptamers that can enhance or inhibit protein activity by binding and apply them to the analysis of homeostatic mechanisms.

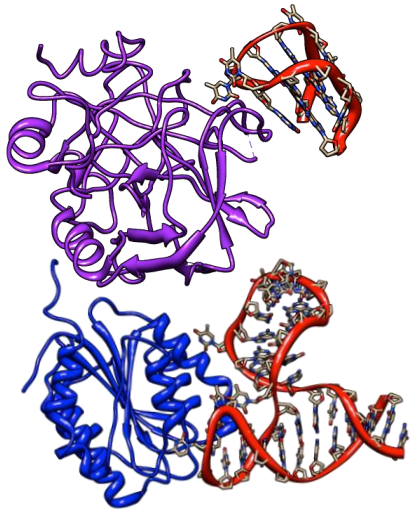

Figure 2. 3D structures of DNA aptamers.

Expected Research Achievements

We aim to broadly apply the concepts of aptamer biology to life science research in the future. To do that, we will construct a research platform that integrates nucleic acid engineering and biology by a cross-disciplinary team consisting of aptamer researchers and brain researchers. Specifically, the team will develop a novel model mouse for analyzing homeostatic pathways by applying DNA aptamers that can control the activity of proteins involved in the brain homeostatic mechanism. We will develop activity-regulated DNA aptamers and introduce the aptamers into the brain using a delivery system that delivers nucleic acids to the brain. Several aptamers that exhibit inhibitory or agonist activity on protein function have been shown to be able to regulate protein function in the mouse/rat. Aptamers that enhance enzyme activity by binding have also been reported in the area leader's research (Figure 3). Therefore, we will develop a basic technology to apply our special knowledges in the development of activity-regulating DNA aptamers to the development of analytical models of homeostasis mechanisms within the research period. This will complete the preparation for the application of the research field of "aptamer biology" to life system research.

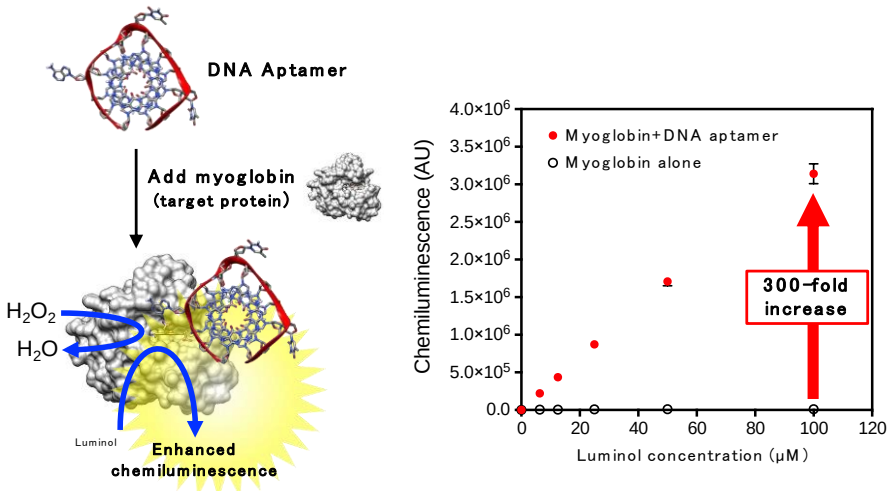

Figure 3. A DNA aptamer that enhances enzyme activity (modified from Nucleic Acids Res 49, 6069-6081, 2021). By developing aptamers that bind near the active center, we expect to obtain aptamers with activity-regulating ability.

Homepage Address, etc.	https://web.tuat.ac.jp/~aptamericbiology/