Light up the protein, light up the world

Kenryo SAKOI

When you hear the word "protein", what does come to your mind? Maybe this word reminds you of dietary supplements to enhance your muscle amount, or bodybuilders drinking such drinks? Sorry, I'm not going to tell you about these topics, but about tiny molecular machinery that controls the function of our body. Proteins, in a biological context, are one of the important components of living organisms. They consist of hundreds to thousands of building blocks called amino acids, formed into large biomolecules with many roles, such as nutrition take-up, moving muscles, etc. Among those various functions, the protein I'm now trying to develop is a sensor to visualize calcium in living cells.

Neither proteins nor calcium themselves are visible even with microscope because they don't show any colors. In order to capture the image or the movie of calcium flow, we combine a calcium sensor protein and a small fluorescent (light-emitting) molecule. Here's the trick: for protein part, we fuse two proteins together. The one protein is a calcium-sensing protein, which changes its structure upon binding to calcium. The other protein is called tag protein, which can be labelled by certain synthetic small molecule. The small molecule is designed so that it can be fluorescent, emitting visible light (for example, green or red) by laser irradiation. In the resulting system, when cellular calcium concentration increases, the protein undergoes structural change and that enables the molecule attached to the protein to be fluorescent. When put inside the cell, these sensors therefore can visualize calcium ion, which itself is not visible with our eyes. I believe that these kinds of tools will help us and neuroscientists understand the mechanism of neuronal signaling, since Ca^{2+} is known to be one of the major components in signal messenger.

Now you may understand the mechanism of the sensor, but you may have a question like “how do you develop such a system?” This is one of the most difficult experimental challenges and, for me, is one of the major reasons to be engaged in doing research in this field. The solutions to the problem can be classified into two approaches: a classic experimental method and a newly emerging computational method.

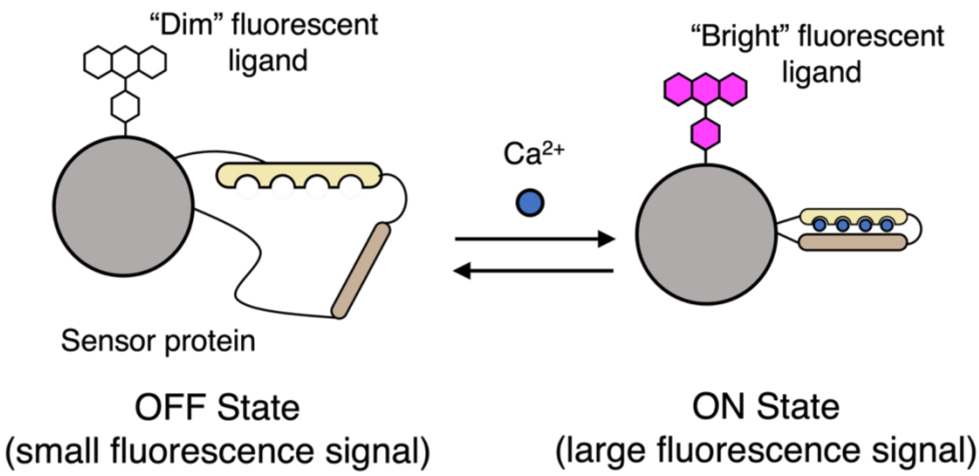

Figure 1. Schematic illustration of the sensor.

The former way involves the technology mimicking evolution found in nature. In this system, we introduce random mutation into our protein and make a large library of mutants. From the pool of candidates, we perform the experiment to test the abilities of the proteins and choose the best one. The best variant is further mutated, and the resultant library is screened. The repeated cycle of the screening is called “directed evolution”, because it looks like the evolution process of living things on this planet, where emergence of some species from other species (speciation) takes place by mutation on one’s gene result in the gain of functions, and they become able to survive under certain condition, leaving their gene to the descendants. This experimental process, actually, is tough and time-consuming. I, actually, find this experimental process quite tough and sometimes feel like a burden. We need to keep repeating the same experimental procedure again and again in order to get a good result. However, I also feel relaxed and enjoy doing this process because we can keep moving forward even without a good rationale. When doing research, sometimes we get stuck in a difficult problem which are too hard to solve in a short period. But, even if we can't come up with a good way to proceed, directed evolution can help us by automatically finding one, because mutations are completely random. My supervisor even says, "directed evolution is like a buying a lottery." For now, my lottery looks very decent.

These days, there have been a breakthrough in the field of computational tools. These tools involve deep-learning, or artificial intelligence (AI) -based software that predicts the result of the experiment and suggest us ideas by itself. Also, there have been tools that simulates the moves of proteins by solving the equation of motion on computer. This is the most interesting thing for me these days. To tell the truth, I'm not familiar with these recently established tools for now and still learning them. However, I feel really happy trying to introduce computational methods in my research, because there are few examples that applied the computational methods to the protein sensor field, meaning that perhaps we can be the first people on history!

You may have been surprised that I'm still learning a lot of things even though I have entered one of the "highest-level" universities in Japan. Actually, I feel that as I get older the more things there are to study. I even wish that I had studied more when I was a child. Here's a lesson I learned as a graduate student: study anything you want. 12-year-old me would think that some things are worth learning and other things are not. I'm now a student of the Chemistry department, but insights on biology is highly required in my research. Now, I’m trying to acquire knowledges about mathematics and physics for extending my research. Also, you need to acquire skills on reading, writing and even speaking in English in order to get yourself and your research known by the audience worldwide, and to pursue the research career. As I stated in this essay, there are many things that we don’t know yet but find interesting and necessary. My message to 12-year-old self is to learn everything that interest you and enjoy your journey!

I didn’t use any AI-based tools in writing this essay.