Learning from Insects

Department of Synthetic and Biological Chemistry, Graduate School of Engineering,
Kyoto University
Professor Masato Umeda

[My basic science approach]

I still remember my anxiety when I joined a university laboratory and started my first research. Because already so many researchers have been studying biology by then, and even now, hundreds of thousands of excellent researchers worldwide are doing research, I wondered if there is anything I can clarify. However, once I began my research, my fears were quickly resolved. We didn’t understand so many things about living things, and the laboratory was full of questions that couldn't be solved and experiments that didn't go as expected. It was well preserved in the head of my mentors who taught me the research and in the laboratory notebooks stored in the laboratory. These unsuccessful experiments prevented us from repeating the same mistakes and served as a starting point for the subsequent investigation and clues to new discoveries.

Because living organisms are so complex and work in mechanisms beyond our imagination, even if we start a project with a certain hypothesis (goal) and spend a long time conducting a series of experiments, we often fail to prove the hypothesis. When we submit such research to so-called top-notch scientific journals in the U.S. and Europe, most of them are rejected for publication because the biological significance of the research results is not clear. However, if the research direction is clear and describes solid facts, it can surely be published in some research journals. If you have what is called a "fall but don't get up for free" mentality, you can still publish the facts obtained from your experiments and preserve and share them as an intellectual property forever. Even scientific journals such as PLOS ONE (Public Library of Science One), which anyone can read without paying a subscription fee and is widely shared by the community, are now publishing articles as "Positively Negative" articles about the results of unsuccessful drug trials and epidemiological experiments.

Basic science takes time. Sometimes, you may feel discouraged. One of the reasons why we can continue despite this is that there is a community of scientists who share the facts discovered during their research as achievements. In this case, finding such a fact is itself an important result, and sharing it with other researchers in the same field can serve as a foundation for the subsequent development. It may also be true for companies to work hard for years until the results meet expectations. In such cases, if the CTO and others create a culture in which failures are shared as important facts, so to speak, and recognized as achievements, the same mistakes will not be made, and aspiring people will be able to recover and continue their efforts even if they are about to break.

Ohsumi Frontier Science Foundation

[About my research]

It is thought that there are more than 10 million species of organisms living on the earth today, and we humans, as one of the animal species, live together with many other organisms. Recently, many scientists were surprised to learn that a great variety of organisms, including bacteria, live inside our bodies (e.g., in the large intestine) and on our body surfaces and that the number of such organisms is more than ten times greater than the number of cells that make up our entire bodies. It has also been shown that an imbalance of symbiotic bacteria can trigger various diseases such as obesity, cancer, and neurological disorders. This fact revealed by modern biology indicates that we do not exist as a unique life form, the primate of all things, but as a symbiosis of many organisms. In order for human beings to survive for a long time to come and lead healthy lives, it is essential to clarify the mechanisms and activities of humans and various other organisms, which is one of the major challenges for basic biologists.

Insects are the most diversified and thriving animal species on earth, accounting for 60% of all multicellular organisms. The reasons that insects have thrived in this way are 1) superior environmental adaptability, 2) miniaturization and acquisition of flying ability, and 3) the achievement of high energy metabolic activity that supports flight. On the other hand, all living organisms are composed of molecules such as proteins and lipids created by the combination of a limited number of atoms such as carbon, hydrogen, and oxygen, and tens of thousands of different chemical reaction systems come together to produce the energy necessary for vital activities. So what mechanisms do insects have that are different from ours? For example, as shown in the figure below, an insect less than 1 mm in length, almost the same as a unicellular animal, a paramecium, has the same internal organs, such as brain, heart, and intestines, as we have. How are these microscopic insects formed? Using Drosophila as a material, our research aims to reveal the secret of insect prosperity by unraveling its molecular mechanisms. Our research to date has demonstrated the ingenious mechanisms of the organism, as shown in the figure below.

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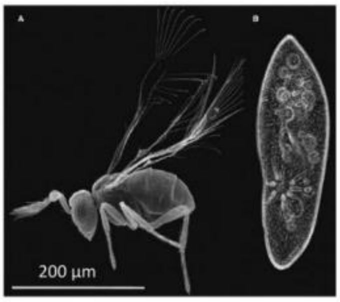
Ultra-small Insects



A: *Megaphragma mymaripenne*
B: *Paramecium caudatum*（ゾウリムシ）
(*Anthro. Struct. Develop.* 41:29. 2012)

Factors contributing to insect prosperity

1. high adaptability to temperature: acquisition of superior thermoregulatory mechanisms and systems to maintain cellular functions over a wide temperature range
2. miniaturization and acquisition of flying ability: acquisition of high cell deformability through unique membrane lipid mechanisms
3. high energy metabolism: energy metabolism via multiple fatty acid transport pathways to mitochondria

Below is a brief description of each study.

(1) Excellent temperature adaptability

Even insects regulate their body temperature by going to the sun or shade. We created a heat-loving mutant (atsugari mutant) that always likes to be in the cold and investigated why it prefers to be in the cold. As a result, we found that the atsugari mutant is highly metabolically active and that Drosophila goes to cold places when its metabolic energy is high and goes to warm places when its energy is low, thereby regulating its body temperature according to its body state (Science 323:1740, 2009). We mammals must constantly eat sufficient food (other organisms). Otherwise, our body temperature will drop, and we will die. In this sense, we are highly flabby creatures, but Drosophila can live in a wide range of temperatures from 0 to 30 degrees Celsius and can be considered an energy-saving, environmentally friendly animal that changes its body temperature according to its physical condition.

(2) Secret of miniaturization

We perform an experiment in which we suck cells with a pipette about 1 micron in diameter to measure the activity of ion channels on the cell membrane. What surprised us was that insect cells were deformed and sucked into that pipette. Mammalian cells are either not sucked into such a pipette at all, or the cell membrane is ruptured if sucked too hard. This observation prompted us to analyze how the membranes of insect and mammalian cells differ in detail at the molecular level. First, we found that the tension of insect cell membranes is less than 1/10 that of mammals, making them incredibly soft and viscoelastic. Furthermore, we discovered that insect cells have a unique protein that constantly flips the lipid molecules that make up the cell membrane in and out of the membrane. It was also found that when this protein is deficient, the cells do not deform as rigidly as mammalian cells. Since cells with this unique property are observed only in small insects, we hypothesize that acquiring a viscoelastic cell membrane with excellent deformability may be advantageous for producing the microscopic body tissues necessary for miniaturization.

(3) High energy metabolic activity

We produce energy by burning lipids called fatty acids in intracellular organelles called mitochondria. A protein called CPT1 functions as a gatekeeper to transport these fatty acids to the mitochondria, and if this protein is deficient, the mammal will die. However, in Drosophila, we found that the animal is completely healthy even without the CPT1 protein and shows no abnormalities in energy metabolism. This observation implies that Drosophila has another mechanism besides CPT1 to transport fatty acids to the mitochondria. Therefore, we investigated a series of genes and found new candidate transport proteins. Insects produce more than a hundred times more energy per unit weight than humans during flight. And the enzyme CPT1 regulates fatty acid transport through a very complex reaction. Still, this pathway alone is not sufficient to provide energy during flight, and we believe that energy is efficiently produced through the protein we have identified. In fact, humans have a similar protein, but it has not been well studied yet, so we will also try to clarify its function in the future.