Unraveling what it means to be alive

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Dive into BDR's intriguing research

RIKEN BDR researchers are carrying out many intriguing and interesting research projects, but it can sometimes be difficult to understand what they are actually doing. Coordinator Hideki meets with researchers to delve behind the scenes of their research.

A step-by-step approach to aging research

This time, I interview research scientist Masaharu Uno. I heard that his research was on aging using worms. Why worms, I wondered as I made my way to go talk to him.

Aging research using worms

First of all, can you tell me what your research theme is?

I am looking at organismal aging and response to environmental stimulus using the *C. elegans* worm. The external environment is continuously changing during an organism's lifespan. And all living animals need to adapt to environmental changes such as temperature and the amount of food available. I'm looking at how these factors affect the lifespan (of worms).

From a layman's perspective, humans and worms appear to be very different.

There are of course many differences, but there are also many points that are conserved between humans and worms. In fact, many genes have been found conserved in both worms and mammals. Thus, I think we can apply our findings from worms to humans.

Why did you choose aging as your research theme?

You and I can consider our bodies to be matured. So naturally, the immediate question would be what will unfold next. Don't you find it mystifying that even though we were born into this world, we all have to die? Wouldn't it be fantastic if we could answer this question?

I think from an evolutionary perspective, people used to view aging as a process that was not strictly regulated. This is because evolution is considered to be a phenomenon in which there is a bias toward ensuring the survival of more offspring. Aging is a process that takes place after the reproductive period, so it can be thought that evolution would not select for extending individual lifespans. As aging is also thought to be just a process in which the physical body deteriorates, it's hard to think there is some system regulating this process.

I see your point. How are you trying to examine this, then?

For example, there is a gene called *daf-2*, and when there is a mutation in this gene, we can observe a doubled lifespan. Downstream of DAF-2, there is a signaling cascade where DAF-16 functions. If you generate a worm with a mutation for both *daf-2* and *daf-16*, the lifespan returns to normal. DAF-2 is a receptor for growth factor IGF-1, and DAF-16 is conserved as transcription factor FOXO in mammals. So we are trying to search for factors regulating aging by using lifespan as an indicator.

Masaharu Uno

Research scientist in Laboratory for Molecular Biology of Aging. After receiving his Ph.D. from the Graduate School of Biostudies, Kyoto University, he moved to RIKEN BDR, where he has been engrossed in the study of aging using *C. elegans*. His hobby is reading. Impressed by his mentor Dr. Eisuke Nishida's extensive knowledge, he has recently been reading five books in diverse genres, from fiction, philosophy and sciences, all at the same time.

Hideki Yakushiji

Partnership-Promotion Coordinator at RIKEN BDR and advisor at Foundation for Biomedical Research and Innovation at Kobe. He joined RIKEN in 2013, after working for several Japanese and international life science and manufacturing companies in areas such as business development. He is now focusing on facilitating collaborations and business development within RIKEN as well as promoting the KOBE Biomedical Innovation Cluster.

Relation between life span and metabolism

You mentioned something earlier about the amount of food, right?

Worms can be found all over the world, and some say that the total mass of all worms on Earth is greater than any other species on this planet. They can feed on almost anything. We breed them with colon bacillus (*E. coli*), but some researchers are known to feed them dog food. They can also eat wood.

I recall reading a news story about eliminating worms from farms and golf courses.

They eat pretty much anything, and will continuously feed if there is food present. But it's well known that their lifespan almost doubles when food is restricted. I'm now trying to examine the relationship between genetic background and food restriction.

Do you remember I mentioned that the *daf-2* mutant has a doubled lifespan? Well, although you can extend it even further with food restriction, the extent of the lifespan extension in *daf-2* mutants by food restriction is smaller than that observed in wild type.

The *daf-2* is a homolog of the Insulin/IGF-1 receptor. IGF-1 is Insulin-like growth factor-1. This suggests that lifespan regulation by food restriction might involve insulin and the IGF-1 signaling pathway, and also leads us to hypothesize that there is a link between lifespan and metabolism.

Are there any other environmental factors that you are applying to worms?

We sometimes use arsenic and hydrogen peroxide solution to place them under oxidative stress, and sometimes use osmotic pressure.

How do you apply osmotic pressure?

This can be done by raising the salinity of the breeding environment. This is kind of interesting, since we have observed that worms bred under

conditions of mild stress can acquire greater resistance to lethal stress.

So if worms have been bred in low food environment, does that mean they can live much longer if they run out of food?

Actually, it's not that straightforward. Worms can actually survive for a long time without food.

Wait, but didn't you say that worms eat anything and that the lifespan of worms is about one month?

Yes, I did say that, but it's a bit more complicated than that. If placed under food restriction during early development, worms will enter a state called dauer, which enables them to survive about three months. The body is covered with a hard cuticle layer and becomes more resistant to environmental stress. When food becomes available, they exit the daur state and resume development.

They can sense food nearby even when enclosed in that shell? How greedy they are!

They can detect foods by smell using sensory neurons that are protrude outside of the cuticle layer. Do you know that a technology is being developed to use worms to detect early-stage cancers? That is how sensitive the olfactory senses of worms are, and some say it is greater than that of dogs.

Research steadily, one step at a time

Was aging research your interest from the beginning?

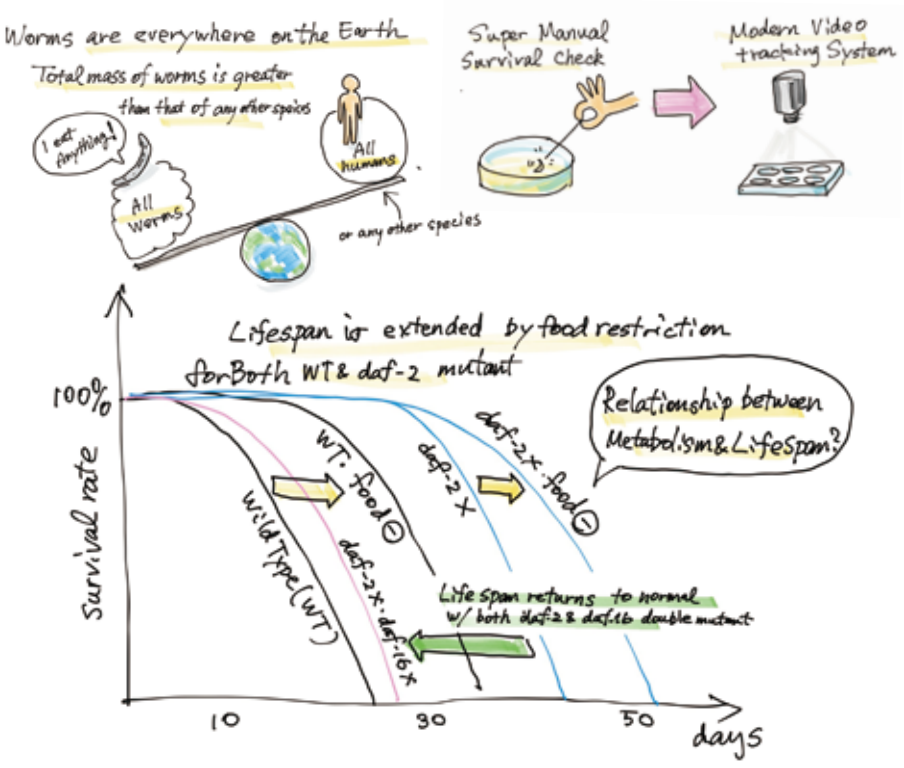
To be honest, I wasn't thinking of using worms to study aging when I was a student. I found the work of the many senior researchers in my lab at Kyoto

University to be very fascinating, and that was what made me want to give it a try. And before I knew it, I had also decided to become a researcher. I think that the lab environment was good for me.

BDR is also now a good environment for me, since there are many researchers here working in diverse areas, from development, regeneration and structural biology to AI and mathematical modeling. I really do enjoy the different seminars held at BDR.

That is good to hear. It also sounds like you are getting some new ideas?

That's right! We use a thin platinum wire to check if a worm is alive or dead. If the worm moves when you poke it, it's alive. If it doesn't move, then it's dead. On a good day, I can check about 1,000 worms using this manual method, but this is not very efficient, right? So, I am now starting to discuss with other researchers about trying to develop a new system to check this by taking daily photos and analyzing the images.



Wow, so the super labor-intensive method is now going to be sophisticated.

This will be really good since worms are transparent and taking photos will give us further information about their internal organs, like a CT scan. We can also track changes in their bodies from day to day. I believe this will help us to see other features of aging that we haven't seen yet.

What kind of things?

One of the difficulties of aging research is the huge differences among individuals.

For instance, imagine that we have 10-day old worms. Some might live five more days, and others maybe ten more days. Now we have them grouped based on when they were born, but we can't tell how long they will live. This is also true for humans—having the same birthday does not mean they will die on the same day. Once we can predict remaining life expectancy, we might be able to see something much different. This is still under discussion, though.

It seems like you have a long road ahead.

Aging involves many factors like diet, genetic background and individual differences. I don't think we can jump straight away into research using higher living organisms such as mice and humans. What we have found so far may only be happening in a particular stage of life. Capturing daily images will be the first step toward grasping the process of aging. For now, I'm focusing on trying to fully understand aging in worms.

I see. Steadily and step by step.

POSTSCRIPT

I found it impressive that he aspired to become researcher because he was awestruck by the researchers around him. The ability to find something interesting, even if it has no direct relation to his/her own research, may be the key to making new discoveries. His step-by-step approach also left a deep impression on me, since many people, including myself, tend to try and leap to the goal.

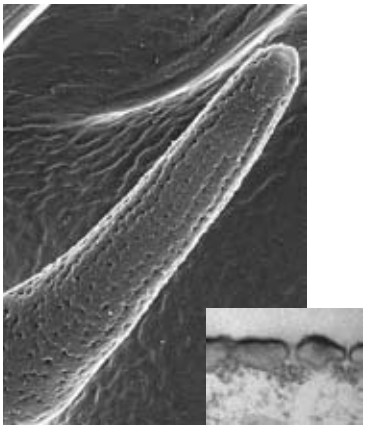
Read other interviews

01

Flies smell through a gore-tex system

Have you ever wondered how fruit flies detect fruit? A research group led by Shigeo Hayashi from the Laboratory for Morphogenetic Signaling has gained important insights into how nanopores on the antennae surface that allow the fruit fly to detect chemicals in the air are formed, and has identified the gene responsible for their development. By using transmission electron microscopy and next-generation genome sequencing, they discovered a gene — named gore-tex — that is responsible for the formation of those pores.

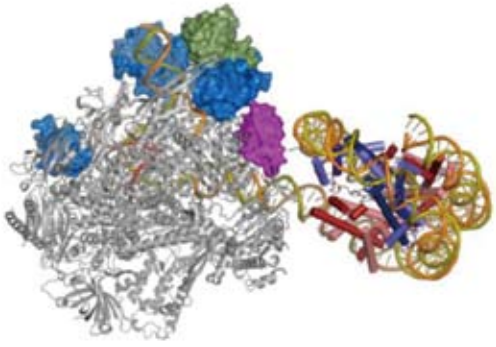
Ando T, Sekine S, Inagaki S, et al. *Curr Biol* 29. 1512-1520 (2019)



02

Elongation factors smooth transcription in the nucleosome

As you read this, an enzyme known as RNA polymerase II is busy transcribing genetic information stored in your DNA into messenger RNA, much of which is then converted into proteins needed for various cellular processes in your body. However, when proteins called elongation factors are not present, the transcription of DNA by RNA polymerase II stalls at several locations within the nucleosome. Shun-ichi Sekine and Haruhiko Ehara from the Laboratory for Transcription Structural Biology have identified two elongation factors that prevent RNA polymerase II from stalling when transcribing in the nucleosome and also reveal insights into how they function.



Ehara H, Kujirai T, Fujino Y, et al. *Science* 363. 744-747 (2019)

03

Combining two spectroscopy techniques reveals how single cells respond to new drugs

The vast majority of potential new drugs never make it past human clinical trials because they are either toxic or do not work. Population-level cell screening, routinely conducted during the early stages of drug development, can miss critical information. This problem could be overcome by screening potential drugs on a single-cell level early on, but is often too costly and time-intensive. Arno Germond and collaborators from the Laboratory for Comprehensive Bioimaging have developed a low-cost alternative by combining two complementary analytical techniques—Raman spectroscopy and mass spectrometry.

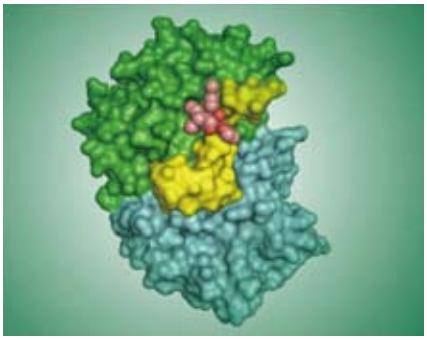
Ali A, Abouleila Y, Shimizu Y, et al. *Anal Chem* 91. 2710-2718 (2019)

04

Natural plant defense could lead to new personalized cancer therapy

The discovery by Takuhiro Ito and his research group from the Laboratory for Translation Structural Biology of why a natural drug compound kills tumor cells—but not the plant from which it is derived—could lead to new personalized cancer therapy. This drug, known as rocaglamide A (RocA), was extracted from the leaves of the Chinese perfume tree *Aglaia odorata* and thought to work by targeting an enzyme called eIF4A, which is needed to produce proteins in cells. The team has discovered the three-dimensional structure formed between RocA, eIF4A1 and target RNA. They showed that eIF4A induces a sharp bend in the long stretch of adenines and guanines in the RNA, creating a molecular cavity that fits the cancer-killing drug like a glove, and discovered mechanistic insights that could help drug developers design potent derivatives of RocA that nestle even more tightly into the cavity.

Iwasaki S, Iwasaki W, Takahashi M, et al. *Mol Cel* 73. 738-748 (2019)

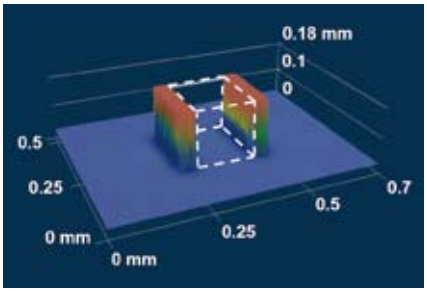


05

Toward micro-hearts: tiny pumps driven by self-organizing cardiomyocytes

Upon first hearing the term, microdevices, many people immediately think of the microchips powering your computer or phone. However, outside of the IT industry, microdevices actually play a substantial part in the biomedical field due to its miniaturization of chemical systems to form microsystems. In microengineering, micropumps are typically driven by external energy sources—but Yo Tanaka and Nobuyuki Tanaka from the Laboratory for Integrated Biodevice, reported the invention of the world's smallest autonomous hybrid pump, powered by cardiomyocytes that self-organize into microtissues. Combining this micropump technology with a fine valve-like structure allows the possibility for Tanaka and his team to create a "micro-heart", a very small pump that is driven only by biological energy sources.

Tanaka N, Yamashita T, Yalikun Y, et al. *Sensor Actuat B-Chem* 293. 256-264 (2019)



Researcher Spotlight

former BDR researcher
Miki Ebisuya
interviewed by Kylius Wilkins
edited by Emily Bian
(University of Wisconsin-Madison Intern)

From Kobe to Barcelona

The Ebisuya group reconstitutes developmental mechanisms by making artificial gene circuits, and studies interspecies differences by comparing organoids of different animals.

"In our lab we take two different synthetic biology approaches, reconstituting or recapitulating developmental mechanisms in vitro to better understand them."

You can read more about their research at the EMBL website:

https://www.embl.es/research/unit/ebisuya/index.html

Q▸ So can you tell me a bit about your new lab in Barcelona and how you were recruited?

A▸ Sure! So the official affiliation is EMBL Barcelona. It's a new site of EMBL, which stands for the European Molecular Biology Laboratory, and its headquarters is located in Heidelberg, Germany. Though EMBL itself is very old, EMBL Barcelona was built two years ago, so it's relatively new. The unit head, James Sharpe, was appointed two years ago, and he started recruiting last year during the first recruitment round. I was recruited in that first round as the first group leader together with Vikas Trivedi. So currently, we only have three groups, but two more, Bernabeu and Haase groups, are joining beginning this October 2019!

Q▸ What is the environment of Spain like? What's the atmosphere of EMBL?

A▸ The environment is wonderful, because we are by the beach we have this beach volleyball league inside the institute. I moved to Barcelona last summer in July, and I live right next to my institute and the beach. So after work, I would go swimming—that was fantastic. Last summer, I would swim nearly everyday! Also, though EMBL Barcelona itself is new, it's in a big research complex and we are on the fourth floor of that building. The other floors are occupied by other institutes and other researchers, which is good because we can interact with each other.

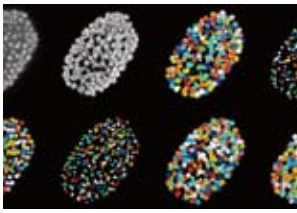
Q▸ How is the transition from RIKEN to EMBL?

A▸ So I actually still have my lab here in RIKEN for another year, but since we are now closing down the lab we are trying to move all the people, equipment, experiments, etc. over. Luckily, I have one Spanish postdoc in my Japan lab who is originally from Barcelona. I've been very thankful to have one postdoc help me set up the new lab and another postdoc help me shut down. And after sending all the equipment to Barcelona, my husband will be joining us here—that's the plan!

Q▸ Is there anything you miss about RIKEN?

A▸ I do! I miss my colleagues, and as I said, currently EMBL Barcelona is very small, but RIKEN is a big institute! The interns are very diverse and I have many wonderful colleagues there. I definitely feel homesick at times. The people at EMBL are really friendly, but the biggest problem is the language barrier, you know? It's fine inside the institute, since everyone can speak English. But renting a house, for instance, is a bit difficult, since my landlord doesn't speak English at all, and so is shopping at the daily market if you don't speak Spanish at all. Yesterday I couldn't say "give me 200 grams of minced meat", ended up in receiving more than 500 grams.

On the cover!



3D microscopic images of *C. elegans* embryo. Nuclei of the approximately 350 cells in the embryo were labeled with a fluorescent marker (top left), and after removing background noise, nuclear region of each cell were identified using computer software.
Image: Lab for Developmental Dynamics

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