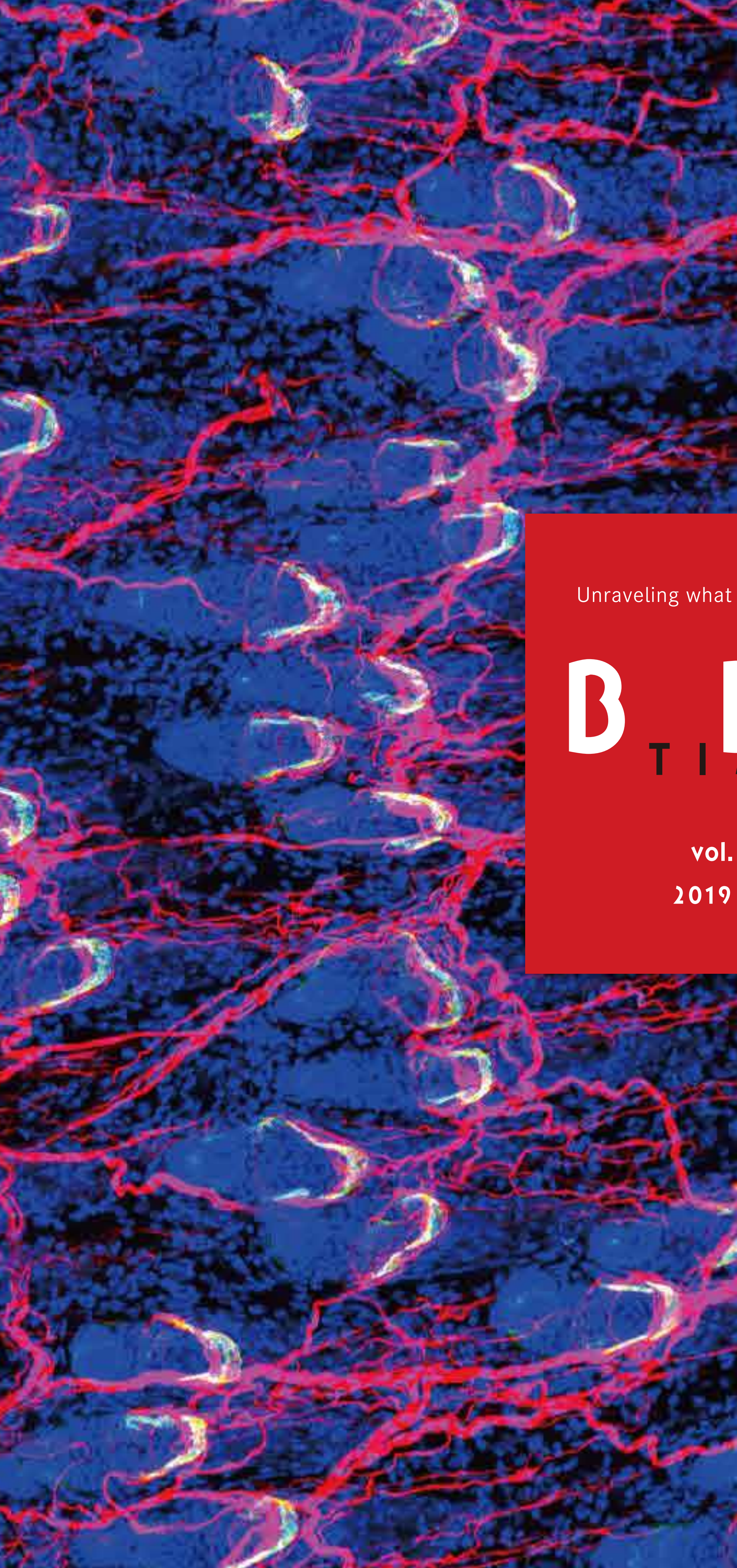

Unraveling what it means to be alive

BDR TIMES

vol.01

2019 SPRING

RIKEN Center for
Biosystems Dynamics Research

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.

Research on hibernation?

Hideki's interest was piqued when he heard that special postdoctoral researcher Genshiro Sunagawa is conducting research related to hibernation. His first impression of Sunagawa was that he looked a bit intimidating...

For safer emergency transportation

I've heard that your research theme is hibernation. Can I ask you, why hibernation?

Now, I am a researcher but I started my career as a pediatrician. When I was working at the National Center for Child Health and Development (NCCHD), I saw some cases where patients could not be transported due to the severity of their condition. In fact, transporting a patient can sometimes be troublesome by causing further complications.

In what kind of situations is transportation difficult?

Patients are attached to tubes and a ventilator, and are under anesthesia. In this condition, even small bumps during transportation could disturb respiration. In worst cases, it will kill the patient, unfortunately. I had been thinking about how we can transport those critical patients more safely. To tell you the truth, hibernation did not come to mind in the beginning.

The fateful encounter

I came across a paper entitled, "Hibernation of primates," just after finishing an overnight shift. I will never forget that moment. It was in 2005. My initial thought after reading it was, "this can be applied to humans as well!" I was so moved by the paper, although this feeling may have been caused by fatigue from working overnight. I decided that year to enter graduate school.

Indeed, it sounds like a fateful encounter.

Yes, it was. By the way, I was mainly specializing in anesthesiology at NCCHD.

Aren't there many anesthetists at such a large hospital?

Of course. But working in ICU requires much knowledge and skills of anesthetization. Once I realized this, I mainly focused on anesthesiology. I worked on hundreds of cases, even though I was only there for two years. This experience is what led me to hibernation research. I will never forget that paper.

Oh, and one more interesting thing was that the primate lived in Madagascar.

Wait. Madagascar is located on the east side of Africa. Primates hibernate even in a such tropical area?

Yes. This was one of the most interesting points in that paper, though I didn't realize it at that time.

Genshiro Sunagawa

Born in Fukuoka. Pediatrician and researcher. After graduating from Kyoto University, he worked as a pediatrician at Osaka Red Cross Hospital and NCCHD. He then entered graduate school and joined the RIKEN Center for Developmental Biology (now part of RIKEN BDR) where he worked on mechanism of sleep regulation. His current research interest is clinical application of hibernation. He hopes to change medicine through hibernation research.

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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.

What exactly is hibernation?

Can you explain what hibernation means?

Recently, hibernation is said to be a survival strategy for animals in which they can lower their metabolism under conditions where energy intake is difficult. Winter is the typical situation, but it is not limited to winter. Even mice can enter this state after starvation.

That's an amazing ability And mice can enter hibernation state just by starvation?

Yes, although it doesn't happen right away.

We, mammalians, have a system for maintaining body temperature at 37°C, which is amazing because it's difficult to maintain that temperature. It's like an air conditioner.

It is easier to maintain body temperature in larger body masses than smaller body masses. Elephants and bears can retain body heat only by producing small amount of heat.

Is that true?

Yes. Oxygen consumption per unit mass of an elephant is equivalent to that of a squirrel in hibernation. Interesting, isn't it?

No brain waves even if the animal is still alive!?

Is there some sort of special trick with the model mice you are using, like genetic modification?

No, we are actually using mouse lines commonly used in research. They are not even a hibernation model. But they can enter hibernation states after starving them for 24 hours with body temperatures dropping to the low 20s from 37°C.

Body temperatures of hibernating animals like squirrels, dormice, and hamsters drop to below 10°C. These hibernating animals also start generating heat once external temperature falls too low. This means that at least some part of the autonomic nervous system remains active. But interestingly, no significant brain waves are detected in this state.

So, is it possible to look at brain waves of mice?

Yes, it's fairly easy. I would really like to look at brain waves of hibernating animals. It would be fascinating if the animal could sense external temperatures in an area of the body besides the brain.

What was the link between anesthesiology and hibernation?

I still don't understand why you thought, "This is it!" when you read the primate hibernation paper.

I see. Let me start by explaining the differences between anesthetization and hibernation. Anesthetization is used to stop three functions during surgery. First is consciousness because, as you know, surgery is stressful. Second is feeling pain, as pain places stress on the body even when unconscious. The last one is muscle strength, since it's dangerous if a patient moves during surgery. But this leads to one problem, which is that once muscle function is lost, breathing also stops. Therefore, a mechanical ventilator is required. This is what we call general anesthesia.

In hibernation, consciousness is likely lost. The animal also likely does not feel pain as there are no detectable brain waves, though we don't know quite well about it. They also lack muscle strength since the body is limp. So, you can see anesthesia and hibernation are quite similar.

When a patient is anesthetized, it means that you are reducing the body's energy requirement —only around a 10 to 20% reduction, though. But, in some hibernating animals, their basal metabolism can drop to 1%, meaning, in theory, the heart only needs to work 1/100 of normal capacity.

Wow, that's an astonishing difference!

Chemical reactions unfolding in the cells of hibernating animals are likely different from non-hibernating ones.

Hibernation needs to be understood at the cellular scale

What do you mean by saying the chemical reactions are different?

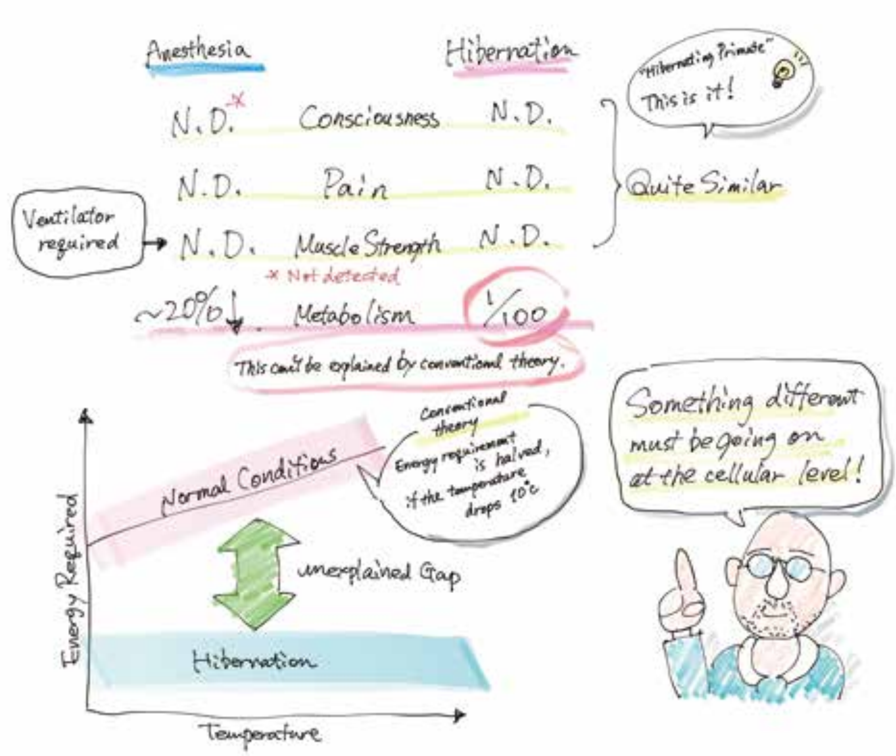
From a chemistry perspective, if the body temperature drops 10°C, energy requirements should also drop to about half. If the temperature drops 30°C, theoretically energy requirements fall to one-tenth to one-eighth of normal conditions, meaning oxygen consumption should also be within this range.

In reality, oxygen consumption drops down to 1/100 of normal conditions in hibernating animals. This observation cannot be explained with conventional knowledge, so something different must be taking place. That is what I really want to know.

So, you are going to address it using a cellular approach, then?

Hibernation is basically linked to metabolism, so I think it's possible to address at the cellular level. This way we can also apply it to human iPS cells and advance research in that arena. I plan to work toward realizing my dreams for hibernation research, and RIKEN's research facilities offers a great environment for advancing that research.

I didn't realize the breadth of hibernation research. Thank you for sharing your intriguing research.



POSTSCRIPT

Sunagawa looked a little rough at first glance, but as our conversation unfolded, his soft-spoken and friendly demeanor made me quickly realize what a nice guy he was, and I could easily picture him as a pediatrician. He can take difficult concepts and break them down into simple terms. Hibernation research is a catchy theme, but initially I couldn't see the link between anesthesiology and hibernation. After talking to him, I think I now understand what drives his research—medical innovation.

Read the full interview ▼

BDR Research Highlights

Research highlights articles from *RIKEN Research* and press releases between April 2018 to February 2019. Read these and other articles on the BDR website.

01

New single-cell RNA sequencing methods could lead to better regenerative therapies

Lab for Bioinformatics Research developed an improved method for analyzing expression of genes by single cells with the potential to enhance regenerative medicine therapy as well as disease research.

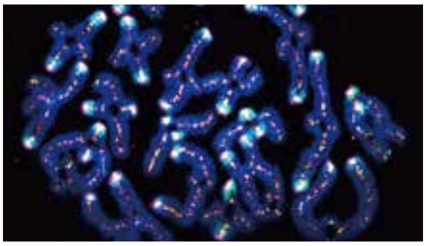
Sasagawa Y, Danno H, Takada H, et al. *Genome Biol* 19(1). 29 (2018)

02

Mechanism stabilizing chromosome pairs during meiosis identified

Lab for Chromosome Segregation show that modification with a protein called SUMO helps maintain proper chromosomal organization in newly produced egg cells.

Ding Y, Kaido M, Llano E, et al. *Curr Biol* 28(10). 1661-1669.e4 (2018)



03

Two essential genes that regulate how much REM sleep we experience

Rapid eye movement (REM) sleep is a mysterious stage of sleep in which animals dream. Lab for Synthetic Biology has identified a pair of genes that regulate how much REM sleep an animal experiences.

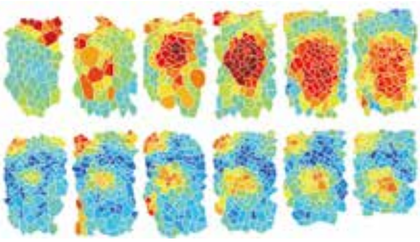
Niwa Y, Kanda GN, Yamada RG, et al. *Cell Rep* 24(9). 2231-2247.e7 (2018)

04

Signaling relays offer an efficient alternative for coordinating embryonic development

Live imaging analysis of developing fly embryos by Lab for Morphogenetic Signaling reveal that a surprising 'switch'-based signaling mechanism governs tissue formation.

Ogura Y, Wen FL, Sami MM, et al. *Dev Cell* 46(2). 162-172.e5 (2018)



05

Getting a grip on the slow but unique evolution of sharks

By decoding the whole genomes of three shark species and comparing them with those of other vertebrate species, Lab for Phyloinformatics solved molecular riddles of their unique life histories and evolutionary paths.

Hara Y, Yamaguchi K, Onimaru K, et al. *Nat Ecol Evol* 2(11). 1761–1771 (2018)

06

Gene *Fam60a* found to play a key role in the developing embryo

Lab for Organismal Patterning revealed that healthy development of an embryo depends on a protein that regulates the DNA of stem cells

Nabeshima R, Nishimura O, Maeda T, et al. *Elife* 7. e36435 (2018)

07

Creating a functional salivary gland organoid

Lab for Organ Regeneration succeeded in growing three-dimensional salivary gland tissue that, when implanted into mice, produced saliva-like normal glands.

Tanaka J, Ogawa M, Hojo H, et al. *Nat Commun* 9(1). 4216 (2018)

08

Evolution of the inner ear: insights from jawless fish

Lab for Evolutionary Morphology has described for the first time the development of the hagfish inner ear. The study provides a new story for inner ear evolution that began with the last common ancestor of modern vertebrates.

Higuchi S, Sugahara F, Pascual-Anaya J, et al. *Nature* 565(7739). 347–350 (2019)

09

Microtubule and kinesin interactions send cellular cargo to the right destination

The molecular mechanism that ensures cellular cargo is transported along the right track has been identified by Lab for Cell Polarity Regulation.

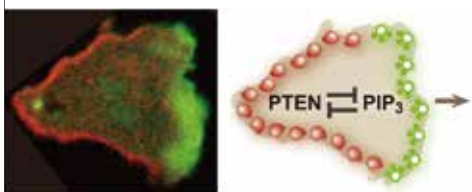
Shima T, Morikawa M, Kaneshiro J, et al. *J Cell Biol* 217. 4164–4183 (2018)

10

Two inhibitory molecules ensure that cells move full steam ahead

Lab for Cell Signaling Dynamics reveal cells move in a single direction due to two mutually inhibiting molecules on their surfaces.

Matsuoka S and Ueda M. *Nat Commun* 9(1). 4481 (2018)



11

Scientists lay foundation for single-cell level understanding of DNA replication

Lab for Developmental Epigenetics developed a new method to examine DNA replication in individual cells, which revealed stability of DNA replication program and higher-order chromatin structure in mammalian cells.

Takahashi S, Miura H, Shibata T, et al. *Nat Genet* 51 (3). 529–540 (2019)

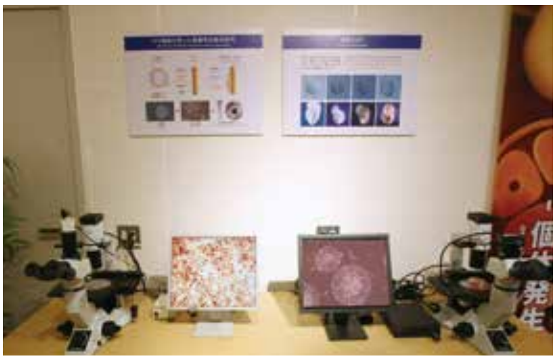
BDR Photo Tour

Introducing interesting research equipment and devices as well as favorite spots at BDR campuses in Kobe, Osaka, Yokohama, and Hiroshima.

BDR Gallery (Kobe Campus)

This exhibit gallery is designed to introduce concepts of "lifecycle research" through displays of research samples, models and movies to visitors to the BDR, such as high school students and delegates from government agencies.

▲ View from the entrance. The room can hold approximately 20 people at one time.

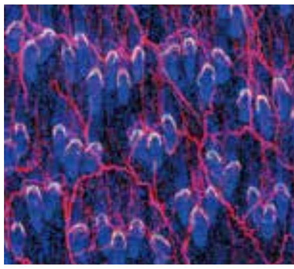


▲ Display of iPS and RPE cells used in retinal regeneration research.

▲ Next to the gallery is a mock laboratory where visitors can observe several model organisms used in research.

◀ Full-scale human mannequin display used to explain whole-body level molecular imaging research.

On the cover!



This image shows how tactile sensation is generated by the skin. Hair follicle stem cells (blue), which are important for hair shaft generation, secrete extracellular matrix proteins (green) that guide the connections of the neural network (red) to the skin, helping the skin to sense mechanical stimulation.
Image: Lab for Tissue Microenvironment

BDR TIMES vol.01
Issued April 15, 2019
Published by RIKEN
Center for Biosystems
Dynamics Research (BDR)
E-mail: bdr-riken@ml.riken.jp
https://www.bdr.riken.jp/en/

RIKEN2019-025