JCB Journal of Cell Biology

PEOPLE & IDEAS

Sara Cuylen-Haering: Cellular soaps to keep neat chromosomes

Lucia Morgado-Palacin

Sara Cuylen-Haering studies the molecular mechanisms driving phase separation of chromosomes and other cellular organelles, with a special focus on biological surfactants.

One of the youngest interns in the biotech industry, Sara Cuylen-Haering just knew when she approached the biotechnology research lab of Bayer as part of the work internship program for secondary education in Germany that she wanted to pursue a career in biosciences. The idea of studying mathematics also crossed her mind but was quickly dropped because it was difficult to picture making a live from it. Thus, Sara enrolled herself in biotechnology at the University of Münster, in North Rhine-Westphalia. While in college and motivated by her internship at Bayer, she did a long industry placement at the research department of the chemical company BASF. The experience was again great, but finding a drug that works or a plant resistant to a given pathogen without understanding the behind-the-scenes mechanism felt incomplete, which drew her to apply for a PhD program in basic research at the EMBL (European Molecular Biology Laboratory) in Heidelberg. Sara joined the lab of Christian Haering, where she combined biochemistry and yeast cell biology to investigate the structural organization of eukaryotic chromosomes. For her postdoc, she moved to Vienna, Austria. In Daniel Gerlich's lab, at the Institute of Molecular Biotechnology, Sara brought in basic and advanced live-cell imaging to her research on chromosome biology and ended up with some exciting findings: "I was lucky that the only hit from a microscopy-based screen for regulators of mitotic chromosome adhesion [Ki-67] had an exciting novel biological function." At that time, she was not keen on becoming a principal investigator (PI), but her publications made quite some impact in the field, and her mentors and peers then convinced her to search for PI positions. She applied to a group leader call from the institute she did her PhD studies in, and it went better than expected: "Since I still knew many people at EMBL, my aim was rather not to embarrass myself than to actually get the job. I did not imagine they would hire me."

Sara then started her own lab in 2017, focused on the molecular mechanisms of genome organization by surfactants and phase-separating proteins. We chatted with her to learn more about her current projects.

Sara Cuylen-Haering. Photo by EMBL/Marietta Schupp.

What interested you about surfactants?

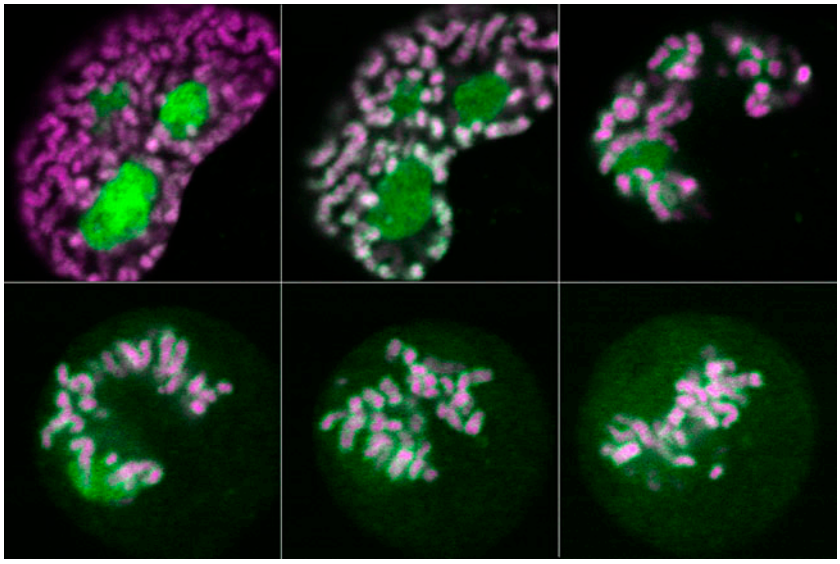
The discovery that membrane-less organelles assemble by liquid–liquid phase separation raises the fundamental question of how such organelles can regulate their size and shape. Liquids generally minimize their surface area and consequently they fuse and round up. However, in cells, many membrane-less organelles have non-round shapes. So, I was very curious to understand how this works. What are the regulators for size and shape of liquid-like condensates/organelles?

In non-biological phase-separated systems, surface-active agents (surfactants) are used to convert a two-phase system of two immiscible liquids (e.g., oil droplets in water) into an emulsion. By titrating the amount of surfactant, the number and size of the droplets can be controlled. While surfactants are widely used in chemical industry, the concept of surfactants or "cellular soaps" is not common in biology. However, my postdoc discovery that a naturally occurring protein can act as a surfactant of mitotic chromatin (Cuylen et al., 2016) raises the intriguing possibility that other organelles might utilize surfactant proteins to regulate their sizes or shapes.

What are you currently working on, and what is up next for you?

We are currently trying to understand the detailed molecular mechanism and regulation of the only known cellular surfactant so-far: Ki-67. We recently discovered that its surfactant activity cannot only be

lmorgado@rockefeller.edu.



Live-cell imaging of Ki-67 (green) during entry into mitosis reveals its re-localization from nucleoli to the surface of mitotic chromosomes (magenta). Image courtesy of the Cuylen-Haering lab.

inactivated but can actually be converted to a glue function. This causes chromosome clustering during exit from mitosis (Cuylen-Haering et al., 2020). We are elucidating the mechanism that underlies this radical switch using cellular assays and, in the future, also by bottom-up in vitro reconstitution assays.

Furthermore, we aim to identify regulators of other membrane-less organelles, such as the nucleolus, using live-cell screening approaches. This is a challenging task since no clear candidates exist, and unbiased genome-wide screening approaches are time-consuming and expensive. We therefore collaborated with Becton Dickinson and the Steinmetz group at EMBL to test and benchmark a novel imaging-enabled sorter that can sort cells based on subcellular phenotypes at unprecedented speed (Schraivogel et al., 2020). We plan to use this technology in the future for unbiased screens for regulators of biological condensates.

What are the most pressing challenges of your field?

The key challenge in the field of phase separation is, in my view, to demonstrate its functional relevance in cells and, if so, to elucidate its function. It becomes more and more obvious that phase separation is ubiquitous and almost every protein can phase separate under certain conditions in the test tube. I anticipate that not every condensate in cells will immediately have a defined biological role. At this point, many studies are still phenomenological and fall short in demonstrating functional impact. The latter is admittable a very hard task, because manipulations that perturb the phase separation properties of a specific protein also potentially affect other functions of that protein.

What kind of approach do you bring to your work?

Our work is very much question driven. All projects in the lab start from an exciting biological observation that we try to understand. However, often our work raises more questions than it provides answers, and we might eventually answer another question than the one we originally aimed to solve.

In general, I think it is very important to keep an open mind and not to be stuck to the original model or hypothesis. I always encourage my students to first think about and then perform the experiments that can destroy our model. We mostly start from an observation made under the microscope, but since we have fantastic service facilities and a uniquely collaborative atmosphere at EMBL, the range of our approaches is not limited to live-cell imaging. For example, we started to collaborate with experts in electron microscopy, cell sorting, CRISPR screening, and protein biochemistry. Addressing the question with the best possible techniques, even if they are not our core expertise, is part of my lab's approach.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

I learned the essentials of science: how to think critically, plan and perform experiments that provide unambiguous answers, include essential controls, rigorously test a model, organize data, write a manuscript or a grant, review a paper, and prepare convincing presentations. While this general scientific skillset is essential for the work of a PI, I also believe that soft skills have become just as important, since mentoring very different personalities with diverse needs is key to a successful lab. I already had the chance to supervise several students during my PhD and my postdoc training, which helped me with this task.

Were there any other challenges you felt unprepared for?

Time management enters a new dimension if you move from a postdoc to PI. You get way more emails and have more meetings, organizational duties, and travel commitments, which are a challenge for time management. On some days I feel frustrated because I only react to emails and requests, and I am not doing any of the work that I had planned. At the end of a workday, my to-do list often becomes longer than shorter, so I need to remind myself that I did do some work but just achieved other things than those I had originally planned.

As many other PIs who recently started their labs, I was unprepared for the pandemic. I had my lab for about two years when the pandemic hit, and I had recruited two new lab members just before the shutdown of our institute. It was very challenging to supervise and motivate group members who had to stay at home. Most of my group members are from abroad. With their family and friends far away—often in different time zones—being isolated at home in a foreign country was very hard for them. Remote coffee video meetings and online Christmas parties were better than nothing but couldn't replace face-to-face interactions.

Any good advice you have been given that helps navigate the PI life?

An excellent advice I got is to quit the email program and only open it during dedicated "email sessions" during the day. This definitely helps to keep focus during the week.

The Cuylen-Haering lab. Photo by EMBL/Kinga Lubowiecka.

In addition, I believe that it is very important to assign clear family times during weekends or vacation, with emails turned off and no job-related work. My family deserves full attention, and for myself, it is also very important to recharge batteries for the coming week. I very much enjoy playing badminton in a local team, which is a great way to clear my mind. If necessary, I assign defined working hours where I efficiently focus on work, but afterwards I again enjoy time with my family. Combining both tasks, like playing with my toddler while trying to discuss over video or writing emails, doesn't work for me and just creates stress—for me and my family.

Yes, getting a good work-life balance is sometimes hard to achieve in science. Is that what you would change of academia, or do you think there are bigger issues that need to be tackled?

In my view, the biggest current issue in academia is that we evaluate scientific output by high-impact publications, citations, h-indices, numbers of papers, or other calculated metrics, despite initiatives like the Declaration on Research Assessment (DORA). Hiring or funding decisions often still rely on these criteria, while the quality of a scientist or a research project cannot be judged simply based on the name of the journal or the number of citations. The need to produce rather than to discover prevents scientists from deciding against going for the challenging projects that often might fail but have the chance to overturn our current thinking. Furthermore, the current philosophy also impacts teaching and training aspects, since only papers are considered as scientific output, while highly trained scientists are not. We really need to judge candidates based on their actual discoveries, their potential, and their mentoring capability, and not only on the impact factor of the journals they have published in.

If you could rewind to your first day as a PI, what would you repeat, if anything?

I spent a huge amount of time at the beginning developing organization schemes for the lab. I programmed a database, compared various electronic lab journals, organized the lab space, labeled everything, wrote general lab protocols. This was a huge time investment at the expense of getting research started quickly, but in retrospect I feel that it was absolutely worth the time, and it helps a lot as the lab grows. If you don't do this at the beginning, it is much harder to implement such schemes later, and information might even get lost with people leaving the lab. I am glad that I took the time at the beginning.

Now taking your whole scientific trajectory into consideration, what has been your biggest accomplishment?

It was the lucky discovery of the first biological surfactant during my postdoc. In my own lab, we are now close to understanding the underlying molecular mechanism in detail, which makes me very proud!

And your biggest accomplishment outside of the lab?

My biggest accomplishment is now 1.5 years old! Having a baby is also the most amazing miracle of biology! Observing a little one grow up and develop is such an exciting experiment. It also helps you to set priorities right and makes you more efficient and less perfectionist.

Any tips for a successful research career?

Do what excites you most, be flexible, and use opportunities! You cannot meticulously plan a scientific career, since science is not predictable. If you are motivated and excited about what you are doing, you will perform best, have the most fun, and have the best chances for a successful career. In science, there are always setbacks. Maybe your hypothesis was wrong, the result of an experiment is not as interesting as you had hoped, or your peers don't appreciate what you do. Don't be disappointed and be flexible to adjust your career plan if alternative opportunities arise. There are other enjoyable and successful careers in science other than becoming a group leader in academia!

References

Cuylen, S., et al. 2016. *Nature*. https://doi.org/10.1038/nature18610

Cuylen-Haering, S., et al. 2020. *Nature*. https://doi.org/10.1038/s41586-020-2672-3

Schraivogel, D., et al. 2022. *Science*. https://doi.org/10.1126/science.abj3013