People & Ideas

Maya Schuldiner: The systems that define us

Schuldiner leverages high-throughput approaches to investigate novel protein functions.

Inspired by her parents, who both worked in academia, Maya Schuldiner knew she wanted to focus on biological or medical studies after high school and her service in the Israeli Army. But just before her first semester of medical school, she took a few months off to travel to the lush beaches in Thailand. In her beach bag were several popular science books her brother had given her for the trip. Reading these, Schuldiner realized that what she really wanted to do was to contribute to new scientific discoveries. Returning days before the start of the semester, she moved metaphorical mountains to get into an undergraduate biology program.

Now, from her lab at Israel's Weizmann Institute of Science, Schuldiner is still moving mountains—this time made of data. Her group uses high throughput screening to investigate novel protein functions (1) and to probe the composition (2), operation (3), and organization (4, 5) of diverse organellar systems, including the endoplasmic reticulum and peroxisomes. We called her to hear more about the gems she's uncovered in her work.

BACK TO BASICS

You did your undergraduate degree and PhD at Hebrew University in Jerusalem…

Yes. During my first semester of undergraduate studies I was taught a course by Professor Nissim Benvenisty, and I fell in love with his work and asked to work in his lab. This is where I met my husband, Oren, who was a master's student in the lab at the time.

When I joined the lab everybody there was working on cancer genetics, with a major focus on the Myc oncogene and its targets. But Nissim offered me a project he'd started during his own PhD studies, trying to understand why mouse embryonic stem cells so easily become teratocarcinomas when they're injected into mice. I was the only person in the lab working on stem cells.

The moment that the derivation of human embryonic stem cells was published, we understood that this was going to be extremely important. We immediately got in the car to get an aliquot of cells from the doctor in Israel, Joseph Itskovitz-Eldor, who was part of the team that first generated them.

Why did you shift your focus as a postdoc?

Some of the first papers in the human embryonic stem cell field were mine, and everybody thought I was completely crazy for leaving. But the field wasn't mechanistic enough for me. It was too descriptive. I wanted to go back to the basics to try and understand what different proteins actually do.

At the time, the yeast genome had recently been sequenced, and we really only knew what about 30% of yeast proteins were doing. The numbers haven't changed that much today, I have to say. We're trying to build this massive pyramid of knowledge on differentiation, tumor transformation and cell-to-cell communication, but we don't understand the basic building blocks: the proteins. It became my dream to understand what each and every protein in the cell is doing.

> "I wanted to find novel methodologies for discovering new protein functions."

One of the reasons I was attracted to Jonathan Weissman's lab for my postdoc was that they were knee-deep into a systematic way of probing protein function. Together with Erin O'Shea they were building collections of every single yeast gene tagged with GFP and with purification tags, and they were doing the first microarrays to uncover the transcriptional output of the unfolded protein response. I wanted to use systematic approaches to define the protein composition of an entire organelle, like the endoplasmic reticulum.

When I started my own lab, I wanted to find novel methodologies for discovering new protein functions. We use high-content screens to uncover functions for proteins that haven't been studied before.

PHOTO COURTESY OF NAAMA PESO

Maya Schuldiner

HIGH CONTENT

For example, your recent work on protein translocation into the ER…

The signal recognition particle (SRP) is an exquisite biochemical machine that perfectly couples protein translation with translocation across the ER membrane, via a channel called the translocon. But there are alternative pathways for getting proteins into the ER. Tslil Ast, a PhD student in my lab, found out that at least 40% of secretory proteins actually do not use SRP at all, and yet are not substrates for other known pathways such as the GET pathway. We recently identified a new pathway that targets these proteins and are preparing to publish about it.

Pathways that don't couple translocation with translation may encounter errors in translocation. For example, we found a novel degradation pathway that we called prERAD, that handles proteins that reach the ER membrane but fail to initiate translocation. Alternatively, translocation might start but then stall, obstructing the translocon. We wanted to figure out how that's resolved, so Tslil created a synthetic protein, which we called Clogger, that would frequently get stuck in the translocon. Together with Susan Michaelis, we discovered that the protease Ste24 cleaves parts of the protein on the cytoplasmic side of the tunnel, enabling the rest of the protein to be retrotranslocated back into the cytoplasm and degraded.

Text by Text and Interview by Kendall Powell
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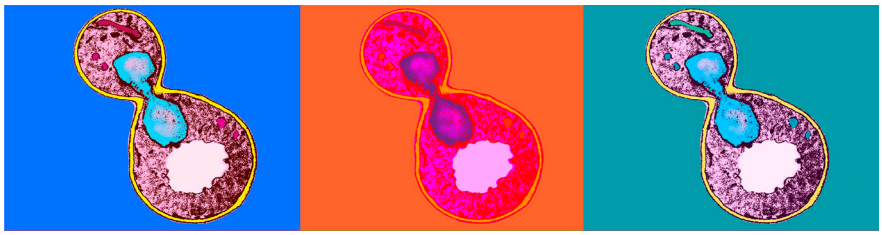

IMAGE COURTESY OF NITAI STEINBERG

Yeast libraries can be used to uncover novel protein functions.

You created Clogger just for the sake of this one screen?

We often spend quite a lot of time thinking about ways to ask questions that haven't been easy to tackle with existing tools, and then creating new tools to systematically screen libraries that we or others have made. For our screens we use a robotic apparatus that automates everything from growth and liquid handling through to microscopy. We've been working with the system for eight years now, and every time we throw a question at this technology, it brings back an interesting answer.

How do you identify where a new approach is needed?

I travel quite a lot to conferences and listen to talks. But instead of writing down for myself what is known, which is what most people do, I write down what isn't known. What are people not saying? What do they not know? Of course, questions like that also come out of our own work. Often when we solve one question, another one arises.

THE IMPORTANCE OF COMMUNICATION

A lot of your lab right now is focused on peroxisomes…

I think what defines my lab is not a single organelle, cellular process, or gene, but really the approach that we take to looking at biology.

We got into peroxisomes serendipitously. We thought we had discovered a protein that was the long sought-after ER glutathione transporter. We were very excited by this until we tagged it and realized that it wasn't in the ER at all; it was in peroxisomes. I hate to admit it, but these organelles hadn't even crossed my mind before then. When I started looking at them I became very excited because they have very nice characteristics for doing systematic cell biology. They're very small; compared with the ER, which contains about 400 proteins, there are only about 90 proteins in peroxisomes. About 50 have unknown functions, which means there's plenty to study. I'm lucky to have a phenomenal research associate, Einat Zalckvar, who's heading this part of the group.

You've shown that peroxisomes make direct contacts with other organelles…

My father studies linguistics, communication, and contact. Maybe that's why I'm so drawn to studying communication within and between cells. My research interest in organellar contacts started during my postdoc. Peter Walter's lab was next door, and Benoît Kornmann was doing a screen to identify the tether creating ER–mitochondria contact sites. I was curious about why there was no severe phenotype when the ER–mitochondria contact sites were disrupted.

> "Being a scientist is not a job. It's a passion, a way of life."

In parallel with Christian Ungermann's group, my lab found a novel contact site between vacuoles and mitochondria that expands to rescue the loss of ER–mitochondria contact sites. Around that time, the mitochondria–plasma membrane contact site was discovered, and it suddenly became clear that there had to be many more contact sites between organelles that have simply been overlooked in the past. We've now made sensors for contact sites—even unknown contact sites—and found that every two organelles in the cell can form contacts under certain conditions.

If you type "cell" into Google, you'll get thousands of pictures, and they all depict the exact same things: organelles floating around in a cytoplasm soup. Actually, the cell looks nothing like that. Our data tell us that every organelle has a very defined geographical locale, tightly embedded within the network of organelles, and that organelle communication is very intense; the chatter is very strong.

We'd like to know what is holding these contact sites together. What are the molecules or information that is being transferred through them? These are the questions that we're now very much excited by in the lab.

Any tips for a successful research career?

Wow. I have many. How long can the list be? [*Laughs*] I think the first one is to take care of yourself by pursuing hobbies, family, or other interests. One has to have a way of detaching from the science and coming back to it with a fresh perspective.

It's also important to find a support system, because science can get lonely. In that regard, find a spouse or partner that you will enjoy going through life and your scientific career with, somebody that will support you and will be a real partner in this life, because being a scientist is not a job. It's a passion, a way of life.

I have three children: Daniel, Noam, and Mattan. People talk often about how difficult it is to combine a career in science with being a parent or being a mother. But I actually think that children are a really good way to balance your life out.

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PHOTO COURTESY OF MAYA SCHULDINER

Schuldiner finds balance hiking with her family in the desert.