People & Ideas

Mónica Bettencourt-Dias: Centered on centrioles

Bettencourt-Dias studies the structures underlying both cilia and the mitotic spindle.

Centrioles lead a double life in most animal cells. They pair up to form the centrosome, the main microtubule-organizing center and director of the mitotic spindle. But, operating under the pseudonym of the basal body, they also act alone to assemble cilia and flagella. With so many cellular processes reliant on these microtubule-based structures, it's no surprise that centriole numbers are carefully controlled throughout the cell cycle.

Mónica Bettencourt-Dias first became interested in centrioles as a postdoc with David Glover at the University of Cambridge when, as part of a screen for cell cycle regulators (1), she identified a kinase called PLK4, whose knockdown resulted in cells with no centrioles at all (2). Echoing the centriole's double life, Bettencourt-Dias also found time during her postdoc to obtain a diploma in science communication from Birkbeck College in London.

Having originally moved to the UK as a PhD student, working on heart regeneration in salamanders with Jeremy Brockes at University College London (3), Bettencourt-Dias returned to her native Portugal in 2006 to set up her own lab at the Gulbenkian Institute. She continues to focus on centrioles, investigating how PLK4 controls their biogenesis (4) and how PLK4 itself is regulated by ubiquitination (5), as well as studying the evolution of centriole assembly (6). In a recent interview, Bettencourt-Dias explained why centrioles continue to be the center of her attention.

CENTRIOLES TAKE CENTER STAGE

Where in Portugal did you grow up?

I grew up in Lisbon, and did my undergrad studies there too. I was always interested in science, maybe because my parents both do research—my father is a mathematician and my mother is a social scientist. Initially I was interested in physics, but then I became interested in how the human body works and how it relates to disease. So I decided to study biochemistry at university.

Then I entered a PhD program at the Gulbenkian Institute. We had a year of classes taught by visiting international faculty—some of the best cell and developmental biologists in the world—and then we had money to go anywhere in the world to do our research, which was really nice.

Why did you choose to work with salamanders?

I was very interested in the cell cycle, particularly in understanding how it is controlled during development. So I decided to work with Jeremy Brockes at University College London on salamander regeneration. Salamanders can regenerate almost everything, from their limbs to their spinal cord. Cells lose their differentiated characteristics and reenter the cell cycle, proliferate, and then differentiate again. I wanted to understand this in the context of heart regeneration.

It was an extremely interesting topic, but there were no genetic tools, and few antibodies as there weren't many people working in that field at the time, though that's starting to change now. For my postdoc, I wanted to work with a different organism, though I was still curious about the cell cycle. So I joined David Glover's lab and began working with *Drosophila*.

> "We have a tent at the festival where we do scientific speed dating."

How did you end up working on centrioles?

We performed a screen for cell cycle regulatory kinases, which was really fun but a lot of work. It wasn't as big as the screens people do now, but we were doing everything by hand back then. David realized that we needed more people, so I had a technician work with me. That was great in terms of learning how to supervise people and organize big projects.

One of the kinases had a really striking phenotype—a complete lack of centrosomes. It was one of those phenotypes where you go to the microscope and immediately know: "This is the thing to work on." We showed that this kinase—PLK4—regulates centrosome number and it opened completely new avenues for studying centriole biology.

Mónica Bettencourt-Dias

ENGAGING THE PUBLIC

You also studied for a diploma in science communication during your postdoc. Why was that?

I've always felt that it's important for scientists to communicate with the public, and with more specialized audiences like the media and politicians. The world is increasingly full of science and technology, and people have to make decisions such as whether to eat genetically modified foods. Those decisions should be based on evidence so I think it's very important for scientists to explain how to think critically and to show how science works. I also think that, since research is largely funded by taxes, it's important that people know what we do with the money. The public should have a say in whether something is worth investing in.

So that's why I did this course, and it was very helpful. Once you know how the media works, it's completely different to speak with journalists because you know the pressures they're subjected to and how you can simplify their work. And it was a lot of fun—I've always liked doing creative stuff, so I really enjoyed interviewing scientists and making TV and radio programs.

Text and Interview by Ben Short
bshort@rockefeller.edu

What science communication activities are you involved in at the moment?
My friends and I regularly organize courses to train scientists to communicate with lay audiences. Among other activities, they're interviewed on camera so they can watch themselves and learn from their mistakes.

There's also a partnership between our institute and a big music festival that occurs nearby. We have a tent at the festival where we do scientific "speed dating." We have scientists at all these tables, and a person from the public sits with them. Every three minutes they change and speak with a different scientist. Some people are really curious but once I had a high school student show up with her parents, and she just told me that she didn't like science. So I asked her, "What *do* you enjoy?", and she said she liked taking pictures. I said, "Oh, we take loads of pictures in science," and then we started talking, and it was really fun.

CENTRAL CENTRIOLE QUESTIONS

Back to the research: How do cells ensure they make the right number of centrioles in each cell cycle?
That's a really important question, and we don't have an answer for it at the moment. Dividing cells normally have two or four, depending on which stage of the cell cycle they're at. Centriole formation is tightly coupled to DNA replication. Proteins that regulate the chromosome cycle are also important for the centriole cycle, but we don't know how they signal to the centrioles. What we do know is that many tumors have abnormal numbers of centrioles, and, although people are still trying to understand whether this is a cause or a consequence of cancer, centriole amplification often occurs early in tumorgenesis.

Scientific speed dating at the Optimus Alive music festival, near the Gulbenkian Institute.

Even if it's not causative, it might be important from a diagnostic point of view.

But there are also cells that don't have any centrioles—like oocytes, which can't form an embryo until a sperm brings in a centriole during fertilization. Then there are cells that have hundreds of centrioles, all of which form cilia that beat in the same direction to generate fluid flow. So different cell types regulate centriole number in different ways.

In some cell types, centrioles aren't needed for cell division. Why is that?
If you look at the eukaryotic tree of life, centrioles exist in all the different branches, but some eukaryotes have lost them. Higher plants like *Arabidopsis*, or certain fungi like fission and budding yeast don't have centrioles, so it's clear that there are other ways of nucleating microtubules and organizing the mitotic spindle. However, centrioles are always there in the species that make cilia and flagella. One idea is that centrioles go to spindle poles as a way to ensure they're faithfully segregated and can make new cilia in the daughter cells. Because centrioles can nucleate and anchor microtubules, certain organisms might have adapted to this so that centrioles became required for mitosis in some cases.

> "We set up a database to map the different centriole-related structures that exist."

Can you learn anything else from studying the evolution of centrioles?
People use evolutionary approaches quite a bit in the centriole field. One reason for that is that the centriole's nine-fold symmetrical structure is extremely conserved throughout eukaryotes. That really forces you to think that there must be something important about this type of organization, and it means you can learn a lot from other organisms.

The molecules that make the structure are also really conserved, so by comparing structures and genomes, you can learn a lot about these proteins. We set up a database called CentrioleDB to map the different centriole-related structures that exist across the eukaryotic tree of life. We started by compiling information from very old literature—beautiful electron microscopy studies from a variety of organisms. But then we realized we didn't know much about all these different species, so now we have more than 20 people throughout the world that are experts in these organisms helping us to annotate the structures. We also have information about the proteomes of different centrioles and cilia, so we can look at the profiles of these structures and compare them with the profile of their components to learn about their assembly.

What else is your lab working on at the moment?
The control of centriole number is a very important question for us, not only in cycling cells, but also in cells like the oocyte that lose their centrioles. We're using *Drosophila*, but also human cells and frog extracts, which allow us to do certain biochemical and imaging experiments that we wouldn't be able to do otherwise. We're also interested in how a centriole becomes a basal body. We're looking at *Drosophila* sperm where the centriole elongates and differentiates into a basal body that can then form the flagellar axoneme.

What do you like to do when you're not in the lab?
The science communication things are a kind of hobby, and I also enjoy photography—I usually have my camera with me everywhere I go. And I love traveling, which you get to do a lot as a scientist. Going to nice places and meeting people is great!

1. Bettencourt-Dias, M., et al. 2004. *Nature.* 432:980–987.
2. Bettencourt-Dias, M., et al. 2005. *Curr. Biol.* 15:2199–2207.
3. Bettencourt-Dias, M., et al. 2003. *J. Cell Sci.* 116:4001–4009.
4. Rodrigues-Martins, A., et al. 2007. *Science.* 316:1046–1050.
5. Cunha-Ferreira, I., et al. 2009. *Curr. Biol.* 19:43–49.
6. Carvalho-Santos, Z., et al. 2010. *J. Cell Sci.* 123:1414–1426.