A Conversation with Mónica Bettencourt-Dias

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Mónica Bettencourt-Dias is a Principal Investigator at the Instituto Gulbenkian de Ciência, Oeiras, Portugal.

Jan Witkowski: You spoke on the first evening about centrioles. Is that what you consider your field? Or do you consider your field more broadly, cell biology?

Dr. Bettencourt-Dias: My field is, broadly, cell biology and cytoskeleton. I'm very interested in centrosomes in cilia. Centrosomes are actually the major microtubule organizing center in animal cells, and they are very tiny: over a hundred times smaller than the diameter of a human hair. But they are very important for the cytoskeleton of the cell. Within the centrosomes, there are structures called the centrioles that also have a different functionality in the cells. They can migrate to the membrane where they form cilia and flagella, which are very important for cell movement, and also to move particles, like expelling particles from our trachea. Cilia also serve as antennas in many of our cells: They are very important to sense light in your eyes, to sense smell, to sense whether you've eaten enough or not in the last meal. They do tons of things in our body, and participate at many times in our life.

Jan Witkowski: In the context of this meeting, they're important for organizing the spindle.

Dr. Bettencourt-Dias: Exactly. With centrosomes, I mostly focus on how cells count the structures, because normally to have accurate chromosome segregation, you would have two centrosomes, one at each spindle pole. What happens in several diseases is that you have a deregulated number. Normally, animal cells control very well the number of these structures—much as they control the amount of DNA that they have—so that when you have cell division, each daughter cell inherits exactly the same amount. Each daughter cell should also inherit exactly the same number of centrosomes: one centrosome per daughter cell. It's very important that cells duplicate these structures in a coordinated fashion with the DNA replication, so that when you have chromosome segregation, you also have centrosome segregation, and you inherit the right amount of DNA *and* the right amount of centrosomes.

Jan Witkowski: Presumably, when the numbers of centrosomes get mixed up, you get inaccurate segregation of chromosomes.

Dr. Bettencourt-Dias: Yes. More than a hundred years ago, Theodore Boveri proposed that a deregulated centrosome number could lead to transformation. You could get a new ploidy, inaccurate chromosome segregation, and then transformation into tumors. Now we know that that's the case. It has been shown very recently that if you have a deregulated centrosome number, you can have inaccurate chromosome segregation and tumors. But we also know that having more centrosomes—not just during cell division, but also in interphase when the cell is not dividing—can be deleterious for our bodies, although maybe not for the cell, because it could have advantages. For example, it can break the adhesions between cells and they will become more invasive, so that's one of the properties that they may get. Also, the nucleation of more microtubules is important for processes like inflammation and many other phenomena.

Jan Witkowski: You do your research on the control of centriole numbers and why there are never two per cell. Centrioles are complicated things, so how do they replicate?

Dr. Bettencourt-Dias: These are beautiful structures. Their structure was elucidated in the '50s, when we started to have electron microscopy. They have this beautiful ninefold symmetry, which is actually conserved throughout the eukaryotic Tree of Life. When you think about DNA replication, you have one strand, and then the other strand forms complementary to the first one, so it's very obvious how it replicates. But centrioles are slightly different. You have one centriole, which is a barrel, and the new centriole forms close by in an orthogonal fashion. There's been a huge discussion whether they actually form in a "templated" fashion, whether one helps the other to form. The self-replication of centrioles and perpetuation of central centrosomes was actually proposed by Boveri and van Beneden. But at the same time, other people saw that these structures can form *de novo*, so they can appear, for example, in sea urchins.

It's not very clear why the centriole leads to the formation of another one close by, given that they can form without any centriole present. The idea that we have now-

adays is that centrioles can self-assemble: if you just have them on their own, at least part of the molecules that constitute centrioles can start forming the beginning of the structure. We think that the parental centriole, the one that already exists, recruits the components that form centrioles, so that it catalyzes the formation of new centrioles close to itself.

Jan Witkowski: But “catalyzes” only in the sense of attracting the necessary components?

Dr. Bettencourt-Dias: Exactly. And then they will do their business. There’re a lot of positive feedback loops that enforce that things will happen there and not elsewhere in the cytoplasm. This is beautiful, because something that already exists dictates the place where the new ones will form, and because you have regulatory molecules localizing there, it will also dictate the time when these things happen.

Jan Witkowski: Does each centrosome have two centrioles?

Dr. Bettencourt-Dias: Exactly. During replication they come slightly apart, and this is also important to regulate the process. Each one of them will form a new “partner” close by, so that when they migrate to opposite poles during mitosis, you’ll have one centrosome, each with two centrioles, at opposite ends of the cell.

Jan Witkowski: What’s the mechanism by which the proteins that form centrioles are attracted to a preexisting one?

Dr. Bettencourt-Dias: About 15 years ago we started to know the molecules that play a role in centriole formation. Before, it was almost impossible to address this problem; now we know what the molecules are. We know that they are recruited, so the ones that exist at the already-existing centriole will recruit the other molecules that are needed to form the new one, and they will perpetuate the structure where it already exists.

Jan Witkowski: But what’s the mechanism by which those proteins that are needed are attracted?

Dr. Bettencourt-Dias: I think it’s just a question of maintenance. If you have molecules that are already there that have affinity for the other ones, they’ll be recruited. I think some of them are not even recruited by microtubules. It’s just that they have more affinity for what is there, so they’ll be retained at the old structure and form a new structure. Of course, a big question is why do they form at a certain time, which is when the DNA’s also replicating, and this is what we are also studying. We want to make the link between these molecules that we have identified that play a role in forming a new centriole, and we want to know whether they are regulated by the cell cycle machinery that also regulates DNA replication, so that the two things are coordinated. What we have identified is that the major cell cycle players—the cyclin-dependent kinases that promote advancing the cell cycle—also regulate these molecules. They actually prevent this structure from being

formed in mitosis; it only starts being formed at the beginning of the next cell cycle.

Jan Witkowski: In mutants that have abnormalities of the cell cycle, do you get abnormalities in centrosome formation?

Dr. Bettencourt-Dias: You can. For example, a major cyclin-dependent kinase, CDK-1, actually prevents centrioles from being formed in mitosis, and in fly mutants for CDK-1, you get many more centrosomes. So, yes.

Jan Witkowski: Are there well-recognized “centrosomeopathies” or “centrioleopathies”?

Dr. Bettencourt-Dias: Definitely. Since the beginning of 2000, there’re a variety of diseases like microcephaly and primordial dwarfism where the mutated genes that are causing the diseases were identified as genes that localize to the centrosome and are important for centrosome biogenesis. We now know that microcephaly is strongly associated: It’s a “centrosome-opathy” because it’s associated with problems with the centrosome and in the division of the stem cells that give rise to the brain. You have more death of cells in the brain that are supposed to populate the brain, therefore there’s a smaller brain. Also, there can be precocious differentiation of stem cells in the brain. Therefore you exhaust the stem cell pool, and you have fewer cells in the brain, and therefore you have a smaller brain. Recently, two groups also linked Zika virus infection to effects in the centrosome that linked also to microcephaly. Definitely, there are centrosome-opathies. Cancer is similar. There were some recent studies pointing that if you have transient deregulation of centrosome number, you can actually induce cancer in mice.

Jan Witkowski: Are centrioles present in all multicellular organisms?

Dr. Bettencourt-Dias: No. Centrioles are very interesting, because if you look throughout the eukaryotic Tree of Life, you see that in all the different branches, you have centrioles. But in many of the different branches, there are species that have lost them. For example, higher plants, some amoebas, some fungi have lost them. But because you have it in all the different branches, it’s most likely that the last common ancestor of eukaryotes already had these structures. Actually, the molecules that are needed to form centrioles are present in all of these different branches, so it’s really very plausible that the last common ancestor already had them.

Jan Witkowski: Even in organisms that no longer have centrioles?

Dr. Bettencourt-Dias: We don’t know exactly how the loss of centrioles occurs. Centrosomes participate in cell division, but actually, the ancestral form of cell division did not rely on centrosomes. Species initially likely had centrioles because they needed to make cilia for movement, because this was critical. Then, because the centrioles were needed for the cilia and the centrioles needed to be symmetrically inherited by the daughter cells, they

became associated with the poles of the spindle so that they could be inherited symmetrically. Once there, they might have been co-opted to participate in cell division in certain organisms. For example, they are not required for somatic cell divisions in the fruit fly, but they are required in embryonic divisions, and also in male meiosis.

Jan Witkowski: Presumably, human cells can't divide without centrioles?

Dr. Bettencourt-Dias: They can divide, even without centrioles. There're many different studies—the first ones using laser ablation of the centrosomes, and more recently knocking down the centriole components because we know the machinery—and they can divide normally. Again, I think it's because there's this ancestral mode of cell division. Basically, you have microtubule nucleation from factors that exist around the chromatin. Once you have microtubules, more microtubules are nucleated from them, forming microtubules that organize

the spindle, so that you have normal chromosome segregation.

However, what happens in human cells is that once you remove the centrioles, they'll actually divide, but then they will arrest in the cell cycle once they don't have centrioles. Human cells have ways to sense whether they have these structures or not, and they will arrest. That's not the case in fly cells. They are fine without centrosomes, and their somatic cells keep dividing.

Jan Witkowski: I seem to recall that there was talk that centrioles had their own DNA.

Dr. Bettencourt-Dias: There's a long history in the centriole field of people looking for DNA and claiming there was DNA. So far, centriole duplication doesn't seem to rely on its own DNA, but there are recent reports claiming that there is RNA for at least some of the centrosomal proteins on the centriole. I think that's part of the future. Even though the question was raised long ago, I think it still needs to be answered.

Cold Spring Harbor Symposia on Quantitative Biology

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Cold Spring Harb Symp Quant Biol 2017 82: 372-374 originally published online March 27, 2018
Access the most recent version at doi:[10.1101/sqb.2017.82.034520](https://doi.org/10.1101/sqb.2017.82.034520)

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