People & Ideas

Helder Maiato: Hot (+)TIPs on mitosis

Maiato studies how microtubule plus-end tracking proteins (+TIPs) influence mitosis.

At the growing end of each microtubule fiber sits a large and varied group of proteins called +TIPs. These proteins have diverse functions, ranging from promoting microtubule growth and stability to mediating interactions with other structures such as the cell cortex or kinetochores.

Helder Maiato began studying +TIPs as a graduate student, focusing his early efforts on the importance of a protein family called CLASPs in mitosis (1). He has shown that CLASPs shape the mitotic spindle by working both at kinetochores (2) and centrosomes (3). But Maiato says he is not satisfied with narrowly studying one protein, so he has broadened his inquiries into other +TIPs (4) and into mitosis more generally (5), as he explained when we reached him at his office at Portugal's Institute for Molecular and Cell Biology in Porto.

THE STARTING LINE

Are you originally from Portugal?

Yes, I grew up in Porto, which is the second largest city in Portugal. My father and mother both worked for an elevator company and didn't have any higher education. I was actually the first member of my family to go to university.

I decided to go to university because I was a very good student in school. I got a lot of encouragement from my teachers to pursue my studies to the highest level and to consider doing research as a career. I had wonderful biology and chemistry teachers, and I always got nice reports from them, although I was always very distracted during classes. That comes with my personality. I'm always in the moon, thinking of something else. [Laughs]

You did your undergraduate and much of your graduate work in Porto…

Because I had grown up there, it was a natural choice to do my studies at the University of Porto. In those days, the first degree at university was basically already a doctoral degree, which could take up to six years of study to complete, depending on the field. I studied biochemistry as my major subject because the biochemistry program was very oriented towards research. It was very selective; at the entire University, only 30 students were admitted to the program.

It was also a little risky because research in Portugal was very limited at that time. But we could see that, after joining the European Union, the country was getting closer and closer to the standards of other EU countries and was starting to invest in research. I was prepared from day one that I would have to leave the country at some point to further my career—with the hope that I could come back, of course. The Portuguese are very attached to their country and to their families. It's a small but very beautiful country. If you asked me if I would like to live anywhere else, I wouldn't trade it for anything.

THE CUTTING EDGE

When did you first encounter CLASP?

I did a rotation project in Claudio Sunkel's lab during the last year of my undergraduate degree to clone and sequence the gene that we now call CLASP. It had come up in a screen of mitotic mutants in *Drosophila*, but we didn't know which gene was associated with the mutation. Once we sequenced the gene and looked for other sequences in the databases, we immediately realized it was conserved in humans. It had a very important role in mitosis, so we were interested in understanding what this protein was doing in human cells. But Claudio is a *Drosophila* geneticist, so we didn't have the tools to look at this.

> "We're trying to obtain the big picture of mitosis as a process."

Fortunately, I had received a fellowship from the Gulbenkian Foundation that allowed me to go to Bill Earnshaw's lab in Edinburgh. There we found that the human homologue CLASP1 localizes to all the interesting structures that a mitosis researcher cares about: it's on kinetochores and on centrosomes, and it binds to the growing ends of microtubules. It binds to the spindle, after anaphase it's enriched in the spindle midzone where microtubules overlap, and it ultimately accumulates at the midbody. CLASP1 was probably the first protein shown to play a role in regulating kinetochore microtubule dynamics. We later showed that it also plays a major role at centrosomes, where it helps the spindle resist the traction forces generated by the chromosomes.

PHOTO COURTESY OF THE CALOUSTE GULBENKIAN FOUNDATION

Helder Maiato

But my general interest has always been mitosis. Nowadays we still work on CLASPs for historical and emotional reasons, but we're trying to look at them from a very broad perspective. I think this is actually one of the problems that the field is facing at the moment: everybody's so specialized in a particular protein or structure that the big picture can be forgotten. We're trying to obtain the big picture of mitosis as a process.

What tools do you use to ask such big-picture questions?

We combine the power of RNAi in cultured cells with special laser microsurgery

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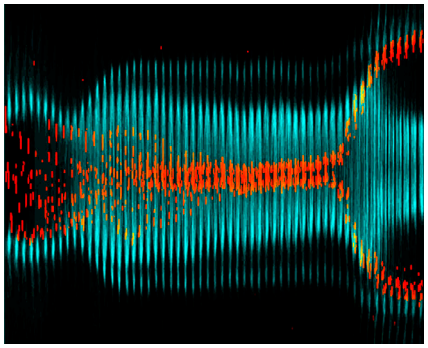

KYMOGRAPH COURTESY OF IRINA MATOS/MAIATO LAB

This kymograph opens a window on how chromosome separation is regulated in time and space.

tools that I learned to use during my postdoc. After working in the UK, I returned to Porto to marry my wife and spent a transition year working with Claudio. Then I went to Albany, New York, to do a postdoc. Officially I was a postdoc with Conly Rieder. But Alexey Khodjakov was starting his own independent group just next door, and we shared all the facilities. So, whenever I saw something striking, I would immediately take it to Alexey, and we would go crazy about it together. [Laughs]

My project in Conly's lab was to extend what we knew about CLASPs, specifically their effects on kinetochore microtubule dynamics, to all +TIPs that were known at the time—there were just a handful of them then, whereas now we have 800 potential +TIPs out there. It was an exciting time and very productive. But without knowing it, we created a monster. We have such a powerful system, and I have many more boiling questions than we can ever hope to address. Besides that, the biggest challenge I've had was to set up the whole laser surgery facility and microscope here when I returned to start my own lab in Portugal.

THE BIGGER PICTURE

What other +TIPs are you studying?

We were motivated to study EB proteins because they were thought to be master microtubule regulators; most, but not all, +TIPs rely on EB proteins for their targeting to microtubule plus ends. Surprisingly, when we perturbed the function of these proteins, we saw that the mitotic phenotypes are fairly mild. That doesn't mean they're unimportant, though.

One member of the family, EB3, becomes critical when cells commit to exit mitosis. That's a very sensitive period for the cell because, during mitosis, epithelial cells round up and lose their attachment to the extracellular matrix. They risk becoming fully detached from the epithelial layer. Our work showed that regulation of microtubule dynamics, particularly through phosphorylation of EB3, is critical to coordinate the rapid re-adhesion of cells after they exit mitosis.

EB3 present on cortically attached astral microtubules has to be dephosphorylated to allow stabilization of the focal adhesions they contact, but EB3 needs to be phosphorylated at the midbody during cytokinesis. So this phosphorylation is changing EB3's properties in a way we don't yet understand.

> "Curiosity is at the heart of being a scientist."

EB3 phosphorylation is controlled by the kinase Aurora B, which is present in a concentration gradient that decreases from the spindle midzone to the poles. A gradient is actually a very efficient way to measure distances or proximity, so we're very interested in the relevance of this gradient to other processes later in mitosis. That's one of the hottest topics that we're pursuing in the lab at the moment.

What are the hot topics outside your lab?

My wife and I have two small kids—a five-year-old daughter and a two-year-old son—and they take up a lot of my energy. Now that they're both old enough to sleep through the night, I'm slowly catching up with my other interests. I am very grateful to have both sets of grandparents nearby; the family support provides a lot of balance to my life. I can keep working at a good pace, in an intensive way, and still feel secure that my children are okay.

That's especially important in these tough economic times. It can be difficult to do science in this setting, especially because it seems that there is not much space anymore for curiosity-driven science. I know grant agencies, politicians, and our peers are always looking for a safety net. They want a hypothesis-driven project, and I'm fine with that, but I think we also need to leave some space for curiosity. If you're a good scientist, you have the instinct and the intellect to distinguish and pursue good ideas of the kind that might take you to something very important. To me, curiosity is at the heart of being a scientist.

1. Maiato, H., et al. 2003. *Cell.* 113:891–904.
2. Maiato, H., A. Khodjakov, and C.L. Rieder. 2005. *Nat. Cell Biol.* 7:42–47.
3. Logarinho, E., et al. 2012. *Nat. Cell Biol.* 14:295–303.
4. Ferreira, J.G., et al. 2013. *J. Cell Biol.* 201:709–724.
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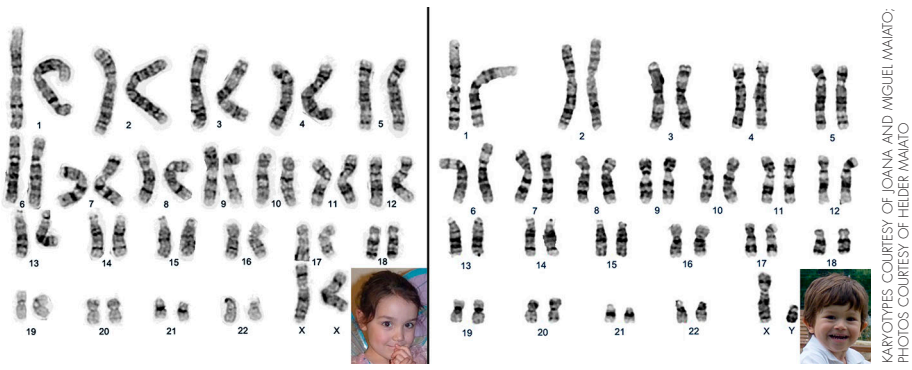

KARYOTYPES COURTESY OF JOANA AND MIGUEL MAIATO; PHOTOS COURTESY OF HELDER MAIATO

Karyotypes for two of Maiato's greatest passions.