People & Ideas

Sue Biggins: How kinetochores keep control of mitosis

Biggins studies kinetochores and the mitotic checkpoint.

During mitosis, it's up to the kinetochores assembled on the centromeres of each chromosome to give a cell the go-ahead to begin anaphase. A kinetochore will only give its ready signal once it becomes attached to and stretched apart by microtubules emanating from both opposing spindle poles. This process, known as the spindle checkpoint, ensures the even distribution of chromosomes between daughter cells.

Spindle checkpoint defects can cause cell death or cancer, which is why Sue Biggins has devoted her career to studying kinetochores (1–3) and centromere biology (4). Throughout her work, Biggins applies a rigorous methodology she learned as a graduate student with Princeton's Mark Rose, who wouldn't even look at experiments that weren't properly controlled. That philosophy guided both her postdoctoral work with Andrew Murray at UCSF (5) and all of her work since. We called her at her lab at the Fred Hutchinson Cancer Research Center in Seattle, Washington, to hear how that hard work is paying off with insights into the big questions of kinetochore biology.

TAKING CONTROL

What first inspired your interest in science?

My father was a biochemist. He worked on photosystem I, and he was really interested in the idea that plant energy could be harvested as an alternative energy source. He never pushed me to go into science, and we didn't really talk about his work, but I noticed that he was very passionate about what he did, and that really rubbed off on me.

Did you always want to be a scientist?

I think I was more interested in music when I was a child. But at some point I got the idea that it would be too difficult to have a career in music, so, when I was an undergrad, I decided to be an MD. I applied to med schools and even did some undergraduate research in human nutrition because I thought that would be a useful way to prepare for medical school. I didn't enjoy the work I was doing on human nutrition, though, because there were so many variables to account for that I found I wasn't very comfortable making conclusions.

Then I did a summer internship at Merck, and it really changed everything for me. I had a great experience and realized that I loved working in the lab. I was working with yeast, and I was excited that I could design experiments in a way that made it easier to reach firm conclusions. So at that point I pulled my med school applications and decided to go to graduate school.

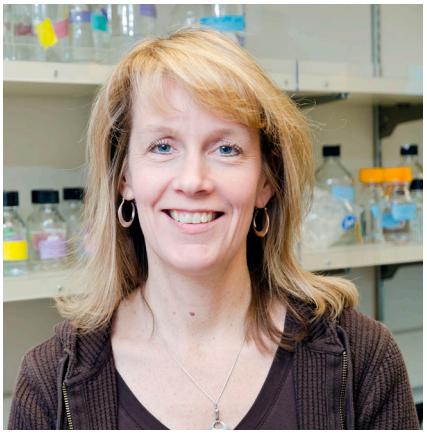
PREPARING THE SYSTEM

Why did you choose Andrew Murray's lab for your postdoc?

I chose Andrew's lab because I was interested in both his work on mitosis and the spindle checkpoint and his ability to push the envelope scientifically. I planned to work on a project I'd designed to isolate factors involved in chromosome condensation from *Xenopus* cell extracts. But right when I arrived at UCSF, another lab isolated condensin, so I had to switch projects.

> "It's very difficult to separate kinetochore attachment and tension."

I kept working in *Xenopus* for a year but found I couldn't stand waiting for the frogs to lay eggs or going through months when all the eggs were bad. It was too unpredictable. So I was really excited when Aaron Straight in Andrew's lab developed a system to fluorescently tag single chromosomes in yeast. That opened the door to a ton of experiments, so I asked Andrew if I could start working on that system instead. A student and I then did a big yeast screen for defects in chromosome segregation, and one of the mutants I got out of that screen was the Aurora kinase Ipl1. I originally thought Ipl1 was going to have something to do with sister chromatid cohesion, and I spent a long time figuring out that that was not what was going on and that Ipl1 regulated kinetochore function instead. But I felt a lot of resistance to this idea when I first proposed it.



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Sue Biggins

Why was that?

Aurora A had been identified in mammals as a protein that regulates spindle poles, and everyone assumed Ipl1 was the yeast version of Aurora A. But Ipl1 clearly carries out functions similar to Aurora B, which does not have a strong role in regulating spindle poles. Instead, Aurora B localizes to kinetochores during mitosis and triggers the spindle checkpoint if the kinetochore is not properly attached to the spindle poles.

How it does this is still controversial because, in vivo, it's very difficult to separate kinetochore attachment and tension. Many people would say that Aurora B is involved in sensing both kinetochore attachment to spindle microtubules and in responding to the tension that develops across the kinetochore after attachment. However, the two are totally coupled: as soon as a microtubule attaches to the kinetochore, the attachment is stabilized, and then the kinetochores come under tension.

Text and Interview by Caitlin Sedwick
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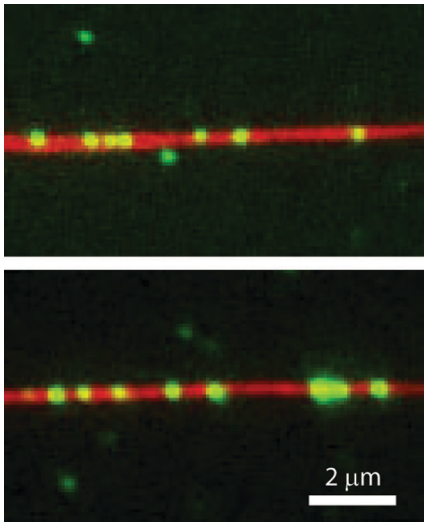

IMAGE COURTESY OF CHIP ASBURY, UNIVERSITY OF WASHINGTON

Purified kinetochores (green) bind microtubules (red) in vitro.

You have to have an attachment to ever come under tension. We've shown that Aurora B destabilizes attachments that lack tension, so we've argued that its role in the checkpoint is indirect.

The question of whether attachment or tension relieves the spindle checkpoint is still far from settled, but we're closer to being able to answer it now. When I first started my lab at the Hutch, we really didn't know many kinetochore proteins, but in the past ten years most major kinetochore components have now been identified. Now I can go back and do some of the more interesting work I always wanted to do, including working with some of Aurora B's substrates and setting up in vitro systems to test its role. Once all the substrates are mapped, it should be possible to figure out if there really are different checkpoint targets for attachment and tension.

READY TO GO

What guides your choices on research subjects?

I try to figure out what the most important questions in the field are and then do whatever has to be done to address those questions. Also, if a project doesn't look like it will have much impact, we'll drop it to work on something more interesting. So I don't just do genetic screens even though I was trained in yeast genetics. If we need a new method to answer an important question, we learn the method.

What new techniques have you taken on because of that philosophy?

The biggest thing that's happened to my lab is that we've started to work with purified kinetochores, so now we can answer some of the outstanding questions about kinetochore biology. There are several different sub-complexes that make up the kinetochore, but how they fit together to regulate the spindle checkpoint or bind to microtubules is unknown. Our approach to studying these questions is to do it in vitro with purified kinetochores.

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I didn't have any biochemistry experience when we set out to purify kinetochores, but thankfully I had a student who really wanted to try it and had the motivation to stick with the project. Also, because I'm at the Hutch, which strongly supports its researchers taking risks to push their fields forward and provides a supportive environment to try new techniques, I had some great colleagues who were willing to help us learn to do it.

Now that we have the pure particles, I've struck up collaborations with other researchers to try to address questions about both kinetochore structure and the biophysics of kinetochore–microtubule interactions. And I can look into other questions, such as how the kinetochore is assembled on centromeric chromatin.

You've also studied what distinguishes centromeric chromatin from regular chromatin…

In yeast, the centromere is defined by the presence of a histone variant, CenH3, which is incorporated into a single nucleosome. We identified a ubiquitin ligase that recognizes CenH3 and degrades it when it appears at the wrong place. We're trying to understand everything about how that process works: for instance, are there features of the chromosome that keep CenH3 from localizing to euchromatin? Or does it easily get incorporated into euchromatin but destroyed by this ligase when it's inappropriately localized?

Can we talk about your interests outside of lab?

Sure, but that'll be a short conversation. [Laughs] The two things that are most important to me are my lab and my family—I have two kids—so I don't have much time for anything else. My son is very active in sports, so whatever time I'm not in lab I spend hauling him around to sports events. [Laughs]

I suppose you could say that I enjoy cooking as a kind of hobby, but fortunately that's not the sort of hobby you have to practice to stay good at. I also run, but I consider that more of a necessity than a hobby. My lab members join me once a year in a charity run, though, and that is fun.

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PHOTO COURTESY OF TOM HENDERSON

Biggins and members of her lab participate in a charity run.