Needhi Bhalla: Chromosomes do the most amazing things

Bhalla studies the regulation of chromosome synapsis during meiotic prophase.

Meiotic cell division is a reductive process that halves the cell's genetic complement in preparation for mating. While analogous to mitotic division, meiosis additionally involves the pairing and crossing-over of homologous chromosomes to generate additional genetic diversity in daughter cells. This is accomplished via a precisely choreographed chromosomal dance, with checkpoints in place to confirm successful completion of the major steps.

Needhi Bhalla is enthralled with the elegant maneuvers that chromosomes execute during meiotic cell division. Her lab uses the nematode *C. elegans* to investigate how cells confirm (1) that their chromosomes have found and synapsed with their homologous partners during meiotic prophase (2–5). Among the molecular regulators of this process are some performers—better known for their roles in the mitotic spindle assembly checkpoint (4, 5)—that make new moves in meiosis, as we learned when we called Bhalla at her lab at the University of California, Santa Cruz.

> "Chromosomes do all this amazing stuff, yet how they do it is still so mysterious."

NO AMBIVALENCE

What's your background?

I grew up on the southern shore of Long Island, just outside of Queens. I heavily identify as a New Yorker, even after living in California for 20 years. There are things I really miss about being in New York. Both my parents came over from India to go to school in the '60s and early '70s when the immigration laws opened up. My father was an engineer for the Air Force and my mother is a nutritionist.

I don't know how many South Asian families you know, but in my family, if you're good at science, it's pretty much assumed that you're going to be a doctor. As an undergraduate I worked in Teri Melese's research lab at Columbia one summer, and it made me realize I really wanted to do research. The question was whether I would do a PhD or an MD/PhD. I knew if I made it into medical school I would be under a lot of family pressure to practice medicine, which I really didn't want to do. I had gotten really excited about cell biology in Teri's lab, and because she had trained at the University of California, San Francisco, which was the pinnacle of cell biology research at that time, I interviewed there. My ambivalence about the MD portion of the program and my enthusiasm about the PhD part was quite evident in my interviews.

Evidently your PhD interviews went well. You did your PhD with Andrew Murray…

The amazing thing about Andrew Murray's lab was that (1) the work he did was so creative and original that there was this sense that you were really answering important questions, and (2) his lab at that time was just a magical place. There was such great energy, and the people who were in the lab then have become some of my lifelong friends. Now we all have families, go camping together, and spend holidays together. I would love to emulate that environment in my own lab.

WATCH THIS!

You studied mitosis in yeast with Murray but switched to meiosis in worms for your postdoc…

In Andrew's lab I became enamored of chromosomes: what they accomplished, and also how they monitor their own behavior. The thing about working with yeast that I absolutely adored was the ability to use genetics to get at the cell biology. The problem with yeast was that we could not see the chromosomes. I decided I wanted to do a postdoc in a genetically manipulatable organism where you could see the chromosomes. The minute I saw chromosomes in *C. elegans* I knew this was what I wanted to do. The chromosomes are highly visible, and the things they do in meiosis are just amazing. That's why I chose to join Abby Dernburg's lab.

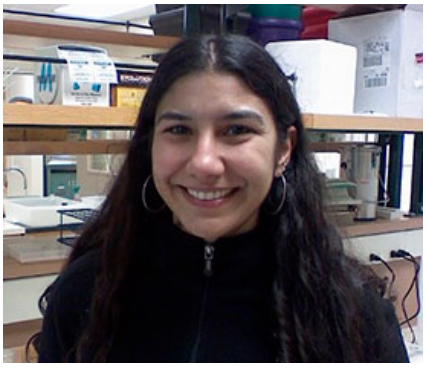

PHOTO COURTESY OF NEEDHI BHALLA

Needhi Bhalla

What did you find so fascinating about meiotic chromosomes in* C. elegans*?

During meiosis, chromosomes have to identify and pair with their unique partner, their homologous chromosome. In some organisms it's likely that recombination—the ability of chromosomes to get a double-strand break and use a recombination intermediate to invade another chromosome—helps promote some of that pairing. But in *C. elegans*, pairing occurs independent of recombination, so chromosomes are somehow able to identify their unique partner, and we have no idea how that works. Once they've identified their partner they assemble something we call the synaptonemal complex, in a process called synapsis. The complex is structurally conserved, with homologous chromosomes separated by about 100 nanometers, but the proteins involved vary between organisms. After synapsis, the chromosomes undergo recombination, and this accomplishes two things: it generates the diversity that underlies sexual reproduction and drives natural selection during evolution. Crossovers also fulfill a much more prosaic role, in that they hold the homologues together so that they can properly biorient on the meiotic spindle. Almost all organisms require at least one meiotic recombination event to proceed to chromosome segregation, but there are also mechanisms that ensure crossovers don't occur too close together. *C. elegans* requires that there be just one crossover per chromosome. Chromosomes do all this amazing stuff, yet how they do it is still so mysterious.

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

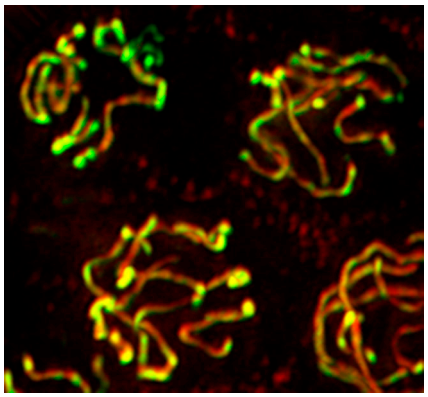

IMAGE COURTESY OF NEEDHI BHALLA

The synapsed (yellow) and unsynapsed (green only) regions of *C. elegans* meiotic chromosomes are easily visualized.

You've focused on the process of synapsis…

C. elegans chromosomes have specialized regions called pairing centers that facilitate the pairing and synapsis of homologous chromosomes, a role that in other organisms may be filled by telomeres. I had come to Abby's lab to work on identifying proteins that might mediate pairing center function. We were working with a mutation called *meDf2*, where the X chromosome's pairing center is deleted, and noticed that pairing centers were essential for pairing and synapsis. If both X chromosomes were missing it, chromosomes wouldn't pair or synapse, whereas if only one X chromosome had it, about half the nuclei would pair and synapse their X chromosomes, and the other half would not. However, these *meDf2* heterozygote worms generated only 10–15% more aneuploid progeny than normal worms, which indicated there was likely some culling mechanism for nuclei with unsynapsed chromosomes.

We hypothesized that if chromosomes can't pair or synapse, then they also can't recombine, and would probably activate the checkpoint that ensures recombination has taken place. But when we mutated known components of the recombination checkpoint, this had no effect. That meant the cells were actually responding to the presence of unsynapsed chromosomes. We realized that animals heterozygous for *meDf2* trigger this synapsis checkpoint, while homozygotes trigger the recombination checkpoint. The pairing center both promotes and somehow monitors synapsis. In my own lab we've sought to identify components of the synapsis checkpoint. For example, we found that a protein called PCH-2 is important for the checkpoint. We're still working to understand its precise function.

One of your early papers showed chromatin itself is involved in the checkpoint…

When chromosomes are unsynapsed, they take on these hallmarks of heterochromatin. It's not quite clear why they do that. What we found is that this might be true for the rest of the chromosomes, but it's not true of the pairing center, and the pairing center's ability to avoid heterochromatinization is likely required for its ability to regulate the checkpoint.

> "It's going to be really exciting to figure out what [SAC components are] doing."

LEARNING NEW STEPS

Spindle assembly checkpoint proteins are also involved?

Right. We recently published work showing that Mad1, Mad2, and Bub3 negatively regulate synapsis and participate in the synapsis checkpoint response. In the spindle assembly checkpoint, these proteins contribute to monitoring kinetochore attachment and are thought to sense when kinetochores are under tension. They may also have other roles. We don't know whether they're doing something similar in meiotic prophase. We looked super hard to see if they were at pairing centers, yet we could not see them there. But we still think they're acting at pairing centers because pairing centers are so important for synapsis. It's also possible that there's something going on at the nuclear envelope that's required for proper synapsis, and these proteins are doing something at the nuclear envelope. It's going to be really exciting to figure out what they're doing.

Whatever they're doing, it's separate from what PCH-2 does…

That's correct. We've shown that spindle assembly checkpoint components and PCH-2 regulate synapsis by independent mechanisms. If we make double mutants, we get more severe defects in synapsis than we see in either single mutant. That's interesting because in the spindle assembly checkpoint, PCH-2 directly regulates Mad2 by disassembling a p31-Mad2 complex to promote checkpoint activation and Mad2's localization to unattached kinetochores. Yet our data indicates Mad2 and PCH-2 act in separate pathways during meiotic prophase. These findings might be reconciled if p31 is not involved in meiotic prophase, or if another protein somehow redirects PCH-2's activity away from p31 at this time. We're currently working on experiments to test these ideas.

What do you do to unwind after tackling these thorny problems all day?

I read. I've loved reading ever since I was a child; I read everything I could get my hands on. Today it's pretty much my coping mechanism [*Laughs*]. I was recently up for tenure, and I realized reading was basically my way of handling my anxiety about it.

Anything you would recommend for others facing tenure?

I love science fiction. I've read a lot of Octavia Butler. I'm really into post-apocalyptic fiction, so I read *The Hunger Games* books. I thought, "Well, these people's lives are harder than mine. I think I can handle tenure, if they can handle a tournament to the death." [*Laughs*]

1. Bhalla, N., and A.F. Dernburg. 2005. *Science.* 310:1683–1686.
2. Lamelza, P., and N. Bhalla. 2012. *PLoS Genet.* 8:e1003089.
3. Deshong, A.J., et al. 2014. *PLoS Genet.* 10:e1004291.
4. Bohr, T., et al. 2015. *J. Cell Biol.* 211:233–242.
5. Nelson, C.R., et al. 2015. *J. Cell Biol.* 211:503–516.

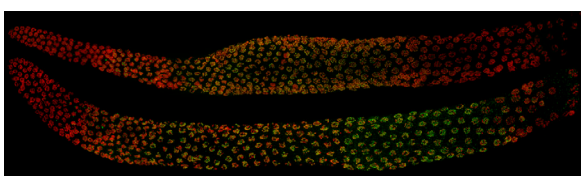

IMAGE COURTESY OF NEEDHI BHALLA

PCH-2 (green) localizes to meiotic chromosomes (red) during meiotic recombination in wild-type (top) and *meDf2* mutant (bottom) *C. elegans* germlines.