People & Ideas

David Pellman: Grasping the geometry of cancer

David Pellman investigates the constraints and advantages that alteration of chromosome number places on dividing cells.

Cells must follow a strict plan to accomplish successful cell division. For most cells, deviations from this plan, like the presence of extra centrosomes or chromosomes, can cause real trouble: cell death, or possibly cancer.

But not everything in life follows a plan. For example, David Pellman says he didn't have any intention to pursue a career in research. In college, he'd decided to go to medical school, but an early taste of research success during a summer project in Hidesaburo Hanafusa's lab (1) sparked an interest in basic science. So, after completing his medical residency, Pellman took a postdoctoral position in Gerald Fink's lab at the Massachusetts Institute of Technology (2), where he learned to leverage yeast genetics to explore the mechanics of cell division. Now, Pellman's lab at the Dana-Farber Cancer Institute is defining how cellular geometry and the scaling of protein concentrations place constraints on dividing cells (3–6). In the process, they've gained important insights into the cellular conditions that accompany deviations from the usual plan for cell division, such as those associated with genome doubling and polyploidy.

NOT ACCORDING TO PLAN

You're trained as an MD?

That's right. I'm not actively taking care of patients now, but I did until six or seven years ago. I did my internship and residency at Children's Hospital in Boston, and I joined the fellowship program at Dana-Farber and Children's Hospital, which has a heavy scientific emphasis. I had already developed an interest in research before I arrived, and the people there really encouraged me to pursue that interest. Eventually I chose to become a cell biologist and focus primarily on research, but that certainly wasn't my plan at first.

What was your plan?

I wasn't the kid who tinkered in the basement with toy chemistry sets. My problem was that I was interested in everything. When I started college, I didn't really know what I wanted to do.

I actually took a year off during college and worked with a violin maker, learning how to build and repair various wooden instruments. I played the guitar and thought it would be fun to work with something I enjoyed, but I discovered that I liked playing the instruments more than I liked making them. I still play guitar, but mostly just at home with my eight-year-old son, who plays the piano.

That year off in college really helped me to focus; I discovered the difference between an avocation and a vocation. When I got back to college after my year off, I decided to go to medical school.

What got you interested in research?

I had a very lucky experience as an undergraduate. Toward the end of college, I took a graduate course in biochemistry from Nick Cozzarelli that I really liked, and that got me interested in the idea of doing research. I was headed back to New York, where I grew up, to spend the summer with my family before starting medical school. I asked Nick to recommend some labs there, and he suggested Hidesaburo Hanafusa's lab. I worked there for the summer on the localization of the viral oncogene Src, and things went really well. I think I actually got a false sense of how science goes because our progress was so rapid. I wish all starting students could have that initial taste of success.

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SKETCH THE APPROACH

Your postdoc took you down a different road, though?

Yes. I was still interested in cancer, but I was also attracted to the idea of drilling down and figuring out how the signaling pathways involved in transformation worked. At the time there was very little information about how signaling pathways operated, and very little ability to manipulate those pathways in mammalian cells. On the other hand, yeast was a very attractive system, because I could use genetics to study individual pathways.

David Pellman

While it's obviously not possible to study cancer in yeast, you can use them to understand how normal cell biological processes work. As my postdoc developed I decided I was going to focus on mitosis and cell division, and since then I haven't looked back. I basically thought that if I was really going to understand abnormal chromosome segregation in cancer, I had to first understand as much as I could about normal cell division mechanisms.

When you started your own lab at Dana-Farber, what questions did you tackle?

When I was a postdoc, Gerry was always telling me, "All you need is a good mutant." Easier said than done. One can get mutants of various sorts, but finding the

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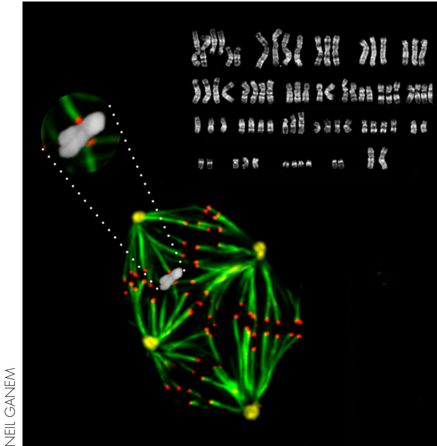
NEIL GANEM

Extra centrosomes (yellow) pass through abnormal geometries, causing spindle microtubules (green) to form abnormal attachments to kinetochores (red) and chromosomes (white).

informative ones can be tricky. One of the first things we did in my own lab was a genetic screen to try to identify new spindle components. This uncovered a number of genes involved in spindle positioning and asymmetric cell division, and perhaps the most interesting was a mutation in a formin gene. When we followed up on that mutant, we quickly found that formins assemble actin structures that form tracts for the polarized transport necessary for building the daughter cell, including the astral microtubules that orient the spindle during asymmetric division.

SCHEMATICS OF CELL DIVISION

How have your interests evolved since?

At one point we were studying a conserved microtubule regulator that in yeast is called Bik1 and in higher cells is called Clip-170. We thought Bik1 had an important role in kinetochore microtubule dynamics and kinetochore-microtubule attachments, so we were disappointed to find that lack of Bik1 doesn't cause striking phenotypes—the yeast are basically fine. Then we noticed that although the Bik1 gene isn't essential in haploid or diploid cells, it's absolutely required in triploid or tetraploid cells. We called this phenomenon ploidy-specific lethality, and it's opened up a lot of questions for us.

For example, genome doublings happen frequently in evolution, and it's still somewhat debated whether they are simply accidents that become fixed or if they're real drivers of evolutionary diversity. The fact that ploidy-specific lethality exists suggests that the genetic requirements are different in genome-doubled versus normal cells. Clearly, there are lots of detrimental aspects to genome doubling, but we'd like to understand whether there are any advantages to it, and if there are any selective pressures for it. Along with that, we'd like to understand how genome doubling or aneuploidy affect cell physiology. There may be a translational angle to this if we can find ways to specifically kill aneuploid cells—a prominent feature of most cancers.

Is there a link between genome doubling and cancer?

Genome doubling can occur through a failure of cytokinesis, which creates tetraploid cells. In 2005 we published a paper showing that cytokinesis failure can promote tumorigenesis in a mouse breast cancer model. One of the things that we observed in that paper was that tetraploid-derived tumors are genetically unstable, a feature that is shared, at least in part, with tetraploid yeast. Of course, many natural tumors are also genetically unstable; they frequently lose or gain entire chromosomes—a phenomenon known as chromosomal instability (CIN). While the significance of CIN is complex and still debated—it's unclear whether it drives the cancer or if it's just something the cancer cells have to put up with—the causes of CIN are much easier to tackle. We can ask, is there a genetic origin for CIN?

> "We can ask, is there a genetic origin for CIN?"

There's an idea that goes all the way back to Theodor Boveri's famous monograph where he suggested that aneuploidy, usually accompanied by centrosome amplification, might somehow cause cancer. He further recognized that cytokinesis failure would be a simple way to generate centrosome amplification. Based on this early work, it was thought that extra centrosomes might drive CIN through the formation of multipolar cell divisions—fragmentation of cells into highly aneuploid progeny. So, Neil Ganem in my lab imaged more than 10,000 cell divisions in various CIN cancer cells, looking for multipolar cell divisions. But he found that multipolar cell division almost never happened and, if it did, it almost always led to unviable cells. Instead, consistent with previous work, we found that extra centrosomes are ultimately bundled into bipolar spindles, but before they are bundled, they pass through a multipolar geometry. This time spent in a multipolar geometry sets up abnormal attachments between kinetochores and spindle microtubules, which in turn causes unequal distribution of chromosomes to daughter cells. So, there is a trade-off: the clustering process allows cells to survive, but the cost is CIN. There may or may not be dedicated CIN genes, but oncogenic mutations that give rise to extra centrosomes can cause geometric problems in spindle assembly that might be a common cause of CIN.

This raises all sorts of interesting questions concerning how cells scale geometric structures and metabolic networks. There are many tissues in the body where polyploidy is actually part of the normal developmental program. We'd really like to understand how and why polyploidy normally comes about, and that's one question we'll be working on next.

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Bundled together: David Pellman and family.