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PEOPLE & IDEAS

Lillian Fritz-Laylin: Keeping up to speed with evolutionary cell biology

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Fritz-Laylin studies the evolution of complex protein networks associated with cell movement.

Lillian Fritz-Laylin's first introduction to science was a part-time job as a bottle washer and media technician while studying philosophy as an undergraduate at the University of California, Berkeley. Although she can still pour superbly uniform agar plates, the best lesson she learned was that: "I love day-to-day life as a biologist. I like using my hands, troubleshooting experiments, and being part of a team. I am incredibly grateful I figured this out, because it turns out that I am a staunch empiricist and philosophy was not a great fit with that aspect of my personality." Fritz-Laylin switched courses to study immunology, but realized mouse work was not for her. She left California for Norwich in the UK to investigate how plants develop innate immunity but returned to University of California, Berkeley, for her graduate studies. In Zac Cande's laboratory, which was named "the zoo," people were working on a wide range of organisms, from maize to mammals. Sequencing the genome of the amoeba *Naegleria gruberi* for her thesis project was the first step on the path to a career in using comparative genomics to find out how eukaryotes evolved the machinery that drives fundamental cell biological processes, such as cell motility. Fritz-Laylin recently established her own research group at the University of Massachusetts, Amherst, where we contacted her to find out more about her scientific journey.

What drew you to study the evolution of cell motility?

I'm often asked how I ended up working on *Naegleria*. It's a great example of how being at the right place at the right time can change everything. Before I joined Zac's laboratory, Scott Dawson had convinced Zac that he should work on *Giardia*. At that time, we thought *Giardia* was the organism furthest away from humans on the eukaryotic tree and I was excited about the possibility that *Giardia* could help us understand very early eukaryotic evolution. But *Giardia* is a parasite and experiences accelerated evolution due to continual founder effects. The Joint Genome Institute's (JGI) Community Sequencing Program offered to sequence another "small" genome, if there was one we wanted. Zac and Scott immediately thought of *Naegleria* because of its remarkable cell biology: it switches from a crawling amoeba with no cytoplasmic microtubules to a swimming flagellate. Right after I joined the laboratory, the JGI requested RNA from amoeba and flagellate cells to make cDNA libraries for gene prediction but no one in Zac's laboratory worked with *Naegleria*. I didn't have a thesis project, so said I would do it and combed old literature for protocols to induce differentiation. The day I looked through our phase microscope at crawling amoebae that had transformed into swimming flagellates, I was hooked. All I wanted to do was understand how these cells transcribe, translate, and assemble an entire microtubule cytoskeleton within an hour as it is such a striking and fast phenotypic switch. My dissertation was on *Naegleria* differentiation (1) and use of the *Naegleria* genome sequence to estimate what very early eukaryotic cells were like (2). The idea of gradual accumulation of complexity in eukaryotes is probably incorrect. Rather, the ancestor of extant eukaryotic cells already had the vast majority of genes and features we now consider eukaryotic, which means these traits are older than we thought.

Lillian Fritz-Laylin. Image courtesy of Scott Dawson.

"The trick is to figure out how best to deal with who we really are, not who we wish we were."

As part of the *Naegleria* project, we used comparative genomics to identify genes that correlate with the ability of cells to crawl like an amoeba or white blood cell. For my postdoc, I joined Dyche Mullins' laboratory at the University of California, San Francisco, with the intention of doing biochemistry on the proteins predicted to control cell crawling. I was particularly interested in understanding how amoebae and white blood cells can move 100 to 1,000 times faster than adherent mammalian cells. I quickly realized there are very practical reasons people study slow cells: if cells move 1,000 times faster, you need to image them 1,000 times faster! I collaborated with Eric Betzig and others to collect high speed 3D datasets using the new lattice light sheet microscope and to figure out how to analyze and render the resulting terabytes of data (3). Our movies made it clear that the typical

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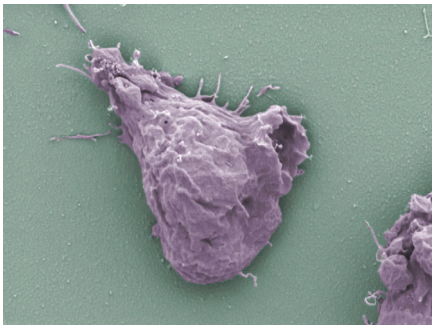

Naegleria gruberi amoebae imaged using scanning electron microscopy. The amoebae are pseudocolored purple. Image courtesy of Katrina Velle.

view of cell migration (2D images taken from overhead) only shows us a tiny fraction of what is happening. Cells are dynamic 3D objects interacting with a 3D world. This context is everything.

What is your laboratory currently working on and what is up next for you?

Right now, my laboratory works on chytrid fungi as well as *Naegleria* because of their amazing cell biology. These "wee beasts" are also important for understanding eukaryotic evolution and represent deadly pathogens. Chytrids are evolutionarily distant from the Dikarya (yeasts and multicellular fungi). They have traits conserved in animals and other eukaryotes that were lost by the Dikarya, including the ability of the cells to crawl and swim. The chytrids we work with, *Batrachochytrium dendrobatidis* (*Bd*) and *Batrachochytrium salamandrivorans* (*Bsal*), are contributing to the massive die-off of frogs and salamanders. I hope understanding how *Bd* and *Bsal* zoospores move helps us fight the spread of these ecologically devastating diseases. *Naegleria* belongs to the Discoba, a group of eukaryotes about as evolutionarily distant from humans as you can get.

Naegleria holds the land speed record for cell crawling: amoebae zip along at speeds up to 120 µm per minute! But these cells have no cytoplasmic microtubules. This is very different from fibroblasts or epithelial cells that require require actin and microtubules to move 1 to 10 µm per hour. *Naegleria*'s extreme speed in the absence of microtubules provides a unique opportunity to understand the role of actin in cell migration. When stressed, *Naegleria* amoebae differentiate into swimming flagellates—a transient form that neither eats nor divides—by building an entire microtubule cytoskeleton from scratch. This process was the first known example of de novo basal body assembly and includes transcription and translation of fairly typical eukaryotic α and β tubulin. The flagellates can rapidly disassemble their microtubule cytoskeleton, recycle the proteins, and return to being amoebae.

Naegleria amoebae undergo a closed mitosis (meaning the nuclear envelope remains intact) with spindles that lack microtubule organizing centers. Unlike the flagellar tubulin that is similar to that of other eukaryotes, the spindle is built from very divergent α and β tubulin proteins. We are collaborating with Patricia Wadsworth's laboratory to understand the evolution and molecular mechanisms of *Naegleria* spindle assembly and chromosome separation. I am really excited about this project because it looks like a case of duplication and divergence, but instead of a single gene, we are talking about a whole microtubule network.

"The day I looked through our phase microscope at crawling amoebae that had transformed into swimming flagellates, I was hooked."

When I was in Dyche's laboratory, I noticed specific actin regulators were almost always conserved in organisms that crawl. There was a peculiar exception: the actin regulators in the genome of the fungus *Bd*. But I could not find any references indicating *Bd* could crawl. I was surprised at how few papers existed on the cell biology of *Bd*, as *Bd* is causing massive die-offs of frogs around the world. I decided to test the hypothesis that conservation of actin regulators could predict the ability of this pathogen to crawl (4). I am so happy I took advantage of the opportunity to study *Bd* because the cell biology of this fungus is amazing. Like other chytrid fungi, *Bd* spores lack cell walls and swim with a flagellum. It turns out that my hypothesis was correct, and *Bd* zoospores crawl as fast as white blood cells. Each zoospore then retracts its flagellum, builds a cell wall, expands its volume over 1,000 fold, and turns into a giant multinucleated syncytium. After cellularization and maturation, flagellated zoospores, each with a single nucleus, worm their way out of the cell wall to start the life cycle again. It is a beautiful series of developmental transitions. We are hard at work looking at how the actin cytoskeleton drives these transitions, particularly cell growth and polarization.

Any tips for a successful research career?

My personal motto for success is: "Know thyself!" The times I've done my best work are when I play to my strengths, while keeping in my mind my weaknesses so I can watch out for them. My mentoring style is to help trainees see their own strengths and weaknesses. We all have them, and there is no use pretending we don't. The trick is to figure out how best to deal with who we really are, not who we wish we were. Every scientist deals with rough patches when experiments aren't working, grants or papers are rejected, or our lives outside of the laboratory are hard. The best career advice I've been given is to "Just keep swimming!"

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3. Fritz-Laylin, L., et al. 2017. *eLife.* 6:e26990.
4. Fritz-Laylin, L., et al. 2017. *J. Cell Biol.* 216:1673–1688.

You are never alone in the Fritz-Laylin laboratory. "Every image you take, every buffer you make, every beaker you break, we'll be watching you." Image courtesy of Lillian Fritz-Laylin.