Ann Miller: Shaping cells and scientists

Marie Anne O'Donnell

Miller studies how the cytoskeleton controls cellular shape change.

Playing volleyball and basketball boosted Ann Miller's competitive drive and leadership traits from an early age, instilling perseverance and a love for "the rush you get from winning, as well as how to deal with losing gracefully." But it was doing arts and crafts projects that inspired an appreciation of "things for their aesthetic beauty and the satisfaction of making things with [her] hands." The skills gleaned from these activities have been valuable at every stage of her scientific career, from mastering laboratory techniques to fueling the drive necessary to pursue competitive research questions.

Miller shifted her original goal of training to be a physician to pursuing biochemistry research after becoming fascinated by the molecular mechanisms that regulate cells and tissues while an undergrad at Gustavus Adolphus College, in St. Peter, MN. As a graduate student in Tony Koleske's laboratory at Yale University, Miller examined the molecular mechanisms by which the Arg (Abl-related gene; Abl2) nonreceptor tyrosine kinase regulates cytoskeletal structure, cell morphology, and motility (1). To continue pursuing her interest in how actin, microtubules, and Rho GTPases coordinately direct dynamic cellular processes, Miller joined Bill Bement's laboratory at the University of Wisconsin-Madison. Miller showed that MgcRacGAP activity is necessary early and throughout cytokinesis to keep RhoA activity focused at the actomyosin contractile ring by a mechanism called Rho GTPase flux (2). In the summer of 2011, Miller began assembling her own research team as an assistant professor at the University of Michigan. We contacted her to learn more.

What first drew you to study the cytoskeleton?

I am fascinated by how the cytoskeleton provides structural support and molecular highways in the cell but also dynamically reorganizes in response to localized signals to generate cell and tissue scale forces. I want to understand how Rho GTPases are activated in space and time to orchestrate actomyosin arrays during diverse cellular functions. Because these actomyosin-dependent processes are dynamic, live microscopy is essential to learn how they work. I love the aesthetic beauty of cells, and one of my favorite things during outreach events is showing children our awesome time-lapse movies of what's going on inside cells. Finally, I am driven by the relevance of our work to cancer biology, as studying the process of epithelial cytokinesis is essential for understanding what goes wrong in cancer.

"Get comfortable with being uncomfortable."

What is your laboratory actively working on?

We're investigating the molecular mechanisms that regulate cytokinesis in epithelia, where cells are connected via cell–cell junctions. Dividing cells and their neighbors undergo major changes in shape and tension at these junctions as the contractile ring pinches the dividing cell into two and these processes are controlled by localized zones of active RhoA. However, there are many questions about how RhoA activation is regulated and orchestrates junction maintenance, remodeling, and tension in dividing epithelial tissues. We're using the epithelium of *Xenopus laevis* embryos as an intact, vertebrate model system for the live imaging of localized Rho GTPase activity, cell–cell junction proteins, and the cytoskeleton.

My laboratory has shown that MgcRacGAP down-regulates RhoA and Rac1 activity at specific regions of epithelial cells, which is necessary for successful cytokinesis and cell–cell junction structure (3). We recently demonstrated that *Xenopus* MgcRacGAP contains an SxIP motif, which binds to the microtubule plus end tracking protein EB1 and is important for proper delivery of MgcRacGAP to its sites of action to locally regulate RhoA activity (4). Additionally, we've investigated how cell–cell junctions are remodeled during cytokinesis in epithelia of the *Xenopus* gastrula and provided the first evidence of how nascent tricellular tight junctions are formed (5). We've also characterized a role for the scaffolding protein Anillin at cell–cell junctions (6) and are determining how Anillin regulates actomyosin structures and contractility at cell and tissue scales. Anillin knockdown increases localized, transient accumulations or "flares" of active RhoA at cell–cell junctions, and we propose that these Rho "flares" make epithelial cells flexible to shape changes during cytokinesis and tissue morphogenesis by repairing local breaks in junctions.

Ann Miller. PHOTO COURTESY OF SUZANNE TAINTER.

What is up next for you?

I'm excited about combining cell biology with developmental biology, tissue mechanics, and mathematical modeling to ask questions about how cell junctions are remodeled in response to cell shape changes in different tension environments in the developing embryo; how Anillin organizes actomyosin organization and contractility; and how Rho flares are initiated and what their consequences are. Andrew Goryachev, Bill Bement, George von Dassow, and I are working on a collaborative project investigating the mechanisms that orchestrate patterning of the cell cortex. Cells can support sustained waves of dynamically coupled Rho activity and actin assembly, which we termed "cortical excitability" (7), and we are taking a multipronged approach to determine the mechanisms underlying cortical excitability.

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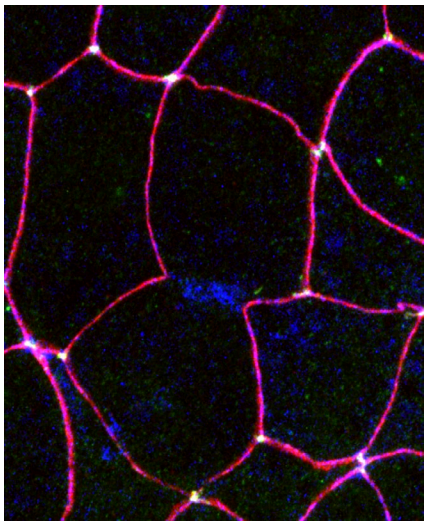

We are interested in how cells maintain and remodel their cell–cell junctions and actomyosin cytoskeleton during cell shape changes such as cytokinesis. Dividing *Xenopus* epithelial cell labeled with probes for F-actin (blue), tight junctions (magenta), and tricellular tight junctions (appear white). PHOTO COURTESY OF TOMOHITO HIGASHI, POSTDOC IN THE MILLER LABORATORY.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

Tony Koleske and Bill Bement were both excellent mentors with very different styles. I've found my own leadership style that combines their influence with my unique perspective. I think developing a sense of teamwork so that each individual feels valued but realizes they have to work collectively toward shared goals in the laboratory is essential. We do a number of things to build camaraderie, including our annual Spirit Week (a tradition passed down from the Bement Lab), playing laser tag, or canoeing down the Huron River (and posting about these laboratory happenings on our instagram feed, themillerlab). Another strategy I use is to provide and discuss a "Lab Expectations" document that lays out my philosophy and expectations for each new laboratory member. I have high expectations, but I also try my hardest to work with each trainee to help them develop as scientists and achieve their goals. I've been incredibly lucky to recruit a smart, creative, hard-working, and fun group of people to work in my lab. The most rewarding thing about being a PI has been the pride I feel in seeing the growth and successes of my lab members.

What has been the biggest challenge in your career so far?

The transition between postdoc and faculty: Deciding which jobs to apply for, the application and interview process itself, and then the exciting, yet overwhelming, feeling of landing my ideal faculty job and thinking, now what? How am I going to get my independent research program off the ground and funded? Everyone feels this way to some extent, yet unfortunately, this is when more women than men leave academic science. If women make that decision because they are more excited about other career opportunities that align better with their skills and interests, that's great! But if women leave the academic path because it seems too hard or incompatible with having a family, I want to say: You CAN do this! For me, having a husband who is a true partner in taking care of our kids as well as access to excellent child care has been essential. One of the great things about running my own laboratory is the flexibility. There's always too much to do and not enough time, but I can choose how I prioritize my time. I think any woman (or man) who wants to be successful in a challenging career has to make sacrifices, but the flexibility of running my own laboratory allows me to find a balance that works for me and my family.

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What is the best advice you have been given?

Tony Koleske told me to "get comfortable with being uncomfortable." First, if you work on research questions that are interesting, there will be competition. However, by finding your niche and unique approach or perspective, you will make a useful contribution, and some level of competition is necessary to push the field forward. Second, as a group leader, I'm thrown into a lot of situations that I don't feel fully prepared for, but the best thing to do is just jump in, seek advice when needed, and figure it out. One of the great things about being a scientist is that I'm constantly learning new things and challenged by the work and the people I interact with; this pushes me to keep growing as a scientist and as a person.

What hobbies do you enjoy?

I love spending time with my family. My husband, Dave Johnson, is a physical therapist and hugely supportive of my career in science. He's been open to moving around the country, understanding of the late nights and travel, listens to my frustrations, offers useful laboratory management advice, and celebrates the good things that happen. We enjoy sports, outdoor activities, music, and theater with our two kids, Grace, who is 8 years old, and Micah, who is 3. I enjoy reading and try to encourage a love of reading "real" paper books in our kids. My favorite book this past year was Lab Girl by Hope Jahren; Jahren's passion for her work and her lyrical descriptions that animate what's going on in the trees and soil around us are inspirational.

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(Top) Ann and her family attending a University of Michigan Women's Volleyball game. PHOTO COURTESY OF DAVE JOHNSON. (Bottom) Ann and her laboratory celebrating a milestone birthday with a frog cake. PHOTO COURTESY OF MATT CHAPMAN.