Megan King: A force to be reckoned with

King's work focuses on the intimate biomechanical link between the nucleus and the cytoskeleton.

PHOTO COURTESY OF MEGAN KING

Megan King

Megan King grew up in rural Vermont, in a town with only a few thousand people and not a single traffic light. The youngest and sole girl in a family of engineers, she was immersed in a world of "geeks" from the start. Though she was programming at a young age, she found herself gravitating toward chemistry and, later, biology and liked very much the connection to the natural world in a way that she felt was absent in engineering and computer programming.

King has since made her way to a less rural town—New Haven, Connecticut—where she operates her own lab in the Department of Cell Biology at Yale University. Her research focuses on the biomechanics of the nucleus and the surrounding cytoskeleton (1). Her work investigates how this link affects the balance of forces within the surrounding tissue and the effects it has on the integrity of DNA (2,3). We contacted her to learn more.

Where did you study before starting your own lab?

I studied biochemistry at Brandeis, where I had the privilege of working in Dr. Susan Lowey's laboratory, focusing on the modulation of myosin by its light chain composition. Much of my fundamental perspective on science was built in those years. After working in biotech for two years, I headed to the University of Pennsylvania to study biochemistry and molecular biophysics in the laboratory of Dr. Mark Lemmon. There, I had the opportunity to try many different experimental approaches, from crystallography to cell biology. I remember my first immunofluorescence microscopy experiment clearly—I fell back in love with the microscope immediately (having first fallen in love with looking at pond water in the seventh grade back in Vermont—thanks, Mr. Parmelee!). So despite enjoying all of the biophysics in Mark's lab, I felt the pull of cell biology strongly. I became hooked on the nucleus and its dynamics and went next to Rockefeller University and the laboratory of Dr. Günter Blobel. In Günter's lab I studied nuclear envelope membrane composition, an area pioneered by his lab for decades. After initially working in cell culture models, I then went on to take advantage of budding yeast (relying on the expertise brought to the lab by my now-husband Patrick Lusk) and then fission yeast (helped out greatly by my colleague Frank Neumann and the rest of Paul Nurse's lab). This was somewhat of a golden period for the reemergence of yeasts as valuable model systems for studying inner nuclear membrane proteins, and this laid the foundation for the work that my lab is pursuing to this day.

> "I have been very unsuccessful at staying in my 'scientific sand box.'"

What was it that first drew your interest to nuclear biomechanics?

I initially became fascinated with the nucleus because it is a self-organized system that undergoes a cycle of dramatic reorganization every cell cycle. In addition, it houses the chromosomes, which behave very differently from other macromolecular complexes due to the sheer size of the chromatin polymer. These different attributes make the nucleus very interesting from its basic biophysical properties on up (4). I then became fascinated with understanding why the nuclear envelope doesn't simply tubulate in response to cytoskeletal forces (like the ER does). The problem of how to efficiently move a nucleus through the cytoplasm while maintaining its integrity is not as simple as it looks at first glance, and we continue to be driven toward understanding the ways that cells meet this challenge.

What is your lab actively working on?

In mammalian models we are very interested in understanding how mechanical information, particularly from adjacent cells or the extracellular matrix, is communicated to the nuclear interior. We are asking how cells respond to these cues to maintain mechanical homeostasis; surprisingly, defects in these mechanotransduction pathways seem capable of driving damage to the DNA, which is a fascinating new area of investigation. An important aspect of this avenue of research will be to define, in detail, how nuclear mechanics are established and modulated. In yeast models we continue to investigate how the nuclear periphery influences genome integrity, with a particular focus on how genomic change can drive adaptation, even at the cost of lost genome integrity. It is a great time to see how these two seemingly disparate fields (nuclear mechanics and genome integrity) are becoming connected, though on the surface they are quite distinct.

What kind of approach do you bring to your work?

The work in my lab tends to be question driven. We will take on learning any technique (or developing a new one) to answer the question at hand. At the same time, it is important to not be naïve about the challenges associated with such an approach. I have been very lucky to have great collaborators—especially Simon Mochrie and Valerie Horsley at Yale—

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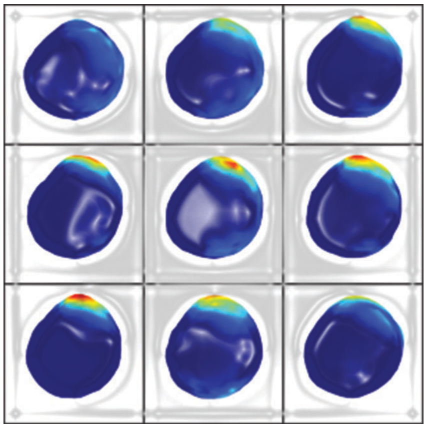

IMAGE COURTESY OF YAO ZHAO AND SARAH SCHREINER

Stylized renderings of nuclear shape fluctuations reconstructed from time-lapse imaging of an *S. pombe* nucleus.

who have allowed us to push our own boundaries in part by taking advantage of their expertise. I have been very unsuccessful at staying in my "scientific sand box." There are costs, but I am starting to accept that I may never change in this respect, and so I will have to learn how to mitigate the negatives and accentuate the positives that come with such a modus operandi.

Was there anything you were unprepared for upon becoming a group leader?

Starting the lab, I thought that the key to success would be about asking the right questions. I've learned quickly that it's really about finding great people to agree to work with you!

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

Putting forward the idea that there is an intimate mechanical crosstalk between the chromatin within the nucleus and the forces generated by the cytoplasmic cytoskeleton. Using a variety of methods and model systems we continue to uncover evidence that the dynamic cytoskeleton can alter chromatin dynamics within the nucleus, both in a general, indirect manner and in specific, directed ways. On the flip side, chromatin itself is critical for the ability of the nuclear envelope to resist deformation by force, particularly the heterochromatin associated with the nuclear periphery. This model has broad implications for various aspects of chromatin biology, including DNA repair, and cellular and tissue mechanics.

Who were the key influences early in your career?

There have been many. My perspective on biophysics, now the foundation for how I think about cell biology, comes directly from my training at Brandeis, both in the classroom (particularly as taught by Chris Miller) and in the laboratory (by Susan Lowey and Guichy Waller). Mark Lemmon's influence on how to communicate science, usually underappreciated but essential, has been critical during my transition to becoming an independent scientist. In terms of combining quantitative biochemical and biophysical approaches with cell biology, Tom Pollard became a real inspiration toward the end of my PhD, and it has been a wonderful experience to join Tom at Yale, with whom I now teach an undergraduate course in cell biology.

"I find it very easy to get carried away with the sheer joy of thinking about science."

What is the best advice you have been given?

It sounds so simple, but Günter Blobel's advice to "focus on the big questions" continues to resonate with me. This principle has been one of the primary drivers for my group to develop new assays—so that we can go after unanswered, big questions. Often this takes patience and investment, but it is very rewarding when you finally succeed!

What hobbies do you have?

Patrick and I are juggling two labs and four kids, so needless to say, there is not much time for hobbies. I have always been a dancer, and I have been lucky over the past few years to find a new dancing home in New Haven. In the summers I also love to garden, although this year I am already way behind!

What has been your biggest accomplishment outside of the lab?

Probably my role as a mentor and teacher. I underestimated how motivating it is to mentor other people. In fact, the time I spend mentoring provides important "fuel" for other aspects of my career. It is funny how you can wake up one day and realize that you are a role model for other young scientists—for me in particular because I am raising four kids.

What excites you about the future of science?

The increasingly interdisciplinary nature of cell biology. I love when these two halves of me—the biophysics/thermodynamics side and the cell biology/microscopy side—collide. In those moments I find it very easy to get carried away with the sheer joy of thinking about science—and these are the moments that make the rest of the challenges worth it.

1. Thiam, H.R., et al. 2016. *Nat. Commun.* 7:10997.
2. King, M.C., and C.P. Lusk. 2016. *Curr. Opin. Cell Biol.* 41:9–17.
3. Stewart, R.M., et al. 2015. *J. Cell Biol.* 209:403–418.
4. Schreiner, S.M., et al. 2015. *Nat. Commun.* 6:7159.

PHOTO COURTESY OF MEGAN KING

King at home with her husband, Patrick Lusk, and their "brood."