People & Ideas

Alpha Yap: Cadherins hold it all together

Yap is interested in how cadherins influence the cytoskeleton—and vice versa.

Homotypic adhesion between surface receptors called cadherins is essential to the integrity of epithelial sheets. But cadherins aren't just passive anchors that allow cells to stick together. Instead, by coupling to the actin cytoskeleton, they can generate tension to affect the structure and resiliency of individual cells and tissues.

How are contractile forces generated at cadherin junctions, and how are forces transmitted across junctions to neighboring cells in the epithelial sheet? Having studied cell–cell adhesions since the start of his research career (1, 2), Alpha Yap has a good appreciation for the complexity of cytoskeletal regulation at cell–cell junctions (3–5) and is now poised to answer these questions. We called him at his lab at Australia's University of Queensland to hear how he's weaving his past experience into new insights on junction structure and function.

A SATISFYING SWITCH

Did you always want to be a scientist?

Well, first I wanted to be a tennis player, but I was too short, had no talent, and had bad vision. Later I wanted to be a professional musician and sing in a choir, but again I lacked talent. My son and daughter somehow have this talent, and my daughter is actually a professional musician, but I think my singing then and subsequently may qualify as cruel and unusual punishment for anyone who hears it. [Laughs] Then in high school, I had an idealized vision of—this sounds terribly pretentious—a scholarly life. So I suppose, deep down, that's what I wanted.

But after high school I went into medicine instead, because in Australia at that time one could go straight to medical school after high school. I took a medical degree and trained in a hospital for several years as a specialist physician and endocrinologist. But then I decided to go to the lab and do a PhD. I still do a little bit of clinical endocrinology, but it's a tiny part of what I do now.

Why did you switch to research?

You know, I don't think I ever made a considered decision to pursue a research career instead of medicine. At some point I just realized that, although there's a profound human satisfaction in helping people and it can be enormously satisfying to reach a diagnosis for a patient, the intellectual satisfaction derived from that is very short-lived. By contrast, a happy research life is sort of a slow burn. In fact, research is frequently frustrating, but for me the intellectual satisfaction in a research career goes deeper. So, I gradually found myself placing more of my emphasis on research than on medicine.

I think that success in science depends on your creativity and your ability to work out problems. The problems that you work out, and your success in doing so, can be very idiosyncratic, so a life in science is one that everyone makes for themselves. There's no mold or career template that we all have to fit into. It depends on taste, personality, and, ultimately, what kind of science you love. For me, that's a very interesting aspect of this career.

STICKING TO ADHESION

Your research career started with the thyroid gland…

As a medical student, I was interested in endocrinology, and my mentor at the time, whom I'd met as one of my lecturers, was a very inspiring figure. He had some projects available on the thyroid gland, so I got the opportunity to do science in the discipline that most interested me. Eventually, questions about the organization of epithelial cells in the thyroid, which are immediately relevant to endocrine physiology, morphed into more general questions, such as how cells and tissues are organized.

> "A happy research life is sort of a slow burn."

PHOTO COURTESY OF LIBBY YAP

Alpha Yap

You pursued similar questions as a postdoc…

I was doing my graduate work around the time—the early '90s—when adhesion had finally become molecular. I wanted to understand more about the cell biology of adhesion and of epithelia, but I thought that I would eventually go back to studying the thyroid gland or the like.

I took a postdoc position in Barry Gumbiner's lab in New York, which, looking back on it, was one of the great formative times of my life. There were so many interesting things going on in Barry's lab, and there were so many interesting, dedicated, creative people there—I learned then how a lab can be much more than the sum of its parts. That was where I first started to realize that the biology of an organ such as the adrenal gland might not be a consequence of particular molecular interactions extrapolated *n* number of times. Rather, the biology might arise from higher-order organization at the cell surface, such as the spatial distribution of adhesion receptors and their interaction with signaling molecules and the cytoskeleton.

So you returned to Australia but not the thyroid…

Yes. My wife and I are both from Australia. We returned there mostly for family reasons but also because I was on a traveling fellowship from the Australian government that provided me with funding back home.

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

The work that I'd done in Barry's lab was about lateral clustering of the cadherin receptor, and I initially thought that I would try to focus on understanding the molecular basis for that. So I got a grant and hired a technician, but, when we started to build reagents to study clustering, we realized that we could use them to ask whether or not signaling modulators are activated when cadherin adhesive bonds are formed.

I feel like my research career moves in five-year blocks. In our first five years, my lab was working on two problems. One was to try to understand signaling pathways that are activated when cadherins are bound. We were particularly interested in the Rac GTPase. The other thing we became interested in was whether cadherins could actually regulate the actin cytoskeleton.

When I was in Barry's lab, we all believed that cadherins bound to actin but that the interaction was kind of passive. But I'd become interested in the notion that cadherin binding could activate proteins like Rac that would ultimately exert an influence on the actin cytoskeleton.

EVERY FIVE YEARS

Has your work been informed by research from the focal adhesion field?

Yes, very much so. But an interesting difference between that field and ours is that the adhesive junction interactions we deal with are actively symmetric. When you study a fibroblast interacting with the extracellular matrix, it pulls on the matrix; the matrix is largely passive. But when a cell pulls on a neighboring cell, its neighbor is potentially active. There's a difference there that may ultimately be very interesting.

And your subsequent five-year blocks?

In the next five years, we looked at actin regulators, and we also became very interested in how cadherins might interact with microtubules. We took each of those subjects as far as we could, but then we reached a point where we couldn't take them any further. It's only in the last five years that many of those tracks have started to converge and make sense in the bigger picture.

How so?

In the past we've studied cortical myosins, which are involved in generating tension at cell adhesions. To generate tension, you need to have strong adhesion coupled to a contractile force generator. We recently did some studies that suggested to us that myosin IIA contributes to adhesion by clustering cadherins—therefore strengthening adhesion—whereas a different myosin, IIB, is the predominant force generator. The reality could be more complex than that; we just don't know yet. But we do know that myosin contractility is regulated by the Rho GTPases, and we've published evidence that other small GTPases such as Rap1 are also involved.

How is the activity of these GTPases regulated? Samantha Stehbens, when she was a grad student in my lab, uncovered something unexpected there. She discovered that dynamic microtubules somehow regulate the zonula adherens or ZA, which is a band found in many epithelia where cadherins concentrate to generate strong adhesion.

That finding led us to a protein called centralspindlin, which was previously understood as a regulator of cytokinesis. The cytokinetic furrow is finely controlled by microtubules, and centralspindlin is a microtubule-binding complex that is localized to the furrow in a microtubule-dependent fashion. We showed that centralspindlin is localized to the ZA in the same way, and we think it's localized there to coordinate the activation and inactivation limbs of the Rho GTPase cycle.

> "We're trying to understand how force is generated at junctions."

Today, my lab members are working toward trying to understand the dynamic way in which the actin cytoskeleton is organized at cell–cell adhesions and how that affects junctional function. We're trying to understand how force is generated at junctions and how adhesions sense and resist force. We can measure those forces by using high-powered lasers to cut a junction and recording its recoil as an index of tension, and we'd like to introduce tension-sensitive FRET biosensors into the proteins that we work on to study molecular-level tension. Ultimately, though, we'd like to understand how these interactions scale up and how forces generated between cells at one junction might affect the cells around them to allow cells to collectively respond to a stimulus.

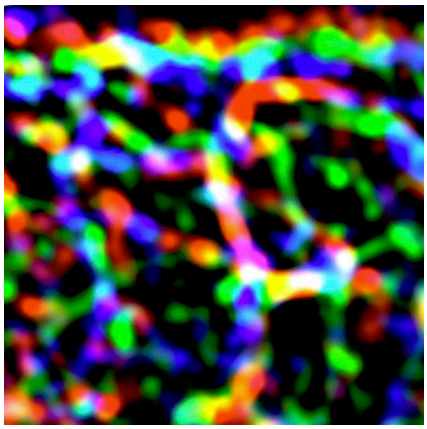

IMAGE COURTESY OF SELWIN WU

E-cadherin (blue), F-actin (green), and myosin II (red) at the lateral cortex of cell–cell junctions.

PHOTO COURTESY OF LIBBY YAP

Yap and his son, David, playing around on the piano.

1. Yap, A.S., et al. 1992. *Exp. Cell Res.* 202:366–369.
2. Yap, A.S., et al. 1998. *J. Cell Biol.* 141:779–789.
3. Stehbens, S.J., et al. 2006. *J. Cell Sci.* 119:1801–1811.
4. Smutny, M., et al. 2010. *Nat. Cell Biol.* 12:696–702.
5. Ratheesh, A., et al. 2012. *Nat. Cell Biol.* 14:818–828.