

Kris DeMali: Fixed on cell adhesion

DeMali, a lady with both feet firmly on the ground, studies the proteins that keep cells rooted.

The connections that cells make with their neighbors and with their extracellular matrix are essential for keeping our bodies in one piece. But the loss or modification of these connections is also essential for numerous processes, such as cell migration and cell division.

How cells control the dynamics of building and destroying their bonds was a question that piqued Kris DeMali's interest during her PhD studies on cell signaling pathways that prompt mitosis (1–3).

So much so, in fact, that she switched her focus to cell adhesion for her post-doctoral studies (4–6).

Now, as a group leader at the University of Iowa, DeMali is continuing her studies into cell adhesion, and is particularly interested in the changes in cell stickiness that are associated with cancer—such as when tumor cells start to metastasize. DeMali, who moved to the

university two and a half years ago with a Howard Temin Award from the National Cancer Institute, was kind enough to loosen herself from the laboratory bench momentarily and talk with us at JCB.

COUNTRY ROOTS

Where did you grow up?

On a small farm in rural Ohio. It was a small dairy operation. We had mostly cattle, plus a few pigs and chickens and a lot of maize.

Did farm life prompt your interest in science and nature?

It probably awakened my interest in science, but I didn't recognize it at that

point. Growing up on a small farm, I wasn't exposed to people who did scientific research. But I liked my science classes in high school, so I thought I'd go to medical school.

You weren't tempted to become a vet?

No! [laughs]. I think people who grow up on farms don't want to be vets.

So how did an interest in medicine turn into an interest in science?

I took a chemistry course during my first semester at the College of Wooster in Ohio, and I met a chemistry professor named Ted Williams who gave me a summer job in his laboratory. I had to identify and dispose of all the unlabeled chemical waste that had accumulated over the years from the experiments that had been performed in the organic teaching laboratory.

That sounds like a lovely job. I can see why you were hooked.

[Laughs]. It was a terrible job, but it actually ended up being quite fun. I started off the summer with a bench full of four-liter bottles filled with unknown organic waste, and it was a real challenge to identify what they were. I progressed pretty rapidly, and because there was still time left in the summer, he let me begin a research project. It was really that summer job that made me stick with science.

UPROOTED

Where did you do your PhD?

I started my PhD at the University of Colorado Health Sciences Center in Denver with Andrius Kazlauskas, studying the downstream signals from the PDGF receptor. About midway through my graduate career, he moved to take a faculty appointment at Schepens Eye Research Institute, affiliated with Harvard Medical School, in Boston. So I moved with him.



Kris DeMali

Were you happy to move?

No, I wasn't happy at all! I was actually quite angry. I had chosen Denver because it was a reasonably sized city to live in. Being from rural Ohio, the thought of living in Boston and not owning a car was quite a scary prospect.

But I made the move, and I quickly learned to love Boston. It was a very exciting place to do science. There were so many seminars going on every day that were directly related to the kind of research that we did, and there was such a big volume of people doing science, that it was a really fun place to be.

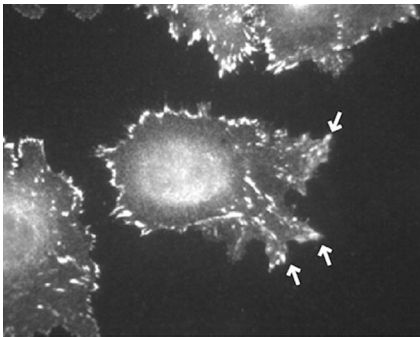
What was your project?

I studied PDGF receptor signaling, and tried to determine how, in certain contexts, it drives cellular transformation. Over the course of my studies I became interested in the fact that transformation has to be accompanied by changes in the adhesive properties of cells. I became so interested that I decided to pursue post-doctoral studies with Keith Burridge, who's a leading cell adhesion researcher at Chapel Hill North Carolina.

How did the project develop in Keith's laboratory?

Because I was changing fields—from growth factor receptor signaling to work-

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At a migrating cell's leading edge vinculin and an actin regulator come together (arrows), enabling the cell to send out protrusions, grab hold of the matrix, and move forward.

ing on adhesion—when I first joined the laboratory, I relied pretty heavily on Keith for project ideas. We began investigating whether or not there was a link between the actin polymerization machinery, Arp2/3, and integrins, which attach cells to the extracellular matrix.

We soon found out there was a link, and it was the integrin-associated protein, vinculin. I then discovered the two are not connected all the time. They only interact when the cell is stimulated by epidermal growth factor, or the extracellular matrix protein fibronectin—such as when the cell has to change its adhesive properties to go through mitosis or to migrate.

NEW ROOTS AND ROUTES

And you're still working on vinculin?

Yes. Most of my post-doc work was focused on cell-to-matrix adhesions, but some people in Keith's laboratory began to study transendothelial migration—when cells such as leukocytes have to squeeze through the endothelial lining of the blood vessels to access the tissues. During this migration the endothelial cells have to alter their cell-to-cell adhesions to let the leukocytes through. That started me thinking about vinculin's role in cell-to-cell adhesions.

Is there evidence of a role for vinculin in cell–cell contact?

There is substantial literature that suggests vinculin plays a role at adherens

junctions. However, most studies are performed using gene deletion approaches, which eliminates vinculin at both cell–matrix and cell–cell adhesion sites. So my laboratory has been devoting a significant amount of time to generating a powerful vinculin knockdown substitution system. First, we knockdown the endogenous vinculin by RNAi and then we add back a fluorescently labeled vinculin.

How does the method differentiate between the cell–cell junctions and the cell–matrix attachments?

The turnover of vinculin in cell–cell adhesions is much more rapid than the turnover in cell–matrix adhesions. When we inhibit ~70–80% of the vinculin, it leaves intact the vinculin at sites of cell–matrix adhesion, and only removes vinculin's function in cell–cell adhesion. Our results show that when we add the fluorescent version of the protein, we are looking at vinculin at the cell–cell junctions.

So what have you discovered?

We're very close to ascribing a function for vinculin at the cell–cell junctions. But we've not published it yet. In short, what we've found is that vinculin is one of the proteins that appears to be involved in dynamic changes in adhesive properties that occur during processes such as transendothelial migration, mitosis, embryonic development, or wound healing.

What's up next for you?

First we want to establish vinculin's function, and then we'll pursue how it fits into the broader context of mitosis, migration, disease, etc. I think those are all exciting avenues to pursue in the future.

We're also interested in what happens to vinculin in cancer, as loss of vinculin is associated with disease progression and poor prognosis. I think one of the things I learned during my graduate and post-doctoral studies is that you just go where the science takes you. So I look forward to being taken down all sorts of paths.

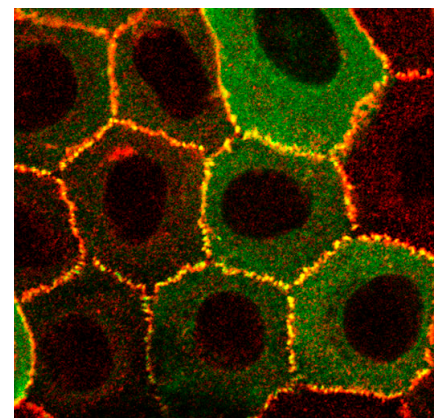
What do you like best about being a PI?

I really love mentoring my students—I have two graduate students and two undergrads. I like conveying to them my excitement about science, but also seeing their own excitement too.

The major challenge for all young PIs, of course, is funding, and I'm no different. But the department I'm in has a strong commitment to mentoring young scientists, and I think that's the key to success in science, especially in the current funding climate. Also, I really like being in Iowa. It's a small college town, and I like that setting. It takes me back to my roots. **JCB**

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Vinculin (green) colocalizes with a cell–cell adhesion protein (red).