FIRST PERSON

First person – Catherine Green Galbraith

First Person is a series of interviews with the first authors of a selection of papers published in Biology Open, helping early-career researchers promote themselves alongside their papers. Catherine Green Galbraith is first author on 'Coupling integrin dynamics to cellular adhesion behaviors', published in BiO. Catherine is an Associate Professor at Oregon Health Science University, Portland, USA, where she runs a lab together with Jim Galbraith, using molecular organization and dynamics to predict how cells make decisions during directional migration.

Catherine Green Galbraith

What is your scientific background and the general focus of your lab?

My lab reflects my multi-disciplinary scientific background. I was trained in bioengineering and applied mechanics, and then did my postdoctoral work in cell biology before joining the National Institutes of Health (NIH). While pursuing my own research at NIH, I also collaborated extensively with Janelia Research scientists Eric Betzig and Harald Hess on the development of photoactivated localization microscopy (PALM) applications, including two-color, live-cell, and 3D iPALM as well as the Bessel sheet microscope. In the fall of 2013 I accepted an Associate Professor position at Oregon Health Science University in Portland, OR, USA.

Our research is currently focused on defining cellular decision processes – decision modules and signaling pathways – that convert extracellular matrix (ECM) probing into directed migration. The overall goal is to understand how specific molecular interactions are coupled to biochemical signals and cellular outputs using a combination of biophysics, quantitative biology and cutting-edge microscopy. We are currently focused in two areas; firstly, defining mechanisms that create patterns of unbound ECM receptor organization, mobility and conformation at the front of cell protrusions to regulate the functionalization of protrusions to probe ECM. And secondly, identifying signaling pathways that bound ECM receptors use to separate the decision to convert an ECM cue into directed migration from the decision to continue to probe the ECM through actin cytoskeletal dynamics. By comparing normal and metastatic cells these studies will explore how cancer cells are able to misinterpret ECM cues and metastasize.

How would you explain the main findings of your paper to non-scientific family and friends?

I would say that this paper demonstrates that what you see is not always what you get. Normally, we say that if we label a molecule with a probe so that we can see it and it still goes where we expect it to go and binds what we expect it to bind, then it is functioning properly. Here, we show that is not always a good assumption. When we look with higher resolution, we see that labeling can change the conformation of the molecule, making it more likely to bind its target. This demonstrates that when we add labels to molecules, it is not adequate to say that the label is non-perturbative if the molecule goes to the right place on the cell — we also need to measure any changes in the function of the individual molecule.

What are the potential implications of these results for your field of research?

Our finding is a cautionary tale for anyone fluorescently labeling molecules. We found that even though a fluorescently labeled protein properly localizes and interacts with known binding partners, labeling can change the state of the protein. Irrespective of whether the alpha or the beta subunit of integrin heterodimers was labeled with a fluorophore, the expressed integrins would localize to adhesion complexes and bind extracellular matrix. However, when the fluorophore was on the beta subunit, the conformation of the integrin was converted into a high-affinity state, slowing the single molecule mobility and increasing interaction with ligand. When visualized with conventional approaches, these changes were not morphologically grossly abnormal and might easily be attributed to biological variability unless the labeled molecules were compared with unlabeled molecules or the molecular localization was confirmed with molecular (nm scale) resolution.

What has surprised you the most while conducting your research?

It always surprises me that people talk about the need for multidisciplinary science, but it seems as though we are still in the early adopter stages. My undergraduate and graduate degrees are in engineering, and engineers apply multiple disciplines to the problem that they are trying to solve. This is how I approach biology, and students always seemed freaked out when I do things like teach them to set up optimized search algorithms to explore parameter space and explain working within the linear range of measurement detectors in order to be able to quantify our biological data.

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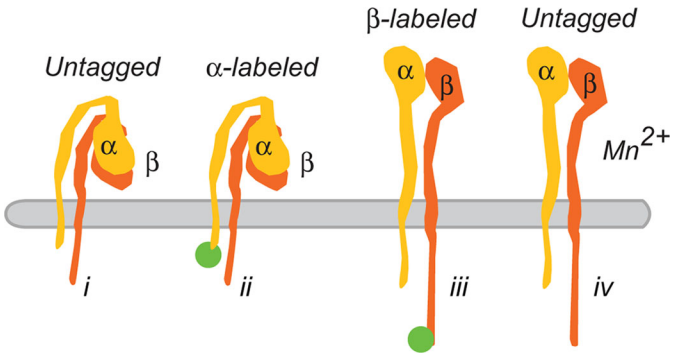

A cartoon model illustrating that integrins properly localize and insert into the membrane irrespective of how they are labeled. However, although labeling the alpha subunit does not perturb molecular behavior, labeling the beta subunit changes the molecular conformation and activates the molecule to increase its affinity for the ligand by exposing the same epitope as treatment with the chemical activator Mn^{2+}.

"My undergraduate and graduate degrees are in engineering, and engineers apply multiple disciplines to the problem that they are trying to solve."

What, in your opinion, are some of the greatest achievements in your field and how has this influenced your research?

The greatest achievements in my field depend upon new technological advances, especially in imaging and quantitative measurements. About 10 years ago, I made the discovery that integrins at the leading edge of migrating cells were in primed configuration; sticky but not yet stuck to ligand. We could make molecular perturbations (siRNA) to try to figure out interacting proteins and mechanisms, but because the actin cytoskeleton at the front of the cell is so dense and has a half-life of about 30 sec, we could not visualize the effects our perturbations had on molecular interactions. At that point in time, single-molecule super-resolution microscopy was being developed, and I was lucky enough to become involved in developing two-color and then live-cell PALM. These were the new technological advances that I needed to make progress on my biological problem and see what was previously invisible.

What changes do you think could improve the professional lives of early-career scientists?

I think that early-career scientists need to be more broadly rather than more narrowly trained. With funding getting tighter every year there is a tendency to force scientists to specialize and narrowly focus earlier and earlier in their careers. I think that this puts scientists at a disadvantage when they are faced with an obstacle in either their science or their career path; they do not have the skill sets to figure out how to forge a new path around the obstacle that leads to the same or perhaps a more interesting end point.

What's next for you?

Now that we have the tools to couple integrin molecular behaviors with conformation and affinity state, the next step is to go back to that discovery we made a decade ago – the leading edge of cells is sticky but not yet stuck – and figure out the mechanism.

Reference

Galbraith, C. G., Davidson, M. W. and Galbraith, J. A. (2018). Coupling integrin dynamics to cellular adhesion behaviors. *Biol. Open* **7**: bio036806.