Harvey McMahon: Ahead of the curve on membrane dynamics

McMahon studies how membranes are bent into shape during vesicle formation and fusion.

The plasma membrane undergoes dramatic shape changes during endocytosis. Starting off as an essentially flat surface, the bilayer becomes increasingly curved before it finally pinches off into the cytoplasm to form an endocytic vesicle. Numerous proteins coordinate this process, many of which have been investigated by Harvey McMahon at the MRC Laboratory of Molecular Biology in Cambridge, UK.

McMahon first became interested in vesicles as a PhD student working on neurotransmitter release with David Nicholls at the University of Dundee (1). During his postdoc with Thomas Südhof at UT Southwestern, McMahon studied the molecular mechanisms of synaptic vesicle fusion (2), but he switched his focus to the endocytic machinery upon starting his own lab in Cambridge. In addition to studying how endocytic cargo is recruited into nascent vesicles (3), McMahon has studied proteins that sculpt the plasma membrane at every stage of endocytosis, from a membrane-shaping F-BAR protein that defines the initial bud site (4) to the dynamin GTPase that releases the completed vesicle into the cytoplasm (5). Many of these proteins contain a crescent-shaped BAR domain (6). McMahon has also returned to exocytosis to study how membrane curvature drives vesicle fusion (7).

> "There's a reason each organelle is shaped the way it is."

In a recent interview, McMahon discussed the arc of his career and how his future research is shaping up.

ON AN UPWARD CURVE

Where did you grow up?

I grew up in Ireland in a small town called Clones. So I guess at some level I was destined to clone! I always wanted to know how things worked. I remember taking my grandfather's pocket watch apart and not being able to put it back together again. During my time at university I started to think about how I could get paid to do something that I really liked doing. And so in my last year I applied for a research assistant's post in David Nicholl's lab that allowed me to study for a PhD at the same time.

What did you do during your PhD?

I showed that the neurotransmitter glutamate was stored in vesicles and was released from these vesicles upon depolarization. I also worked on the effects of toxins like tetanus and botulinum toxins on the brain. That got me interested in molecular mechanisms: I asked myself, "What are these toxins actually targeting to shut down synaptic transmission?" So I moved to Tom Südhof's lab at UT Southwestern for my postdoc, because he had his hands on many of the potential target proteins.

What did you discover during your time in Dallas?

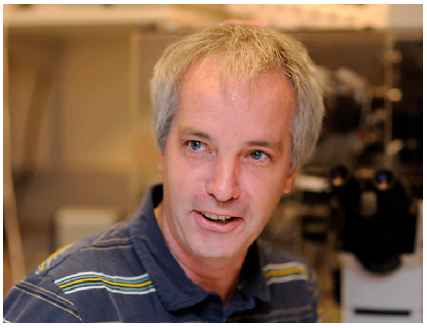
I was isolating what we had termed the core complex in vesicle fusion, which turned out to be the same as Jim Rothman's SNARE complex. It contained the three central components—syntaxin, SNAP-25, and synaptobrevin—and we showed that the complex was SDS resistant. But I found that there were other components associated with the complex that weren't SDS resistant. That was the complexin family, and I worked on the complexins' function in SNARE assembly and synaptic vesicle release.

I was also very interested in the hypothesis that the machinery involved in synaptic vesicle fusion would be involved in fusing other types of vesicle and that there were ubiquitous versions of all of these synaptic proteins. I chose to look at synaptobrevin and ended up cloning its counterpart cellubrevin, which is involved in exocytosis throughout the body.

A BEND IN THE ROAD

Why did you switch to working on endocytosis in your own lab?

One reason was that we knew that you need to efficiently recycle synaptic vesicles in order to get further rounds of exocytosis. So we really wanted to look at the opposite side of the coin to vesicle release.



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Harvey McMahon

And ultimately that led to your interest in membrane bending…

Yeah. We started to look at components of clathrin-mediated endocytosis. I never liked the idea that a molecule such as clathrin, which doesn't bind directly to membranes, could actually shape the membrane. It didn't make sense to me from a biophysical standpoint. So we decided to look at the direct membrane-binding proteins associated with clathrin-mediated endocytosis.

The first one we looked at was AP180, which caused a small level of membrane invagination in vitro. But when we looked at epsin it was much more startling. We crystallized epsin and found that it has an amphipathic helix that inserts into the bilayer to bend the membrane. It seemed inconceivable that epsin was the only protein doing this, so we went on to look at other molecules.

But our findings meant we could no longer think of membranes as a fluid mosaic of lipids and proteins; they must have a certain level of structure for the insertion of an amphipathic helix to bend them. So membranes are right at the fore of our thinking these days. We've recently gone back to exocytosis to ask what role membranes play in that process as well. We now talk about curvature stress—the idea that membranes are stressed by proteins—and that this stores up energy that can drive membrane trafficking processes forward.

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Text and Interview by Ben Short
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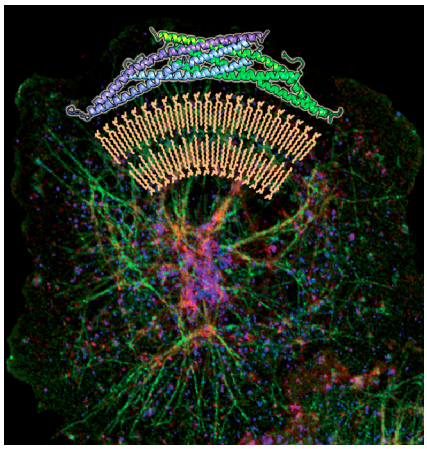

IMAGE COURTESY OF HARVEY McMAHON

The BAR domain of amphiphysin bends membranes, pulling out membrane tubules (green) in cells.

You recently described a protein that acts at the very earliest step of clathrin-mediated endocytosis…

If you want to make a clathrin-coated vesicle, you have to start bending the membrane at a very early stage. To do that, you need a protein that can take a flat membrane and gradually mold it into something that's much more curved, so it goes through a whole series of transitions. You should have a very strong phenotype if you knock out the protein that does that. But all the proteins we'd worked on in the past—epsins, amphiphysins, and so on—showed relatively mild phenotypes when they were depleted.

So we turned our attention to the F-BAR family of membrane-shaping proteins and started doing structural biology on many of them. There was some serendipity here because the first one that crystallized was FCHo2, and that turned out to colocalize completely with clathrin-coated vesicles. It's not actually incorporated into them, though, which is why people hadn't found it before.

FCHo2 is a protein that binds to an almost flat membrane, and, as it concentrates itself, it achieves a much higher curvature. Then it twists on the membrane and achieves a higher curvature still. So it's a protein that can adapt to a range of curvatures and thereby promote the early stages of membrane invagination. When we decrease FCHo2 expression, we get less endocytosis, and, when we increase its expression, we get more.

How is vesicle budding coordinated with cargo recruitment?

What makes clathrin so unique is the fact that it has a central organizer—the AP2 complex in the case of the plasma membrane—and a whole series of accessory proteins. We think that almost every clathrin accessory protein, if it interacts with and bends the membrane, will actually be a cargo adapter as well. In other words, the cell doesn't waste its time making proteins that bend the membrane without also bringing in cargo. So the whole thing integrates efficiently, and you can change the properties of the vesicle very easily by changing those accessory adapters in different cell types.

SHAPING THE FUTURE

Are there any principles that apply to all membrane-bending mechanisms?

Proteins that insert an amphipathic helix or some other domain into membranes tend to have a very strong effect on membrane shape, whereas a protein that scaffolds the membrane from the outside has a much weaker effect unless the protein oligomerizes. But I wouldn't call this a general principle because I think there are lots more possibilities. I actually think that we have only discovered the tip of the iceberg of proteins that affect membrane curvature. My feeling is that almost every membrane-binding protein, at some level, will influence membrane shape.

What are you working on now?

We're tremendously excited about clathrin-independent endocytosis. There are many different entry routes into the cell. Are they connected to particular signaling events or trafficking to a particular compartment? We think that they are. One way to get a handle on these different routes is to understand curvature. If you have a handle on the curvature mechanisms, you can modulate the pathways, as we can with FCHo2 and clathrin-mediated endocytosis.

We're still interested in the mechanisms of membrane fusion. We're trying to take the same network approach that we used to understand clathrin-mediated endocytosis to understand how the many different proteins involved in fusion can work together.

In general, although we're beginning to understand how membranes and organelles are shaped, we are still intrigued about how this relates to function. Membranes aren't just barriers—they all have shapes inherent to every organelle. And that shape is important—there's a reason each organelle is shaped the way it is. We just haven't figured all those reasons out yet.

What is the* Imagining the Brain *project?

Imagining the Brain is a public engagement initiative that aims to inspire the talented cohort of young artists in Cambridge schools to communicate the latest thinking in science, especially neuroscience. Yvonne Vallis from my lab gives talks on exciting topics to local schools, especially on subjects that the students say are really relevant to them. We put on a public exhibition of their artwork; the material from this initiative is being used all over the world, and examples are found on our web site (http://www.endocytosis.org/ImaginingTheBrain/).

We are absolutely committed to encouraging young people to look at science in a new way, and the feedback we've had has been brilliant. In fact, I just got an email yesterday saying, "I just got accepted into Cambridge, having been enthused about science through you," which is really great!

1. McMahon, H.T., and D.G. Nicholls. 1991. *J. Neurochem.* 56:86–94.
2. McMahon, H.T., et al. 1995. *Cell*. 83:111–119.
3. Schmid, E.M., et al. 2006. *PLoS Biol.* 4:e262.
4. Henne, W.M., et al. 2010. *Science*. 328:1281–1284.
5. Marks, B., et al. 2001. *Nature*. 410:231–235.
6. Peter, B.J., et al. 2004. *Science*. 303:495–499.
7. Martens, S., et al. 2007. *Science*. 316:1205–1208.

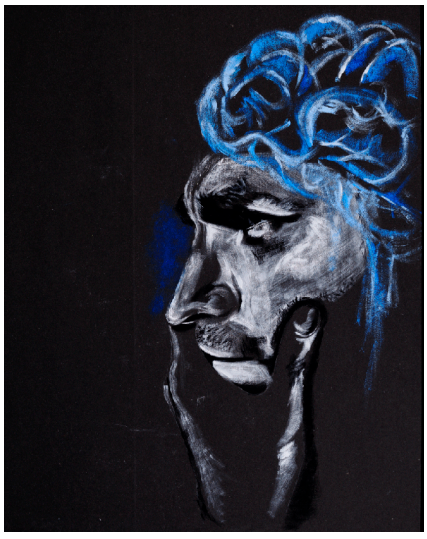

IMAGE COURTESY OF MU-CHEN CHIANG

"Scanning Beyond the Flesh," a submission to the *Imagining the Brain* project.

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