

## Heidi McBride: Mitochondria are well connected

McBride studies mitochondrial dynamics and mitochondrial trafficking with other organelles.

At the mention of mitochondria, do you visualize little lozenge-shaped organelles that sit passively in the cytoplasm, quietly brewing up ATP and only getting to do something exciting after being enlisted in an apoptotic cascade? That image, comforting though it may be, is woefully incomplete.

In fact, says McGill University's Heidi McBride, mitochondria are highly dynamic organelles that form an extensive network in the cell and that react to alterations in cellular homeostasis with dramatic physiological and morphological changes (1, 2). She should know, because she's studied mitochondrial biology since the start of her career (3), and her work has helped change the way other scientists view the organelle. McBride's lab has also shown that mitochondria are intimately connected to other organelles and to membrane trafficking pathways (4–6). Her group is currently exploring how these connections might impact phenomena as diverse as neurodegeneration and heart disease, she told us when we spoke with her recently.

### A NEW FIELD

#### *How did you decide to pursue a career in science?*

In high school I played a lot of music—saxophone, clarinet, flute, and piano—because I had to cover a lot of instruments in different stage, symphonic, and jazz bands. My music teacher encouraged me to go to McGill because of their music program, and I almost decided to study music when I went there for university. But I'd loved my science classes in high school, too. I remember being especially interested when we started to learn about photosynthesis because I grew up on a farm and it was fascinating to me how plants could make fuel from sunlight. I decided there would probably be more jobs in science, so I majored in biochemistry.

As an undergraduate I did lab work with John Bergeron, who is a cell biologist here

at McGill. Then I ended up doing my PhD with Gordon Shore, who was a good friend of John Bergeron's, because the things he had taught in my classes about mitochondrial protein import and the biogenesis of organelles had really caught my interest. My marks in school were never great, but Gordon was a farmer and knew I grew up on a farm, so I guess he hired me because he thought I'd work hard. [Laughs]

My main claim to fame in graduate school was the work I did showing that the transmembrane domains of some mitochondrial proteins can function as signal anchor sequences that target them to the mitochondrial outer membrane.

#### *You switched fields for your postdoc...*

Absolutely, because in 1996 when I got my PhD you couldn't really do a postdoc in mitochondrial cell biology. Even though we had no idea how mitochondria divide or move about in the cell, it wasn't obvious where to go to study those topics. People thought mitochondria were boring and we already knew everything about them: They make ATP. The import receptors had been identified, so many of the import labs were slowing down or switching to study apoptosis.

During my PhD I had become interested in how mitochondria move about inside the cell and communicate with the nucleus and

other organelles. At that time, many groups were reporting exciting discoveries about vesicular transport and how signal transduction cascades may modulate vesicle behavior, but

there was not much discussion about what regulates mitochondrial movement. Jodi Nunnari and that whole cohort of people who would go on to make major discoveries in mitochondrial biology were just one postdoc generation ahead of me, but the field was dormant when I started my postdoc.

Instead, I decided to study with Marino Zerial at the EMBL to learn about the building blocks of membrane dynamics: to understand how membranes move and how

**"Oh, they do a beautiful dance."**



Heidi McBride

PHOTO COURTESY OF HEIDI MCBRIDE

this is integrated with cell signaling. It was a transformative experience for me, extremely intense and inspirational. This experience fueled my return to mitochondrial dynamics in 2000 as an independent scientist at the University of Ottawa Heart Institute.

### A DYNAMIC DANCE

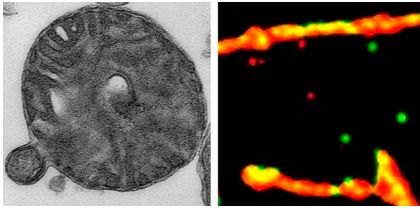
#### *What does one see when viewing mitochondria through a microscope?*

Mitochondria look like a network of worms. Depending on the cell type they may be more fragmented than contiguous, but—oh, they do a beautiful dance. Everyone who comes into the lab, even my six-year-old son, remarks on it. They move, they fuse, and they branch and turn around very rapidly. And they're doing all this while interacting with other organelles: the ER, endosomes, and so on. So they have to communicate a lot, and their behavior is highly regulated. We've been looking at the role of SUMO and various mitochondrial signaling pathways in regulating this behavior.

Early on we were looking at a protein called dynamin-related protein 1, or Drp1, which was known to be involved in mitochondrial fission. At the time it wasn't known how Drp1 activity was controlled. Then we identified SUMO1 in a yeast two-hybrid screen for Drp1 interactors back in the early 2000s. That was kind of frightening at first because SUMO is a transient modification that's nearly impossible to track, but we found that SUMOylation stabilizes Drp1 on mitochondria, especially during programmed cell death when mitochondria have to fragment.

SUMOylation becomes very stable during apoptosis but is lost during the cell cycle.

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**Left: Electron microscopy captures a vesicle budding off a mitochondrion. Right: Distinct mitochondrially derived vesicle populations contain different mitochondrial proteins (pyruvate dehydrogenase, red; Tom20, green) lying outside mitochondrial tubules.**

So we asked: What are the other SUMOylation substrates on mitochondria, and what enzymes regulate this process? We've been working on that for a decade. I wouldn't say we're there yet, but it's been a good ride.

#### *What about the other side of mitochondrial dynamics, fusion?*

My lab had spent a long time perfecting a mitochondrial fusion assay based on split-luciferase complementation. My colleagues at the Ottawa Heart Institute told me that the best currency of cellular stress is oxidized glutathione, so we threw that into our assay and got a massive stimulation of mitochondrial fusion. Then we looked at the mitofusins GTPases that drive fusion, and it turns out that the mitofusins undergo a disulfide-based switch that I think basically primes them for fusion.

Mitochondria have to fragment during apoptotic cell death, or have to be chewed up by autophagy, so the thinking in the field is that mitochondrial fusion may take place as an intermediate response to cell stress to protect against dying. Normally, in a homeostatic tissue, the stress will pass and everything goes back to normal. But there is some tipping point we don't really understand between when mitochondria are hyper-fused and the cell can still recover and when chronic stress flips the cell into death paradigms, where mitochondria fragment, their cristae remodel, and the cell is poised for death.

#### **INTERCONNECTED INTEROPERATION** *How do mitochondria engage with other organelles and trafficking pathways?*

Several years ago we were trying to find the mitochondrial SUMO E3 ligase on

mitochondria. We were systematically screening proteins with membrane domains and ring fingers that could be ubiquitin ligases or SUMO E3 ligases when we stumbled on a protein that we call MAPL and other people call MUL1 or MULAN. MAPL overexpression caused mitochondria to fragment, which was consistent with our idea about SUMO promoting fission. But my student kept showing me pictures of MAPL fluorescence in small dots everywhere in the cell. Eventually we used electron microscopy to figure out what was going on, and we were completely shocked to see these clear, electron-dense budded structures—vesicles—coming off the mitochondria. I'd never seen anything like it!

It took us a long time to figure out where these vesicles were going because they only go to a subpopulation of peroxisomes. Peroxisomes and mitochondria are intimately linked by a set of master regulator genes that control both mitochondrial and peroxisomal biogenesis. We theorize that these vesicles are part of a functional triad of metabolic flux between the ER, mitochondria, and the peroxisome.

#### *Under what conditions do these vesicles appear?*

Production of peroxisome-targeted vesicles isn't regulated by stress but does seem to be cell type dependent. This makes sense because peroxisomes also play cell type-specific roles, for example, in the production of bile in liver cells and of myelin in neurons. Interestingly, we've found that retromer complex containing VPS35 is required to generate these vesicles. Vps35 loss-of-function mutations are known to cause Parkinson's disease, so we wonder whether failure to traffic out of mitochondria is also implicated in neurodegeneration.

#### *You've shown that another population of vesicles traffics to lysosomes...*

From our imaging analysis, we knew there were more vesicles that did not target peroxisomes but rather were destined for lysosomes. We developed an in vitro reconsti-

tution system and showed that these vesicles are stimulated by stress and are enriched for oxidized proteins. There's significant traffic from mitochondria to lysosomes at steady state, so we think this is a mechanism that allows mitochondria to remove localized chunks of dysfunctional membrane and proteins. This pathway requires two additional Parkinson's related genes, PINK1 and Parkin, further fueling the concept that mitochondrial vesicle transport is likely implicated in disease.

I recently relocated my lab to McGill to expand my collaborative interactions with scientists working on Parkinson's, immunology, and heart disease. I've always wanted to take our work in a more translational direction, but the field was mechanistically limited until now. Luckily, the professors who trained me at McGill no longer think of me as Gordon's kid. [Laughs] But we still have a lot of work to do in trying to convince other cell biologists that mitochondria are part of their stories. When people start putting mitochondria in their pictures of endosomal, ER, and Golgi traffic, we will have done our jobs.

**"When people start putting mitochondria in their pictures...we will have done our jobs."**

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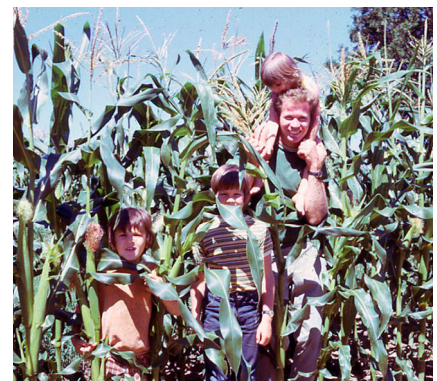


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**With Heidi on his shoulders, Heidi's father Izett stands beside her brothers Hugh and Kirby in their Westmeath, Ontario, cornfield in 1971.**