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First person – Stephen Coscia

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping researchers promote themselves alongside their papers. Stephen Coscia is first author on 'Myo19 tethers mitochondria to endoplasmic reticulum-associated actin to promote mitochondrial fission', published in JCS. Stephen is a PhD student in the lab of Dr Erika Holzbaur at the University of Pennsylvania, where he uses microscopy to study regulation of mitochondrial dynamics by the cytoskeleton.

How would you explain the main findings of your paper in lay terms?

Critical to cellular health is the proper regulation of mitochondrial division (or 'fission'), and we investigated how this process occurs. Often fission occurs where mitochondria contact another organelle – the endoplasmic reticulum (ER). These sites are maintained by ER-anchored actin filaments, but it is unclear how so. We reasoned that this 'F-actin' must be engaged by a mitochondrial protein and hypothesized that myosin 19 (Myo19) serves this role. Supporting our hypothesis, we found that in cultured cells, depletion of Myo19 led to more interconnected mitochondria, whereas overexpression of Myo19 led to fragmented mitochondria. This overexpression phenotype was dependent on (1) Myo19's ability to bind F-actin, (2) the presence of proteins that generate F-actin at mitochondria–ER contacts, and (3) the protein that completes fission, which is Drp1. Finally, we found that Myo19 depletion reduced mitochondria–ER contacts. Altogether these data indicate that Myo19 tethers mitochondria to ER-associated actin to promote mitochondrial fission, and the study raises several questions. Chief among them is in what ways is mitochondrial fission regulated via Myo19? We look forward to future work on this topic.

Were there any specific challenges associated with this project? If so, how did you overcome them?

We wanted to examine if Myo19 maintains mitochondria–ER contacts, and since our lab has a lot of experience with light microscopy, our first approach was to fluorescently label mitochondria and the ER in cultured cells and then assess the degree of overlap between these two organelles. Hindering the success of this experiment, however, we found the diffraction-limited ER signal occupied much of the cytosolic space at baseline. At the same time, I was grant writing and was prompted to think of alternative methodologies to incorporate into the project, which led me to an excellent paper from the lab of Dr Jeffrey Golden where the authors implemented a split-luciferase mitochondria–ER contact reporter. This reporter emits luminescence whenever mitochondria and the ER are in close proximity, so its intensity is informative in a manner not influenced by the diffraction limit. Dr Golden was kind enough to send us the necessary constructs, and we found luminescence was decreased with Myo19 knockdown, consistent with our hypothesis that this protein maintains mitochondria–ER contacts.

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Stephen Coscia

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

Myosin family proteins can convert chemical energy into mechanical energy by processing ATP and in turn swinging a rod-like 'lever arm' domain. This capability is key to the function of most myosins, allowing them to transport cargo, generate tension across F-actin, etc. Thus, we assumed that Myo19's full mechanochemical cycle was essential to this motor's ability to fragment mitochondria. Surprisingly, mitochondria still fragmented upon overexpressing a Myo19 mutant that had a shortened lever arm. One explanation was that lever arm swinging is dispensable for Myo19-mediated mitochondrial fission, and that the 'motor' is really just functioning as a nucleotide-sensitive tether. Follow-up experiments supported this hypothesis, adding Myo19 to the short list of myosins for which simply F-actin binding and unbinding can be sufficient. I'm glad we kept an open mind for the unexpected.

Why did you choose Journal of Cell Science for your paper?

Our reasons for choosing JCS for our paper were twofold. First, there had been great papers on Myo19 in the journal, and we wanted to build off the findings they detailed. Second, we appreciated that these papers were far from the only ones in JCS that featured exciting results and rigorous science, and we hoped our paper fit this same mold.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

Each of the senior authors on the paper have served as mentors, providing critical guidance to the science but also helping outside of the lab. Outside of the lab, through classes, journal clubs or just

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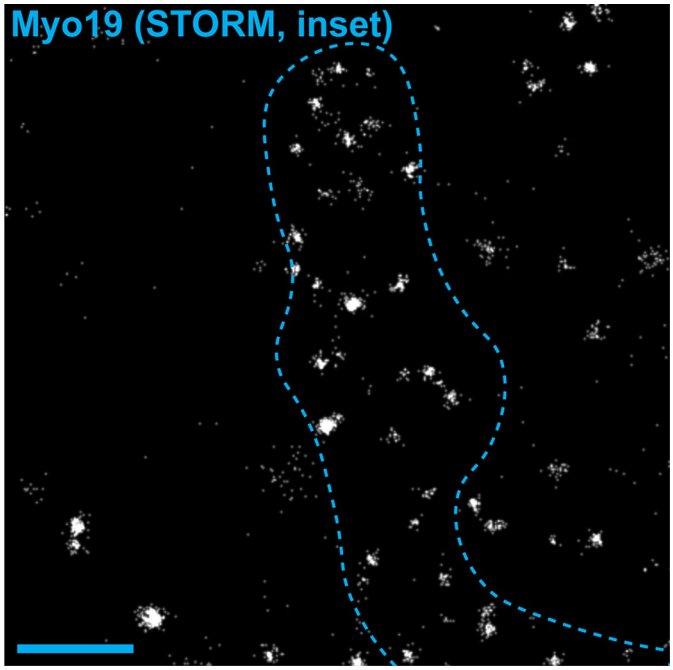

Stochastic optical reconstruction microscopy image of endogenous myosin 19. The dotted blue line represents the outline of an individual mitochondrion. Scale bar: 0.5 µm.

informal conversations, they've shared their perspectives on papers or themes in the field, and they've showed me the value and power of mechanistic cell biology. My thesis advisor Dr Erika Holzbaur has often urged me to 'go deep' with my scientific pursuits, and I hope my dissection of Myo19's involvement in mitochondrial fission reflects this advice.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

Early biology courses and research experiences gave me a general interest in a science career. I felt the subject matter was interesting in its own right and also appreciated how those in science possessed a special ability to help others by advancing the borders of medicine. Still, instrumental to committing to a career in science was attending the American Society for Cell Biology annual meeting for the first time. There, I saw the breadth of work being done and got excited to jump in.

Who are your role models in science? Why?

Over the course of graduate school, I have met scientists at all levels (graduate student, post-doc and professor) who are fearless in their work, always willing to learn something new, and also generous colleagues, who take the time to mentor others with no strings attached. I feel lucky to have met so many of these people throughout my PhD, and know I will try to emulate their approach to science throughout my career.

Tell us something interesting about yourself that wouldn't be on your CV

Late in college, I made a 180 degree turn in my studies, switching from history to biology. I still love the former subject though – historical non-fiction is my preferred pleasure reading material and sometimes I just look over old maps for fun!

Reference

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