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FIRST PERSON

First person – María Gabriela Otero

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Maria Gabriela Otero is the first author on 'Proteasome stress leads to APP axonal transport defects by promoting its amyloidogenic processing in lysosomes', published in Journal of Cell Science. María conducted the research in this article while a PhD student in the lab of Tomás Falzone at the Instituto de Biología Celular y Neurociencias, Universidad de Buenos Aires, Argentina, but is now a postdoc in Tyler Pierson's lab at the Board of Governors Regenerative Medicine Institute – Cedars-Sinai Medical Center, Los Angeles, USA, investigating pediatric neurological disorders.

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

Among other features, the brain of a patient with Alzheimer's disease is characterized by the abnormal accumulation of fragments of the amyloid precursor protein (APP) that stick and clump together in the form of plaques. This accumulation was suggested to be caused by failures of the cell's 'garbage disposal', the protein degradation system in neurons. APP is massively distributed and is constantly moving within the cell using a 'highway' to reach its final destination where it performs its function. What would happen within a neuron if APP cannot be distributed correctly? In the paper, we show that impairments in the garbage disposal system redirect APP from the highway and trap it in the cell body, making it unable to function where it is needed. In addition, once the protein is trapped, its fragmentation begins. This occurs by means of a novel and coordinated cross-talk between different systems involved in protein degradation. We suggest that this excessive and abnormal accumulation of APP fragments may contribute to the formation of the plaques mentioned above and, therefore, to the onset of the disease.

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

We wanted to test if proteasome impairment modifies cleavage of the transmembrane protein APP at the plasma membrane in living cells. To solve this challenge we partnered with Valeria Levi, who showed us how to perform a fluorescence cross-correlation spectroscopy analysis. This method, based on the analysis of intensity fluctuations, allowed us to measure dynamic processes in the cell under physiological conditions. We transfected cells with N- and C-terminus fluorescently double-tagged APP, which allowed us to see changes in the full-length protein. The intensity of each colour was collected simultaneously and the fluctuations analysed with or without treatment.

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

My 'eureka' moment was when I saw live imaging for the first time. Seeing organelles moving throughout an axon back and forth like cars on the highway was incredible. I remember that day like it was yesterday.

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María Gabriela Otero

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

We chose Journal of Cell Science for its long-standing tradition of publishing ground-breaking basic research on experimental cell biology. Our work fits perfectly with the journal scope, and our previous work that described the axonal transport properties of the proteasome complex for the first time was published in Journal of Cell Science (Otero et al., 2014). We thought it would be an excellent opportunity to complete the story with this newly discovered role of the proteasome complex in axonal transport regulation of APP. These new findings describe an important molecular pathway that bridges protein degradation defects and Alzheimer's disease progression.

"Seeing organelles moving throughout an axon back and forth like cars on the highway was incredible."

Have you had any significant mentors who have helped you beyond supervision in the lab?

I'm thankful to my PhD mentor Tomas Falzone. He gave me freedom to think and conduct the experiments, but he was always willing to discuss the results and talk about future experiments. He was supportive and patient at all times, and taught me to be critical of my own work.

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?

I knew that I wanted to pursue a career in science when I took a chemistry course in high school. I was fortunate to have a truly inspiring teacher who went above and beyond teaching academic content – she would also let us experiment with her and show us how to apply chemistry in our daily lives. She not only shared her

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knowledge with me, but also passed on her passion for chemistry, teaching and research.

Who are your role models in science? Why?

I cannot pinpoint anyone in particular. My role models in science have been the people with a drive to help others and shows passion for their work, critical thinkers humble enough to teach and spread their knowledge, the ones who can step back and admit their mistakes, and most importantly, the people that can be patient and persistently reach for their goals.

What's next for you?

I've started my postdoc investigating pediatric neurological disorders. In the future, I would like to continue my research in the cell biology field and start my own laboratory.

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

I consider myself an experimenter, inside and outside the lab. When I'm not working, I love trying new things, whether it's visiting places I've never been, going to different beaches, preparing recipes that let me combine ingredients in novel ways or just hitting the open road with no destination in mind.

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