

FIRST PERSON

First person – Ana Julia Fernández-Alvarez and María Gabriela Thomas

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. Ana Julia Fernández-Alvarez and María Gabriela Thomas are co-first authors on 'Smaug1 membrane-less organelles respond to AMPK and mTOR and affect mitochondrial function', published in JCS. Ana Julia and María Gabriela (Gabi) are both Research Associates in the lab of Graciela Boccaccio at Fundación Instituto Leloir, Buenos Aires, Argentina, where they investigate the cellular biology of RNA granules.

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

A.F.-A. and M.G.T.: Here we dive deeply into the understanding of the function of a protein called Smaug1. We have been studying this amazing protein for years, and we still have a lot to learn. We know it binds RNA, keeping it in a sort of 'dormant' state, i.e. preventing the mRNA to be translated into proteins. We also know that Smaug is widely expressed in all organisms and cell types, and what is even more intriguing, Smaug and related proteins form 'biocondensates' or 'membrane-less organelles' (MLO). Smaug MLOs belong to a growing family of novel cellular bodies whose formation and function are just beginning to be known. In the present paper, we show that Smaug MLOs have an outstanding function in the regulation of mitochondrial respiration. Disruption of Smaug MLO formation dramatically affects mitochondrial morphology and function. Our results strongly suggest that Smaug MLOs serve as knobs that coordinate the biogenesis of the respiratory machinery. Relevant to this, defective Smaug function is known to affect muscular and neuronal cells, which are highly dependent on mitochondrial respiration as a source of energy. Our aim is to continue our work on expanding our findings to different physiological systems.

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

A.F.-A.: The first challenge during our research was silencing the expression of Smaug1 protein. Canonical silencing using certain siRNAs resulted in an increased level of mRNAs in our cellular system. After several trials, we finally found a combination of 3'UTR-targeted siRNA that produced a significant decrease in protein expression. We believe this effect is due to the expression of alternative isoforms. We found that the siRNAs that produced a misleading effect were targeting inside or near the alternative second exon, which further codifies a circular RNA. To address the mechanisms implicated by this issue is part of our future plans.

M.G.T.: Another challenge was the acquisition of live-cell movies. At that time, there was a new microscope in our institute, equipped with a heated platform and a controlled CO₂ flux chamber, and it was



Ana Julia Fernández-Alvarez (right) and María Gabriela Thomas (left)

the first time we performed this type of experiment. We had to learn how to grow the cells in small chambers and how to take sequential images without losing the Smaug1 MLOs' plane. The most difficult part was to treat the cells with the different drugs without moving the platform. It was really amazing when we finally got it and it was the beginning of a series of very inspiring experiments!

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

M.G.T.: Yes! My 'eureka' moment was when I realized that the mitochondrial phenotype changed dramatically after silencing Smaug. In control cells, mitochondria are large and elongated, like a plate of spaghetti. After Smaug silencing, mitochondria became fragmented, like a plate of gnocchi!

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

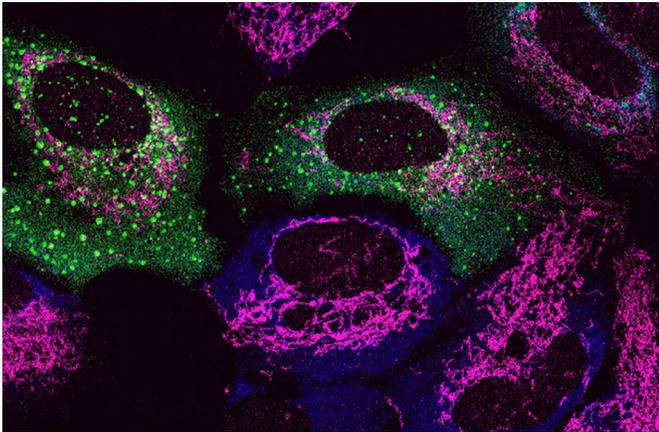
A.F.-A. and M.G.T.: Journal of Cell Science is well known in the field of cell biology and publishes very nice and solid articles. JCS is definitely one of our favourites when choosing papers for our journal club, and we felt that it was perfect for our paper. We have previously published in JCS. The submission process was always challenging and the interaction with the editorial board turned into exciting improvements. We are proud of being part of JCS.

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

M.G.T.: We both work together with our PI Graciela. We complement each other in a magnificent way. Ana does all the molecular experiments and most of the biochemical work, and I focus on the imaging.

A.F.-A.: We work like a real team!

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Smaug1 MLOs observed under the 63× objective of the confocal microscope in the cytoplasm of U2OS cells. Mitochondria (magenta) are elongated and branched and EIF3 η (blue) remains cytoplasmic and not condensed at basal conditions. Smaug1 MLOs are in green.

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?

A.F.-A.: I first got excited by science at high school when I had my first chemistry classes. Getting to discover the amazing universe of chemical processes was what caught my attention at the beginning. Thanks to an old family friend, I finally decided to study biochemistry at the University in Buenos Aires and there I got interested in cell biology and decided to follow a scientific career. The difficult economic situation in our country around 2000 motivated me to move to Spain to do my PhD, where I met my first laboratory director. His enthusiasm while telling the story of the production of a protein crystal as if it was a Hollywood film definitely settled my path into science.

M.G.T.: I went to a high school that specialized in biology and I really enjoyed learning about all the processes related to human biochemistry and biology. I studied biochemistry at Universidad Nacional del Sur in my hometown, Bahía Blanca. When I was finishing my degree, I got a scholarship to work in a scientific laboratory as a student, and this was the beginning of this adventure! Then I moved to Buenos Aires for my PhD and I am still here. In all those steps, I had the chance to meet very

enthusiastic people who encouraged me to continue in this fascinating world.

Who are your role models in science? Why?

M.G.T.: I don't have a specific role model; I admire all those scientists, specifically women, who work hard to succeed in the academic world. It is especially difficult to maintain the balance between work and family, without being pushed away from the scientific system. Additionally, we live in a low-income country and it is really hard to get funding here! So I really admire all those colleagues that make it.

What's next for you?

A.F.-A.: I really like academia and I am not planning to leave it at all. Besides the Smaug project where a lot of work is still to be done, I am currently working on a new amazing project on the dynamics of stress granules, which we hope will be part of a new paper.

M.G.T.: I will continue working on Smaug; we still have many experiments to do! I have a research position in the National Council for Scientific and Technical Research, so I will continue advancing my career in academia.

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

A.F.-A.: I am mother of two children who are slowly becoming a little bit more independent, which allowed me to start to entertain myself with two very different hobbies. First, I started to study photography and I am happy to develop very nice images of my family and friends. More recently, I started playing soccer, something not only fun but healthy!

M.G.T.: I have an entertaining hobby. I make trencadís and venetian mosaics. I decorate stuff from small things to relatively large murals. I really love it! I also workout three times a week to keep myself healthy. Last year, I studied some photography together with Ana, but clearly she is much better than me! My family, the most important thing to me, includes my two kids, a husband and a dog. You can see that I never get bored!

Reference

Fernández-Alvarez, A. J., Thomas, M. G., Pascual, M. L., Habif, M., Pimentel, J., Corbat, A. A., Pessoa, J. P., La Spina, P. E., Boscaglia, L., Plessis, A. et al. (2022). Smaug1 membrane-less organelles respond to AMPK and mTOR and affect mitochondrial function. *J. Cell Sci.* **135**, jcs253591. doi:10.1242/jcs.253591