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FIRST PERSON

First person – Shweta Yadav

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. Shweta Yadav is the first author on 'RDGBα localization and function at membrane contact sites is regulated by FFAT–VAP interactions', published in Journal of Cell Science. Shweta is a post-doctoral associate in the laboratory of Prof. Juan Botas at Baylor College of Medicine, Texas, USA, investigating neurodegenerative diseases.

Shweta Yadav

How would you explain the main findings of your paper to non-scientific family and friends?

All living organisms are made up of small functional units, called cells. Cells can be considered as factories or organizations, which have multiple specialized sections and/or units with specialized roles to perform (called organelles). Although each unit works independently, they need to talk to each other in order to shape the final output of the organization. The work presented in the paper describes the detailed mechanism of how two organelles of the cell, the plasma membrane (PM) and the endoplasmic reticulum (ER), transfer information in order to maintain their ability to respond to outside stimuli. There are two broad messages: first, cells have evolved ways to increase the efficiency of inter-organelle information transfer by bringing them in close proximity at specialized sites known as 'contact sites'. The work presented in the paper describes how a protein functions to transfer molecules across the PM–ER contact sites at these sites and is essential for signalling. Second, during the course of evolution, the same protein modules (domains or motifs) are often found in combination with other proteins, in order to impart specialized functions and properties. For example, we show that a single protein domain, the phosphatidylinositol transfer protein domain (PITPd), is synthesized by the cell as part of a multi-domain protein in order to impart spatial enrichment and to regulate its activity.

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

Yes, there were a couple of challenges. The project was aimed at understanding the function of lipid transfer proteins, which had been identified in *in vitro* assays. These proteins were hypothesized to transfer single lipid molecules, which is difficult to visualize *in vivo*. *Drosophila*, as a model organism, offered great help in understanding the molecular basis of the function of these proteins *in vivo* by complementing the findings of biochemical assays performed *in vitro*. One specific challenge – which laid the foundation of this paper – was an unexpected result that was obtained during the course of our study. It was an established notion in the field that the PITP domain of the retinal degeneration B (RDGB) protein was key to its activity and sufficient to support its function *in vivo*. However, we noticed that the PITP domain failed to support its function in some specific experiments. Our observation initially seemed to go against the published results, although a detailed analysis helped to clarify the differences between our obtained data and previously published results. Subsequent experiments to understand the basis of this failure to rescue through the PITP domain indirectly highlighted the significance of another cellular specialization of photoreceptors, namely sub-surface cisternae, as a means to adapt to conditions where cells are continuously exposed to bright light.

"It was exciting to find something new, which went against the established dogma"

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

RDGB is a large protein with multiple domains besides the PITP domain, but it was accepted in the field that only the PITP domain was important and the rest of the protein was dispensable *in vivo*.

Shweta Yadav's contact details: Botas Lab, Suite 1050, NRI building, 1250 Moursund Street, Baylor College of Medicine, Texas, U.S. 77030.
E-mail: shweta@ncbs.res.in

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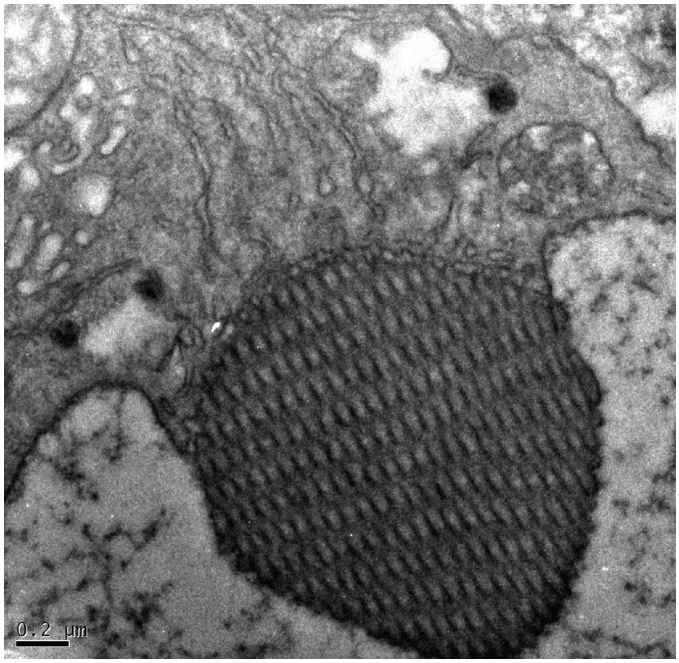

EM showing the apical membrane (rhabdomere) of the y photoreceptor. Tubules of ER can be seen near the base of the rhabdomere, making stable PM–ER contact sites.

Why would the cell spend so much energy in synthesizing a large protein when only a small segment performs its function? I lived with this accepted notion until I found this failure of complete rescue with the PITP domain in one of the experiments with modified light exposure of flies. It was exciting to find something new, which went against the established dogma, but it also gave me a hard time. Since the results were the opposite of what's accepted in the field, I had to wait to report it and to be patient until I could nail down the molecular basis of the results I had obtained.

Have you had any significant mentors, and how have they helped you?

I am thankful to my PhD mentor, Dr Raghu Padinjat, for his guidance and support. I learnt a lot under his mentorship. The present manuscript is an outcome of the intellectual freedom that I received in the lab. I am also thankful to Prof. Shamshad Cockcroft for critically reviewing the manuscript in its initial stages and for giving suggestions.

"…we should not keep negative and unexpected observations to ourselves just because we cannot explain them"

What's the most important piece of advice you would give first-year PhD students?

A PhD is a learning experience. Failures and unexpected results are part of the training and should always be accepted with a positive attitude. One should try to look for lessons that can be learnt from failures. We often anticipate results based on our hypothesis, but one should always be open to alternative or negative results as sometimes they point towards less understood and exciting findings. I think we should not keep negative and unexpected observations to ourselves just because we cannot explain them.

What changes do you think could improve the professional lives of early-career scientists?

One of the biggest challenges for early-career scientists is the shift from doing bench work to organizing and running a lab. We often don't get assistance or prior training for this. Depending on the scientific group in which one has worked before, people get different exposure to management skills. It would be great to introduce ways to train people during their post-doctoral work, thereby increasing their confidence.

What's next for you?

I have finished my PhD from National Centre for Biological Sciences (NCBS, India) and have recently joined Juan Botas's lab at Baylor College of Medicine, in Texas, for my post-doctoral research. Here, I will be working on neurodegenerative diseases.

Reference

Yadav, S., Thakur, R., Georgiev, P., Deivasigamani, S., Krishnan, H., Ratnaparkhi, G. and Raghu, P. (2018). RDGBα localization and function at membrane contact sites is regulated by FFAT–VAP interactions. *J. Cell Sci.* **131**, jcs207985.