

FIRST PERSON

First person – Amit Sharma

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. Amit Sharma is first author on 'Transgelin-2 and phosphoregulation of the LIC2 subunit of dynein govern mitotic spindle orientation', published in *JCS*. Amit conducted the research described in this article while a PhD student in Dr Sivaram V. S. Mylavarapu's lab at the Regional Centre for Biotechnology, NCR Biotech Science Cluster, Haryana, India. He is now a post-doctoral fellow in the lab of Dr Laurence Pelletier at the Lunenfeld Tanenbaum Research Institute, Toronto, Canada, where his area of interest is cell division and cancer.

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

Most cells divide through a highly dynamic but tightly regulated process known as mitosis to help the body grow and develop properly. Mistakes during mitosis lead to aberrant growth and development, and often to deadly diseases like cancer. One key event early during mitosis is the proper positioning and orientation of the mitotic spindle within the mother cell, a process crucial to deciding the proper axis of body growth, organ development and maintenance of stem cells. The mitotic spindle largely consists of thread-like dynamic microtubules that radiate outward from the two nucleating centres at its two ends, the 'spindle poles'. To properly orient the spindle within the mother cell, similar to a hammock being properly tied between two trees, sufficient numbers of microtubules must nucleate and radiate outward from each pole, and then be 'captured' by proteins resident at the cell boundary (cortex), thus anchoring the spindle to the cortex. The intracellular transport motor dynein, a multi-protein assembly present both on spindle poles and at the cortex, is indispensable for both these processes of microtubule nucleation and cortical capture to orient the spindle. Through our research, we have identified two new mechanisms used by the dynein motor to orient the mitotic spindle. First, we showed that a specific chemical modification (phosphorylation at amino acid residue 194) of the LIC2 protein component of dynein must occur in the mitotic cell for the spindle poles to remain intact and nucleate sufficient numbers of microtubules. Second, we discovered a new interaction accomplice of dynein located at the cortex, transgelin-2, which helps maintain proper levels of two crucial cortical capturing proteins, LGN and NuMA, thereby helping to properly orient the mitotic spindle. This is a new function discovered for transgelin-2, which was otherwise known to help string together the fibrous actin skeleton of the cell at the cortex. Our study suggests that the functions of dynein in ensuring proper spindle orientation and completion of cell division may be more intricately regulated than we had known so far.

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

One of the biggest challenges was to identify new protein interactors of the LIC2 dynein motor protein that performed specific roles in



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mitosis and mitotic spindle orientation. We found some of the interactors of LIC2-dynein, which could be potential interactors with a specific role in mitosis. To ascertain the role of these proteins, we performed extensive live-cell and fixed-cell imaging and analysed the data for various interactors. Through this process, we discovered that transgelin-2 is a novel interactor of LIC2-dynein that has a role in mitosis by regulating spindle orientation by regulating the localization of cortical machinery (LGN-NUMA) at the cell cortex. Our study also shows that the two closely related vertebrate dynein complexes (LIC2-dynein and LIC1-dynein) could sometimes interact with unique interaction partners to perform unique, non-overlapping functions in mitosis.

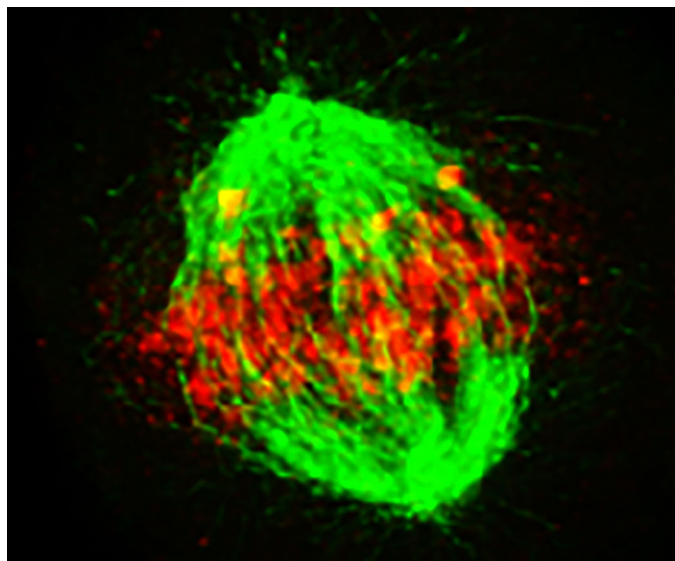
When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

The most important and striking result for me was the mis-localization of the cortical machinery (LGN-NUMA), which captures astral microtubules, upon depletion of transgelin-2. This gave us the hint about the possible molecular mechanism for the regulation of spindle orientation. Ultimately, we found that it is likely to be the fine balance between LIC2-dynein, which carries spindle orientation molecules towards the pole, as opposed to transgelin-2, which stabilizes these cortical molecules at the cell cortex.

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

Journal of Cell Science has a good reputation in the field of cell biology. Most of the articles in this journal are of high quality and have made significant contributions in their respective fields. Moreover, the review process at *JCS* is thorough, quick and transparent, which help improve the manuscript significantly and scientists/authors to publish their work in quick time.

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The mitotic spindle of a metaphase HeLa cell. The image shows the spindle and astral microtubules (green) and the kinetochores (red).

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

My PhD supervisor Dr Sivaram V. S. Mylavarapu has had a significant contribution in shaping my career and helping in developing critical and independent thinking, which is an essential ingredient for any scientist to be successful later in their research projects. He always pushed us to read a lot of new articles related to our work. He always used to say “you are the driver of your own project”. This holds true, in the sense that he is there to guide us, but in the end, it is you who has to think about your project and experiments in detail. In the end, I would say it was great to have a mentor like him. He always guided and supported me during troubled times in the experiments. His encouraging words were always helpful to motivate me to plan and perform experiments meticulously and reproducibly.

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 think it is my inquisitiveness to know about new things that happen around us. Similarly, in science there are a lot of things that we still do not understand fully. So, every day, there is the challenge to find something new. Moreover, doing science gives me autonomy and problem-solving skills. I enjoy being in science and I think the most interesting things are the positive results that you get sometimes after facing several failures.

Who are your role models in science? Why?

There are many role models in science; it is hard to pinpoint one role model. But I think the scientists in the bygone eras are the real role models. The way they thought about problems was amazing, in the sense that despite the lack of today’s facilities in that time, they made great contributions to humanity, such as the discovery of gravitational forces (Newton) and the discovery of antibiotics (Alexander Fleming). We are still using their concepts to build further knowledge.

What’s next for you?

Currently, I am working as a post-doctoral fellow in Mount Sinai hospital in Toronto. I would like to continue my career in academia, since academia offers the freedom to work on problems that interest you. The industry requires more streamlined and goal-oriented work, which is quite necessary to combat disease, as we are seeing now with the global COVID-19 outbreak. However, I believe that I would be able to make my best contributions to science and humanity when I have the freedom to study something that excites me, which is more likely to be possible in academic research.

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

In my free time, I like to explore new places and party with friends. I enjoy watching and playing badminton, cricket and chess. These hobbies help me in rejuvenating and relaxing after hectic lab work schedule.

Reference

Sharma, A., Dagar, S. and Mylavarapu, S. V. S. (2020). Transgelin-2 and phosphoregulation of the LIC2 subunit of dynein govern mitotic spindle orientation. *J. Cell Sci.* **133**, jcs239673. doi:10.1242/jcs.239673