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FIRST PERSON

First person – Ashok Kumar

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. Ashok Kumar is the first author on 'A predicted unstructured C-terminal loop domain in SIRT1 is required for cathepsin B cleavage', published in Journal of Cell Science. Ashok performed the research in this article while working as a postdoctoral research fellow in the lab of Mona Dvir-Ginzberg at the Hebrew University of Jerusalem, Israel. He is now a research associate in Prabodh Kapoor's lab at the University of Texas, USA, investigating how post-translational modifications regulate gene expression and their impact on metabolic disease in the context of ATP-dependent chromatin remodellers such as INO80.

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

The cell is the basic unit of life. It contains DNA, RNA, proteins and many other cellular components performing their jobs in a directed way, in the same way that actors playing their role in a movie are controlled by a director. If the director is doing a good job then that will produce the best outcome from the actors, but sometimes directors are also stressed or influenced by the actors. Sirtuin1 (SIRT1) is one of the proteins that regulates many other proteins by controlling their performance. This work focused on the structure of SIRT1 and how it works together with a protein-cutting molecular 'scissor' called cathepsin under inflammatory stress and ageing. Cathepsin levels increase under conditions of inflammation and cut SIRT1 at one of its unstructured regions. This cut generates an inactive fragment called 75SIRT1, as previously reported by the Dvir-Ginzberg group to play a part in the age-related joint disease osteoarthritis. We removed this unstructured component from SIRT1 and were able to generate a novel mutant that maintains many of SIRT1's activities, yet renders the mutant resistant to the molecular scissors. To summarize, we tried to provide a superpower for the movie director (SIRT1) in the form of the ability to close the set (a mutant form of SIRT1) so that interference from the actors (cathepsins) is minimized.

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

The challenge in this project was to test the hypothesis that cleavage of full-length SIRT1 (flSIRT1) occurs at a specific amino acid (H533) site, as previously described by the Dvir-Ginzberg group. When examining different tissues we were able to see slight shifts in the cleaved variant (75SIRT1) surrounding this 75 kDa region, indicating that the sequence is not a strong contributor to cleavage, which we were able to later confirm by point mutation of H533. Molecular modelling and docking of flSIRT1 with cathepsin B provided the first insight indicating that a structure embedded in SIRT1 is susceptible to cleavage, which was unexpected based on our previous work. This was confirmed after ablating this region and generating a SIRT1 mutant that is resistant to cathepsin B cleavage.

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Ashok Kumar

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

During my PhD, I was exposed to the high-quality work published in Journal of Cell Science, and hoped that someday my work would also be showcased in this journal. I am glad that our work passed the rigorous review process and was found to be suitable for the journal. I believe that the review process is thorough yet efficient and provides an excellent platform for early-career scientists to promote their quality research.

"These interactions motivated me to serve humanity by making significant contributions to research."

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

I would say Prof. Mona Dvir-Ginzberg was the first mentor who really understood me and my capabilities. I came to her with knowledge in molecular and structural biology, and she provided me with all the opportunities to explore molecular biology and learn epigenetics and cell biology. Her immense support and scientific guidance helped me to continue my journey in further exploring chromatin dynamics. Her input in this study was very helpful in accomplishing the project objectives. She is helpful, friendly and always thoughtful to her students.

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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?

The turning point of my academic career was qualifying for a master's program with a competitive scholarship to study at Guru Jambheshwar University of Science and Technology at Hisar, Haryana, India. I got the opportunity to complete my master's project in the Department of Food Irradiation and Processing laboratory at the Bhabha Atomic Research Centre, Mumbai, India. There, I was exposed for the first time to highly impressive scientists who challenged me intellectually during my time at this renowned institute. These interactions motivated me to serve humanity by making significant contributions to research. Working in such an environment for four months prompted my interest in a scientific career and helped me decide to pursue a PhD.

Who are your role models in science? Why?

My role model in science is Dr A. P. J. Abdul Kalam, the 11th President of India and a nuclear scientist who developed ballistic missiles in India and thus made great contributions to India's national security. He started his journey in a small village but went on to achieve the Bharat Ratna, India's highest civilian honour. His ideology made a major impact on my life and drove me in my career path.

What's next for you?

I am undertaking my second postdoc at University of Texas Health Science Center at Tyler, Texas, USA, in the area of proteins involved in chromatin remodelling. I am currently exploring the role of ATP-dependent chromatin remodellers in cancer biology and also trying to understand the function of nuclear actin and its post-translational modifications in the context of gene regulation.

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

I believe in spirituality and like to meditate, which helps me keep calm and focused. I love cooking and making delicious dishes for my loved ones and am inspired by the Indian chef Sanjeev Kapoor.

Reference

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