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FIRST PERSON

First person – Varun Jayeshkumar Shah

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. Varun Jayeshkumar Shah is the first author on 'CRL7^{SMU1} E3 ligase complex-driven H2B ubiquitination functions in sister chromatid cohesion by regulating SMC1 expression', published in Journal of Cell Science. Varun is a PhD student in the lab of Dr Subbareddy Maddika at the Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad, India, investigating the role of LisH-domain-containing proteins in the assembly of multi-subunit E3 ligase complexes.

Varun Jayeshkumar Shah

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

Cells are the basic functional units of our bodies. In order to grow, organisms make new cells through the process known as cell division. The cell cycle involves two phases – the first phase, interphase, is where the cell grows, duplicates everything and prepares itself for cell division. The second phase is mitosis, where actual division of the cell occurs. The information regarding when to divide and grow is retained in the genetic material of the cell, which is stored in the form of chromosomes. These chromosomes are thread-like structures comprising DNA and protein, located in the nucleus of the cell. During the interphase preparation step the chromosomes are duplicated, resulting in the generation of paired matching chromosomes. These two copies of the chromosomes are generally held together by a ring-like structure called a cohesin ring. Various proteins, such as SMC1a, SMC3, SCC1 and SCC3, are part of this complex. When the cell enters mitosis, these paired chromosomes are faithfully separated into two daughter cells. To allow equal distribution of chromosomes into daughter cells, the parent cell needs to remove these rings from the chromosomes. In our study, we have identified enzymatic machinery (CRL7^{SMU1}) that is required for the synthesis of one of the cohesin ring complex proteins, SMC1a. Consequently, we showed that loss of CRL7^{SMU1} complex proteins in cells resulted in unequal distribution of chromosomes followed by defective cell division.

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

In the early days, we were quite successful in figuring out that CUL7 can act as a scaffolding protein, DDB1 as an adaptor protein and SMU1 as a substrate recognition protein of the cullin RING-type E3 ligase (CRL) complex. However, identification of the substrate and the E3 ligase associated with the complex was challenging. The presence of multiple E3 ligases in the list of SMU1 purified protein complexes was puzzling and pushed us to investigate which one acts as the E3 ligase of the complex. I performed various pull-down and co-immunoprecipitation experiments, identifying RNF40 as the E3 ligase of the complex. However, that was not the end of our challenges, as we later struggled to identify the substrate of the complex. Finally, through knockdown and interaction studies we identified that H2B is a substrate of the CRL7^{SMU1} complex.

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

There were many eureka moments at different stages of the project but I would like to highlight two of them here. The first was the time when I found that SMU1 assembles a new CRL-type E3 ligase complex – CRL7^{SMU1}. The second one was when I observed that loss of all CRL7^{SMU1} complex proteins resulted in defects in sister chromatid cohesion.

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

I am fortunate to have been surrounded by great mentors throughout my career. My current mentor, Dr Subbareddy Maddika, has played a significant role in shaping my career as a researcher. His remarkable patience, quest for critique, reasoning and constant learning are qualities I would like to pursue. Additionally, he understands my weaknesses and strengths, and has helped me to improve on both a professional and personal front. He has been a source of constant motivation (especially when I was feeling low) and inspiration. I have also been lucky to have mentors like Dr Neeraj Singh, Dr Rupesh Jha and Dr Jagneshwar Dandapat, who have always given me unconditional support and guidance, and encouraged me to do my level best.

Varun Jayeshkumar Shah's contact details: Centre for DNA Fingerprinting and Diagnostics, Nampally, Hyderabad 500 001, India.

E-mail: varun@cdfd.org.in

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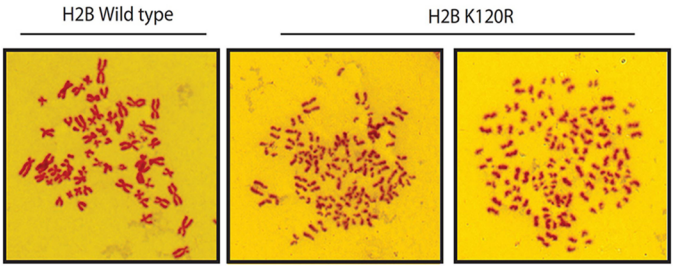

Chromosome spreads prepared from HeLa cells transfected with H2B wild type and K120R mutant.

“…a student first needs to learn how to choose the right question.”

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

The scientific question that you want to address matters the most in research. That’s why I believe a student first needs to learn how to choose the right question. Once the question is decided, students need to invest most of their time in meticulous planning and execution of experiments where hard work, perseverance and patience matter the most. Additionally, be curious, be thorough with the literature and develop a passion for asking questions, as these are the qualities that will take you to the next level. Finally, learn the art of communicating science because this skill makes a huge difference in the scientific career of any researcher.

What’s next for you?

Currently, I am writing up my thesis and will be submitting soon. After that, I will be looking for suitable postdoc positions where I can utilize my expertise and address unanswered questions in the broad field of cell biology.

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

Apart from science, I like to run and listen to music.

Reference

Shah, V. J. and Maddika, S. (2018). CRL7^{SMU1} E3 ligase complex-driven H2B ubiquitination functions in sister chromatid cohesion by regulating SMC1 expression. *J. Cell Sci.* **131**, jcs213868.