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FIRST PERSON

First person – Imke Mandemaker

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. Imke Mandemaker is first author on 'Histone H1 eviction by the histone chaperone SET reduces cell survival following DNA damage', published in JCS. Imke conducted the research described in this article while a PhD student in Dr Jurgen Marteijn's lab at the Department of Molecular Genetics, Erasmus MC, Rotterdam, The Netherlands. She is now a Postdoc in the lab of Prof. Andreas Ladurner at the Biomedical Center Munich, Ludwig-Maximilians-Universität, Munich, Germany, investigating the dynamic regulation of chromatin.

Imke Mandemaker

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

The blueprint of our cells, the DNA, is continuously threatened by damaging agents. These can come from outside sources like cigarette smoke, but are also produced during normal cellular processes. Luckily, our cells have several mechanisms to repair DNA and thereby prevent the formation of mutations. We studied a protein called SET, and observed that when SET is removed from cells they become resistant to DNA damage. We observed that SET affects chromatin; the structure of DNA wrapped around proteins called histones. Depletion of SET leads to enhanced amounts of one of these histone proteins, called H1, on the DNA. This enhanced binding of H1 was causing the resistance, as SET depletion did not affect survival in cells with low levels of H1. Initially, we hypothesized the resistance of SET-depleted cells would be the result of enhanced repair; however, we did not observe differences in repair efficiency. Instead, we found that there is a reduced activation of apoptosis, a controlled form of cell death, and show that SET is involved in the same pathway as p53, one of the key proteins in activating apoptosis. We think that SET is involved in stimulating cell death in cells that cannot reliably repair all DNA lesions, thereby preventing formation of mutations.

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

The biggest challenge in this project was, like in many projects, to find the mechanism. We quickly found that SET knockdown (KD) did not affect nucleotide excision repair; but how did it stimulate survival after DNA damage? I tested many different inhibitors, pathways, cell lines and KDs, but no matter what I targeted, SET KD cells always showed enhanced resistance. It wasn't until the last few months of my PhD that we found the connection with H1 and p53, which allowed me to wrap up the project.

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

The first colony-survival experiment that I did to find out whether SET was involved in the DNA damage response has stuck with me the most. Usually, targeting a protein involved in the DNA damage response will make the cells sensitive to DNA damage. The fact that we observed resistance was therefore very striking. It was not until I had done the experiment three times that we really believed the results. At that moment, we knew that we had a new interesting project in our hands.

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

We find it very important that our work is published in an international peer-reviewed journal. The Journal of Cell Science publishes a nice array of fundamental cell biology papers and we felt that our manuscript would fit in perfectly.

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

All my supervisors so far have really helped me to further develop as a scientist and as a person. In my PhD, both Prof. Wim Vermeulen and Dr Jurgen Marteijn have taught me so much. They have always encouraged me to be independent and gave me the freedom to follow my own ideas. Even though I have now moved on to another lab, they are still there to advise me on the future steps in my career. My current supervisor, Prof. Andreas Ladurner is also very supportive. He allowed me to start my own independent research project and supports me to further develop my soft skills.

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?

When I first learned about DNA in high school, I was immediately intrigued. I find it amazing how the complexity of an organism, with all molecular pathways, is encoded by just the four different bases that make up our DNA. By doing research, I can keep discovering new things about how our cells work at a molecular level. I also feel that by doing science, I contribute to our society. Moreover, doing science just makes me happy. I love performing experiments and trying to put all the pieces of the puzzle together.

Imke Mandemaker's contact details: Biomedical Center Munich, Department of Physiological Chemistry, Ludwig-Maximilians-Universität, Munich, Germany.
E-mail: imke.mandemaker@bmc.med.lmu.de

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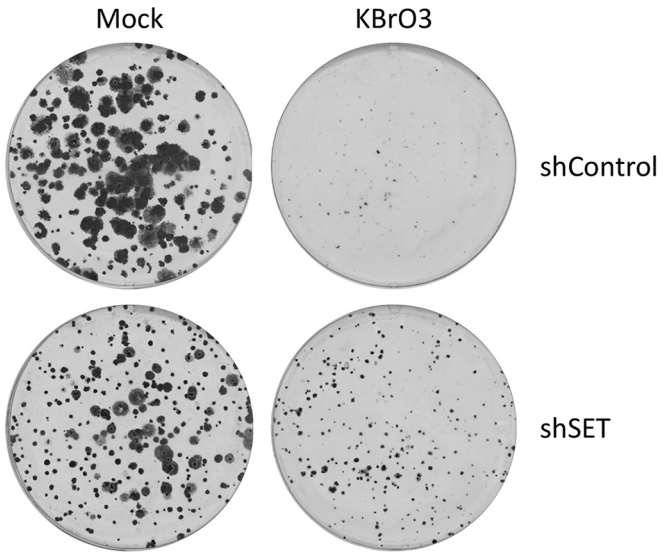

Colony survival assay of mouse embryonic stem cells showing that cells in which SET is depleted are more resistant to DNA damage than control cells.

Who are your role models in science? Why?

I get my inspiration from other people who are simply excited about science; this could be a PI or a PhD student. Luckily, I have had the opportunity to do my PhD in a department full of these kinds of people. I don't have one specific role model, but it is the environment, mentality, collaboration, supervision and atmosphere that I have experienced in this department that I use as a guideline.

What's next for you?

Currently, I am working as a postdoc in the lab of Andreas Ladurner. Munich is a very stimulating place to do chromatin research, as there are many established chromatin labs which perform highly collaborative research. My current work revolves around finding out how the elusive tumour suppressor protein macroH2A is incorporated into chromatin.

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

In my free time I play volleyball, both indoors and on the beach. Doing sports really helps me to clear my head and relax after a day in the lab.

Reference

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