© 2018. Published by The Company of Biologists Ltd | Journal of Cell Science (2018) 131, jcs218446. doi:10.1242/jcs.218446

FIRST PERSON

First person – Thibault Courtheoux and Alghassimou Diallo

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. Thibault Courtheoux and Alghassimou Diallo are joint first authors on 'Aurora A kinase activity is required to maintain an active spindle assembly checkpoint during pro-metaphase', published in Journal of Cell Science. Thibault is a postdoc and Alghassimou a PhD student in the lab of Dr Claude Prigent at IGDR-UMR, Université de Rennes, France, investigating cell division and mechanisms leading to chromosome instability and cancer.

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

T.C.: To divide, human cells needs to 'catch, attach and separate' 23 pairs of chromosomes. This very dynamic process occurs during cell division in less than an hour and requires precision; if even one chromosome is not correctly attached, the cell will delay chromosome separation and become 'paused'. Each unattached chromosome will recruit proteins to activate the pause signal, like a red traffic light. In this article, we showed that Aurora A (a catalytic protein involved in the early stages of mitosis) is involved in maintaining this traffic light on 'red'. We then used a drug or made a genetic modification to inactivate Aurora A in the presence of unattached chromosomes. Surprisingly, the traffic light stopped working and cells divided again, losing or gaining chromosomes to become genetically unstable, as in cancer.

A.D.: Throughout life, cells are renewed by division. The biological mechanism by which a so-called 'mother' cell produces two genetically identical 'daughter' cells is the cell cycle. During this cycle, the cell sets up monitoring mechanisms like the spindle assembly checkpoint (SAC) that allows for an equal distribution of chromosomes between the two daughter cells (chromosome segregation). It thus prevents genetic instability, which is one of the causes of cancer. These monitoring mechanisms are regulated by proteins like Aurora A kinase, whose roles in early mitosis are well established. We have shown that Aurora A kinase activity is required to maintain activity of the SAC monitoring mechanisms during cell division. Inhibition of Aurora A induced unequal chromosome segregation.

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

T.C.: To study and identify new protein functions during mitosis, it is necessary to synchronize cells and precisely localize this protein. To overcome this challenge, I combined mitotic arrest with super-resolution microscopy of cells expressing GFP-tagged Aurora A proteins at endogenous levels. Using a nano-booster to enhance GFP signal after fixation, we localized Aurora A at the kinetochore.

A.D.: Inhibition of Aurora A prevents the formation of the bipolar spindle with the result that it was impossible to investigate its function beyond this stage. To remedy this, we used a 'chemical genetics' approach to study, *in vivo*, the role of the Aurora A kinase in the later phases of mitosis. This involved creating an allele-sensitive mutant of Aurora A (as-Aurora A) to make it sensitive to a specific inhibitor that has no other targets in the cell. This inhibitor (1-Na-PP1) very rapidly and specifically inhibits as-Aurora A kinase at very precise moments of the cycle. Thus, as-Aurora A kinase could be inhibited just prior to metaphase. By inhibiting as-Aurora A kinase at this stage of mitosis, an original role of the kinase in maintaining active SAC has been demonstrated.

Thibault Courtheoux

"I remember that day like it was yesterday, because it was when the 'science virus' infected me."

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

T.C.: During my PhD, I was watching a chromosome failing to segregate in fission yeast, trying to understand what was happening when I suddenly thought 'if this chromosome is not moving in the right direction, it is because it is attached to both mitotic poles (merotelic attachment)'. I remember that day like it was yesterday, because it was when the 'science virus' infected me. It was also the

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Journal of Cell Science (2018) 131, jcs218446. doi:10.1242/jcs.218446

Alghassimou Diallo

beginning of another challenge: to convince my PhD supervisors. Twelve years later, I am still working on chromosome dynamics with the same desire to contribute to science.

A.D.: The most striking result for me was the disruption of the localization of Mad2 after inhibition of Aurora A kinase. Indeed, we observed a drastic decrease or disappearance of Mad2 at kinetochores and its strong enrichment at the poles of the bipolar spindle. Using immunofluorescence, we found that despite mitotic defects, the cells expressing as-Aurora A kinase did not arrest in prometaphase. The fall of the mitotic index in the absence of Aurora A kinase activity indicates that the cells escape from the SAC and exit from mitosis.

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

T.C.: Yes! I had the chance to undertake my PhD in Sylvie Tournier's and Yannick Gachet's team in Toulouse (Laboratory of Cellular and Molecular Biology Control Proliferation, France). Their patience and passion were a great opportunity for me. They gave me all I needed to overcome my technical limitations and escorted me to the end of my PhD with kindness, always putting my interests before theirs. I wish all young scientists could meet researchers like Sylvie and Yannick in their careers, and so I try to follow their example when I supervise students.

A.D.: My PhD supervisor was 'The Boss', Dr Claude Prigent. I greatly appreciated his pragmatism, his open-mindedness and his welcome of foreign PhD students with his legendary smile. His great expertise in the field of cell cycle research and scientific rigor put me in a favorable environment to complete my thesis project. Each phenotype observed had to be fixed after several repetitions (more than five times) then validated by different approaches. And, in each experiment, it was necessary to check all the steps even if the phenotype was observed.

"Never lose sight of the purpose of your thesis project, avoid distraction because a PhD is a moment of joy but also a moment of doubt, failure and questioning"

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

T.C.: Trust yourself, give all your energy to your project, explore new questions and rapidly acquire valuable technical expertise so that others in your field will refer to you for advice.

A.D.: You must believe and be convinced that you can only succeed by working hard. Never lose sight of the purpose of your thesis project, avoid distraction because a PhD is a moment of joy but also a moment of doubt, failure and questioning. Be up-to-date with the publications in your research field, participate actively in your lab's scientific meetings and broaden your horizons by interacting with researchers working on other subjects.

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

A.D.: For someone like me, coming from an underdeveloped country, the priority is getting funding to carry out a research project, because research is incredibly expensive. Financial and material support in the form of equipment is fundamental. As a result, having access to international financial support is crucial because underdeveloped countries do not always have the means to properly fund research. Also, it is crucial to have a good mentor who has a sense of how to coach junior foreign researchers and put them in the best position to start their career and professional success.

What's next for you?

T.C.: I am looking for a permanent position at CNRS (France). My middle-term goal is to lead my own team, working on ubiquitylation during mitosis as a non-degradative regulatory mechanism.

A.D.: My most ardent wish is to find a position in a university conducive to research (teaching and scientific research) or in a lab (postdoc) to pursue and advance some interesting results obtained during my thesis that are not included in this article.

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

T.C.: When experiments are not working (more often than expected), I enjoy putting science to the side and going fly-fishing: a sunny spring day, observing insects in the water and trying to mimic them as closely as possible. After several hours, with or without fish, my battery is fully charged and I'm ready for new challenges.

A.D.: I like to keep informed by following national and international news. I am also interested in the animal world and watch a lot of wildlife documentaries. The protection of the environment and the preservation of animal and forest species really speaks to me.

Reference

Courtheoux, T., Diallo, A., Damodaran, A. P., Reboutier, D., Watrin, E. and Prigent, C. (2018). Aurora A kinase activity is required to maintain an active spindle assembly checkpoint during pro-metaphase. *J. Cell Sci.* **131**, jcs191353.