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FIRST PERSON

First person – Samantha Salvage

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. Samantha Salvage is first author on 'Ion channel gating in cardiac ryanodine receptors from the arrhythmic RyR2-P2328S mouse', published in JCS. Samantha conducted the research described in this article while a postdoc with James A Fraser, Physiological Laboratory, University of Cambridge, UK and visiting postdoc with Angela F Dulhunty's lab at The Australian National University, Acton, Australia. She is now a postdoc in the lab of Antony P. Jackson at the Department of Biochemistry, University of Cambridge, UK, investigating cellular and molecular determinants of cardiac conduction and their implications for arrhythmogenesis.

Samantha Salvage

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

The release of Ca^{2+} ions from their stores in heart cells is important in normal heart rhythm as it initiates muscle contraction – the pumping mechanism. This Ca^{2+} release occurs via ryanodine 2 receptors (RyR2), which form channels between the store and the cell. Genetic mutations in RyR2 channels can disrupt their tightly controlled action, resulting in abnormal Ca^{2+} leak into the cell that can trigger abnormal heart rhythms, in particular those associated with emotional stress and/or physical exertion – known as catecholaminergic polymorphic ventricular tachycardia (CPVT). We identified a mechanism that contributes to this abnormal activity in a RyR2 mutation that is associated with some cases of human CPVT. These mutant channels exhibited an increased sensitivity to levels of Ca^{2+} that are normal in heart cells, which resulted in increased RyR2 activity. This increased activity was due to channel activation at lower than normal Ca^{2+} concentrations and, in a previously undescribed phenomena, persisted, such that Ca^{2+}-dependent inactivation was incomplete. Together, this results in a higher likelihood of excess Ca^{2+} release. These effects were observed in the absence of adrenaline, which mimics emotional stress or physical exertion, suggesting that this mutation could result in uncontrolled Ca^{2+} release leading to abnormal heart rhythms even at rest, as seen in humans with RyR2 CPVT mutations. With physical exertion or emotional stress this situation would be greatly exacerbated, increasing the likelihood of the severe and potentially fatal rhythm characteristic of CPVT.

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

The main challenge for me in this particular project was the lipid bilayer RyR2 channel recordings. We were using preparations from murine hearts, which give limited material, and channel incorporation into the bilayer appeared to be more variable, often taking much longer than with RyR2 from larger animal hearts and with reduced bilayer stability. Members of the Dulhunty group provided great supervision and support, and, together with the patience and perseverance that is crucial for single-channel experiments, I was able to successfully acquire a suitable amount of data for this work.

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

Recording single-channel RyR2 activity was totally new to me and it was particularly exhilarating the first time I successfully recorded from one of these channels, seeing their rapid opening and closing on screen as it was happening. Then performing the same recordings on the mutant channels and with the addition of certain agents was possibly more exciting; the responses were quite different and began to give clues as to the underlying mechanism of the phenotype.

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

Journal of Cell Science is an excellent journal in the field of cell biology. A number of strong scientific reports have been published in Journal of Cell Science within our field, in particular with respect to RyR(2) structure and function, and so we were confident we would reach our audience! Further to this, the Dulhunty group have published several works with Journal of Cell Science in recent years and have found the review process to be incredibly thorough, fair and rational.

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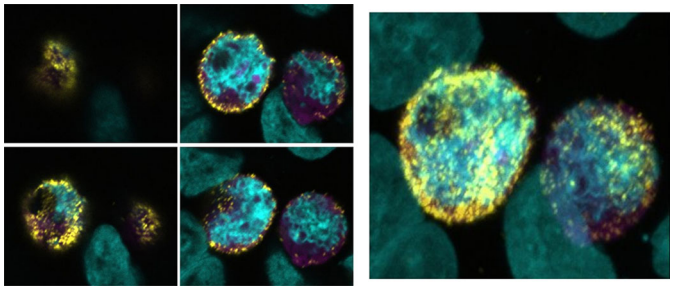

Nav1.5 clustering at the cell surface membrane. Proximity ligation assay (PLA) in HEK293 cells expressing Nav1.5 tagged with green fluorescent protein (magenta) and Nav1.5 tagged with HA (not visualised). PLA signal (yellow) is produced when the two Nav1.5 proteins co-localise to within 30 nm of each other; here seen at the cell surface. The four images on the left show different planes. The right-hand panel is a 3D reconstruction of many planes. Cell nuclei are depicted in cyan.

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

I have been privileged to have had very talented and encouraging mentors. Indeed, this project would not have happened without Dr James Fraser, who was supportive of me undertaking this work in another laboratory, and Professor Angela Dulhunty, who fully welcomed me into her group and provided considerable advice both in the project and for my stay in Australia. Taking hold of, and looking out for, career-developing opportunities (such as collaborative research projects and conference presentations) no matter how daunting they may appear, is something that has also been actively encouraged by my current PI, Dr Antony Jackson, and Professor Chris Huang.

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 have always loved problem solving and understanding how things work, particularly in biology. Then during my undergraduate degree I completed a professional training year in a research group at the University of Eastern Finland. This took me out of my comfort zone and involved working in an unfamiliar research environment on a defined project with questions that hadn't been answered before – which is quite different to the typical lab practical classes you're exposed to in an undergraduate degree. It was without a doubt one of the best experiences, both academically and personally, which I would thoroughly recommend to any student who has the opportunity.

Who are your role models in science? Why?

My role models (there are too many to mention all of them) in science are people who have managed to achieve a successful and productive research career, while maintaining a good balance with their personal life, whether that is juggling a family or pursing specific hobbies and interests. I think this can be very challenging and is not something to be underestimated.

What's next for you?

Our work on the RyR2-P2328S variant additionally led to findings of Ca^{2+}-mediated downregulation of the cardiac Na^{+} channel ($Na_v1.5$), the function of which is important to the electrical activity which subsequently triggers the release of Ca^{2+} from RyR2 channels. Currently, I am carrying out research investigating mechanisms of $Na_v1.5$ regulation in the lab of Dr Antony Jackson, and plan to develop my own research line looking at the interplay between these aspects.

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

I enjoy cycling as well as travelling and visiting new places. I have a particular soft spot for Italy and am currently trying to learn some Italian in my spare time.

Reference

Salvage, S. C., Gallant, E. M., Beard, N. A., Ahmad, S., Valli, H., Fraser, J. A., Huang, C. L.-H. and Dulhunty, A. F. (2019). Ion channel gating in cardiac ryanodine receptors from the arrhythmic RyR2-P2328S mouse. *J. Cell Sci.* **132**, jcs229039. doi:10.1242/jcs.229039