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FIRST PERSON

First person – Avinash Persaud

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. Avinash Persaud is the first author on 'Dynamin inhibitors block activation of mTORC1 by amino acids independently of dynamin', published in Journal of Cell Science. Avinash is a research associate in the lab of Daniela Rotin at The Hospital for Sick Children, Toronto, Canada, investigating mTORC1 signaling and the function of the ubiquitin ligase Nedd4.

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

The mammalian target of rapamycin complex 1 (mTORC1) is a complex of proteins that coordinates both external stimuli coming from the blood and internal cellular processes and, in doing so, plays an important role in the regulation of cell growth and survival in our bodies. mTORC1 is activated by main signals including essential amino acids, particularly leucine. Leucine is thought to account for ∼20% of our dietary protein intake and approximately one-third of muscle protein and, thus, plays an important role in protein synthesis, particularly through the activation of mTORC1.

By using genetic and pharmacological approaches, we investigated and quantitated the different routes of leucine entry into cells, and determined their contributions towards mTORC1 activation. Surprisingly, we also discovered that the pharmacological inhibitor Dynasore completely abolished mTORC1 activation – an unpredictable off-target effect of the drug. Upon further investigation, we showed that Dynasore acts at two specific stages of mTORC1 activation: (i) it mislocalizes mTORC1 within the cell and (ii) it inhibits Akt, a protein known to activate mTORC1. Since mTORC1 plays a vital role in the regulation of cell growth, conceivably, the misregulation of this signaling network results in several disease states, including cancer. As a precaution – although compounds such as Dynasore or chemically modified forms of it can be attractive models for the development of new therapeutic drugs that inhibit mTORC1 and, hence, metabolic diseases – a more comprehensive analysis has to be undertaken to determine its specific off-target and/or side effects.

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

One challenge of this project was to elucidate how mTORC1 is inhibited by Dynasore. By using several dominant-active and dominant-negative protein constructs that play a role in mTORC1 localization and activation, I was able to decipher which signaling pathways were affected by dynasore. This approach allowed me to ascertain where dynasore was acting within these signaling pathways and, eventually, the protein targets themselves.

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Avinash Persaud

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

The recruitment of mTORC1 to the lysosomal membrane through Rheb (in the presence of amino acids) was only partially impaired by dynasore in my experiments; I, therefore, expected to see a corresponding partial activation of mTORC1 by amino acids. Instead, dynasore completely abolished mTORC1 activation. Thus, I hypothesized that dynasore must be also targeting the TSC1/TSC2–Rheb axis that is also necessary for mTORC1 activation. Indeed, I discovered that Akt, a positive regulator of Rheb and mTORC1, was inhibited by dynasore; and I was able to partially rescue this inhibition by using a dominant-active form of Rheb.

"…exciting discoveries are born from unexpected results and this is what makes science intriguing."

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

Without a doubt, Dr Daniela Rotin has been a significant mentor both throughout my PhD and my current studies. She has provided me with the necessary tools and guidance to facilitate my research interests and, more importantly, a greater appreciation for knowledge and continuous personal development.

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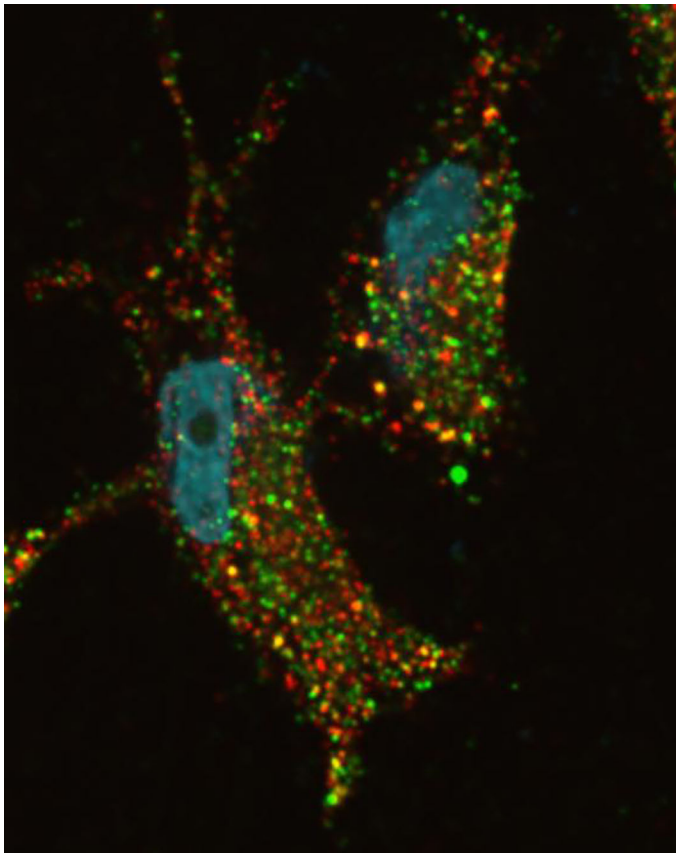

Reduced lysosomal localization of mTOR in the presence of dynasore. The nucleus is stained cyan, lysosomes (LAMP1) green and mTOR (anti-mTOR) red.

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

I would advise first-year PhD students to not become despondent or frustrated when experiments do not go according to plan or yield unexpected results. Lots of exciting discoveries are born from unexpected results and this is what makes science intriguing. Not only in your first or fourth year is trouble shooting and critical thinking an important part of science, but also of life. How we approach these situations in the lab can translate into how we approach life in general.

"…opportunities that foster collaborations and networking with other scientists would help […] early-career scientists"

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

I believe that opportunities that foster collaborations and networking with other scientists can help to develop the professional lives of early-career scientists, as this would expose them to various scientific techniques and ideas that aid the development of their critical thinking skills, while providing a more dynamic work environment for their projects and publications.

What's next for you?

I am always interested in new innovative research projects as science is always evolving, and would like to further my career within research.

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

I am a very family-oriented and spiritual person and owe a lot of my advances and accomplishments to these values.

Reference

Persaud, A., Cormerais, Y., Pouyssegur, J. and Rotin, D. (2018). Dynamin inhibitors block activation of mTORC1 by amino acids independently of dynamin. *J. Cell Sci.* **131**, jcs211755.