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FIRST PERSON

First person – Marco Travaglio

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping researchers promote themselves alongside their papers. Marco Travaglio is first author on 'Increased cysteine metabolism in PINK1 models of Parkinson's disease', published in DMM. Marco is a PhD student at the University of Cambridge in the lab of Luis Miguel Martins at the MRC Toxicology Unit in Cambridge (UK), and interested in developing novel therapeutic targets for Parkinson's disease.

Marco Travaglio

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

Parkinson's disease (PD) is a complex condition that has attracted a large amount of research in recent times because of its increasing prevalence in our society. Although most cases of the disease occur sporadically, meaning that no gene or mutation can be linked to its development, a few cases can be traced back to individual genes. Interestingly, mutations in some genes lead to very similar changes in the brain of PD patients affected by the more common, sporadic form of the disease. Among these genes is *PINK1*, a gene mostly involved in maintaining the correct functioning of mitochondria, the organelles often referred to as the cell's powerhouses. We know what mutations in this gene do but don't know how to fix them.

In our study, we show that flies and human cells carrying a mutation in *PINK1* consume a larger than usual amount of cysteine, a naturally occurring amino acid that is mostly found in high-protein food. This increased cysteine metabolism coincides with a decrease in glutathione, an antioxidant normally produced from cysteine and needed by cells to combat substances that damage cells in PD. Because the changes in cysteine levels are large and consistent in flies and cells, we hypothesized that cysteine may be central to how mitochondria cope with damage when PINK1 stops working in PD.

What are the potential implications of these results for your field of research?

There are currently several clinical trials investigating the positive effects of cysteine or similar compounds for PD patients. The main implication of our study was to provide additional evidence to the beneficial role of cysteine in fighting dangerous changes in the brain of PD patients. Our and other studies conclusively prove that cysteine has a very important but often neglected role in the cascade of events that leads to the development and progression of PD. More studies are needed but I think our study provides a good proof of concept.

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

The main advantage of using flies is that you can address multiple scientific questions quickly and with little resources. Flies are also incredibly useful genetic model systems, which means that you can manipulate the expression of certain genes relatively easily. The disadvantage is that, sometimes, it's hard to extrapolate your findings to the human body, in which the added complexity of sometimes invalidates the findings produced in flies. This is why we compared our findings to a human cell model, i.e. specifically induced pluripotent stem cells derived from a PD patient. This is, indeed, the main advantage of this human cell model: its cells allow for a direct investigation of what the disease does in human beings. In the future, we may even create therapeutics for individual patients by using these cell models. The main disadvantage is that these cells are very difficult to culture in the lab. They require expert handling, there is a limit to how many cells you can culture at the same time, and it takes a long time for them to develop and differentiate into neurons.

What has surprised you the most while conducting your research?

I was surprised by how striking the similarities were between flies and human cells. I was expecting some level of comparability, given that I was looking at changes in the expression of the same gene (*PINK1* in human and pink1 in fly), but I did not expect changes in Pink1 expression to yield such similar phenotypes. I was also surprised by the large drop in cystine levels in the extracellular medium of the human cells. The protocol for the differentiation of these cells requires to change the medium every day so I did not expect to see such a large decrease given the constant supply of fresh medium.

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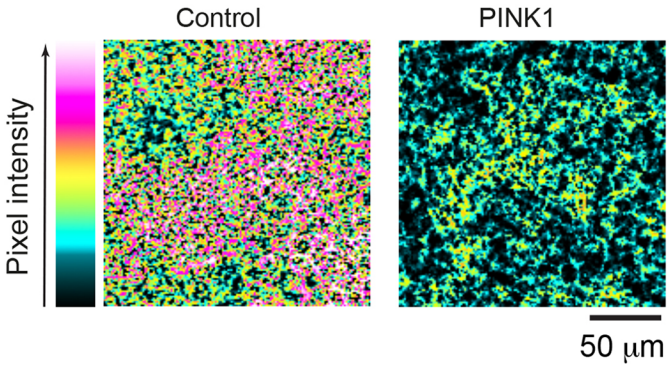

Representative immunofluorescence images showing a loss in mitochondrial membrane potential in PINK1-mutant NPCs (PINK1).

Describe what you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

The most significant challenge is to develop a unifying theory of PD that encompasses observations obtained from different models and genetic mutations. If we can find a common mechanism that explains how PD develops and progresses in humans, it would be easier to target it. However, my observations are limited to the systems and models we used for our experiments. This means that I can only make conclusions for the models that I worked with and that the results might be different for other mutations linked to PD. We need more collaboration between scientists to address critical challenges that extend to all patients with PD, regardless of whether they have a PINK1 mutation or not.

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

Greater transparency on experimental results and data collection could have a very big impact on how the community serves patients and healthcare providers, but communication silos and zero-sum games, where the publication becomes the aim and not the mean, create self-perpetuating cycles of inefficiencies and failures in clinical trials and beyond.

What's next for you?

I will continue to push the boundaries of science in a different capacity. I have recently joined IQVIA, where my work focuses on advising pharmaceutical industry associations and institutions on prominent policy projects.

Reference

Travaglio, M., Michopoulos, F., Yu, Y., Popovic, R., Foster, E., Coen, M. and Martins, L. M. (2023). Increased cysteine metabolism in PINK1 models of Parkinson's disease. *Dis. Model. Mech.* **16**, dmm049727. doi:10.1242/dmm.049727