

FIRST PERSON

First person – Lucía Zacchi

First Person is a series of interviews with the first authors of a selection of papers published in *Disease Models & Mechanisms*, helping early-career researchers promote themselves alongside their papers. Lucía Zacchi is first author on 'Early-onset torsion dystonia: a novel high-throughput yeast genetic screen for factors modifying protein levels of torsinAΔE', published in *DMM*. Lucía is a post-doctoral fellow at The University of Queensland, Brisbane, Queensland, Australia, investigating the molecular machinery involved in the secretory pathway and how to manipulate it for medical and biotechnological applications.

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

All cells from all organisms translate the genetic code into proteins, and these must be produced correctly to ensure survival. To understand this concept, think of a cell as a car factory, and of every piece of the car as a different protein; for a car to function, each piece must be properly made and assembled, e.g., the tires should be round, not square. For this reason cells tightly control the quality of protein production. Genetic or environmental factors that impair the function of quality control mechanisms lead to severe human diseases. Similarly, some mutations that lead to faulty proteins (like square tires) can cause disease either because they are cleared by quality control mechanisms (none of the protein remains in the cell; i.e. no tires for the cars) or because they escape quality control (faulty proteins may interfere with normal cell function; i.e. substandard cars are produced). Different proteins engage different components of the quality control machinery. Understanding how the quality control system works in normal conditions or during disease is important from general biological, clinical and biotechnological perspectives.

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

Our goal was to design a method that would allow us to: 1) identify new genes involved in quality control, and 2) identify genes involved in the quality control of specific proteins. In this paper, we present this new method: an automated genetic screen that allows for the efficient, rapid and systematic analysis of the effect of each gene in an organism on the ability of cells to produce a specific protein of interest. The method uses baker's yeast as the model organism and the protein torsinAΔE (associated with the neurological disease dystonia) as the specific protein of interest. We identified over 300 yeast genes required to produce normal levels of torsinAΔE in yeast cells. Some of these genes could eventually become therapeutic targets for dystonia in the future. Many of the genes identified belong to cellular processes previously unconnected to quality control. These unexpected findings are one of the strengths of



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unbiased screen approaches and may lead to a better understanding of this beautifully complex machinery. Finally, one notable difference between our method and most other yeast genetic screens is that ours does not screen for changes in cell growth, but rather for changes in protein levels. This is important, as it allows for a genetic screen when the overproduction of the protein of interest causes no growth defect. This was the case of our torsinAΔE–yeast system. Thus, our screen considerably expands the capability of this powerful biological system to inform on relevant biological questions, both regarding the physiology of the yeast itself but also as a tool to explore our own biology.

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Dystonia is the third most common movement disorder and is characterized by involuntary muscle contractions that can lead to abnormal postures. One of the most severe forms of dystonia is early-onset torsion dystonia (EOTD), which starts during childhood and can affect all the limbs in the body. Although many EOTD-associated genetic components are known, it is still unclear how EOTD develops and what cellular defects are associated with it. In addition, the known mutations associated with EOTD are necessary but not sufficient for disease onset; other unknown factors are required. For this reason, it is not possible to design pharmacological approaches to correct or prevent the cellular defects associated with EOTD.

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To overcome this hurdle, our approach did not focus on the EOTD cellular defects, but on the mutated proteins. The best-studied EOTD mutant, torsinAΔE, is more rapidly cleared from the cell than the wild-type torsinA variant by the quality control mechanisms. This suggests that torsinAΔE engages different quality control components than torsinA, and if those could be identified, they could be pharmacologically modulated to help the cell eliminate torsinAΔE and maintain torsinA. In a targeted set of experiments, we had previously shown that our torsinAΔE–yeast could inform on cellular components required for torsinAΔE production in human cells. Our new screen was perfectly suited to expand this search to the entire yeast genome to identify additional, novel, perhaps unexpected cellular factors that impact torsinAΔE protein production. The advantage of this approach is that the pharmacological modulation of these factors would be independent of the unknown downstream cellular defects caused by the combination of torsinAΔE and the additional unknown factors.

“[...] the rise of proteomics as a versatile and extremely useful tool will significantly help in overcoming many of the current biochemical hurdles to study this (and any) disorder”

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

Yeasts are easy to manipulate, they are economical, reliable and there is a wealth of ‘omics’ data and molecular tools available for research. A large percentage of the yeast genes are homologous to human genes and findings are translatable to humans, explaining why yeast has informed on the biology of an impressive number of disease-associated genes. Furthermore, the scientific yeast community is open and friendly, which I believe are two key components to effective and ethical scientific progress.

The drawback of yeast as a model for dystonia is that yeast cannot reproduce the complexity of a multicellular organism.

Further, yeast does not express some of the known proteins that interact with torsinA and are required for torsinA ATPase activity. Nevertheless, yeast is a great system to explore the questions we are interested in answering, since a large proportion of the components of the quality control mechanisms under study are conserved between yeast and humans.

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 field of dystonia must address the question of what are the cellular defects that lead to the disease. The way to do this effectively is to study cells from patients. Fortunately, the enormous technological advances in the last decades in stem cell research and tri-dimensional tissue culture (‘brains in a dish’) will allow researchers to ask these questions. Furthermore, the rise of proteomics as a versatile and extremely useful tool will significantly help in overcoming many of the current biochemical hurdles to study this (and any) disorder.

The other challenge that all scientists face is obtaining funding. Most funding is allocated to the research of neurodegenerative diseases. But research on less prevalent diseases is also important and funding through federal agencies may benefit from higher diversification. Dystonia research not only helps alleviate the suffering of patients and their families (including the chronic psychological and economical burden), but it also provides key biological information that can have useful ramifications on other diseases with overlapping symptoms. Luckily there are foundations such as the Dystonia Medical Research Foundation (www.dystonia-foundation.org), the Parkinson’s and Movement Disorder Foundation (www.pmdf.org) and the Michael J. Fox Foundation (www.michaeljfox.org), among others, that support the research of this severely debilitating disease.

Reference

Zacchi, L. F., Dittmar, J. C., Mihalevic, M. J., Shewan, A. M., Schulz, B. L., Brodsky, J. L. and Bernstein, K. A. (2017). Early-onset torsion dystonia: a novel high-throughput yeast genetic screen for factors modifying protein levels of torsinAΔE. *Dis. Model. Mech.* **10**, doi:10.1242/dmm.029926.