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FUTURE LEADER TO WATCH

Future leader to watch – Roman Zug

First Person is a series of interviews with the first authors of a selection of papers published in Biology Open, helping early-career researchers promote themselves alongside their papers. Roman Zug is first author on 'Developmental disorders caused by haploinsufficiency of transcriptional regulators: a perspective based on cell fate determination', published in BiO. Roman is a postdoc in the Department of Biology at Lund University, Sweden, investigating the developmental regulatory systems that underlie phenotypic variation and evolution, and the interrelationships between both.

Roman Zug

What is your scientific background and the story of how you got to where you are today?

I studied biology at Humboldt University of Berlin, focusing on theoretical evolutionary biology. I then did my PhD with Peter Hammerstein at the Institute for Theoretical Biology, also at Humboldt University, working on *Wolbachia*, symbiotic bacteria that manipulate the biology of their arthropod hosts in bizarre ways. While modelling the evolutionary dynamics of *Wolbachia* and their hosts, I became increasingly interested in the developmental and regulatory mechanisms underlying these interactions, and in evolutionary developmental biology (evo-devo) in general. That's why I decided to pursue a postdoc project that combines evolutionary biology, developmental biology, and systems biology. I was awarded a postdoctoral fellowship from the Deutsche Forschungsgemeinschaft (DFG) to work with Tobias Uller at Lund University. In Lund, I analyzed the origins of discrete phenotypic plasticity (e.g. wing polyphenisms in insects) by modelling the evolution of the underlying gene regulatory network (GRN), with a focus on bistable switches. During this research, I realized that bistable switches also play an important role during human development, and that this might help to explain why so many developmental disorders are caused by haploinsufficiency of transcriptional regulator genes. The resulting hypothesis is the centrepiece of the Future Leader Review.

What is the most important take-home message of your Review?

Many human birth defects and neurodevelopmental disorders such as autism and schizophrenia are caused by loss of function of a single copy of transcription factor and other regulatory genes. This dosage sensitivity (called haploinsufficiency) is remarkable because, for most genes, a single copy is sufficient for normal function. I argue that dosage sensitivity is an inherent feature of cell fate decisions, and I propose the hypothesis that developmental disorders result from disrupted bistability (the ability to switch between two stable steady states) in the gene regulatory network of the underlying cell fate decision.

What has surprised you the most while researching this Review?

I think it's fascinating that disorders as diverse as autism, congenital heart defects, immunodeficiencies and disorders of sex development can be traced back to the same type of defect, i.e. disrupted bistable switches in the GRN of the associated cell fate decision (acknowledging, of course, that these disorders can also have other causes). But then again, it is perhaps not too surprising that disrupting such a fundamental process as cell fate determination can affect basically any organ or tissue. Rather, given that most of these disorders are quite rare, I think what's really stunning is how robust development is by and large!

What do you feel is the most important question that needs to be answered to move the field forward?

Many transcription factors that show haploinsufficiency in humans don't do so in other species, e.g. in mice. This means that heterozygous loss-of-function mutations in these genes will elicit a disease phenotype in humans, but not in mice. This is important not least because mice are the most commonly used animal model for studying human disease. The reason for these differences in dosage sensitivity is still unclear. One idea is that the differences stem from evolutionary divergence of the regulatory architecture between the two species. Elucidating this puzzle will not only increase our understanding of gene regulatory evolution but is also likely to improve translational research in the context of developmental disorders.

"Excellent mentoring empowers ECRs to follow their interests, develop new projects, and make the right career choices."

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Biology Open (2022) 11, bio059178. doi:10.1242/bio.059178

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

I believe that strong mentoring is key for early-career researchers (ECRs) to grow both professionally and personally. Excellent mentoring empowers ECRs to follow their interests, develop new projects, and make the right career choices. Of course, much of this comes down to the mentors themselves, their personality, and the atmosphere they create in their research group. But establishing and expanding mentorship programs in universities and other research institutions is also important. Finally, as many ECRs are likely to undergo periods of financial hardship, I think it's crucial for them to be able to publish also at times when they have no funding. Therefore, the opportunity provided by Biology Open to publish Future Leader Reviews for free is absolutely spot on!

What's next for you?

We've just finished a follow-up article in which we argue that loss of function of transcriptional regulator genes represents a crucial link between the evolution and dysfunction of human cognitive and social traits. The argument is based on the haploinsufficiency of those genes, which makes them particularly sensitive to loss-of-function mutations. It's also tempting to investigate theoretically the idea that differences in dosage sensitivity between species are due to regulatory divergence. More generally, I think it's worthwhile to further explore the role of dosage-sensitive genes in adaptive evolution. Definitely some fun projects in the pipeline!

Reference

Zug, R. (2022). Developmental disorders caused by haploinsufficiency of transcriptional regulators: a perspective based on cell fate determination. *Biology Open* **11**, bio058896. doi:10.1242/bio.058896