© 2023. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2023) 16, dmm050153. doi:10.1242/dmm.050153

FIRST PERSON

First person – Mark Hanson

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. Mark Hanson is first author on 'Antimicrobial peptides do not directly contribute to aging in *Drosophila*, but improve lifespan by preventing dysbiosis', published in DMM. Mark conducted the research described in this article while working as a postdoctoral researcher in Prof. Bruno Lemaitre's lab at École Polytechnique Fédérale de Lausanne (EPFL), Switzerland. He is now a Research Fellow in the lab of Prof. Ben Longdon at University of Exeter, Penryn, UK, investigating the evolution of immune systems to learn how our body's defences are adapted to the world around them.

Mark Hanson

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

Overactivation of the body's immune system is often to blame for a number of diseases including autoinflammatory diseases and age-related inflammation. Part of your body's defences are antimicrobial products, such as 'antimicrobial peptides' (AMPs). These genes work a bit like antibiotics, keeping our body's microbes in check with their potent cell-killing activity. But it has been unclear if having too strong an AMP response could be detrimental to your own cells, not just to microbes. If these inflammation-regulated antimicrobials really were harming yourself when overactivated, they could be the principal actors behind auto-inflammatory or age-associated diseases like inflammatory bowel disease (IBD) or neurodegenerative diseases (for example, dementia). Taking advantage of recent genetic techniques, we finally performed systematic tests of whether AMPs make a difference to the aging process in fruit flies. Ultimately, we found that these genes do contribute to aging by regulating the gut microbiota. However, we did not find convincing evidence that lifespan changed for the better in flies depleted of their AMPs, even in germ-free conditions. Thus, AMPs of fruit flies do not seem to have clear negative effects on the aging process. Our study is not the final say on this interesting question, but it provides some of the first gene-deletion evidence for the importance of AMPs in aging and lifespan. Our results suggest these genes do impact aging, but only indirectly through their positive effects on regulating the microbiota, and not by harming the body's own cells during age-associated inflammation.

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

There is a great interest in what causes the body's deterioration with aging, particularly regarding neurodegenerative disorders. The NF-κB inflammatory response has been implicated in neuronal development and pruning, behavioural responses and neurodegenerative syndromes. Aging is also associated with microbiota dysbiosis, which can have negative consequences on an individual's health. As key target genes of NF-κB signalling, AMPs have long been suspected to contribute to inflammatory and age-associated diseases. However, these small genes were difficult to target with classic genetic approaches. Using CRISPR, we could systematically delete the genes encoding AMPs in fruit flies, testing their impact on aging in the presence or absence of the microbiota for the first time. Our results suggest that, while these genes are highly upregulated upon aging, they are not harming the body in a significant way. Instead, AMPs are key to maintaining control over the microbiota with aging, and in the absence of AMPs, microbiota bacteria grow out of control and harm their host.

"[…] flies have the same innate immune system as humans and other animals, but lack the adaptive immune system of vertebrates."

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

The genetic tractability of *Drosophila* has allowed the first systematic characterization of AMPs in an animal model. *Drosophila*'s other great strength in immune research is also a weakness when viewed in a different light: as invertebrates, flies have the same innate immune system as humans and other animals, but lack the adaptive immune system of vertebrates. On the one hand, combined with *Drosophila*'s powerful genetic tools, this allows the delicate dissection of how innate immune mechanisms operate without worrying about the possible interference of learned

Mark Hanson's contact details: Centre for Ecology and Conservation, University of Exeter, Penryn Campus, Treliever Road, Penryn TR10 9FE, UK.
E-mail: m.hanson@exeter.ac.uk

Disease Models & Mechanisms (2023) 16, dmm050153. doi:10.1242/dmm.050153

***Drosophila melanogaster* as a model for aging.** How host autoimmunity contributes to age-related diseases is of great interest to slow disease progression and improve the quality of life. AMPs, effector molecules of the innate inflammatory response conserved from humans to fruit flies, have been of great interest for their potential to inflict autoimmune damage in aged individuals. We tested the idea that AMPs could be contributing to the aging process using *Drosophila* fruit flies, as these genes are upregulated upon aging. As expected, we found that antimicrobial peptides are key to keeping the host microbiome under control during aging. However, we did not find evidence of a negative role for AMPs on lifespan in the absence of microbes, suggesting that these genes do not have significant autoimmune effects in the absence of microbe-associated damage upon aging. Our results suggest that AMP upregulation upon aging is correlated with age-associated diseases, but it is unlikely to be the root cause.

immunity in the study system (which can contribute to noisiness in the data, and different results among research groups using e.g. mouse models). On the other hand, this also means the fly model does not involve important immune memory factors contributing to aging and inflammation in human diseases. In this instance, testing the potential impact of AMPs on aging, the absence of adaptive immune responses is key to get a clear picture of what the intrinsic effects of AMPs are on lifespan.

What has surprised you the most while conducting your research?

Independently of our research question, we discovered a cryptic viral infection that significantly impacted our results, causing premature mortality. Depending on which strains of flies were infected with this cryptic virus, we could have drawn entirely different conclusions from our results. This sort of finding follows many conversations about the reproducibility of aging studies, in which the 'rescue effect' of a given drug or treatment is only seen when one compares the overall lifespan to a genetically consistent control but not necessarily a long-lived individual. In fly research, the striking impact of this cryptic infection could help make sense of a number of conflicting past results or, at least, paint them in a new light. But to our main study question – we genuinely thought some specific AMPs would be detrimental to lifespan, given previous studies demonstrating artificial overexpression can do things like damage neurons, induce mitochondrial stress or reduce lifespan. However, we found this was not the case in standard rearing conditions.

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

Generally speaking, there is a tendency to focus on powerful genetic techniques or drug interactions in aging, even prioritizing these factors over the baseline health of the animals being studied. Differences between lab groups, strains of animal and study systems also make for a lot of noise, leading to conflicting or exaggerated results across some studies, although it is impossible to know which studies have exaggerated results without the benefit of years of hindsight. I think a significant advance that will come in the next 10 years, one which we take in our own study, is to stop comparing results strictly to the 'best' genetic controls, and instead compare to what is expected for a healthy individual. For instance, it is not necessarily so striking if one can take a short-lived animal (e.g. ∼60 years in human terms) and extend its lifespan by 10%. The field's most significant advances will come when we identify the factors to take a long-lived animal (e.g. ∼80 years in human terms), and extend their lifespan even further. At that point, we will have discovered important factors regulating aging that should be of fairly universal importance.

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

Academic career stability is an essential and underappreciated shortcoming of the many issues scientists face – and it is discussed plenty! We are churning out more and more PhDs and yet, somehow, we still cannot find reviewers for articles, and PIs can share plenty of frustrating stories about searching for postdocs. More than the low salary compared to the salaries posted for industry jobs, there simply is not a career prospect in academia without shooting for the moon: less than 5% achieve a stable career position with a university, and only a tiny fraction of that is made up of PhDs becoming professors. We need more long-term research scientist positions, lab managers and senior researchers who can support professors without needing to secure everything involved with running their own groups. Not only would this make for stable career prospects, it would also reduce the competition for grant funding among senior researchers, thereby avoiding cumulative centuries – millennia even – of wasted people-power spent in grant writing and reviewing efforts.

What's next for you?

In November 2022, I started a Research Fellow position at the University of Exeter, Cornwall, in the UK. My funded project investigates how immune signalling networks evolve. Specifically, I am asking: how do novel connections between immune pathways come to be? What are the common mechanisms that generate novel immune signalling connections, and can we begin to learn to predict them? Currently, there is a very poor understanding of how novel infectious diseases (like SARS-CoV-2) translate across species. Predicting potential disease reservoirs is key to future public health efforts, including the management of ongoing (SARS-CoV-2) and emerging pandemic pathogens.

Reference

Hanson, M. A. and Lemaitre, B. (2023). Antimicrobial peptides do not directly contribute to aging in *Drosophila*, but prolong lifespan by preventing dysbiosis. *Dis. Model. Mech.* dmm049965. doi:10.1242/dmm.049965