Advances in understanding the complex molecular biology underlying ageing have brought this science to an important tipping point. **Dr Aric Rogers** talks about his lab and how interventions that successfully extend life in animal models may be used to intervene in human ageing.

**What is the overarching goal of research into the biology of ageing?**

In a broad context, researchers like myself seek to understand mechanisms responsible for increased lifespan in animal models. These are important for us to comprehend because molecular genetics shows that we have a lot more in common with these animal models than not. The high level of conserved molecular genetics leads to conserved molecular function among species, thereby making it possible to apply our findings to improve human health and longevity.

**Can you discuss what fuels your investigation of the ageing process?**

All of us are subject to the decline in health associated with ageing and many believe that there is nothing that can alter this process. What helps fuel my investigation is the knowledge that we can actually influence lifespan – we’ve done it in numerous animal models. Our lab uses the tiny roundworm *Caenorhabditis elegans*, which has been utilised to find interventions that result in a vast increase in lifespan. As ageing researchers, we strive to understand the mechanisms at work behind such interventions. We can then begin to look for treatments that mimic the effect in humans.

**Dietary restriction (DR) increases lifespan in a number of animal models. How is your lab using DR to understand the potential for human ageing interventions?**

There are a number of different forms of DR that are known to increase lifespan. Although caloric restriction is a type of DR, there are other types of DR that do not reduce caloric intake but do increase lifespan, such as protein restriction and every other day feeding. Our lab is looking very closely at a type of DR in the nematode *C. elegans* that increases lifespan and changes gene expression at a point of regulation that happens just prior to protein synthesis. These changes are important for mediating the positive effects associated with DR.

**Which age-related diseases do you hope your research will ultimately help to combat?**

One of the wonderful realisations to come out of research into the basic mechanisms of ageing is that most of the interventions found to increase lifespan also increase healthspan and delay the onset of major age-related diseases. This has huge implications for how we as a research community might refocus already stretched resources in an effort to decrease incidence of diseases such as cancer and diabetes.

**You have received some highly competitive grant awards, including an American Federation of Aging Research Postdoctoral Fellowship and a K99/R00 Transition to Independence Award from the National Institute on Aging. How important has this funding been to your research?**

This funding has been instrumental in establishing the line of research we are involved in and in helping start my own lab. I have been fortunate so far, as this is a challenging time for scientists trying to obtain funding for government-sponsored research. My lab is part of a larger effort at the Mount Desert Island Biological Laboratory (MDIBL) to open new doors between the world of science and business, facilitating the rapid transfer of what we learn in the lab to therapeutic applications to improve human health. The hope is that these partnerships will increase the rate at which health-promoting therapeutics are made available and help fill in the gap left by reduced funding from government sources.

**How does being a part of the Davis Center for Regenerative Medicine and Biology at MDIBL enhance your research?**

I was attracted to MDIBL by the possibility of joining the Davis Center with its focus on ageing and regeneration. It has strategically leveraged itself to be at the forefront of research aimed at improving health and quality of life as we age. Their focus can be broken down into two parts: one involves enhancing the ability of cells and organs to maintain healthful status; the other is geared to improving the ability to regrow lost or damaged tissues. My lab is focused on advancing the first of these areas of investigation in order to slow age-related decline and increase healthful lifespan in humans. By combining what we learn from both of these branches of research, we will have the best chance of optimising human health and longevity.
The key to longevity

Seeking to understand how dietary restriction and inhibition of protein synthesis slows ageing, a team at Mount Desert Island Biological Laboratory in Maine is studying how gene expression is remodelled at different points of regulation under conditions that extend lifespan.

MAJOR ADVANCEMENTS IN medicine have extended average human life expectancy. However, maximum lifespan remains unchanged and an increasingly ageing population is still vulnerable to age-related illnesses including arteriosclerosis, diabetes, Alzheimer’s and Parkinson’s.

Dr Aric Rogers and his team at the Mount Desert Island Biological Laboratory (MDIBL), Maine is using animal models to understand mechanisms capable of prolonging lifespan and preventing or delaying the onset of age-related diseases. The group hopes to be able to apply their findings to help improve human health, ultimately resulting in an increase in both average and maximum healthy lifespan. The research is already beginning to shed light on changes that take place under dietary restriction (DR) and alteration of protein synthesis with the potential to extend life and abate the onset of age-related illnesses.

LIFESPAN EXTENDING INTERVENTIONS

From their work and the work of a number of other top-notch researchers in the field, the team has come to the conclusion that genetic inhibition of certain pro-growth genes during adulthood can significantly increase lifespan in model organisms from yeast to mammals – specifically, certain factors involved in protein synthesis. Because the specific proteins that are created in cells are part of a controlled process, inhibition of factors involved in protein synthesis can also affect which proteins are manufactured, as Rogers elaborates: “This preference turned out to be important for increased lifespan and for that observed in a genetic model of dietary restriction”. Encoded in our genes are the blueprints for proteins that determine how we respond to the environment. “Genes must be carefully expressed at the right time and in the right amount. For genes to be expressed, they must be transcribed (copied) and then translated (decoded) to synthesise new proteins,” he explains. Therefore, the two critical points for regulating gene expression are transcription and translation.

In the past, most research into the relationship of gene expression with growth and disease were measured at the transcription level. The importance of regulating gene expression at points after transcription was often not investigated. However, current studies show that a number of age-related diseases are caused by deregulation of gene expression at the level of translation, when the protein encoded by a gene is actually made. Rogers and his team are looking at post-transcriptional gene expression ‘switches’, figurative buttons that may alter the rate of age-related health decline and illnesses. By manipulating these switches through the development of novel treatments, the researchers aim to prevent or reverse translational deregulation of gene expression.

STUDIES OF LONGEVITY

One line of investigation in the Rogers lab looks to understand how DR slows ageing. Despite diet playing a key role in lifespan and overall health, experts are only just beginning to understand the true complexity of the changes that occur during this intervention. “We know that responding to changes in nutrient availability involves cellular processes that affect gene expression at the post-transcriptional level,” highlights Rogers. “Despite these facts, we still do not understand...
the full range of changes that take place at the level of gene expression downstream of transcription, nor is it understood how such changes contribute to ageing.” It is therefore essential for the team to obtain a clearer understanding of these changes.

Previous studies emphasised the importance of regulating translation of messenger RNAs (mRNAs) to affect lifespan. To understand the alterations in gene expression that occur at this level, Rogers is using as a diagnostic a method that combines genome-wide analysis of the translation state with next-generation sequencing technology to determine the mechanisms of differential expression under DR. The combination of the two technologies is cutting-edge and allows for an unparalleled level of gene expression resolution in comparison to earlier methods used to investigate such mechanisms controlling longevity.

Research in Rogers’ lab is also exploring the effect of inhibiting mRNA translation on ageing, as he further elaborates: “We showed robust lifespan extension upon suppression of IFG-1, the Caenorhabditis elegans orthologue of eukaryotic translation initiation factor (eIF)-4G, a factor that positively regulates mRNA translation. We have adapted translation state array analysis (TSSA) methods to investigate changes in the translome upon suppression of IFG-1”. Advances in the project have led to the publication of Rogers’ results, demonstrating a vast number of differentially translated mRNAs important for lifespan extension.

To elucidate the crucial role of differentially translated mRNAs to lifespan, it was necessary to suppress expression of certain growth and development genes. mRNA length could account for part, but not all, of the differences in translation regulation. Further examination suggests that cis-regulatory elements – that is, short nucleotide motifs within the mRNA transcripts themselves – may account for differential translation that cannot be attributed to mRNA length. Rogers thinks that understanding the contribution of cis-regulatory elements to differential translation when ifg-1 is suppressed will be important for explaining extended lifespan under this condition and for developing treatments aimed at targeting these mechanisms of control.

**GOLDEN AGE OF DISCOVERY**

A relatively new member of MDIBL, Rogers was attracted to the growing centre by scientists with a shared interest in ageing and regeneration. Indeed, by combining their knowledge of the subject, the researchers are perfectly poised to conduct investigations on healthy lifespan and aim to make great advancements in the arena of human health, including novel interventions aimed at strengthening the ability of human tissues and organs to maintain their integrity.

The Rogers lab and other labs at MDIBL are making use of high-throughput methodologies and cutting-edge equipment to discover mechanisms that control ageing and regeneration. Specifically, Rogers and his team are utilising a mix of massive parallel sequencing, or deep sequencing, to measure translation via gene transcripts that are separated according to their relation to the translation machinery. This method enables the researchers to characterise components within the transcripts that demonstrate their suitability to be used in the production of new proteins. The laboratory is deepening its insight into the control of gene expression at this level and hopes to use this knowledge to design novel treatments capable of modulating gene expression to benefit health and to increase longevity.

**BEYOND CURRENT UNDERSTANDING**

Rogers was recently awarded a sizeable grant to help finance his project at MDIBL. The Pathway to Independence Award, bestowed by the National Institute on Aging, part of the National Institutes of Health, has funded his previous research and will do the same for the next three years. Equally supportive of Rogers’ work is the MDIBL Director, Dr Kevin Strange, who reveals: “Aric’s arrival heralds great things for the Davis Center at MDIBL. He’s a top notch researcher whose work shows definite potential for understanding, and possibly manipulating, factors that help determine how long we live”.

Looking ahead, Rogers intends to build on his previously published evidence. Independently, these findings suggest genetic inhibition of a particular translation factor and a genetic form of DR could regulate increases in lifespan by overlapping mechanisms. He is optimistic and confident that his team is following some promising leads which will deliver exciting results.

**INTELLIGENCE**

**CONSERVED MECHANISMS OF LIFESPAN EXTENSION**

**OBJECTIVES**

To understand how life-extending interventions work across different species and to apply what is learned to extend human health and longevity. The lab is currently focused on interventions involving dietary restriction and modulation of protein translation and the underlying mechanisms that lead to increased lifespan and healthspan.

**KEY COLLABORATORS**

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