Sue-ji collected several natural strains of c. elegans

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Sue-Ji HongThe rate at which human individuals age is variable and has a complex genetic basis. Likewise, this variation is observed in nematode worms. Naturally occurring genetic variation within two genes influences the rate of decline in several age-related behavioural functions. Caenorhabditis elegans is a nematode worm that has become a prominent model organism to study ageing. Although initial studies on C. elegans focused on identifying genes that influenced lifespan, measuring lifespan gave no indication as to whether an organism was ageing in a healthy or unhealthy manner. Whilst healthy ageing is characterised by a slower, moderate decline in physiological functions, unhealthy ageing is characterised by a rapid and severe decline.

Some individuals will age healthily or unhealthily, and this natural variation is partly contributed by genetic factors, that is, variation caused by the differences in the genomes amongst individuals. Due to the complex genetic basis that underlies this variation, the specific factors that controlled healthy ageing had not been identified previous to this study presented by Yin et al.. In this study, the researchers demonstrated that natural variation in two genes have been shown to modulate ageing rates in various strains of C. elegans.

Since studies on C. elegans can be comparable to studying human individuals in a population, identifying such genes that influence ageing rates in C. elegans can give insight as to why individuals experience different ageing rates and why some can preserve physiological functions as they age whilst others cannot. This is of important medical significance as ageing is a major risk factor for several neurodegenerative diseases such as Alzheimer’s

and Parkinson’s. As this study has revealed the first genetic pathway that influences natural variation in ageing rate, it may lead to a better understanding of improving health span in an ageing population.

Furthermore, it could allow for development of early interventions that have significant impacts for the prevention or progression of age-related neurodegenerative diseases. Yin et al. collected several natural strains of C. elegans whereby the genome sequences of these strains had several variable sites whereby the sequence differed, thus creating genetic variation. These variable sites are known as polymorphisms and can be linked to certain biological traits, although establishing clear links between them has been difficult due to the complex genetic basis that underlies these traits. The researchers found that during ageing, different C. elegans strains underwent distinct rates of decline in virility (mating efficiency), feeding behaviour and locomotion (movement).

The researchers found that polymorphisms within the novel neuropeptide-coding gene regulatory-gene-for-behavioural-ageing-1 (rgba-1) and its neuropeptide receptor gene npr-28, influenced the rate of decline of virility. These genes are involved in neuropeptide signalling pathway. As C.

elegans age, their serotonin and dopamine levels decrease due to the decreased expression of the BAS-1 enzyme that synthesises them (3). The decreased expression of BAS-1 has previously been shown to contribute to the decline in virility during ageing of some C. elegans strains (4).

In this study, Yin et al. found that polymorphisms in rgba-1 accounted for changes in BAS-1 expression levels which, in turn, regulated the rate of decline in virility. The study revealed that rgba-1 encodes for four neuropeptides which are protein-like signalling molecules used by neurons for communication (5). Although neurons are the primary source of neuropeptides, glial cells (which physically support and insulate neurons) can also release such signalling molecules to modulate neuronal function.

Interestingly, Yin et al. demonstrated that only neuropeptides released by glial cells (but not those released by neurons) prevented age-related declines in virility. rgba-1 neuropeptides bind to the NPR-28 receptor encoded by npr-28. The researchers revealed that npr-28 was specifically expressed in neurons that produced the neurotransmitters serotonin and dopamine. Polymorphisms within npr-28 modulated the rate of decline in virility during ageing.

Whilst rgba-1 neuropeptides are unique to C. elegans, NPR-28 receptors are related to the receptors that bind to human neuropeptides nociception and somatostatin hence, these receptors are also involved in modulating neuronal function. Through population genetic analysis, the researchers suggest that variation in ageing rates have been due to emergence of new genes (rgba-1), and process of natural selection. rgba-1 and npr-28 were shown to be under a type of natural selection process which reduces/eliminates genetic variation amongst individuals. Furthermore, the study showed that, in contrast to previous thoughts, evolutionary selection of genes conferring benefits in early life may also be advantageous in later life

by extending health span or lifespan, or both. Lastly, the researchers showed that rgba-1 and npr-28 could act on other mechanisms to modulate the decline in virility during male ageing. The mitochondrial unfolded protein response (UPRmt) has previously been associated with lifespan extension.

In this study, researchers showed that when the RGBA-1-2b neuropeptide binds to the NPR-28 receptor, it inhibited the UPRmt which increased the rate of ageing. Yin et al. have made tremendous progress by revealing how genetic variation and a neuropeptide signalling pathway can modulate the rate of ageing. However, the next challenge will be to determine whether neuropeptides have a role in regulating the rate of ageing in humans. Understanding the role of neuropeptide signalling on the rate of human ageing could lead to development of therapeutics against neuropeptide receptors. As these receptors belong to the G-protein coupled receptor family (a common drug target), targeting such receptors may potentially prevent unhealthy ageing.

For example, Parkinson’s is characterised by a reduction in dopamine levels through the death of dopamine-releasing neurons. Further studies could investigate whether this reduction is mediated by neuropeptide signalling and since the researchers did not elucidate whether UPRmt exists in dopamine-producing neurons, perhaps this could be a point of focus for further research as if it were to exist, increasing activation of UPRmt could potentially delay decline in dopamine levels and hence the onset of Parkinson’s. Moreover, since rgba-1 and npr-28 were shown to only regulate certain aspects of healthy ageing, the role of other mechanisms involved in

this process have yet to be elucidated. Figure 1: Neuropeptide signalling modulates rate of age-related traits... Yin et al.

demonstrate that in Caenorhabditis elegans, glial cells release four neuropeptide signalling molecules which are encoded by rgba-1. These bind to a neuropeptide receptor 28 that are encoded by npr28 and activate signalling within another neuron. Genetic variation within these rgba-1 and npr28 affects the rate in decline of male mating efficiency, known as virility.