Meeting report

Addressing the age-old question of old age

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A report on the Second International Conference on Functional Genomics of Ageing, Hersonissos, Greece, 28 April-1 May 2004.

The 'Second International Functional Genomics of Ageing' meeting brought together a veritable 'who's who' of top people in the field of ageing research. Organized by Jan Vijg and Yousin Suh (both at University of Texas Health Science Center, San Antonio, USA), the meeting's aims were to provide information on recent advances in research into the biology of ageing and on how functional genomics approaches can be used to identify processes and pathways that influence ageing and longevity. Several interesting themes emerged at the meeting and there were many exciting presentations.

Demographic studies of ageing

Several presentations at the meeting examined ageing from a demographic point of view. As explained by Steve Austad (University of Idaho, Moscow, USA), the longevity of any species can be thought of as the product of several parameters, two of which are frailty (a measure of intrinsic vulnerability to death) and senescence (the rate of change in frailty over time). These two parameters can also be thought of as the instantaneous 'risk' of death and the rate at which that risk increases throughout life, respectively. By performing ageing studies using large cohorts, parameters such as frailty and senescence can be measured in different populations (Figure 1). From demographic data, it is possible to address the mechanism by which life-extending treatments work: do they decrease frailty or do they decrease senescence?

William Mair and Linda Partridge (University College London, UK) described the use of demographic analysis to study the effects of dietary restriction and reduced temperature - two environmental factors that extend lifespan in *Drosophila melanogaster*. They discovered that these interventions operate in intrinsically different ways: dietary restriction extends lifespan by lowering the intrinsic frailty throughout life, whereas lower temperature extends lifespan by reducing the rate at which flies senesce (Figure 1b,c). Strikingly, the protective effects of dietary restriction could be induced at any point during life. By shifting flies from full feeding to conditions of dietary restriction and measuring changes in age-specific mortality, Mair showed that previously fully-fed flies switched almost immediately to having the same (reduced) risk of death as flies that had been under dietary restriction throughout their adult life (Figure 1b). This effect is not due to reduced fecundity, which is a common effect of dietary restriction, and implies that the life-extending properties of dietary restriction may be due to alterations in an 'ageing program'. This finding has far reaching consequences, as dietary restriction has been shown to extend lifespan in every system it has been tested in, including mammals.

Ageing and inflammation

A demographic view of human ageing was also presented by Caleb Finch (University of Southern California, Los Angeles, USA) who showed that the longer lifespans exhibited by successive human generations are due entirely to reduced frailty throughout life. The mortality curve for successive generations is shifted down, but there is no change in the rate of senescence. It is well known that life expectancy from birth has increased as a result of reduced infant mortality, but what had not previously been noted was a correlation between infant-mortality rate and late-life mortality. This correlation implies that whatever aspect of life history has changed to reduce mortality during the infant period also makes for much more 'robust' adults as well. Finch hypothesized that the early process that has now changed is the incidence during infancy of inflammatory induction as a result of disease, infection or injury. In this view, people are now living longer than ever because we experience less infection and disease as babies, which results in us carrying less of an

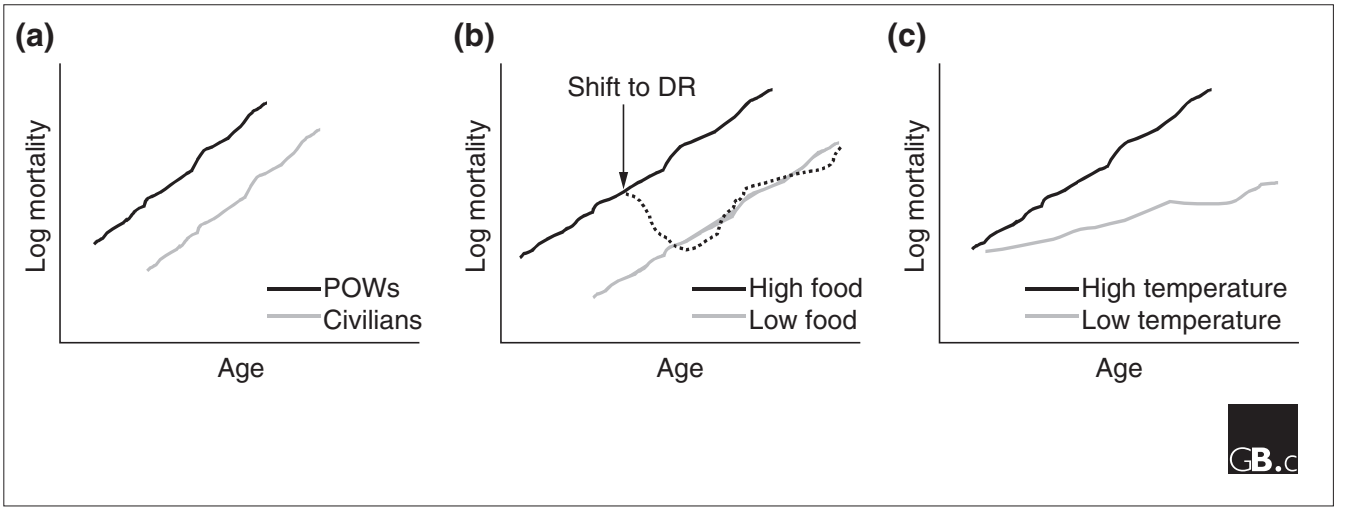

Figure 1
Demographic survival analysis. Treatments that increase lifespan can do so by either reducing 'risk', which results in a shift of the survival curve downward and to the right, or by reducing senescence, which results in a decrease in the slope of the mortality curve. **(a)** The mortality rate of Australian prisoners of war (POWs) in Japanese concentration camps during World War II compared with that of civilians in Australia between 1944 and 1945 (adapted from Finch *et al*., *Science* 1990, **249:**902-905). The mortality rate is the same for both populations, as illustrated by the curves having the same slope, but the POWs experienced a much greater intrinsic risk than their civilian counterparts, resulting in an upward shift of the mortality curve. **(b,c)** Dietary restriction (DR) and temperature extend lifespan to similar degrees, but demographic analysis shows that they do so by very different mechanisms in *Drosophila melanogaster*. Dietary restriction extends lifespan by shifting the survival curve (b), whereas temperature extends lifespan by changing the slope of the curve (c). Strikingly, shifting flies from high-food to low-food conditions results in an immediate reversal of the survival curve to low-food rates (broken line in (b)), implying that there is some inherent 'risk' associated with the high-food diet and that dietary restriction can protect against this.

'inflammatory load' throughout life. This idea is very appealing, as the process of inflammation is linked to many diseases that cause morbidity and mortality, such as rheumatoid arthritis, atherosclerosis, diabetes and Alzheimer's disease.

Several other presentations during the meeting also implicated the inflammatory response as a prime candidate for a process that shortens lifespan. Nir Barzilai (Albert Einstein College of Medicine, New York, USA) presented evidence that adiponectin, a fat-derived peptide that has insulin-sensitizing and anti-inflammatory properties, is expressed at much higher levels in human centenarians and their offspring. The expression of this peptide is normally negatively correlated with the amount of fat present in the body (it is up-regulated with leanness, and down-regulated with fatness). The action of this peptide is consistent with the life-extending properties of dietary restriction, a regime under which animals have very small fat stores, and with the morbidity associated with excessive fat.

Continuing the theme, Jim Nelson (University of Texas Health Science Center, San Antonio, USA) presented a very nice study on dietary restriction in mice and the effects it has on the inflammatory response. Dietary restriction is known to result in increased stress resistance, longevity, and attenuation of the inflammatory response, and mice undergoing dietary restriction have increased levels of circulating corticosterone. As corticoids are known to counteract inflammatory responses, the elevated levels of plasma corticoids during dietary restriction are a prime suspect for mediating these effects. To study this, Nelson and co-workers performed elegant studies using a corticosterone releasing hormone (CRH) knock-out mouse model, which shows a drastically reduced corticoid response, together with hormone-replacement therapy. They found that CRH deficiency does indeed prevent the inflammatory attenuation normally observed during dietary restriction, and they are in the process of examining whether elevated corticoid levels are necessary for the long lifespan of mice undergoing dietary restriction. Taken together, these three studies all point towards inflammation as a process that may exemplify the 'antagonistic pleiotropy' theory of ageing: although inflammation is beneficial early in life to prevent infection and disease, the results of inflammatory processes later in life can be detrimental and lead to premature ageing.

Ageing in yeast

The baker's yeast *Saccharomyces cerevisiae* has recently become an important model system for both ageing and cancer cell biology. Ageing in yeast can be measured in terms of chronological lifespan (the amount of time that passes until a yeast cell can no longer form a colony), and in terms of replicative lifespan (the number of times a yeast cell can

divide). Previous work has shown that dietary restriction can extend the replicative lifespan of yeast and that this effect is dependent on the activity of the NAD-dependent protein deacetylase, Sir2. Additionally, over-expression of Sir2 in yeast results in a dramatic increase in replicative lifespan. The effects of Sir2 on lifespan appear to be conserved, as over-expression of the *Caenorhabditis elegans* homolog, Sir-2.1, results in marked increases in lifespan in the worm as well.

A presentation on yeast ageing at the meeting has now brought into question some of these earlier findings about the role of Sir2. One of the problems with the yeast model system is the lack of a uniform genetic background for ageing studies. A mutation that extends lifespan in a short-lived genetic background but not in a longer-lived one is unlikely to be informative about the ageing process. In this case the extended lifespan is likely to occur because the mutation is rescuing some type of 'sickness' in the short-lived strain. To address this question, Brian Kennedy (University of Washington Medical School, Seattle, USA) has systematically examined in a long-lived genetic background the effects of 42 genes reported to regulate either chronological or replicative ageing. Whereas most mutations that shortened lifespan still had the same effect, only 5 of 12 mutations that had been reported to lengthen lifespan still did so in the long-lived strain. Kennedy also examined the interplay between dietary restriction and Sir2. Over-expression of Sir2 in a long-lived strain did still increase lifespan (although to a lesser extent), but in contrast to earlier studies, Kennedy showed that dietary restriction appears to act independently of Sir2 in the long-lived strain. These data illustrate the importance of establishing a standard genetic background for ageing studies in yeast.

Overall, the meeting brought together some of the worlds best bio-gerontologists for a terrific four-day review of ageing research. Work presented at the meeting highlighted several emergent themes that could prove very exciting in future studies. The conference was organized in association with the Elsevier journal *Mechanisms of Ageing and Development*. Invited papers, as well as selected, edited submitted presentations will be published in a special edition of the journal.