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*Introduction*

# The new science of ageing

Thanks to improvements in hygiene and healthcare, human life expectancy in developed countries has been increasing at a steady rate of about 2.5 years per decade since the middle of the nineteenth century [1]. People are staying healthier as they go through middle and older age and, as a result, they are living longer. Although this crowning achievement of human civilisation should be celebrated as such, it is receiving a decidedly mixed press. The reason is that more people are now living long enough to experience the loss of function and diseases of older age. Ageing is the major risk factor for all of the predominant killer diseases, including cardiovascular disease, cancer and neurodegeneration, and the main burden of ill health is now falling on the older section of the population. However, until recently, the complexity of the ageing process has made it appear an unpromising target for experimental analysis or medical intervention. At best, a piecemeal approach to the problems of ageing has seemed feasible [2].

Research into ageing has undergone a revolution in recent years, with the discovery that mutations in single genes can increase lifespan in laboratory animals. Rather than simply extending the moribund period at the end of life, these genetic interventions often keep the animals in a state of youthful health and vigour for longer, and in mice they produce a broad-spectrum maintenance of function and freedom from disease as the animals age. Mechanisms of ageing also show strong evolutionary conservation, with mutations in related genes extending the lifespan of distantly related organisms, such as budding yeast, nematode worms, fruit flies and rodents [3,4]. These striking findings suggest that protecting against the ageing process can increase healthy lifespan and they have opened up the prospect of a broad-spectrum, preventative medicine for the diseases of ageing in humans [5]. The aim of the Discussion Meeting 'The new science of ageing' was to explore these new findings, with an emphasis on identifying key areas for future research.

Cynthia Kenyon [4] opened with the history of the discovery of the first long-lived mutants in the nematode worm *Caenorhabditis elegans*, and the finding that the genes involved encoded an insulin/insulin-like growth factor signalling (IIS) pathway. This effect of IIS is conserved during evolution, because similar mutants in fruit flies and mice have subsequently been shown to extend lifespan [4,6]. IIS matches nutrient-consuming processes, such as growth, metabolism and reproduction, to nutrient availability. It acts systemically in multicellular organisms, and may indeed have evolved with the advent of multicellularity. The closely connected Target of Rapamycin (TOR) pathway, which is present in yeast as well as in multicellular animals, senses amino acids, and also plays an evolutionarily conserved role in ageing [7]. Rapamycin, a potent and specific inhibitor of TOR, has recently been shown to extend lifespan in mice, a clear proof of principle for the use of pharmacological intervention into the ageing process [8]. Brian Kennedy discussed how mutations in TOR signalling extend lifespan in yeast, nematodes, fruit flies and mice [9], exploring the downstream signalling and effector mechanisms at work, including altered AMPK activity and translation, AMPK activity, autophagy, mitochondrial function and stress response. As with IIS, elucidating the precise modulation of TOR signalling, the tissues in which altered signalling is important and the combination of downstream effectors that act to extend lifespan will be a challenge requiring both incisive experiments and integrated modelling approaches. In mice, many of the mutations that extend lifespan alter growth hormone (GH) and IGF-1 signalling. Andrzej Bartke [10] pointed out that extension of lifespan is most robust in mice mutant for GH signalling itself. As with IIS and TOR signalling, the potential downstream effectors are numerous and include stress resistance, antioxidant defence, alterations to insulin, IGF or TOR signalling, reduced inflammation and altered mitochondrial function. These pathways have highly pleiotropic effects, not all of them desirable (for instance, reduced IIS can both impair wound healing and cause diabetes), and it will be important to understand the extent to which these different effects can be separated from each other by intervention at a suitable level in the signalling networks.

Work on the role of these pathways in human ageing is in its infancy, but developing rapidly. Eline Slagboom *et al.* [11], Heather Wheeler & Stuart Kim [12] and Nir Barzilai *et al.* [13] described work on both the phenotypes and genotypes associated with exceptional longevity in human study cohorts. Intriguingly, long-lived humans show a phenotypic resemblance to animals subject to dietary restriction and have a particularly low incidence of diabetes. Although genetic influences on human lifespan are small, at least some of the genes involved are human orthologues of ones shown to be important in animal lifespan, particularly

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the key IIS effector FoxO forkhead transcription factor. Interestingly, genes that affect lifespan seem in general to be different from those that confer susceptibility to specific ageing-related diseases.

A systems level approach to ageing has barely begun, but already functional genomic approaches are yielding new insights. For instance, gene expression profiles change with age in the human kidney, and individuals with youthful expression profiles for their chronological age also have youthful looking kidneys [14]. For these kinds of functional genomic approaches to reach their full potential, extensive databases and powerful methods of bioinformatic analysis will be needed, issues addressed by Janet Thornton [15]. Tom Kirkwood [16] addressed the challenge of applying a systems approach to the complexity of the ageing phenotype and its modification during extension of lifespan, illustrated by modelling of the interplay between mitochondrial dysfunction, telomere shortening and DNA damage in cellular senescence.

One of the most remarkable phenomena of ageing is that rejuvenated offspring are produced by ageing parents. The processes of spatial quality control that cause damaged cellular components to be retained in the parent, thus rejuvenating the offspring but causing the parent to age, were discussed by Thomas Nyström [17]. Great strides have been made, particularly in budding yeast in identifying damaged molecules that undergo asymmetrical segregation and the genes and mechanisms involved. The role of cellular senescence in organismal ageing was addressed by Maria Blasco [18], who considered the role of telomeres. In normal mice, artificially driven expression of telomerase leads to a slightly increased incidence of cancer. By contrast, if telomerase is similarly expressed in mice where resistance to cancer is augmented by overexpression of tumour suppressors, lifespan is extended, and this extension depends upon the catalytic activity of telomerase. This result implies that deficiencies in the maintenance of telomeres are normally limiting for mouse lifespan. Ageing of stem cells may be complex, and, in part, a consequence of ageing of the local and systemic environment, as well as of the stem cells themselves. Tom Rando [19] analysed the evidence for one mechanism by which stem cells may retain their regenerative potential in tissues, namely unequal partitioning of chromosomes at mitosis according to the age of their template DNA strands. Although the data broadly support the idea that stem and other progenitor cells retain the original DNA strand, with the new copy with its replication errors going to the offspring cell, the exact mechanisms and functional significance of the asymmetry await discovery. Little is known of the rate of accumulation of non-replicative errors on the parent DNA strand, which could be an important cause of damage in long-lived cells. Nor is it yet known whether lifespan-extending mutations modify the asymmetrical division of molecular damage or the maintenance of telomeres.

Although so far it has only scratched the surface, experimental work with the model organisms is starting to reveal exactly how amelioration of the ageing process protects against the diseases of ageing. Andrew Dillin [20] discussed work in *C. elegans* and the mouse, demonstrating that animal mutants for IIS are protected against neurodegenerative disease by amelioration of their proteotoxic aetiology. Interestingly, mutations that reduce IIS with or without increasing lifespan can protect against neurodegenerative disease, and it will be important to understand the exact relationships between these two outputs of the pathway. Dominic Withers [21] discussed how reduced IIS and TOR signalling produce a broad-spectrum improvement in health during ageing in mice. For instance, several long-lived mouse mutants are protected against cognitive and motor decline, adiposity, cancer, bone loss and glucose intolerance; the last is particularly striking given that some of these mouse models are insulin resistant when young. Understanding how a single mutation can have such profound effects on health during ageing is a major challenge for research in this area.

The aim of research into ageing is to improve the health of older humans. David Gems [22] considered the ethical implications of extending human lifespan, and concluded that the ethical imperative to free people from the diseases of ageing far outweighs the potential negative social consequences of increased lifespan. However, amelioration of ageing by medical intervention will require the development and testing of drugs that target the gene products that have this effect. Such an undertaking would pose major challenges for the pharmaceutical industry. William Evans [23] discussed some of these. Drug trials would have to be conducted over a long period and with older people, who often have complications from multiple chronic diseases and polypharmacy. Furthermore, a broad spectrum improvement in health is not an outcome that would currently motivate a drug trial and nor is frailty a recognised medical problem. In practice, these considerations may be the major obstacles to the translation of the science of ageing into improvements in the health of older people. However, pressure from the growing population of older people may nonetheless change the face of geriatric medicine in the not too distant future.

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