CURRENT KEY DEVELOPMENTS

Growing up in ageing

TBL Kirkwood, *director, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne*

Email: tom.kirkwood@newcastle.ac.uk

Early steps

My introduction to the science of ageing came about by chance, through a brief conversation in an elevator at the National Institute for Medical Research (NIMR) in Mill Hill, London, with geneticist Robin Holliday. Fresh from university, I had very recently joined the staff of the National Institute for Biological Standards and Control, which was in the process of being formed out of two former divisions of the NIMR. Holliday knew that I had trained in mathematical biology and he had an idea about the ageing of human cells in culture that had a strong mathematical flavour to it. Within a few months we jointly published a paper proposing the 'commitment theory' of cellular ageing,[1] which offered an explanation of the striking contrast between the finite growth of normal, diploid human fibroblasts (the Hayflick limit) and the indefinite growth of malignantly transformed cells. This led quickly to a major experimental test of the theory's predictions.[2] Meanwhile, I had also become interested in the underlying molecular mechanisms that might be responsible for driving cells to age, particularly the idea that deterioration might be caused by a feedback of errors in the cells machinery for synthesising macromolecules.[3] Curious about why ageing should occur, I was able to connect my two lines of interest in the cellular and molecular mechanisms of ageing with the logic of Darwinian evolution. The result was a paper proposing what soon came to be known as the 'disposable soma' theory – the hypothesis that, under pressure of natural selection, organisms evolved to put only limited effort into somatic maintenance and repair, reserving special measures for the germline.[4] The significance of the disposable soma theory was that for the first time it was possible to unite within a single framework an explanation of both why and how (in mechanistic terms) ageing occurs.

At the National Institute for Medical Research

During the 1970s, research on biomedical aspects of ageing was an extremely sparse affair. Despite a flurry of activity that had occurred in the 1950s, much of it recorded in the series of Ciba Foundation Colloquia on Ageing, there were very few active groups anywhere in the world, and only a tiny handful in the UK. The general opinion was that ageing was too complicated a subject to offer the hope of any real progress, and there was almost no recognition that the intrinsic biology of ageing might contribute to the pathogenesis of age-related frailty, disability and disease. Nevertheless, in 1981 I was able to secure a tenured scientific position at the NIMR, albeit one that required me to include other interests than ageing within a general portfolio of mathematical biology research. The latter included some interesting work on bacterial growth and on the kinetics of how viral infections might be modulated by defective interfering virus particles, as well as some formative steps in the newly emerging discipline of bioinformatics. In 1988, I was able to form and direct a new Laboratory of Mathematical Biology, within which I could explore some of the particular implications of the disposable soma theory, notably with regard to the prediction that ageing should have multiple underlying mechanisms that might interact in important ways with each other.[5,6] The disposable soma theory was also developed very considerably with regard to its broader implications for the mechanisms and comparative biology of ageing.[7–9]

The first UK chair in biological gerontology

Although research within a well-established environment like the NIMR had many advantages, it became clear that significant expansion of ageing research did not conform to the current strategic priorities of the institute. In 1993, I accepted an appointment as professor of biological gerontology at the University of Manchester. In a farsighted 1969 article on the problem of biomarkers of ageing, Alex Comfort, whose book *The biology of senescence* had been an inspiration to me, had lamented the lack of a university chair on the subject of biological ageing in any British university.[10] At last, Comfort's wish had been realised.

The years at Manchester coincided with a significant expansion of research in the biology of ageing, aided in great measure by a specific science of ageing initiative funded by the Biotechnology and Biological Sciences Research Council (BBSRC). As funding became somewhat easier to obtain and the field began to grow in status, significant new results began to be published from groups around the world, including our own. Of particular significance from my group were the demonstration that, as predicted by the disposable soma theory, the capacity of cells to withstand molecular stresses was positively correlated with species' longevity, thereby supporting the idea that longevity was regulated by investments in somatic maintenance and repair,[11] and the discovery of important functional changes with ageing in tissue stem cells. First steps were also taken to map out approaches to investigating approaches to human longevity,[12,13] and a study of British aristocrats over many centuries confirmed the existence of an evolutionary trade-off between human fertility and longevity.[14]

The Institute for Ageing and Health

Being keen to work in an environment offering scope to establish real critical mass in ageing research, I moved in 1999 to the Institute for the Health of the Elderly (IHE) at Newcastle

University. The IHE, whose name was soon changed to the Institute for Ageing and Health, was founded on a platform of excellence in geriatric medicine and in dementia research. Its expansion after 1999 to include a major programme on the biology of ageing has led to the creation of a substantial, multidisciplinary research environment which includes biologists, clinicians, technologists and social scientists. Funding was quickly obtained for a new building, the Henry Wellcome Laboratory for Biogerontology Research, completed in 2003. This has been followed in rapid succession by four further buildings which together began the formation of an integrated biomedical Campus for Ageing and Vitality. In addition to new buildings, expansion of research was made possible with research funding from the BBSRC to create the Centre for Integrated Systems Biology of Ageing and Nutrition, spearheading the study of complexity in ageing[15]; the Wellcome Trust for the Clinical Ageing Research Unit directed by David Burn; the UK Research Councils Lifelong Health and Wellbeing initiative for the Centre for Brain Ageing and Vitality directed by Doug Turnbull; and the National Institute for Health Research for the Biomedical Research Centre on Ageing directed first by Chris Day and now by Patrick Chinnery. At the same time, there was opportunity to influence the national agenda for ageing research as specialist adviser to a House of Lords Science and Technology Select Committee inquiry into ageing in 2005 and through a Government Office for Science Foresight report on Mental Capital Through Life.[16,17] In February 2010, Newcastle University was awarded the Queen's Anniversary Prize for Higher and Further Education for its programme of research on ageing and health.

Future prospect

Research on the underlying mechanisms of ageing is now a major discipline within the life sciences, recognised as a priority by most of the major funding agencies. The frequency with which research articles appear in the highest impact general scientific and medical journals is a clear sign of the transformed status of the field. Nevertheless, immense challenges are still to be addressed, including the mechanistic complexity of the ageing process, its diversity of effects in cells and tissues, the genetics of longevity, and the fascinating relationship between intrinsic ageing and the many diseases to which it gives rise. It has been exciting to have experienced this transformation in research on ageing from its days as a scientific rarity to one of the biggest growth areas in biomedical science. It is about time.

References

1 Kirkwood TBL, Holliday R. Commitment to senescence: a model for the finite and infinite growth of diploid and transformed human fibroblasts in culture. *J Theor Biol* 1975;53:481–96.
2 Holliday R, Huschtscha LI, Tarrant GM, Kirkwood TBL. Testing the commitment theory of cellular ageing. *Science* 1977;198:366–72.
3 Kirkwood TBL, Holliday R. The stability of the translation apparatus. *J Mol Biol* 1975;97:257–65.
4 Kirkwood TBL. Evolution of ageing. *Nature* 1977;270:301–4.
5 Kowald A, Kirkwood TBL. Towards a network theory of ageing: a model combining the free radical theory and the protein error theory. *J Theor Biol* 1994;168:75–94.
6 Kowald A, Kirkwood TBL. A network theory of ageing: the interactions of defective mitochondria, aberrant proteins, free radicals and scavengers in the ageing process. *Mut Res* 1996;316:209-236.
7 Kirkwood TBL. Repair and its evolution: survival versus reproduction. In: Townsend CR, Calow P (eds), *Physiological ecology: an evolutionary approach to resource use*. Oxford: Blackwell Scientific Publications, 1981:165–89.
8 Kirkwood TBL. Comparative and evolutionary aspects of longevity. In: Finch CE, Schneider EL (eds), *Handbook of the biology of aging*. New York: Van Nostrand Reinhold, 1985:27–44.
9 Kirkwood TBL, Cremer T. Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. *Hum Gen* 1982;60:101–21.
10 Comfort A. Test-battery to measure ageing-rate in man. *Lancet* 1969;27:1411–5.
11 Kapahi P, Boulton ME, Kirkwood TBL. Positive correlation between mammalian life span and cellular resistance to stress. *Free Radical Biology Med* 1999;26:495–500.
12 Schächter F, Cohen D, Kirkwood TBL. Prospects for the genetics of human longevity. *Hum Gen* 1993;91:519–26.
13 Schächter F, Faure-Delanef L, Guénot F *et al*. Genetic associations with human longevity at the APOE and ACE loci. *Nature Gen* 1994;6:29–32.
14 Westendorp RGJ, Kirkwood TBL. Human longevity at the cost of reproductive success. *Nature* 1998;396:743–6.
15 Kirkwood TBL. A systematic look at an old problem. *Nature* 2008;451:644–7.
16 Beddington J, Cooper CL, Field J *et al*. The mental wealth of nations. *Nature*. 2008;455:1057–60.
17 Kirkwood TBL, Bond J, May C, McKeith I, Teh M. *Foresight Mental Capital and Wellbeing Project. Mental capital through life: future challenges*. London: Government Office for Science, 2008.

Sarcopenia and some simple approaches to modifying the consequence of ageing

Sarah (Sallie) Lamb, *professor of trauma rehabilitation, Nuffield Department of Rheumatology and Orthopaedic Surgery, University of Oxford and director and professor of rehabilitation, Warwick Clinical Trials Unit, University of Warwick*

Email: S.Lamb@warwick.ac.uk

In popular culture, and from the time of the ancient Greeks, aging has traditionally been associated with declining physical and cognitive vitality.[1] The size and profitability of the 'anti-ageing' industry indicates the desire of many people to stave off the apparently inevitable cosmetic and functional insults of time. Potential remedies range from creams, elixirs, vitamin tonics and supplements, to the fountain of youth portrayed in the 1980s film *Cocoon*, in which the residents of a retirement village sample the delights of rejuvenation. The emerging culture of celebrity in the 21st century provides glowing examples of older actors, actresses and so on, who attest to the power of diet, exercise and a handy cosmetic surgeon. Such experiences of aging are by no means universal, but open a portal to understanding how progress in exercise physiology and prescription over the last 20 years provide real hope of enhancing the experience of aging.