Biogerontology (2010) 11:507–511
DOI 10.1007/s10522-010-9288-1

OPINION

# Longevity mutants do not establish any "new science" of ageing

**Robin Holliday · Suresh I. S. Rattan**

Received: 31 May 2010 / Accepted: 2 June 2010 / Published online: 15 June 2010


**Abstract** The biological reasons for ageing are now well known, so it is no longer an unsolved problem in biology. Furthermore, there is only one science of ageing, which is continually advancing. The significance and importance of the mutations that lengthen the lifespan of invertebrates can be assessed only in relationship to previous well-established studies of ageing. The mutant strains of model organisms that increase longevity have altered nutrient signalling pathways similar to the effects of dietary restriction, and so it is likely that there is a shift in the trade-off between reproduction and maintenance of the soma. To believe that the isolation and characterisation of a few invertebrate mutations (as well as those in yeast) will "galvanise" the field and provide new insights into human ageing is an extreme point of view which does not recognize the huge progress in ageing research that has been made in the last 50 years or so.

**Keywords** Ageing · Lifespan · Gerontogenes · Model systems · Evolution

R. Holliday
Australian Academy of Sciences, c/o 12 Roma Court, West Pennant Hills, NSW 2125, Australia

S. I. S. Rattan (✉)
Laboratory of Cellular Ageing, Department of Molecular Biology, Aarhus University, 8000 Aarhus, Denmark
e-mail: rattan@mb.au.dk

## Biogerontology: an ongoing science of ageing

The Royal Society of London recently organized a 2 day Discussion Meeting on "The new science of ageing." It will be published in the Philosophical Transactions of the Society. In the announcement of the meeting, part of the synopsis included the following:

> *Research into ageing has been galvanized by the discovery of single-gene mutations that extend healthy lifespan of laboratory animals and that delay multiple, age-related diseases. Evolutionary conservation of these genetic effects allows the use of invertebrates to understand human ageing. This meeting will discuss the scientific challenges and the prospects for a broad-spectrum, preventative medicine for age-related disease*
> http://royalsociety.org/the-new-science-of-ageing/.

In this article we question the validity of this approach to understanding human ageing on the following grounds. First, we think the title of the meeting is inappropriate. It suggests that "the new science of ageing" in some way replaces previous research on ageing, with the implication that this research constitutes an old science of ageing. It cannot be disputed that there is only one science of ageing, which is continually advancing. Second, the significance and importance of the mutations that lengthen the lifespan of invertebrates can be assessed

only in relationship to previous well-established studies of ageing. These have lead to many strong conclusions, and in particular, the reasons why ageing exists in almost all animals (Hayflick 2007; Holliday 1995; Holliday 2006; Kirkwood 2005). Third, despite what the synopsis of the Royal Society states, it is a gross overstatement to write that the mutants "delay multiple, age-related diseases"; - what age-related diseases do *Caenorhabditis elegans* and *Drosophila* really have? There is almost no documentation of this. The very limited knowledge of age-related diseases in selected invertebrates, has to be contrasted with the *huge* amount of information about human age-related diseases.

## Survival, maintenance, reproduction and longevity

The energy resources available to an animal come from its food, but the way these resources are used is not the same in all animals. Nevertheless, in all animals which age there are three major features of its life history that require energy. The first is essential for all these animals: general metabolism, respiration, movement, feeding and excretion. The second is reproduction, including in many cases parental care. The third is development to an adult and then maintenance of adults during the period when reproduction can occur. A given period of reproduction is followed by senescence, ageing and death. The first allocation of resources is reasonably constant (with some exceptions, such as animals which do not move because they are anchored to a substrate). The second and third allocation of resources is extremely variable. Thus there are animals that produce large numbers of offspring, but have short lifespans because they allocate fewer resources to maintenance of the adult body. Other animals produce fewer offspring, but invest resources in maintaining the adult for a longer period of time. Therefore there is a trade-off between the second and third allocation of resources, which is seen in many different taxonomic groups. Evolution and habitat determine the animal's life history strategy, and the balance between reproduction and longevity. This will in turn depend on the likelihood of survival of young and adult individuals in their natural environment. High mortality correlates with short lifespans and low mortality with long lifespans. Also, fecundity is inversely related to longevity (Holliday 1995).

## Longevity extension and trade-off

At first sight, it seems paradoxical that the reduction in resources brought about by dietary restriction (DR) often leads to an increase rather than a decrease in lifespan (reviewed in (Le Bourg and Rattan 2006)). The explanation is that DR diverts resources from reproduction to maintenance. It is an evolutionary adaptation (Holliday 1989; Kirkwood and Shanley 2005; Shanley and Kirkwood 2006; Turturro and Hart 1991). In a natural environment, the food supply may often fluctuate. During a period when food is scarce, it is disadvantageous to attempt to breed, and advantageous to survive by investing what resources are available in preserving the integrity of the soma, or body. Then when more food resources become available reproduction can begin again. Chronic DR over a lifetime delays age-associated disease and the onset of senescence. DR until the control animals cease to breed, and then the provision of a full diet allows these animals to reproduce at a later age than the control animals. Additionally, the molecular mechanisms for the lifespan extending effects of DR range from transcriptional and translational changes to post-translational modifications, and mild stress-induced hormesis (reviewed in: Everitt et al. 2010; Rattan 2008a, b).

There are now many genetic mutations that alter longevity in various model systems. The first gene mutation resulting in the extended lifespan of an organism was the *age-1* mutant in the nematode *C. elegans* (Friedman and Johnson 1988; Johnson 1990). Since then a large number of putative gerontogenes or longevity genes have been reported in yeast, *C. elegans*, *Drosophila* and rodents, which when experimentally mutated to lose function result in the extension of average and maximum lifespan of the organism (Rattan and Singh 2009). The methods used for the identification of such genes include induction of mutations and deletions by irradiation and chemical mutagens, alterations in gene expression by knockout, by homologous recombination, and reduction in gene expression by RNAi-induced abrogation of translation (Curran and Ruvkan 2007; Olsen et al. 2006; Panowski et al. 2007).

It is important to note that in these studies, an extension of lifespan occurred when one or multiple interventions resulted in the reduction or total inhibition of the activity of one or more genes. Some of the main pathways whose loss-of-function is shown to associate with extended period of survival are: (i) energy generation and utilization in mitochondrial respiratory chain; (ii) nutrition and hormonal sensing and signalling including insulin/insulin-like growth factor-1 (IGF-1) and its target forkhead transcription factor FOXO, transcriptional silencing by sirtuin-mediated histone deacetylase; and (iii) translational interference through target of rapamycin (TOR), which is a kinase that integrates signals from nutrients and growth factors, and regulates cell growth and the progression of cell cycle (Hipkiss 2008; North and Sinclair 2007). Similarly, several mutant mice strains with defects in growth hormone (GH) pathways, including deficiencies of GH levels and GH receptor, have extended lifespans (Fontana et al. 2010; Kenyon 2010; Longo 2009; Vijg and Campisi 2008). In *C. elegans* two of the main genes in which induction of mutation(s) leading to the loss of function results in the modulation of lifespan are IGF-1 tyrosine kinase receptor daf-2 and forkhead transcription factor daf-16, which appear to work antagonistically. For example, whereas a loss of daf-2 activity extends longevity, the loss of daf-16 suppresses that effect. Further comparative analyses of such genetic mutants in worms, flies and rodents indicate that the pathway of insulin/IGF-1 signalling (IIS) may be a key regulator of longevity (Kenyon 2010; Longo 2009).

Although theses studies have demonstrated longevity-extending effects of various genes in controlled laboratory conditions, there is very little information available on the basic process of ageing in terms of the rate and extent of occurrence and accumulation of macromolecular damage and its physiological consequences in these animals. There is also almost no information available as to what is the physiological price paid for inactivating such genes whose normal function is a part of the general metabolism and signalling (Van Voorhies et al. 2006). There is some evidence that laboratory-protected longevity mutants in *C. elegans* have reduced Darwinian fitness when competing with the wild type worms under nutritionally challenging conditions (Chen et al. 2007) Similarly, klotho-induced insulin resistance and the paradox of the insulin/IGF-1 signalling pathways in longevity extension seriously question the practicality of such gene manipulations in humans (Rincon et al. 2004; Unger 2006; Van Voorhies et al. 2006).

Studies have also been performed in which the effects of adding one or multiple copies of various genes, that leads to the increased expression of their gene products, has resulted in the extension of lifespan in model systems worms, fruitflies, rodents and cultured cells. Some such transgenic manipulations include the addition of antioxidant genes superoxide dismutase (SOD) and catalase, $NAD^+$-dependent histone deacetylases sirtuins, forkhead transcription factor FOXO, heat shock proteins, heat shock factors, protein repair methyltransferases, and klotho which is an inhibitor of insulin and IGF1 signalling (Fontana et al. 2010; Kenyon 2010; Longo 2009; Schriner and Linford 2006; Vijg and Campisi 2008).

It is striking that mutant strains of these organisms that increase longevity have altered nutrient signalling pathways (Partridge 2010). Therefore a strong argument can be made that their effects are similar to DR (Fontana et al. 2010) and that they shift the trade-off between reproduction and maintenance of the soma. These signalling pathways seem to be conserved in invertebrates and mammals. It can be said that the DR lifespan phenotype is a *phenocopy* of mutants that extend lifespan. It could also be said that these mutants are *genocopies* of DR. It might also be expected that some mutants would increase lifespan by slowing down metabolic rate. In invertebrates this might be an effect comparable to lowering the temperature, which is known to often increase longevity (Economos and Lints 1986), but not always (Norry and Loeschcke 2002; Olshansky and Rattan 2005). Others mutants may have slower development, which also stretches out the lifespan (Economos and Lints 1985; Finch 2009; Ishii et al. 1994). The effect of DR on longevity was discovered in mice more than 75 years ago, and only recently in *C. elegans* and *Drosophila*. It can be said to be the only environmental effect that extends lifespan. The fact that mutants exist that mimic DR is interesting and important, but it cannot be said to constitute a "new biology of ageing" (Partridge 2010).

Ageing is a complex process affecting molecules, cells, tissues, organs, as well as physiological

homeostasis/homeodynamics (Rattan 2007). It is not always realized that the maintenance of the soma is also very complex. In mammals it includes DNA repair, defences against free radicals, breakdown of defective proteins, proofreading in the synthesis of macromolecules, the immune system, detoxification, wound healing, epigenetic controls in differentiated cells, and the defenses against cancer. Each maintenance mechanism is a discipline in its own right, but the study of ageing encompasses them all. It is therefore obvious that there are very large numbers of genes that encode the many components of maintenance, and these depend on the investment of resources. There is now much evidence from comparative studies that the efficiency of different maintenance mechanisms correlates with the animal lifespan (Holliday 1995; Holliday 2006). It is also clear that ageing is multicausal. This follows from the fact that the ageing phenotype is complex, and there may be a gradual failure of many maintenance mechanisms (Holliday 1995; Holliday 2006; Rattan 2006).

## Polygenic determinants of ageing and longevity

The polygenic control of ageing is also shown by experiments with *Drosophila* in which there is selection for longevity (Luckinbill 1998; Rose 1991). The starting population is outbred and heterozygous for many gene loci. The offspring from the oldest breeding females are selected for the next generation, and this selection is continued. After several generations of selection the longevity of the population became significantly greater than that of the starting population (up to two-fold). It is also known that human lifespan is under polygenic control (Yashin et al. 2000). There are single genes that cause premature ageing, but no single genes in humans have been reported so far that significantly increase longevity (Rattan and Singh 2009). It is also clear that evolution for reduced or increased longevity can occur within major taxonomic groups, and this selection is not acting on a small number of genes, but on many.

The biological reasons for ageing are now well known, so it is no longer an unsolved problem in biology (Hayflick 2007; Holliday 2006; Kirkwood 2005). Future research will attempt to unravel in detail the many causes of ageing and allow the development of preventative measures that will reduce the incidence and severity of age-associated diseases (Rattan 2005; Rattan 2008a, b). To believe that the isolation and characterisation of a few invertebrate mutations (as well as those in yeast) will "galvanise" the field and provide new insights into human ageing (http://royalsociety.org/the-new-science-of-ageing/; Partridge 2010) is an extreme point of view which does not recognize the huge progress in ageing research that has been made in the last 50 years or so.

## References

Chen J, Senturk D, Wang JL, Müller HG, Carey JR, Caswell H, Caswell-Chen EP (2007) A demographic analysis of the fitness cost of extended longevity in Caenorhabditis elegans. J Gerontol Bio Sci 62A:126–135

Curran SP, Ruvkan G (2007) Lifespan regulation by evolutionarily conserved genes essential for viability. PLoS Genet 3:e56

Economos AC, Lints FA (1985) Growth rate, life span in Drosophila. V. The effect of prolongation of the period of growth on the total duration of life (J.H. Northrop, 1917). revisited. Mech Ageing Develop 33:103–113

Economos AC, Lints FA (1986) Developmental temperature and lifespan in *Drosophila melanogaster*. I. Constant developmental temperature: evidence for physiological adaptation in a wide temperature range. Gerontol 32: 18–27

Everitt AV, Rattan SIS, Le Couteur DG, de Cabo C (eds) (2010) Calorie restriction, aging and longevity. Springer, New York

Finch CE (2009) Update on slow aging and negligible senescence–a mini-review. Gerontology 55:307–313

Fontana L, Partridge L, Longo VD (2010) Extending healthy life span–from yeast to humans. Science 328:321–326

Friedman DB, Johnson TE (1988) A mutation in the age-1 gene in Caenorhabditis elegans lengthens life and reduces hermaphrodite fertility. Genetics 118:75–86

Hayflick L (2007) Biological aging is no longer an unsolved problem. Ann NY Acad Sci 1100:1–13

Hipkiss A (2008) Energy metabolism, altered proteins, sirtuins and ageing: converging mechanisms? Biogerontology 9:49–55

Holliday R (1989) Food, reproduction and longevity: is the extended lifespan of calorie-restricted animals an evolutionary adaptation? BioEssays 10:125–127

Holliday R (1995) Understanding ageing. Cambridge University Press, Cambridge

Holliday R (2006) Aging is no longer an unsolved problem in biology. Ann NY Acad Sci 1067:1–9

Ishii N, Suzuki N, Hartman PS, Suzuki K (1994) The effects of temperature on the longevity of a radiation-sensitive mutant *rad-8* of the nematode *Caenorhabditis elegans*. J Gerontol 49:B117–B120

Johnson TE (1990) Increased life-span of age-1 mutants in *Caenorhabditis elegans* and lower Gompertz rate of aging. Science 249:908–912

Kenyon CJ (2010) The genetics of ageing. Nature 464:504–512
Kirkwood TBL (2005) Understanding the odd science of aging. Cell 120:437–447
Kirkwood TB, Shanley DP (2005) Food restricticon, evolution and ageing. Mech Ageing Dev 126:1011–1016
Le Bourg E, Rattan SIS (2006) Special issue: can dietary restriction increase longevity in all species, particularly in human beings? Introduction to a debate among experts. Biogerontology 7:123–125
Longo VD (2009) Linking sirtuins, IGF-I signaling, and starvation. Exp Gerontol 44:70–74
Luckinbill LS (1998) Selection for longevity confers resistance to low-temperature stress in *Drosophila melanogster*. J Gerontol Biol Sci 53A:B147–B153
Norry FM, Loeschcke V (2002) Temperature-induced shifts in associations of longevity with body size in *Drosophila melanogster*. Evolution 56:299–306
North BJ, Sinclair DA (2007) Sirtuins: a conserved key unlocking AceCS activity. Trends Biochem Sci 32:1–4
Olsen A, Vantipalli MC, Lithgow GJ (2006) Checkpoint proteins control survival of the postmitotic cells in *Caenorhabditis elegans*. Science 312:1381–1385
Olshansky SJ, Rattan SIS (2005) At the heart of aging: is it metabolic rate or stability? Biogerontology 6:291–295
Panowski SH, Wolff S, Aguilaniu H, Durieux J, Dillin A (2007) PHA-4/Foxa mediates diet-restriction-induced longevity of C. elegans. Nature 447:550–555
Partridge L (2010) The new biology of ageing. Philos Trans R Soc Lond B Biol Sci 365:147–154
Rattan SIS (2005) Anti-ageing strategies: prevention or therapy? EMBO Reports 6:S25–S29
Rattan SIS (2006) Theories of biological aging: genes, proteins and free radicals. Free Rad Res 40:1230–1238
Rattan SIS (2007) Homeostasis, homeodynamics, and aging. In: Birren J (ed) Encyclopedia of gerontology. Elsevier Inc, UK, pp 696–699
Rattan SIS (2008a) Hormesis in aging. Ageing Res Rev 7:63–78
Rattan SIS (2008b) Increased molecular damage and heterogeneity as the basis of aging. Biol Chem 389:267–272
Rattan SIS, Singh R (2009) Gene therapy in aging. Gene Ther 16:3–9
Rincon M, Muzumdar R, Altmon G, Barzilai N (2004) The paradox of the insulin/IGF-1 signaling pathway in longevity. Mech Age Dev 125:397–403
Rose MR (1991) Evolutionary biology of aging. Oxford University Press, New York
Schriner SE, Linford NJ (2006) Extension of mouse lifespan by overexpression of catalase. Age 28:209–218
Shanley DP, Kirkwood TB (2006) Caloric restriction does not enhance longevity in all species and is unlikely to do so in humans. Biogerontology 7:165–168
Turturro A, Hart RW (1991) Longevity assurance mechanisms and calorie restriction. Ann NY Acad Sci 621:363–372
Unger RH (2006) Klotho-induced insulin resistance: a blessing in disguise? Nat Med 12:56–57
Van Voorhies WA, Curtsinger JW, Rose MR (2006) Do longevity mutants always show trade-offs? Exp Gerontol 41:1055–1058
Vijg J, Campisi J (2008) Puzzles, promises and a cure for ageing. Nature 454:1065–1071
Yashin AI, De Benedictis G et al (2000) Genes and longevity: lessons from studies of centenarians. J Gerontol Biol Sci 55A:B319–B328