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Beyond the evolutionary theory of ageing, from functional genomics to evo-gero

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By the mid 1970s, the mechanisms by which ageing can evolve had a secure theoretical basis in population genetics. Here, we discuss how subsequent evolutionary work has focussed on testing and extending this theory, and on attempting to integrate it with other emerging facets of the biology of ageing, such as genetic studies of long-lived mutants and of phenotypic plasticity in ageing, such as in response to nutritional status. We also describe how functional genomic studies are providing new insights into the evolutionary forces shaping genome evolution and lifespan control. Future challenges include understanding the biochemistry of longevity and how its failure generates ageing and associated diseases, and the determination of the genetic basis of lifespan evolution and the great plasticity that it displays.

Introduction

The evolution of ageing presents a paradox for evolutionary biologists because a disadvantageous trait, namely a decline in reproductive prospects with age, has a demonstrated genetic basis and undergoes evolutionary change. Work on the evolution of ageing began over a century ago, resulting in a secure theoretical basis in population genetics with considerable empirical support [1,2]. A largely parallel body of work in biogerontology has produced descriptions of the phenotypes of ageing and experimental analysis of their mechanistic basis [3–6]. There have also been some interactions between these two approaches: for example, the phenomenon of cellular senescence, which can result in the presence of useless or even damaging cells in the dividing tissues of older humans, can be understood as a side-effect of a mechanism for preventing cancer [4,7]. In a similar vein, several of the neurodegenerative diseases of ageing, such as Huntington's and Alzheimer's, might arise as a result of the inadequacy of energetically expensive cellular defence mechanisms [8].

These findings are beginning to put phenotypic flesh on the genetic bones of the idea that ageing can evolve as a side-effect of traits that are beneficial at younger age, as postulated by the pleiotropy theory for the evolution of ageing. Work on startling cases of phenotypic plasticity in the natural world, where individuals of the same genotype differ greatly in their rate of ageing, for instance the extreme longevity of social insect queens relative to workers of the same genotype [9,10] and of parasitic relative to free-living forms [11], have begun to reveal mechanisms that can produce dramatic switches in the rate of ageing [12,13]. However, the intellectual traditions of evolutionary biology and biogerontology have tended to work independently of one another. We argue here that recent, experimental findings in biogerontology have paved the way for evolutionary approaches to make a substantial contribution to the biology of ageing and, ultimately, to medicine.

Why does ageing evolve?

The intrinsic decline in function that occurs during ageing appears to be caused by the accumulation of damage, particularly at the molecular level. As far as we know, no genes have evolved specifically because they cause damage to accumulate, and the evolution of ageing can therefore be understood only as a side-effect of other causes of evolutionary change. The mechanisms by which ageing can evolve were first elucidated by J.B.S. Haldane [14], P.B. Medawar [15] and G.C. Williams [16]. Extrinsic hazards from disease, predation and accidents mean that even potentially immortal organisms will die. Genetic effects that become apparent only later in life encounter a reduced force of natural selection, because not all their bearers will survive to express them. Haldane pointed out that late-onset genetic diseases in humans, such as Huntington's disease, encounter only weak selection, because most reproduction is complete by the age of onset [14]. Ageing could therefore result from the accumulation under mutation pressure of age-specific, deleterious mutations. In addition, if some mutations have pleiotropic effects, with beneficial effects in youth, such as high fecundity, but also with a higher subsequent rate of ageing, then they could be incorporated into the population by natural selection, which will act more strongly on the early, beneficial effect. Thus, variation in the rate of ageing would result from the readjustment of a tradeoff between youthful benefits and the subsequent rate of ageing. Both processes imply that faster ageing will evolve where the extrinsic hazard to adults is greatest, a hypothesis in general supported by the data [1,2,17].

Recent work on the evolution of ageing has highlighted extensions to the theory. Changes in extrinsic hazards can

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affect population density, which can in turn alter the expression of life-history traits, such as fecundity and survival, and, hence, modulate how a change in hazard affects the intensity of selection on different age classes [18]. In addition, the force of natural selection can stay the same or even increase over at least part of the adult period, for instance if there is growth and, hence, an increase in fecundity with age [19,20]. This could lead to the evolution of absent or negative senescence, for which there is some empirical evidence [5,19,21]. Transfer of resources between generations can also be important, particularly because it can result in selection for post-reproductive survival [22–25].

Long-lived mutants: a challenge to evolutionary biology?

Evolutionary theory makes clear predictions about the role of genes in ageing. For example, ageing is a non-adaptive process and, therefore, is not programmed in the sense that development is. The rate of ageing is also determined by the activities of the genes that contribute to the maintenance of viability and to fecundity. This polygenic basis could make the rate of ageing difficult to modify and, in particular, to slow down. If a mutation in a single gene slowed down the accumulation of one form of damage, all the other processes of damage accumulation would continue unaltered, leaving the rate of ageing little changed. Indeed, detailed study of the human ageing process has shown that it is highly complex, with multiple, tissue-specific forms of damage increasing in incidence with age. This complexity could imply that there are multiple, independent pathways of damage accumulation, rather than a single ageing process.

These arguments suggest that it should not be possible to investigate ageing using a mendelian genetic approach. However, during the early 1980s, Michael Klass set out to isolate long-lived mutants using the nematode *Caenorhabditis elegans*. Surprisingly, he succeeded [26]. Yet, despite this extraordinary achievement, he concluded that his findings must somehow be wrong; it appears that he was taught the evolutionary error of his ways. Soon afterwards, he left academic science for a successful career elsewhere [27]. However, his results stood up to the scrutiny of others. As Tom Johnson discovered, several of Klass' long-lived mutants contained mutations in the gene *age-1* (GenBank accession number: NM_064061). Thus, the wild-type *age-1* gene acts to increase the rate of ageing, halving the maximum lifespan of the adult worms [28].

At first sight, *age-1* appears to present a challenge to the evolutionary theory of ageing. Here, we have programmed ageing controlled by a single gene; it could hardly be clearer. So can the evolutionary theory survive this blow? The existence of *age-1* presents three problems [29]. First, how could the wild-type, life-shortening allele increase fitness? Second, how can the apparently programmed ageing caused by *age-1* be accounted for? Finally, how can the rate of ageing be controlled by a single gene?

The increased lifespan in *age-1* and related mutants in *C. elegans* is likely to be associated with reduced reproductive fitness. Lifetime fecundity is not increased and can be reduced, and the age of first reproduction is sometimes delayed or even prevented by the inappropriate formation of a dauer larva, a dormant larval stage that, in the wild type, is produced only in response to food shortage or crowding [30]. Little is known about the ecology of *C. elegans* but it seems likely that, in nature, the worm encounters cycles of boom and bust, doing much of its reproduction under the former conditions. Under these circumstances, early reproduction is favoured. Recent experimental work has confirmed that the mutants reduce fitness [31–33]; thus the wild-type *age-1* allele increases fitness by reducing dauer larva formation and speeding up and increasing adult reproduction.

What about programmed ageing? The *age-1* gene encodes part of a cellular signalling pathway that regulates dauer formation [6], an invertebrate insulin/insulin-like growth factor (IGF)-like signalling (IIS) pathway that is homologous to the more familiar pathways of mammals. IIS pathway genes control lifespan, which is therefore genetically determined. Discussions of programmed ageing are confused by the fact that 'programmed' means more than one thing. On the one hand, it refers to cases where gene action orchestrates a concerted process, as in development or programmed cell death (apoptosis). On the other, it means that a trait is affected by genetic variation. Arguably, ageing is programmed in the second but not the first sense [34], and, therefore, the existence of *age-1* and similar mutations does not necessarily imply that the wild-type alleles of the genes have been selected because they cause ageing.

How can lifespan be controlled by a single gene? Two possibilities are, first, that the mutations that extend lifespan are in genes whose products regulate the activity of many other genes and, second, that these genes do not in fact control the rate of ageing.

Mutations in genes encoding constituents of the IIS pathway can extend lifespan not only in *C. elegans,* but also in the fruit fly *Drosophila melanogaster* and the mouse *Mus musculus* [35]. There is therefore much interest in understanding the mechanisms by which IIS modulates lifespan. The principal effector of IIS pathway action on lifespan in *C. elegans* is a transcription factor, DAF-16 (abnormal in dauer larva formation 16), encoded by *daf-16* (GenBank accession number: NM_001026427). Microarray analysis of genes regulated by DAF-16 to extend lifespan implies that ~10% of genes in the genome are regulated, directly or indirectly [36]. This suggests that longevity is a highly polygenic trait (Figure 1). Functional analysis of IIS-regulated genes supports this view: in long-lived IIS mutants, some genes are upregulated (and therefore longevity associated) whereas others are downregulated (potentially life shortening). Recently, Murphy and co-workers showed that knockdown of longevity-associated genes frequently leads to small but significant reductions in lifespan in long-lived IIS mutants. Moreover, knockdown of genes associated with short lifespan frequently causes slight increases in lifespan. Thus, the large effects of reduced IIS on longevity appear to result from the cumulative effect of many genes with small effects on lifespan [37]. Comparable information from other mutations that extend lifespan in *C. elegans* and from long-lived mutants in other organisms

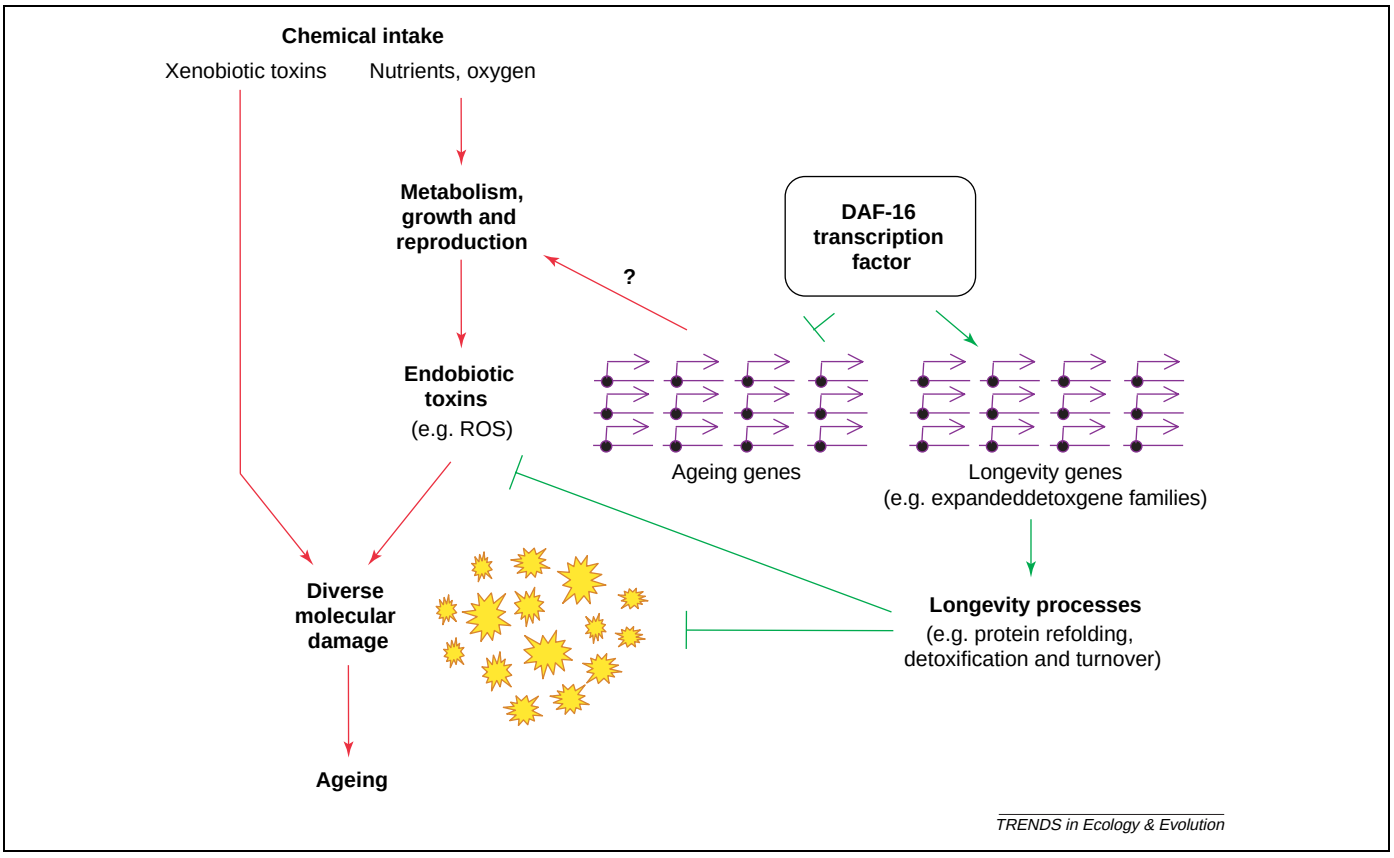


Figure 1. Molecular basis of ageing and longevity. Single gene mutations that affect longevity act via multiple target genes. The figure details a hypothetical view of the relationship between insulin–IGF-1 signalling, the genes that it regulates, growth, reproduction, molecular damage and longevity. Arrows represent the promotion of, and T bars inhibition of, the change shown. As depicted, molecular damage results from diverse stochastic mechanisms. DAF-16 stimulates the expression of numerous genes specifying a range of somatic maintenance processes, which promote longevity. However, it also switches off genes that promote ageing, although the mode of action of these genes is less clear. Here, we suggest that metabolism, growth and reproduction increase damage (arrow with question mark). Abbreviation: ROS, reactive oxygen species.

is needed to determine whether this conclusion applies more broadly.

A more radical possibility is that the mutations that increase lifespan do not slow down ageing. Recent work on another means of extending lifespan, dietary restriction (DR), has shown that, in *Drosophila* at least, DR acts acutely to reduce death rate [38]. For example, the mortality rate of flies switched from high to low food concentration drops rapidly, rather as if they recover from the effects of something in the food that is noxious at high concentrations. The physiological basis of this acute risk effect is not yet understood, but it is different from slowing the accumulation of the unrepaired damage that accumulates during ageing, which is not expected to be reversible [39]. It is not yet clear where the mutations that extend lifespan sit with respect to this dichotomy between amelioration of acute risk of death and of accumulation of damage. The time is ripe for a comparative investigation of the mechanisms by which lifespan is affected by evolved differences (i.e. between populations or species), evolved phenotypic plasticity, single-gene mutations and environmental interventions, such as DR. However, it will be necessary to develop the tools to investigate new model organisms that present substantial, evolved variation in lifespan. The standard laboratory model organisms thrive in laboratory conditions in part because of their rapid and copious reproduction. These traits are not in general characteristic of long-lived organisms. Application of the tools of biogerontology to these different sources of variation in lifespan will greatly increase our understanding of the biology of ageing and the potential for intervention in the process.

Mechanisms of extension of lifespan by mutations

Studies of genes regulated by IIS are providing clues about the biological processes by which single gene mutations increase lifespan. Various processes have been implicated in longevity assurance, from autophagy (the orchestrated destruction and removal of cellular macromolecules and organelles) to anti-oxidant and anti-bacterial defences [36,37,40–42]. Gene categories that are enriched among genes upregulated in long-lived adult *C. elegans* were recently identified by RNA expression profiling [36], and included many linked to cellular maintenance; for example, small heat shock proteins (smHSPs). HSPs have previously been shown to be important in longevity assurance [43–45]. Also present were four major gene classes of cellular detoxification (i.e. drug detoxification): cytochrome P450s (CYPs), short-chain dehydrogenase-reductases (SDRs), uridine diphosphate (UDP)-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs). These enzymes act in concert in the series of reactions leading to detoxification and excretion from the cell of lipophilic and electrophilic xenobiotic and

endobiotic toxins [46]. Thus, detoxification appears to be elevated in long-lived adult *C. elegans* [36]. This suggests that the toxins that detoxification eliminates normally limit lifespan and that this detoxification process assures longevity. Consistent with this, the overexpression of an IIS-regulated GST that detoxifies lipid-peroxidation products increases lifespan in *C. elegans* [47,48].

One suggested mode of action of evolutionary tradeoffs in controlling lifespan is that cellular maintenance processes consume energy and that natural selection results in the preferential allocation of resources to reproduction [49]. Additionally, processes such as reproduction might generate molecular and cellular damage [29]. Either way, inadequate resource investment in somatic maintenance would result in a 'disposable soma', subject to ageing [50,51]. Detoxification and HSP function both consume a considerable amount of energy. Thus, failure to invest sufficient resources in these maintenance processes might lead to faster rates of ageing [52].

Molecular damage and genome evolution

As well as microarray analysis, other aspects of functional genomics are providing insights into the mechanisms that control the rate of ageing. The sequencing of genomes is revealing a large, hitherto unseen side of the genetic complement: large gene families in which mutation of individual members generates little or no mutant phenotype. Many of these gene families show rapid rates of evolution, and a tendency to proliferate into large lineage-specific gene expansions [53–55]. A shared feature of many such gene families is a role in coping with a molecularly diverse environment. This includes olfaction and chemosensation, immune defence against infectious agents and parasites, and detoxification of toxins. For example, the largest gene family in *C. elegans* is that of G protein-coupled receptors involved in chemosensation, of which there are some 1300, and which evolve rapidly [56]. Other such rapidly evolving gene families include those of drug detoxification, mentioned above (CYPs, SDRs, UGTs and GSTs), which also undergo rapid diversification. In many organisms, a high proportion of the genes in the genome are members of such rapidly diversifying gene families; for example, ~50% in *C. elegans* and ~30% in *Drosophila melanogaster* [54].

A central axiom of the biology of ageing is that it is the result of stochastic damage, particularly at the molecular level. Functional genomic studies tell us that much molecular evolution is driven by the need to cope with a rapidly changing chemical environment. This raises an important question about ageing that is relevant to evolutionary and mechanistic biology: how do somatic maintenance processes deal with the chemical diversity of the molecular damage that is central to ageing? One must assume that the forms that damaged biomolecules and environmental toxins can take are almost limitless. Molecular recognition is essential to biological function, whether it involves interactions between proteins domains, between enzyme and substrate, or antibody and antigen. How can a genome evolve to deal with the near-infinite structural diversity of molecular junk? A good illustration of how serious a problem this is the contrast between the properties of the enzymes catalase and UGT (Box 1).

Future challenges: ageing and disease, evo-gero

Ageing is a major risk factor for many human diseases, including cardiovascular disease and a range of neurodegenerative diseases, and has been described as 'the most potent of all carcinogens' [57]. Studies of the mechanisms

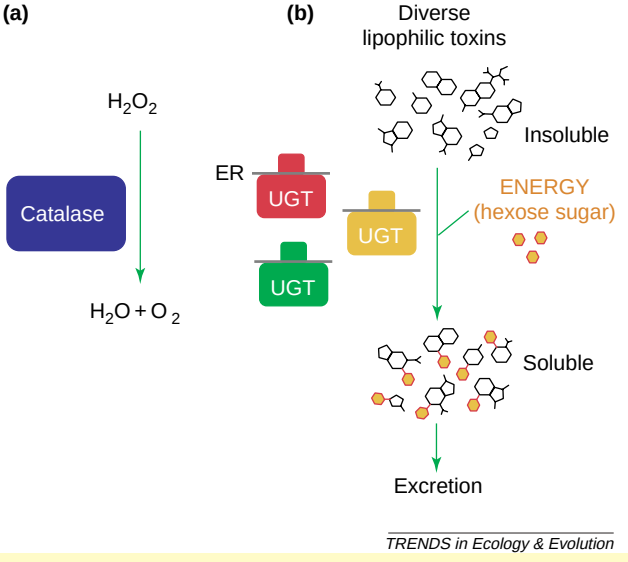
Box 1. The challenge to the genome of chemical diversity: a tale of two enzymes

Functional genomic analysis of genes with altered expression in long-lived *Caenorhabditis elegans* mutants suggests that longevity assurance biochemistries protect against a range of toxins and molecular damage [36,37]. The problem of the complexity of molecular damage can be illustrated by comparing the enzymes catalase and UGT.

Catalase breaks down hydrogen peroxide H_2O_2, a potentially damaging ROS, with very high efficiency and without requiring energy input (e.g. NADH or ATP), producing a product that comprises harmless cellular constituents (i.e. molecular oxygen and water) (Figure Ia). This high level of efficiency has presumably evolved thanks to the ubiquity of hydrogen peroxide in living systems.

In stark contrast are UGTs, which are mainly associated with the smooth endoplasmic reticulum via which their products are excreted from the cell [46]. A major function of UGTs is to attach a hexose sugar group (taken from UDP–glucuronic acid) to otherwise insoluble lipophilic toxins to render them soluble enough to be excreted [46] (Figure Ib). UGTs typically have broad substrate specificity and many different isoforms, presumably to deal with diverse and novel targets requiring detoxification (drug metabolism). They are also remarkably profligate in terms of energy use: each molecule that is detoxified requires a hexose sugar (~30 ATP equivalents). Moreover, once they have done their work, their product still needs to be excreted from the cell and the organism. Relative to catalase, UGTs seem remarkably inefficient and wasteful enzymes, and their existence is testimony to the difficulty that the genome faces in the chemical diversity of damaged and toxic molecules [52].

The contrast between these two enzymes suggests a principle: the more diverse, or rare, given forms of toxin or molecular damage are, the more energetically costly it is likely to be for the cell to protect itself against them. This implies a law of diminishing returns, which could explain the force of the selective pressure to cut costs of somatic maintenance [50,51], leading to more rapid ageing.



by which the rate of ageing can be slowed down should inform our understanding of how the ageing process increases disease susceptibility.

It appears that the evolved inadequacy of longevity assurance mechanisms leads to ageing and, consequently, to the diseases of ageing. This implies that the processes that these mechanisms suppress, and those that cause age-related diseases are one and the same, at least to some degree. Understanding this nexus between longevity assurance, ageing and disease is a major challenge (Figure 2).

Some inroads have already been made into addressing these issues. For example, several neurodegenerative diseases (e.g. Parkinson's, Alzheimer's and Huntington's) are associated with the accumulation of cellular aggregates (reviewed in [8]). This suggests that the ontogeny of some diseases of ageing involves an ageing-associated decline in protein-folding homeostasis. Models of these three diseases are under investigation in laboratory organisms such as *C. elegans* and *Drosophila*; for example, a Huntington's disease model has been developed in *C. elegans* (Box 2). These path-finding studies demonstrate that the tools of model organism biogerontology could lay bare the links between longevity assurance mechanisms, ageing and ageing-related disease. They also show how Huntington's disease, which helped inspire the evolutionary theory of ageing, continues to inform our understanding of ageing.

Another major challenge is to uncover the genes and processes that determine the differences in lifespan among animal species. Animal lifespans vary to a remarkable degree, and can evolve rapidly. For example, the common

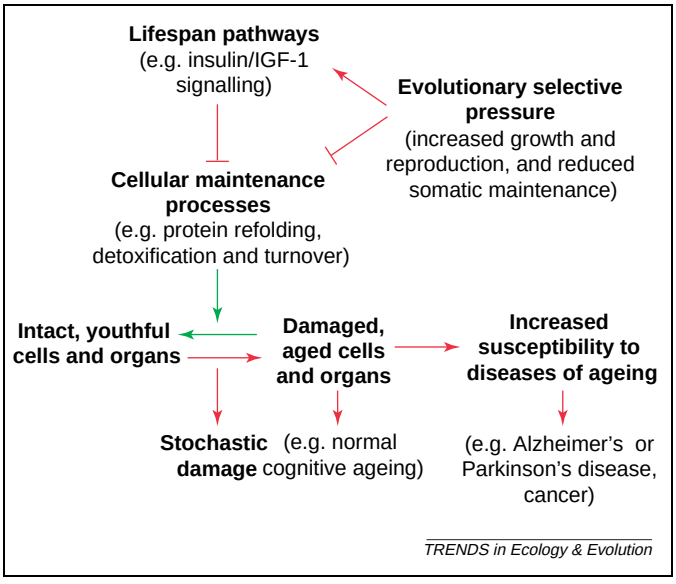


Figure 2. Longevity assurance, ageing and disease. New studies of the biology of ageing are revealing processes that control when and how fast ageing occurs, such as insulin–IGF-1 signalling [6], cellular senescence [4], protein refolding [43–45], autophagy [41] and phase 1 and 2 detoxification [36,37,52]. These represent major points of intervention against ageing-related disease. As shown here, lifespan pathways control improved cellular maintenance, which leads to slowed ageing (e.g. slowed normal cognitive ageing) and protection against diseases of ageing (e.g. neurodegenerative diseases of ageing, such as Alzheimer's and Parkinson's disease, and cancer). Ageing can evolve via selection to reduce investment in energetically costly somatic maintenance processes and instead to increase early fitness traits such as growth and reproduction [50,51]. Arrows denote stimulation, and T bars inhibition, of the process indicated. Red and green denote changes leading to ageing and longevity, respectively.

Box 2. How ageing sets the timing of onset of Huntington's disease

Huntington's disease is a progressive neurodegenerative condition that usually strikes in middle age and is caused by an autosomal dominant mutation. At the molecular level, it results from expansion of polyglutamine (polyQ) tracts in the protein huntingtin, which cause protein aggregation. The role of ageing in this aggregation has been explored using transgenic *Caenorhabditis elegans* expressing green fluorescent protein (GFP) linked to polyQ tracts of varying lengths [58]. In worms with short polyQ tracts, the GFP remains soluble, such that the worms have a diffuse green glow. By contrast, in worms with long polyQ tracts, the GFP aggregates, such that the worms are speckled fluorescent green and display abnormal movement. The most interesting worms are those containing polyQ tracts of intermediate length (Q40). In young worms, the GFP is diffuse, but as they age, the GFP becomes speckled, and the worms begin to move abnormally, thus recapitulating the late-age onset of Huntington's disease in humans.

What is it that changes during ageing that leads to polyQ-GFP aggregation? The tools developed for studying ageing provide the means to explore this question. Interestingly, mutation of the IIS gene *age-1*, which extends lifespan, also suppresses polyQ-GFP aggregation [58]. Moreover, polyQ-GFP aggregation was increased by lowering expression levels of several genes encoding small heat shock proteins [43]. Similarly, in *Drosophila*, overexpression of HSP70 suppresses polyQ-mediated neurodegeneration [59]. Taken together, these results imply that HSPs act on common processes underlying ageing and age-related disease, apparently involving a progressive failure of normal protein-folding mechanisms (i.e. protein-folding dyshomeostasis).

ancestors of *Homo sapiens* and chimpanzees walked the Earth only some 5.4 million years ago, yet our maximum lifespan is twice that of our closest living relative (~110 years versus ~59 years). Do the genes and processes that have been the focus of model organism work (e.g. IIS and cellular detoxification) also specify species differences in ageing? Do they also control the remarkable phenotypic plasticity of lifespan seen in, for instance, social insects? Answering these questions will require an approach analogous to that used in understanding the evolution of differences in development that lead to differences in anatomy (i.e. evolutionary developmental biology, or evo-devo). One might naturally refer to such an approach as evolutionary gerontology (or evo-gero) (Box 3).

Conclusions

The past two decades since the first issue of *TREE* have seen a complex dance between the older evolutionary biology of ageing and the younger, model organism-based biogerontology. At times, evolutionary theory has even acted as an obstacle to the development of lifespan genetics, for example by predicting that single gene mutations with large effects on lifespan should not exist. This failure of evolutionary biology provides important lessons, for example, that evolutionary biologists should not underestimate the intricacies of biological systems.

Biogerontology has revealed layer after layer of complexity: for example, the regulation of lifespan by neuroendocrine and cellular signalling pathways, which act via transcriptional regulation of a large number of target genes and processes, which themselves suggest a vast chemical complexity involved in the biology of damage. It has also revealed biologies whose multiple

Box 3. Evolutionary gerontology (evo-gero)

We are beginning to understand the biologies of ageing and longevity that correspond to the evolutionary concept of antagonistic pleiotropy. Such an understanding opens the way to investigate the biological mechanisms underlying the evolution of the wide variation in ageing rates among animal species.

For example, what sorts of processes are altered when longevity evolves, for example, in humans among the higher primates, or the African porcupine *Hystrix cristata* among rodents (Figure I)? Are the types of process involved similar or different in different animal lineages? For example, do the determining processes include cellular senescence, insulin–IGF-1 signalling, protein refolding, turnover processes or detoxification?

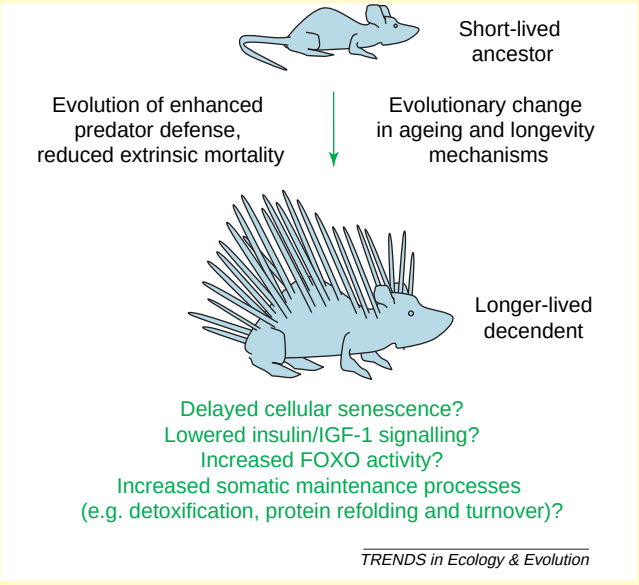


Figure I. What are the biological mechanisms underlying lifespan evolution? Here, the evolution of spines reduces predation, leading to evolution of increased longevity. The African porcupine *Hystrix cristata* is the longest-lived rodent, and can live over 20 years in captivity.

effects at different stages of adulthood might correspond to the evolutionary prediction of antagonistic pleiotropy, including cellular senescence [7], insulin–IGF-1 signalling [31–33] and drug metabolism [52]. Many challenges lie ahead: to apply model organism genetics, functional genomics, and evo-gero to understand the core biology of ageing, and how it controls the plasticity in ageing, evolved differences in lifespan and, most importantly, the roots of ageing-related disease. There is much to do.

Acknowledgements

The brevity of our review of this burgeoning field means that there are some promising avenues that we not described here. We hope that any colleagues that this has affected will understand, and forgive us this neglect. We thank the BBSRC and the Wellcome Trust for supporting our work.

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