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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

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