OPINION

Programmed and altruistic ageing

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Abstract | Ageing is widely believed to be a non-adaptive process that results from a decline in the force of natural selection. However, recent studies in *Saccharomyces cerevisiae* are consistent with the existence of a programme of altruistic ageing and death. We suggest that the similarities between the molecular pathways that regulate ageing in yeast, worms, flies and mice, together with evidence that is consistent with programmed death in salmon and other organisms, raise the possibility that programmed ageing or death can also occur in higher eukaryotes.

'Ageing' describes all of the time-dependent changes that occur in the molecules, cells and tissues of an organism, whereas 'senescence' can be defined as the subset of those changes that negatively affect the functions of the organism[1]. However, because the term ageing is more widely used than senescence to define detrimental age-dependent changes, we will use ageing throughout this review[1,2]. Ageing occurs in organisms that range from yeast to humans, but also in non-living systems such as automobiles. Do organisms become 'rusty' and age like cars or is there a genetic programme that guarantees that a specific age is reached?

Gerontologists widely support theories of ageing that are based on the non-adaptive accumulation of stochastic damage to macromolecules that is caused by oxygen and other toxic species following the decline of the force of natural selection and the consequent decline in protection and repair mechanisms with increasing age[3,4]. However, a series of pioneering genetic studies that were carried out in yeast, worms, flies and mice over the past 15 years have shown that lifespan can be extended by threefold or more through mutations that force entry into phases that are normally entered under conditions of starvation[5,6]. These findings indicate that a genetic programme might regulate the level of protection against stochastic damage, and therefore the length of time an organism remains healthy. Another possibility — and the focus of this review — is that a programme can promote ageing and death for altruistic reasons (the 'programmed and altruistic ageing' theory). There are two possible explanations for such altruistic behaviour — one explanation is that it benefits closely related organisms that have acquired mutations that increase their ability to grow and survive, the other is that it benefits the group as a whole.

Recent studies of the unicellular organism *Saccharomyces cerevisiae* raise the controversial possibility that programmed and altruistic ageing might occur, and that this might be an adaptive process that benefits small sub-populations of closely related mutants[7–9]. Here we review the programmed and altruistic ageing theory and the recent experimental evidence that supports it.

Theories of ageing

In this section, we will briefly discuss how each of the different theories of ageing fits the data that have been generated by studies of lifespan in model systems. Although these theories clearly provide different views on how and why ageing and death occur, they also overlap.

The free radical theory. The free radical theory of ageing proposes that the reactive oxygen species that are produced as part of normal metabolism cause ageing by slowly damaging macromolecules, organelles and cells[10,11]. It is now widely accepted, and we agree, that free radicals are a principal mediator of ageing[10,11]. However, a fundamental question to be addressed is whether free radicals and other insults are the primary cause of ageing, or whether ageing and death occurs mostly after a putative programme that regulates protection, repair and replacement systems becomes less efficient. We discuss this issue in later sections.

The disposable soma theory. It was August Weismann who suggested that chemical and mechanical damage is, in principle, reparable to an arbitrarily high standard of faithfulness[12]. However, theories of metabolic trade-off offer an explanation of why molecular repair mechanisms might have limited effectiveness. The disposable soma theory takes these metabolic trade-offs into account. According to this theory, the repair of stochastic damage requires caloric energy, and competing metabolic demands for this energy have forced natural selection into an optimization process in which compromises between longevity and growth or reproduction are inherent[13]. Consistent with this theory, trade-offs that include decreased fertility or growth are observed in most but not all long-lived mutant organisms[5].

In disagreement with this theory is the observation that caloric restriction, and not increased caloric intake, has been observed to extend lifespan in a diverse range of species[14]. However, it is possible that a reduction in nutrient availability increases rather than decreases the energy that is available for somatic maintenance by saving the energy that is normally invested in growth and reproduction[14,15]. Further studies are necessary to determine whether the disposable soma theory might explain ageing, alone or in combination with other theories.

The antagonistic pleiotropy theory. There is also the possibility of purely genetic trade-offs, as described by the antagonistic pleiotropy

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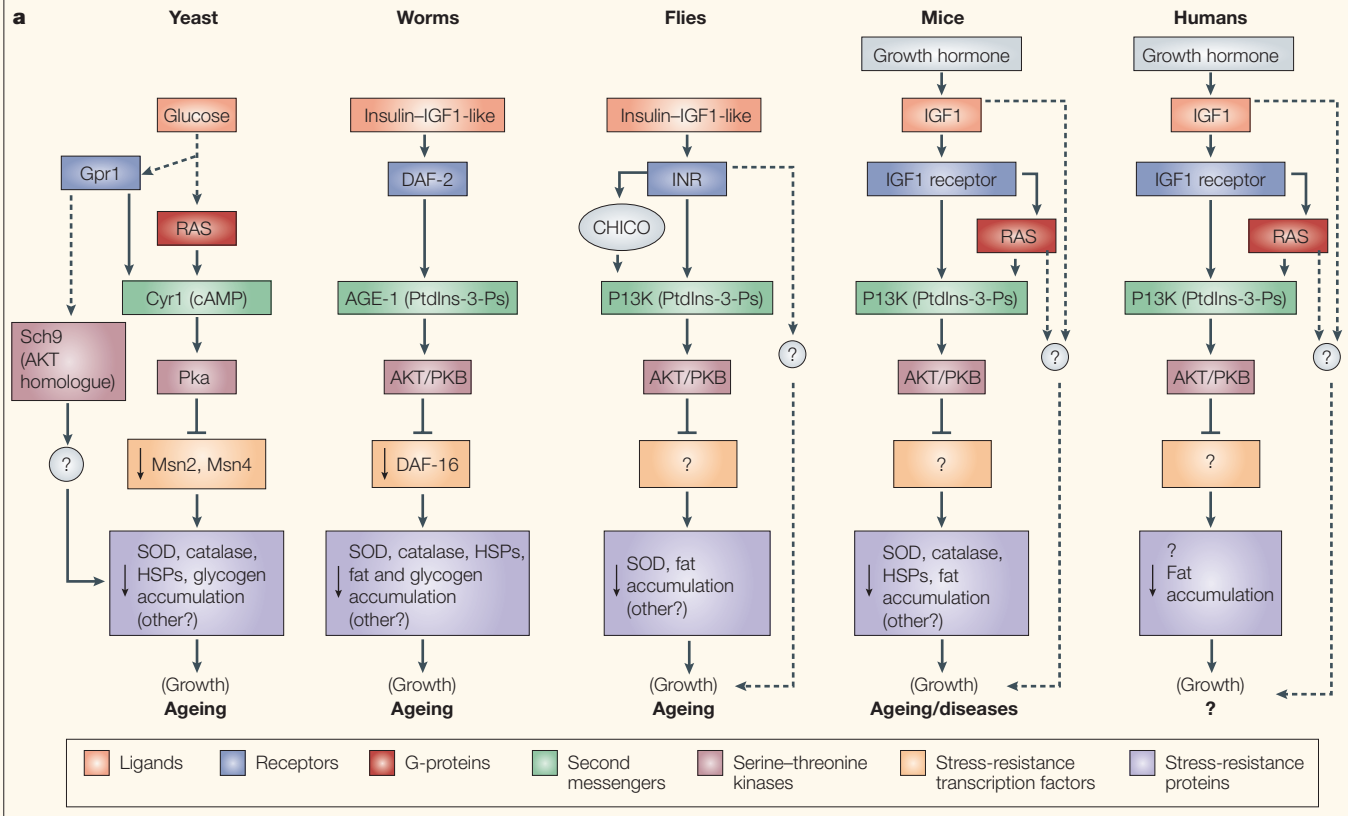
Box 1 | **Longevity pathways in yeast, worms, flies and mice**



Following pioneering studies that resulted in the isolation of long-lived *Caenorhabditis elegans* mutants[58,59], the genes that mediate the extension of chronological lifespan were discovered in both nematodes and *Saccharomyces cerevisiae*[46,60–62]. The yeast and worm longevity pathways share several homologous proteins, including superoxide dismutases (SODs), catalase, heat shock proteins (HSPs) and serine–threonine kinases such as Sch9 and protein kinase A (Pka) in yeast, and AKT-1/AKT-2 (v-akt murine thymoma viral oncogene homologues 1 and 2) and SGK-1 (serum and glucocorticoid inducible kinase homologue) in the worm[5,63], and analogous proteins regulate longevity in fruitflies and mice (see panel **a**). In mice, mutations that decrease the level or activity of IGF1 (insulin growth factor 1) extend lifespan by up to 65% compared with that of the wild type, and cause dwarfism[64–67]. The high-stress-resistance phenotype also seems to be regulated by the IGF1 pathway in mammals[68–70] (see panel **a**). In yeast, worms, flies and mice, mutations that extend lifespan also cause the accumulation of glycogen, fat, or both (see panel **a**). IGF1 deficiency also increases fat accumulation in humans[5]. Notably, in mammals, fat is the main carbon source during long periods of starvation (hibernation), whereas glycogen provides glucose only during short periods of fasting. Therefore, the switch between glycogen storage in long-lived yeast and fat storage in long-lived metazoans is consistent with the role of longevity regulatory pathways in inducing accumulation of the carbon source to maximize long-term survival during periods of starvation. The similarities between the yeast, worm and fly longevity regulatory pathways suggest that portions of these pathways have evolved from a common set of starvation-response genes in ancestral organisms.

Panels **b–d** show wild-type (left) and long-lived 'dwarf' (right) yeast, flies and mice with mutations that decrease glucose or insulin–IGF1-like signalling. Yeast *sch9* null mutants form smaller colonies (panel **b**). *sch9* mutants are also smaller in size, grow at a slower rate and survive three times as long as wild-type yeast. *chico* homozygous mutant female flies are dwarfs and have an increased lifespan of up to 50% (panel **c**). Chico functions in the fly insulin–IGF1-like signalling pathway. The GHR/BP mice are dwarfs that are deficient in IGF1 and show a 50% increase in lifespan (panel **d**). Other yeast and worm mutants show lifespan extension of more than 100%, but do not have detectable growth defects (see text). Fly and mouse images courtesy of D. Gems and A. Bartke, respectively.

AGE-1, ageing alteration 1; cAMP, cyclic AMP; Cyr1, adenylate cyclase; DAF-2/-16, abnormal dauer formation 2 and 16; Gpr1, G-protein coupled receptor 1; INR, insulin-like receptor; Msn2/4, multicopy suppressors in a temperature-sensitive SNF1 protein kinase mutant of *Saccharomyces cerevisiae*; PKB, protein kinase B; PtdIns-3-Ps, phosphatidylinositol-3-phosphates; PI3K, phoshatidylinositol 3 kinase; Ras, Harvey rat sarcoma virus oncogene.

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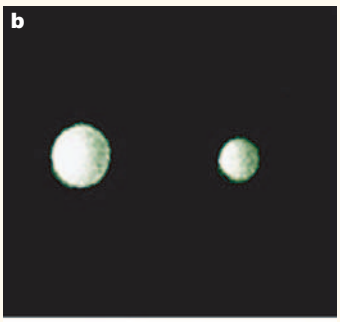

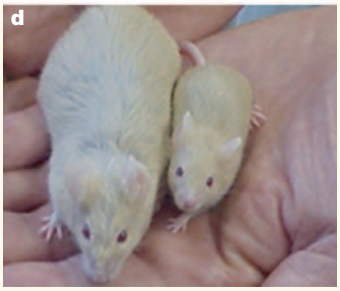

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theory: alleles that cause a decline in vitality late in life might be selected if they carry benefits early in life, so that the net result for fitness is positive[16,17]. However, this theory is not consistent with the observation that some life-extending mutations do not cause obvious growth or fertility disadvantages (BOX 1). For example, yeast that lack *RAS2* (Harvey rat sarcoma virus oncogene 2), and certain *Caenorhabditis elegans daf-2* (abnormal dauer formation 2) mutants, survive for more than twice as long as controls but grow and reproduce normally[5]. Nevertheless, it is possible that the defects that cause a significant reduction in fitness might not be easily detectable[4]. For example, in *C. elegans* the *age-1* (ageing alteration 1) mutation, which increases lifespan, does not cause a measurable reproductive disadvantage, but impairs the ability of the worms to undergo cycles of feeding and starvation[16]. In fact, a broad class of life-extending mutations in the *daf-2* gene has been found to carry costs that are associated with resistance to starvation[17]. Similarly, *S. cerevisiae* mutations that extend lifespan negatively affect the ability of populations to adapt to changing environments[8]. Therefore, further studies are required to determine whether decreased fitness is a necessary trade-off for lifespan extension.

The mutation accumulation theory. Alleles that are detrimental at late ages might find their way into the genome as part of the mutational load. The mutation accumulation theory proposes that the force of selection declines with age, and the weakness of selection might cause mutations that have deleterious effects late in life to accumulate in the genome[18]. This theory has lost favour in recent years because of the limited evidence to support it[13,19], and also because the data provide stronger support for the antagonistic pleiotropy theory[16,17]. However, it is premature to rule out that the accumulation of late-acting alleles could contribute to ageing.

The programmed longevity theory. The identification of many mutations that extend lifespan in model systems (BOX 1) supports the existence of what we will call a putative 'longevity programme'. During periods of starvation, this programme would allow organisms to exceed their normal lifespan by entering a 'maintenance mode' (during which somatic maintenance is upregulated) that is associated with changes such as hypometabolism, high stress-resistance and low or no fertility (BOX 1). Life-extending mutations affect this programme so that individuals enter the maintenance mode irrespective of the environmental conditions[5,6]. Therefore, the programmed longevity theory discussed here is consistent with a role for free radicals in causing age-dependent damage, but proposes that the primary cause of ageing is the genetically programmed inactivation or decline in a system that normally prevents damage by regulating protection, repair and replacement of genes.

Although much of the data that relate to the causes of ageing can be explained by established evolutionary theories, several studies are also consistent with the existence of programmed longevity. When fruitflies are calorie-restricted (an intervention that extends lifespan) for just two days at two different ages, their mortality is indistinguishable from that of flies that are calorie-restricted for life[20]. Similar results are observed when chronologically ageing yeast are calorie-restricted (V.D.L., unpublished observations). Late-onset calorie restriction also extends lifespan in both mice and rats (BOX 1), although the number of animals used and the type of data reported so far are not sufficient to determine the effect of calorie restriction on mortality[21,22]. It is possible that the reversed mortality rates of *Drosophila melanogaster* that have been switched to calorie restriction are a consequence of a reversal of the damage[20]. However, the ability of repair and replacement systems to reverse the damage accumulated since birth so rapidly would argue that organisms normally maintain a sub-optimal level of protection.

Furthermore, yeast and flies that overexpress superoxide dismutases and catalases, which scavenge free radicals, survive only approximately 5–30% longer than wild-type flies[23–25], whereas mutations in central nutrient-response pathways cause a twofold to threefold lifespan extension[5,26,27]. Similarly, overexpression of antioxidant enzymes causes little or no lifespan extension in mice[28,29] (BOX 1). If free radicals were the primary cause of ageing we would expect the effect of antioxidant enzymes on lifespan to be closer to that of mutations in signal-transduction genes. Therefore, the data are consistent with the existence of programmes that optimize the 'normal' lifespan and that can respond to starvation conditions by extending longevity through the regulation of many repair and protection systems including, but not limited to,

Box 2 | **Altruism and group selection**

We argue that programmed ageing could be maintained by selection at the group level (group selection). Darwin proposed that natural selection can operate at more than one level, but most evolutionary biologists generally believe that selection operates on the level of individual organisms[32]. Group selectionism enjoyed some support before the 1960s but almost disappeared from the literature after Williams[71], Maynard Smith[72] and Hamilton[31] provided alternative explanations for the observations that were made by Wynne-Edwards[33] and others in support of altruistic behaviour (reviewed by Shanahan[73]). Wynne-Edwards had concluded that animal population numbers remain stable because animals regulate reproduction on the basis of nutrient availability[33]. For this regulation to occur, the individual would have to consider the welfare of the group before deciding whether to reproduce or not. Maynard Smith argued that even if certain groups altruistically reduced reproduction, an egoist would eventually infect and take over the altruistic group[72].

Great advances have been made since the contributions of Williams and Maynard Smith. Based on the Price equation, a theory of multilevel selection has developed, which was spearheaded by the work of Wilson[32]. Nevertheless, the individual cost of programmed death is sufficiently great and the group benefit sufficiently diffuse that quantitative models that are based on multilevel selection do not support the evolution of ageing programmes through these mechanisms. Theory and observation both indicate that when populations outgrow their food supply, mass starvation can be rapid and lethal. Local extinctions that result from overpopulation might support a kind of population-level selection that is strong and rapid enough to overpower the individual costs of programmed ageing[34].

It is possible that even if most of the altruistic groups are invaded by a selfish organism, the remaining altruistic groups would have an advantage over the non-altruist, provided that the disadvantage created by egoism eventually causes extinction. It is also possible that the altruistic groups have evolved protective systems that are aimed at keeping the selfish organisms out. Therefore, altruistic genes could be inherited together with a protective or surveillance system with the purpose of keeping the selfish organisms out. In fact, when programmed ageing occurs in the altruistic *Saccharomyces cerevisiae*, the medium is acidified to pH 3.5 (REF. 8), which prevents the growth of competing organisms.

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Box 3 | **Theoretical arguments against programmed ageing**

Most evolutionary biologists believe that programmed ageing cannot result from natural selection, as it is currently understood to operate. Almost 50 years ago, evolutionary theorists established several arguments against this theory. First, the contribution of ageing to individual fitness is wholly negative. Second, the contribution of ageing to population-level fitness is too indirect and too diffuse to be important in selection dynamics, and therefore ageing cannot be affirmatively selected as an adaptation. Third, ageing can be readily understood in terms of the declining force of selection pressure with age. Fourth, selection that operates on genetic trade-offs is predicted to favour early fertility at the expense of robust protection against deterioration (this is known as antagonistic pleiotropy). Fifth, metabolic trade-offs constitute another opportunity for the body to divert energy towards early fertility at the expense of repair and maintenance functions (this is known as the disposable soma theory). And finally, even without trade-offs, genetic load would be expected to be heaviest in the genes for which their deleterious effects manifest only late in life (this is known as the mutation accumulation theory).

antioxidant enzymes[30]. The identification of the longevity programme might be particularly important for the identification of the primary regulators of ageing and age-related diseases (BOX 1).

The programmed and altruistic ageing theory. The programmed and altruistic ageing theory presented here proposes that ageing is programmed so that organisms age and die to benefit related individuals or their group. An ageing and death programme that benefits closely related organisms can be explained by kin selection[31]. By contrast, death for the benefit of unrelated organisms is explained by group selection[32,33] (BOX 2). Theoretically, ageing could provide long-term benefits at the group or population level that include population stabilization, enhanced genetic diversity, a shortening of the effective generation cycle and acceleration of the pace of adaptation[8,34]. Local extinctions from overpopulation might support a kind of population-level selection that is strong and rapid enough to overpower the individual costs of programmed ageing[34] (BOX 2). These benefits have not previously been invoked to explain features that have the appearance of ageing programmes because the force of group selection is thought to be too slow and too weak to oppose the direct costs to the individual. However, we propose that although theories that evoke group selection and altruism are problematic (BOX 3), they do provide a natural framework for interpreting various recent experimental findings, which other theories are obliged to regard as anomalies.

The remainder of this article will describe the experimental evidence from yeast that supports the existence of programmed ageing, and discuss the implications of this model. We will also discuss how programmed ageing might occur under only certain environmental conditions in populations of unicellular eukaryotes, and speculate whether programmed ageing occurs in higher eukaryotes.

Evidence for altruistic ageing

In our view, the following are important requirements for demonstrating the theory of programmed ageing: the identification of mutations that can significantly extend lifespan (described in BOX 1); the similarities between normal ageing and mammalian apoptosis; evidence for the benefit that is provided by the ageing programme (for example, a correlation between lifespan and the ability of a population to adapt to changing environments); the identification of a sequence of molecular processes that are required to cause normal ageing and death; and the demonstration that the programme occurs both under conditions that mimic those encountered in natural environments and in organisms that are isolated from natural environments.

Phenoptosis. The lives of many cells in multicellular organisms seem to follow a Samurai principle: it is better to die than to be wrong. Complex biological systems are equipped with programmes that eliminate portions of the system that become dangerous or unnecessary for the system as a whole. One mechanism of programmed cell death is apoptosis — this is characterized by distinctive morphological changes in the DNA, nucleus and cytoplasm. Apoptosis is involved in ontogenic development, anticancer defence, immune responses and other physiological processes.

For unicellular organisms, the idea of programmed cell death becomes theoretically problematic because we are talking about the death of a whole organism — or phenoptosis[35]. However, in the past 10 years, several studies have indicated that a form of programmed death that is similar to mammalian apoptosis occurs in the unicellular organism *S. cerevisiae*. When the anti- or pro-apoptotic mammalian proteins BCL2 (B-cell leukaemia/lymphoma 2) or BAX (BCL2-associated X protein) are expressed in *S. cerevisiae* they rescue cells from death or stimulate it, respectively[9,36,37]. Indeed, the overexpression of the human anti-apoptotic BCL2 protein in yeast delays ageing and death in both wild-type cells and cells that lack superoxide dismutases[9]. In addition, certain mutations in the *S. cerevisiae* genome cause death that is similar to mammalian cellular apoptosis[36,38,39], and harsh treatments (such as H_2O_2 and acetic acid) induce a form of death in yeast that also resembles apoptosis[40,41]. More recently, the identification of an *S. cerevisiae* caspase-like protease that is involved in the apoptotic cascade strengthened the claim that apoptosis occurs in yeast[42]. Other studies indicate that the plant antibiotic osmotin and yeast sexual pheromone can cause the death of yeast in an apoptosis-like manner[43].

Pheromone-dependent death in yeast has been shown to involve several consecutive components that share features with apoptosis. These include pheromone-receptor activation; a mitogen activated protein kinase cascade; protein synthesis; stimulation of mitochondrial respiration and an increase in energy coupling; a strong elevation of mitochondrial membrane potential; a burst of production of reactive oxygen species in the mitochondrial respiratory chain; the decomposition of mitochondrial filaments; and the collapse of the mitochondrial membrane potential and cytochrome *c* release from mitochondria[44,45]. These biochemical changes are similar to those that were previously identified in studies of chronologically ageing *S. cerevisiae*, which included activation of the Ras and Sch9 pathways, mitochondrial superoxide generation and loss of mitochondrial function[25,26,46]. Notably, a form of programmed death has also been described for bacteria: it was shown that damaged DNA activates a signalling pathway that causes autolysin-mediated death[47].

Benefits of ageing for kin or for the group. Several studies support our hypothesis that the programmed ageing and death of populations of billions of *S. cerevisiae* can promote the adaptation of some members of the population to changing environments by affecting DNA-mutation frequency and the nutritional environment.

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As in higher eukaryotes, chronological ageing in yeast is determined by monitoring time-dependent mortality and loss of functions such as reproduction[48]. Chronological lifespan is normally determined by measuring the survival of a population of billions of non-dividing yeast that are grown in a glucose or ethanol-containing medium[48]. Ageing in yeast can also be measured by counting the number of daughter cells that are generated by an individual mother cell (this is called replicative lifespan)[49], although the results presented in this article are mostly from assays that measure chronological lifespan.

In studies of chronologically ageing yeast, after 90–99% of the population dies, a small sub-population of better-adapted mutants regrow by using nutrients that are released from the dead cells[8]. This regrowth phenomenon (the doubling of viable organisms within a chronologically ageing population) might be similar to the 'gasping' phenomenon that can be observed in chronologically ageing bacteria[50]. It is possible that the composition of the growth medium changes as a consequence of the non-adaptive death of old cells, selecting for rare mutants that previously had low fitness. However, the results indicate that the death of most of the population and regrowth of the mutants is part of an evolved programme.

Mechanisms of programmed and altruistic ageing. The evidence for apoptotic-like death in yeast leads to the question of whether components of the apoptotic process might be involved in an ageing programme. Many of the features of apoptosis — including chromatin condensation, phosphatidylserine externalization, increased generation of oxidants and caspase activation — are observed in ageing yeast populations before death[7,8,26]. However, it is also possible that particular cellular mechanisms fail with age in yeast and other organisms, and that multicellular organisms have evolved to take advantage of existing 'death mechanisms' to cause apoptosis.

The frequency of regrowth that is observed in studies of chronological lifespan in yeast is inversely correlated with the lifespan of the population[8]. Populations that have an increased lifespan and a higher frequency of mutations (because they overexpress both the superoxide dismutase (*SOD1*) and catalase genes) have been observed to have a reduced frequency of regrowth[8]. Similarly, the frequency of regrowth is reduced in populations of long-lived yeast that lack the *RAS2* or *SCH9* genes, which have an increased chronological lifespan, a reduced number of age-dependent DNA mutations and reduced levels of superoxide[8] (FIG. 1). Does ageing in yeast promote the adaptive regrowth of new mutants?

If superoxide toxicity and premature ageing do favour adaptive regrowth we would expect that, at least under certain conditions, a further increase in superoxide levels and mortality rates could increase adaptive regrowth. This is what is observed — yeast populations that have mutations in the *SOD1* gene (mutations that decrease protection against superoxide) have high DNA-mutation frequencies and die early, but show almost twice the frequency of regrowth compared with wild-type populations[8]. Therefore, it seems that the lack of functional *SOD1* accelerates the superoxide-induced DNA damage, as well as the death of most of the cells, the remains of which become nutrients for mutants within the population that are better-adapted to the new environment.

Based on computational simulations and experimental evidence, this higher mutation frequency is predicted to be an important factor that favours adaptive regrowth, and is consistent with the activation of a pro-ageing/pro-mutation programme[8] (FIG. 1). Indeed, it is difficult to explain why wild-type cells would already have sub-optimal protection against DNA damage when they are young if ageing and death were not programmed. One possibility, which is consistent with the disposable soma theory,

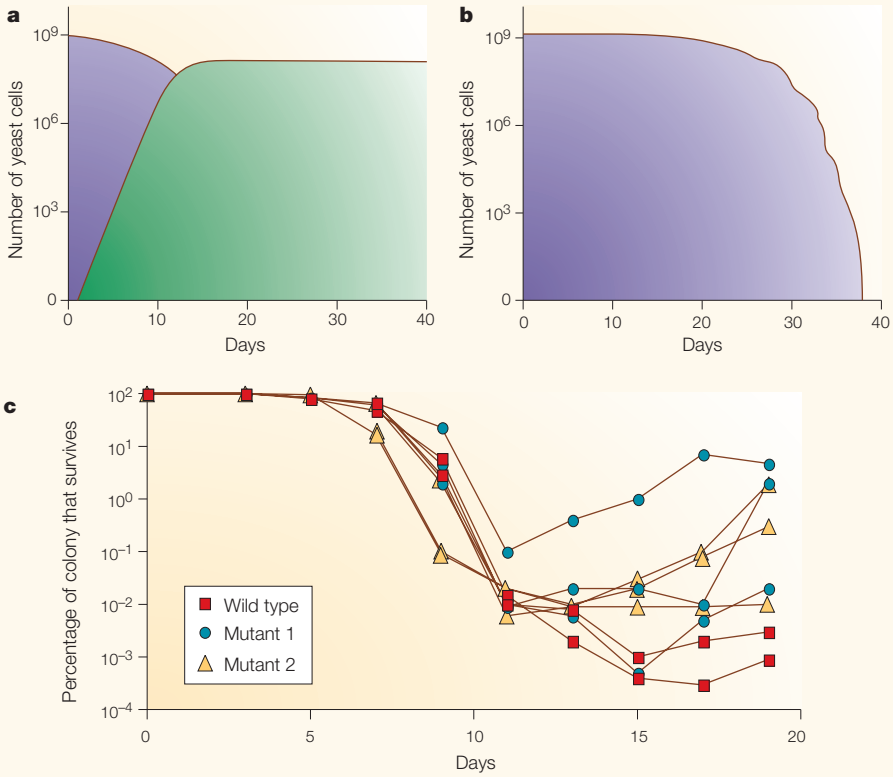

Figure 1 | **Computational simulations of stochastic and programmed ageing in *Saccharomyces cerevisiae*. a** | The results of a computational simulation for programmed ageing that shows the survival of wild-type yeast cells (blue) and the regrowth of a mutant population (green). The initial population consisted of 10^9 cells, which had a frequency of spontaneous DNA mutations of 1 in every 10^9 cells (based on the experimental population size). This regrowth result was observed in 52% of the 100 simulations. **b** | The results of a computational simulation for stochastic ageing that shows the survival of a long-lived population (blue) (which has a mutation in the gene *SCH9*). We assumed that the long-lived *sch9Δ* mutants age stochastically, so that ageing is no longer controlled by a programme. The computational simulation of the survival and regrowth of the *sch9Δ* mutation shows that regrowth occurs in only 0.4% of 1,000 simulations. The age-dependent spontaneous DNA-mutation frequency is derived from experimental data of yeast with a mutation in the gene *SCH9*. These computational simulations are consistent with the experimental results that extended longevity, reduced DNA-mutation frequency, and reduced release of nutrients that negatively affect adaptation. **c** | The survival and adaptive regrowth of wild-type cells and two different regrowth mutants that were isolated in previous experiments (mutant 1 and mutant 2 have mutations in unidentified genes). The regrowth mutants have an adaptive advantage (they grow earlier) compared with wild-type cells, and the shape of this graph is similar to the green area in panel **a**. Modified, with permission, from REF. 8 © (2004) Rockefeller University Press.

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is that the energy available is not sufficient to increase DNA repair to the level of the long-lived mutants. However, in studies of chronological lifespan, the yeast cells do not divide and so do not invest energy into reproduction. Furthermore, the frequency of DNA mutations in young cells is twice as high as that of long-lived mutants, even though metabolic rates are comparable[8,25]. If wild-type cells do not have sufficient energy to invest in DNA repair, but *sch9Δ* and *ras2Δ* mutants do, it is not clear what other functions wild-type cells are activating. These results indicate that the Ras and Sch9 pathways could promote adaptive regrowth, in part, by increasing the generation of superoxide and DNA-mutation frequency. So it seems that, under the conditions tested, a long lifespan causes an adaptive regrowth disadvantage for mutants within the population. A programme might have evolved to optimize the regrowth conditions for the mutant(s).

Further evidence for a programme that reduces survival to optimize the fitness of related organisms comes from competition experiments. In direct competition in the same flasks, wild-type cells outcompete long-lived cells that overexpress Sod and catalase, which are themselves out-competed by the short-lived mutants that lack Sod[8]. Similarly, in direct competition, mutants that lack the yeast caspase-like protease Yca1 (also known as Mca1), which mediates oxygen-stress-dependent apoptosis, are out-competed by wild-type cells[7]. It is possible that the inability of the population of long-lived mutants to compete against wild-type organisms is independent of an ageing and death programme. However, we feel that it would be surprising if the association between increased superoxide levels, markers of apoptosis, a shorter lifespan and the frequency of regrowth was not part of an adaptive mechanism. It would also be surprising if the role of Yca1 in adaptation was not linked to programmed death[7].

As mentioned above, one possibility is that programmed ageing has evolved in response to kin selection[31] and that older yeast cells undergo programmed cell death to benefit related individuals. However, the regrown population reaches only approximately 10% of the number of cells present in the original population[8], which is not consistent with the kin selection theory[31]. Another alternative is that the long-lived genetic variety does not become fixed because of an individual fitness cost of the long lifespan. As discussed earlier, it is possible that the long-lived mutants for which fitness is apparently normal might have deficiencies that are difficult to detect. However, we think that the fact that many long-lived mutants show growth or reproductive defects, but some do not, indicates that although a trade-off between extended lifespan and growth or reproduction might be common, it is not necessary.

Wild-type strains and environmental conditions. The medium-dependent death and regrowth of yeast, which has been described above, occurs in at least three laboratory wild-type strains, but also in diploid budding yeast that is isolated from grapes and in laboratory strains that are incubated in 'grape extracts'[8]. This indicates that age-dependent death and regrowth are not artefacts that are caused by laboratory conditions or strains.

Notably, programmed and altruistic ageing and death do not seem to occur under all conditions. In fact, under severe calorie restriction (incubation in water), yeast organisms enter a longer-lived mode, which might or might not be programmed[9]. We speculate that the decision concerning whether to undergo programmed ageing, at least in *S. cerevisiae*, depends on whether the availability of nutrients and other conditions make the ageing programme beneficial or deleterious to the fitness of the group.

Programmed and altruistic ageing in higher eukaryotes. Although the existence of programmed and altruistic ageing has not yet been demonstrated experimentally in higher eukaryotes, many studies of semelparous plants and animals indicate that it might occur[51]. As was noticed by Wallace, and subsequently discussed extensively by Finch[1], some organisms die shortly after reproduction. For example, in the mite *Adactylidium*, the young hatch inside the mother's body and eat their way out[52]; the female *Octopus hummelinck* stops eating when her offspring are released from the eggs[53]; and bamboo can live for 15–20 years, reproducing vegetatively, but then dies immediately after the ripening of the seeds (for a discussion see REF. 35). The Pacific salmon, which is one of the best-studied examples of rapid senescence and sudden death, dies suddenly after spawning[1]. Originally this kind of death was thought to be caused by excessive energy consumption when swimming in the river for a long distance against the current[14,15]. This explanation seems to be incorrect because ageing and death does not occur if the gonads or adrenal glands are removed[54] and sudden death is observed even when the river is short and the current is weak[55]. The authors of this last study proposed that, analogous to the altruistic ageing and death of yeast, sudden death of the Pacific salmon increases the food that is available for invertebrates which, in turn, provide food for young fish[1,55]. Another possibility is that this strategy evolved through kin selection and that, consistent with Hamilton's inclusive fitness theory[31], the sudden death of salmon and other organisms might directly benefit the offspring, and so is a strategy that maximizes a female's own fitness[1].

Conclusion

The wide scepticism about group selection and the difficulties associated with the experimental demonstration of programmed and altruistic ageing eclipsed the ideas of pioneers of evolutionary biology such as Wallace, who first proposed that death can be programmed, and Weismann, who later developed the idea[12]. Today, Wallace and Weismann's critics often cite Medawar to conclude that ageing could not be an evolved process because, under natural conditions, most organisms die of diseases or predation before they become old[4,13,18].

However, we feel that the evidence that populations of *S. cerevisiae* die to benefit a few mutants indicates that population genetic theory could be underestimating the potency of group selection. Could a putative ageing programme also have evolved to make older higher eukaryotes less competitive than younger ones? Could a similar strategy have evolved in mammals that normally die before reaching old age[32]? Because a small loss of function can cause a statistically significant increase in death rate, the effect of ageing in wild animals could begin in relatively young individuals, which is confirmed by the increase in death rates in wild animals that begins at puberty[56]. Because ageing contributes to death that is caused by, for example, predators and infections before middle age, the existence of programmed ageing in mammals cannot be ruled out on the basis that most organisms die of disease or predation before they become old. Although any claim that humans are programmed to age and die would be highly speculative, we believe that as a hypothesis it suggests fruitful avenues for biological and even medical research.

"There can be no doubt that a tribe including many members who…were always ready to aid one another, and to sacrifice themselves for the common good would be victorious over most other tribes; and this would be natural selection."[57]

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1. Finch, C. E. *Longevity, Senescence, and the Genome* (University Press, Chicago, 1990).
2. Martin, G. M., Austad, S. N. & Johnson, T. E. Genetic analysis of ageing: role of oxidative damage and environmental stresses. *Nature Genet.* **13**, 25–34 (1996).
3. Nemoto, S. & Finkel, T. Ageing and the mystery at Arles. *Nature* **429**, 149–152 (2004).
4. Austad, S. N. Is aging programmed? *Aging Cell* **3**, 249–251 (2004).
5. Longo, V. D. & Finch, C. E. Evolutionary medicine: from dwarf model systems to healthy centenarians. *Science* **299**, 1342–1346 (2003).
6. Kenyon, C. The plasticity of aging: insights from long-lived mutants. *Cell* **120**, 449–460 (2005).
7. Herker, E. *et al.* Chronological aging leads to apoptosis in yeast. *J. Cell Biol.* **164**, 501–507 (2004).
8. Fabrizio, P. *et al.* Superoxide is a mediator of an altruistic aging program in *Saccharomyces cerevisiae*. *J. Cell Biol.* **166**, 1055–1067 (2004).
9. Longo, V. D., Ellerby, L. M., Bredesen, D. E., Valentine, J. S. & Gralla, E. B. Human Bcl-2 reverses survival defects in yeast lacking superoxide dismutase and delays death of wild-type yeast. *J. Cell Biol.* **137**, 1581–1588 (1997).
10. Harman, D. A theory based on free radical and radiation chemistry. *J. Gerontol.* **11**, 298–300 (1956).
11. Balaban, R. S., Nemoto, S. & Finkel, T. Mitochondria, oxidants, and aging. *Cell* **120**, 483–495 (2005).
12. Weissmann, A. *Essays upon Heredity and Kindred Biological Problems* (Claderon, Oxford, 1889).
13. Kirkwood, T. B. Understanding the odd science of aging. *Cell* **120**, 437–447 (2005).
14. Mitteldorf, J. Can experiments on caloric restriction be reconciled with the disposable soma theory for the evolution of senescence? *Evolution Int. J. Org. Evolution* **55**, 1902–1905; discussion 1906 (2001).
15. Shanley, D. P. & Kirkwood, T. B. Calorie restriction and aging: a life-history analysis. *Evolution Int. J. Org. Evolution* **54**, 740–750 (2000).
16. Walker, D. W., McColl, G., Jenkins, N. L., Harris, J. & Lithgow, G. J. Evolution of lifespan in *C. elegans*. *Nature* **405**, 296–297 (2000).
17. Jenkins, N. L., McColl, G. & Lithgow, G. J. Fitness cost of extended lifespan in *Caenorhabditis elegans*. *Proc. Biol. Sci.* **271**, 2523–2526 (2004).
18. Medawar, P. *An Unsolved Problem in Biology* (HK Lewis, London, 1952).
19. Shaw, F. H., Promislow, D. E., Tatar, M., Hughes, K. A. & Geyer, C. J. Toward reconciling inferences concerning genetic variation in senescence in *Drosophila melanogaster*. *Genetics* **152**, 553–566 (1999).
20. Mair, W., Goymer, P., Pletcher, S. D. & Partridge, L. Demography of dietary restriction and death in *Drosophila*. *Science* **301**, 1731–1733 (2003).
21. Merry, B. J. Molecular mechanisms linking calorie restriction and longevity. *Int. J. Biochem. Cell Biol.* **34**, 1340–1354 (2002).
22. Partridge, L., Pletcher, S. D. & Mair, W. Dietary restriction, mortality trajectories, risk and damage. *Mech. Ageing Dev.* **126**, 35–41 (2005).
23. Sun, J. & Tower, J. FLP recombinase-mediated induction of Cu/Zn-superoxide dismutase transgene expression can extend the life span of adult *Drosophila melanogaster* flies. *Mol. Cell. Biol.* **19**, 216–228 (1999).
24. Sun, J., Folk, D., Bradley, T. J. & Tower, J. Induced overexpression of mitochondrial Mn-superoxide dismutase extends the life span of adult *Drosophila melanogaster*. *Genetics* **161**, 661–72 (2002).
25. Fabrizio, P. *et al. SOD2* functions downstream of Sch9 to extend longevity in yeast. *Genetics* **163**, 35–46 (2003).
26. Fabrizio, P., Pozza, F., Pletcher, S. D., Gendron, C. M. & Longo, V. D. Regulation of longevity and stress resistance by Sch9 in yeast. *Science* **292**, 288–290 (2001).
27. Tatar, M. *et al.* A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science* **292**, 107–110 (2001).
28. Gallagher, I. M., Jenner, P., Glover, V. & Clow, A. CuZn-superoxide dismutase transgenic mice: no effect on longevity, locomotor activity and 3H-mazindol and 3H-spiperone binding over 19 months. *Neurosci. Lett.* **289**, 221–223 (2000).
29. Schriner, S. E. *et al.* Extension of murine lifespan by overexpression of catalase targeted to mitochondria. *Science* **308**, 1909–1911 (2005).
30. Bredesen, D. E. The non-existent aging program: how does it work? *Aging Cell* **3**, 255–259 (2004).
31. Hamilton, W. D. The genetical evolution of social behaviour. *J. Theor. Biol.* **7**, 1–16 (1964).
32. Wilson, D. S. Human groups as units of selection. *Science* **276**, 1816–1817 (1997).
33. Wynne-Edwards, V. C. *Animal Dispersion in Relation to Social Behaviour* (Oliver & Boyd, Edinburgh, 1962).
34. Mitteldorf, J. in *Proc. 9th Int. Conf. Simulation Synthesis Living Systems* (MIT Press, Boston, 2004).
35. Skulachev, V. P. in *Topics in Current Genetics* Vol. 3 (eds Nystrom, T. & Osiewacz, H. D.) 191–238 (Springer, Heidelberg, 2003).
36. Jin, C. & Reed, J. C. Yeast and apoptosis. *Nature Rev. Mol. Cell Biol.* **3**, 453–459 (2002).
37. Ligr, M. *et al.* Mammalian Bax triggers apoptotic changes in yeast. *FEBS Lett.* **438**, 61–65 (1998).
38. Skulachev, V. P. Programmed death in yeast as adaptation? *FEBS Lett.* **528**, 23–26 (2002).
39. Frohlich, K. & Madeo, F. Apoptosis in yeast — a monocellular organism exhibits altruistic behaviour. *FEBS Lett.* **473**, 6–9 (2000).
40. Madeo, F. *et al.* Oxygen stress: a regulator of apoptosis in yeast. *J. Cell Biol.* **145**, 757–767 (1999).
41. Ludovico, P., Sousa, M. J., Silva, M. T., Leao, C. & Corte-Real, M. *Saccharomyces cerevisiae* commits to a programmed cell death process in response to acetic acid. *Microbiology* **147**, 2409–2415 (2001).
42. Madeo, F. *et al.* A caspase-related protease regulates apoptosis in yeast. *Mol. Cell* **9**, 911–917 (2002).
43. Narasimhan, M. L. *et al.* A plant defense response effector induces microbial apoptosis. *Mol. Cell* **8**, 921–930 (2001).
44. Severin, F. F. & Hyman, A. A. Pheromone induces programmed cell death in *S. cerevisiae*. *Curr. Biol.* **12**, R233–R235 (2002).
45. Pozniakovsky, A. I. *et al.* Role of mitochondria in the pheromone- and amiodarone-induced programmed death in yeast. *J. Cell Biol.* **168**, 257–269 (2005).
46. Longo, V. D. *The Pro-Senescence Role of Ras2 in the Chronological Life Span of Yeast.* Thesis, Univ. California (1997).
47. Lewis, K. Programmed death in bacteria. *Microbiol. Mol. Biol. Rev.* **64**, 503–514 (2000).
48. Fabrizio, P. & Longo, V. D. The chronological life span of *Saccharomyces cerevisiae*. *Aging Cell* **2**, 73–81 (2003).
49. Jazwinski, S. M. The genetics of aging in the yeast *Saccharomyces cerevisiae*. *Genetica* **91**, 35–51 (1993).
50. Zambrano, M. M., Siegele, D. A., Almiron, M., Tormo, A. & Kolter, R. Microbial competition: *Escherichia coli* mutants that take over stationary phase cultures. *Science* **259**, 1757–1760 (1993).
51. Mitteldorf, J. Aging selected for its own sake. *Evol. Ecol. Res.* **6**, 1–17 (2004).
52. Kirkwood, T. B. & Cremer, T. Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. *Hum. Genet.* **60**, 101–121 (1982).
53. Wodinsky, J. Hormonal inhibition of feeding and death in octopus: control by optic gland secretion. *Science* **198**, 948–951 (1977).
54. Robertson, O. H. & Wexler, B. C. Histological changes in the organs and tissues of senile castrated kokanee salmon (*Oncorhynchus nerka kennerlyi*). *Gen. Comp. Endocrinol.* **2**, 458–472 (1962).
55. Zyuganov, V. V. Long-lived parasite prolonging life of his host. *Dokl. Acad. Nauk* (in the press).
56. Loison, A., Festa-Bianchet, M., Gaillard, J. M., Jorgenson, J. T. & Jullien, J. M. Age-specific survival in five populations of ungulates: evidence of senescence. *Ecology* **80**, 2539–2554 (1999).
57. Darwin, C. *The Descent of Man* (John Murray, London, 1871).
58. Friedman, D. B. & Johnson, T. E. A mutation in the *age-1* gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. *Genetics* **118**, 75–86 (1988).
59. Kenyon, C., Chang, J., Gensch, E., Rudner, A. & Tabtiang, R. A *C. elegans* mutant that lives twice as long as wild type. *Nature* **366**, 461–464 (1993).
60. Morris, J. Z., Tissenbaum, H. A. & Ruvkun, G. A phospatidylinositol-3-OH kinase family member regulating longevity and diapause in *Caenorhabditis elegans*. *Nature* **382**, 536–539 (1996).
61. Longo, V. D., Gralla, E. B. & Valentine, J. S. Superoxide dismutase activity is essential for stationary phase survival in *Saccharomyces cerevisiae*. Mitochondrial production of toxic oxygen species *in vivo*. *J. Biol. Chem.* **271**, 12275–12280 (1996).
62. Lin, K., Dorman, J. B., Rodan, A. & Kenyon, C. *daf-16*: An HNF-3/forkhead family member that can function to double the life-span of *Caenorhabditis elegans*. *Science* **278**, 1319–1322 (1997).
63. Longo, V. D. & Fabrizio, P. Regulation of longevity and stress resistance: a molecular strategy conserved from yeast to humans? *Cell. Mol. Life Sci.* **59**, 903–908 (2002).
64. Brown-Borg, H. M., Borg, K. E., Meliska, C. J. & Bartke, A. Dwarf mice and the ageing process. *Nature* **384**, 33 (1996).
65. Flurkey, K., Papaconstantinou, J. & Harrison, D. E. The Snell dwarf mutation *Pit1*^{dw} can increase life span in mice. *Mech. Ageing Dev.* **123**, 121–30. (2002).
66. Holzenberger, M. *et al.* IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* **421**, 182–187 (2003).
67. Coschigano, K. T., Clemmons, D., Bellush, L. L. & Kopchick, J. J. Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. *Endocrinology* **141**, 2608–2613 (2000).
68. Brown-Borg, H. M. & Rakoczy, S. G. Catalase expression in delayed and premature aging mouse models. *Exp. Gerontol.* **35**, 199–212 (2000).
69. Brown-Borg, H. M., Rakoczy, S. G., Romanick, M. A. & Kennedy, M. A. Effects of growth hormone and insulin-like growth factor-1 on hepatocyte antioxidative enzymes. *Exp. Biol. Med.* **227**, 94–104 (2002).
70. Sharma, H. S., Nyberg, F., Gordh, T., Alm, P. & Westman, J. Neurotrophic factors influence upregulation of constitutive isoform of heme oxygenase and cellular stress response in the spinal cord following trauma. An experimental study using immunohistochemistry in the rat. *Amino Acids* **19**, 351–361 (2000).
71. Williams, G. C. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* **11**, 398–411 (1957).
72. Maynard Smith, J. Group selection and kin selection. *Nature* **201**, 1145–1147 (1964).
73. Shanahan, T. The troubled past and uncertain future of group selectionism. *Endeavour* **22**, 57–60 (1998).

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