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Understanding the Odd Science of Aging

Reviews

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Evolutionary considerations suggest aging is caused not by active gene programming but by evolved limitations in somatic maintenance, resulting in a build-up of damage. Ecological factors such as hazard rates and food availability influence the trade-offs between investing in growth, reproduction, and somatic survival, explaining why species evolved different life spans and why aging rate can sometimes be altered, for example, by dietary restriction. To understand the cell and molecular basis of aging is to unravel the multiplicity of mechanisms causing damage to accumulate and the complex array of systems working to keep damage at bay.

Introduction

Aging is arguably the most familiar yet least well-understood aspect of human biology. Each of us quickly acquires knowledge of the aging process, first by observing what it does to others and then by experiencing its effects ourselves. Most can offer some kind of theory as to why aging exists and how it is caused. However, most of these ideas are substantially, if not entirely, incorrect. In particular, there is a widespread but erroneous tendency to regard aging as programmed. As we shall see, there is scant evidence for the existence of such a program, and there are powerful arguments why it should not exist. Part of the oddity of aging science thus derives from the fact that we must begin by dismantling important preconceptions about why aging occurs.

The second oddity about aging is its inherent complexity. Almost every aspect of an organism's phenotype undergoes modification with aging, and this phenomenological complexity has led, over the years, to a bewildering proliferation of ideas about specific cellular and molecular causes. An attempt by Medvedev (1990) to rationalise the multiplicity of hypotheses resulted in a listing of more than 300 "theories" of aging. Fortunately, recent advances have resulted in significant simplification of the theoretical underpinnings of aging research, and this, combined with the greatly increased power of experimental techniques to investigate the phenomenological complexities of the senescent phenotype, has helped clear a path toward unravelling the workings of the aging process. Nevertheless, the intrinsic complexity of aging remains a significant challenge to understanding how aging is caused.

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Because aging occurs for nonintuitive reasons and unfolds in complex ways, theory plays an unusually pivotal role in its research. This review examines and critically assesses the current framework of ideas about why and how aging happens. It then considers some of the ways in which aging rate can be modified, and it concludes by examining some of the instances that push the boundary of our understanding of the aging process.

Setting the Stage

Before addressing aging theory in detail, we shall begin by considering three instances in which something of the oddity of aging is revealed. The first arises when we look at genetic effects on life span. There is a clear heritable component in human longevity (Cournil and Kirkwood, 2001), and, in recent years, large numbers of genes affecting longevity have been identified in organisms such as the nematode *Caenorhabditis elegans*. Indeed, the existence of single genes having major effects on longevity in *C. elegans* supports, at first sight, the idea of programmed aging. But if genes program aging, they do so only very loosely. There are significant differences in aging phenotype even between monozygotic human twins (Finch and Kirkwood, 2000), and, in *C. elegans*, even when genotype and environment are controlled, the variation in aging phenotype and in individual life span is enormous (Herndon et al., 2002; Kirkwood and Finch, 2002). This is in sharp contrast to the developmental process in this organism, which is so precisely regulated that each adult has just 959 somatic cells.

At the cellular level, it has been known for 40 years that normal, differentiated cells such as fibroblasts have a limited division potential before undergoing so-called "replicative senescence." This is in contrast to malignantly transformed cells, which can divide indefinitely. In human cells, the difference is largely due to the presence or absence of telomerase, suggesting that normal cells may be programmed to undergo senescence, perhaps as a protection against tumor formation. But, if programmed, the programming is again very loose, because there is a large variation in the rates of senescence of individual cells within the population. The idea that telomere loss through the end replication problem that arises in the absence of telomerase is a mechanism to "count" cell divisions, which thereby controls a cell senescence "clock," although widely held, does not comfortably fit the facts. Stress-induced DNA damage appears to be more important than the end replication problem for determining the rate of telomere erosion (von Zglinicki, 2003).

One of the most widely studied phenomena in aging research, known for 70 years, is the effect of dietary restriction (DR)—underfeeding without malnutrition—in extending life span in laboratory rodents and other species. The effects are substantial, resulting in as much as a 50% increase in rodent longevity. When gene expression is compared in DR and normally fed animals, a

wide array of genes is found to be altered in expression (Weindruch et al., 2002). However, in spite of a considerable amount of research effort, the mechanisms underlying life extension through dietary restriction are still highly uncertain (Merry, 2002).

Why Does Aging Occur?

To ask why aging occurs is to enter the realm of evolutionary biology, which increasingly is seen to be important for understanding health and disease (Stearns, 1999). In the case of aging, the challenge to evolutionary theory is to explain why aging occurs in spite of its obvious drawbacks. Aging is commonly characterized as a progressive, generalized impairment of function, resulting in an increasing vulnerability to environmental challenge and a growing risk of disease and death. It is also usually accompanied by a decline in fertility. Thus, aging is associated with major age-related losses of Darwinian fitness, posing the puzzle of why it has not been more effectively opposed by natural selection. As Williams (1957) tellingly observed, "It is remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed."

Is Aging Programmed?

When pressed to explain why aging occurs, in spite of its obvious disadvantages, the hypotheses most frequently advanced are that it benefits the species by preventing overcrowding and/or facilitating further evolution by securing a turnover of generations. These ideas echo Weismann (1889), who reasoned, "Worn out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound." From such thinking comes the notion that there are processes that actively mold the senescent state, driven by genes *for* aging. Given the perennial nature of the program idea, it is important to rehearse briefly the chief arguments why it is flawed:

(1) Data on age-related mortality patterns in wild animal populations reveal that, in many species, individuals rarely survive to ages when senescent deterioration becomes apparent (Medawar, 1952; Lack, 1954; Finch, 1990). For most natural populations, extrinsic mortality (due to accidents, predation, starvation, disease, cold, etc.) is such that death occurs well before "old age." This means that (a) there is no requirement for aging to weed out "worn-out individuals"; b) there is no evidence that aging in fact serves as a significant mortality force in the wild; and (c) there can have been scant opportunity to evolve genes specifically for aging, even if they were beneficial, since natural selection would not normally "see" them in action.
(2) The idea, as stated by Weismann (1889), is circular. It supposes that older individuals are worn out, perhaps reproductively exhausted, when its very purpose is to explain why such age-related decline should occur.
(3) The suggested benefits from aging are ones that serve the interests of the species or group. Whenever a benefit at the *group* level is assumed to supersede the contrary interests of the *individual*, any evolutionary hypothesis must confront the problem of "cheating." Individuals in whom the aging program was inactivated by mutation would benefit from the sacrifice of others, while enjoying any fitness advantage that might accrue from immortality. Such mutations would therefore be expected to spread. Although attempts have been made theoretically to explore the evolution of programmed aging and death in spatially structured populations (e.g., Travis [2004]), no convincing arguments have been advanced to support the general evolution of aging through such a mechanism.

If the theoretical arguments against programmed aging are felt to be insufficient, compelling as they are, it is noteworthy that, although hundreds of mutations have been found to extend longevity in *C. elegans*, no combination of mutations has yet been found which *abolishes* aging altogether. From a purely empirical standpoint, this suggests either that the program for aging is extraordinarily robust or that it does not exist.

Evolutionary Genetics

If aging is not programmed, how has it evolved and how can we account for genetic effects on aging? A satisfactory solution to this problem was first offered by Medawar (1952), who saw that, if attrition of population numbers through extrinsic mortality makes it hard to see how any program for age-related death might have evolved, it also shows that natural selection is essentially powerless to influence survival at older ages. Medawar's idea, now known as the "mutation accumulation" theory, proposed that late-acting alleles arising by de novo germline mutation could, at best, be acted against only weakly by natural selection, even if they adversely affected key traits like survival and reproduction. Thus, over successive generations, they might accumulate within the genome. Any individual who happened to escape the hazards of extrinsic mortality for long enough would experience the actions of these late-acting mutations as aging, and the same would of course be true for individuals reared in protected environments. [N.B. The mutation accumulation should not be confused with the somatic mutation theory (see below), which postulates the accumulation of *somatic* mutations arising through genome instability during a single generation.]

Additionally, Williams (1957) postulated the existence of pleiotropic genes of a special sort having opposite effects on fitness at different ages such that their effects were beneficial in early life, when natural selection is strong, but harmful at later ages, when selection is weak. This idea is now known as the "antagonistic pleiotropy" theory.

Together, the mutation accumulation and antagonistic pleiotropy theories provide the backbone for much of the current thinking about the evolutionary genetics of aging (Kirkwood and Austad, 2000; Partridge and Gems, 2002). Attempts to identify genes of these kinds have, however, had only mixed success to date. Evidence for mutation accumulation remains both limited and controversial (Shaw et al., 1999), while evidence for antagonistic pleiotropy, although stronger, is as yet lacking in details. Writing in 1957, Williams acknowl-

Figure 1. Organisms Face Tough Choices

According to the Darwinian imperative of natural selection, organisms must optimize their use of metabolic resources to maximise their fitness by production of progeny. To achieve this, resources must be allocated between competing processes such as growth, storage, reproduction, and maintenance and repair.

edged that convincing examples of antagonistically pleiotropic genes were hard to find, and he therefore illustrated his idea with a hypothetical mutation having a favorable effect on bone calcification during development but which expresses itself in a subsequent somatic environment in the calcification of the connective tissue of arteries. Although the number of gene mutants that extend life in mice, fruitflies, and nematodes and at the same time have detrimental early life effects is growing (e.g., Jenkins et al. [2004]), a recent review assessing the evidence for the existence of individual genes with antagonistic pleiotropic effects concluded that, at present, the repertoire of clear-cut instances "remains thin" (Leroi et al., 2005)

Evolutionary Physiology

If there is, as yet, limited evidence for the existence of specific genes of the types proposed by mutation accumulation and antagonistic pleiotropy, there is extensive support for the kinds of physiological connections of the kind envisioned by Williams (1957). In the physiological context, it may be more useful to think of these in terms of trade-offs, without specifying the underlying genetic structure in detail. The likely physiological basis for such trade-offs has been most explicitly developed within the "disposable soma" theory (Kirkwood, 1977; Kirkwood and Holliday, 1979; Kirkwood and Rose, 1991). The disposable soma theory was based on asking how the organism should optimally allocate its metabolic resources, chiefly energy, between the maintenance and repair of its soma and the other functions that it must carry out in order to maximise its Darwinian fitness (Figure 1). The necessity for trade-off arises because resources allocated to one function are unavailable to another.

Somatic maintenance needs only to be good enough to keep the organism in sound physiological condition for as long as it has a reasonable chance of survival in the wild. For example, since more than 90% of wild mice die in their first year (Phelan and Austad, 1989), any investment of energy in mechanisms for survival beyond this age benefits at most 10% of the population. Nearly all of the mechanisms required for somatic maintenance and repair (DNA repair, antioxidant systems, etc.) require significant amounts of energy (ATP). Energy is scarce, as shown by the fact that the major cause of mortality for wild mice is cold, due to failure to maintain thermogenesis (Berry and Bronson, 1992). The mouse will therefore benefit by investing any spare energy into thermogenesis or reproduction, rather than into better capacity for somatic maintenance and repair, even though this means that damage will eventually accumulate to cause aging. The three-year lifespan potential of the mouse is sufficient for its actual needs in the wild, and yet it is not excessive, given that some mice will survive into their second year and that age-related deterioration will become apparent before maximum life span potential is reached. Thus, it makes sense to suppose that the intrinsic life span of the mouse has been optimized to suit its ecology. The idea that intrinsic longevity is tuned to the prevailing level of extrinsic mortality is supported by extensive observations on natural populations (Ricklefs, 1998). Evolutionary adaptations such as flight, protective shells, and large brains, all of which tend to reduce extrinsic mortality, are associated with increased longevity.

Unlike the evolutionary genetic theories, which simply delineate the temporal aspects of genes that might explain aging, the disposable soma theory makes specific predictions about the biology of aging, as follows:

(1) Aging results from accumulation of unrepaired cellular and molecular damage through evolved limitations in somatic maintenance and repair functions. Such damage accumulates throughout life (from the time when somatic cells and tissue first begin to form).
(2) Longevity is controlled primarily through genes that regulate the levels of somatic maintenance and repair functions. Note that there is no necessary assumption that these genes switch to lower levels of maintenance and repair (which would smack of programmed aging); rather, it is the set point of the genes that determines the rate at which damage accumulates.
(3) Immortality of the germline may require elevated levels of maintenance and repair in germ cells, as compared with somatic cells. This is evidently fulfilled in the case of telomerase, and recently it has been shown that mouse embryonic stem cells downregulate multiple mechanisms for cell maintenance as they undergo differentiation (Saretzki et al., 2004).
(4) The mechanisms of cellular and molecular aging are inherently stochastic (i.e., strongly influenced by chance); this may explain the marked variability in aging phenotypes, noted earlier.
(5) There are likely to be multiple kinds of damage contributing to aging, which will be regulated by a complex network of maintenance and repair functions.
(6) The allocation of resources to maintenance and repair is determined by evolutionary optimization, and the allocation strategy may need to be plastic to respond to individual variations in circumstances of the organism during its life cycle (e.g., fluctuating food supply).

How Aging Is Caused

Aging is highly complex, involving multiple mechanisms at different levels. We will first consider the theories about molecular mechanisms underpinning age-

related cellular deterioration and then examine how aging affects cell and tissue homeostasis.

Molecular Mechanisms of Aging

At the molecular level, evidence suggests that several of the most important mechanisms involve damage to macromolecules. Some of the major theories that have been proposed to explain aging are the following:

Somatic Mutation Theory

Numerous studies have reported age-related increases in somatic mutation and other forms of DNA damage, suggesting that the capacity for DNA repair is an important determinant of the rate of aging at the cell and molecular level. There is a general relationship between longevity and DNA repair (Promislow, 1994). This is particularly well illustrated by studies on the enzyme poly (ADP-ribose) polymerase-1 (PARP-1), which is a key player in the immediate cellular response to stress-induced DNA damage (Bürkle, 2001). Higher PARP-1 activity levels are associated with longer life spans both between and within species (Grube and Bürkle, 1992; Muiras et al., 1998).

Telomere Loss Theory

In many human somatic tissues, a decline in cellular division capacity with age appears to be linked to the fact that the telomeres, which protect the ends of chromosomes, get progressively shorter as cells divide (Kim et al., 2002). This is due to the absence of the enzyme telomerase, which is normally expressed only in germ cells (in testis and ovary) and in certain adult stem cells. Some have suggested that in dividing somatic cells telomeres act as an intrinsic "division counter," perhaps to protect us against runaway cell division as happens in cancer but causing aging as the price for this protection (Campisi, 2005). While the loss of telomeric DNA is commonly attributed to the so-called "end replication" problem—the inability of the normal DNA copying machinery to copy right to the very end of the strand in the absence of telomerase—it has been found that stress, especially oxidative stress, has an even bigger effect on the rate of telomere loss (von Zglinicki, 2002), telomere shortening being greatly accelerated (or slowed) in cells with increased (or reduced) levels of stress.

Mitochondrial Theory

An important connection between molecular stress and aging is suggested by the accumulation of mitochondrial DNA (mtDNA) mutations with age (Wallace, 1999). Age-related increases in the frequency of cytochrome c oxidase (COX)-deficient cells, which are associated with mtDNA mutation, have been reported in human muscle (Müller-Höcker, 1989; Brierley et al., 1998), brain (Cottrell et al., 2000a, 2000b), and gut (Taylor et al., 2003). Cells in which mtDNA mutation reaches a high level are likely to suffer from impaired ATP production, resulting in a decline in tissue bioenergenesis.

Altered Proteins Theory and Waste Accumulation Theory

Protein turnover is essential to preserve cell function by removing proteins that are damaged or redundant. Age-related impairment of protein turnover is indicated by the accumulation over time of damaged proteins, and there is evidence that an accumulation of altered proteins contributes to a range of age-related disorders, including cataract, Alzheimer's disease, and Parkinson's disease. Protein turnover involves the functions of chaperones, which help to sequester and, if possible, restore denatured proteins, and proteasomes, which recognize and selectively degrade damaged and ubiquitinated proteins. With aging, there is evidence for functional declines in the activities of both proteasomes (Carrard et al., 2002) and chaperones (Soti and Csermely, 2003). These declines may be part of a more general failure, through overload, of cellular "waste disposal" processes (Terman and Brunk, 2004).

Network Theories of Aging

Much of the early proliferation of aging theories arose from a tendency to see the different hypotheses as *competing* to explain how aging occurs. The disposable soma theory suggests that multiple kinds of damage will accumulate in parallel within cells, since the same logic limits the investment in each of a wide range of maintenance and repair functions (Figure 2A). Although the multiplicity of aging mechanisms is now widely acknowledged, the reductionist nature of experimental techniques means that, in practice, most research is still narrowly focused on single mechanisms. This is severely limiting because, although for each of the theories outlined above evidence can be found that the kinds of molecular and cellular lesions it predicts do occur during aging, for *none* of them is there evidence that the theory is, by itself, sufficient to account for age-related frailty, disability, and disease. This has led to recent initiatives to develop "'network" theories of aging in which the contributions of the various mechanisms are considered together, thereby allowing for interaction and synergism between different processes (Kirkwood et al., 2003). Furthermore, such network models can highlight important differences between "upstream" mechanisms that set a process in train and "end stage" mechanisms that dominate the cellular phenotype at the end of its life (Kowald and Kirkwood, 1996). For example, a gradual accumulation of mtDNA mutations, occurring over years, might lead to a steady increase in the production of reactive oxygen species (ROS) and a gradual decline in energy production. Although the build-up of mtDNA mutations initiates the process, what ultimately destroys the cell is that eventually a threshold is reached where homeostatic mechanisms collapse. Understanding these connections is likely to be important in developing effective interventions against age-related cellular deterioration.

A further attraction of the network approach is that, although the various mechanisms comprising the network are likely to operate to some degree in all cell types and in all species, there may be important differences concerning which mechanisms are more important. All cells share a basic vulnerability to damage affecting key macromolecules such as DNA and proteins, particularly when this damage arises from generic sources such as endogenous oxidative stress caused by ROS. However, cells in actively proliferating tissues are more vulnerable than postmitotic cells to suffer somatic mutations and telomere erosion because of the repeated requirement for DNA replication. Conversely, postmitotic cells are more vulnerable to accumulation of aberrant proteins and metabolic wastes through failure of turnover processes, since, in dividing cells, any

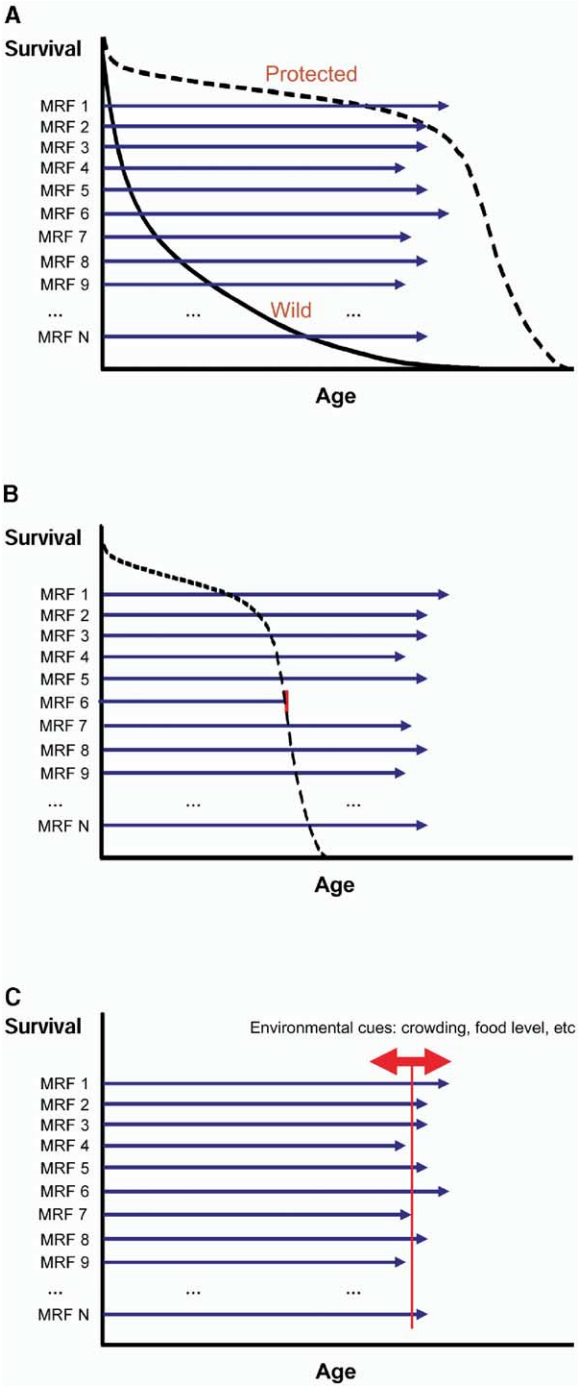

Figure 2. Maintenance and Repair Determine Longevity

(A) According to the disposable soma theory of aging, the optimal investment in somatic maintenance and repair functions (MRF) is expected to be only what is needed to maintain the body for as long as it has a reasonable chance of survival in the wild environment, where extrinsic mortality pressures are high. The lines for individual MRFs indicate the period of "longevity assured" before the limitations of that MRF result in an intolerable burden of damage. The number, N, of MRFs is potentially large, and, although they are all subject to similar selection, there is likely to be some variation from MRF to MRF in the periods of longevity assured, both within and across individuals within the population.

(B) Mutation of a gene responsible for a particular MRF will lead to accelerated accumulation of damage and a shortened life span.

(C) Where organisms are subject to significant environmental variability, they may have evolved high-level regulatory genes that can sense changes in environmental conditions and coordinately regulate multiple MRFs.

such accumulation will be diluted by the synthesis of new cellular constituents during mitosis. Thus, although the network of mechanisms underlying cellular aging may share common components across all cell types, the relative importance of these components may differ. Furthermore, if dividing cells reduce their rate of division in later life as a consequence of intrinsic molecular aging, they may then undergo a corresponding shift in the balance between different mechanisms of molecular damage accumulation. Similar considerations apply to differences between species that may differ in the extent of cell renewal or exposure to specific types of molecular damage.

Cellular Aging

If damage drives the underlying age-related deterioration in cell function, a range of interesting consequences and questions arises at the cellular level. First, it is expected that there will be considerable microheterogeneity within aging tissues, since damage is inherently stochastic. Thus, damaged cells are likely to coexist alongside relatively undamaged cells, and one of the major unresolved issues concerns the frequency of seriously damaged cells that might be required to produce significant impairment of tissue function (Kipling et al., 2004). Study of the phenomenon of in vitro replicative senescence is largely concerned with cultures in which all of the cells have reached the limit of their division potential. This situation will not be reached in vivo, however, and so it is important to understand how some cells reach the senescent state before others and what effect this may have on tissue homeostasis. Also, caution needs to be exercised in drawing conclusions from studies based on ex vivo culture of cells from aged tissues, since these procedures will automatically select for the least damaged cells and may not be sufficiently representative of the aged tissue itself.

An important question concerns the cellular response to damage. In some contexts, notably among stem cells of highly proliferative tissues such as bone marrow and gut epithelium, damaged cells pose a significant threat to the organism's health because of their potential to give rise to large numbers of mutant, potentially malignant daughter cells. This is presumably why such cells tend to respond to DNA damage by initiating apoptosis. In the case of gut epithelial stem cells, even a very low dose (0.1 Gy) is sufficient to initiate apoptosis (Marshman et al., 2002). It may be significant that, in aged mice, these stem cells, which exhibit some functional deterioration already, show increased levels of apoptosis in response to low-dose genotoxic stress (Martin et al., 1998a, 1998b). In general, in tissues where apoptosis is used to delete damaged cells, increased levels of apoptosis in aged organs are likely to reflect higher background levels of accumulated cellular damage. Once again, it is important to use our theoretical

understanding of aging to assign the right direction to the causal arrow. If aging were programmed, then the increased levels of cell death seen in some organs and tissues might be evidence for the action of the program. However, the more likely explanation is that the cell deaths reflect the actions of protective mechanisms that evolved to delete occasional, dangerously damaged cells in young animals. These mechanisms will be called into play much more often in aged tissues in which the background accumulation of damage is greater and the resulting loss of cellularity may itself accelerate senescent decline. This late deleterious side effect of a process that is beneficial in earlier life is of little consequence for natural selection, providing a good example of the underlying principle of antagonistic pleiotropy.

While induction of apoptosis makes theoretical sense when damaged cells pose a particular threat, as is evidently the case for tissue stem cells, a less costly alternative is to induce permanent cell cycle arrest through cellular senescence. The facts that senescence may be induced directly by stress (stress-induced premature senescence; Toussaint et al. [2002]) and that even when telomere loss is involved this is significantly linked with stress exposure (von Zglinicki, 2002) suggest that a primary function of cellular senescence is to arrest cycling cells that are sufficiently stress exposed that their continued division would pose a threat.

The balance between deleting and preserving damaged cells appears to be particularly important for optimizing the trade-off between aging and cancer. This was elegantly demostrated in a study by Tyner et al. (2002) of mice in which a mutant form of p53 showed constitutive activation. Heterozygotes between mutant and wild-type p53 showed increased p53 activity and had greatly reduced cancer incidence. However, they also showed faster aging. Their shortened life spans were accompanied by accelerated age-related reduction in mass and cellularity of various tissues, including spleen, liver, kidney, and testis. Accelerated age-related losses were also noted in skin thickness, hair growth, wound healing, and stress resistance (to anesthesia and to 5-fluorouracil treatment in hematopoietic precursor cells).

Campisi (2005) has suggested that replicative senescence itself might be viewed as an example of antagonistic pleiotropy, in which the early-life benefit of enhanced cancer resistance is paid for by the late-life cost of tissue aging. There is certainly something in this idea, and the actions of p53 reveal it to be perhaps the clearest example of an antagonistically pleiotropic gene (Leroi et al., 2005). However, the relationship between replicative senescence and aging appears more complicated than simply a case of antagonistic pleiotropy.

The trade-off mediated by p53 is about how the organism deals with cells that are damaged already. Underlying this trade-off is the deeper question of how much the organism invests in DNA maintenance itself. As we have seen, long-lived organisms invest in better DNA maintenance. The benefit of this is seen both in slower aging and delayed incidence of cancer, since genome instability contributes to both these processes. Since human cells are much less susceptible to cancer than mouse cells, the best cancer avoidance strategy for a mouse, other things being equal, would be to invest in the level of DNA maintenance enjoyed by humans. However, other things are not equal, and each species has balanced the costs and benefits of its investments in DNA maintenance to suit its own ecological circumstances. What we see, therefore, is a combination of two principles at work. First, there is the question of how much effort should be put into protecting cells from damage; this is answered most directly by the logic of the disposable soma theory. Second, there is the question of what to do about damaged cells; this is answered through trade-offs between cell survival/proliferation, senescence, and death by optimizing the costs and benefits of the various options.

In summary, current theoretical understanding suggests that, as cells age, they tend to accumulate damage. The rate at which damage arises is dictated, on the average, by genetically determined energy investments in cellular maintenance and repair, at levels optimized to take account of evolutionary trade-offs. Long-lived organisms make greater investments in cellular maintenance and repair than short-lived organisms, resulting in slower accumulation of damage. In order to manage the risk presented by damaged cells, particularly the risk of malignancy, organisms have additionally evolved mechanisms, such as tumor suppressor functions, to deal with damaged cells. The actions of such "coping" mechanisms will frequently involve a second tier of trade-offs.

Modifying the Rate of Aging

The discovery in 1997 that the gene whose mutation is responsible for the human progeroid condition known as Werner syndrome (WS) was a DNA helicase fitted well with the idea that an accumulation of DNA defects contributes to aging. Cells from WS subjects are characterized by genome instability, rapid cell senescence, and increased cancer risk. Thus, *WRN* mutation is like cutting short one of the lines securing the body's maintenance and repair (Figure 2B). The same concept applies to an approach that has been used recently to investigate, in transgenic mice, genes whose failure might contribute to accelerated aging, particularly those involving defects in DNA maintenance and repair functions such as WRN, Ku80, ERCC1, and telomerase (Hasty et al., 2003). Similar approaches have also been used to produce premature "aging" in mice expressing defective mitochondrial DNA polymerase, thereby producing an mtDNA mutator phenotype (Trifunovic et al., 2004), and defects in A-type lamins (Mounkes et al., 2003).

The attractions of such models are obvious: they exaggerate a specific type of molecular damage, demonstrate a clear cause-and-effect relationship, and provide experimental models to assess interventions. However, there are important caveats. The model will only truly represent accelerated aging if the specific lesion it generates is a natural part of the spectrum of lesions that arise during the "normal" aging of the wild-type. If this condition is not fulfilled, the genetic alteration may produce pathology and reduce life span yet have little or nothing to do with the aging process. In

this regard, it is noteworthy that the pathobiology of most premature-aging mouse models differs in some respects from that seen in normal aged mice, just as WS differs from normal human aging. Second, even if the lesion is of a kind that occurs during normal aging, its specific amplification means that potential interactions with other lesions contributing to normal aging are likely to be missed. Assessing interventions within a model where one kind of lesion dominates the aging process will not necessarily translate to the situation that arises in the normally aged animal.

Plasticity in the Natural Regulation of Aging Rate

The evolutionary theories of aging predict that potentially many genes influence aging rate. Thus, it was an important challenge when it was found that a range of single gene mutations have big impacts on life span in model organisms like *C. elegans* (Guarente and Kenyon, 2000; Johnson et al., 2002) and that insulin and insulin-like growth factors play a central role in modulating aging in this and other species (Tatar et al., 2003; Holzenberger et al., 2003; Bluher et al., 2003; Gems and Partridge, 2001). How could a central regulator of aging be reconciled with the notion of a large number of distinct mechanisms, and, indeed, did not the existence of such regulation suggest a kind of program?

The puzzle of how to control multiple genes governing aging rate was considered theoretically in earlier discussions about the rates of evolutionary divergences of species life spans (Cutler, 1975; Martin, 1979; Kirkwood, 1985). However, the new discoveries gave fresh impetus to the problem as well as pointing to likely solutions. The evolutionary explanation of aging rests on the principle that natural selection has sought to optimize the allocation of metabolic resources across core processes like growth, reproduction, and maintenance. Over evolutionary time scales, these allocations can respond to pressures of natural selection. But what happens if, for example, environmental circumstances change within an organism's lifetime and the previous allocation is no longer optimal?

Some of the most important environmental variation concerns the level of nutrient availability, and so it makes sense, if the capacity to vary metabolic allocations in response to changing circumstances has evolved, first that insulin signaling pathways should be involved and second that this regulatory plasticity should be most clearly observable within the context of changes in resource availability.

One of the clearest examples of a plastic response to altered circumstances is seen in the phenomenon of dauer formation in *C. elegans*. The *C. elegans* dauer larva is a long-lived stress-resistant dispersal form, which develops in response to overcrowding. An insulin/IGF-1-like gene, *daf-2*, heads a gene regulatory pathway controlling the switch into the dauer form. This acts through controlling a master regulator, *daf-16*, which itself appears to regulate several hundred genes controlling an array of maintenance functions including stress responses, protein turnover, and antimicrobial resistance (Murphy et al., 2003). Thus, although the nematode regulates its rate of aging through a large number of maintenance and repair functions, these are subject to high-level control through a signaling system that has evolved to sense the quality of the environment and to tune the investments in maintenance accordingly (Figure 2C).

A similar regulatory system appears also to be involved in the response to dietary restriction. Dietary restriction is observed to cause slowing of aging and extension of life in many species (Merry, 2002). One hypothesis as to why this occurs is that animals have evolved a response to temporary fluctuations in resource availability, in which energy is diverted from reproduction to maintenance functions in periods of food shortage, thereby enhancing survival and retaining reproductive potential for when conditions improve (Harrison and Archer, 1988; Holliday, 1989). This is consistent with the general upregulation of maintenance functions that is seen during DR, at least in rodents (Weindruch et al., 2002). The idea that the response to dietary restriction represents some kind of evolved strategy to switch resource allocation in response to need should not be accepted without critical assessment. Does the organism in fact increase its Darwinian fitness by this means, or is the effect merely an unselected byproduct of metabolic perturbation induced by food shortage? In order to test the evolutionary plausibility of the idea that the rodent dietary restriction response has been subject to evolutionary regulation, Shanley and Kirkwood (2000) made a detailed quantitative assessment using a dynamic resource allocation model informed by detailed physiological data. This revealed that there is indeed reason to suppose that the dietary restriction response has been shaped by natural selection.

A third example of regulatory control of aging is seen in colonial insect species such as ants and bees in which the different castes may have very different life spans even though they share the same genes (Chapuisat and Keller, 2002; Omholt and Amdam, 2004). In the case of the honey bee (Omholt and Amdam, 2004), the worker population consists of a hive bee caste performing a multitude of tasks inside the nest and a forager caste collecting food and other resources from outside. Workers emerging in spring and midsummer have a mean lifespan of about 25–35 days, of which about two thirds is spent as a hive bee before switching to become a forager. Winter bees emerge when the sources of nectar and pollen diminish at the end of the productive season and normally live 6–8 months. Winter bees are exposed to lower levels of extrinsic mortality and differ from summer bees in several physiological respects, which can be related to differential resource allocation. Furthermore, when a summer beehive worker switches to a foraging role, additional changes occur, consistent with the idea that the risk-exposed forager becomes more "disposable."

Pushing the Boundaries of Our Understanding of Aging

Within this review so far, significant attention has been given to explaining why the idea of programmed aging is unsound and how evolutionary theory explains the widespread occurrence of aging despite the lack of a program. The importance of a strong, coherent theoret-

ical framework for aging research is that it provides a means of integrating a highly disparate set of experimental models and observations. Theory must, however, be continually challenged, and we now consider some of the apparent exceptions that test the rules.

Semelparous Organisms

Semelparous (once-only reproducing) species, like Pacific salmon, are commonly said to exhibit programmed aging and death. This interpretation of the rapid postreproductive death of semelparous organisms is unlikely, however, to be correct. The rapid deterioration of Pacific salmon after mating is a byproduct of a life history that has been geared by natural selection to stake everything on the success or failure of a single bout of reproduction. The first phase of a semelparous life history is devoted to growth and to acquiring the resources necessary for reproduction. As soon as the signal to reproduce is triggered, a massive effort is made to mobilize all available resources to maximize reproductive success, even if this leaves the adult so severely depleted or damaged that death ensues. Once a species has evolved down the pathway that results in semelparity (this is most likely to occur where ecological circumstances decree that the chance of surviving to breed again would in any case be small), there is no reason to hold back resources for postreproductive adult survival. Although instances may conceivably occur where the death of the adult directly benefits its young (Kirkwood, 1985), there is little evidence that semelparous organisms are *actively* destroyed once reproduction is complete; they tend simply to fall apart. They are, in effect, extreme examples of the "disposable soma."

Extrinsic Mortality and Life Span

A central prediction from the evolutionary theories of aging is that the level of extrinsic mortality determines the rate at which the force of natural selection wanes with increasing age and that this in turn influences the rate of aging. In a more hazardous environment, late-acting deleterious mutations should accumulate at earlier ages and the soma become more disposable, and vice versa. Thus, a recent study on patterns of senescence in populations of guppies exposed to different levels of extrinsic risk (Reznick et al., 2004), which ran counter both to theoretical expectation and to previous studies in this and other species on the relationship between descreased extrinsic mortality and delayed senescence (Ricklefs, 1998), provides an intriguing challenge. In fact, such examples highlight that the underlying theory is more complex than often appreciated and that genetic models may need to take account of factors such as population density effects that can modulate the straightforward relationships between extrinsic mortality and evolution of aging rate (Abrams, 2004).

Nonaging Species

A number of multicellular organisms, including *Hydra*, exhibit very slow or negligible rates of senescence (Finch, 1990). In the case of *Hydra*, individual animals were observed over a period of 4 years to show no age-related deterioration, either in terms of survival or reproduction rates (Martinez, 1998). This is most likely linked to the fact that *Hydra* are capable of undergoing complete regeneration from almost any part of their structure, implying that germ cells permeate the body so comprehensively that *Hydra* has no true distinction between germline and somatic tissue. In an earlier test of the idea that the presence or absence of aging should be linked with possession or not of a soma, Bell (1984) showed that organisms lacking a distinction between germline and soma showed no tendency to age, unlike those with such a distinction. In the case of species having clear distinctions between germline and soma yet negligible rates of aging, at least so far as has yet been observed, further research is clearly needed.

Aging in Unicellular Organisms

Given the evidence just cited that the presence or absence of aging in multicellular organisms tends to be linked to possession or not of a distinct soma, it might be supposed that unicellular organisms, which lack a soma (in the commonly understood sense), should be immortal. However, during the 1980s, the budding yeast *Saccharomyces cerevisiae* became firmly established as an experimental model for research on aging. In this case, one might stretch a point and suggest that the "mortal" mother cell can, in a sense, be seen as soma, whereas the smaller bud that becomes the daughter can be seen as germline (Lai et al., 2002). The same argument might even include the bacterium *Caulobacter crescentus*, which divides asymmetrically and also exhibits a form of aging (Ackermann et al., 2003). The case gets harder, however, when we note recent reports of aging in fission yeast *Schizosaccharomyces pombe* (Barker and Walmsley, 1999) and *Escherichia coli* (Stewart et al., 2005).

The resolution to this seeming paradox comes from looking more closely at what we have been learning about the molecular and cellular basis of aging. The origin of the aging process in multicellular animals arose from the division of labor between germline and soma (Weismann, 1889). As soon as the germline/soma distinction evolved, only the germ cells carried the responsibility for forming individuals of the next generation, freeing somatic cells to become specialists such as neurons, muscle cells, or cells in the lens of the eye. This came at a price, however, because the soma then became disposable. What Stewart et al. (2005) have shown is that a division of labor exists even in *E. coli*, highlighting the fundamental importance of reproductive *asymmetry* in creating a context for aging to evolve (Kirkwood, 1981; Partridge and Barton, 1993). The germline/soma distinction is a *sufficient* instance of such asymmetry, but it is not a *necessary* one. Although *E. coli* appears to divide symmetrically, in molecular terms it does not in fact do so. One daughter cell receives the old cell pole, the other cell receiving a new pole. The difference is apparently enough to cause a decline in fitness of the daughter that receives the old pole and thus does not benefit from the complete renewal of its molecular structures.

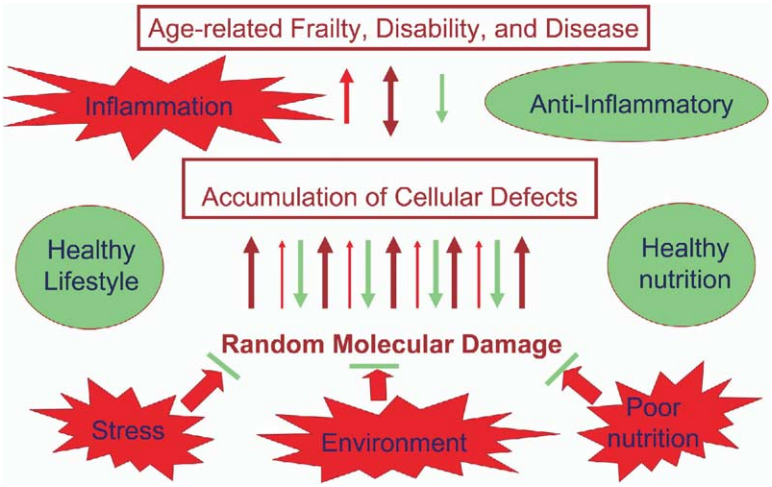

Figure 3. Damage and Aging

Underlying the aging process is a lifelong, bottom-up accumulation of molecular damage. Such damage is intrinsically random in nature, but its rate of accumulation is regulated by genetic mechanisms for maintenance and repair. As cell defects accumulate, the effects on the body as a whole are eventually revealed as age-related frailty, disability, and disease. This model accommodates genetic, environmental, and intrinsic chance effects on the aging process. Genetic effects are expressed primarily through maintenance functions, while environment (including nutrition and lifestyle) can either increase or help to decrease the accumulation of molecular damage. Cellular defects often cause inflammatory reactions, which can themselves exacerbate existing damage; thus, inflammatory and antiinflammatory factors can play a part in shaping the outcomes of the aging process. Green color and arrows indicate effects that counter damage accumulation; red color and arrows indicate contrary effects. Brown arrows indicate damage that arises as a byproduct of intrinsic biochemical reactions, errors, and thermal noise.

Conclusions

Although it is entirely understandable to try and see the semblance of a program in aging, the arguments against the existence of any such program are compelling. Far from being programmed to die, organisms are programmed for survival. The reason that aging occurs is in essence quite simple. Life exists far from thermodynamic equilibrium. Its stability is constantly threatened by a wide array of internal and external stressors, and, in these circumstances, things tend to fall apart rather quickly unless actively maintained. Keeping the soma going requires constant effort, and this, in the long run, is unwarranted—in terms of natural selection, there are more important things to do. Thus, programming for survival ultimately fails, and it is this that results in aging (Figure 3).

How aging actually plays out, however, is quite complex, and there are many features of the aging phenotype that can give an appearance of programming. Indeed, part of the attraction of antagonistic pleiotropy to many, both within and beyond the aging field, may be the way in which it suggests that aging happens for a *purpose*. The purpose is not aging, per se, but the early benefit for which the pleiotropic gene is selected. In this sense, it is possible even to see aging as being program driven, like development, even though the program evolved for some other reason.

One of the problems with this view, though, is that there are, in fact, very few clear-cut examples of candidate pleiotropic genes other than p53. Even for p53, its primary function, as we have seen, is more about "managed decline." A second problem is that even the kind of indirect programming that antagonistic pleiotropy implies fails to explain the extraordinary variability of the aging phenotype, unless we suppose that the pleiotropic genes regulate maintenance and repair. This, however, would be to equate antagonistic pleiotropy with the disposable soma theory. Although it is possible to press the kinds of gene actions envisaged by the disposable soma theory into the mold of antagonistic pleiotropy (Kirkwood and Rose, 1991), the fit is awkward. This is because the genes in question are for repair functions, which are uniformly beneficial. What one has to argue in order to make them fit antagonistic pleiotropy is that the early benefit comes from *not repairing too much*, which seems to stretch the concept that Williams (1957) originally had in mind for such genes. It is surely easier to talk simply of trade-offs. Such terminology extends more naturally into considering the kinds of regulatory control of aging rate that appear to operate via insulin signaling pathways and in social insects like honey bees and which are most naturally accommodated within the evolutionary physiology framework of the disposable soma theory.

Perhaps the central paradox of aging science is that it is concerned to understand a process that occurs universally within our own species (and many others) and yet runs directly counter to the underlying driving force of living systems, the power of natural selection to support and sustain life. Aging is, above all, about the failure of living systems to keep going. Such systems do not, as a rule, give up the struggle easily, and we may anticipate that, in learning how aging erodes and eventually overwhelms our survival mechanisms, we will learn a great deal more about how these mechanisms are organized.

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