Genes and Aging – II

The genes that control ageing

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A belief that ageing and longevity are governed by genetic factors has led to growing excitement that research on the human genome will soon uncover the genes for ageing and – who knows? – open the path to longer lives for us all. But what is the evidence that genes control ageing and how realistic is it to expect that the "new genetics" can secure for us a modern-day elixir of youth?

The confidence that genes affect ageing comes from several lines of evidence. First, there is the obvious fact that different species have different life spans, and where better to look for the underlying causes than their genomes. Second, there are clear life span differences between different inbred strains of animals, such as mice and rats held in identical environments, differing only in their genes. Third, when we examine human populations it really does seem to be true that the best recipe for a long life is to choose your parents carefully. Longevity shows a statistical tendency to run in families, and the life spans of identical twins are more similar to each other than life spans of non-identical twins. Fourth, and the subject of much recent research, simple organisms like fruit flies and nematode worms have revealed a range of gene mutations that markedly affect the length of life.

The evidence for a genetic contribution to ageing is therefore compelling, but intriguingly all these studies point to only weak genetic specification of individual life span. In humans, genes account for only about a quarter of what determines individual length of life. In other species, the picture is much the same. So what kinds of genes control longevity? And how come they do so in such an indecisive way?

One of the most successful tools for teasing apart these puzzles is Darwin's theory of evolution by natural selection. Ageing is widespread among animal species but by no means universal, and not all species age in the gradual way that we do. Some organisms, like the freshwater *Hydra*, show no signs of ageing at all. Others like the Pacific salmon age all at once, just as soon as their once-in-a-lifetime chance of reproduction has come and gone. In the case of the Pacific salmon, the rapid post-reproductive death of the adult appears to be driven by sex

hormones. If a salmon has its reproductive organs removed, it cannot of course reproduce but it lives much longer.

So is ageing the price paid for sex? And are ageing and death programmed to tie in with reproduction, for example, to provide living space for the next generation? The answer to the first question, we shall see, is 'sort of'. The answer to the second is a definite 'no'. Understanding why and how ageing evolved will tell us much about the nature of the genes that are involved and how these shape the life history, particularly the relationship between reproduction and survival. In fact, we are discovering that each of the diverse life history patterns seen in nature can be understood as variants on a single theme. This theme, considered from the point of view that existence can be explained in terms of purpose, is that genes look after themselves first and have few reservations about treating their products - our bodies - as disposable.

A simple observation, pointed out half a century ago by Peter Medawar, puts paid to the general idea that old organisms are programmed to lay down their lives in order to provide living space for their young. Extensive field studies show that it is rare to find old animals, that is animals in which the ageing process is significantly advanced, in nature. Most animals in the natural world die young. From a population of newborn wild mice, nine out of ten of them will be dead before age ten months even though half of the same animals reared in captivity would still be alive at age twenty-four months. Thus, ageing is in an important sense an artifact of protected environments, even though the potential to age is deeply ingrained.

The fact that ageing is rarely seen in natural animal populations tells us immediately that it did not evolve to control population size. Since animals do not, for the most part, live long enough for ageing to exert any effect on their survival, we can discount the population-control argument. Furthermore, because animals die young, natural selection cannot exert a direct influence over the process of senescence. It is thus hard to see how any direct programme for ageing, driven perhaps by an 'ageing gene', might have evolved.

Instead of being programmed to die, organisms are programmed to survive. The trouble is that in spite of a formidable array of mechanisms that strive to keep us alive, including programmed cell death which in adults serves mainly to delete unwanted or damaged cells, these mechanisms are not good enough to allow us to last indefinitely. The key to understanding why

this should be so, and what governs how long a survival period should be catered for, comes from looking again at the data from survival patterns in the wild. If ninety percent of wild mice are dead by the age of ten months, any investment in programming survival much beyond this point benefits at most ten percent of the population. This immediately suggests that there will be little evolutionary advantage in building long-term survival capacity into a mouse. The argument is further strengthened when we observe that nearly all of the survival mechanisms required by the mouse to combat intrinsic deterioration, such as damage to their DNA, require metabolic resources. Metabolic resources are scarce, as evidenced by the fact that the major cause of mortality for wild mice is cold, due to failure of their bodies to produce enough heat to maintain their body temperature. From a genetic point of view, the mouse will benefit more by investing any spare resource into heat generation or reproduction rather than by boosting its DNA repair capacity to a better level than it requires.

This concept, with its explicit focus on evolution of optimal levels of cell maintenance, is termed the ‘disposable soma’. In essence, the disposable soma theory predicts that the investments in durability and maintenance of somatic, that is non-reproductive tissues, are sufficient to keep the body in good repair through the normal expectation of life in the wild environment but no better than that, although some measure of reserve capacity is to be expected. Thus, it makes sense that mice, with ninety percent mortality by ten months, have intrinsic life spans of around three years, while humans, who probably experienced something like ninety percent mortality by age fifty in our ancestral environment, have intrinsic life spans limited to about one hundred years. The distinction between somatic and reproductive tissues is important because the reproductive cells, also known as the germ line, must be maintained at a level that preserves viability across the generations, whereas the soma needs to serve only a single generation. At once, we can understand the apparent immortality of *Hydra*. The usual mode of reproduction in *Hydra* is vegetative, by forming asexual buds. This is facilitated by the fact that germ or stem cells permeate its body, which gives it almost limitless powers of regeneration. Although individual *Hydra* can and do die, their immortality is very real in the sense that individuals have been observed for long periods of time without showing signs of intrinsic ageing. The principle that absence of a clear distinction between soma and germ line correlates with absence of ageing, and vice versa, has been confirmed in other species.

The disposable soma theory identifies the likelihood of death from external causes as the primary driver in the evolution of longevity. If this is high, as in the mouse, the average survival period is short and there is little selection for a high level of maintenance. Any spare resources should go instead towards reproduction. Consequently, the organism is not long-lived even in a protected environment. Conversely, if the level of extrinsic mortality is low, selection is likely to direct a higher investment in building and maintaining a durable soma. Comparative studies bear this prediction out at both the ecological and molecular level. Adaptations, such as wings, protective shells or a large brain, that reduce death from external causes are linked with increased longevity as seen in bats, birds, turtles, and humans. Even at the molecular level, cells from the longer-lived mammals have greater capacity to withstand stress than cells from shorter-lived species. This ties in well with a range of studies demonstrating greater capacity for DNA repair in longer-lived mammals.

The last decade has seen a surge of activity aimed at identifying genes controlling ageing in invertebrates such as the nematode worm and the fruitfly. It was in nineteen eighty-eight that the first mutant gene conferring an increase in life span in nematodes was detected and since then the number of such genes has steadily climbed, now standing at around twenty. A particular advantage of worms for this kind of work, in addition to their short life span of around twenty days for wild-type worms under standard culture conditions, is that this species mainly reproduces as a self-fertilising hermaphrodite. This facilitates the isolation of new strains with a very high degree of genetic uniformity.

By the middle nineteen nineties it had been found that the original longevity mutant, appropriately named *age-1*, showed unusual resistance to a wide range of environmental stresses, an observation subsequently reproduced for many of the other longevity-conferring mutations. This is directly consistent with the finding that longevity and stress-resistance are positively associated in mammals. Furthermore, life extension has since been demonstrated in nematodes and fruitflies in which the activity of their stress-resistance genes has been artificially increased. A side-effect of this work has been a revival of interest in a phenomenon known as hormesis, where a low dose of a damaging agent such as heat or radiation increases survival. In nematodes and fruitflies, hormetic effects are particularly clear.

While the high level of genetic uniformity in nematode stocks has been of advantage in identifying longevity-conferring mutations, a different approach has been used to explore the

genetics of ageing in fruitflies by applying artificial selection to outbred populations. In outbred populations, the existence of variation in genes that control the rate of ageing should, in principle, allow selection for sub-populations that age more slowly. There is, however, an inherent problem in selecting for long life. By the time you know which flies lived the longest, they are of little use for breeding! This problem was overcome in two ways. First, selection was applied not to longevity directly but to the capacity to lay eggs at older ages. By discarding eggs laid before a certain age, the experiment imposed a selection for late fecundity. After twenty generations of selection, this procedure resulted in populations whose life span had been increased by thirty percent or more. The second trick exploited the fact that temperature affects fruitfly life span; flies live longer at lower temperatures. Sibling groups of flies were divided into sub-groups, one maintained at high temperature, the other at low temperature. Those at high temperature died quickly, so those that lived longest could be quickly identified. Meanwhile their siblings maintained at low temperature were still fully fertile and could be selected for further breeding. This second procedure worked particularly well producing thirty percent life span increases within just six generations of selection.

If both selection experiments and artificially induced gene modifications can so readily produce major increases in life span, it might seem that longevity could be enhanced at will. But there was a price. In the case of fruitflies, the downside of evolving longer lives was revealed in a reduced reproductive rate. In most of the selection experiments, the long-lived populations that were produced had significantly reduced overall fertility, particularly in the earlier stages of life, which in nature are the most important. Nematodes have shown less obvious fitness costs from increased life span but the costs are there to be found. An experiment that pitted long-lived *age-1* mutants against the wild-type in mixed populations found that when the worms were exposed to intermittent stress, mimicking conditions likely to arise in nature, the wild-type won out even though the *age-1* worms have greater individual capacity to survive acute stresses in non-competitive situations.

The principle that a price is paid for longevity holds true in fruitflies and nematode worms, but what about us? To test the possibility that humans, too, might show a negative correlation between longevity and fertility, birth and death records for more than thirty thousand British aristocrats who lived and died between the eighth and nineteenth centuries have been examined. Although aristocrats are not a typical sub-group of the population they were chosen

because they are far better documented than the general population and they have always enjoyed the best living conditions. If you want to study biological determinants of longevity, it is of little use to study a population whose lives are often cut short by hardships associated with poverty. It was found that there was a tendency for the longest-lived individuals to have had smaller family sizes and higher levels of infertility. Studies based on historical records are necessarily limited in the kinds of questions they can answer. Nevertheless, this finding has since been repeated in other populations.

Current studies in humans are focusing on the growing numbers of centenarians among us. Centenarians are interesting for the information that these exceptionally long-lived individuals might provide about the genes influencing human longevity. Several recent studies have found evidence for genetic differences between centenarians and the general population. Activity levels of a key enzyme which reacts to DNA damage within minutes of a stress being applied, have been shown to be higher in centenarians. This is in line with an earlier study showing that activity levels of this enzyme correlate with mammalian species life span, longer-lived species having higher levels. Thus it appears, at least in this case, that the same genetic factor can contribute to differences in life span between and within species.

Huge advances in our knowledge of genes involved in ageing are promised by the human genome project and similar projects in other species. In addition to information about gene sequences, large amounts of data will emerge from techniques that can compare patterns of the activity of genes in old versus young tissues or those with and without age-related diseases. But this avalanche of data will require careful interpretation. A major challenge in evaluating the large numbers of genes that are likely be picked up by these techniques will be to distinguish which of the many differences are involved in the ageing process, and which are a consequence of it.

It is the intrinsic nature of how genes control life span that explains the relatively low precision of the genetic specification of life span. Genes for longevity do not simply count out our days and then kill us. They endow us with a given level of protection against damage. How long we actually keep going is then strongly influenced by things like lifestyle – the foods we eat and the exercise we take – as well as by luck.

The major themes emerging from our present understanding of the genes that control ageing are: that ageing is not programmed but results from the gradual accumulation of random

somatic damage; and that the rate of ageing, and hence longevity, is set by the efficacy of maintenance and repair processes. A growing body of data supports these themes but a great deal more work still needs to be done to identify the actual genes which are involved, how they are regulated, and how they interact with each other.

Finally, what about those Pacific salmon and their sudden post-reproductive death? Is this not programmed ageing and does it not confound the evolutionary theory? Actually the answer is 'no'. Pacific salmon have evolved what is called a 'semelparous' life history, in other words they have all their offspring at once. If you evolve down the semelparous path your life consists mostly of acquiring resources and readying yourself for the big day. When that day comes, it is important to mobilise all possible metabolic resources to ensure reproductive success, even when this is destructive to the soma. Sometimes, somatic tissue is even sacrificed directly to feed the young. In other words, the semelparous soma is the ultimate disposable soma. What is programmed is big-bang reproduction with death as a side-effect of little or no consequence; it is not programmed ageing. On the other hand, it may not be a bad way to go.