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Forum

The biological basis of ageing: a brief guide

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Abstract

Improved understanding of genetics and the protective mechanisms that have evolved at the cellular level now makes it possible to present a unified hypothesis of the biology of ageing. Previously, two opposing theories of ageing – "genetic-programming" theory and "wear-and-tear" theory – led to apparently divergent research thrusts. The recognition that both theories are aspects of the same phenomenon – at different levels of cell function – allows a deeper understanding of the contribution that each school has made to present notions of the biology of ageing.

In a 1974 review article on "The longevity of cultured human cells", Leonard Hayflick noted that it is remarkable that so little research is being done on the biology of ageing, "...despite the universality of the problem" (Hayflick, 1974:1). Whereas fame and fortune attracted scores of top-grade scientists into immunology – the scale of the HIV-industry is unprecedented – and clinical medicine, the biological sciences of gerontology have lain fallow. Until recently.

Over the past decade significant new insights into the biological basis of ageing have come about. These insights stem from improved understanding of the ever-increasing complexity of the genetic codes that determine the development of the organism throughout life, as well as great advances in our understanding of cell biology. Thus, it has become possible to marry two previously opposing sets of hypotheses on the cause of ageing: the "genetic-programming" theories and the "wear-and-tear" theories (Meier, 1984) may now be regarded as comprising different levels of the same phenomenon.

In this brief guide the principal lines of evidence sustaining the aforementioned theories of ageing are reviewed and their convergence towards a unified hypothesis is demonstrated.

Programmed cell death

In 1952 Medawar put forward the notion that lifespan is determined by the absence of evolutionary selection pressures after the fertile years (Medawar, 1952). Thus a genetic basis for life-span was assumed; the focus of Medawar's (1952) argument turned on possible evolutionary mechanisms which would cause such genes to arise in any given species. The most influential hypothesis for the mode of acquisition of genes that would have a destructive effect in later life was put forward by Williams, who, in 1957, coined the term "antagonistic pleiotropy" (Williams, 1957). By this mechanism genes that confer some significant advantage during the early years of an individual's life (genes that would thereby secure the better survival of members of the species who carry that gene) have, as an irrelevant (in evolutionary terms) "side-effect", the potential to cause harmful effects resulting in death after the fertile years. An example of this mechanism may be seen in genes which may cause a woman to commence secreting oestrogen at a younger age, thus increasing her fertility – an advantage for the species. However longer exposure to oestrogen also has the effect of increasing the likelihood of breast cancer. Thus, the same genes which give fertility advantages in early maturity also reduce the average life-span of affected individuals. If the frequency of this group of genes is high enough in the species (humankind), the average life-span of women will be significantly reduced, while fertility will be significantly enhanced.

Ageing in a test tube

The first experimental evidence in support of genetically programmed cell death was produced by an imaginative series of experiments by Hayflick and Moorhead (1961). This seminal work relied on culture techniques whereby cells are harvested from a human foetus and plated on a culture medium. Such cells would grow and divide to cover the surface of the medium; on plating a sample of these cells, they would again divide to cover the surface of a new culture medium. However re-plating could be repeated only approximately 50 times, by which time the cells began to show features of senescence and failed to re-divide. If the original sample of cells were harvested from an older individual, the number of potentially successful re-platings would be approximately proportionately reduced (Martin, Sprague & Epstein, 1970).

Although these and subsequent experiments based on Hayflick's model served to sustain interest in the notion of genetically programmed cell death, some inherent flaws in the experimental design to some extent invalidate the findings. Kirkwood (1977) has suggested that since the experimental procedure requires only a small sample of cells to be harvested for re-plating in every cycle, this would lead to the "diluting out" of senescent cell lines. Thus, there would be a tendency to over-represent healthy cell lines, leading to an

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over-estimation of the organism's mean cell-dividing potential and, by extension, an over-estimation of the species' potential life-span.

Youthful worms

The nematode *Caenorhabditis elegans* provides gerontologists with an extremely useful model for studying their subject. This small (1,2 mm long) soil-dwelling worm consists of only ca. 1 000 cells. As a result of intensive investigations during the past 18 years, almost its entire genetic code (consisting of only 100 million base pairs) is now known (Johnson & Lithgow, 1992). Amazingly, all the 959 somatic cells in the hermaphrodite and all 1 031 cells in the male form are, with a few exceptions, completely determinate, i.e. subject to a remarkably rigid developmental programme, controlled by their genes. These features, along with the advantage of having a hermaphrodite form, permitted significant advances in studies on gerontogenes – genes that determine the mean life-span of the species. Selective in-breeding techniques have allowed several groups of workers to breed long-lived strains with mean increases of life-span of up to 70 %. Studies of these strains suggest that the genes coding for long life are recessive and rely on the non-expression of the gene's dominant counterpart. Work towards identifying the exact location of the responsible gene(s) is well under way. Final proof of its correct identification is likely to be forthcoming within the next few years. However there is little doubt that a gene which codes for longevity has been created through selective breeding in *C. elegans*.

Progeric children

Unfortunately, the opportunity to study the ageing process in humans by investigating the genetic mutations that cause progeria has been rather less well exploited than that of the biology of *C. elegans*. Consequently it is unknown whether these conditions are heterogenous at the genetic level. Little is known about the nature of the metabolic errors that occur in such individuals. To distinguish true instances of accelerated ageing from discrete inborn errors of metabolism leading to early death, Casarett (1959) proposed that progeroid mutants should show features of accelerated ageing in all organ systems. At least two human disease syndromes satisfy this criterion. Hutchison-Gilford progeria is inherited by a spontaneously arising dominant genetic mutation, whereas Werner's Syndrome is caused by an autosomal recessive gene. It has been shown that cell lines from patients suffering from either syndrome have diminished replicative life-spans when investigated by the Hayflick model. Both conditions produce excessive concentrations of a chemical substance, hyaluronic acid, which suggests that there may be a similar underlying genetic mechanism responsible for the somatic effect of dramatically accelerated ageing (Johnson, 1988).

In summary, at least three lines of investigation may be held to support the view that ageing is at root determined by genes that are heritable: that the difference between humankind and a thousand-year-old redwood tree is more to be found in the genes that determine cell division and has less to do with environmental toxins.

Environmental toxins

The world is a hostile place and is becoming more so by the day. From the increased UV-light exposure due to ozone depletion, exposure to herbicides and asbestos, and cumulative environmental radiation exposure, our cells, specifically the DNA-molecules within their nuclei, are constantly under assault. Ever since life began in the primordial, tepid, saline ocean, cells have had to devise methods to resist chemical and radiation attacks by maintaining a stable, hygenic *milieu interieur*. Apart from a vast diversity of external attacks, cells have to deal with the many toxic molecules produced as by-products of their own metabolism. Among these, the most damaging are a class of highly reactive molecules called oxygen radicals or oxidants (Morley, 1992), which are produced in large quantities as the cell metabolizes glucose, other nutrients and specialised molecules – e.g. the neurotransmitter dopamine. It has been estimated that the DNA molecules of a cell are subjected to 10 000 attacks by such oxidants every day.

Cells have evolved two methods to deal with such attacks: repair and defence.

Repair mechanisms

At least three cellular repair-systems have been identified. First, when DNA reproduces itself (replicates) the process is very accurately done by a system of "proofreading" and correction of errors. Second, the cell is able to recognize and repair "spontaneously" arising damage to its DNA, i.e. damage as a result of chemical reactions, such as de-amination and depurination. Third, the cell has alternative mechanisms to repair DNA which is damaged by external agents, such as radiation (Boerrigter, Wei & Viig, 1992). Highly sophisticated as these repair systems are, their functioning is accompanied by two inescapable features: they demand a significant amount of energy to run and they are not 100 % accurate. These features form the molecular biological basis of evolution: the occurrence of DNA damage and the inaccuracy of repair give rise to genetic mutations, ultimately leading to the occurrence of new species. The energy cost of DNA repair gives rise to selection pressures which may determine the success or failure of such new species in a given environment.

Defence mechanisms

Although the need to maintain a stable internal environment, with respect to pH, osmolality, temperature, etc., for the optimal functioning of all the cell's chemical reactions has been recognized for many decades, it has only recently been recognized that oxygen radicals are particularly malevolent towards DNA molecules. Not surprisingly, several mechanisms to neutralize the effects of these radicals have evolved, the most potent of which is the chemical superoxide desmutase. This molecule is able to scavenge oxygen radicals within the cell, so preventing them from attacking strategically important molecules such as DNA. What would the effect be if a subspecies of animal arose which had a superabundance of superoxide desmutase?

In the course of studies on longevity Rose (Rose, 1984; Rusting, 1992) used selective in-breeding techniques on fruit flies (*Drosophilia melanogaster*) to breed a strain that has a mean life-span almost twice as long as the wild parent strain. Not only do flies of the "superior strain" live longer, they are also able to demonstrate greater stamina by being able to remain airborne longer and to withstand greater environmental stresses. Upon chemical analysis it was found that the new strain had an unusually active variant of the anti-oxidant enzyme superoxide desmutase in their cells. In a remarkable feat of "convergent evolution", or, possibly, preservation of a primordial defence mechanism, the long-living strains of *C. elegans* referred to earlier were also found to produce high concentrations of superoxide desmutase.

Apart from superoxide desmutase, cells produce or concentrate from the diet a wide variety of molecules that mop up harmful chemicals, or have the sole purpose of breaking down damaged cellular molecules. These include anti-oxidants

(glutathione peroxidases, catalases, Vitamin E, beta carotene, uric acid, Vitamin C and metal chelators), enzymes involved in protein repair (proteinases, proteases, peptidases), enzymes involved in lipid repair (phospholipases, acetyltransferases, glutathione peroxidase, glutathione transferase) and enzymes involved in DNA repair (exonucleases, endonucleases, glycosylases, polymerases and ligase) (Rusting, 1992).

The united hypothesis

An essential point to realise is that all the aforementioned enzymes that have evolved to protect the cell from damaging substances are under direct genetic control. Thus, the effectiveness with which the organism weathers a life-time's environmental stresses ("the slings and arrows of outrageous fortune"), is dependent on the genetic make-up of the species – by way of a better or poorer ability to control the damage. The genetic make-up of the species lies at the root of the "accumulation of toxins" theory of ageing. Equally, while genes do exist that specifically curtail life-span, such as those found in progeria, it is likely that their harmful effects are expressed in cells by a failure to synthesize enzymes that normally limit the damage of harmful metabolites, or by an excessive production of such harmful metabolites.

The two classical hypotheses regarding the causation of ageing may therefore be seen as different aspects of the same phenomenon, describing different levels of the cell's physiology: genetic make-up and gene expression.

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