Ageing Genes: Gerontogenes

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Secondary article

Article Contents

- Introduction
- Nature of Ageing Genes
- Candidate Gerontogenes
- Gerontogene Therapy

The term 'gerontogenes' refers to an altered state of those genes that influence ageing and longevity, the vitagenes. The idea of gerontogenes is in line with the evolutionary explanation of the ageing process as being caused by the absence of maintenance and repair, rather than an active, evolutionarily selected process.

Introduction

The highly complex phenomenon of ageing is now reasonably well understood in descriptive terms. A large body of data clearly shows that ageing has many facets. Individually no tissue, organ or system (with the exception of thymus) becomes functionally exhausted even in very old organisms, and it is their combined interaction and interdependence that determines the survival of the whole. From an evolutionary point of view, the essential lifespan of a species is the time required to fulfil the Darwinian purpose of life; that is, successful reproduction and continuation of generations. The later period of survival, achieved generally in protected environments and characterized by progressive ageing, is an emergent phenomenon because of the inability of the maintenance and repair pathways to continue to work efficiently. Therefore the genes that influence ageing and longevity are those that have evolved in accordance with the life history of a species for assuring its essential lifespan. Such genes are known as longevity assurance genes or vitagenes.

Nature of Ageing Genes

Evolutionary theories of ageing and longevity discount the notions of adaptive nature of ageing and its selection as an advantageous trait for the individual. Furthermore, the diversity of the forms and variations in which age-related alterations are manifested suggest that the progression of ageing is not programmed or deterministic but is stochastic in nature. Yet, ageing appears to have a genetic component of some kind. The role of genes in ageing is indicated by (1) an apparent limit to maximum achievable lifespan within a species; (2) some heritability of lifespan as evident from studies on twins; (3) human genetic mutants of premature ageing syndromes; and (4) some gene association with extreme longevity.

The paradoxical situation of the genetic aspects of ageing and longevity on the one hand, and the stochastic nature of the progression of the ageing phenotype on the other, can be resolved by developing radically novel views about the nature of genes for ageing, termed gerontogenes.

However, the term gerontogenes does not refer to any 'real' genes for ageing but to an altered state of longevity assurance genes or vitagenes, which gives the appearance of being the genes for ageing. Most importantly, the idea of gerontogenes as altered vitagenes is in line with the evolutionary explanation of the ageing process as being an emergent phenomenon caused by the absence of eternal maintenance and repair, instead of being an active process selected during evolution.

Candidate Gerontogenes

Two kinds of gene action are postulated to be responsible for the emergence of the ageing phenotype. The first considers the role of late-acting mutations which are already present at the time of fertilization and birth, and show their deleterious effects after the period of growth, development and maturation. The second category of gene action is referred to as the antagonistic pleiotropy, which involves genes selected for beneficial effects during early development but which have harmful effects in postreproductive life when they escape the force of natural selection. In both cases, these genes were not selected as the real genes to cause ageing, but manifest themselves only as virtual gerontogenes due to their involvement in the progression of ageing.

Although the essential lifespan of different species may differ by several orders of magnitude, there is very little or no difference in the structure, function and activity of the so-called housekeeping genes involved in basic metabolic processes. Therefore the genetic differences in lifespan are mainly due to the differences in the genes involved in maintenance and repair processes.

Evidence that the maintenance and repair pathways are the determinants of longevity comes from comparative studies performed on species with widely varying lifespans, and from experiments performed to retard ageing and to prolong the lifespan. These genetic pathways include the

Table 1 Putative gerontogenes affecting ageing and longevity

Organism	Putative gerontogene	Identity/function
Saccharomyces cerevisiae	*LAG1*, *LAG2*	47-kDa and 78-kDa transmembrane domain containing proteins
	RAS-1, *RAS-2*	Stimulates inositol phospholipid turnover; participates in MAP kinase pathway
	UTH4	Homologous to Pumillio protein of *Drosophila*
	Sir complex	Transcriptional silencing of telomeres and HM loci; histone deacetylase
Caenorhabditis elegans	*age*-1	Phosphatidylinositol-3 (PI3) kinase
	daf-2	Insulin receptor-like protein
	daf-16	Hepatocyte nuclear factor-3 (HNF-3) Forkhead family of transcription factors
	tkr-1	Tyrosine kinase receptor-1
Drosophila	Methuselah	G-protein coupled receptor
Mouse	Klotho	Membrane protein β-glucosidase
Human	Werner's gene WRN	DNA helicase

efficiency of deoxyribonucleic acid (DNA) repair, the fidelity of genetic information transfer, the efficiency of protein degradation, the extent of cellular responsiveness to stress, and the capacity to protect from damage induced by free-radicals and oxidation. Similarly, anti-ageing effects of several hormones, vitamins, a dipeptide carnosine, modified amino acids, and modified nucleic acid bases such as kinetin are also mainly due to the effects of these chemicals on maintaining, stimulating or recovering the efficiency of repair pathways. Genetic selection of *Drosophila* for longer lifespan also appears to work mainly through an increase in the efficiency of maintenance mechanisms, such as antioxidation potential and stress tolerance. The identification of long-lived mutants of the nematode *Caenorhabditis elegans* is also accompanied by an increased resistance to oxidative damage, an increase in the activities of superoxide dismutase and catalase enzymes, and an increase in thermotolerance.

Until now, several putative gerontogenes have been reported for various ageing systems, including yeast, nematodes, insects and mammals (**Table 1**). Additionally, genetic linkage studies for longevity in mice have identified major histocompatibility complex regions, and quantitative trait loci on human chromosomes 7, 10, 11, 12, 16, 18 and 19 as putative gerontogenes. In human centenarians, certain alleles of HLA locus on chromosome 6, different alleles of *APO-E* and *APO-B*, and *DD* genotype of angiotensin-converting enzyme have been linked to their long lifespan.

The diversity of the genes associated with ageing and longevity of different organisms indicates that, whereas the genes involved in repair and maintenance pathways may be important from an evolutionary point of view, each species may also have additional 'private' gerontogenic pathways which influence its ageing phenotype.

Gerontogene Therapy

Gerontogene therapy directed towards the overall ageing process seems to hold little promise. Assuming that there are only 50 genes which constitute the network in which they interact with each other, this gives rise to 2^{50} or 10^{15} (a million billion) possibilities of their interacting and influencing each other. Even at the level of a single cell zygote, let alone the billions of cells in an adult human being, interfering with such a complex network and improving upon what is already a 'normal' combination for that particular individual (in the absence of any obvious genetic diseases) is a mission impossible.

Further Reading

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