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Molecular biology of ageing

Ageing is broadly defined as an intrinsic, deleterious, progressive, cumulative and universal process that occurs in all organisms after they attain adulthood. Research on ageing is relatively a new field, at least in comparison to development. Besides, it is an enormously complex problem because one needs to find out what goes wrong with fully developed organisms, which are not only multicellular but have several types of organs that perform entirely different functions, after they have attained adulthood. For understanding development, however, one begins from a single cell and follows up how it divides, gives rise to various types of cells and organs, and becomes an adult. Despite a late start, research on biochemical and molecular aspects of ageing has made significant advances since 1980s, thanks to the utilization of the techniques of molecular biology and genetic engineering.

That fact that all members of a species have a more or less fixed maximum life span, various stages of the developmental period are well-timed, long-lived members of a species have long-lived progeny, etc. indicate that ageing has a genetic basis. The variability in the life spans of the members of a species is due to various types of extrinsic and intrinsic factors that they encounter during their life span such as reproduction, nutrition, temperature, radiation, pollution, free radicals, etc. Moreover, different organs of an individual begin to age at different times and at different rates, and all individuals of a species do not age the same way. So it is unlikely that there is a single 'master' gene or switch that causes ageing. Products of one organ influence the functioning of one or more organs. Thus the functioning of various organs *in vivo* is interrelated. Hence researchers have taken up different model systems to unravel the basic cause of ageing at the level of genes. Genetic studies have been carried out by breeding experiments on the fruitfly, *Drosophila*, and the free living nematode, *Caenorhabditis*, to look for genes that determine longevity and metabolic rates. Molecular biology techniques are being used to find out how the expression and regulation of genes that control specific functions *in vivo* change after adulthood, and what roles specific regions of these genes play in these processes as organisms such as rat, mice, bird, insects age. *In vitro* studies are also being done using fibroblast cells of normal individuals and of those suffering from genetic diseases such as Werner syndrome and progeria to find out what molecular changes occur as the cells stop dividing. Since mitochondria have genes that code for subunits of several respiratory enzymes, and mutations in these genes cause diseases, these organelles are the subject of intensive studies in several laboratories. This issue of *Current Science* carries a special section (**pages 859–901**) that brings together recent studies on various model systems to understand the molecular basis of ageing.

That longevity of individuals of a species is determined by genetic factors is well established. The longevity of *Drosophila* and *C. elegans* has been extended by different types of laboratory manipulations. But extended longevity without extended metabolic rate and activity would defeat the objective of the research on ageing, which is aimed at extending the period of activity of organisms. Usually extended longevity phenotypes are associated with an increased resistance to certain types of environmental stress, and resistance to a stress involves one or more genes. Arking exposed *Drosophila* to the biomarker, paraquat, a bipyridyl herbicide, that generates free radicals in the cell, and found that the expression of three genes including Cu–Zn–SOD, necessary for resistance to free radicals, was elevated in the adult of the flies which have long life span. Thus, resistance to oxidative stress and increased longevity are directly related (**page 859**).

One of the objectives of ageing research is to understand why various functions progressively decline after adulthood, and whether they are due to alterations in specific genes that are responsible for these functions. Understanding the gene–function (genotype–phenotype) relationship requires that both are quantifiable. Once the relationship of a function (phenotype) is established with one or more genes, it would be possible to understand how and why the gene expression changes and whether it can be manipulated. Kanungo and colleagues have shown how the expression of the genes for fibronectin (FNT) protein that is required for cell–cell interaction, morphogenesis and wound healing in the rat, and the genes for ovalbumin and vitellogenin (VTG) which are required for egg formation in the bird declines after adulthood, and they show that this is due to the decrease in the levels of nuclear proteins that bind to specific sequences in their promoter regions to regulate their expression (**page 865**). Fujita and colleagues show that a senescence marker protein (SMP 30) that binds to calcium and is involved in its regulation in the liver and kidney declines in an androgen-independent manner during ageing in the rat. They have characterized the gene for SMP 30, which has several *cis*-acting elements that may be involved in the regulation of its expression (**page 872**). It would be interesting to know what factors regulate its expression.

Since ageing of an organism is due to ageing of cells and tissues, several workers have isolated individual cells from tissues and organs, made them divide *in vitro* for long periods to study the changes in their function as they grow old and cease to divide. It has to be kept in mind that these cells are separated from their organizational hierarchy, and are without the influence of other organs to which they are subjected to *in*

vivo through the internal milieu. Hence such cells are not in a normal physiological state. Nevertheless, cells isolated from humans and other organisms at different stages of development and of different life spans have provided useful information about the changes in their intrinsic properties as they grow old *in vitro*.

Riabowol and colleagues have analysed the roles of several genes that either shift the cells *in vitro* to cease multiplication and senesce, or continue multiplication and get immortalized. They show that hyperphosphorylation of serum response factor contributes to loss of Fos transcription factor and senescence. Furthermore, a certain cell-cycle specific cyclin or loss of tumour suppressor gene leads to immortilization and tumorigenesis. Using different cell types as models they have studied the role of telomerase which is active in immortal cells, but is inactive in senescent cells (**page 878**). On the other hand, Gonos and colleagues have studied genes involved in signal transduction in fibroblast cells in culture, and report that the *c-fos* gene, which is expressed in dividing cells, is downregulated in aged cells. Retinoblastoma (Rb) protein is a tumour suppressor. In the underphosphorylated state it is active and suppresses cell division. In senescent cells Rb is not phosphorylated. Several novel genes such as prohibitin that block DNA synthesis, and vimentin that is overexpressed in senescent cells have been cloned (**page 884**).

Mitochondria are organelles that are essential for energy production aerobically. They are the only other organelle outside the nucleus in animals that has a genome which codes for several respiratory enzymes. The mitochondrial DNA (mtDNA) is not protected like the nuclear DNA by histones and nonhistones. Wei and his colleagues show (**page 887**) that there is increase in the production of reactive oxygen species and free radicals in mitochondria due to a decrease in the antioxidants and free radical scavenging enzymes like superoxide dismutase during ageing. This causes mutations such as deletion and oxidative modification in mtDNA. Such mutated genes produce defective respiratory enzymes and impair the metabolic rate. Even the nuclear DNA is subjected to damage like strand cleavage and base modification due to various factors such as free radicals, ionizing radiation, chemicals, etc. However, the presence of DNA repair enzymes alleviates this problem partially. It has been shown earlier that species having longer life span have a greater DNA-repair capacity. Rao (**page 894**) shows that both single and double strand breaks occur in the DNA as a function of age in all types of cells. The latter type of breaks are more lethal to the cell, and when they reach a critical level, the cell undergoes apoptotic death.

Thus studies on various model systems and use of different molecular methods have provided a substantial amount of insight into how changes in gene function cause ageing. Hopefully, these and newer approaches would unravel the basic cause of ageing at the level of the genome to manipulate the function of genes. This would help in the prolongation of the active period of organisms or defer the onset of ageing.

M.S. Kanungo

Understanding locomotion

To move is to live, at least in the animal kingdom to which we belong. In his article on 'Locomotion: Dealing with friction' (**page 826**), V. Radhakrishnan moves over a great deal of ground indeed in his pursuit of the many facets – engineering, physics, biology of how animals and birds, and we, and our machines move. The setting ranges from space, in which one can only push against a part of oneself that has to be sacrificed, to dense liquids in which bacteria battle enormous forces (on their scale). One might be aiming at speed, or at staying moving for the longest time, or traveling the greatest distance. The unifying theme is friction, in all its diverse forms. This wide ranging review has a perspective cutting across conventional categories. The insights, comparisons, and numbers which it provides will probably surprise and inform even people who have thought about some of these things.

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