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# The biology of aging

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The incidence of overall mortality and several degenerative diseases, including hip fracture, stroke, heart failure and Alzheimer's disease increase exponentially with aging. Mortality begins to rise exponentially at about age 28 reaching a maximum human lifespan of about 120 years for women and 115 for men.

The mass of several systems, including muscle, bone, brain and kidney decreases with age, but the amount of fat in organs, such as muscle and bone marrow increases with aging. Many physiological functions decline steadily with age, including total energy expenditure, amount of spontaneous movement, gait speed, muscle strength and endurance, maximum heart rate, cognitive function, glomerular filtration rate, decline steadily with age. Decreased amount and speed of movement, decrease in muscle mass, accumulation of cellular garbage (damaged proteins and organelles), cellular and nuclear disorganization, and wrinkling are features of aging in many species, from worms to mice to humans.

## Caloric restriction, rate of living and free radicals

In model organisms, caloric restriction consistently prolongs lifespan and slows many physiological changes with age. (In poikilotherms, similar changes are produced by decreasing temperature). This observation spawned and supports the 'rate of living' theory of aging: production of energy damages proteins, DNA, and mitochondria. This damage accumulates to cause dysfunction of cells and organs.

The most popular explanation for aging is we 'rust'. The *free radical* or *oxidative damage* theory proposes that long-lived post-mitotic cells, such as cardiac myocytes and neu-

rons, progressively degenerate because aerobic metabolism, that is essential to life, necessarily generates oxygen radicals that damage other macromolecules. Indeed, oxidative phosphorylation generates one oxygen radical (such as O<sub>2</sub><sup>-</sup>) for every 50 to 1,000 molecules of ATP produced from ADP. These oxygen radicals particularly damage mitochondria (where the >90% of these reactions take place), but may also damage other parts of cells. Most, but not all studies in all tissues, find that mitochondrial DNA damage increases and mitochondrial energy production decreases with aging. The theory would predict that bolstering anti-oxidant defences, such as increasing levels of superoxide dismutase (SOD) and treating with antioxidant vitamins, would slow aging, decrease the incidence of age-related diseases and prolong lifespan. Increasing SOD expression has prolonged the lifespan of some model systems, but human trials of antioxidants have consistently produced no or even harmful effects on risks of diseases.

## Entropy

The 2<sup>nd</sup> law of thermodynamics (essentially, entropy increases with time) says that all macromolecular systems become less organized with time. Faster rates of metabolism and generation of heat will inexorably decrease the order and organization of molecular structures. This process – entropy – will limit or decrease the efficiency of cellular functions and cause errors of DNA and protein transcription and other processes.

## Insulin signaling

Caloric restriction also decreases insulin production as well as IGF-1 production and experiments in worms, flies and mice have shown that decreasing insulin signaling and production of growth hormone and IGF-1 (and their homologues) consistently prolongs lifespan and slows many features of aging. This might work by reducing the 'rate of living' or generation of oxidative damage, but other experi-

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ments show that decreased insulin signaling has other effects that may mediate its benefits, including increasing heat shock proteins that clear damaged macromolecules.

### Neuroendocrine control of aging

Besides the effects of growth hormone, some have postulated that aging may result, at least in part, by decreasing hypothalamic-directed production of other hormones, such as sex hormones, DHEA or prolactin. There has been meager to no support for this hypothesis in humans, but recent experiments in *C. elegans* showed that ablation of neurosensory cells prolonged lifespan by decreasing production of a yet-to-be-identified hormone.

### Cellular ‘clock’ and cell senescence

Discovery of the ‘Hayflick’ phenomenon – that fibroblasts double about 30 times then become senescent – gave birth to the theory that the lifespan of animals is limited by this internal clock. However, this principally applies to cells that proliferate such as osteoblasts and enterocytes. Telomeres (nucleotide ‘caps’ at the end of chromosomes) shorten with each cell division reaching a critical length that induces cell senescence.

One study found that short telomeres predicted higher mortality popularized this theory. But mutations causing extremely short telomeres (DKC) cause grey hair, premature death, often due to marrow failure and severe infections but have only a few features of aging (including osteoporosis).

### Cellular damage

The residues of damaged proteins and organelles accumulate with aging and this cellular garbage can interfere with normal cell function. Lysosomes digest and recycle the constituents of damaged proteins and mitochondria but this process is incomplete. Lipofuscin, a complex of lipid and protein, accumulates in long-lived cells and with aging, an increasing proportion of cells in tissues, such as skin, contain lipofuscin deposits.

### Inflammation and aging

Circulating levels of many pro-inflammatory cytokines, such as IL-6, increase with aging. They cause insulin resistance and have been associated with an increased risk of mortality, especially from cardiovascular disease, and have been associated with poor neuromuscular function and frailty. These cytokines are produced from inflammatory responses to infections, foreign antigens, and damaged native proteins. They are also produced by visceral fat and by senescent cells. Interestingly, senescent cells also produce relatively large amounts of IL-6.

### Miscellaneous ‘causes’ of aging

DNA becomes increasingly methylated with aging, which can suppress transcription of numerous genes, but its relationship to features of aging and mortality are not known. Progeria is very early onset of many features of aging due to mutation of the LMNA gene that causes abnormal protein scaffold around the inner edge of the nucleus and build-up of LMNA protein within the nucleus. The role of LMNA in normal aging is unknown.

### Slowing human aging

In general, slowing the fundamental process of aging would reduce overall mortality and increase healthy lifespan to a greater degree than would reducing the risk of specific diseases such as cancer or cardiovascular disease.

A small (CALERIE) trial in humans showed that 25% reduction in caloric intake decreased metabolic rates, improved insulin sensitivity, increased mitochondrial biogenesis and decreased markers of oxidative damage of DNA. Observational studies have found that exercise has been associated with decreased mortality from multiple causes. It is not certain whether and how regular exercise might slow aging. Searches for molecular fountains of youth are underway in model organisms and early phase trials in humans.

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