

Research on Aging Background and New Directions

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*How long have people wondered
about their own lifespan?*

*We don't know, but we do have
about one hundred years of
recognizable science.*

Observations and Insights

It started with observations of different species. In 1908, Max Rubner wrote that large animals live longer and use fewer calories per gram of body mass than smaller animals (although there are many exceptions such as long lived birds). This gave rise to the “rate of living theory,” i.e. you live longer the slower you burn. Living longer, however, is not our only concern. Indeed, there is a difference between longevity and aging. We want quality of life, not just a long life. The idea of a “health-span” distinguishes a long life of disability from good health until the point of an abrupt death.

Caloric Restriction

Our first real insight into mechanisms of aging came in 1935, when Clive McCay and colleagues found that restricting the calorie consumption of lab rats by 30-40% led to a 20-40% increase in life span. While smaller, the rats were generally healthy, except there was a downside: the rats had decreased fertility. This concept has continued to intrigue researchers. In recent years, various groups have found genetic mimics of the calorie restricted rat, of which I will say more; mutations known as *pit1*, *prop1*, *GHRBP*, and *GHRHR*. These mutations are known to affect the utilization and activity of growth hormone (GH). Involvement of the GH axis is plausible because manipulating these genes doesn't only give you a visible outcome, or phenotype, it gives you physiological and mechanistic changes resembling those seen in caloric restriction.

Rust vs. Toast Models

Another important development was the 1956 theory of Denham Harman, that aging was related to free radical damage. Free radicals are highly reactive oxidants, produced internally or through such external influences as UV radiation. Oxidation of iron yields rust... do we “rust” as we age? Or do the carbohydrates in our cells oxidize like the “browning” of toast and other foods? The body normally protects itself from reactive oxidant species by using enzymes to inactivate them. Flies and worms that are genetically programmed to make excessive amounts of superoxide dismutase and other antioxidant enzymes live longer, and delay the physiological signs of aging. It has, however, been difficult to extend these observations to mammals, and many experts doubt that free radicals are causal.

DNA and Aging

As we began to understand the central role of DNA in biology, the question arose of its relationship to aging. Organisms have the capability to repair DNA damage – up to a point – but breaks and mutations can accumulate over time. Sometimes, inability to repair DNA damage results in cancer. Leo Szilard proposed in 1959 that DNA damage was responsible for aging. Because reactive oxygen species originate from the mitochondria, by 1972, the focus of this theory narrowed to mitochondrial DNA. So far, we have been unable to untangle cause from effect.

Other insights have arisen from unfortunate experiments of nature, the human progeroid syndromes, in which children appear to age at a rapid rate. One form is Werner's syndrome, caused by a recessive mutation in the gene *WRN*. The gene carries information to produce an enzyme, known as a RecQ helicase. Work remains to be done, but it is intriguing to note that this enzyme may be involved in DNA repair. Another form of progeria is Hutchinson-Gilford's syndrome. The mutation in this disease is also an enzyme, lamin A/C. Its function is as yet unknown but may be involved in the inner membrane of the cell nucleus – where, of course, the DNA is found.

Living Longer

So far, the only sure way we can make an existing, genetically normal mammal live longer is by calorie restriction (CR). And we know more about how CR *doesn't* work than how it does. It does not act by slowing metabolism, by increasing exercise or by decreasing the percentage of body fat. CR interacts with the neuroendocrine system; we don't know how, but the indications are that it is through GH and/or a substance whose production it stimulates, insulin-like growth factor (IGF) -1.

Non-mammalian species have provided powerful models for study. One is the worm, *c. elegans*. As in *drosophila*, its genome is well known, and a large number of mutations has been identified which affect lifespan. These worms have a single receptor for both insulin and IGF-1. In

1993, Cynthia Kenyon described a mutation of the receptor gene, *daf-2*, in which the worms lived two to six times as long as controls. Again, the spotlight is on the GH/IGF system.

The Ames Dwarf Mouse & Longevity

A major paradigm shift occurred in 1996 with the publication, by Holly Brown-Borg and colleagues, describing the Ames dwarf mouse. This is a mutation in a single gene (*prop1*) that extends lifespan 50 to 65%. The mice are 1/3 normal size, not sick, but are infertile. Relative to their size, they are not calorie restricted. In fact if you restrict their caloric intake, you extend life span even more, to about 75%. So the effects of the mutation and diet are separate. These mice remain active as they get older, and some cellular processes do not show the expected age-related deterioration. Even some behavioral measures seem to be protected; for example, the mutant mice have less age-related decline in memory than wild-type peers. And – they have low blood insulin levels.

Recently developed techniques allow scientists to “knock out” or prevent expression of a gene in specific tissues, rather than an entire animal. If the gene whose mutation causes Ames dwarfism is knocked out only in fat tissue, the mice still live 18% longer. Their hormonal profile shows deficiencies in prolactin, thyroid-stimulating hormone, and GH. Because of other lines of evidence pointing to GH in aging, more attention has been focused on GH than the others.

There is a human condition, Laron dwarfism, comparable to the knocking out of the GH receptor. There are few good data on human GH receptor deficiency, as it is seen mostly in countries where lifespan is generally short and record-keeping unreliable, but they do seem to live longer than their peers.

Centarian Studies

Yet another line of thinking comes from centenarian studies here in the United States. Screening for genetic variation has yielded an excess of variants affecting lipoproteins (cholesterol ester transfer protein, CETP; apolipoprotein C-3) and insulin sensitivity (adiponectin).

Cancer vs. the Aging Process

Growing knowledge about cancer has also shed light on aging processes, beyond the interface of DNA repair. The concept of aging at the cellular level goes back to 1965. Leonard Hayflick found that as cells divide in culture, they eventually become “senescent” and stop dividing. In this process, chromosomes of the cultured cells shorten by losing their ends, called telomeres, like beads popping off a necklace. Maintenance of telomeres is under control of an enzyme, telomerase. Cancer cells have telomerase and don't stop dividing. Giving back telomerase to cells in long-term culture can prevent telomere shortening and senescence. However, we don't yet know which is cause or effect.

Conclusion

I hope I have shown you that multiple metabolic and physiologic pathways have been implicated in the basic biology of aging. Most likely, several of these acting together are responsible for what we see as the aging process. Thus, understanding these cellular processes has tremendous potential for treating and preventing human disease and disability.

Since this is Bryn Mawr, I must end with an example from the ancients, as related by Steven Austad (p. 36):

“In Greek mythology, two Trojan youths renowned for their beauty were kidnapped by Eos, the randy dawn goddess, to be her lovers. They met very different fates. Ganymede was soon stolen away from Eos by an equally enthralled Zeus, who made the lad feel like a god, forever young and beautiful. Eos managed to keep Tithonus for herself and asked Zeus that he be granted eternal life, but in a famous oversight she neglected to point out that what she really meant was eternal youth. In one of those malicious pranks to which Greek gods were prone, Zeus did give Tithonus eternal life but allowed him to continue aging. Eventually he became feeble, withered and demented, until Eos could no longer stand it and turned him into a grasshopper.

The fates of Ganymede, long-lived yet still youthful, versus Tithonus, long-lived but increasingly decrepit, illustrate two extreme scenarios about how increased longevity during the next century could play out.”

Bibliography

Note: In this talk I have drawn extensively on two reviews:

1) De Magalhaes, JP “Open minded scepticism: inferring the causal mechanisms of human ageing from genetic perturbations,” *Ageing Research Reviews* 4:1-22 (2005)

2) Austad SN, “A Biologist’s Perspective: Whence Come We, Where Are We, Whither Go We?” in *Enduring Questions and Changing Perspectives in Gerontology*. D.J. Sheets et al. (Eds). New York, Springer, 2005, pp. 29-62.

Other references available on request.