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BIOLOGY OF AGING

Learning objectives:

At the completion of the lecture, you should be able to:

1. Define antagonistic pleiotropy
2. Give the rationale for why the "disposable soma" theory of aging can be treated as an example of antagonistic pleiotropy
3. Name four premature aging syndromes, two of which are known to affect DNA repair enzymes
4. Describe why patients with diabetes are thought to show accelerated aging of some tissues (advanced glycation products)
5. Give the rationale for how the free radical theory of aging contributes to the mitochondrial damage theory of aging
6. Explain how replicative aging can be an anticancer mechanism
7. Describe how telomere shortening causes replicative aging
8. List the major mechanism by which cancer cells escape the limits of replicative aging
9. Give the rationale for how a "feast and famine" life history strategy could explain why caloric restriction extends the lifespan of rodents

A. Introduction to Aging

Mean human life span has increased dramatically, while maximum life span has stayed constant at approximately 110-120 years. As medical treatments and sanitation improves, an increasing fraction of the population is living longer.

In 1990, 340 million people in the world were 65 or older. In 2050, that number is predicted to be 2.5 billion. Centenarians are the fastest growing segment of our population. If you are a general internist, 70% of your practice will be with patients over 65. In 1999, it is estimated that $573 billion will be spent in health care costs for age-related diseases in the US.

Major age-related diseases include Alzheimer's disease, arthritis, cancer, diabetes, cardiovascular disease, osteoporosis and stroke. Recent dramatic increases in average life span have resulted from prevention of "premature deaths" due to early diagnosis and treatment for some of these disease, but the change in life expectancy as of age 80 has changed relatively little since 1960.

Although increased susceptibility to disease accompanies aging, aging is more than just the ravages of disease. Most physiological functions show some decline during aging. Although most declines are relatively linear, the collective effect is exponential. Mathematically, aging can be described as an exponential rise in the age-specific mortality rate. For humans, the probability of death doubles every eight years. The "system-wide" nature of this process can be seen by the almost superposable curves for death from all causes versus deaths from pedestrian accidents as a function of age. Aging can be viewed as a progressive decrease in reserve capacity and a progressive approach towards a threshold of frailty, so that there is an increasing probability that any crisis, which could be weathered when young, now results in death.

B. Antagonistic pleiotropy

1. Natural selection is relatively unconcerned about events that happen late in the life span. Once one has produced sufficient offspring to have a reasonable probability of maintaining your genes,

each additional offspring is statistically less important. The extreme position is that to a first approximation natural selection doesn't operate during the post-reproductive period.

2. Antagonistic Pleiotropy. Because the force of selection is strong early in life and declines thereafter, traits that confer an early advantage but have deleterious late effects will nonetheless be selected. ("Pleiotropy" means "multiple effects", thus "Antagonistic Pleiotropy" means good and bad effects competing with each other).

C. The auto mechanic's guide to aging

1. Good maintenance costs $$$: replace hoses/belts/oil regularly.
2. Don't buy new tires just before you sell the car.
3. It's wasting money to manufacture a car in which the transmission always fails before the engine: design specifications should have everything break down at the same time (after, for example, 100-120 thousand miles for most American cars).

D. Biological applications of the auto mechanic's guide

1. Maintenance and repair are costly. Proteins denature spontaneously at body temperature, and usually rates of turnover are faster than this rate. Rates of protein turnover do decline as a function of age. Since each cell division reduces the accumulation of most damaged molecules (other than DNA) by 50%, cellular turnover is an effective maintenance mechanism of getting rid of damage. Protection against oxidative damage, protein cross-linking, maintaining a high fidelity of DNA synthesis and repair, tumor suppression mechanisms, immune competency etc. are all examples of important maintenance and repair systems.
2. There is a strong inverse correlation between different species in the rates of annual mortality and the life span. This reinforces the concept that if your probability of being killed is high, you are genetically better off investing your resources in reproduction rather than long term survival.
3. The trade-off between maintenance/repair versus reproduction has been called the "disposable soma" theory (i.e., you don't need to maintain your body longer than it takes to reproduce your body is disposable). This can be regarded as an application of antagonistic pleiotropy, in which the early benefits of investing in reproduction rather than maintenance/repair result in the adverse effects of declining physiology as we outlive our "natural" life spans.
4. There are many different life-history strategies, and many things will be different in different species. For example, the adult mayfly has no mouthparts, lives for one day, and can be viewed as a flying pair of gonads whose sole purpose is reproduction. It is our mammalian bias that describes the mayfly as only living for a day, for most of its life span is spent in larval stages and for the mayfly the adult stage is clearly only the means for producing more larval stages. The 17-year cicada is another example of this concept.

E. Specific aging theories

1. DNA damage. Damage to DNA occurs over time. There are very strong correlations with the ability to correct such damage (for example, UV-induced DNA repair) and life span. Several human genetic syndromes that have premature aging components have been found to result from defects in enzymes involved in DNA metabolism: Werner's syndrome is due to deletions in a helicase, while Ataxia Telangiectasia mutations lie in a gene involved in checkpoint arrest following double-strand breaks.
2. Cross-linking/glycation. Sugars such as glucose can non-enzymatically react with and cross-link proteins such as collagen, and there are very tight correlations between age and the degree of cross-linking. Many of the vascular problems in diabetes can be attributed to glycation in the walls of the blood vessels. Ophthalmologists can virtually predict your age (in the early forties) when cross-linking in the lens becomes sufficient to make you farsighted and require reading glasses. Altered elasticity due to cross-linking is proposed to contribute to many of physiological declines of aging.

3. Free radicals. Free radicals are produced during oxidative metabolism, are highly reactive and damage lipids (producing lipid peroxides), DNA, and to a lesser extent proteins. There are a series of enzymes that scavenge and remove free radicals (catalase, superoxide dismutase, glutathione peroxidase), and there are correlations between life span in different species and the activity of these enzymes. Transgenic flies over-expressing catalase and superoxide dismutase have 30% longer life spans. Vitamins A, E and C are antioxidants as is zinc. Many health food stores tout their beneficial effects for preventing aging, and although little good data is available there are significant numbers of scientists involved in aging research who take antioxidants.

   Lipofuscin, the "age pigment", consists primarily of lipid peroxidation products. The role of cell turnover in diluting the accumulation of damaged molecules is well illustrated by the fact that lipofuscin accumulates almost exclusively in postmitotic cells such as neurons and cardiac muscle. No correlations between lipofuscin accumulation and disease have been found, but it is a good marker of age.
4. Mitochondrial damage. The efficiency of DNA repair in mitochondria is vastly inferior to that of nuclear DNA. Mutations in oxidative metabolism not only decrease energy generation but increase free-radical production, leading to accelerating rates of damage/mutation. Since mitochondria must manufacture some of their proteins using specific mitochondrial tRNAs, a deletion that eliminates any one of them totally blocks the synthesis of all mitochondrial encoded proteins. Mitochondrial mutations do increase as a function of age, especially in non-dividing tissues. Regular exercise has been shown to ameliorate the age-related decreases in muscle mitochondrial function, possibly by stimulating mitochondrial turnover.
5. Cellular Senescence.
   a. Normal diploid cells have a limited capacity to proliferate. Cells from older donors proliferate less than those from young donors. Cells from patients with premature aging syndromes (Progeria, Werner's syndrome, Ataxia Telangiectasia, Down's syndrome) all show a reduced life span of their cells in culture.
   b. Cultured cancer cell lines are immortal. Cancers are estimated to generally need 4-6 mutations to escape normal controls and become invasive, many of which are recessive. At 20 divisions per mutation, hundreds of divisions are probably required. A major function of cellular senescence is thought to be to prevent cancer by providing insufficient cell divisions to accumulate these changes.
   c. Antagonistic pleiotropy. Limiting cell divisions limits both "regeneration" (the ability to respond to trauma) and turnover (required for normal maintenance and repair). The number of permitted divisions "should" be set at just enough to provide adequate maintenance throughout the average expected life span in the wild, since increased repair capacity must be balanced against decreased cancer protection.

F. Mechanisms of cellular senescence

1. The "end-replication problem": since lagging-strand synthesis requires an RNA primer, DNA polymerase can't replicate the region between the last Okazaki priming event and the end of the chromosome.
2. Telomeres
   a. Composed of many kilobases of TTAGGG repeats
   b. Protects the ends from being recognized as a broken chromosome needing repair and involved in chromosome pairing during meiosis.
   c. In conjunction with telomerase, helps solve the end-replication problem.
3. Telomerase: a ribonucleoprotein composed of a protein subunit that contains reverse transcriptase activity and an RNA that serves as the template for the addition of TTAGGG repeats.
   a. Is active in germ cells and thus maintains telomere length.
   b. Is turned off completely or down-regulated (in stem cells) during development.

c. This results in telomere shortening every time a cell divides, which provides the counting mechanism for cellular senescence. Telomeres are long in fetal tissues, and shorten progressively as a function of aging.

4. The two-stage mechanism for cellular senescence.
   a. Mortality Stage 1 (M1). Cells stop dividing when there are still several kilobases of telomeric repeats left.
      i. "Activation" of p53 and pRB cause growth arrest: p53 is a protein involved in signaling DNA damage and causing a checkpoint arrest in DNA synthesis. pRB (the Retinoblastoma Protein) is involved in regulating the cell cycle. It must be phosphorylated by the CDK/cyclin complex (which is inhibited by p16) before cells exit G1 and begin S phase.
      ii. Viruses such a Human Papilloma Virus type 16 (strongly associated with cervical carcinomas) express proteins that bind both p53 and pRB, block their action, and allow cells to bypass M1 and continue dividing.
      iii. Defects in p53 (or other proteins involved in p53 action such as mdm2) and pRB (or other proteins involved in pRB action such as p16) are present in most human cancers.
      iv. Induction of M1 is probably caused by one or a few telomeres lacking sufficient repeats and inducing a DNA damage signal.
   b. Mortality Stage 2 (M2).
      i. If cell can bypass M1, they continue to divide and telomeres continue to shorten. They divide until terminal shortening results in lack of protection of the chromosome ends, resulting in end-to-end chromosome fusions, non-disjunctions, chromosome scrambling and failures of cell division.
      ii. Rarely, cells can escape M2 by developing a way of restoring and maintaining telomere length. Usually, this occurs by re-expressing or upregulating the activity of telomerase (probably due to mutations in the pathway by which telomerase was repressed). Occasionally, a poorly understood "alternative pathway" (probably involving recombination) is induced.
5. Expression of telomerase can immortalize normal cells
6. Telomerase and Cancer: 85-90% of all tumors express telomerase activity
7. Telomerized normal cells do not exhibit properties associated with cancer cells
8. Prospects for cancer diagnosis, screening and therapy

G. Caloric restriction

1. Feeding rodents a balanced diet reduced by 30% compared to normal intake results in a 30-50% extension of life span:
   a. Decreased free radical production
   b. Decreased DNA damage
   c. Increased rate of protein turnover. This counterintuitive result ("wasting" energy on turnover) is consistent with "feast and famine" life-history strategy:
      i. Reproduce like mad over the summer, then simply survive over the winter.
      ii. Thus, invest in reproduction and skimp on maintenance/repair in the summer, then do the opposite in the winter.
      iii. Spores in yeast, dauer formation in c. elegans: mutations in dauer formation affecting increased resistance to stress/free radicals extend lifespan in c. elegans
      iv. Amenorrhea in high performance women athletes.

H. Human Aging

a. Lungs: decreased elastic recoil leads to decreased oxygenation
b. Heart: decreased heart rate and thicker walls lead to decreased cardiac output
c. Bone: alterations in the rates of formation versus removal lead to osteoporosis
d. Kidney: decreased filtration leads to altered sodium and volume retention and drug excretion.

e. Hearing: buildup of wax, calcification of joints of bones of middle ear, nerve changes lead to hearing loss (presbycussis)

H. Conclusions

" All of the above." Evolutionary considerations suggest that all of the maintenance and repair mechanisms should be "tuned" to the natural life span of the organism and that all of them should be contributing to the overall phenotype of aging. The ability of caloric restriction to "reprogram" a large series of mechanisms as part of an alternative life history strategy establishes that the efficiency of these mechanisms is not immutable or approaching an intrinsic limit (like the speed of light), but is subject to biological regulation. Understanding the details of the mechanisms and how to medically intervene and increase their efficiency may change the fundamental process of aging and increase both health span and life span.

Recommended reading:

The Clock of Ages by John J. Medina, Cambridge University Press, Cambridge, 1996

Successful Aging by John W. Rowe and Robert L. Kahn, Pantheon Books, NY, 1998