Molecules and Aging : A Unified Molecular Explanation of the Aging Process and Possible Intervention Strategies

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Summary of the Lecture to be Presented by Dr. Arun K. Roy, the University of Texas Health Science Center at San Antonio, at the Annual Meeting of the Korean Society for Gerontology

Life in its most primitive form is thought to have begun almost three billion years ago and during this early stage there was no ozone layer in the atmosphere to shield the planet from the intense UV radiation. Carl Sagan, the noted planetary scientist once estimated that it would have only taken a fraction of a second to kill the modern-day bacteria with 100% efficiency if they were exposed to such an environment. Thus, it is indeed surprising that life not only was able to originate from such a hostile environment, but it could also evolve into amazingly complex forms. This has been made possible by a careful selection of strategies for constant repair of damaged biomolecules. Acumulative deficit in the balance between the rate of repair and the rate of damage, in functional term is reflected as AGING.

Sources of these damages are many, and sometimes they come from unpredictable corners. Nature has, therefore, wisely opted to circumvent the problems of aging by reproductive rejuvenation of the species, rather than, fighting for immortality of the individual. There are four major predictable causes that can inflict macromolecular damage within a living cell. These damages require constant repair for survival of both the individual and the species. These include : 1) the intrinsic thermodynamic instability of certain macromolecules, 2) effects of UV and ionizing radiations, 3) biochemical byproducts that can be toxic, and 4) covalent, nonenzymatic adduct formation between small and large molecules.

Large biomo lecules, such as enzymes, in most cases, require specific shape or conformation and that particular conformation may be thermodynamically unstable so that with time, it tends to change into a more stable but unfortunately less active or inactive form. Problems with harmful radiations have already been mentioned ; and for us, this harmful effect may only be of consequence to exposed tissues, such as the skin. The last two items appear to be the most important factors in inflicting age dependent damages to our body. Oxygen on its way to releases energy from various substrates can generate highly reactive free radicals. Water, which is the universal medium for life can promote hydrolysis, $\times$10,000 purine and 500 pyrimidine bases are kicked off the DNA from a cell every day. Glucose, the most predorminant energy source, can stick to large molecules and eventually make them functionally inactive. Other metabolic intermediates can also be harmful to the cell. Several enzymes such as superoxide dismutase, catalase, glutathione reductase etc. are continuously kept busy to neutralize

the free radicals.

Both proteins and nucleic acids contain free amino groups that can nonenzymatically react with the aldehyde groups of the sugar-forming protein aggregates and DNA adducts. These macromolecules gradually lose their biological activities. About half of the proteins in the brain of an older invididual may be biologically inactive. Furthermore, a large number of unidentified ligands can covalently attach to the nucleic acid bases, and in non-dividing cells of specialized tissues like the heart and the brain, this can become problematic with time.

Even the primitive life forms like the bacterium E. coli has developed and elaborate repair system to prolong its life, long enough to complete multiple cycles of replicative propagation. Despite these repair strategies, the fact remains that the genetic material(DNA in most cases) requires an old template to produce a duplicate copy. Age dependent accumulation of any unrepaired damages, particularly on this old DNA strand, eventually becomes intolerable leading to the death of its bearer.

The higher forms of life that contain duplicate sets of genes(diploid organisms) have been able to cope with the aforementioned problems with a greater success by perfecting the sexual mode of reproduction. At the molecular level sex involves exchange of chromosomes from two different partners(outcrossing) and meiotic recombination(a process of cell division where close physical association between the two homologous chromosomes facilitate repair of double-strand DAN damages). Outcrossing allows masking of a defective gene inherited from an aged or otherwise damaged sex partner. While recombination allows efficient repair of double-strand DNA guided by the extra copy of a homologous normal chromosome. Sexual mode of reproduction is, therefore, an effective strategy not only for mltiplication but also for vertical transmission of a rejuvenated genome.

During the formation of germ cells, two highly efficient double strand DNA reapir processes are made feasible. One is the sister chromatid exchange where a large chunk of DNA jumps from one chromatid to the other, exchanging badly damaged genes for good ones. And the second is the recombinational repair where the physical proximity of two chromosomes, brought together by the melotic process, allows the missing information of one of the chromosomes to be corrected with the original information copied from the homologous partner.

Even with elaborate and efficient repair processes, mistakes do occur. Minor damages that persist are selected against through programmed cell ceath during development and release of only the near perfect gametes. All germ cells before their release for participation in the reproductive process undergo careful selection. For example, in the case of a human female only one out of 10,000 germ cells is selected to be released. That is to say about 500 ova are released during the reproductive life of a woman while the lest of the 5 million or so undergo programmed cell death. The unusual radiation sensitivity of both male and female germ cells during their developmental stages also attests to this careful selective scrutiny. Although the germ cells are extensively repaired through rejuvenation, and carefully examined for any remaining damages, such an elaborate process is too costly and not affordable for other cells of the body, especlally those that are allowed to differentiate into highly specialized forms to perform certain difficult functions and cannot be easily replaced by duplication. These cells(that include cells of the brain and heart) progressively accumulate age-dependent demages and ultimately become nonfunctional. When engouth of them become inefficient, the organism fails and death occurs.

The maximum life span potential of each individual species is genetically programmed and depe-

nds on 1) the specific rates of aging, 2) the duration required to assemble the reproductive structures and, 3) the evolutionary overload on the senescence phenotype. Although every species has its own genetically predetermined Maximum Life Span Potential(MLSP), very few individual members ever make it to that point. As a general rule, the MLSP amounts to about 10 times the period needed to attain the initial reproductive competence. One of the areas of emphasis of the aging research is to retard the rate of aging, allowing an extension of healthy life closer to the maximum life span potential-specially in the case of man. Two different approaches are currently being expiored. The first one involves calorie restriction and has been tested in various animal models with consistent results. Limiting the caloric intake to about 60% of the level consumed by their and libitum fed cohorts allows laboratory animals to live about 30% longer wih more viality reflected in almost every biological parameters examined so far. Although the exact mechanism for this effects is presently uncertain, it is reasonable to assume that limited caloric intake slows down oxygen and glucose metabolism with the production of less oxygen radicals and glucose adducts that can cause protein crosslinking and enzyme inactivation.

The second approach uses pharmacological agents to block certain chemical reactions that are known to cause age-dependent damages to macromolccules. Glucose, thc key energy source of thc living cell can chronically react to proteins to from aggregates and impair their functions. Aminoguanidine, a chemical agent, prevents such glucose-mediated cross-linking of proteins and is being clinically tested in patients with diabetes where the delcterious effect of glucose is specially problematic. Activated oxygen in the form of free radicals is highly reactive and can initiate uncontrolled chemical reactions. Despite efficient cellular mechanisms to neutralize free radicals, somc escapc inactivation and cause macromolecular damage. PBN(N-tert-butyl-a-phenyl nitrone) is an effective trapping agent for free radicals. It reacts with free radicals and produces a stablc nitroxyl product. Administration of PBN to old animals causes a decrcase in the oxygen mediated damage to brain proteins and results in a significant improvement in the mcntal faculty of experimental animals.

Thus, advances in the understanding of the molecular mechanisms of aging have not only allowed us to dcvelop a unified explanation of thc process itself, it is also helping to design strategies for retarding the rate of aging. Results of these studies have important societal implications for extending the healthy life span.