Current Research in a Central Mechanism Theory of Senescence:

Toward an Anti-Aging Drug?

Abstract: Aging seems to consist of a collection of afflictions that increase as we grow older, eventually bringing death. But there may be some central mechanism in the aging process that triggers many of these seemingly separate, individual ailments. Scientists are looking at two genetic mechanisms, either or both of which may influence the advent of senescence in humans. One is the endocrine regulation of aging by insulin-like signals. There may be genes that code for hormones that stress reproduction over genomic maintenance. Studies with worms, flies, and mice all indicate that silencing expression of those genes and facilitating expression of other genes that stress somatic repair and maintenance over growth and reproduction, slows the aging process and maintains health much longer in individual organisms. A second area that is being studied is the damaging effects reactive oxygen species (free radicals) on cellular health and genomic stability; this could be a major cause of aging. Caloric restriction may extend life-span by attenuating the oxidative stress caused by normal metabolism. Researchers are looking for drugs that would facilitate these anti-senescence mechanisms in humans.

In the words of the blues song, "Everybody wants to go to heaven, but nobody wants to die (Nix, 1971)." A corollary of this theory might be that nobody wants to go through the aging process, either, with its prospect of Alzheimer's, cancer, heart disease, diabetes, shortsightedness, reduced motor capacities, wrinkled skin, etc. Average life-span has greatly increased in the past century, from 48 years in 1900 (Arking, 2003) to 77 years in 2000, in the United States (CDC, 2003). However, the actual process of aging, bringing with it manifestations of one or more of the afflictions mentioned above, has not changed at all.

In longevity research today, scientists are not looking at aging so much in terms of simply adding years to maximum life expectancy; this is already happening with improvements in sanitation,

nutrition, medical intervention in disease, and so on. Researchers are instead more interested in studying the mechanism of senescence, defined as "the time when age-associated deficits are manifested" (World Health Network, 2004). Medical records of the elderly seem to indicate that aging consists of a series of "independent degenerative processes leading to disease and ultimately death" (Hekimi and Guarente, 2003). Instead of trying to remedy each of these individual ailments, researchers are seeking a way to increase longevity by delaying the process of senescence as a whole. Current research suggests that the the rate of aging in an organism is not fixed, and that we may be able to alter the basic mechanism that drives the aging process (Barrett, 2003). The bundle of diseases which are symptoms of senescence may to some extent be manifestations of this central process, which may in fact be regulated by a limited number of genetic processes. Studies show that in the worm C. elegans, most of all of the various aging processes can be significantly slowed and a much longer life-span achieved by making changes in only a few genes. This finding points to a central mechanism for senescence (Hekimi and Guarente, 2003) (Kingsland, 2003).

The aging process would seem to be sitting in evolution's blind spot. The prime directive of evolution, the standard of "Darwinian fitness," is for an organism to pass as many copies of its genome as possible to the next generation. Organisms are selected for traits that will allow them to survive to reproductive age and then to successfully generate viable offspring. The mechanism of natural selection will not select for or against gene expression that manifests after the organism is past its reproductive age; these traits are not relevant to the organism's Darwinian fitness (Arking, 2003). On the one hand, this suggests that senescence is inevitable: long-lived genetic variants will not be selected for, since they are expressed in a post-reproductive phase (Vaupel et al 2003). On the other hand, it indicates that there is no specific evolutionary reason for senescence to occur, and opens the door to examining possible genetic alternatives to the current standard aging scenario (Arking, 2003).

An organism needs energy for reproduction and growth, and it needs energy for maintenance and repair, both at an organismal and at a cellular level. Even in the best of times, there might not be enough metabolic energy available to maximally fulfill both those functions, leaving a choice of which function to devote energy resources to (Arking, 2003). Since Darwinian fitness revolves around reproduction, organisms that devote more resources to reproduction, at the expense of cellular maintenance and repair, will be selected. If there were a change that could be made to shift that balance later in life, for instance by expressing a different set of genes, the phenotypic shift would not be supported by natural selection, since it occurs in the post-reproductive part of life. Therefore, "maximum (Darwinian) fitness takes place at a repair level lower than that required for indefinite somatic repair, and organisms die. This is the so-called disposable soma theory" (Arking, 2003).

As it turns out, there may be just such a genetic choice going on that leads to senescence. Of the dozens of genes that affect mammalian longevity, many of them are regulated by hormonal signals (Tatar et al, 2003). This insulin-like signaling system appears to be activated by an insulin-like peptide, insulin-like growth factor 1 (IGF-1). Differences in the level of IGF-1 can turn on or off two entirely different sets of genes, one which activates increased growth and reproduction, and another which promotes maintenance and repair (Arking, 2003). In an important study that opened the door for much of the current aging research, Cynthia Kenyon et al looked at the daf-2 gene, a gene in C. elegans which encodes a hormone receptor quite like the receptor that binds IGF-1 in humans. They found that a mutation in the daf-2 gene in C. elegans causes fertile, active mutants to live more than twice as long as the wild type. They hypothesized that these findings indicate a lifespan-regulation mechanism, since the daf-2 gene regulates many other downstream genes (Kenyon, 1993). Studies built on their work indicate that, in both yeast and worms, suppression of genes that promote growth increases longevity and promotes protection from metabolic stress-related deterioration (Longo and Finch, 2003).

Studies of mice have also demonstrated this similarity between daf-2 function and IGF-1 signaling (Longo and Finch, 2003). Dr. Kenyon, professor of biochemistry and biophysics at the University of California San Francisco, states, "... genes downstream of this receptor do lots of different things. Some of them code for proteins that protect animals from all sorts of stresses, chaperones that help other proteins fold correctly, and antioxidant proteins such as catalase and superoxide dismutase. Then there are those that encode proteins that kill bacteria, and metabolic genes. But you have a single hormone receptor, the IGF-1/insulin receptor, and a transcription factor commanding between 50 and 100 genes that directly affect the aging process" (Kingsland, 2003).

A related area of aging research is looking at the cumulative deleterious effects of mitochondrial production of reactive oxygen species (ROS), commonly known as "free radicals" (Martin et al, 2003). The ongoing accumulation of damage to somatic cells is seen to be a major cause of senescence, and ROS may be the principle long-term cause of that damage (Hasty et al, 2003). During the normal and necessary production of ATP by the mitochondria, electrons sometimes escape from the electron transport chain and combine with oxygen in the area to create ROS, which are highly reactive ions containing oxygen and unpaired electrons. One aging theory maintains that as the mitochondria, where most free radicals are produced, sustains ongoing damage from ROS, it both loses its efficiency in creating ATP and also creates more and more ROS, increasing damage further. Eventually, the cells become starved for energy, and the tissue systems they constitute begin to break down, leading to degeneration and/or disease in the organism (Weinbruch, 1996).

DNA is another major target of ROS. "More than 100 different types of oxidative DNA lesions have been described, ranging from base modifications to single- and double-strand DNA breaks and interstrand cross-links" (Hasty et al, 2003). Genomic stability and integrity is a key factor in health and long life, while gene expression that is very unstable can lead to death (Arking, 2003).

Specifically, damage to telomeres could promote senescence. Telomeres are the long ends of eukaryotic chromosomes that contain repetitive base pairs and specialized proteins. They function to protect the chromosome from degrading and connecting to or forming recombinations with other chromosomes. They also bind proteins that may contribute to DNA repair. Exceptionally short or damaged telomeres in mammals appear to lead to non-functional, senescent cells. Studies in mice lacking telomerase RNA (mTR) have shown that this mutation can cause manifestations of premature aging as well as chromosomal fusion, indicating genomic instability (Hasty et al, 2003).

ROS damage to DNA interferes with the crucial transcription and replication processes in ways that can cause cells to stop growing, die, or possibly mutate to a cancerous form. This disruption of gene expression by ROS-induced DNA damage is very likely a significant factor in the overall aging process (Hasty et al, 2003).

Here, once again, we encounter the energy-production balance: growth and reproduction versus repair and maintenance. The same free radicals which are responsible for cellular and genetic damage also have physiological benefits having to do with fitness and growth factor signal transduction. This hormonal signaling pathway, which we encountered earlier, stimulates reproductive fitness while at the same time suppressing repair factors; specific antioxidant enzymes such as superoxide dismutases and catalase are decreased by IGF-1 (growth factor hormone). However, inactivation of these signaling pathways increases protection against damage caused by ROS, as well as other cellular stress (Longo and Finch, 2003).

Many studies have shown that caloric restriction, the practice of greatly reducing the number of calories delivered by a diet while maintaining optimal nutritional levels, increases longevity in yeast, worms, and mice. One theory postulates that caloric restriction slows metabolism, thus

slowing mitochondrial activity and slowing the production of free radicals. Experiments in mice have shown that caloric restriction also stabilizes genetic expression (Alder and Underwood, 2004), which, as we saw above, is related to both ROS damage of DNA and manifestations of senescence. The effect of caloric restriction may be a genetic survival mechanism to shift energy from reproduction to maintenance in times of scarcity, when reproduction would present problems and the organism needs to marshal all its resources for individual physical survival (Hekimi and Guarente, 2003).

It should be emphasized that the delay of senescence, whether through inhibited insulin-like pathways, reduced cellular ROS damage, or caloric restriction, does not just tack extra time onto the end of an organism's lifespan. In many of the studies cited above, the experimental animals not only lived longer than average, but also remained healthier longer, both in absolute length of time and in percentage of their lifespan (Barrett, 2003). According to Ron Bailey, science correspondent for Reason magazine, "The point of aging research is not to enable us to be older longer but rather (to) allow us to be younger longer" (Barrett, 2003). Caloric restriction studies of mice have shown them to live 30% longer then die quickly, having remained healthy during the extended life period. Similarly, studies in humans have shown that the longer the life span, the shorter the final illness (Dominus, 2004). So while current research may bring us longer life, increased quality of life during those extra years is perhaps an even more important result.

"Sounds good," you say. "So when does this research produce the anti-aging pill?" For those of us further along in our life cycle, the encouraging news is that anti-senescence actions may be effective even when begun later in life. Studies with flies showed that introducing caloric restriction later in life produced the same longevity increases as those in flies on CR since the beginning of life (Vaupel et al, 2003). Introducing caloric restriction in middle-aged mice increased their maximum longevity by 10-20 percent, with the added benefit that it reduced the possibility of developing cancer (Weinbruch, 1996).

Caloric restriction, with its unfortunate side effect of constant hunger, seems the perfect embodiment of the joke, "you might not live forever, but it will seem like it." However, there may be ways to enjoy the benefits of caloric restriction without the growling stomach. A compound found in red wine, resveratrol, has been found to affect the IFG-1 pathway to delay senescence in worms (Kingsland, 2003) and also to increase lifespan in yeast by 60% (Dominus, 2004) (Alder and Underwood, 2004). In another study, the drug 4-phenylbutyrate increased lifespan in fruit flies by suppressing an enzyme that represses a cell's stress reducing genes (Arking, 2003).

Simon Melov et al were able to increase the lifespan of C. elegans by 44 percent by administering superoxide dismutase/catalase mimetics which ameliorate ROS cellular damage. They concluded that, "It appears that oxidative stress is a major determinant of life-span and that it can be counteracted by pharmacological intervention" (Melov, 2000). This possibility has several biotech firms racing to find a drug that will safely stimulate in humans the senescence-delaying mechanisms described above.

There is much work to be done, however, as most of the drug interventions tested so far have had unacceptable side effects. For instance, tests of the compound known as 2D, while providing some of the longevity benefits of caloric restriction without the hunger, also tended to slow metabolism to the point of cardiac arrest, "an undesirable side effect in a drug intended to prolong life" (Alder and Underwood, 2004). In addition, there are practical and ethical considerations to explore; Science magazine considers public debate on issues surrounding aging to be "essential" (Martin et al, 2003). Concerns about overpopulation, the social and economic impact of the shift in demographics, the disparate impact on industrial versus developing nations, the possibility that anti-aging pharmacology would only be available to the rich, and other potential impacts of increased longevity on society all need to be considered (Barrett, 2003) (Dominus, 2004). Nevertheless, scientific exploration of the central mechanisms for aging will undoubtedly

continue. It is producing exciting and promising research that could lead to extension of lifespan in humans.

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