Prevention of Age-related Diseases and Extension of Healthy Life

The gist of a project proposed by

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Here I propose to develop new sensitive non-invasive methods for quantitative measure of real biological age and the changes in biological age of each individual undergoing changes in his/her life style. This research project is part of M. Radman's vast project revealed in the Extended Abstract, notably the identification of inborn genetic weaknesses present in different forms in each and every person at the level of susceptibility of individual proteins to oxidative inactivation.

Two biological clocks determine the destiny of all living species and organisms: (1) The universal clock of genetic change in the germ line, common to all species (evolutionary destiny), and (2) The species-specific somatic clock determining the kinetics of emergence of age-related diseases and the life span of individual organisms (individual destiny). The chemistry of these biological clocks is not known, and this project proposes to study both clocks.

New Methods

We have recently developed methods for:

(A) Measuring global genomic mutation rates in any living cell, including the germ line cells (*M. Elez, I. Matic & M. Radman, Current Biology, in press*). The chemistry of the germ-line clock is clearly DNA chemistry, but we do not know the causes of DNA changes (mutations) assuring adaptive evolution of species.

(B) Measuring the somatic clock, i.e., the fundamental biochemical event(s) responsible for the progressive loss of biological fitness in the course of aging (so-called intrinsic aging). We found that the chemistry of the somatic clock is protein chemistry, i.e., the accumulation of protein damage due to the oxidation (carbonylation) of their amino acids ("corrosion") causing loss of

protein function and/or decreased precision of interactions among proteins (*A. Krisko & M. Radman, submitted; A. Krisko, M. Leroy, M. Radman & M. Meselson, submitted*). The test of proteome damage and cell fitness can be called "bio-gerontometry".

The Biology of Robust Species

Some rare species (e.g., bacteria like *Deinococcus radiodurans* and small aquatic animals Bdelloid Rotifers and Tardigrada) show stunning resilience to stresses such as extreme radiation, toxic chemicals and years of radical dehydration (desiccation), that kill most species hundred times over. By studying the molecular biology of such species, we found that their robustness is due to the evolved prevention of the oxidative damage to cellular proteome – the functional entity of life – not to prevention of DNA damage. The anti-oxidant protection against proteome damage is due to the synthesis of small molecular weight (<3 kDa) molecules that prevent or scavenge the effects of reactive oxygen and nitrogen species (ROS and RNS).

The protective molecules from robust species protect equally effectively proteomes from resistant and sensitive species. This trans-species protective activity is the basis of our hope that that such protective entities may protect the human proteome from debilitation damage caused by radiation, chemicals and possibly age. Hence, a perspective of slowing down the rate of aging and all age-related diseases, or "geronto-therapy".

The "Biology of Human Destiny" and the Individualized Preventive Medicine

Clearly, being overweight, smoking and consuming alcohol is deleterious to human health. But, why some individuals, healthy and athletic at young age, and living a healthy life style, die relatively early of some disease, whereas others doing the opposite (e.g., Winston Churchill) live long and lucid life?

What is the nature of constitutive weaknesses that often run in families and are expressed only at advanced age? Is it possible that everybody's "silent polymorphism", silent at young age when people are still healthy, becomes progressively "loud" (i.e., phenotypic) at advanced age when disease becomes evident? What is the cause and can we measure it? We believe to be on the

track of answering this question.

With the laboratory of Thomas Nystrom in Goteborg, we have shown that subtle changes in protein structure can drastically increase the susceptibility to oxidative damage (carbonylation) *(Dukan et al. PNAS (2000) 97: 5746-5749; Fredricksson et al., Genes Dev. (2007) 21:862-74*). Recently, we have observed that naturally occurring "morphs" (single amino acid substitution) of a protein related to Parkinson's disease can show increased susceptibility to carbonylation by 15-fold. The *in vitro* susceptibility of this protein to H_2O_2 induced carbonylation correlates with the early onset of the disease in the patient. The tentative interpretation is that – at advanced age when global protein carbonylation increases exponentially (*Oliver et al., JBC (1987) 262:5488-5491*) – individual polymorphic proteins start "burning out" by oxidation at different rates in different individuals causing eventually the deficit of their function and disease. In other words, although healthy at young age, we are all predisposed to some diseases that will appear at advanced age with similar exponential Gompertz kinetics and eventually cause our death. Can such predispositions be identified at young age?

Here is an experimental strategy: If we could detect and diagnose individual's inborn susceptibilities to spontaneous and induced protein carbonylation in most individual protein spots in 2D gels, we may be in the position of reading in young persons their health-related destiny at advanced age.

Suppose that we would succeed in this predictive diagnostic. What can we do with and about it? First, apply the common sense preventive life style, and second, that the only known effective biological anti-oxidant complex from the robust species would act as such in humans.

Since we are obviously all predisposed to suffer from some specific disease(s) before the onset of other diseases, everybody would want to take the anti-oxidant treatment. What can be expected from such treatment?

Extension of Healthy Life: Young at 100 years?

Almost all proteins are "turned-over", i.e., synthesized and then broken down. Therefore, the measured level of carbonylation in human fibroblasts results from the steady-state of incurred

protein carbonylation and the selective breakdown of carbonylated proteins by the dedicated 20S proteasome (which is also made of proteins that are subject to carbonylation). Therefore, if the anti-oxidant complex from robust species is taken chronically, and is effective, then the old oxidized proteins would eventually get degraded and the protected newly synthesized proteins would be maintained at low level of oxidative damage. Therefore, if one indulges in "gerontotherapy" by consuming small m.w. antioxidant protectors from robust species (in A, iv)), such treatment could stop, or even reverse, the aging process and thus prolong healthy longevity.

This is of course a science fiction scenario, but human life span keeps increasing 6 hours every day without implementation of any particular plan or strategy (). The virtue of this project is the simplicity of concepts and the feasibility of experiments. Everything that looks so complicated in aging could become but a detail of this simplicity. For instance, we find that DNA repair is limited by the level of oxidative damage to repair proteins with direct consequence to genomic integrity. Chromosomal telomeres may be shortening with age because the enzyme telomerase becomes inactivated by oxidative damage, etc.

Amusing questions

Interesting questions arise relative to this project. While people should enjoy to be long lived and healthy, is there any positive societal interest in prolonging healthy human life? Given the monumental expenditures for and budgetary deficits of health care, prevention of diseases would liberate considerable government and insurance funds for other priorities. When should one start the rejuvenation treatment, before or after the menopause? The population growth would presumably slow down which may be beneficial to humanity's destiny. Already slow human biological evolution should somewhat slow down, but young centenarians could generate an explosion in cultural evolution.