Iranian J Publ Health, Vol. 37, No.3, 2008, pp.1-8

Review Article

Gene and Aging

**DD Farhud [1], M Aghasi [2], H Sadighi [1]*

[1] Genetic Clinic, Vallie Assr Sq, 16 Keshavarz Blvd, Tehran 14, Iran
[2]Dept. of Nutrition, Iran University of Medical Science, Iran

(Received 8 Jan 2008; accepted 17 Aug 2008)

Abstract

Collection of multiple processes that increase the chronological age of an organism leading to death is defined as aging, and even though important, it is poorly understood. Recent research has shown that aging is due to biochemical and genetic changes, in interaction with environmental effects, including diet and nutrition. Most knowledge on aging is based on genetic model system, but its molecular mechanisms are still not very clear. Discoveries in molecular biology have made way to look for candidate genes influencing lifespan. Furthermore, new investigations have stressed on the roles of mitochondria as the major generators and direct targets of reactive oxygen species. This paper reviews some recent literature on genes and aging in model system, then discusses the role of mitochondria and nutrients in human aging.

Keywords: *Gene, Aging, Reactive oxygen species, Free radical*

Introduction

Aging, a difficult process to define, is believed to be progressive and accumulative deleterious changes, compromising physiological processes leading to death (1).

Investigations on this still poorly understood process have shown that aging is due to biochemical and genetic changes, in human and model organisms, alongside the environmental effects, such as food habits. Most knowledge on aging is based on genetic model system, but its molecular mechanisms are unknown (2, 3). Longevity is considered to be heritable, that is 25 to 50 percent of individual variability being considered to be related to genetic factors (4). The genetic influence is, to some extent, revealed by rare genetic premature aging conditions and heritability estimates of longevity in normal populations (1). Studies of aging coefficient in various population groups have helped in clarification of the genetic influence (5, 6). Recent developments in molecular biology have made it possible to search for candidate genes that may influence lifespan (7, 8). A different class of genes involved in aging, is related to production and scavenging of molecules known as reactive oxygen species (ROS), providing further reason for acceptance of mechanistic theory of aging, or the free radical theory (9). As mitochondria are the main generators and direct targets of ROS in the cells, it is believed that oxidative stress and damage in mitochondria are contributory factors in aging. Investigations so far has produced evidence that mitochondrial functions decline in aging and degenerative diseases, concluding that antioxidant systems and nutrients may have important effects on aging (10, 11). Hence, it can be concluded that aging is a consequence of complex interactions of genes, environment, lifestyle and chance (12).

This review article considers some recent literature on genes and aging in model system, and the role of mitochondria and micro-nutrients in human aging.

Discussion

Collective multiple processes that increase chronological age and probability of death is called aging of an organism. This means that in a population age structure outnumber old ones (2).

Aging remains a poorly understood process due to its complex but gradual physiological and homeostatic decline. Recent research has somehow

***Corresponding author:** Tel/Fax: +98 21 88950184, E-mail: farhud@sina.tums.ac.ir

clarified biochemical and genetic processes and controls that strongly influence aging (3).

Aging is a non-adaptive process in which the genes affecting its rate either do not affect fitness or have been selected due to beneficial effects early in life. The suggestion of this evolution theory of aging, goes on to express that aging is influenced by many genes and caused by various physiological and molecular processes (2).

Knowledge of aging mechanism is mostly based on genetic model system. *Saccharomyces cerevisiae*, yeast, dies after a finite number of divisions which is by budding, that is, the number of divisions defines the lifespan. Mutation of SGS1, a homologue of the human WRN helicase gene, shortens lifespan. SIR2, a histone deacetylase- encoding gene and RAS2, a homologue of the mammalian RAS proto-oncogene are examples of genes which control the yeast lifespan and may show links between nutritional sensing, gene expression and cell division (2).

Multiple genetic pathways determine lifespan in invertebrates. Multiple endo- or paracrine signals, such as insuline-like signaling pathways determine the lifespan of nematode roundworm *Caenorbabditis elegans*. The pathway responds to nutrition pheromone sensory signals and also signals coming from the somatic gonad and the germline. These pathways also regulate formation of a non-responding diapauses life cycle stage (the donar larvae) during development and it forms in response to food deprivation and other adverse conditions. Mutations can result in altered body size and fertility, and some, age mutations, like daf-2 gene, encoding insulin receptor-like protein increase lifespan. Additional daf mutations can produce lifespan extentions of 300%. Also, these mutations confer resistance to environmental stressing factors, such as heat and UV radiation. Mutations of such pathways are highly pleiotropic, concerning with fitness, lifespan, fertility and body size. Single genes also have effects on lifespan and environmental stressors (2).

Caloric restriction (CR) whether started early or later in life, and growth hormone repression, GH/insulin- like growth factor- 1 insulin axis, have increased lifespan in animal model system. Also, genes involved in the GH/IGF-1 signaling pathways can increase lifespan, supporting evolutionary conservation of molecular mechanisms. Insulin and insulin-like growth factor-1 (IGF-1)- like signaling and molecules involved in its following steps have shown to be associated with lifespan in fruit flies and nematodes, and further, mammalian models with reduced GH and/or IGF-1 have been shown to have increased lifespan as compared to controlled siblings. These investigations have shown that genetic alteration can keep the organism healthy and disease- free for longer periods and reduce age related pathologies, similar to observations in caloric restricted individuals, concluding that these mutations extend lifespan and improved healthy and quality of life as the organism ages (13).

The molecular mechanisms of aging are unknown (2). Genetic and environmental factors have large effects on aging and lifespan. Diet can have profound effects on lifespan of organisms; however, the mechanism is still not fully understood. Inactivity of myriad single genes is found to significantly increase the lifespan of organisms (7, 8). The modes of action of these genes would be clarified by identification of the pathways that they are involved with. Production and scavenging of reactive oxygen species (ROS) molecules are carried out by another type of genes involved in the aging process. This evidence supports the mechanistic theory of aging, the free radical theory (9). Correlated phenotypes of longevity and oxygen radical theory of aging, in which produced ROS cause the accumulation of damaged macromolecules, are consistent, as in organism *C. elegans*. Age mutants resist oxidative stress and over express some genes encoding antioxidant enzymes like superoxide dismutase (SOD) and catalase. Engineered strain of *D. melanogaster*, with additional copies of genes encoding these enzymes, show extended lifespan. Mice with mutated $p66^{shc}$ gene have 30% extended life and are resistant to oxidative stress (2).

The SHE gene, named after Src and collagen homologous regions, has shown to be related to lon-

gevity in mice. Alterations of $p66^{shc}$ specific region cause change in resistance to apoptosis in reaction to oxidative stress and intracellular oxidant level (14). Methylation of the $p66^{SHC1}$ promotor decreases its expression level (15) playing role in longevity (16). Its high expression level is shown to be related to carcinogenesis and metastasis in human tumor tissues (17). The $p66^{SHC1}$ function is related to the function of tumor suppressor protein p53 (18). These two regulate levels of intracellular ROS and apoptosis. Loss of p53 causes genomic instability and renders cells to becoming cancerous. Therefore, induction of apoptosis causes premature aging and insufficient induction produces cancer (19). It is thought the major mutations are not tolerated by $p66^{SHC1}$ because they alter its function and its role in tumor suppression is disrupted. Subtle mutations, on the other hand, prolong the effect, as reduced apoptosis leads to greater reserve capacity by number of divisions' competent stem cells. Increase of lifespan is caused by increased resistance to oxidative stress by up-regulation of forkhead activity. This stimulates ROS scavenging and repair of oxidative damage. Because Activation of $p66^{SHC1}$ decreases forkhead activity, It is believed that the beneficial valine allele is associated with mild decrease of $p66^{SHC1}$ activity levels. They, therefore, may explain the role of $p66^{SHC1}$ in human longevity (14).

Aging rates are determined by pleiotropic aging rates genes with strong correlation between extended lifespan, altered life history, lowered fitness and increased stress resistance. The type of genes that modulate aging rate indicates that aging is influenced by endocrine signals, intracellular signaling pathways, metabolic regulators and stress response factors, such as antioxidant enzymes (2).

Energy metabolism in aerobic organism is by glycolysis, the Kreb's cycle and electron transport chain. The latter or the oxidative phosphorylation system (OXPHOS) is carried out in the inner membrane of mitochondria and is responsible for production of ATP, generation of ROS and regulation of cell death. Five complexes in the inner membrane, the respiratory chain, transfer electrons with O_2 as the final acceptor. This electron transport system consists of more than 80 subunits and need more than 100 additional genes (20).

Reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide and hydroxyl radicals, produced by electron transport system, attack and damage a variety of cellular entities, causing wholly or partly different cellular pathologies. Oxygen is converted to O_2^-, some from complex II, by genetic influence. This indicates the age-related complex II deterioration produced O_2^- and accelerates aging (20). Fig. 1. schematic illustration of the mitochondrial role in human aging and mitochondrial disease (21).

Under normal physiological condition, 1-5% of the oxygen is converted to the reactive oxygen species (ROS) and free radicals due to incomplete reduction by one-electron transfer reactions in mitochondria. They are usually disposed of by the coordinate function of the antioxidant defense system consisting of free radical scavenging enzymes SOD, GPx and CAT together with a number of small-molecular-weight antioxidants. If escaped, they may cause oxidative damage (strand breakage and base modification) and mutation to mtDNA molecules that are attached, at least transiently, to the inner membranes (21).

Chronic elevation in levels of reactive oxygen species damages various components of the electron transport system, producing an even higher levels and rates of ROS, resulting cellular and organismal aging. Reduction of metabolism reduces ROS production and increase lifespan (22).

ROS can cause mutation of genes such as tumor suppressor genes and oncogenes, leading to cellular transformation, as the importance of O_2^- is discussed in cancer, differentiation and aging. Oxidative stress from mitochondria have important role in apoptosis and cancer (14).

Thus, as mitochondria are the major generators and direct targets of ROS, it is well believed that the oxidative stress and damage in mitochondria are contributing factors to aging. Data in recent years have shown that mitochondria bioenergetic function decreases as the age of postmitotic cells,

such as brain, heart and muscle, increases (10, 11, 23). It is also accepted that mtDNA mutations increase with age, but since each is generally less than 5%, it is thought that this, together with a wide spectrum of deletions of mtDNA, (30) as seen in skeletal muscles, severely impair the mitochondrial respiration and oxidative phosphorylation (23-25). Low activity of cytochrome c oxidase was seen in skeletal and heart muscle fibers of elderly (26, 27). Recently, mtDNA mutations and oxidative DNA damage were found to increase the aging of human lung and skin (28).

The genetic role in aging can be better revealed by syndromes such as Huchinson-Guilford progenia syndrome (HGPS), in which premature aging become apparent some time after birth, and Werner syndrome (2). Wiedemann-Rautenstrauch Syndrome (WRS), a premature aging syndrome, has several characteristics of aging at birth (1). It is believed that genetic factors cause 25 to 50 percent variations in human lifespan, but the loci are unknown (4). Gene association studies have shown that some alleles are associated with longevity (2). Centenarians, for instance, are less likely to have genetic and environmental exposures associated with decrease lifespan and death at earlier ages. This is called *demographic selection*, as apolipoprotein Eε4 allele, associated with heart and Alzheimer disease is rare in concentrations (27), but the ε2 variant of the APOE gene is over-represented in the same population, but is also associated with type III and IV hyperlipidemia (2).

Studies in model organisms have demonstrated that components of insulin and insulin-like signaling pathways are involved in the regulation of lifespan. We provide evidence suggesting that variants of the gene encoding insulin-degrading enzyme (IDE) may be influencing human lifespan. We have employed a variety of models and diverse samples that reproducibly indicate the relative change in IDE genotype frequency across the age spectrum as well as allow the detection of association with age-at-death. A tenable molecular basis of this is suggested by the observation of genetic association with both fasting plasma insulin levels and IDE mRNA expression. Across populations the emergent genetic model is indicative of over- dominance, where heterozygotes of critical markers have increased IDE mRNA expression and insulin levels, and this is reflected in diminished heterozygosity at advanced age. A critical and replicating feature of this study is that change in IDE genotype frequency with advancing age appears to be occurring only in men, and this is supported in that insulin levels are only associated with IDE in men. Results suggest a relationship between a gene that is intimately involved in insulin metabolism and the determination of lifespan in humans, but over-dominance and gender specificity will be important parameters to consider clarifying the biological importance of these findings (29).

Cell culture studies show characteristics of aging. *In vitro* cultured cells undergo only a limited number of divisions, or replicative senescence. The nondividing cells show, among other characteristics such as extracellular secretion of metalloproteinases, matrix degrading enzymes. Such cells contribute to functional deficits. Shortening of chromosomal telomeres during replication, take place in senescent cells, preventable *in vitro* by restoration of telomerase, the telomere synthesizing enzyme (2).

Family and twin studies confirm the influence of genes on lifespan. Increasing number of centenarians make it possible to study the effects of candidate genes on lifespan, with now more available procedures of molecular biology (30).

Table 1 summarizes the genes whose polymorphisms have been analyzed in more than one gene-longevity association study (only the post-1980 literature is considered), and table 2 summarizes the genes whose polymorphisms have been analyzed in association with longevity in one study only (30).

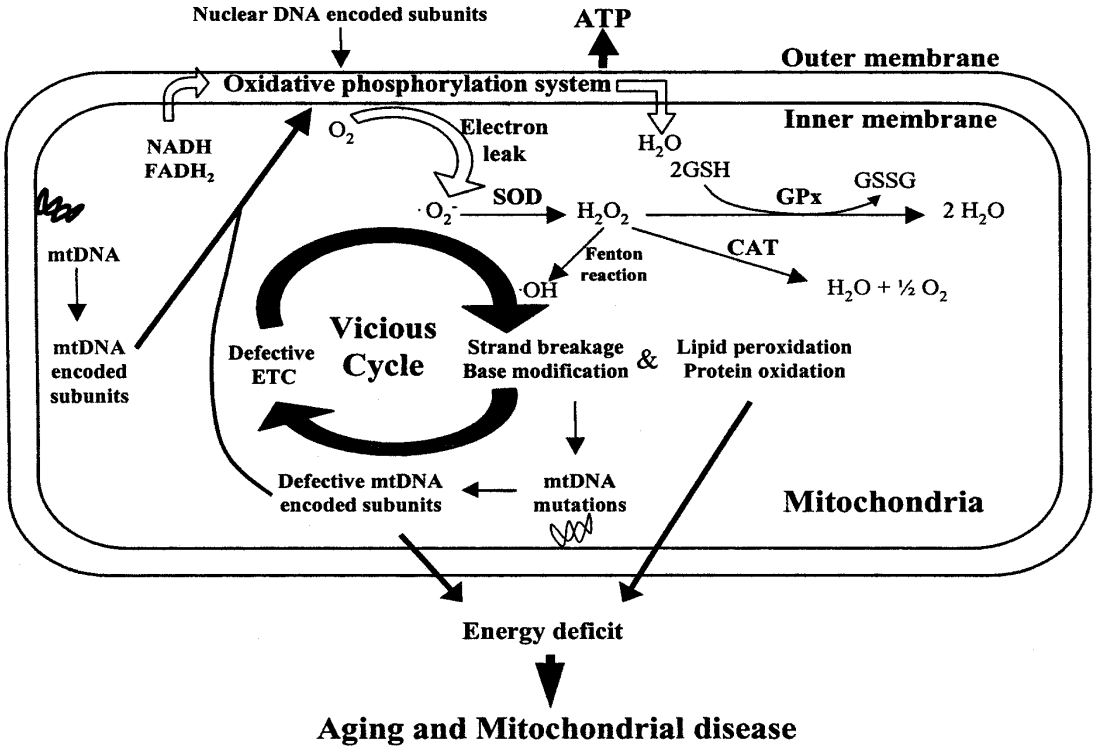

Fig. 1: A. schematic illustration of the mitochondrial role in human aging and mitochondrial disease.

Table 1: Genes whose polymorphisms have been analyzed in association with longevity in more than one study [a]

Gene	Function	Disease associated	Longevity association
ApoE	Lipoprotein metabolism (apoprotein of HDL, VLDL)	AD, CVD	Yes (Louhija et al., 1994; Kervinen et al., 1994; Schachter et al., 1994; Zhang et al., 1998; Gerdes et al., 2000) No (Bader et al., 1998)
ApoB	Cholesterol homeostasis (sole apoprotein of LDL)	CAD	Yes (Kervinen et al., 1994; De Benedictis et al., 1997, 1998a)
ApoA-IV	Lipoprotein metabolism (apoprotein of HDL, VLDL)	AD?	Yes (Merched et al., 1998; Pepe et al., 1998)
ACE	Angiotensin converting Enzyme	MI, CI, AD, EH	Yes (Schachter et al., 1994; Faure-Delaneff et al., 1998) No (Bladbjerg et al., 1999; Heijmans et al., 1999a)
CYP2D6, CYP2C19	Cytochrome P450 gene family	PD? cancer susceptibility	Yes (Bathum et al., 1998) No (Agundez et al., 1997; Yamada et al., 1998; Muiras et al., 1998a)
HLA class I and class II	Immune response	Immune disorders	Yes (Proust, 1982; Takata et al., 1987; Dorak et al., 1994; Ma et al., 1997; Akisaka et al., 1997; Ivanova et al, 1998a; Ricci et al., 1998)

Fig. 1: Continued…

			No (Izaks et al., 1997)
P53	Tumor suppressor gene	Cancer susceptibility, Apoptosis	No (Bonafe` et al., 1999a,b)
Factors V, VII, PAI-1	Blood coagulation and fibrinolysis proteins	MI, thromboembolia	Yes (Mari et al., 1996; Mannucci et al., 1997) No (Bladbjerg et al., 1999; Heijmans et al., 1999a; Meiklejohn et al., 2000)
Fibrinogen	Plasma coagulation factor	CAD	Yes (Mari et al., 1996) No (Mannucci et al., 1997; Bladbjerg et al., 1999)
Prothrombin	Blood coagulation and prothrombin protein	MI	Yes (Mari et al., 1996) No (Bladbjerg et al., 1999)
MTHFR	Homocysteine methylation	CVD Cancer susceptibility?	Yes (Faure-Delaneff et al., 1997; Matsushita et al., 1997; Kluijtmans et al., 1999; Todesco et al., 1999) No (Galinsky et al., 1997; Harmon et al., 1997; Brattstrom et al., 1998; Bladbjerg et al., 1999; Rea et al., 2000)
Mitochondrial DNA	Oxidative Phosphorylation	Mitochondrial diseases, CAD?, diabetes?, PD?, AD?	Yes (Tanaka et al., 1998; Ivanova et al., 1998b; De Benedictis et al., 1999)
PARP	DNA repair, apoptosis	???	No (De Benedictis et al., 1998b; Muiras et al., 1998b; Cottet, 2000)

[a] AD, Alzheimer's disease; CVD, Cardiovascular disease; CAD, Coronary artery disease; MI, Myocardial infarction; CI, Cerebral infarction; EH, Essential hypertension; PD, Parkinson disease (30).

Table 2: A brief review of genes whose polymorphisms have been analysed in association with longevity in one study only[a]

Gene	Function	Disease associated	Longevity association
TPA (Tissue plasminogen Activator)	Fibrinolytic/thrombolytic response	MI? Stroke	No (Bladbjerg et al., 1999)
AGT (Angiotensinogen)	Renin–angiotensin system	EH, CVD, CAD, CHD	No (Bladbjerg et al., 1999)
GP2b3a	Blood coagulation	CVD	No (Bladbjerg et al., 1999)
TPO (Thyroid Peroxidase)	Thyroid metabolism	???	No (De Benedictis et al., 1997)
TH (Thyrosine Hydroxilase)	Catecholamine Synthesis	???	Yes (De Benedictis et al.,1998b)
SOD2 (Superoxide dismutase 2)	ROS scavenging, apoptosis	???	Yes (Tan et al., 2001)
WRN (Werner)	DNA helicase	Werner syndrome	No (Castro et al., 1999)

[a] MI, Myocardial infarction; EH, Essential Hypertension; CVD, Cardio-vascular disease; CAD, Coronary artery disease; CHD, Co (30).

Genetic studies, especially twin studies, suggest that normally the role of genes is to enable the individual to age successfully. However, there are non genetic factors, like environment, behavior and physiological processes (such as diet, exercise, smoking, physical and chemical contacts), required for the successful aging, even though, there are genes that affect these mediating factors making indirect effects on successful aging. Also, there are gene-environment interactions that play important roles in successful aging through social support (4).

Diet has various important effects on health and lifespan. It has been clearly shown that diet has interactions with genome, causing alterations in gene expression. Nutrigenomics is a new approach to understanding molecular mechanism of diet in health and aging. Transcriptional profiling techniques, in mode of action of energy (caloric) restriction, nutritional modulation of DNA damage and repair, and nutritional modulation of epigenetic markings, are the present investigational methods. Epigenetic-mediated changes in gene expression in relation to dietary and other types of exposures is an important molecular mechanism in relating environment and genome, resulting the cell function and hence, health in the course of life (31).

Acknowledgements

The study was partly financially supported by ISMO.

The authors declare that they have no conflict of interests.

References

1. Arboleda G, Ramı´rez N, Arboleda H (2007). The neonatal progeroid syndrome (Wiedemann- Rautenstrauch): A model for the study of human aging. *Experimental Gerontology*, 42: 939-43
2. Lithgow GJ (2001). Aging, Genetics of Academic Press.
3. Fraser HB, Khaitovich P, Plotkin JB, a¨a¨bo S, Eisen MB (2005). Aging and gene expression in the primate brain. *Plos Biol*, 3(9): e274.
4. Glatt SJ, Chayavichitsilp P, Depp C, Schork NJ, and Jeste DV (2007). Successful Aging: From Phenotype to Genotype. *Biol Psychiatry*, 62: 282-93.
5. Farhud DD, Sadighi H, Pour-Jafari H, Sheibani AM (1998). Aging coefficient in different religious groups in Iran. *Iranian J Publ Health*, 27(1-2):1-8.
6. Farhud DD, Pour-Jafari H (1999). Aging coefficient in different provinces of Iran. *Iranian J Publ Health*, 27(1-2)(Persian Articles): 13-20.
7. Hekimi S, Guarente L (2003). Genetics and the specificity of the aging process. Science, 299: 1351-54.
8. Hughes KA, Reynolds RM (2005). Evolutionary and mechanistic theories of aging. *Annu Rev Entomol*, 50: 421-45.
9. Beckman KB, Ames BN (1998). The free radical theory of aging matures. *Physiol Rev*, 78: 547-81.
10. Wei YH (1998). Oxidative stress and mitochondrial DNA mutations in human aging. *Proc Soc Exp Biol Med*, 217: 53-63
11. Ozawa T (1997). Genetic and functional changes in mitochondria associated with aging. *Physiol Rev*, 77: 425-64.
12. Puca AA, Chatgilialoglu C, Ferreri C (2007). Lipid metabolism and diet: Possible mechanisms of slow aging. *The International Journal of Biochemistry & Cell Biology*, 04.003.
13. Berryman DE, Christiansen JS, Johannsson G, Thorner MO, Kopchick JJ (2008). Role of the GH/IGF-1 axis in lifespan and healthspan: Lessons from animal models. Growth Horm IGF Res, 05.005.
14. Mooijaart SP, Heemst DV, Schreuder J, Gerwen SV, Beekman M, Brandt BW, Slagboom PE, Westendorp RG.J (2004). Variation in the SHC1 gene and longevity in humans. *Experimental Gerontology*, 39: 263-26.

15. Ventura A, Luzi L, Pacini S, Baldari CT, Pelicci PG (2002). The p66^{shc} longevity gene is silenced through epigenetic modifications of an alternative promoter. *J Biol Chem*. 277: 22370-376.
16. Purdom S, Chen Q M (2003). p66^{shc}: at the crossroad of oxidative stress and the genetics of aging. *Trends Mol Med*, 9(5): 206-210.
17. Jackson JG, Yoneda T, Clark GM, Yee D (2000). Elevated levels of p66^{shc} are found in breast cancer cell lines and primary tumors with high metastatic potential. *Clin Cancer Res*, 6(3): 1135-39.
18. Trinei M, Giorgio M, Cicalese A, Barozzi S, Ventura A, Migliaccio E, Milia E, Padura IM, Raker VA, Maccarana M, Petronilli V, Minucci S, Bernardi P, Lanfrancone L, Pelicci PG (2002). A P53-p66^{shc} signalling pathway controls intracellular redox status. Levels of oxidation-damaged dna and oxidative stress-induced apoptosis. *Oncogene*, 21(24): 3872- 78.
19. Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, et al. (2002). P53 mutant mice that display early ageing-associated phenotypes. *Nature*, 415 (6867): 45-53.
20. Ishii N, Ishii T, Hartman PS (2006). The role of the electron transport gene SDHC on lifespan and cancer. *Experimental Gerontology*, 06.037.
21. Wei YH, Lu CY, Wei CY, Ma YSH Lee HCH (2001). Oxidative Stress in Human Aging and Mitochondrial Disease-Consequences of Defective Mitochondrial Respiration and Impaired Antioxidant Enzyme System. *Chinese Journal of Physiology*, 44(1): 1-11.
22. Oberley LW, Oberley TD (1988). Role of antioxidant enzymes in cell immortalization and transformation. *Mol Cell Biochem*, 84: 147-53.
23. Lenaz G, D'Aurelio M, Pich MM, Genova ML, Ventura B, Bovina C, Formiggini G, Castelli GP (2000). Mitochondrial bioenergetics in aging. *Biochim Biophys Acta*, 1459: 397-404.
24. Kopsidas G, Kovalenko SA, Kelso JM, Linnane AW (1998). An age-associated correlation between cellular bioenergy decline and mtDNA rearrangements in human skeletal muscle. *Mutat Res*, 421: 27-36.
25. Papa S (1996). Mitochondrial oxidative phosphorylation changes in the life span: Molecular aspects and physiopathological implications. *Biochim Biophys Acta*, 1276: 87-105.
26. Müller-Höcker J (1989). Cytochrome *c* oxidase deficient cardiomyocytes in the human heart: an age-related phenomenon. A histochemical ultracytochemical study. *Am J Pathol*, 134: 1167-73.
27. Müller-Höcker J (1990). Cytochrome *c* oxidase deficient fibers in the limb muscle and diaphragm of man without muscular disease: an agerelated alteration. *J Neurol Sci*, 100: 14-21
28. Lu CY, Lee HC, Fahn HJ, Wei YH (1999). Oxidative damage elicited by imbalance of free radical scavenging enzymes is associated with large-scale mtDNA deletions in aging human skin. *Mutat Res*, 423: 11-21.
29. Hong MG, Reynolds CH, Gatz M, Johansson B, Palmer JC, Gu HF, Blennow K, Kehoe PG, Faire UI, Pedersen NL, Prince JA (2008). Evidence that the gene encoding insulin degrading enzyme influences human lifespan. Hum Mol Genet, 17(15): 2370-78.
30. Benedictus GD, Tan Q, Jeune B, Christensen K, Ukraintseva SV, Bonafe M, Franceschi C, Vaupel JW, Yashin AI (2001). Recent advances in human gene-longevity association studies. *Mechanisms of Ageing and Developm*ent, 122: 909-920.
31. Mathers JC (2006). Nutritional modulation of ageing: genomic and epigenetic approaches. *Mech Ageing Dev*, 127(6): 584-89.