



## Physiological mechanisms involved in longer life span!

\*Karthek R. Balapala<sup>1</sup>, Madhu Thota<sup>2</sup>

<sup>1</sup>Assistant Professor in Physiology and <sup>2</sup>Tutor in Pharmacology, Maharajah's Institute of Medical Sciences, Vizianagaram, India

Received: 10-10-2016 / Revised Accepted: 20-12-2016 / Published: 01-01-2017

### ABSTRACT

Past research indicated association between social relations and longevity among humans. Decline in mitochondrial function with alterations in the nuclear chromatin are seen in old age. Ageing in animals is associated with multiple organ dysfunction, while age related degeneration formed the major factor in human ageing. Low levels of circulating methionine were noticed in naked mole-rats that lived longer, suggesting they had a natural life-extending phenotype akin to that observed among the methionine-restricted animals. Health improving interventions contributed to a better life span. Different rates of ageing are seen among humans of different families and those with exceptional survival give prospective to comprehend why some people age at a slow rate than others. Objective of this review is to identify the key factors that promote longevity.

**Keywords:** Longevity; Molecular genetics, Nutrition; Reactive oxygen species



### INTRODUCTION

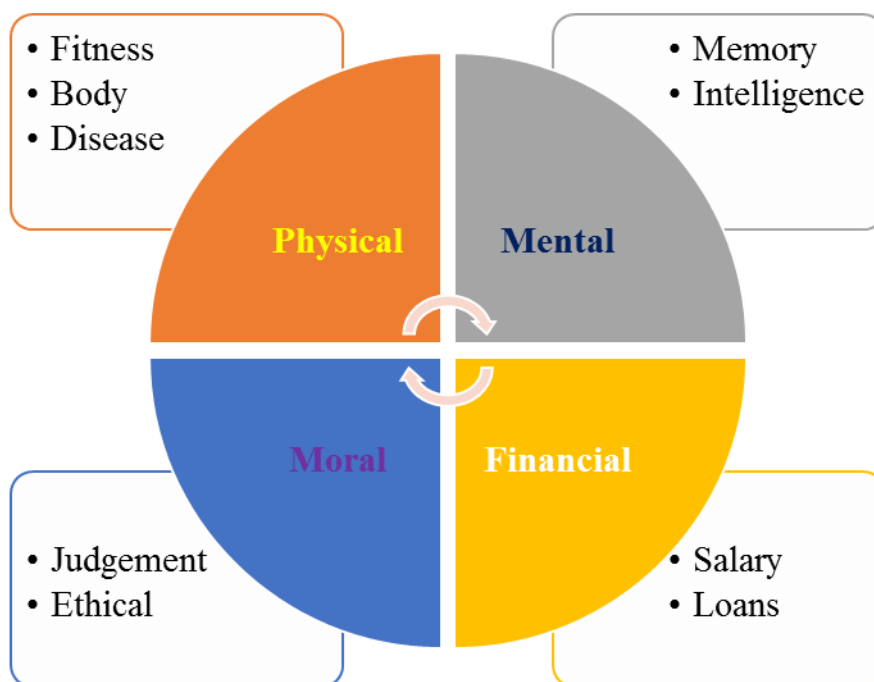
Higher levels of linguistic agency envisaged greater life-span in prominent physicists, historians, American presidents and psychologists. These results did not characterize to varying degrees of positive emotion, negative emotion, or social interaction, quantified in terms of other linguistic categories <sup>(1)</sup>. Genetic variation in connective tissue growth factor gene (CTGF) and epidermal growth factor receptor gene (EGFR) contributed to the fruition of higher old age in Japanese. Excess of heterozygotes were noted among the longevity cases, consistent with heterozygote advantage in living to extreme old age <sup>(2)</sup>. Dietary restriction (DR) extended life span and reduced reproduction among animals, as per the disposable soma hypothesis, suggesting that longevity was a result of reduced investment in reproduction and increased nutrient allocation to the soma, granting an increase in cellular maintenance. The study done by Heck MJ, Pehlivanovic M et al., 2016., revealed that DR did not alter nutrient allocation instead attenuated protein oxidation, an observation inconsistent with that of the basic predictions of disposable soma hypothesis <sup>(3)</sup>. *Cytorace-9* flies lived longer than those of *Cytorace-3*, when pathogenic infections were absent. Nevertheless, when these *Cytoraces* were confronted with

different pathogenic microbes, the trend was reverse. Long-lived *Cytorace-9* survived worse than the short lived *Cytorace-3* after infection with pathogens that was attributed to a reduction in its immune response <sup>(4)</sup>.

Study done among Chinese and Japanese done by Tanisawa K, Arai Y et al., identified CLEC3B p.S106G as a novel longevity-associated variant, pushing up the novel hypothesis that tetranectin, encoded by CLEC3B, had a critical role in human longevity and aging <sup>(5)</sup>. In vivo SkQ1 alleviated the negative effects of raised mitochondrial reactive oxygen species production on longevity. Was not effective when reactive oxygen species production was reduced before by other means <sup>(6)</sup>. Dietary restriction (DR), involving moderate attenuation in food intake, perked up the aging health thus extending the life span in various species. Specific nutrients, but not the total calories, intervened the effects of DR, among which the key role was played by protein and specific amino acids (AAs). Modulation of specific dietary AAs influenced traits such as growth, reproduction, physiology, longevity and health among animals <sup>(7)</sup>. NAD(+) precursor nicotinamide riboside NR delayed the senescence of neural stem cells SCs and melanocyte SCs thus prolonging the life span of mice. The study suggests that strategies that

conserve cellular NAD(+) reprogrammed the dysfunctional SCs in mammals that alleviate life span<sup>(8)</sup>. Some sensory neurons caused attenuation of life span in *Caenorhabditis elegans* by differential regulation of the expression of a

specific insulin-like peptide (ILP), INS-6. Also, treatment with food-derived cues and optogenetic activation of sensory neurons, alleviated the ins-6 expression thus decreasing life span<sup>(9)</sup>.



**Fig 1: Factors of well being and longevity**

Chronological life span (CLS) extension depended on initial concentrations of ammonium and glucose in growth medium, while the other nutrients were not limiting. Glutamine, induced CLS shortening similar to ammonium, even though this effect was not seen with low nitrogen source urea. Ammonium reduced yeast CLS independently of the metabolic process activated during aging, either respiration or fermentation. Ammonium also induced replication stress inhibiting a proper cell cycle arrest in G0/G1 phase<sup>(10)</sup>. Mark-recapturing with genetic sampling extended the longevity of an elasmobranch species with the increase in life span estimate of the lemon shark *Negaprion brevirostris*. This means higher vulnerability and a longer recovery time due to exploitation<sup>(11)</sup>. Modulation of the methionine metabolic network increased the life span-from yeast to humans. The study done by McIsaac RS1, Lewis KN et al., 2016., revealed that sulfur amino acids and the concomitant transsulfuration pathway had a privileged role<sup>(12)</sup>. Level of hepatic phosphorylated endoplasmic reticulum associated stress markers eIF2 $\alpha$  and IRE1 $\alpha$  were inversely related to serum ascorbate and life span. Study suggests that vitamin C modulated longevity and endoplasmic reticulum stress response in *Gulo*-/- mice<sup>(13)</sup>. Study that explored the mechanism of captopril, also analyzed

the *acn-1* gene that encodes the *C. elegans* homolog of ACE. Reduction in the activity of *acn-1* increased the mean life span. Reducing the activity of *acn-1* also delayed the age-related degenerative changes and increased stress resistance, suggesting that *acn-1* influenced aging. Captopril did not extend further the lifespan of animals with reduced *acn-1*<sup>(14)</sup>. Choosing diverse survival values as end points had a tremendous influence on the estimated contributions of rectangularization and life span extension to the raise in life expectancy in a study done by Schalkwijk FH, Koopman JJ et al., 2016<sup>(15)</sup>.

#### ROLE OF BIOCHEMICALS IN AGING

Less knowledge and research has been done to analyse how metabolic activity and epigenetic modifications change as organisms reach midlife. Decrease in activity of the acetyl-CoA-synthesizing enzyme ATP citrate lyase (ATPCL) as well as the histone H4 K12-specific acetyltransferase Chameau level, increased the observed aging-associated changes and advanced longevity in *Drosophila melanogaster*<sup>(16)</sup>. Social isolation raised the risk of inflammation by equal amounts as that of physical inactivity during adolescence. Effect of this social isolation on hypertension overwhelmed that of

clinical risk factors like diabetes in old age <sup>(17)</sup>. Review study done by Creevy KE1, Austad SN et al., 2016., discussed the age-specific patterns of morbidity and mortality in companion dogs, and explored if this evidence supported the longevity dividend (LD). Companion dogs showed a high capability as a model system to facilitate in depth research on LD <sup>(18)</sup>. Cellular aging was associated with decrease in NAD+. Restoration of NAD+ reversed the phenotypes of aging by induction of cellular repair and stress resistance. Study indicates that intracellular NAD+ concentrations assured in promoting longevity. Low cellular NAD+ concentration had a negative effect on life span <sup>(19)</sup>. Calorie restriction (CR) up-regulated daily expression of Bmal1 and its downstream target genes Periods. The study revealed BMAL1 as an important mediator of CR. Thus the activation of BMAL1 can associate CR mechanisms with biologic clocks <sup>(20)</sup>.

No increase in life span of F344 rats occurred with the level of dietary restriction (DR). Low level of DR affected the life span. Rodent study done by Richardson A1,2, Austad SN et al., 2016., gave implications suggesting that a modest reduction in calories would show health benefits in humans <sup>(21)</sup>. Extension of life-span due to reduced vitellogenesis and enhanced lysosomal lipolysis needed nuclear hormone receptors (NHRs) NHR-49 and NHR-80. This suggested some novel roles for these NHRs in lysosomal lipid signaling. Dietary-restricted worms and mice showed a decrease in the expression of VIT (vitellogenin) and hepatic APOB (apolipoprotein B), respectively, indicating a conserved longevity mechanism <sup>(22)</sup>. Limitation of specific amino acid, methionine imitated the effects of DR with extension of life span among experimental organisms. Beneficial effect of methionine-restricted diet, the molecular pathways involved in longevity promoting interventions was revealed <sup>(23)</sup>.



**Fig 2: Factors of premature ageing**

Growth hormone signaling attenuation increased life span among lab mice. Decrease in dietary intake of methionine, resulted in life-span extension among rats and mice. Comparison of two interventions was done in the study done by Brown-Borg HM., 2016 <sup>(24)</sup>. Gene sequencing resulted in breakthrough of functional gene variants that sustained many centenarian phenotypes. Such studies laid road to the developments of strategic drugs to delay aging and prolonging longer health span <sup>(25)</sup>.

**CAENORHABDITIS REMANEI AND BIOMOLECULES OF AGING**

Flavin-containing monooxygenase enzymes (FMOs) were found conserved in eukaryotes and induced by multiple life span-extending interventions among mice. Study indicates that these enzymes had a critical role to supporting longevity and health among diverse phyla like *Caenorhabditis elegans* <sup>(26)</sup>. Folic acid (FA) inhibited mechanistic target of rapamycin (mTOR) and insulin as well as insulin growth factor 1 (IGF-1) signaling pathways that control oxidative stress levels and life span. The expression levels of stress-

and life span-relevant gerontogenes and oxidative enzymes like superoxide dismutase 3 (SOD-3) and glutathione S-transferase 4 (GST-4), were enhanced to decrease the intracellular reactive oxygen species (ROS) damage, thus delaying the aging process<sup>(27)</sup>. Rapamycin induced a longer life span and smaller size in males, but individual fitness was not affected. In female nematode *Caenorhabditis remanei*, size and fitness were negatively affected with increased life span only with higher concentrations of rapamycin. Study results revealed that rapamycin affected key life-history traits in a sex-specific manner<sup>(28)</sup>. A novel phytomolecule Acacetin 7-O- $\alpha$ -l-rhamnopyranosyl (1-2)  $\beta$ -D-xylopyranoside (ARX) effect was tested on worms with mutations. Study showed that ARX-mediated life-span extension involved mechanisms linked with DR and maintenance of cellular redox homeostasis. Study reported on longevity-promoting activity of ARX in *C. elegans* mediated by DR-regulating genes and stress<sup>(29)</sup>.

Male gender showed positive effect on survival of adult male relatives (fathers and brothers) but not female blood relatives of centenarians in United States. Lower life span was noted in centenarian siblings-in-law than the life span of centenarian siblings and did not related to centenarian gender. Wives of male centenarians (who share lifestyle and living conditions) had better survival than the wives of centenarians' brothers<sup>(30)</sup>. Longer life span made the evolution of cooperation more possible, such that promiscuous cooperative species had lived longer. The study results indicate the importance of promiscuity in cooperative breeders and elucidate the pivotal role of life-history traits in the evolution of cooperative breeding. Hence cooperation can evolve through a blend of indirect and direct fitness benefits<sup>(31)</sup>. Bioactive dietary components exercised their effect through selective inflammatory pathways thus impinging on genetic and metabolic changes. Hence, dietary components that modulate glucose and insulin levels, including any other mediator that activate nuclear factor- $\kappa$ B, could trigger also inflammation through common pathway master switches<sup>(32)</sup>. No association was found between longevity and THO1 and CSFIPO loci. Instead association between longevity and autosomal short tandem repeats (STR) markers D12S391, D22S1045, and DS441 was noticed in the study done by Bediaga NG1, Aznar JM et al., 2015. 6 out of the 21 STRs studied displayed different allelic frequencies. Hence the genomic portrait of the human longevity is indeed complex and might be shaped by numerous genomic loci<sup>(33)</sup>. No tendency to die early was seen in those first serving at an earlier age or those serving first at a later age to die later than expected among the tested 430 men who were elected to serve in the House of Representatives for the 71st U.S. Congress in 1929-

1930 who alive during 1930. Study done by McCann SJ., 2015., indicated that developmental aspects of the concomitants, prerequisites, and consequences of early career achievement peaks vigorously augmented the conditions for an earlier demise<sup>(34)</sup>.

## ECOLOGICAL FACTORS

Genetic diversity metrics played a critical role in restoring and mitigating the seagrass *Posidonia oceanica* along the coastal marine systems. But the exceptional longevity of individuals made temporal mismatch that suggested incorrectly a good meadow health status, when gradual deterioration of allelic diversity went unnoticed in the study<sup>(35)</sup>. Larger moth species showed longer life span, thus sustaining a physiological rather than ecological explanation of such relationship. Traits of reproductive season and larval diet breadth, could not explain the species-specific lifespan values. Hence strengthening the the dominance of physiological determinants of longevity greater than ecological ones<sup>(36)</sup>. Specific nutrients like amino acids and interactions among balanced nutrients played a critical role in aging biology. Study done by Raubenheimer D, Simpson SJ et al., 2016., indicated how a method of Geometric Framework for nutrition, aided in understanding the nutritional interactions of animals with their environments in nutritional ecology. This was possible by clearly distinguishing the roles of calories, nutrient balance and individual nutrients<sup>(37)</sup>. Mortality pattern in reptile tyrannosaurs were found analogous to the humans of 18th-century. The study results indicate that tyrannosaurs might live longer years to undergo aging before maximum lifespan achieved. Their longevity strategy seemed to be more alike to the big birds rather than 18th-century humans<sup>(38)</sup>. A 14-year field study done on wild Damaraland mole rats, *Fukomys damarensis* indicated that workers had a strong but unusual effect on lifespan in offspring. Animal groups with larger workforces displayed higher rates of offspring recruitment but maintaining high juvenile survival rates. Relationships might have favored the evolution of the delayed dispersal, cooperation, morphological specialization, and the patterns of unusual longevity characterizing these societies. On the other hand, the offspring reared by larger workforces also showed slower growth rate<sup>(39)</sup>. Study done with greenhouse population revealed that a short-term metal exposure of gravid females negatively affected the life history variables among their off springs. This influenced the population dynamics among life-bearing fish species. Both factors of maternal copper exposure and maternal cadmium exposure caused fewer broods and longer gestation time period. There were not any changes

in brood size, inter-brood interval, life span or time-to-sexual-maturity<sup>(40)</sup>.

## CONCLUSION

CTGF and EGFR genetic variations accorded to the attainment of greater old age among Japanese. Tetranectin, encoded by CLEC3B, showed a critical function in human aging and longevity. Occurrence of neurodegenerative and age related diseases among humans depended on the metabolic responses. Molecular approaches that conserve cellular NAD(+) might reprogram the

dysfunctional SCs, thus alleviating the total life span in mammals. Social isolation heightened the risk of inflammation by equal amounts as that of physical inactivity during adolescence. Effect of social isolation was more severe than that of any clinical risk factors on hypertension. The homeostatic responses used by the animals during variations in the nutritional environment and their consequences such as lifespan and reproduction, provide researchers an understanding of evolutionary processes in a multi-dimensional nutritional environmental context.

## REFERENCE

1. Robinson MD, Bair JL, Persich MR and Moen NR. "Linguistic Agency and Life-Span Longevity". *Psychosom Med.* 2016 Apr 29.
2. Donlon TA, Morris BJ et al. "Association of Polymorphisms in Connective Tissue Growth Factor and Epidermal Growth Factor Receptor Genes With Human Longevity." *J Gerontol A Biol Sci Med Sci.* 2016 Jun 30. pii: glw116.
3. Heck MJ, Pehlivanovic M et al. "Life-extending Dietary Restriction Reduces Oxidative Damage of Proteins in Grasshoppers but Does Not Alter Allocation of Ingested Nitrogen to Somatic Tissues". *J Gerontol A Biol Sci Med Sci.* 2016 Jun 15. pii: glw094.
4. Sinam YM, Chatterjee A et al. "A newly evolved *Drosophila* Cytocrome-9 shows trade-off between longevity and immune response". *Infect Genet Evol.* 2016 Jun 13;44:1-7.
5. Tanisawa K, Arai Y et al. "Exome-wide Association Study Identifies CLEC3B Missense Variant p.S106G as Being Associated With Extreme Longevity in East Asian Populations". *J Gerontol A Biol Sci Med Sci.* 2016 May 6. pii: glw074.
6. Tsybul'ko E, Kremontsova A et al. "The Mitochondria-Targeted Plastoquinone-Derivative SkQ1 Promotes Health and Increases *Drosophila melanogaster* Longevity in Various Environments". *J Gerontol A Biol Sci Med Sci.* 2016 May 10. pii: glw084.
7. Soultoukis GA and Partridge L. "Dietary Protein, Metabolism, and Aging". *Annu Rev Biochem.* 2016 Jun 2;Vol. 85. pp.5-34.
8. Zhang H, Ryu D et al. "NAD<sup>+</sup> repletion improves mitochondrial and stem cell function and enhances life span in mice". *Science.* 2016 Jun 17. Vol. 352. Iss.6292. pp.1436-43.
9. Artan M, Jeong DE et al. "Food-derived sensory cues modulate longevity via distinct neuroendocrine insulin-like peptides". *Genes Dev.* 2016 May 1. Vol. 30 Iss.9. pp.1047-57.
10. Santos J, Leitão-Correia F, Sousa MJ and Leão C. "Nitrogen and carbon source balance determines longevity, independently of fermentative or respiratory metabolism in the yeast *Saccharomyces cerevisiae*". *Oncotarget.* 2016 Apr 26. Vol. 7. Iss.17. pp. 23033-42.
11. Brooks JL, Guttridge TL et al. "Using genetic inference to re-evaluate the minimum longevity of the lemon shark *Negaprion brevirostris*". *J Fish Biol.* 2016 May. Vol. 88. Iss. 5. pp. 2067-74.
12. McIsaac RS, Lewis KN et al. "From yeast to human: exploring the comparative biology of methionine restriction in extending eukaryotic life span". *Ann N Y Acad Sci.* 2016 Jan. Iss. 1363. pp. 155-70.
13. Aumailley L, Warren A et al. "Vitamin C modulates the metabolic and cytokine profiles, alleviates hepatic endoplasmic reticulum stress, and increases the life span of *Gulo*<sup>-/-</sup> mice". *Aging (Albany NY).* 2016 Mar. Vol. 8. Iss.3. pp. 458-83.
14. Kumar S, Dietrich N and Kornfeld K. "Angiotensin Converting Enzyme (ACE) Inhibitor Extends *Caenorhabditis elegans* Life Span". *PLoS Genet.* 2016 Feb 26. Vol. 12. Iss. 2:e1005866.
15. Schalkwijk FH, Koopman JJ et al. "Disentangling rectangularization and life span extension with the moving rectangle method". *Ann Epidemiol.* 2016 Mar. Vol. 26. Iss. 3. pp. 218-21.e2.
16. Peleg S, Feller C et al. "Life span extension by targeting a link between metabolism and histone acetylation in *Drosophila*". *EMBO Rep.* 2016 Mar. Vol. 17. Iss. 3. pp. 455-69.
17. Yang YC, Boen C et al. "Social relationships and physiological determinants of longevity across the human life span". *Proc Natl Acad Sci U S A.* 2016 Jan 19. Vol. 113. Iss. 3. pp. 578-83.: 10.1073/pnas.1511085112. Epub 2016 Jan 4.
18. Creevy KE, Austad SN et al. "The Companion Dog as a Model for the Longevity Dividend". *Cold Spring Harb Perspect Med.* 2016 Jan 4. Vol. 6. Iss. 1. a026633.
19. Poljsak B and Milisav I. "NAD<sup>+</sup> as the Link Between Oxidative Stress, Inflammation, Caloric Restriction, Exercise, DNA Repair, Longevity, and Health Span". *Rejuvenation Res.* 2016 Mar 16.

20. Patel SA, Chaudhari A et al. "Circadian clocks govern calorie restriction-mediated life span extension through BMAL1- and IGF-1-dependent mechanisms". *FASEB J*. 2016 Apr. Vol. 30. Iss. 4. pp. 1634-42.
21. Richardson A, Austad SN et al. "Significant life extension by ten percent dietary restriction". *Ann N Y Acad Sci*. 2016 Jan. Iss. 1363. pp. 11-7.
22. Seah NE, de Magalhaes Filho CD et al. "Autophagy-mediated longevity is modulated by lipoprotein biogenesis". *Autophagy*. 2016. Vol. 12. Iss. 2. pp. 261-72.
23. Lee BC, Kaya A and Gladyshev VN. "Methionine restriction and life-span control". *Ann N Y Acad Sci*. 2016 Jan. Iss. 1363. pp. 116-24.
24. Brown-Borg HM. "Reduced growth hormone signaling and methionine restriction: interventions that improve metabolic health and extend life span". *Ann N Y Acad Sci*. 2016 Jan. Vol. 1363. pp. 40-9.
25. Milman S, Barzilai N. "Dissecting the Mechanisms Underlying Unusually Successful Human Health Span and Life Span". *Cold Spring Harb Perspect Med*. 2015 Dec 4. Vol. 6. Iss. 1. a025098.
26. Leiser SF, Miller H et al. "Cell nonautonomous activation of flavin-containing monooxygenase promotes longevity and health span". *Science*. 2015 Dec 11. Vol. 350. Iss. 6266. pp. 1375-8.
27. Rathor L, Akhoun BA et al. "Folic acid supplementation at lower doses increases oxidative stress resistance and longevity in *Caenorhabditis elegans*". *Age (Dordr)*. 2015 Dec. Vol. 37. Iss. 6. pp. 113.
28. Lind MI, Zwoinska MK et al. "Sex-specific Tradeoffs With Growth and Fitness Following Life-span Extension by Rapamycin in an Outcrossing Nematode, *Caenorhabditis remanei*". *J Gerontol A Biol Sci Med Sci*. 2016 Jul. Vol. 71. Iss. 7. pp. 882-90.
29. Asthana J, Yadav D et al. "Acacetin 7-O- $\alpha$ -l-rhamnopyranosyl (1-2)  $\beta$ -D-xylopyranoside Elicits Life-span Extension and Stress Resistance in *Caenorhabditis elegans*". *J Gerontol A Biol Sci Med Sci*. 2015 Oct 3. pii: glv173.
30. Gavrilov LA and Gavrilova NS. "Predictors of Exceptional Longevity: Effects of Early-Life and Midlife Conditions, and Familial Longevity". *N Am Actuar J*. 2015. Vol. 19. Iss. 3. pp. 174-186.
31. Downing PA, Cornwallis CK and Griffin AS. "Sex, long life and the evolutionary transition to cooperative breeding in birds". *Proc Biol Sci*. 2015 Oct 7. Vol. 282. Iss. 1816. pp. 20151663.
32. Ricordi C, Garcia-Contreras M and Farnetti S. "Diet and Inflammation: Possible Effects on Immunity, Chronic Diseases, and Life Span". *J Am Coll Nutr*. 2015. Vol. 34 Iss. 1. pp. 10-3.
33. Bediaga NG, Aznar JM et al. "Associations between STR autosomal markers and longevity". *Age (Dordr)*. 2015 Oct. Vol. 37. Iss. 5. pp. 95.
34. McCann SJ. "Life Expectancy Can Explain the Precocity-Longevity Hypothesis Association of Early Career Success and Early Death". *J Genet Psychol*. 2015. Vol. 176. Iss. 6. pp. 414-9.
35. Jahnke M, Olsen JL and Procaccini G. "A meta-analysis reveals a positive correlation between genetic diversity metrics and environmental status in the long-lived seagrass *Posidonia oceanica*". *Mol Ecol*. 2015 May. Vol. 24. Iss. 10. pp. 2336-48.
36. Holm S, Davis RB et al. "A comparative perspective on longevity: the effect of body size dominates over ecology in moths". *J Evol Biol*. 2016 Aug 18.
37. Raubenheimer D, Simpson SJ et al. "Nutritional ecology and the evolution of aging". *Exp Gerontol*. 2016 Apr 16. pii: S0531-5565(16)30096-1.
38. Weon BM. "Tyrannosaurs as long-lived species". *Sci Rep*. 2016 Jan 21. Vol.6.19554.
39. Young AJ, Jarvis JU, Barnaville J and Bennett NC. "Workforce Effects and the Evolution of Complex Sociality in Wild Damaraland Mole Rats". *Am Nat*. 2015 Aug. Vol. 186. Iss. 2. pp. 302-11.
40. Cazan AM and Klerks PL. "Effects on life history variables and population dynamics following maternal metal exposure in the live-bearing fish *Gambusia affinis*". *Ecotoxicology*. 2015 Apr. Vol. 24. Iss. 3. pp. 626-35.