УДК 575.24:613.98+577.7

Adv. Gerontol.–2003.–Vol. 11.–P. 34–42

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HOW THE ANALYSIS OF GENETIC MUTATIONS CAN HELP US TO SOLVE BASIC PROBLEMS IN GERONTOLOGY? I. LIFE EXTENDING GENETIC MODIFICATIONS IN ROUND WORM C. elegans

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The results of recent molecular biological studies of aging and longevity confirmed substantial genetic contribution to the life span. The analysis of these findings showed substantial role of specific mutations in genes involved in regulatory processes on both the extra- and intracellular levels. We suggest that difference in responses of intact and mutant animals to the same set of environmental signals may be useful to clarify contribution of organism-environment interactions into the rate of aging, mortality and longevity of respective organisms. In our opinion such clarification is important for better understanding the origin of natural senescence and its dependence on external conditions.

Key words: aging plasticity, life-extending mutations, environmental influences.

Almost all tissues in adult organisms are continuously degraded and become rebuilt at the cellular and/or molecular level. With aging, this delicate balance becomes shifted in favor of degradation along with deceleration of protein and cell turnover. These events can render the bodies less reliable, more frail and prone to age-related morbidity and mortality — the main features of senescence. The reason of such imbalance and turnover deceleration constitutes the central question of gerontology.

The most commonly used free radical theory and telomere/telomerase hypothesis of aging are failed to explain non-pathological senescence. Telomerase activity was found in all stem-like somatic cells and age does not significantly alter the capacity for telomerase induction in such kind of somatic cells as human lymphocytes [42, 86]. Hence, the pure telomere shortening hypothesis of aging meets some difficulties and has to be modified. Moreover, recent studies have implicated reactive oxygen species (ROS) as the natural second messengers along with cAMP, Ca^{2+}, and phospholipid metabolites contributing to signal transduction from membrane receptors of extracellular signaling ligands to intracellular systems involved in gene transcription control (see reviews [25, 94]). The rate of ROS generation in cells is under strict control of several hormones, cytokines, and growth factors. Therefore uncontrolled antioxidant therapy will also inhibit essential cellular functions [47].

For these reasons up to now the following classic statement of G. Williams remains topical — «It is indeed remarkable that after the seemingly miraculous feat of morphogenesis a complex metazoan organism should be unable to perform the much simpler task of merely maintaining what is already formed» [100]. We want to call attention to a possible answer on aforementioned question by means of some theoretical approaches based on the intrinsic (genetic) and extrinsic (environmental) influences on aging and longevity.

Genetic/environmental influences on aging and longevity

The interplay of genetic makeup and environmental influences is known to be complex, with important and sometimes irreversible consequences for the development and maintenance of living beings' phenotypes. Therefore fundamental to evolutionary biology is the tendency for organisms to become increasingly adapted to those environments to which they are most commonly exposed [75, 76].

The detection and processing of environmental cues just as the adequate response to these signals are crucial for the survival of the individual. It is thus not surprising that a large number of different tissues and organs belonging to physiological systems are adjusted to the most probable range of natural environmental pressure characterizing selected ecological niche. This is because organism reacts as a whole on a set of external influences by means of certain changes in numerous regulatory systems at the physiological levels as well as via some changes in signal transduction pathways at the cellular level. Part of such changes may, in principle, modify the aging pattern according to concrete circumstances. For this reason study of natural aging process by means of observation or investigation of animals in captivity as well as human beings in highly com-

fortable conditions would be both artificial and potentially misleading [20, 33].

Recent findings emphasize the importance of signaling in the regulation of life history traits. This opens an opportunity to modulate organisms' aging and life span without changing environmental conditions towards more adequate ones in laboratory experiments. Such modulation may be important in the cases when it is difficult or impossible to create experimental conditions adequate to minimal (possibly near zero) aging rate.

In fact, modified products of properly mutated genes involved in regulatory control circuits can (in some cases) faulty transform inadequate external cues of artificial experimental conditions to the regular reaction of an organism on the quite natural environment. The latter may favor the life span extension by means of aging deceleration and/or an increase in stress resistance.

In this paper we outline around fifty such kind of genes the modified products or overexpression of which extends longevity of laboratory reared worm Caenorhabditis elegans and offer most plausible explanation of the phenomenon. In the second paper on this topic we describe life span extending mutations in budding yeast Saccharomyces cereviseae (23 genes), fruit fly Drosophila melanogaster (12 genes) and domestic mice Mus musculus (6 genes).

Pertinent modified genes of nematode

Round worm nematode Caenorhabditis elegans was a first laboratory entity with significantly extended life span due to mutation in some genes [28, 54]. The first mutated genes were *age-1* which extends life span around 70% [28], and *daf-2* which doubles life span of animals with this mutation [54]. The products of these genes belonged to the highly conserved insulin/IGF-1 signal transduction pathway. Since then there were found around half hundred genes (of roughly 600 °C. elegans genes) modifications of which reliably extend life span. These gene modifications were picked up from available publications and Internet databases such as SAGE KE and corresponded to the different control pathways. They are represented alphabetically in Table 1.

Below we briefly outline these gene modifications:

age-1 or *daf-23* (mutation) — encodes PI-3-kinase (catalytic subunit-p110) of insulin-like growth factor signal transduction pathway. Recessive allele increases life span up to 70—100% in axenic culture [2, 68, 78]. Mutant is dauer constitutive [36] displays lower low brood size and increased embryonic lethality [93]. *age-1* mutants also have elevated levels of superoxide dismutase and catalase activities [97].

Table 1

Life span extension in C. elegans via genetic modification

Involved genes	Life span extension in percents	References
1. *age-1* (mutation)	100%	[28, 68, 98]
2. *age-2* (mutation)	15–20%	[102]
3. *ceinsulin-1* (mutation)	30–40%	[52]
4. *che-2* (mutation)	50%	[6]
5. *che-3* (mutation)	50–100%	[6]
6. *che-11* (mutation)	40%	[6]
7. *che-13* (mutation)	40%	[6]
8. *clk-1* (mutation)	30%	[58]
9. *clk-2* (mutation)	12–25%	[58]
10. *clk-3* (mutation)	24–37%	[58]
11. *daf-2* (mutation)	100%	[54]
12. *daf-6* (mutation)	50%	[6]
13. *daf-9* (mutation)	52–74%	[32, 48]
14. *daf-10* (mutation)	60%	[6]
15. *daf-12* (mutation)	9,2%	[32]
16. *daf-16* (overexpression)	20%	[40]
17. *daf-19* (mutation)	50%	[6]
18. *daf-21* (mutation)	50%	[61]
19. *daf-28* (mutation)	10–15%	[66]
20. *des* (mutation)	60%	[41]
21. *eat-1* (mutation)	10–30%	[59]
22. *eat-2* (mutation)	20–30%	[59]
23. *eat-3* (mutation)	10%	[59]
24. *eat-6* (mutation)	15–40%	[59]
25. *eat-13* (mutation)	30%	[59]
26. *eat-18* (mutation)	15–60%	[59]
27. *ef-2-k* (mutation)	25–30%	[72, 81]
28. *glp-1* (mutation)	30%	[7]
29. *gro-1* (mutation)	29%	[59]
30. *hg25* (mutation)	13–17%	[103]
31. *hg96* (mutation)	26–15%	[103]
32. *hg246* (mutation)	17–29%	[103]
33. *INS* human (overexpression)	25%	[78]
34. *ins-1* (overexpression)	25%	[78]
35. *isp-1* (mutation)	60–100%	[23]
36. *mec-8* (mutation)	60%	[6]
37. *mes-16* (mutation)	60%	[7]
38. *osm-1* (mutation)	40%	[6]
39. *osm-3* (mutation)	100%	[6]
40. *osm-5* (mutation)	100–150%	[6]
41. *osm-6* (mutation)	40%	[6]
42. *pdk-1* (mutation)	60%	[74]
43. *pgl-1* (mutation)	35%	[7]
44. *rad-8* (mutation)	30%	[46]
45. *sir-2.11* (overexpression)	50%	[92]
46. *spe-10* (mutation)	20%	[22]
47. spe-26 (mutation)	60%	[69]
48. *tax-4* (mutation)	100%	[6]
49. *tkr-1* (overexpression)	40–100%	[70]
50. *unc-4* (mutation)	100%	[30]
51. *unc-13* (mutation)	150%	[30]
52. *unc-26* (mutation)	30–50%	[59]
53. *unc-31* (mutation)	70–150%	[2, 30]
54. *unc-32* (mutation)	170%	[30]
55. *unc-64* (mutation)	70–150%	[2, 30]
56. *unc-76* (mutation)	50%	[30]

age-2 (mutation) — gene function unknown. Gene has not been mapped or cloned. Mutation increases life-span by approximately 15—20% [102]. A Gompertz analysis suggests that mutation extends life span by reducing the initial mortality rate. An *age-1* age-2 double mutant strain lives longer than either single mutant and exhibits a longer life-span at 25 °C than at 20 °C. Mutant exhibits normal motility and reduced fertility [102].

ceinsulin-1 or *ins-18* (mutation) — encodes insulin-like ligand predicted to bind DAF-2 [37]. Homologue of mammalian insulin/insulin-like growth factor [52]. RNAi mutants display an increased life span of around 30—40% [52]. RNAi animals are slow growing but do not display any dauer phenotypes [52].

che-2 (mutation) — encodes so-called WD40 (or beta-transducin) repeats involved in a wide variety of important protein/protein interactions [29]. Loss of function mutants extend life span up to 50% [6]. Mutants are chemotactic defective, slightly small and defective for osmotic avoidance. Ciliated neurons have abnormal stunted ultrastructure. Mutants are dauer defective [77, 96].

che-3 (mutation) — encodes cytosolic dynein heavy chain. Required for proper structure of sensory cilia [99]. Loss of function extends life span 50-100% depending on the allele. Life span extension is suppressed by *daf-16* [6]. Mutants have defective sensory neurons [34, 77] and are defective in dye filling [77, 87]. Mutants are dauer defective [96].

che-11 (mutation) — gene not cloned. Loss of function increases life span up to 40% [6]. Mutants are dye filling defective, defective in osmotic avoidance and dauer formation, and have irregular amphid cilia [77].

che-13 or che-9 (mutation) — gene not cloned. Loss of function mutation increases life span up to 40% [6]. Mutants are dye filling defective and have severely shortened axones and ectopic assembly of ciliary structures and microtubules in many sensory neurons; mutants are defective in osmotic avoidance and dauer defective [77].

clk-1 (mutation) — encodes protein required for ubiquinone biosynthesis [50]. Has strong similarity to the human ubiquinone biosynthesis protein COQ7 / CLK-1. Loss of function mutation increases adult life span by 30%. Mutation of both *clk-1* and *daf-2* results in a nearly 5-fold (500%) increase in life span [58]. Mutations in *clk-1* are highly pleiotropic resulting in an average lengthening of embryonic development, post-embryonic development, and adult rhythmic behaviors such as defecation, swimming, and pharyngeal pumping [101]. Overexpression increases mitochondrial activity and shortens life span [26]. *clk-1* mutants require a dietary source of coenzyme Q [49].

clk-2 or *rad-5* (mutation) — encodes homologue of S. cereviseae protein TEL2. Involved in regulating telomere length [12, 62] and DNA damage response [1]. At 20 °C, development is slowed down and adult life span is extended by 12%. At 18 °C by 25% [58]. Mutant shows slow growth and rhythms similar to *clk-1*. Profound maternal and zygotic rescue. Mutation is embryonic lethal at 25 °C and results in some lethality at all temperatures [58]. Mutation of *clk-2* affects telomere length. One report states that *clk-2* mutation results in shorter telomeres [62]; however a second report contradicts this and claims that mutation of *clk-2* results in elongated telomeres while overexpression shortens telomeres [1]. Recently, CLK-2 was found to be identical to RAD-5, a DNA damage checkpoint protein.

clk-3 (mutation) — function unknown. Gene has not been cloned. At 20 °C, development is slowed down and adult life span is extended by 24%. At 18 °C — by 37% [58]. Mutant shows slow growth and rhythms similar to *clk-1*. Profound maternal and zygotic rescue [58].

daf-2 (mutation) — encodes insulin-like / IGF-1 tyrosine kinase receptor [56]. Mutation of *daf-2* increases life span more than 100% [54]. Mutation of *daf-2* in combination with a mutation of *daf-12* results in a nearly 300% increase in life span. [60]. *daf-2* mutants are dauer constitutive [80] and display reduced brood size [31, 93]. *daf-2* mutants synergize with germ line ablation for life span [44] and also show synergy with *clk-1* mutants for life span [58]. All phenotypes of *daf-2* are suppressed by mutation of *daf-16* [24, 31, 54, 60, 93]. Mutation of *daf-2* also results in increased expression of SOD-3, the Mn-superoxide dismutase [43].

daf-6 (mutation) — gene not cloned. Loss of function extends life span up to 50% [6]. Mutants are dauer defective, chemotaxis defective, osmotic aviodance (osm), males mate poorly and mutants are dye filling defective [77]. Mutants have defective sheath cells causing the amphid and phasmids pores to be closed.

daf-9 (mutation) — encodes cytochrome P450 related to vertebrate steroidogenic hydroxylases [35, 73]. Some mutations of *daf-9* increase life span to 52% [32] or even to 74% [48]. Sensory neurons, hypodermis and somatic gonadal cells expressing *daf-9* identify endocrine tissues [32]. Mutants are dauer defective, have abnormal reproductive development and molting defects [32, 48].

daf-10 (mutation) — gene not cloned. Loss of function mutation increases life span up to 60% [6]. Mutants are dauer defective, dye filling defective, octopamine deficient and have abnormal chemotaxis and osmotic avoidance. Mutants also display abnormal sensory anatomy, especially amphidial neurons and sheath cells, and cephalic neurons. Males do not mate [77].

daf-12 (mutation) — encodes nuclear hormone receptor regulated by sterols [5]. Alone, *daf-12* modestly shortens mean life span [31, 60], but slightly increases maximal life span up to 9,2% [32]. DAF-9 may be a primordial

sterol-metabolic enzyme and DAF-12 its sterol-regulated nuclear receptor partner [32]. Like *daf-9 daf-12* mutants have similar larval defects. Activity of *daf-12* is *daf-9* regulated and hormonally specified [5].

daf-16 (overexpression) — encodes Forkhead transcription factor [63]. Loss of function allele shortens life span. Some alleles have life span equal to wild type. *daf-16* is required for life span extension by mutation of *daf-2* or *age-1* [54]. Overexpression of *daf-16* modestly increases life-span (~20%) [40]. *daf-16* mutants are dauer defective [80]. Mutation of *daf-16* completely suppresses all the phenotypes of *daf-2* and *age-1* mutants, including life span extension, dauer arrest, reduced fertility, and viability defects [24, 54, 60, 93]. *daf-16* mutations suppress the long life span of the amphid neuron mutations [6]. *daf-16* mutations also suppress life span extension of animals that have a germ line ablation [44]. Sex-specific life span potential requires *daf-16* [30].

daf-19 or *daf-24* (mutation) — encodes RFX-type transcription factor [88]. Loss of function increases life span up to 50% [6]. Mutants are dauer constitutive, dye-filling defective, and lack sensory cilia [19, 80].

daf-21 or hsp90 (mutation) — encodes an heat shock protein 90 (Hsp90), a chaperone protein that stabilizes many diverse protein targets [14]. *daf-21* mutation is an unusual allele and extends life span up to 50% [61], but a null mutation is lethal [14]. *daf-21*(p673) mutants have an assortment of sensory defects and reduced fertility, but otherwise grow nicely in the laboratory. Genetic analysis has indicated that *daf-21* acts at the same step as daf-11 (encodes a transmembrane guanylyl cyclase) in the dauer formation pathway [91], and daf-11 and *daf-21*(p673) mutants have nearly identical defects in sensing odorants [96]. Furthermore, the suppression of the *daf-21*(p673) Daf-c phenotype by 8-bromo-cGMP suggests that the *daf-21*(p673) mutation, like daf-11 mutations, reduces cGMP levels.

daf-28 (mutation) — gene not cloned. Semi-dominant mutation increases life span by 10-15% [66]. *daf-28* mutant is dauer constitutive [67].

des (mutation) — encodes unidentified protein involved in execution of common necrotic process in C. elegans [41]. Both des(bs29) and des(bs30) mutants exhibit approximately 60% increase in life span [41]. A life-span extension was similar to that observed for *age-1*(hx546) mutants [28].

eat-1 (mutation) — gene not cloned. Loss of function extends life span 10-30%. Life span extension is proposed to be similar to caloric restriction [59]. Defects in pharyngeal feeding behavior [9].

eat-2 (mutation) — encodes nicotinic acetylcholine receptor subunit. Loss of function extends life span 20-30%. Life span extension is proposed to be similar to caloric restriction [59]. *eat-2* mutants can synergize with *daf-2* mutants, but not *clk-1* mutants, for life span. Life span extension by *eat-2* is not suppressed by a *daf-16* mutation [59]. Defects in pharyngeal feeding behavior [9].

eat-3 (mutation) — gene not cloned. The *eat-3*(ad426) allele extends life span by 10%. Life span extension is proposed to be similar to caloric restriction [59]. Defects in pharyngeal feeding behavior [9].

eat-6 (mutation) — gene not cloned. Mutations in *eat-6* extend life span by 15-40%. Life span extension is proposed to be similar to caloric restriction [59]. Defects in pharyngeal feeding behavior [9].

eat-13 (mutation) — not cloned. The *eat-13*(ad522) allele extends life span by 30%. Life span extension is proposed to be similar to caloric restriction [59]. Defects in pharyngeal feeding behavior [9].

eat-18 (mutation) — gene not cloned. Mutations in *eat-18* extend life span by 15-60%. Life span extension is proposed to be similar to caloric restriction [59]. Defects in pharyngeal feeding behavior [9].

ef-2-k (mutation) — encodes a new kind of protein kinase [83]. This enzyme phosphorylates and inactivates eucaryotic translational elongation factor-2 (eEF-2), inhibiting synthesis of all proteins [82, 83]. Disruption of *ef-2-k* significantly increases rates of overall protein synthesis and degradation in nematodes [72, 81]. It was found (in collaboration with N. Tavernakis and M. Driscoll) that C. elegans lacking eEF-2 kinase have significantly (25—30%) increased both median and maximal life span [72, 81]. Conversely, over-expression of *ef-2-k* in worms shortens life span [72, 81]. These results provide the first direct evidence that an increase in protein turnover can retard aging and extend life span. Strikingly, eEF-2 kinase activity is decreased in starved nematodes, suggesting that up-regulation of protein synthesis via decreased eEF-2 kinase activity can contribute to the extension of life span by dietary restriction [72, 81].

glp-1 (mutation) — encodes receptor for a germ line-proliferation signal that is produced by the distal tip cells of the somatic gonad [39, 55, 89]. *glp-1*(qu158) animals are defective in germ line proliferation and have a life-span that is extended about 30% relative to wild-type animals [7]. This life span extension requires *daf-16*. Two alleles of *glp-1* that cause over-proliferation of germ line cells, *glp-1*(oz112gf) and *glp-1*(q485), result in a shortened life-span [7]. In *glp-1* mutants, Z2 and Z3 generate only a few germ cells, which enter meiosis and differentiate as sperm [8].

gro-1 (mutation) — gene not cloned. Loss of function extends life span at 18 °C by 29% and slows growth [58]. Post-embryonic growth rate greatly reduced. Mutant has increased resistance to heat-shock and tends to avoid bacterial lawn [58].

hg25 (mutation) — unknown gene from the heat-shock-resistant mutant strain HG25 [103]. The median life span of HG25 was 13% longer than that of the wild-

type strain N2 (P<0,025). The maximum life span of HG25 was 17% longer than that of the wild-type strain N2 [103]. Mutant has a normal appearance with normal locomotive, feeding and mating behavior and a same fertility [103].

hg96 (mutation) — unknown gene from the heat-shock-resistant mutant strain HG96 [103]. The median life span of HG96 was 26% longer and the maximum life span of HG96 was 15% longer than that of control [103]. Mutant has a normal appearance with normal locomotive, feeding and mating behavior but exhibits lower fertility than the wild-type [103].

hg246 (mutation) — unknown gene from the heat-shock-resistant mutant strain HG246 [103]. The median life span of HG96 was 17% longer and the maximum life span of HG96 was 29% longer than that of control [103]. Mutant has a normal appearance with normal feeding behavior but develops more slowly and exhibits lower fertility than the wild-type [103].

INS or Human Insulin (transgene overexpression) — this transgene encodes human insulin. Expression of human insulin under an inducible heat shock promoter increases worm life span by 25% [78] Can also enhance the life span extension of a *daf-2* mutant [78].

ins-1 (overexpression) — encodes insulin-like protein [78]. Increased dosage of *ins-1* under its own promoter as well as a heat shock promoter increases life span by 25% [78]. Can also enhance the life span extension of a *daf-2* mutant [78]. Overexpression of *ins-1* also causes an increase in dauer formation [78]. Can also enhance dauer formation of a *daf-2* mutant [78].

isp-1 (mutation) — encodes iron-sulfur protein of mitochondrial complex III. Mutation of *isp-1* results in reduced oxygen consumption and increased resistance to oxidative stress. This mutation leads to 60% increase in mean life-span and 100% increase in maximum life-span. An *isp-1 daf-2* double mutant has a life-span that is longer than either single mutant, but the life span extension of the double mutant is not additive relative to each single mutant [27].

mec-8 (mutation) — encodes RNA-binding protein splicing factor. Regulates alternative splicing of *unc-52* [65]. Recessive loss of function allele extends life span by 60% [6]. Mechanosensory defective. Defective dye filling of sensory neurons [64].

mes-16 (mutation) — encodes protein required for early asymmetric divisions of the germ line [13]. *mes-1(bn7)* animals that lack germ cells have a life-span that is extended by approximately 60% compared to mes-1(bn7) animals that are fertile [7]. This life-span extension requires *daf-16*. Homozygous mes-1 mutant progeny from homozygous mutant mothers are sterile [17].

osm-1 (mutation) — sequence not available. Loss of function mutation increases life span up to 40% [6]. Mutants are defective in chemotaxis, dye filling and dauer formation. Mutants also have short axonemes and ectopic assembly of ciliary structures and microtubules in many sensory neurons [77].

osm-3 (mutation) — encodes kinesin motor domain. Required for dauer formation [96], and mediates osmotic avoidance and chemotaxis [89]. Recessive loss of function alleles can extend life span. Life span extension suppressed by gonad ablation but not germ line ablation [6]. Mutants do not form dauers in response to starvation [96]. Mutants have defective cilia [96] and are defective in chemosensory response and chemotaxis [89].

osm-5 (recessive) — encodes member of the TPR family. Required for dauer formation and recovery [66, 96]. Loss of function can increase life span 100—150% [6]. In addition to being dauer defective, loss of function mutants are chemotaxis defective [11]. and dye filling defective [87]. Dauer defective phenotype is suppressed by *daf-2* [96].

osm-6 (mutation) — gene function required for dauer formation and recovery [66, 96]. Loss of function mutation increases life span up to 40% [6]. In addition to being dauer defective, loss of function mutants are chemotaxis defective [11, 21] and dye filling defective [19]. They have extremely shortened axonemes, ectopic assembly of ciliary structures and microtubules in many sensory neurons [77].

pdk-1 (mutation) — Serine/threonine kinase. Required to prevent dauer arrest [74]. Loss of function alleles extend life span by 60% [74]. Mutants are dauer constitutive and a gain of function allele can suppress *age-1* dauer constitutive phenotype [74]. Dauer constitutive phenotype of *pdk-1*(sa680) is suppressed by *daf-16* [74].

pgl-1 (mutation) — encodes component of germ line P-granules. *pgl-1*(bn101) animals that are sterile have a life-span that is approximately 35% longer than wild type animals. Fertile *pgl-1*(bn101) animals have a wild type life-span [7]. PGL-1 is required for fertility and proliferation of germ line cells [53].

rad-8 (mutation) — gene not cloned. Mutation of *rad-8* increases life span by approximately 30% [46]. *rad-8* mutants are hypersensitive to UV radiation, but not X-rays or MMS [38].

sir-2.1 (overexpression) — encodes homolog to NAD-dependent histone deacetylases from S. cerevisiae and *M. musculus* [45]. Multi-copy array extends life span by up to 50% [92]. Life span extension by multi-copy array acts in the insulin-like signaling pathway: it is suppressed by a mutation in *daf-16*, does not synergize with *daf-2* and synergizes with the TGF-b mutations for dauer formation [92]. Overexpression of yeast homolog, *Sir2p*, extends replicative life span in S. cerevisiae [51].

spe-10 (mutation) — gene not cloned. Mutation of *spe-10* results in a 20% increase in mean life span on solid

media [22]. Mutants have a temperature sensitive defect in sperm development [85]. Life span correlates with thermotolerance and UV resistance [22].

spe-26 (mutation) — encodes Kelch family (actin binding) protein. Required for normal spermatogenesis [95]. Loss of function extends life span by 60% [69]. Mutants show reduced fertility [95] and increased resistance to UV radiation and temperature [69].

tax-4 (mutation) — encodes protein which forms heteromeric cyclic nucleotide-gated channel along with Tax-2 [18]. Recessive, loss of function allele can increase life span up to 100%. Life span extension is suppressed by *daf-16* and gonad ablation [6]. Mutants are thermotaxis and chemotaxis defective [11, 57]. Mutants are slightly dauer constitutive and form dauers at 27 °C [18].

tkr-1 or *old-1* (overexpression) — encodes tyrosine kinase receptor [70]. Overexpression increases life span 40-100% [70]. Overexpression causes increased resistance to heat and UV irradiation but does not affect fertility or development [70]. Transcription of old-1 is increased in *age-1* and *daf-2* mutants [71]. old-1 is transcriptionally regulated by *daf-16* [71].

unc-4 (mutation) — encodes neuronal homeodomain transcription factor. Mutation has no significant effect on hermaphrodite life span [59]. Life span of *unc-4*(e120) males is extended relative to hermaphrodites approximately 2-fold [30]. Mutants are uncoordinated [16].

unc-13 (mutation) — encodes factor involved in synaptic transmission [79]. Mutation increases male life span approximately 150%. No effect on hermaphrodite life span [30]. Mutants are uncoordinated [16].

unc-26 (mutation) — gene not cloned. Mutations in *unc-26* extend life span by 30—50%. Life span extension is proposed to be similar to caloric restriction [59]. Mutants are uncoordinated, slow and have defects in pharyngeal pumping [9, 16].

unc-31 (mutation) — gene unknown. Homolog of vertebrate CAPS, a calcium binding protein required for exocytosis [4]. Increases hermaphrodite life span by approximately 70% and increases male life span by 150% [2, 3, 30]. Mutants are uncoordinated [16] and exhibit a dauer constitutive phenotype [2]. Mutant worms are lethargic, feed constitutively, are defective in egg-laying, and produce dauer larvae that fail to recover [9].

unc-32 (mutation) — encodes vesicular ATPase alpha subunit. Increases male life span about 170%. No effect on hermaphrodite life span [30]. Mutants are uncoordinated [16].

unc-64 (mutation) — encodes syntaxin homolog that interacts with synaptobrevin [84]. Mutation increases hermaphrodite life span by approximately 70% and increases male life span by 150% [2, 3, 30]. Mutants are uncoordinated [16] and exhibit a dauer constitutive phenotype [3].

unc-76 (mutation) — encodes FEZ family protein. Involved in axon-axon interactions. *unc-76(e911)* allele extends male life span approximately 50%. No effect on hermaphrodite life span [30]. Mutants are uncoordinated [23].

It is easy to see from the foregoing sketch of mutations that the most of these genes encode products which are involved in the intracellular signal transduction pathways as well as in the extracellular parts of physiological control systems of an organism. They can accept, process and transduce environmental signals into appropriate organism-wide physiological, behavioral, morphogenetic, reproductive and other system responses. Besides some of these genes are directly involved in regulation of defense mechanisms. For example, antioxidant enzyme activities are under strict hormonal control [15], which in turn highly depend on external influences.

Conclusion

The outline of above life-extending gene modifications in model animals led us to the most plausible conclusion that these long-lived laboratory mutants partially resemble many features of genetically normal animals made long-lived by means of positive environmental influences. It may be so due to 'useful' distortion in the signal pathways of mutants living in favorite and artificial laboratory conditions. These conditions usually lead to accelerated aging and deadaptation of living beings.

The studies of such genetic modifications are important as they provide a unique view on the mechanisms of life span determination. They may also shed light on possible range of plasticity for both the rate of aging and stress resistance — the two areas of research that are crucial in understanding of the nature of longevity and mechanisms of its modulation by external and internal factors.

Acknowledgements

We are thankful to all members of the Laboratory of Advanced Statistical Methods at the Max Planck Institute for Demographic Research (MPIDR) for valuable comments. A.V. Khalyavkin thanks James W. Vaupel for the opportunity to complete this research at the MPIDR. This work was partly supported by NIH/NIA grant PO1 AG08761.

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Успехи геронтол.–2003.–Вып. 11.–С. 34–42

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КАК АНАЛИЗ ГЕНЕТИЧЕСКИХ МУТАЦИЙ МОЖЕТ ПОМОЧЬ В РАЗРЕШЕНИИ ФУНДАМЕНТАЛЬНЫХ ПРОБЛЕМ ГЕРОНТОЛОГИИ? I. ГЕНЕТИЧЕСКИЕ МОДИФИКАЦИИ, ПРОДЛЕВАЮЩИЕ ЖИЗНЬ КРУГЛЫХ ЧЕРВЕЙ C. elegans

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Результаты последних молекулярно-биологических исследований старения и долголетия подтвердили значительность генетического вклада в продолжительность жизни. Анализ имеющихся данных выявил существенную роль особых мутаций генов, продукты которых вовлечены в процессы регуляции как на внеклеточном, так и на внутриклеточном уровнях. Мы предположили, что разница в реакциях интактных и мутантных животных на сходные совокупности сигналов окружающей среды может быть полезна для прояснения вклада взаимодействий организм–среда в особенности старения, смертности и долголетия соответствующих организмов. По нашему мнению, подобное прояснение важно для лучшего понимания происхождения естественного старения и его зависимости от внешних условий.

Ключевые слова: пластичность старения, продлевающие жизнь мутации, влияние окружающей среды.