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Genetics and epigenetics of aging and longevity

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Evolutionary theories of aging predict the existence of certain genes that provide selective advantage early in life with adverse effect on lifespan later in life (antagonistic pleiotropy theory) or longevity insurance genes (disposable soma theory). Indeed, the study of human and animal genetics is gradually identifying new genes that increase lifespan when overexpressed or mutated: gerontogenes. Furthermore, genetic and epigenetic mechanisms are being identified that have a positive effect on longevity. The gerontogenes are classified as lifespan regulators, mediators, effectors, housekeeping genes, genes involved in mitochondrial function, and genes regulating cellular senescence and apoptosis. In this review we demonstrate that the majority of the genes as well as genetic and epigenetic mechanisms that are involved in regulation of longevity are highly interconnected and related to stress response.

Introduction

During aging, vital bodily functions such as regeneration and reproduction slowly decline. As a result, the organism loses its ability to maintain homeostasis and becomes more susceptible to stress, diseases, and injuries. A loss of essential body functions leads to age-associated pathologies, which ultimately cause death.

Traditionally, there have been many theories of aging, proposing underlying mechanisms of how aging evolved. The major evolutionary theories of aging are the theory of programmed death,[1-3] the mutation accumulation theory of aging,[4,5] the antagonistic pleiotropic theory of aging,[6] and the evolutionary maintenance (see ref. 7 for a review). Weisman initiated the theoretical approach to the evolution of aging, arguing that natural selection inheritably "programs" death to limit individual lifespan and to clear space for new generations. His view was challenged by Haldane, Medawar, and Williams, who proposed that aging is more stochastic then programmed, because the forces of natural selection diminish with adult age, most rapidly after the peak of reproduction. Hamilton published theoretical work in 1966, deriving a mathematical equation that later became known as "Hamilton's forces of natural selection" and showing that forces of natural selection indeed decline with age, which was later confirmed experimentally using *Drosophila* (see ref. 8 and references therein for a review). The mutation accumulation theory of aging postulates that the mechanism of aging evolved through the evolutionary accumulation of germinal mutations with small harmful effects, which do not appear until old age, and thus avoid the negative pressure of natural selection.[4,5] The first theory that proposed gerontogenes was the theory of antagonistic pleiotropy.[6] Williams postulated positive evolutionary selection of genes that have favorable effects in early life stages but adverse effects in late life (after reaching reproductive success). Indeed, now we know that mutations in many genes important for growth and development (e.g., PI3K, mTOR, see below) can prolong life of model organisms (yeasts, nematodes, flies, and mice). Disposable soma theory, a special case of the theory of antagonistic pleiotropy,[9] predicts the existence of genes that control the redistribution of energy resources from body maintenance to growth and reproduction. According to this theory, repair of cellular damage requires energy, competing for energy needs with reproduction. Therefore, in favor to the growth and development conditions of existence, longevity-assurance genes reduce their activity or are temporarily turned off, and aging speed increases. As predicted by this theory, longevity assurance genes exist, as confirmed by experimental overexpression of some antioxidant, DNA-, protein-, and cellular-repair genes, which prolong the lifespan of model animals (fruit flies and mice).

Identification of dozens of genes with mutations that prolong life supports another evolutionary theory, "longevity program" theory.[10-14] The longevity program could have arisen in the evolution so the organisms can survive in conditions of short-term extreme environmental stress (overheating, overcooling, overpopulation, reducing caloric intake). Under stress, the program allows the body to exceed its normal lifespan by entering "maintenance mode". This is associated with such modifications as increased stress resistance, downregulation of the biosynthesis of structural proteins, suspension of growth, and reproduction. Indeed, the survival rate of offspring in circumstances of short-term adverse changes in the environment will be minimal, so it is to evolutionary advantage to reallocate resources to extended longevity of adults, which can start breeding after the

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improvement of the environmental conditions. For example, *C. elegans* is showing that genetic program by actively promoting longevity of adults at cold temperatures.[15] Artificially induced pro-longevity mutations affect this program, so that individuals go into stress-resistant mode independently of the exogenous conditions. As we shall see, the analysis of large amount of experimental data shows that most of the molecular pathways of longevity are associated with increased stress tolerance.

According to accumulation of the errors theory, aging has been viewed as a mechanical exhaustion and accumulation of errors. This model suggests that accidental errors and stress caused by environmental factors result in metabolic abnormalities, increase in free radical production and macromolecular damage at both cellular and tissue levels (**Fig. 1**).

At the same time, it is known that moderate stress could have beneficial effects stimulating innate defense resources of the body, thereby boosting its ability to cope with higher stress levels and slowing down aging.[16,17] This is the so-called lifespan hormesis effect.[18,19] For instance, in our experiments, we observed the role of DNA repair genes and heat shock protein genes in radiation hormesis in fruit flies.[20-22] Moderate stress stimulates expression of genes responsible for stress-resistance promoting prevention or elimination of genetic errors, including the novel and spontaneous ones, thereby delaying the aging process (**Fig. 2**). On the other hand, prolonged or severe stress exposure exhausts the defense mechanisms, causing drastic accumulation of errors and physiological abnormalities, accelerating the process of aging (**Fig. 2**).

Aging research has undergone dramatic expansion in recent years, with the discovery of gerontological genes, or gerontogenes, members of conserved biological pathways across species that increase lifespan when overexpressed or mutated. This discovery led to a renewed interest in understanding how aging is regulated and opened up a new field developing pharmacological treatments that can extend healthy lifespan and slow down human aging process, pioneered by Cynthia Kenyon and Linda Partridge.[23-27]

Genetics of Aging and Longevity

Identification of gerontogenes—the genes controlling aging and longevity—typically involves model organisms to screen for mutant strains whose rate of aging differs significantly from that of a control group.

The two most efficient methods for identifying new genes are: (1) loss of function: lifespan increases when the gene is inactivated; (2) gain of function: lifespan increases in a mutant with an overexpressed candidate gene.

The phenotypic characteristics that are evaluated are increase in longevity, or emergence of functional aberrations associated with aging (e.g., the dynamics in behavioral responses, elevation of cellular levels of lipofuscin, etc.). In order to accelerate these studies, stress factors can be employed, typically a heat shock or oxidative stress, because stress resistance is frequently linked with life extension.[28] Some of the genes, like LMNA, whose mutant version leads to decreased longevity, may be used to find clues for ameliorating age-related diseases.[29] However, the most valuable gerontogenes that may ultimately lead to prospective drug candidates for life extension are the genes whose overexpression or polymorphisms lead to increased longevity of the organism.

Using various model organisms, hundreds of genes whose activity was altered in long-lived mutants have been identified. The following signaling pathways are involved in regulating the aging process: insulin/IGF-1, PI3K, TOR, MAPK, AMPK, PKC, NF-κB, TGF-β, Notch and WNT. Under favorable environmental conditions, these signaling cascades control energy balance, cellular plasticity, and the mechanisms supporting homeostasis, growth, and reproduction.[30] However, under harsh conditions, the hormonal stimulation of growth is blocked, while stress-resistance proteins are activated. These pathways are evolutionary conserved from invertebrate to mammals.[31]

Lifespan regulators

The most studied pathway in the aging field is the insulin-like signaling pathway. Upon insulin-like growth factor (IGF-1) binding to its receptor, IGF-1 receptor (IGF-1R), the intracellular phosphoinositol-3-kinase (PI3K) is activated, leading to formation of the downstream intermediate phosphoinositide-3,4,5-triphosphate. The latter binds to 3-phosphoinositid-dependent kinase 1 (PDK-1), which, in turn, phosphorylates and activates the kinases Akt/PKB and SGK-1 that control regular growth processes in the cell. At the same time, the stress-resistance factors, such as FOXO transcriptional factor, are inactivated (see the ref. 28 for review).

It is known, that centenarians are more sensitive to insulin while maintaining low blood levels.[32] Insulin-like signaling activity as well as the expression level of insulin-like peptides are reduced in long-lived nematodes, mice, and humans.[33-36] Heterozygous mice and humans harboring mutation in a gene encoding receptor for IGF-1 live longer than usual.[35,37] Mutations in genes encoding for substrates of insulin receptor 1 and 2 result in the extended lifespan in *Drosophila* and mouse.[38-40] Mutations in genes encoding kinases PI3K, AKT/PKB, and PDK are associated with a prolonged life in animals.[41-43] Activity of phosphatases such as PTEN, SHIP1, and SHIP2, counteracting the function of PI3K, also promote longevity.[36] Insulin-like signaling inhibits the mechanisms of stress response regulated by FOXO transcription factor. FOXO activity, together with the activity of FOXO-dependent genes, including PEPCK, Hsps, and MnSod, results in life extension.[44,45] Another FOXO-dependent gene, GADD45, when overexpressed, leads to a prolonged lifespan and stress resistance in *Drosophila* and is also associated with a number of age-dependent pathologies in humans.[22,46,47]

Mutation in a gene encoding kidney hormone Klotho leads to a shortened life in mice, while its overexpression promotes longevity. Klotho suppresses the effect of the insulin/IGF-1 signaling pathway, reinforcing the resistance to oxidative stress at the cellular and organismal levels, thereby promoting longevity.[48]

A characteristic feature of long-lived *Drosophila* with the reduced insulin signaling activity is high lipid level.[49] Lipid metabolism is downregulated with time, leading to age-dependent diseases such as metabolic syndrome and atherosclerosis. Dyslipidemia is associated with altered activity in a number of genes. Hormones regulating lipid metabolism,

such as adiponectin,[50] leptin,[51] ghrelin,[52] and resistin[53] play an important role in age-related diseases and longevity.

Lifespan mediators

Peroxisome proliferator-activated receptors (PPARs) are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily. PPAR forms a heterodimer with its partner, the retinoic acid receptor X (RXR), which, upon ligand stimulation, binds target DNA sequences called peroxisome proliferator response element (PPRE) to induce gene transcription. PPAR ligands comprise fatty acids and their derivatives. PPARα is expressed in tissues, where a high level of mitochondrial oxidation of fatty acids is required, such as liver, kidney, heart, skeletal muscle, and in blood vessels. PPARα is activated by fatty acids, eicosanoids, 15-d prostaglandin, and oxidized fatty acids. PPARα regulates genes promoting lipid oxidation and metabolism of lipoproteins, such as main apo-lipoprotein of high density, Apo A-1. Through these activities, PPARα function antagonizes the metabolic syndrome and aging in general.[54] Pparg-2 (Nr1c3) is activated by fatty acids in an adipose tissue and is known as one of the longevity genes in mammals.[55] Pparg-2 plays central role in enhancing insulin sensitivity in the tissue, while at the same time, it stimulates adipogenesis and takes part in neoplastic processes such as intestinal cancer.

Lifespan effectors

The expression levels of lipogenesis controlling enzymes such as ATP-citrate and acetyl-CoA carbolase,[56] as well as cytosolic phospholipase A2 and phospholipase C-y1,[57,58] are reduced with age. On the contrary, overexpression of genes responsible for β-oxidation of fatty acids leads to life extension in *Drosophila melanogaster*.[59]

A characteristic feature of centenarians is the presence of large lipoprotein particles and raised level of high-density lipoproteins.[60] Gene encoding proteins involved in triglyceride transport such as apolipoprotein E4[61] and apolipoprotein D[62] are also associated with aging and longevity. It has been demonstrated in *Drosophila* that overexpression of human ApoD as well as its own homolog GLaz, lead to a longer life.[63,64]

In response to calorie restriction, the metabolic networks adjust by switching to an economy regime. Upon cellular energy deprivation, the NAD^+-dependent deacetylases such as SIRT1 and HDAC1, 3, and 4, are activated, and it was shown that elevating levels of their expression prolongs lifespan.[65] AMPK, the sensor of cellular AMP level, is another factor promoting longevity.[66] Contrary to that, TOR kinase is activated in the presence of amino acids and accelerates aging; inhibiting TOR kinase activity leads to an extended lifespan in mice.[67] Also, a knockout of RSK3/S6 protein kinase, which is activated by mTOR, resulted in long-lived mice.[68] PHA-4/FOXA transcription factor serves as a mediator of calorie restriction effects and promotes life extension in *C. elegans*.[69]

Housekeeping genes

Excessive protein biosynthesis is toxic for cells and leads to stress in endoplasmic reticulum.[70] Reduced expression of initiation factors eIF4E, eIF4G, eIF4E-BP resulted in extended lifespan in both worms and mice.[71] The activities of several systems responsible for clearing up the damaged or excessive proteins, such as proteasome 20S C2[72] and the lysosomal and autophagy systems,[73] are reduced with age. In model organisms, the overexpression of genes encoding proteins of regulatory proteasome subunit[74] and autophagy proteins[75] lead to life extension. Other enzymes involved in regulation of the lifespan are certain E3-ubiquitin ligases.[76,77] Mitochondrial proteins are the most sensitive (susceptible) to oxidative damage. Overexpressing a mitochondrial chaperone Hsp22 in *Drosophila* resulted in life extension,[78] and over-activation of mitochondrial protease LON in fungi *Podospora anserina* prolonged its lifespan.[79]

About 50% of proteins associated with aging and longevity are involved in signal transduction mechanisms.[80] For example, TGF-β signaling pathway is reduced (downregulated) in long-lived worms.[34] When muscles age, a pathological activation of Wnt signaling is observed.[81] In long-living sea urchins, Notch signaling pathway activity is increased with age.[82] The role of stress response associated with MAP kinase signaling cascade in regulating the lifespan has been recently elucidated: various small GTPases initiate MAP kinase signaling during stress and cellular aging.[83] . Overexpression of p38MAP kinase extended *Drosophila* lifespan.[84] The activity of kinases MEK1, MEK2, ERK1, and ERK2 was elevated (higher) in B-cell precursors in aged mice.[85] In *Drosophila*, elevation in the levels of stress-activated protein kinase SAPK/JNK causes life extension,[86] while GSK3 kinase inhibition leads to cellular aging.[87]

Genes involved in mitochondrial functions

Another group of genes playing an important role in aging are those regulating the free radical production. Some of these genes facilitate an extra production of free radicals. Mice lived longer when a gene, p66Shc, the mitochondrial target of p53 in response to oxidative stress, was eliminated from their genome.[88] The same effect on extending the lifespan was achieved in nematodes

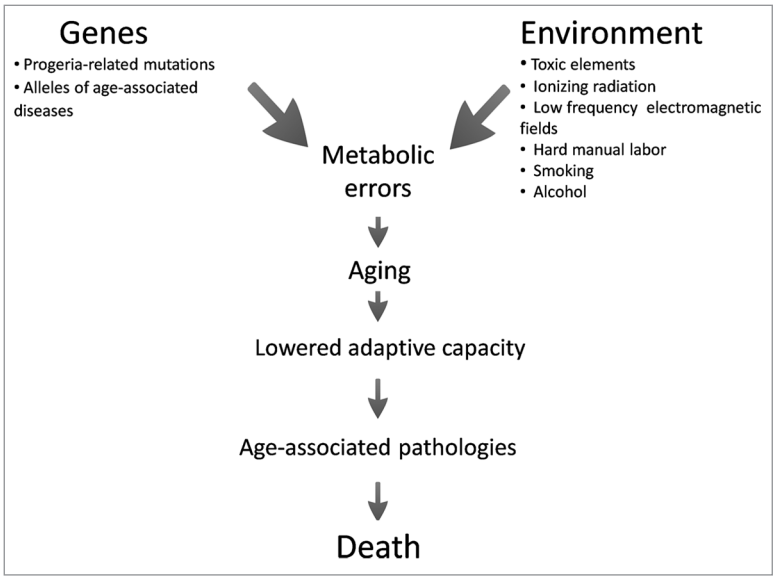

Figure 1. The effect of environmental and genetic factors on aging and the formation of age-dependent diseases.

carrying a mutation in Clk-1 gene regulating the biosynthesis of a component from electron transport chain in mitochondria and an antioxidant ubiquinone, as well as in mice heterozygous for the same gene.[89] Mitochondrial uncoupling proteins UCP-1, -2, and -3 reduce the formation of active oxygen species in mitochondria.[90] Oxidative stress sensors VDAC1 and VDAC3 play role in lifespan in different organisms.[91]

Enhanced activity in a number of proteins involved in antioxidant protection has also been proposed to promote longevity. In a course of cellular response to the oxidative stress through MAP kinase-signaling cascade, SKN-1 transcription factor is activated. SKN-1 activity is elevated in long-lived nematodes, mice, and flies.[92] When genes encoding for peroxyredoxin II (*Jafrac 1*) and peroxyredoxin 5 (*dPrx5*), which are responsible for controlling peroxide levels in a cell, were overexpressed in *Drosophila*, the flies lived longer.[93,94] Overexpression of Mn-SOD is also beneficial for life extension in flies and mice in number of cases.[95] Overexpressing Cu/Zn SOD in neurons extends life in *Drosophila*.[96] Transgenic mice carrying a copy of mitochondrial catalase have shown delayed changes in aging markers in the heart in rodents.[97]

Genes regulating cellular senescence and apoptosis

In humans, a large number of genes undergo change in their expression with aging (**Fig. 2**). Some of these genes are downregulated as growth and development slow down, while other genes become activated in the course of pro-inflammatory and stress responses, which arise due to accumulation of damage and errors at the levels of cells and tissues.

Epigenetics of Aging and Longevity

Epigenetic marks on DNA and chromosomes

One of the main reasons for change in gene expression during aging is epigenetic regulation, which includes alterations in the methylated states of regulatory DNA sequences, covalent modifications of histone proteins, and the expression of regulatory non-coding RNAs. Epigenetic theory of aging is a rapidly developing modern concept postulating that non-adaptive epigenetic alterations are fundamental to aging. It is well established that epimutations accumulate with age, leading to activation of genes normally downregulated epigenetically.[98,99] Genetically identical twins, as they age, exhibit significant differences in genome methylation pattern, leading to differences in gene expression and, ultimately, lifespan.[100,101] Variations in epigenetic markers among different cells within the same tissue of an organism are increased with age.[102] A global demethylation of DNA sequence repeats, such as mobile genetic elements, occurs with aging,[103] as well as the local hypermethylation of promoters of genes transcribed by RNA polymerase II, such as rRNA.[104,105] Senescence is accompanied by the formation of nuclear regions called senescence-associated heterochromatin foci (SAHF). These foci are determined by the recruitment of heterochromatin proteins and Rb protein to E2F-dependent promoters of proliferative genes, leading to the repression of E2F target genes.[106] During aging, the activities of methyltransferases DNMT1 and DNMT3a[107] as well as deacetylase SIRT1[108] are reduced, while the activities of histone demethylases Jmjd3[109] and Jarid1b[110] are enhanced. These changes result in non-adaptive alterations of epigenetic landscape, thereby changing gene expression and leading to aging.

Non-coding RNA

Non-coding RNAs include small RNAs, such as microRNAs and piwi-interacting RNAs, and a wide range of long non-coding RNAs (lnc RNAs).

MicroRNA

The aging process has become a potentially important target in cancer therapy after realization that cancer cells can be induce to undergo aging-type responses under stress of chemotherapeutics.[111] In a search of appropriate age-related biomarkers, the role of microRNA (miRNA) in induction, regulation, and fine-tuning of the aging process has been discovered.[112] miRNAs represent a class of small RNAs that play very important roles in various biological processes in health and in the development of human diseases through specific posttranscriptional downregulation of gene expression. One of the microRNAs, miR-34a, has been designated as an aging marker in several tissues and system. Boon et al. has shown that miR-34a is upregulated in the aging heart, and that miR-34a inhibition reduces cell death and fibrosis following acute myocardial infarction.[113] The results of Boon et al. identified miR-34a and its target PNUTS as a key mechanism that regulates cardiac contractile function during aging by inducing DNA damage responses and telomere attrition. Klotho is an anti-aging protein in mice that regulates pathways classically associated with longevity, such as insulin/IGF-1 and Wnt signaling. Protein expression of Klotho decreases in normal aging of mice. In silico analysis has identified miRNA-339 and miRNA-556 to bind to 3′

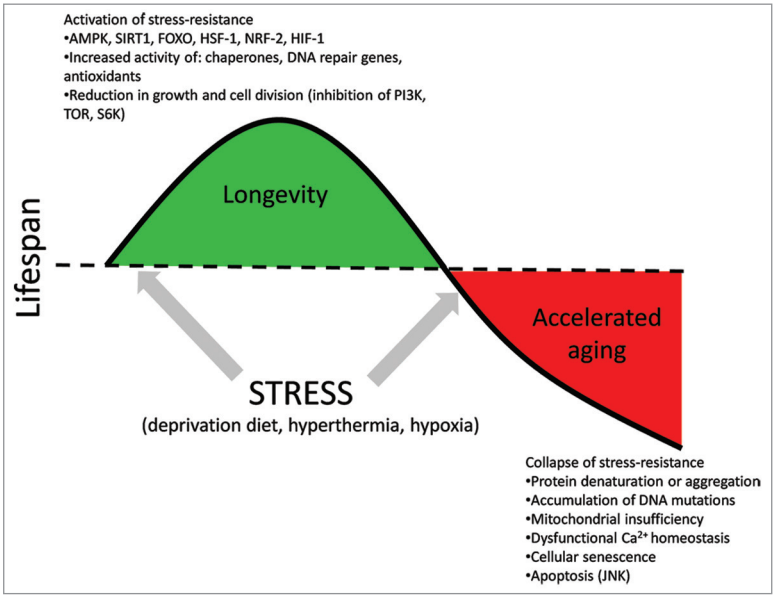

Figure 2. Stresses of various magnitudes affect aging rate and lifespan through different mechanisms.

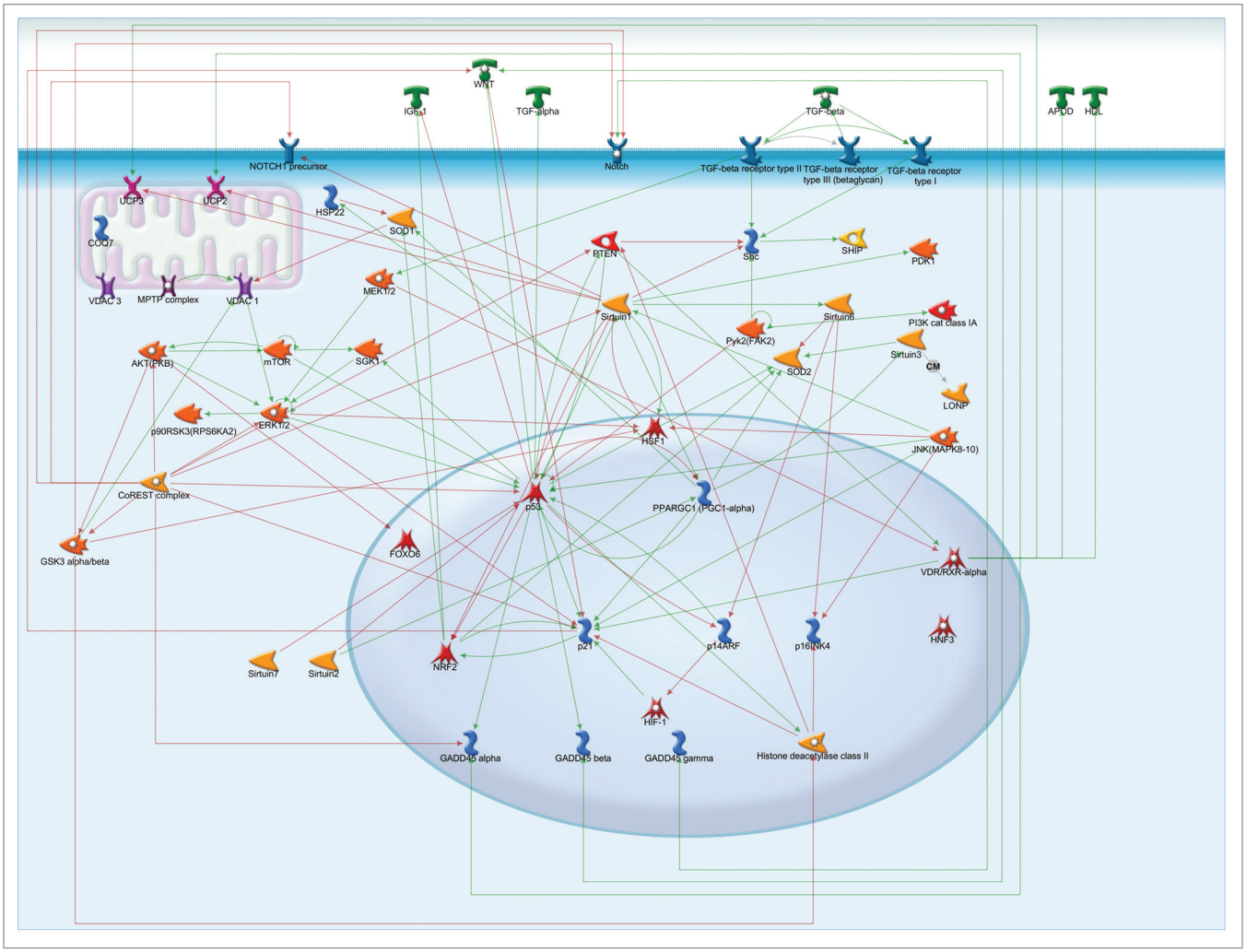

Figure 3. Longevity genes involved in stress response. The relationship between proteins is depicted with arrows, where green and red represent activation and inhibition, respectively.

untranslated region of Klotho mRNA. In vitro results confirmed that these miRNAs can directly decrease Klotho protein expression, indicating that these miRNAs might be playing a role in age-related downregulation of Klotho mRNA in vivo.[114] In addition to intracellular miRNAs, there is a novel category of circulatory miRNAs that can be considered as a completely new intercellular and system level communication. Accumulated evidence suggests that circulatory miRNAs can exert 2 opposite roles, activating as well as inhibiting inflammatory pathways (inflamma-miRs). Several of the circulatory miRNAs seem to be common for the major age-related diseases that share a chronic, low-level proinflammatory status, such as cardiovascular disease, type 2 diabetes mellitus, Alzheimer disease, rheumatoid arthritis, and cancer.[115]

Long noncoding RNAs

The role of long non-coding RNAs (lncRNAs) in aging has been suggested in the work of Chang et al., in which he was studying gene expression changes of aged and rejuvenated human skin. He found that skin aging was associated with a significantly altered expression level of 2265 coding and noncoding RNAs, of which 1293 became "rejuvenated" after broadband light treatment. Rejuvenated genes (RGs) included several known key regulators of organismal longevity and their proximal long noncoding RNAs.[116] Abdelmohsen et al. described identification of senescence-associated long non-coding RNAs (SAL-RNAs). He looked at the lncRNAs that are differentially expressed during replicative senescence of human diploid WI-38 fibroblasts by RNA-seq. SAL-RNA1 (XLOC_023166) has been identified as putative age-delaying lncRNA, since its reduction with small inhibitory RNAs (siRNA) induced rapid aging changes of the fibroblasts, such as large cell morphology, positive β-galactosidase activity, and upregulation of p53.[117]

Pathway Analysis

The longevity genes described in this paper were separated into categories using Gene Ontology (GO), and their interactions were analyzed using GeneGo Metacore.

Most of the longevity genes described are related to stress response. The major regulatory hubs in stress response were

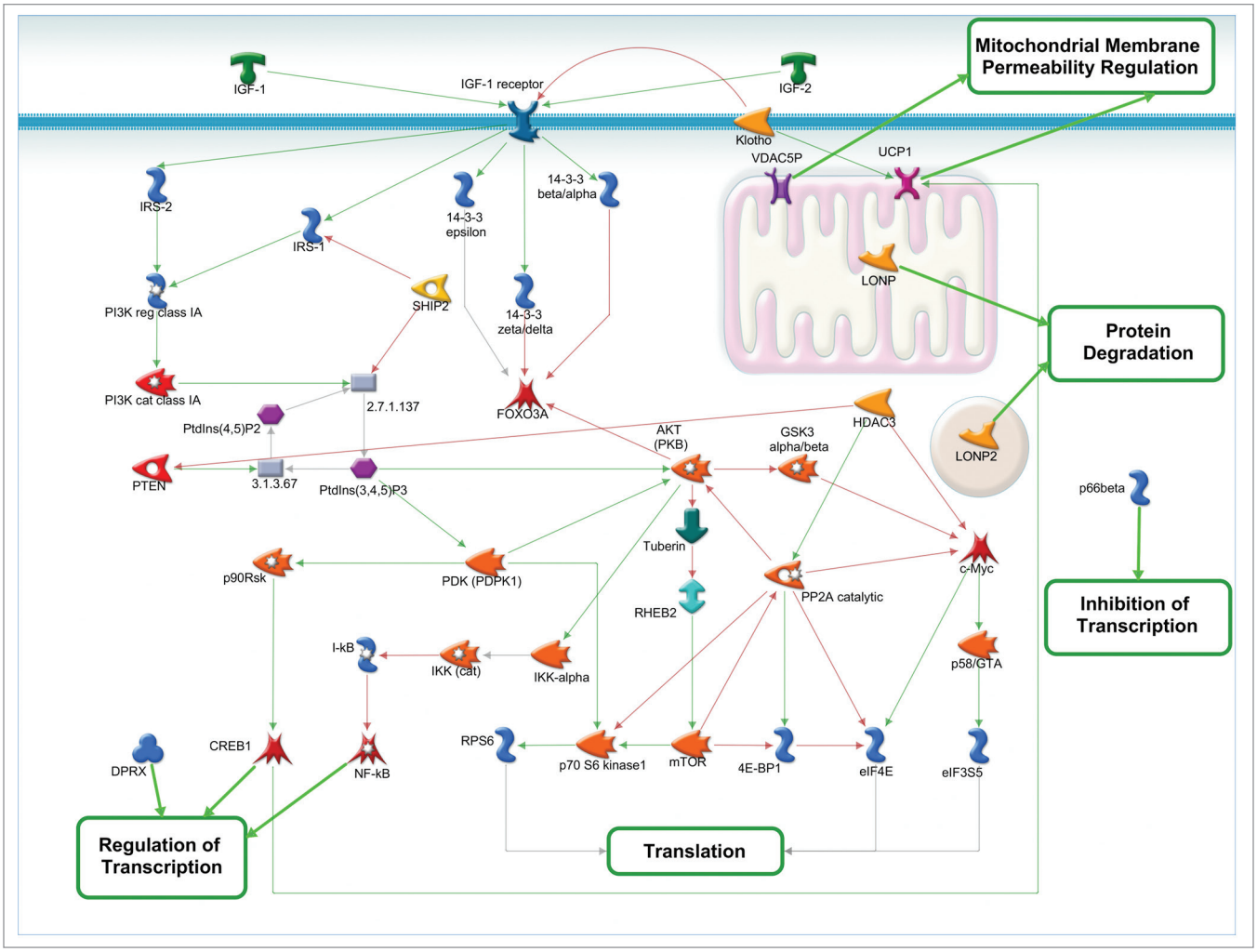

Figure 4. IGF-1-mediated signaling combined with longevity proteins that are not directly involved in stress response.

P53, Sirtuin 1, P21, HSF1, and the CoREST and VDR/RXR-α complexes (**Fig. 3**).

The VDR/RXR-α complex, a complex including over 20 elements, mainly PPAR and RXR, upregulates many proteins in the GADD45 family, P21, APOA1, APOD, WNT 4 UCP2, and UCP3. On the contrary, all of the interactions of the CoREST complex are downregulatory. It downregulates GADD45 α, P53, P21, ERK1/2, PTEN, AKT (PKB), GSK3 α/β complex, Notch pre-cursor, and NOTCH.

There are few genes that do not relate to stress response and are not classified as such in GO (**Fig. 4**). To get a deeper understanding of their action, we combined these genes with insulin-like growth factor signaling pathway. IGF binding, the tyrosine kinase activity of IGF-1 receptor, leads to the phosphorylation of several substrates, including the insulin receptor substrate family of proteins (such as insulin receptor substrate 1 and 2 [IRS-1 and IRS-2], SHC [Src homology 2 domain containing] transforming protein 1 [Shc], and some others).

After phosphorylation these proteins activate downstream signaling through the phosphatidylinositol 3-kinase (PI3K) or GRB2/SOS/H-Ras pathways. Activation of these pathways initiates metabolic cascades that result in the inhibition of apoptosis, activation of several transcription factors (CREB1, NK-κB), stimulation of protein synthesis via activation of ribosomal protein S6 kinase (p70 S6 kinase 1), mTOR, c-Myc, and also enhances glucose uptake, glycogen synthesis, and lipid storage. One of the anti-apoptotic pathways is mediated by 14-3-3 proteins. Three members of the 14-3-3 family of proteins (14-3-3 β/α, 14-3-3 zeta/delta, and 14-3-3 epsilon) interact with the IGF-1 receptor and in tandem with AKT (PKB) inhibit major stress response transcriptional factor FOXO3A. To simplify the schematic, we left out the GRB2/SOS/H-Ras and some of the anti-apoptotic pathways activated by IGF-1. Both HDAC3 and catalytic PP2A downregulate c-Myc, one of the major oncogenes, which may be one of the possible mechanisms for increased longevity in mammals. Both LON peptidases (mitochondrial LONP and peroxisomal LONP2) involved in protein degradation process, along with transcriptional repressor p66 beta and divergent paired-related homeobox protein (DPRX), have no direct interactions with other components of the network. Membrane protein Klotho directly activates only mitochondrial uncoupling protein 1 (UCP1), which facilitates

Table 1. Life extension in model organisms

Gene	Human homolog	Organism	Wild-type lifespan	Life extension (%)	Mechanism	Gender	References
daf-2	IGFR-1	*Caenorhabditis elegans*	14.9 ± 0.1 d	83.0%	Gene inactivation leads to disruption of insulin signaling	N/A	118
age-1	PI3K	*Caenorhabditis elegans*	16 ± 2 d	~1000%	Gene inactivation leads to disruption of insulin signaling	N/A	41
bec-1	beclin	*Caenorhabditis elegans*	22.4–31.1 d (mean lifespan)	−15–30% (across 6 trials)	Gene inactivation leads to disruption of autophagy	N/A	119
hsf-1	HSF	*Caenorhabditis elegans*	13.8 ± 0.5 d	22.0%	Gene overexpression leads to activation of the heat shock promoter	N/A	120
daf-16	FOXO	*Caenorhabditis elegans*	23.2 ± 0.8 d	−27.0%	Gene inactivation leads to disregulation of stress response machinnery	N/A	120
let-363	TOR	*Caenorhabditis elegans*	10 d	250.0%	Gene inactivation leads to disruption of insulin signaling	N/A	121
sgk-1	SGK	*Caenorhabditis elegans*	14.7 ± 0.3 d	61.0%	Gene inactivation leads to disruption of insulin signaling (as sgk-1 acts in parallel with AKT kinases) and better stress response.	N/A	122
hcf-1	HCFC1	*Caenorhabditis elegans*	14.3 ± 0.1 d	28.0%	Gene inactivation leads to activation of stress response by daf-16/FOXO	N/A	123
jnk-1	JNK	*Caenorhabditis elegans*	16.8 ± 0.2 d	−21.7%	Gene inactivation leads to disruption of stress response by daf-16/FOXO	N/A	124
jkk-1	JKK1	*Caenorhabditis elegans*	16.8 ± 0.2 d	−20.9%	Gene inactivation leads to disruption of stress response by daf-16/FOXO	N/A	124
akt-1 akt-2	AKT1 AKT2	*Caenorhabditis elegans*	14.7 ± 0.3 d	19.0%	Simultaneous inactivation of these genes leads to disruption of insulin signaling	N/A	122
sod1	SOD1	*Caenorhabditis elegans*	18 d	33% (averaged across trials 1 and 2)	Overexpression of sod1 activates longevity-promoting transcription factors.	N/A	125
sod2	SOD2	*Caenorhabditis elegans*	19 d	10% (averaged across trials 5 and 6)	Overexpression of sod2 activates longevity-promoting transcription factors.	N/A	125
dSir2	SIRT1	*Drosophila melanogaster*	37 d	57.0%	Overexpression of dSir2 enhances energy metabolism	female	126
dSir2	SIRT1	*Drosophila melanogaster*	41 d	32.0%	Overexpression of dSir2 enhances energy metabolism	male	126
chico	InRS	*Drosophila melanogaster*	44 d	47.7%	Gene inactivation leads to disruption of insulin signaling	female	38
InR	InR	*Drosophila melanogaster*	N/A	85.0%	Gene inactivation leads to disruption of insulin signaling	female	127
dFOXO	FOXO	*Drosophila melanogaster*	Varies across trials	19.4% (averaged across trials)	Overexpression of dFOXO leads to disruption of insulin signaling	female	128
dFOXO	FOXO	*Drosophila melanogaster*	Varies across trials	15.5% (averaged across trials)	Overexpression of dFOXO leads to disruption of insulin signaling	male	128

Table 1. Life extension in model organisms (continued)

Gene	Human homolog	Organism	Wild-type lifespan	Life extension (%)	Mechanism	Gender	References
dPTEN	PTEN	*Drosophila melanogaster*	57 d	17.4%	Overexpression of dPTEN leads to disruption of insulin signaling	female	128
dPTEN	PTEN	*Drosophila melanogaster*	51 d	19.6%	Overexpression of dPTEN leads to disruption of insulin signaling	male	128
hsp22	HSP22	*Drosophila melanogaster*	60 ± 3 d	32.0%	Overexpression of hsp22 increases cell-protection against oxidative injuries	male	78
sod2	SOD2	*Drosophila melanogaster*	77.8 ± 5.7 d and 74.7 ± 5.1 d	−9.5% and −7.4%	Overexpression of SOD2 caused decrease of mitochondrial H2O2 release and enhancement of free methionine content essential for normal biological processes.	male	129
sod1	SOD1	*Drosophila melanogaster*	27 d	>66%	Overexpression of sod1 in motorneurons enhances RO metabolism	male	130
mTOR	TOR	*Drosophila melanogaster*	N/A	30.0%	Overexpression of dominant negative form of TOR alters stress responses translation and/or mitochondrial function	male	131
dS6K	S6K	*Drosophila melanogaster*	N/A	29.0%	Overexpression of dominant negative form of S6 kinase alters stress responses translation and/or mitochondrial function	male	131
IGFR-1	IGFR-1	*Mus musculus*	568 ± 49 d	33.0%	Gene inactivation leads to disruption of insulin signaling	female	37
IGFR-1	IGFR-1	*Mus musculus*	585 ± 69 d	16.0%	Gene inactivation leads to disruption of insulin signaling	male	37
p66shc	p66	*Mus musculus*	761 ± 19.02 d	30.0%	Disactivation of p66 contributes to increased cellular and organism oxidative stress resistance	male and female	88
Klotho	KLOTHO	*Mus musculus*	715 ± 44 d	20.0 and 30.8% (transgenic lines EFmKL46 and EFmKL48)	Gene inactivation leads to disruption of insulin signaling	male	48
Klotho	KLOTHO	*Mus musculus*	697 ± 45 d	18.8 and 19.0% (transgenic lines EFmKL46 and EFmKL48)	Gene inactivation leads to disruption of insulin signaling	female	48
Arf	p19	*Mus musculus*	113.8 ± 2.4 wk	16.0%	Hypothetically activation of Arf/p53 module provides anti-cancer and anti-aging effect detecting cellular damage.	male and female	132
SIRT6	SIRT6	*Mus musculus*	851.3 ± 24.9 and 724.0 ± 35.0 d (transgenic lines 55 and 108)	14.8% and 16.9% (transgenic lines 55 and 108)	Overexpression leads to higher levels of IGF-binding protein 1 and altered phosphorylation levels of major components of IGF1 signaling	male	133

Table 1. Life extension in model organisms (continued)

Gene	Human homolog	Organism	Wild-type lifespan	Life extension (%)	Mechanism	Gender	References
p63	p63	*Mus musculus*	121 wk (median lifespan)	−21.5%	p63 deficiency activates widespread cellular senescence with enhanced expression of senescent markers SA-β-gal PML and p16INK4a	male and female	134
Brca1	Brca	*Mus musculus*	713 ± 146 d	−8.0%	Gene inactivation leads to hypersensitivity to DNA damaging agents and consequently genomic instability of cells	female	135

the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane. It's known that Klotho overexpression extends lifespan, whereas loss of Klotho accelerates the development of aging-like phenotypes, but the exact mechanisms are still rather vague.

The effects of the interventions associated with the genes in **Figures 3 and 4** on life extension of model organisms are summarized in **Table 1**.

There are many genes in the pathways related to stress response where overexpression led to life extension. In *Drosophila*, overexpression of the stress response gene dGADD45 led to up to 73% increases in lifespan. In both *C. elegans* and *Drosophila*, inactivation of TOR signaling led to 250% and 30% increases, respectively. Major lifespan increases across all species were achieved by interventions into the interconnected IGFR-1 and TOR pathways, with IGFR-1 inactivation in mice resulting in up to 33% and Age-1 (PI3K) inactivation in *C. elegans* producing up to 1000% average life extension.

Aging Research Trends

To better understand the general trends in aging genetics, the funding and citation information for the longevity genes in **Figures 3 and 4** was collected using the International Aging Research Portfolio (IARP) system[136] as well as the NCBI PubMed system.

The names of human genes and animal homologs were used as search terms for the IARP system to produce the total funding amounts of grants with grant applications containing these search terms. The process was repeated using the gene name, "AND", and "aging" as search terms. The same process was performed in PubMed to compile the number of citations for each gene. While the exact funding amounts and the number of published papers for each gene may differ, **Table 2** illustrates the general trends.

PubMed was also queried with the name of each gene and the name of each gene "AND" "aging" to identify the year of the first citation and the year of the first citation with "aging" in the abstract.

The science of aging genetics is a comparatively new field. P53 was discovered in 1979 and implicated in aging in 1987. On average, genes in **Table 2** were discovered 21 years ago, and it took 9.7 years between the first citation and the first citation with "aging".

The approximate amount of funding spent on genes related to aging is at over $8.5 billion, with over 195 thousand citations, with the most funding spent on genes involved in stress response. On average approximately 7.4% of the funding was spent on projects with "aging" in the grant application, and this was consistent across all 3 categories. The average amount of funding per citation was over $43.9 thousand.

The largest amount of funding spent on a single gene with "aging" in the grant abstract was $195 million, which represents fewer than 5% of the total funding spent on P53 research. SIRT1 and homologs is the only gene with over $100 million spent on analyzing its role in aging, with just under 14% of the funding spent on non-aging-related projects.

Most of the genes related to aging and longevity were associated with other biologic processes, and most of the funding and publications citing these genes are related to areas other than aging.

Conclusion

Based on the analysis of current knowledge on evolutionarily conserved genetic regulation of aging and longevity, it has been possible to generate a functional classification of genes controlling lifespan[137]

(1) Lifespan "regulators." These act as switches of ontogenetic programs and are responsible for sensing and transmitting external environmental signals: synthesis, response, and transmission of hormones belonging to insulin-like pathway and secondary lipophilic hormones. A large fraction of these genes promote growth and reproduction while suppressing stress resistance. However, some of these genes stimulate stress response (see Klotho for an example).

(2) "Mediators" include kinases, protein deacetylases, and transcription factors. These genes are controlled by regulators and are responsible for switching stress response programs depending on the environmental signals, such as food availability, overpopulation (crowding), light and temperature conditions, and irradiation or endogenous oxidative stress. Mediators act

Table 2. Summary of the available funding and citation data

Process	Gene	Funding	Citations	F/C	F/TF	AF	AF/TF**	YFC	YFCA	FC-A	A-T
Cellular response to stress	TP53 or P53 or Dmp53	$4 027 210 538	68 834	$58 506	46.97%	$195 599 425	4.86%	1979	1987	32	8
	MAPK14	$458 530 482	1706	$268 775	5.35%	$23 968 444	5.23%	2001	2006	10	5
	MAPK8	$424 571 226	1196	$354 993	4.95%	$22 578 844	5.32%	2000	2000	11	0
	SOD1 or sod-1	$274 749 561	4128	$66 558	3.20%	$46 503 534	16.93%	1975	1985	36	10
	SOD2 or sod-2	$203 094 775	1374	$147 813	2.37%	$28 305 859	13.94%	1973	1985	38	12
	CDKN1A	$131 529 936	10 438	$12 601	1.53%	$13 032 831	9.91%	1993	1993	18	0
	SIRT1 or sir2 or dSir2	$116 967 665	3052	$38 325	1.36%	$101 117 219	86.45%	1984	1999	27	15
	MAPK1 or mpk1	$103 268 829	11 237	$9190	1.20%	$8 223 868	7.96%	1982	1993	29	11
	HDAC6	$101 832 683	474	$214 837	1.19%	$-	0.00%	1999	2006	12	7
	MAPK9	$32 669 688	252	$129 642	0.38%	$368 385	1.13%	1994	-		
	HDAC2	$31 533 278	802	$39 318	0.37%	$-	0.00%	1997	2001	14	4
	RXRA	$30 032 747	356	$84 362	0.35%	$1 848 693	6.16%	1992	2011	19	19
	WNT5A	$27 790 400	862	$32 239	0.32%	$ -	0.00%	1993	2000	18	7
	GSK3 or sgg	$27 250 742	1372	$19 862	0.32%	$2 505 572	9.19%	1980	1995	31	15
	MAPK10	$17 683 286	88	$200 946	0.21%	$1 216 021	6.88%	1991	-		
	GADD45A	$12 777 259	482	$26 509	0.15%	$1 296 966	10.15%	1995	1999	16	4
	GADD45G	$7 537 188	69	$109 235	0.09%	$2 062 285	27.36%	1998	2010	13	12
	FOXA3 or HNF3G or TCF3G	$5 315 519	119	$44 668	0.06%	$ -	0.00%	1990	1999	21	9
	MAPK12	$1 438 384	68	$21 153	0.02%	$ -	0.00%	1992	-		
	SIRT7	$1766	51	$35	0.00%	$1766	100%	2000	2005	11	5
	Total Stress Response	**$6 035 785 952**	**106 960**	**$56 430**		**$448 629 712**	**7.43%**				
Insulin-like signaling	MTOR or TOR	$821 029 426	23 778	$34 529	9.58%	$68 845 232	8.39%	1975	1988	36	13
	PPARG	$213 853 403	10 059	$21 260	2.49%	$15 193 855	7.10%	1993	1994	18	1
	AKT1 or akt-1	$121 140 702	5408	$22 400	1.41%	$7 246 805	5.98%	1977	1999	34	22
	PPARA	$74 581 825	750	$99 442	0.87%	$1 120 366	1.50%	1993	2002	18	9
	AKT2 or akt-2	$71 265 752	875	$81 447	0.83%	$2 598 915	3.65%	1987	1999	24	12
	RXRA	$27 790 400	356	$78 063	0.32%	$1 848 693	6.65%	1992	2011	19	19
	HDAC5	$24 234 263	310	$78 175	0.28%	$986 700	4.07%	1999	2002	12	3
	SHC1	$16 912 072	898	$18 833	0.20%	$1 238 936	7.33%	1992	1997	19	5
	HDAC9	$5 844 910	106	$55 141	0.07%	$-	0.00%	2001	2002	10	1
	GSK3A	$2 120 564	150	$14 137	0.02%	$-	0.00%	1995	2013	16	18
	EIF4EBP1 or d4EBP	$608 042	818	$743	0.01%	$-	0.00%	1994	2006	17	12
	Total Insulin Stimulus	**$1 379 381 359**	**43 508**	**$31 704**		**$99 079 502**	**7.18%**				

Table 2. Summary of the available funding and citation data (continued)

Process	Gene	Funding	Citations	F/C	F/TF	AF	AF/TF**	YFC	YFCA	FC-A	A-T
Regulation of translation	MTOR or TOR	$821 029 426	23 778	$34 529	9.58%	$68 845 232	8.39%	1975	1988	36	13
	AKT1 or akt-1	$121 140 702	5408	$22 400	1.41%	$7 246 805	5.98%	1977	1999	34	22
	MAPK1	$96 943 128	11 067	$8 760	1.13%	$8 223 868	8.48%	1991	1993	20	2
	EIF4E	$69 771 228	2392	$29 169	0.81%	$3 935 384	5.64%	1991	2001	20	10
	PTK2B	$44 532 289	298	$149 437	0.52%	$-	0.00%	1995	2010	16	15
	EIF4G1 or EIF4G	$3 998 998	970	$4123	0.05%	$911 650	22.80%	1995	2001	16	6
	EIF4EBP1 or d4EBP	$608 042	818	$743	0.01%	$-	0.00%	1994	2006	17	12
	Total Reg. of Translation	**$1 158 023 813**	**44 731**	**$25 889**		**$89 162 939**	**7.70%**				
Total		**$8 573 191 124**	**195 199**	**$43 920**		**$636 872 153**	**7.43%**				

F/C, funding per citation; F/TF, funding for a specific gene as percentage of total funding; AF, funding for projects with the specific gene name and "aging" in the grant application; YFC, year of first citation; YFCA, year of first citation with "aging" in the abstract; FC-A, the time between first citation of the gene and citation with "aging"; A-T, the time between 2013 and the time of the first citation of the gene with "aging" in the abstract.

either as tissue-specific regulators of effector genes or directly controlling protein activity or lifetime. Mediators also interact among themselves, stimulating or inhibiting one another's activity.

(3) "Effectors" are stress-resistance genes, including heat shock proteins, antioxidants, protein and DNA damage repair proteins, proteasome components, calpains, autophagy proteins, innate immunity, detoxification of xenobiotics, and metabolic regulators. Overexpression of these genes is usually correlated with extended lifespan. Often, the effectors act in additive manner, becoming activated by distinct "mediators" and extending lifespan under stress conditions. However, a number of "mediators" suppress "effectors" activity.

(4) Housekeeping genes. These act ubiquitously at every stage of life and are responsible for supporting cellular structure, respiration, synthesis of amino acids, lipids, nucleotides, etc. Mutations in these genes are either lethal or result in pathologies. Under stress conditions, some of the housekeeping genes are temporarily repressed by "mediators", which allows saving energy and resources for "effectors" and extending lifespan.

(5) Genes involved in mitochondrial function. These are components of electron transport chain, Krebs cycle, uncoupling proteins, clk-1 gene in nematodes. These genes regulate energy metabolism, the level of free radicals, and also apoptosis.

(6) Genes regulating cellular senescence and apoptosis (p53, p21, p16, pRB). These genes are responsible for cancer prevention, cell cycle regulation, and elimination of extra or malignant cells during early ontogenesis and maturity. Cellular senescence (replicative or stress-induced) of dividing cells or excessive elimination of postmitotic cells is a pleiotropic side effect of aging.

How do all these new developments in the new science of aging and discovery of genes that drastically alter longevity fit in with classical evolutionary theories? Which one is standing the test of time and new developments in the field of aging? At this point in time it appears that each of them is holding bits of truth, and each of them is explaining the evolution and mechanism of aging using dualistic principles (adaptive/nonadaptive, molecular/organismic, etc.). There is a newer theory proposed that offers an integrated theory of aging that helps us to better grasp similarity rather than differences among all these processes, the fractal theory of aging.[138] The fractal theory is based, first, on the multilevel nature and complexity of aging, as well as self-similarity of those levels. Another important property of a fractal is a combination of stochastic and regular traits. The fractal principle of aging manifests in a combination of random (i.e., aging rates) and regular (i.e., sequence of geriatric changes) traits. Thus, according to this theory, aging can be defined as an age-dependent fractal increase in the number of deviations from homeostasis at the molecular, subcellular, cellular, tissue, and systemic levels. Actually, what would be highly desirable at this point in time is a unified theory of aging that would offer experimentally testable predictions. If we are able to mathematically describe the aging for one (e.g., cellular) level or one biological trait on a small interval of time, this model could be extrapolated to predict the aging at all other levels of organization of life, including individual lifespan. Substituting the model parameters with experimental measurements could lead to finding of biomarkers of aging rate and efficiency of anti-aging interventions.

Our pathway analysis shows that most of the gerontogenes are members of the stress response pathways and confirms the existence of genetics "longevity program". As a rule, genes, regulators of the longevity program, which suppress mild stress response as well as mutations that make some of those pathways less efficient, provide life-extension benefits. Mild

overexpression of effector longevity genes involved in stress response to DNA, protein, or other cellular damages (e.g., Hsps, Sod, GADD45, ATGs) prolongs lifespan. While moderate stress induces "longevity program" by stimulating expression of life-assurance genes and promoting prevention or elimination of errors, chronic or acute stress exposure exhausts the defense mechanisms and therefore accelerates aging. Pro-aging and anti-aging gene-determined processes exist on all levels of the organismal system—from molecules to systems (metabolic, endocrine, immune, inter-cellular communication). Their multi-level organization, the interpenetration of levels, a combination of regular and stochastic elements is what makes the process of aging a fractal process.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed

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