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Signaling pathways and effectors of aging

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1. ABSTRACT

Aging leads to and is associated with aberrant function of multiple signaling pathways and a host of factors that maintain cellular health. Under normal conditions, the prolongevity, 5' AMP-activated protein kinase (AMPK), is dedicated to the homeostasis of metabolism and autophagy for removal of damaged cellular compartments and molecules. A host of sirtuin family of molecules, that extend life-span, regulate metabolism and repair DNA damage, and possess either mono-ADP-ribosyltransferase, or deacylase activity. Another group of pro-longevity factors, include FOX (forkhead box) proteins, a family of transcription factors that regulate the expression of genes involved in cell growth, proliferation, differentiation, and longevity. Nicotinamide phosphoribosyltransferase (NAmPRTase or Nampt) catalyzes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide (NMN), a requisite step for production of NAD^+, which is known to increase longevity. Loss of Klotho, a transmembrane enzyme that controls the sensitivity of the organism to insulin and suppresses oxidative stress and inflammation, leads to premature aging in mice. Hydrogen sulfide and transsulfuration pathways are crucial to the long life and are required in protection of cells against damage. Aging also leads to the imbalanced activation of other pathways and factors including p53, insulin and IGF signaling, P13K/AKT, mTOR, PKA, RAS, RTK, MEK, ERK, MAPK, CRTC-1/CREB and NFκB. Such aberrant cellular functions, disturb cell metabolism, derail

autophagy and other housekeeping actions, inhibit cell division, induce inflammaging and immunosenecence, cause stem cell exhaustion and induce either senescence, apoptosis or cancer.

2. INTRODUCTION

Aging becomes evident in all human beings by loss of the ability to reproduce, and extensive damage and loss of function in organs, tissues, cells. Although, it is not argued that, the age related diseases, are not the cause rather are the consequence of aging, many have argued that, changes and damages that occur at the cellular level, play a causative role in aging. However, the current cell-centric hypotheses of aging merely explain, some but not all, hallmarks of aging in biological systems (1-6). Thus, the most proximal and fundamental causes of aging have remained as major conundrums in biology (7-9). Here, I summarize the signaling pathways and molecules that maintain the cellular homeostasis and health. However, the function of these pathways progressively gets corroded and such aberrant functions, ultimately, lead to an imbalanced signaling and activation of molecules that cause cells to senesce, and if the damage is severe, to induce apoptosis or initiate the processes that lead to tumorigenesis.

3. SIGNALING PATHWAYS AND EFFECTORS OF AGING

3.1. AMPK

AMPK is a serine/threonine protein kinase and central regulator of cellular and organismal metabolism that resides at the heart of cellular functions including growth, autophagy, polarization, and metabolism in eukaryotes. AMPK senses energy requirement of cells, inhibits anabolic pathways, promotes catabolic pathways and induces ATP production. AMPK is a highly conserved energy sensor comprised of a catalytic α and regulatory β and γ subunits which are differentially expressed and assembled in mammalian tissues. AMPK is activated by allosteric regulation by the increased levels of AMP, ADP and NAD^+ which restores and maintains cellular ATP (10-12). AMPK is also activated by upstream kinases including transforming growth factor-β-activated kinase 1 (TAK1) which can activate AMPK by phosphorylating the catalytic α subunit at Thr^{172}, serine/threonine kinase 11 (LKB1), and by Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) (13-15).

AMPK is activated in response to normal physiological signals including exercise, hormones, and phytochemicals as well as a host of pathological conditions. Activation of AMPK can be contextual, for example, AMPK can be activated or inhibited by developmental and environmental cues, or by adiponectin, ghrelin and leptin in a tissue specific manner (16-17). AMPK is de-activated by protein phosphatases (PP), such as PP2A, PP2Cα and Ppm1E (18-28). During stress, AMPK drives energy production by stimulation of use of glucose and fatty acids and reduces energy consumption by inhibiting protein, cholesterol and glycogen synthesis (10-11).

AMPK also inhibits oxidative stress by induction of mitochondrial UCP2 which represses superoxide production and inflammation (23-26). Activation of AMPK also induces the expression of thioredoxin, a disulfide reductase and prevents the oxidation of cysteine residues in proteins. It has been suggested that anti-oxidative effects of AMPK is also mediated by activation of Nuclear factor erythroid 2-related factor 2 (Nrf2)/SKN-1 signaling and by the induction of expression of anti-oxidative heme oxygenase-1 gene via Nrf2 signaling (27). It appears that AMPK acts, in concert, with Nrf2 and FoxO3a axis in endowing a stress resistant phenotype in long-lived animals.

AMPK and its orthologue in *C. elegans*, AMP-activated kinase-2 (AAK-2) control and extend life-span and health-span by an integrated signaling network that includes metabolic homeostasis, enhancement of stress resistance by FoxO/DAF-16, Nrf2/SKN-1, and Sirt1 signaling pathways, autophagy via the mTOR and ULK1 pathways, inhibition of inflammatory response by inhibition of NFκB signaling and is assigned to cellular housekeeping. Overexpression of AAK-2/AMPK has extended the life-span in *C. elegans* and *D Melanogaster* (28-32). In mice, the knockout of α1 ($AMPK\alpha^{1-/-}$) and α2 ($AMPK\alpha^{2-/-}$) led to different

outcomes, and only the α2 catalytic subunit of AMPK, has a negative impact on the health-span. This subunit, which was shown to play a major role as a fuel sensor, leads to high plasma glucose levels, low plasma insulin concentrations, insulin-resistance and reduced glycogen synthesis in the muscle (33).

Unfortunately, such a valuable pathway is eroded by aging, depriving cells from the host of functions that maintain their youthful state, leading to increased oxidative and ER stress, reducing autophagic removal of damaged cellular components, allowing for emergence of inflammation (inflammaging) and loss of energy homeostasis leading to accumulation of hyperglycemia and fat causing a metabolic syndrome including development of insulin resistance, diabetes obesity, and cardiovascular disease (10, 34). This loss of function of AMPK in aging has been tested by AICAR treatment and physical exercise that increased the activity of AMPKα2 in the muscles of young and not old rats (35). Consistent with this, the activation of AMPK induced by muscle contractions, was shown to be repressed in muscles of old mice (36). Similarly, aging impaired AMPK activation and suppressed insulin-stimulated glucose uptake in rat skeletal muscles (37). The deficiency of AMPK exacerbated aging-induced myocardial dysfunction (38). In mouse brain, although, the baseline activity of AMPK was higher in old animals as compared to their younger counterparts, cerebrovascular stroke stimulated an increase in AMPK activity in young mice but not in the old mice (27). Although the precise mechanism that hampers the AMPK activity in aging tissues is not clear, certain factors which are known to diminish this response, include nutritional factors, some hormones and inflammation that is present in aged tissues (39).

3.2. FOXO

The FOXO family of transcription factors are characterized by a conserved DNA-binding domain, the so-called 'Forkhead box', or FOX. Based on the sequence similarity, this family includes more than 100 members in humans, classified from FOXA to FOXS (40-43). Invertebrates, have only one FOXO gene (daf-16 in the worm and dFOXO in flies) and mammals have four genes named FOXO1 (FKHR), FOXO3 (FKHRL1), FOXO4 (AFX), and FOXO6 (44-45). The four mammalian isoforms of FOXO family appear to have distinct, yet, overlapping functions that can mask the loss of function of the individual FOXO factors (46).

FOXO proteins act primarily as transcriptional activators that bind to the consensus core recognition motif, TTGTTTAC, and their activity is inhibited by the IIS pathway, whereas, the down-regulation of this pathway, in response the harsh environmental conditions, leads to FoxO activation (47-52).

FOXO members interact with many different pathways namely, SIRT1, AMPK, insulin/PI3K/Akt, c-Jun NH2-terminal kinase (JNK), and inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) pathways. FOXO1, 3 and 4 have several effectors including IIS pathway and PI3K-AKT signaling (47, 53). Insulin or IGF-1 both trigger PI3K and then serine/threonine kinase, AKT, that phosphorylates FOXO factors at three conserved residues. This leads to the exit of FOXO factors from nuclei and their transport to the cytoplasm, an event that leads to a suppression of FOXO-dependent transcription of target genes (54-56). However, in the absence of Insulin or IGF-1 signaling, FOXOs are translocated into the nucleus and activate FOXO dependent gene expression. In addition to PI3K/PKB-AKT, other kinases, including AMPK, JNK, and IKKβ can also phosphorylate FoxO, establishing their roles as a master-switch, critical to cellular responses (51). The FOXO factors can undergo post-translational modifications such as phosphorylation, acetylation, deacetylation, methylation, or ubiquitination and such changes modify their DNA binding and transcriptional activity (51-52).

One of the first evidence that linked FOXO to longevity was shown for DAF-16 in *C. elegans,* an orthologue of mammalian FoxOs (57-58). DAF-2 pathway, which corresponds to the mammalian insulin/IGF-1 signaling (IIS), down-regulates the activity of FoxO/DAF-16 transcription factor, both in mammals and *C. elegans*. Thus, it became clear that such a pathway might shorten life-span. Indeed, loss-of-function mutations of DAF-2 pathway doubled the life-span of *C. elegans* (57-58). In flies,

overexpression of dFOXO has been shown to be sufficient to increase longevity (46). Following mutations in the insulin/PI3K/Akt pathway, worms that lack daf-16 or flies that lack dFOXO, were viable but did not show an increase in life-span. Several studies have also revealed APOE and FOXOs (FOXO1 and FOXO3) to be “longevity genes” (59-66).

The actions of FOXOs on life-span appear to be rooted in their evolutionarily conserved roles in regulation of glucose and lipid metabolism which allows cells to adapt to stress such as starvation (67-69). Low glucose (low insulin drive), low insulin (reduced strength of the insulin signal) and FoxO activation all induce a similar metabolic shift. FoxOs increase insulin sensitivity and induce expression of the insulin receptor and IRS2 (70). FOXOs appear to be a “master-switch” for adaptation of cells and organisms to food scarcity, ensuring their metabolic stability by opposing many of the functions of IIS pathway and by induction of cell cycle arrest and quiescence, which is reminiscent of the Dauer state in *C. elegans* (71).

Importantly, FOXOs are critically responsive to the oxidative environment in cells by upstream regulatory pathways of FOXO or directly by sensing oxidation and reduction state of cysteine residues, the so-called cellular redox state. In response to this read-out, FOXOs increase the anti-oxidant capcity of cells through enzymes that degrade reactive oxgyen species such as catalase, manganese superoxide dismutase (MnSOD) and GADD45 (72-77). Besides upregulation of anti-oxidative stress capacity, FoxO activation or low insulin both activate Peroxisome Proliferator-activated receptor Gamma Coactivator 1α (PPGC-1α), a nutrient sensing system that increases mitochondrial biogenesis and induces a shift in metabolism from reliance on carbohydrate towards fat (78). Thus, it is clear why de-activation of this pathway increases the ROS in age related pathologies including atherosclerosis (78-79).

FOXOs also regulate apoptosis and inflammation, endow cell resistance, and regulate, through unknown mechanisms, the protein maintenance, the so-called proteostasis that is impaired by aging (52, 56, 80-84). Whereas the impairment of PI-3K/AKT-PKB signaling causes FoxO activation, the enhanced PI-3K/AKT-PKB unleashes an inflammatory state by inducing NFκB through activation of the IKK (85).

FOXOs affect the expression of genes involved in autophagy and mitophagy, and more specifically, FOXO1 and FOXO3 have been shown to activate autophagy (52). The importance of autophagy and mitophagy in the function of FOXOs is supported by studies that show that defects of autophagy are associated with premature aging in animal models (86-92).

Ubiquitin-proteasome system, that removes short-lived and regulatory proteins, is also subject to regulation by FOXOs, a process that is impaired in aging and neurodegenerative disorders such as Parkinson's, Alzheimer's, or Huntington's disease (93-96). The mode of action of FOXOs on this system appears to be due to upregulation of ubiquitin ligases and by controlling the composition of the proteasome (97-100). AMPK-induced stimulation of FoxO/DAF-16, Nrf2/SKN-1, and SIRT1 signaling pathways all have been shown to improve cellular stress resistance (101).

Similar to other cells, stem cells are also subject to control by FOXOs and such regulation appears to be significant in the ability of these factors to impact tissue regeneration. For example, deletion of Foxo3a leads to the exhaustion of hematopoietic stem cells as a result of their constant exit from quiescence, an effect that can be prevented by increasing the redox state by administration of N-acetylcysteine (102). Moreover, FOXOs control the major stemness factors, OCT4 and SOX2 that maintain pluripotency of human ESCs (103).

3.3. Sirtuins

The life preserving effects of dietary restriction appears to engage the transulfuration pathway, H_2S production, Nicotinamide adenine dinucleotide (NAD^+), sirtuins and AMPK. Exogenous administration of H_2S has been shown to be beneficial and afforded *C. elegans* health-promoting effects including stress resistance and improved

thermotolerance and led to a 70% increase in life expectancy (104). It was shown that such an effect required NAD^+-dependent deacetylase, sir-2.1 (105). We showed that while the production of H_2S decreases with senescence, the replicative senescence can be delayed by exogenous H_2S in human cells in a NAMPT/SIRT1 dependent manner (106). Increasing the H_2S to physiological levels, upregulated the *hTERT*, increased telomerase activity and increased population doublings (106).

Members of the Silent information regulator (SIRT) 1 family of NAD^+-dependent deacetylases act as silencers of gene expression by the deacetylation of histones and control ribosomal DNA recombination, and DNA repair, and confer chromosomal stability and longevity in multiple organisms and are essential to the beneficial effects inducible by dietary restriction (DR) (107-108). SIRT1, the best characterized mammalian sirtuin, deacetylates many non-histone proteins and impacts numerous physiologic processes, including apoptosis, metabolism, and stress resistance (109). There are experimental evidence that have implicated the Sir2 homologs in mammals (SIRT1–SIRT7) as mediators of key effects of caloric restriction (CR) during aging (110-111). SIRT1, SIRT6, and SIRT7 show sub-nuclear localization; SIRT2 is predominantly cytoplasmic; whereas SIRT3, SIRT4, and SIRT5 appear to reside in the mitochondria (112). Mammalian SIRT1 is closely related to Sirt2 which is required in yeast to maintain a silent chromatin state of the ribosomal RNA genes and telomeres. The Sirt2 expression diminishes with replicative aging allowing transcription and recombination of rRNA genes which are known to cause toxicity and to limit replicative life-span in yeast cells (113-114). SIRT1 is an evolutionarily conserved deacetylase that targets histones and several transcription factors, and is known to act as an energy sensor, that is responsive to AMP and NAD^+, increases the intracellular concentration of NAD^+ by increasing Nampt (115-117). The downstream target of SIRT1 include PGC-1α, FoxO1 and FoxO3. SIRT1 deacetylates and subsequently increases the activity of LKB1 kinase, an upstream activator of AMPK (118). SIRT1 is stress responsive, and localizes at DNA damage sites such as DNA breaks to repair the damage. Following damage, the trans-localization of SIRT1, from basal target genes, allows expression of a number of genes whose expression is known to increase with age (119). Thus, continuous damage and environmental stress, vacate normal chromatin occupancy of DNA by SIRT1 and trigger sequential and progressive changes in chromatin state over time, including accumulation of chromosome breaks, mutations, and loss of the youthful gene expression patterns. SIRT1 signaling appears to underlie some of the effects of CR such as stress resistance (120).

Besides SIRT1, the chromatin-associated sirtuin, SIRT6, targets chromatin by transcription factors, maintains telomeres and replicative activity and is required for longevity. SIRT6-deficient mice, although are small and appear relatively normal after birth, exhibit premature aging and show sudden drops in serum glucose and IGF-1 levels, defects in bone mineral density which are reminiscent of osteoporosis, curved spine (kyphosis), loss of subcutaneous fat, lymphocyte depletion, and severe metabolic defects (121-124). SIRT6 directly interacts with NFκB subunit, RelA, and is recruited by RelA to promoters of genes. This leads to deacetylation of H3K9Ac, a key event that promotes removal of RelA and abolishes further NFκB signaling (122). SIRT6 inhibits the expression of several NFκB dependent genes by modulating their chromatin structures whereas its depletion leads to a premature aging phenotype in keratinocytes (122-123). In SIRT6 deficient cells, hyperacetylation of H3K9 at the promoters of the target genes, increases RELA promoter occupancy, and enhances NFκB-dependent modulation of gene expression and leads to cellular senescence and apoptosis. However, such a deficiency, has not been associated with telomeric dysfunction (124). Haplo-insufficiency of RelA has been shown to decrease the early lethality and degenerative syndrome of Sirt6-deficient mice (122). Thus, SIRT6 is thought to lie at the crossroad of aging, rejuvenation, and epigenetics (125).

3.4. NAMPT

In *Saccharomyces cerevisiae*, the PNC1 gene is part of the NAD salvage pathway, that encodes a nicotinamidase that depletes cellular nicotinamide by converting NAM to nicotinic acid (vitamin B3). PNC1 gene is thought to be a master

"longevity regulatory gene" that translates a variety of environmental stresses into life-span extension by activating the sirtuin family of longevity deacetylases (126). Overexpression of *PNC1* increases Sir2-mediated silencing and leads to about 50% increase in the replicative life-span in this yeast (127-128). A decrease in glucose concentration, from 2% to 0.5% is sufficient to increase PNC1 levels by ~4-fold. Interestingly, *PNC1* levels are also increased by more than 4-fold in response to low amino acids, heat stress, and osmotic stress, conditions that are known to extend the life-span in yeast (128). Thus, it is thought that CR induces life extension in yeast through activation of PNC1 and Sir2 (126). It has been proposed that Nicotinamide phosphoribosyltransferase (Nampt), also known as Pre-B-cell colony-enhancing factor (PBEF) or Visfatin is the functional equivalent of PNC1 gene in mammals (126, 129-132). Based on the homology between Nampt and the nadV gene of *Haemophilus ducreyi*, Rongvaux *et al.* proposed and then confirmed that Nampt acts as a nicotinamide phosphoribosyltransferase (NaMPRTase) (130). Nampt is inducible by nutrient deficiency and stress, regenerates NAD^+, controls sirtuins, and supports response to damage and increases life-span (132-133).

Nampt is the rate limiting enzyme that salvages NAD^+ from nicotinamide (126, 129-132). Replicative senescence leads to the decreased expression and activity of NAMPT in smooth muscle cells in culture. Loss of NAMPT and synthesis of adequate supply of NAD^+ occur with aging, and this in turn, reduces SIRT1 activity, leading to cellular senescence (134). Artificial inhibition of NAMPT by its inhibitor, FK866, leads to premature senescence whereas forced induction of Nampt, suppresses age dependent increase in p53 expression, increases the rate of p53 degradation, raises the activity of SIRT1, delays senescence and increases life-span in these cells, an effect that can be inhibited by the dominant negative form of SIRT1 (135).

3.5. Klotho and FGFs

Klotho gene, is named after the spinner, one of the three goddesses, Klotho, Lachesis, and Atropos that according to the Greek mythology, control the life-span of every mortals who, respectively, spin, measure, and cut the thread of life (136). *klotho* gene is comprised of 5 exons, giving rise to a single-pass transmembrane protein with a short 10-amino acid-long intracellular domain, that is highly expressed in the brain, kidney, parathyroid and pituitary glands. The ectodomain of Klotho protein, released in a soluble form (sKlotho) to the blood, cerebrospinal fluid and urine, exerts functions that are distinct from the transmembrane protein (137). sKlotho regulates the activity of ion channels and growth factor receptors including insulin/IGF-1 receptors. In 1997, the klotho gene, was identified to be mutated in the klotho mice, that show pre-mature aging and age related pathology, characterized by hypogonadism, ectopic calcification, impaired bone mineralization, premature thymic involution, skin atrophy, pulmonary emphysema, neuro-degeneration, hearing loss, higher levels of serum phosphorus, calcium, and active vitamin D (1,25-dihydroxyvitamin D3) and lower levels of serum glucose, and an extremely shortened life-span (136-137). Mice homozygous for the mutated klotho allele ($KL^{-/-}$ mice) although initially appear to be normal for 3 to 4 weeks, they start to show premature aging as evidenced by multiple age-related disorders including skin and muscle atrophy, osteoporosis, arteriosclerosis, and pulmonary emphysema, and die prematurely around two months of age (136, 138-139). While, a defect in Klotho gene expression in mice, leads to degeneration of age sensitive processes, the aging phenotypes can be reversed by inhibiting insulin and IGF1 signaling, suggesting, that Klotho-mediated inhibition of insulin and IGF1 signaling, contributes to its anti-aging properties (139).

The evidence in humans supports the action of Klotho as an aging suppressor since single-nucleotide polymorphisms in the human *KLOTHO* gene have been show to be associated with altered life-span, altered risk for coronary artery disease, osteoporosis and stroke (140-147). On the other hand, the overexpression of Klotho extends life-span (139). Mice that carried the *EFmKL46* or *EFmKL48* transgenic alleles of Klotho that were fed *ad libitum*, although did not show a substantial difference in growth from wild-type mice nor changes in blood glucose levels, had higher blood levels of insulin,

likely due to insulin resistance, and lived substantially longer than their wild counterparts and generated fewer offsprings than wild-type breeding pairs (139). Male and not female transgenic mice showed significant reduction in insulin and IGF1 tolerance tests. Moreover, while Klotho peptide did not inhibit the binding of $^{(125I)}$insulin or $^{(125I)}$IGF1, it suppressed ligand-stimulated autophosphorylation of insulin and IGF1 receptors in a dose-dependent manner, leading to inhibition of intracellular insulin and IGF1 signaling (139). Also, it was shown that inhibition of insulin and IGF1 signaling can rescue $KL^{-/-}$ induced phenotypes from age-related pathologies, namely, ectopic calcification, hypogonadism, skin atrophy, pulmonary emphysema, and arteriosclerosis (139).

Fibroblast growth factors (FGF), namely FGF19, FGF21, and FGF23, act in an endocrine fashion and regulate energy and homeostasis of bile acids, glucose, lipid, phosphate, and vitamin D and all require presence of Klotho in target tissues (146). Transmembrane Klotho is an obligate co-receptor for FGF23, a bone-derived hormone that forces secretion of phosphate into urine. In mice, Klotho deficiency leads to reduced klotho levels, hypotrophy of cells in the anterior pituitary gland that secrete GH, and decreased activity of GH/IGF-1 axis and premature aging. Mice, that lack FGF23, retain phosphate and also show a premature-aging syndrome, showing a link between phosphate metabolism and aging. The aging induced phenotype by Klotho is related to ability of klotho to regulate GH, since Ames dwarf and Snell dwarf mice that lack GH live much longer than their normal siblings, and exhibit delayed aging. Targeted disruption of the GH receptor/GH-binding protein gene (GHR-KO mice), the so-called "Laron dwarf mice," are GH resistant and live much longer than their normal counterparts. These mice exhibit increased hepatic sensitivity to insulin, reduced insulin, reduced plasma glucose, lowered hepatic synthesis of IGF-1. They also generate a reduced level of ROS and exhibit an increased resistance to oxidative stress leading to improved antioxidant defense mechanisms, and reduced oxidative damage (147). These long-lived dwarf mice share many phenotypic characteristics that are inducible by CR.

β-Klotho protein is also predominantly expressed in the liver, pancreas and adipose tissues where FGF21 regulates metabolic functions by activating AMPK-SIRT1 signaling and adaptive responses to CR (148). FGF21 signals through classic FGF receptors, which act as tyrosine kinases, more preferably, the FGFR1c/β-Klotho complex. FGF21 is strongly induced in the liver by prolonged fasting and plays a key role in eliciting and coordinating the adaptive starvation response including enhancing insulin sensitivity, decreasing triglyceride concentrations, stimulating hepatic gluconeogenesis, fatty acid oxidation, and ketogenesis and weight loss (148).

3.6. Hydrogen sulfide and transsulfuration pathways

The trans-sulfuration and its upstream and downstream pathways are critically important in an array of diverse metabolic functions requisite to organismal homeostasis. This involves active transfer of thiol and methyl groups in a large number of biochemical processes that are vital to normal function of DNA, RNA and proteins in mammalian cells. The ancestral trans-sulfuration metabolic pathway in bacteria exists as a forward pathway that transfers thiol groups from cysteine to homocysteine to a reverse pathway which exists only in mammalian cells and involves the transfer of the thiol group from homocysteine back to cysteine. The essential amino acid, methionine, is activated, in an ATP-dependent manner, by methionine adenosyltransferase, to form S-adenosylmethionine (SAM). SAM donates a methyl group by methyltransferase, to yield S-adenosylhomocysteine (SAH), followed by formation of homocysteine (149-150). The homocysteine can either be re-methylated back to methionine using a methyl group donated by methyl tetrahydrofolate (MTHF), or is converted to cysteine via trans-sulfuration pathway and generates cystathionine by conjugating it with serine. This pathway is also crucial to the conversion of cysteine to major cellular antioxidant species, which include GSH, glutaredoxins, thioredoxins, taurine, and peroxiredoxins as well as hydrogen sulfide (H_2S) which is vital to life due to its antioxidant, anti-inflammatory and other cyto-protective properties.

Due to its paramount importance, H_2S is formed by at least three enzymatic reactions as well as by chemical means (151). While or cystathionine β-synthase (CBS) generates H_2S and serine as a by-product, cystathionine-γ-lyase (CGL, also known as cystathionase, CTH, or CSE), by using cysteine as the substrate, generates H_2S and produces pyruvate, and NH_3 as by-products of this reaction (152-154). The activity of CBS is enhanced by binding to the carboxy-terminus of SAM and glutathionylation of Cys^{346}, while it is suppressed by nitric oxide (NO) and carbon monoxide (CO) that bind to a heme group at its amino-terminus (153-154). A third enzyme, 3-mercaptopyruvate sulfurtransferase (3MPST or 3MST) produces H_2S by an enzymatic action involving cysteine aminotransferase (CAT), and by virtue of using D-amino-acid oxidase (DAO), generates H_2S from D-cysteine in presence of thioredoxin (153-154).

Glutathionylated CBS increases the production of cysteine and H_2S, which, in turn, promotes the production of other antioxidant species. For example, glutathione, a major antioxidant and reducing agent is produced in mitochondria by the metabolism of H_2S by sulfide quinone oxidoreductase (SQR). Metabolism of H_2S is also important to the formation of poly-sulfides that act as major cellular reservoirs for H_2S. Hydrogen sulfide (H_2S) exists in free form (20%), and dissociates readily in water and produces H^+, a large (80%) amount of HS^-, and trace amounts of S^{2-} (153-154). H_2S-derived sulfur sulfhydrates the reactive cysteine residues of target proteins and enzymes and changes their activity. Together, H_2S and other antioxidants as well as sulfane sulfur protect cells against diverse forms of injuries (155). For example, oxidative stress is a positive regulator of the trans-sulfuration pathway and it activates CBS, promotes conversion of methionine to cysteine and increases synthesis of GSH which protects cells by oxidation, by generating glutathione persulfide (GSSH or GSS^-). Cys^{346} of CBS can also be oxidized to a sulfenic acid which then reacts with glutathione.

H_2S exhibits a classical U-shaped dose response with negative impact at supra and sub-physiological levels and positive effect at physiological doses ranging from protection from ischemia-reperfusion injury to life-span extension (153-156). Exposure to a high concentration of H_2S leads to eye and olfactory irritation, neurotoxicity, inhibition of electron transport chain (ETC), respiratory distress, headache, edema and death (157). Dysregulated endogenous H_2S metabolism results in a range of pathologies from inflammation to β cell dysfunction and diabetes. Reduced levels of H_2S are associated with negative consequences. For example, mice with genetic defects in endogenous H_2S generating enzymes, CGL, or CBS have been shown to be susceptible to hypertension, neurodegenerative disorders, and vascular complications associated with diabetes and osteoporosis (158-161). There are additional evidence that supports the protective effect of H_2S in organ systems and age induced pathologies including a hypoxia-resistant reduced metabolic rate leading to suspended animation resembling torpor, reducing blood pressure by its action in causing vasodilation, protection against ischemia-reperfusion injury, improving glucose tolerance and insulin sensitivity, delaying cognitive decline in animal models of Alzheimer's disease, and increasing longevity in yeast, worms, and mammalian cells (106, 162-169). The generation of ROS is increased in knockouts of *MPST-1*, a major enzyme that drives the production of hydrogen sulfide in *C. elegans*. This deficit in the short lived animals could be overcome by the administration of H_2S donor, GY4137, which resulted in an extended life-span (170). This treatment also delayed the onset of detrimental impact of senescence as assessed by pharyngeal contraction and defecation (170).

3.7. p53

The p53 is a transcription factor with potent tumor suppressor properties that is known to regulate a large number of genes with effects on stress, metabolism, cell cycle, apoptosis, senescence and autophagy (171-178). p53 regulates mitochondrial energy metabolism and mitochondrial biogenesis (179). p53 also controls the mitochondrial integrity by inducing Mieap, a protein which removes oxidized proteins from mitochondria (180).

p53 is a potent inducer of antioxidant defense proteins and decreases aging-associated

oxidative stress (181). Different stresses trigger the phosphorylation of Ser-20 at the trans-activation domain of p53 protein (182). Unfortunately, the transcriptional activity of p53, p53-dependent apoptosis and efficiency of p53 in response to cellular stress, are significantly impaired by aging (183). The reduced p53 functional activity during aging has been attributed to decreased autophagy, and increase in oxidative stress, antagonistic effect of NFκB on p53 function and NFκB induced enhancement of the inflammatory responses (85, 174, 184-186).

In response to energy deficiency, AMPK activates p53 by phosphorylating it at Ser-15 causing cell cycle arrest (187). On the other hand, enforced expression of AMPKα2 increases the transcription of p53 gene and enhances its phosphorylation at Ser-46 leading to apoptotic cell death (188). Thus, activation of p53 comes at a cost since cells with active p53 undergo either cellular senescence or apoptosis (189).

By virtue of reducing development of cancer, p53 is considered to be an aging suppressor and aids in the extension of the life-span (190-192). The p53-deficient mice do not lend themselves to examine the role of p53 in aging since they die early from malignancy. However, two strains of mice that express full-length p53 along with the C-terminal fragment of p53 have shown premature aging (192). On the other hand, a null mutation in p66Shc, that is associated with an impairment of p53 and p21 stress response showed, a 30% increase in life-span (193). The activation of Arf/p53 pathway, likely by increased expression of antioxidant genes, delayed the aging process and reduced age-related damages in mice (194).

It is thought that some of the effects of p53 on organismal aging are mediated by autophagy (195-196). Cytoplasmic p53 represses autophagy whereas nuclear p53 has the opposite effect and stimulates the transcription of DNA-damage regulated autophagy modulator 1 (DRAM1) and Sestrin 2 proteins (186). It has become clear that while increased autophagy extends the life-span, its repression can lead to the accumulation of damaged molecules with an adverse effect on health-span and life-span (186, 197-198). p53 participates in autophagy by activation of mTOR and production of ROS (199-200).

Some of the effects of p53 on aging might be directed at IIS and mTOR pathways, known to induce aging or through MDM2, a major component of IIS and PKB/AKT kinase pathway (201). However, transgenic mice with an elevated p53 activity that exhibit high levels of circulating IGF-1 and tissue-activated IIS, have been shown to be both short- and long-lived (192, 202).

3.8. Growth hormone, insulin and insulin growth factor (IGF)

The evolutionarily conserved and ancient insulin and insulin-like growth factor (IGF) signaling (IIS) controls longevity and plays a major role in the growth, differentiation and metabolism, in response to changing environmental conditions and nutrient availability. Mutations that limit the extent of insulin/IGF-1 signaling dramatically increase life-span in *C. elegans, Drosophila melanogaster* and in several mouse models. After being hatched, *C. elegans* undergoes four successive juvenile (larval) stages before they mature to an adult hermaphrodite worm (203). During food scarcity, crowding and high temperature, the larvae of *C. elegans* exit the cycle of growth and development at the third larval stage, postpone reproduction and form the so called dauer larva which, under laboratory conditions, can survive up to eight times longer than normal (204). Daf mutants are often long-lived and exhibit dauer-like features, such as enhanced resistance to stress and/or changes in the metabolism of carbohydrates, lipids and amino acids. Cloning and sequencing of the daf mutants identified genes that exhibited a strong homology to components of the mammalian insulin and insulin-like growth factor (IGF) signal transduction cascade (IIS) (57-58, 150, 205). In *C. elegans,* in response to food or the sensory perception of food, insulin signaling leads to the secretion of multiple, insulin-like peptides that bind to a common single insulin/IGF-1 like tyrosine kinase receptor (DAF-2). Whereas reduction of function mutations in *daf-18* phospatase, a homologue of the mammalian phosphatase and tensin homolog, PTEN, abolished the life-span extensions of *daf-2* and *age-1* mutants, the reduction-of-function

mutations in *daf-2*, and the kinase components of the IIS pathway down-regulated IIS cascade in *C. elegans* and these animals remained active and youthful much longer than normal and their life-span was increased in by more than twofold (206).

Although the core of the insulin/IGF-1 signaling pathway is conserved in invertebrates to mammals, the mammalian IIS signaling has greatly increased in its complexity in the latter species (207). This increased complexity has made it difficult to separate the roles of growth hormone (GH), insulin, and IGF-1 in longevity. Yet, genetic and metabolic characteristics that are associated with a healthy life-span suggest that the IIS pathway is involved in setting the mammalian longevity. Reduced GH, insulin and IGF-1 signaling due to various mutations have been associated with long-lived phenotypes in mice (206). *FIRKO* mice, that lack the insulin receptor in adipose tissues, are also long lived and show reduction in fat depots and reduced age related loss of insulin sensitivity (208). Reduced IGF-1 signaling, due to mutation of its receptor, led to increased resistance to oxidative stress and long lived phenotypes in *Igf1r*$^{+/-}$ females, but not males (209). Whereas, mutation in *Klotho,* shortened life-span in mice, its overexpression, which inhibits IIS pathway, extended their life-span (136, 139).

GH which is released by the anterior pituitary gland controls mammalian growth and regulates the biosynthesis and release of IGF-1 by the liver and peripheral tissues. Four dwarf mouse models *Prop1df/df* , *Pit1dw/dw*, *GHRHRlit/lit* and *GHR*$^{-/-}$ that exhibited reduced IGF-1 production, reduced circulating levels of insulin and glucose and enhanced insulin sensitivity, were are long-lived (210-213). Longest life-extension has been seen in mouse mutants, the so-called GH deficient hypopituitary dwarfs and the GH resistant *GHR*$^{-/-}$ dwarfs, that show defective GH/IGF-1 and/or insulin. Enhancement of insulin sensitivity and reduced insulin levels appear to be the primary reasons for the longevity phenotype of these mice as well as in wild type mice that are subjected to caloric restriction (214).

In humans, it has been difficult to show the relationship of the GH/insulin/IGF-1 signaling to the longevity due to the complexity of these pathways. It can be speculated that low glucose, low insulin and preserved insulin sensitivity may represent key metabolic features of a human longevity phenotype. Defects in insulin signaling has led to insulin resistance and diabetes and defects in GH/IGF-1 caused defects in growth and an increased risk of cardiovascular disease (207, 213). Yet, there are telltale signs that GH/insulin/IGF-1 signaling plays a role in human aging. For example, there are several common polymorphisms in IIS genes that were associated with longevity and in Italian centenarians, genotype combinations at *IGF-IR* and *PI3KCB* genes, were associated with lower free IGF-I plasma levels (207, 214-216). Centenarians of Ashkenazi Jewish heritage that showed overrepresentation of heterozygous mutations in the IGF-1R gene had a small stature and elevated levels of serum IGF-1 (207, 214-216).

3.9. P13/AKT

Phosphatidylinositol 3-kinase (PI3K), along with AKT serine/threonine protein kinase and mTOR which is downstream of the insulin/PI3K pathway, are all involved in conveying the metabolic and mitogenic signals. P13Ks are a set of evolutionarily conserved and multi-faceted enzymes in flies to mammals that generate 3′ phosphoinositides from phosphatidylinositol in response to growth factors that together with mTOR appear to play a role in aging and life-span (217). The most common form, PI3K IA, is a functional heterodimer comprised of one catalytic and one regulatory unit, encoded by p85α, p85β, and p55γ genes (218-220). Adapter proteins, such as insulin receptor substrate proteins (IRS1-4), by binding to the tyrosine residues, activate PI3K and AKT, which regulate downstream targets including GSK3β and mTOR (221-222).

Activated PI3K phosphorylates and activates and localizes its down-stream mediator, AKT, to the plasma membrane (222). AKT, in turn, can activate a number of other factors and pathways including FOXO, and mTOR (222-223). Activation of AKT is essential to the PI3K-dependent regulatory pathways that participate in cellular response to oxidative stress whereas inactivation of DJ-1, a *Drosophila* homologue, impairs phosphatidylinositol

3-kinase/Akt signaling and response to oxidative stress (224-225). The pharmacological inhibition of PI3K, or induced expression of dominant-negative AKT induces cell death during oxidative stress (226-228). High cholesterol intake which impairs insulin signaling, increases serine phosphorylation of IRS1, PI3K and AKT activities, and increases oxidative stress (229).

Mutations in some genes that regulate P13K have been shown to extend life-span. For example, in *C. elegans*, the mutation in the catalytic sub-unit homologue of mammalian P13K, Age-1 or loss of CHICO, a *Drosophila* insulin receptor substrate protein, have led to increased life-span (230-232). Reducing the activation of the PI3K/AKT/mTOR pathway significantly increases the longevity in mice as well (233). Common variants of both FOXO3A and AKT1 were associated with longer life-span in three independent Caucasian cohorts (233-234). Residing down-stream from P13K/AKT, the activity of mTOR appears to be low in centenarian individuals (235). Thus, longevity seems to be intimately linked to the reduced activity of the IIS/PI3K/AKT/mTOR pathways, suggesting that these signaling pathways are important targets for pharmacological manipulation for extension of life (236).

3.10. mTOR

mTOR is a 289-kDa serine-threonine kinase that senses cellular nutrient levels. mTOR integrates both intracellular and extracellular signals and serves as a central hub for cell metabolism, growth, proliferation and survival (237). De-regulated mTOR has been described in diverse age related diseases such as type 2 diabetes (238-240). Moreover, there is by now, substantial evidence that mTOR is a negative regulator of life-span. In *Drosophila melanogaster*, life extension can be achieved by the overexpression of TOR suppressors, dTsc1 of dTsc2, or expression of dominant-negative forms of dTOR or dS6K 38. By using genetic manipulation, it was shown that depletion of TOR (*let-363*) or RAPTOR (mTORC1 protein member; *daf-15*) by RNA interference (RNAi) in *C. elegans* or deletion of SCH9, a S6K homologue in *Saccharomyces cerevisiae*, extends life-span in both models (241-243).

The central role of mTOR along with insulin and insulin growth factor 1 (IGF-1) in regulating life-span is attributable to the actions of these signaling networks as a sensor of nutrients. Such pathways including insulin, IGF-1, P13L/AKT, RAS, RAF, MEK, and ERK, all converge on mTOR, making it central to regulation of amino acid availability, mitochondrial metabolism and biogenesis, rate of protein synthesis and proteostasis, lipid synthesis and energy utilization and homeostasis, cellular senescence, unfolded protein response, autophagy, and proteosomal degradation (244). mTOR is now considered to be essential in delaying the development of age related pathologies and in the life extension by strategies such as calorie restriction (238). One of the prime examples that nutrition has a significant impact on aging has been shown by introducing calorie restriction of the diet without causing malnutrition in animals. Such measures have been able to extend life-span and health-span in rodents to monkeys (245-249). Food scarcity drives the larvae of *C. elegans* to enter a dauer stage that remain metabolically in-active for months until the environmental conditions become hospitable to life. Thus, halting metabolism effectively increases life-span of animals in dauer stage for months (250). Obtaining such metabolic arrest also allows the seeds and spores of bacteria and fungi to gain considerable extension of life for at least 2000 years when preserved in amber and for millions of years in high salt (251-252).

3.11. PKA

The multi-unit holoenzyme, Protein Kinase A (PKA), has four regulatory sub-units (RIα, RIβ, RIIα, RIIβ) and three catalytic sub-units (Cα, Cβ, Cγ) that show a varied tissue distribution and cellular expression (253-254). In mammals, nutrients are sensed by a G-protein (GEF) that activates adenylyl cylase (AC) (255). AC produces cAMP, which binds to the regulatory subunits of the PKA, releasing the catalytic subunits which either interact with other signaling proteins, or enter the nucleus and activate gene transcription. Activated PKA phosphorylates serine and

threonine residues and mediates the signal transduction of G-protein-coupled receptors (255).

The regulation of oxidative stress, mitochondrial function, and cell survival appear to require the joint participation of AMPK and PKA signaling (256). The regulation of mitochondrial function and oxidative stress by the mitochondrial-directed scaffold of PKA, requires dual-specificity A-kinase anchoring protein 1 (D-AKAP1)(256). The actions of AMPK and PKA are down-regulated in age related pathologies including diabetes, cardiovascular diseases and ischemia and the protective effect of type II regulatory subunit of PKA (PKA/RII*β*) as well as D-AKAP1 diminishes by their reduced mRNA levels in adipocytes and subcutaneous adipose tissues by obesity (257-258). On the other hand, reducing total caloric intake to 20–40% of normal intake which leads to life-span extension, has been attributed to involve down-regulating effect on mTOR-S6 kinase pathway, insulin and insulin-like signaling (IIS) as well as its effect on Ras/cAMP/PKA/Rim15/Msn2/4 and the Tor/Sch9/Rim15/Gis1 pathways (259-262). It is noteworthy that the anti-aging effect caused by the in-activation of both pathways is much more potent than that caused by CR alone (263-264). In yeast, CR and peroxiredoxin promote longevity and H_2O_2-resistance through redox-modification of PKA (265). BMH1 14-3-3 protein, which extends chronological life-span in *Saccharomyces cerevisiae*, appears to act by activating the stress response and by virtue of genetically interacting with CR and conserved nutrient-sensing TOR- and PKA-signaling pathways (266).

In eukaryotic cells, intracellular pH is significant to protein folding, enzyme activity, vesicle trafficking, and organellar function and integrity as well as aging. For this reason, the pH is exquisitely and dynamically regulated in tissues and cells by multiple mechanisms such as the plasma membrane H^+-ATPase, Pma1 and the vacuolar V-ATPase. Both PKA and the TORC1-Sch9 axis regulate the proton pumping activity of the V-ATPase and possibly Pma1 and, in turn, the proton pump acts as a second messenger for availability of glucose by the V-ATPase to PKA and TORC1-Sch9 (267). The replicative and chronological aging in yeast appear to require three kinases: Sch9, PKA and TOR (268). The stress response proteins, namely transcription factors Msn2 and Msn4, that lead to increased longevity, are associated with decreased activity of either Sch9, PKA, or TOR (268).

The impact of Sir2 on DR-mediated extension of life also depends on cAMP-PKA and casein kinase 2 (CK2) signaling in yeast (269). Sir2 partially represses the transcription of life-span-associated genes, such as PMA1 (encoding an H^+-ATPase) and many ribosomal genes, an effect that is inhibited by active cAMP-PKA and CK2 signaling (269).

Mutations that decrease the activity of the Ras/Cyr1/PKA pathway extend longevity and increase stress resistance by activating transcription factors Msn2/Msn4 and the mitochondrial antioxidant enzyme superoxide dismutase (Sod2) (270). Additional evidence for the involvement of PKA in aging has been shown in male and not female mice that lack the regulatory RIIβ subunit (271). These mice have extended life-span, show reduced insulin resistance, and protection against age related pathologies including cardiac dysfunction and hypertrophy, weight gain, and enlargement of liver. These positive impacts of PKA inhibition appear to involve AMPK, and β-adrenergic pathway (271).

Since PKA is part of the signaling cascade that regulates metabolism and aging processes and for this reason is an ideal target in anti-aging strategies. Hydralazine, a FDA-approved drug used for the treatment of high blood pressure and heart failure, has recently been shown to increase the life-span in *C. elegans* in high glucose or stress conditions. These actions of hydralazine appear to involve activation and improved mitochondrial function and metabolic homeostasis via the SIRT1/SIRT5 axis and the NRF2/SKN-1 pathway and by targeting, binding and stabilizing the catalytic sub-unit of PKA (272). Similarly, the life extension by lithocholic acid (LCA) in yeast appears to involve the cAMP/protein kinase A (cAMP/PKA) as well as adaptable target of rapamycin (TOR) and signaling pathways that are under the stringent control of calorie usage (273). LCA extends the life-span by a housekeeping longevity assurance program that is

not purely governed by the adaptable pro-aging TOR and cAMP/PKA pathways. Rather, LCA modulates longevity by reduced lipid-induced necrosis and mitochondrial induced apoptosis, by altering oxidation-reduction processes in mitochondria, enhancing stability of nuclear and mitochondrial DNA and promoting resistance to oxidative and thermal stress (273).

3.12. RAS, RTK, MEK, ERK, and MAPK

RAS genes, which encode small 21 kDa (p21) GTPase proteins, were originally identified as viral genes that account for the highly oncogenic properties of RNA tumor viruses and which appear at a high frequency in a large number of human cancers and are risk factors for age related disorders such as cancer, diabetes, as well as cardiovascular and neurodegenerative diseases (274-278). Ras protein family in mammals include N-RAS, H-RAS, K-RAS4A and K-RAS4B. Ras encompasses a large superfamily of proteins that are involved in signal transduction, conveying signals from surface bound receptor tyrosine kinases (RTKs) in response to cytokines, growth factors and hormones and which integrates with RTK, MEK, ERK, and MAPK pathways (279). Ras proteins are binary molecular switches, that cycle through an in-active GDP-bound and active GTP-bound states. The cytoplasmic tail of the activated RTKs recruit the Grb2 adaptor protein which binds to the Ras-GEF, SOS, and this, in turn, localizes Ras to the activated RTK-bound complex. Significant structural changes in switch regions of I and II components of Ras that exists in an active GTP-bound conformation, forms a GTP-dependent interface. In this conformation, Ras binds downstream effector molecules including Raf, which initiates a phosphorylation cascade via MEK and the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK). Activated ERK phosphorylates multiple cytoplasmic and cytoskeletal proteins, including MAPK-activated protein kinases and ribosomal S6 kinase (280-281). Finally, ERK activated by Ras signaling translocates to the nucleus, phosphorylating and activating several transcription factors including members of the E-twenty-six (ETS) transcription factor family (282). Ras proteins are involved in cell division and differentiation to metabolism, senescence and apoptosis (283). In yeast, the Ras proteins are part of the nutrient signaling pathway that includes cyclic AMP (cAMP) and protein kinase A (PKA) (284). Ras proteins are regulated by the activities of guanine nucleotide exchange factors (GEFs) that catalyze the replacement of GDP by GTP and GTPase activating proteins (GAPs) that increase the rate of GTP hydrolysis (285-286).

Given their broad actions, it is not surprising that Ras proteins are directly or in-directly involved in aging and in replicative life-span in different species from fungi, flies, and worms to mammals. For example, two Ras homologues, RAS1 and RAS2 in *Saccharomyces cerevisiae* influence both replicative and chronological life-span and deletion of RAS1 has been shown to extend the replicative life-span whereas deletion of RAS2 extends chronological life-span (284, 287-288). Such life-extension by deletion of Ras has been attributed to their effects by endowing stress resistance by Sch9 in yeast and by Msn2/Msn4 and Sod2m which are activated in response to RAS-cAMP-PKA signaling, in *Saccharomyces cerevisiae* (241, 281, 289-290). Both MSN2 and MSN4 are considered to be the link between calorie restriction and sirtuin-mediated life-span extension in *Saccharomyces cerevisiae* (291). Genetic inhibition of either Ras or ERK has been shown to extend the life-span in *Drosophila melanogaster* (292). Expression of an activated form of AOP, a transcriptional repressor that is inhibited by Ras activation, also has led to extension of life-span in this fly (293). Similarly, Trametinib, an inhibitor of the upstream kinase, MEK which also inhibits ERK, extended life-span in *Drosophila* (292). Similarly, in *C. elegans*, Ras Let-60 protein has been shown to modulate the effects of insulin/IGF-1 in aging (294). Mice that were deficient for *RasGrf1*, which acts downstream of insulin and IGF-1 receptors, were long-lived, and showed increased SIRT1 expression, lower circulating IGF-1 levels and resistance against oxidative stress, and development of cancer (295-296). However, since RasGrf1 also has an affinity for other ligands, including Rac, Rho, it is not clear that the longevity induced by RasGrf1 deficiency is merely through specific inhibition of Ras (277, 278, 297). The genetic variants of *HRAS1* and *APOE*, which

interact synergistically, are associated with extended health-span and life-span in humans (298-299). Costello syndrome, that arises in humans due to mutations in *HRAS* , is characterized by a short stature, failure to thrive, and oftentimes is associated with premature aging (300). Finally, HGPS that is associated with progeria and shortened life has been shown to be associated with up-regulation of mTOR, IGF1R, IP3, and ERK, showing that HRAS and activity of its downstream effector, ERK, are involved in human aging (301).

3.13. CRTC-1/CREB

CREB and its co-activators, cAMP-response element binding protein (CREB)-regulated transcription co-activators (CRTC)s, have emerged as sensors of hormonal and metabolic signals, energy homeostasis, and endoplasmic reticulum (ER) mediated stress (302-303). In mammals, CRTCs are co-activators of CREB-mediated gene expression (303). More importantly, after their activation, CREB and CRTCs are involved in mediating the effects of feeding as well as fasting signals on the expression of metabolic programs in insulin-sensitive tissues. Besides CRTC, many kinases, e.g. protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinases II/IV and p90 ribosomal S6 kinase, p90RSK, activate CREB-mediated gene transcription (303-304). It is notable that among these, the inhibition of PKA signaling, has been shown to enhance health-span while other studies have shown a link between the activation of calcineurin through dysregulation of Ca^{2+} and accelerated aging whereas calcineurin deficiency which increases autophagy, extends the life-span in *C. elegans* by altering the expression of *bec-1* and *atg-7* (263, 305-308).

To increase the transcription of target genes, the in-active, phosphorylated cytoplasmic CRTC gets activated by dephosphorylation by protein phosphatases such as calcineurin, and following this activation, migrates to the nucleus where it binds to CREB factors (309). The nuclear translocation of CRTC-1 is blocked by phosphorylation by AAK-2/AMPK, an effect that is associated with increase in life-span in *C. elegans* showing that factors that inhibit the CRTC-induced CREB activation pathway are involved in the regulation of aging (303).

The CREB co-activator, TORC2, has been found to regulate fasting glucose metabolism, to stimulate the gluconeogenic program along with the forkhead factor FOXO1 and to endow stress resistance in *Drosophila* (310-311). TORC2 activation appears to underlie the effect of starvation in *Drosophila* (311). Moreover, the life-span extension in *C. elegans* is mediated by the CRTC-1 and CREB through AMPK and catecholamine by reprogramming the mitochondrial and metabolic signals (303, 312).

CRTCs modulate organismal aging in *C. elegans* and appear to be involved in age-related diseases in humans. CRTCs have been implicated in neurodegenerative diseases and their deregulation appears to increase the risk of age related pathologies including Alzheimer's disease, and Huntington's disease (313-316). Activation of the CRH-1/CREB axis by CMK-1/CaMKI in the AFD thermosensory neurons appears to regulate the life-span in *C. elegans* at warm temperatures (317).

3.14. NFκB

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is required for adaptive changes in gene expression and tissue homeostasis (318). NFκB is responsive to oxidative stress, DNA damage, immune activation and growth regulatory signals, and controls cell proliferation, innate and adaptive immunity, inflammation, and apoptosis. Interestingly, *NFKB*1 gene in humans resides within a genetic locus on chromosome four that is associated with human longevity (319).

NFκB appears to be important in aging processes that are associated with inflammation during aging, the so-called inflammaging. Inflammatory response is initiated by activation of NFκB in macrophages which aggravates much of age related metabolic disturbances (320). Several age-related metabolic disorders, e.g. obesity, type 2 diabetes and atherosclerosis have been shown to lead to chronic inflammation due to increased NFκB signaling, a process that can be effectively

suppressed by AMPK leading to FoxO signaling and AMPK activators including some non-steroidal anti-inflammatory drugs, e.g. aspirin and flufenamic acid (26, 321-322). DNA-binding activity of NFκB complexes are significantly increased with aging leading to an increase in levels of p52 and p65 components of NFκB complex in several tissues of mice and rats (323-325). NFκB actively interacts with several regulators of aging. For example, FoxO factors, FoxO3a and FoxO4 are effective inhibitors of NFκB signaling and can prevent immune responses (326-327). FOXO3a, a homolog of the longevity gene *DAF-16 in C. elegans,* which is also strongly associated with human longevity, represses NFκB nuclear translocation and transcriptional activity (326, 328). SIRT1, that deactivates NFκB by binding and deacetylating the p65 RELA, is known to underlie the life extension by calorie restriction (329).

The NFκB signaling is also subject to regulation by Nrf2 which reduces inflammatory response and conversely, the p65 component of NFκB complex binds to the Kelch-like ECH-associated protein 1 (Keap1) protein, and inhibits Nrf2 signaling. This, in turn, leads to increased localization of Keap1 into the nuclei and consequently reduces the binding of Nrf2 to its target sites (330). Decrease or deficiency in Nrf2 signaling during aging increases the inflammatory phenotype (331). Paradoxically, *in vitro* sustained pharmacological activation of Nrf2 in fibroblasts promotes the deposition of a matrix rich in plasminogen activator inhibitor-1 (PAI-1) that induces senescence (332). The *in vivo* sustained pharmacological activation of Nrf2 in fibroblasts promotes wound healing but also induces tumors in the skin. However, it can not be ruled out that such effects might be due to off-target effects of the drug.

An emerging concept is that aging is not a passive process, rather, age dependent disorders require active maintenance. Although it is not clear why NFκB gets activated during aging, diverse lines of studies show that NFκB appears to enforce and is required for the persistence of the global transcriptional program and tissue phenotypes that are hallmarks of aging. The analysis by using microarray of *cis*-regulatory motifs across nine tissue types in humans and mice revealed fourteen motifs that predict age dependent gene expression. Among these, the role of NFκB was tested by its inducible blockade in the epidermis of aged mice. The results were consistent with the idea that continuous activation of NFκB, which controls cell cycle exit and gene expression, is required for the maintenance of tissue specific aging and that blockade of NFκB reverses the age related gene expression signature, leads to resumption of cell proliferation and reduces senescence (333). In support of adverse effects of NFκB in aging, there are also *in vitro* studies that show that NFκB regulates cellular senescence (334-337). Activation of NFκB can lead to age related complications ranging from insulin resistance, to muscle atrophy and amyloid-beta toxicity (338-340). Therefore, it follows that although aging results from a lifetime of sequential accumulation of damage that lead to senescence and halt the proliferation and cellular functions, such changes are reversible by inhibition of NFκB that maintains the aging phenotype. The effect of NFκB is likely not mediated through a small number of genes, rather, expression of many target genes must be controlled to impart a youthful phenotype. This has been shown for DAF-16 that targets hundreds of genes and extends life-span in *C. elegans*. Mere inhibition of single genes, that are controlled by DAF-16, had a significantly less effect, as compared to the RNA interference induced inhibition of a wide range of genes that participate in stress response and metabolism (55).

4. CONCLUSIONS

We have witnessed a great advance in our understanding of aging, the signaling pathways that are implicated and the downstream effectors that are required for cellular homeostasis. However, our knowledge regarding the main and proximal cause of cellular alterations that lead to the age related decline in cellular functions and the real cause of aging have, thus far, eluded us. It is greatly hoped, that we can prolong a healthy life-span, reduce the age related pathologies that place a significant economic burden on our societies, and to devise strategies to reverse aging.

5. REFERENCES

1. Shay JW, Wright WE. Hallmarks of

telomeres in ageing research. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. Jan 211. (2):114-23. (2007)
DOI: 10.1002/path.2090
PMid:17200948

2. Pawelec, Graham. "Hallmarks of human "immunosenescence": adaptation or dysregulation?. " 9-15. (2012)
DOI: 10.1186/1742-4933-9-15
PMid:22830639 PMCid:PMC3416738

3. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. Jun 6 153. (6):1194-217. (2013)
DOI: 10.1016/j.cell.2013.05.039
PMid:23746838 PMCid:PMC3836174

4. Michan S. Calorie restriction and NAD?/sirtuin counteract the hallmarks of aging. Frontiers in Bioscience. (Landmark Edition). Jun 1 19:1300-19. (2014)
DOI: 10.2741/4283
PMid:24896352

5. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. Jun 6 153. (6):1194-217. (2013)
DOI: 10.1016/j.cell.2013.05.039
PMid:23746838 PMCid:PMC3836174

6. Guerville F, Barreto PD, Ader I, Andrieu S, Casteilla L, Dray C, Fazilleau N, Guyonnet S, Langin D, Liblau R, Parini A. Revisiting the Hallmarks of Aging to Identify Markers of Biological Age. The Journal of prevention of Alzheimer's disease. Jan 1:1-9. (2020)

7. Liochev SI Reflections on the Theories of Aging, of Oxidative Stress, and of Science in General. Is It Time to Abandon the Free Radical. (Oxidative Stress) Theory of Aging? Liochev SI Antioxid Redox Signal. Jul 20 23. (3):187-207. (2015)
DOI: 10.1089/ars.2014.5928
PMid:24949668

8. Gems D, de la Guardia Y Alternative Perspectives on Aging in Caenorhabditis elegans: Reactive Oxygen Species or Hyperfunction? Antioxid Redox Signal. Jul 20 19. (3):321-9). (2013)
DOI: 10.1089/ars.2012.4840
PMid:22870907 PMCid:PMC5395017

9. Zimniak P What is the Proximal Cause of Aging? Front Genet. 3:189. (2012)
DOI: 10.3389/fgene.2012.00189
PMid:23056007 PMCid:PMC3455862

10. Steinberg GR, Kemp BE. AMPK in health and disease. Physiological reviews. Jul;89(3):1025-78. (2009)
DOI: 10.1152/physrev.00011.2008
PMid:19584320

11. Hardie DG. AMP-activated protein kinase-an energy sensor that regulates all aspects of cell function. Genes & development. Sep 15;25(18):1895-908. (2011)
DOI: 10.1101/gad.17420111
PMid:21937710 PMCid:PMC3185962

12. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nature cell biology. Sep;13(9):1016-23. (2011)
DOI: 10.1038/ncb2329
PMid:21892142 PMCid:PMC3249400

13. Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Mäkelä TP, Alessi DR, Hardie DG. Complexes between the LKB1 tumor suppressor, STRADa/ß and MO25a/ß

are upstream kinases in the AMP-activated protein kinase cascade. Journal of biology. Dec 1 2. (4):28. (2003)
DOI: 10.1186/1475-4924-2-28
PMid:14511394 PMCid:PMC333410

14. Hurley RL, Anderson KA, Franzone JM, Kemp BE, Means AR, Witters LA. The Ca2+/calmodulin-dependent protein kinase kinases are AMP-activated protein kinase kinases. Journal of Biological Chemistry. Aug 2 280. (32):29060-6. (2005)
DOI: 10.1074/jbc.M503824200
PMid:15980064

15. Momcilovic M, Hong SP, Carlson M. Mammalian TAK1 activates Snf1 protein kinase in yeast and phosphorylates AMP-activated protein kinase *in vitro*. Journal of Biological Chemistry. Sep 1 281. (35):25336-43. (2006)
DOI: 10.1074/jbc.M604399200
PMid:16835226

16. Mantovani J, Roy R. Re-evaluating the general. (ized) roles of AMPK in cellular metabolism. Febs Letters. Apr 6 585. (7):967-72. (2011)
DOI: 10.1016/j.febslet.2010.12.015
PMid:21182839

17. Lim CT, Kola B, Korbonits M. AMPK as a mediator of hormonal signalling. Journal of molecular endocrinology. Feb 1 44. (2):87. (2010)
DOI: 10.1677/JME-09-0063
PMid:19625456

18. Richter EA, Ruderman NB. AMPK and the biochemistry of exercise: implications for human health and disease. Biochemical Journal. Mar 1 418. (2):261-75. (2009)
DOI: 10.1042/BJ20082055
PMid:19196246 PMCid:PMC2779044

19. Steinberg GR, Kemp BE. AMPK in health and disease. Physiological reviews. Jul 89. (3):1025-78. (2009)
DOI: 10.1152/physrev.00011.2008
PMid:19584320

20. Marley AE, Sullivan JE, Carling D, Abbott WM, Smith GJ, Taylor IW, Carey F, Beri RK. Biochemical characterization and deletion analysis of recombinant human protein phosphatase 2Ca. Biochemical Journal. Dec 15 320. (3):801-6. (1996)
DOI: 10.1042/bj3200801
PMid:9003365 PMCid:PMC1218000

21. Gimeno-Alcañiz JV, Sanz P. Glucose and type 2A protein phosphatase regulate the interaction between catalytic and regulatory subunits of AMP-activated protein kinase. Journal of molecular biology. Oct 10 333. (1):201-9. (2003)
DOI: 10.1016/j.jmb.2003.08.022
PMid:14516753

22. Hardie DG. AMP-activated protein kinase-an energy sensor that regulates all aspects of cell function. Genes & development. Sep 15 25. (18):1895-908. (2011)
DOI: 10.1101/gad.17420111
PMid:21937710 PMCid:PMC3185962

23. Xie Z, Zhang J, Wu J, Viollet B, Zou MH. Upregulation of mitochondrial uncoupling protein-2 by the AMP-activated protein kinase in endothelial cells attenuates oxidative stress in diabetes. Diabetes. Dec 1 57. (12):3222-30. (2008)
DOI: 10.2337/db08-0610
PMid:18835932 PMCid:PMC2584127

24. Li XN, Song J, Zhang L, LeMaire SA, Hou X, Zhang C, Coselli JS, Chen L, Wang XL, Zhang Y, Shen YH. Activation of the AMPK-FOXO3 pathway reduces fatty acid-induced increase in intracellular

reactive oxygen species by upregulating thioredoxin. Diabetes. Oct 1 58. (10):2246-57. (2009)
DOI: 10.2337/db08-1512
PMid:19592618 PMCid:PMC2750236

25. Yang Z, Kahn BB, Shi H, Xue BZ. Macrophage a1 AMP-activated protein kinase. (a1AMPK) antagonizes fatty acid-induced inflammation through SIRT1. Journal of Biological Chemistry. Jun 18 285. (25):19051-9. (2010)
DOI: 10.1074/jbc.M110.123620
PMid:20421294 PMCid:PMC2885183

26. Salminen A, Hyttinen JM, Kaarniranta K. AMP-activated protein kinase inhibits NF-kB signaling and inflammation: impact on healthspan and lifespan. Journal of molecular medicine. Jul 1 89. (7):667-76. (2011)
DOI: 10.1007/s00109-011-0748-0
PMid:21431325 PMCid:PMC3111671

27. Liu XM, Peyton KJ, Shebib AR, Wang H, Korthuis RJ, Durante W. Activation of AMPK stimulates heme oxygenase-1 gene expression and human endothelial cell survival. American Journal of Physiology-Heart and Circulatory Physiology. Jan 300. (1):H84-93. (2011)
DOI: 10.1152/ajpheart.00749.2010
PMid:21037234 PMCid:PMC3023251

28. Voss M, Paterson J, Kelsall IR, Martín-Granados C, Hastie CJ, Peggie MW, Cohen PT. Ppm1E is an in cellulo AMP-activated protein kinase phosphatase. Cellular signalling. Jan 1 23. (1):114-24. (2011)
DOI: 10.1016/j.cellsig.2010.08.010
PMid:20801214

29. Apfeld J, O'Connor G, McDonagh T, DiStefano PS, Curtis R. The AMP-activated protein kinase AAK-2 links energy levels and insulin-like signals to lifespan in C. elegans. Genes & development. Dec 15 18. (24):3004-9. (2004)
DOI: 10.1101/gad.1255404
PMid:15574588 PMCid:PMC535911

30. Curtis R, O'Connor G, DiStefano PS. Aging networks in Caenorhabditis elegans: AMP-activated protein kinase. (aak-2) links multiple aging and metabolism pathways. Aging cell. Apr 5. (2):119-26. (2006)
DOI: 10.1111/j.1474-9726.2006.00205.x
PMid:16626391

31. Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans healthspan via AMPK, LKB1, and SKN-1. PloS one. Jan 18 5. (1):e8758. (2010)
DOI: 10.1371/journal.pone.0008758
PMid:20090912 PMCid:PMC2807458

32. Funakoshi M, Tsuda M, Muramatsu K, Hatsuda H, Morishita S, Aigaki T. A gain-of-function screen identifies wdb and lkb1 as lifespan-extending genes in Drosophila. Biochemical and biophysical research communications. Feb 25 405. (4):667-72. (2011)
DOI: 10.1016/j.bbrc.2011.01.090
PMid:21281604

33. Viollet B, Andreelli F, Jørgensen SB, Perrin C, Flamez D, Mu J, Wojtaszewski JF, Schuit FC, Birnbaum M, Richter E, Burcelin R. Physiological role of AMP-activated protein kinase. (AMPK): insights from knockout mouse models. 31, 216-219. (2003)
DOI: 10.1042/bst0310216
PMid:12546688

34. Lage R, Diéguez C, Vidal-Puig A, López

M. AMPK: a metabolic gauge regulating whole-body energy homeostasis. Trends in molecular medicine. Dec 1 14. (12):539-49. (2008)
DOI: 10.1016/j.molmed.2008.09.007
PMid:18977694

35. Reznick RM, Zong H, Li J, Morino K, Moore IK, Hannah JY, Liu ZX, Dong J, Mustard KJ, Hawley SA, Befroy D. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. Cell metabolism. Feb 7 5. (2):151-6. (2007)
DOI: 10.1016/j.cmet.2007.01.008
PMid:17276357 PMCid:PMC1885964

36. Ljubicic V, Hood DA. Diminished contraction-induced intracellular signaling towards mitochondrial biogenesis in aged skeletal muscle. Aging cell. Aug 8. (4):394-404. (2009)
DOI: 10.1111/j.1474-9726.2009.00483.x
PMid:19416128

37. Qiang W, Weiqiang K, Qing Z, Pengju Z, Yi L. Aging impairs insulin-stimulated glucose uptake in rat skeletal muscle via suppressing AMPKa. Experimental & molecular medicine. Aug 39. (4):535-43. (2007)
DOI: 10.1038/emm.2007.59
PMid:17934342

38. Turdi S, Fan X, Li J, Zhao J, Huff AF, Du M, Ren J. AMP-activated protein kinase deficiency exacerbates aging-induced myocardial contractile dysfunction. Aging cell. Aug 9. (4):592-606. (2010)
DOI: 10.1111/j.1474-9726.2010.00586.x
PMid:20477759 PMCid:PMC2910211

39. Viollet B, Horman S, Leclerc J, Lantier L, Foretz M, Billaud M, Giri S, Andreelli F. AMPK inhibition in health and disease. Critical reviews in biochemistry and molecular biology. Aug 1 45. (4):276-95. (2010)
DOI: 10.3109/10409238.2010.488215
PMid:20522000 PMCid:PMC3132561

40. Paik JH, Kollipara R, Chu G, Ji H, Xiao Y, Ding Z, Miao L, Tothova Z, Horner JW, Carrasco DR, Jiang S. FoxOs are lineage-restricted redundant tumor suppressors and regulate endothelial cell homeostasis. Cell. Jan 26 128. (2):309-23. (2007)
DOI: 10.1016/j.cell.2006.12.029
PMid:17254969 PMCid:PMC1855089

41. Jacobs FM, Van der Heide LP, Wijchers PJ, Burbach JP, Hoekman MF, Smidt MP. FoxO6, a novel member of the FoxO class of transcription factors with distinct shuttling dynamics. Journal of Biological Chemistry. Sep 19 278. (38):35959-67. (2003)
DOI: 10.1074/jbc.M302804200
PMid:12857750

42. Zanella F, Link W, Carnero A Understanding FOXO, new views on old transcription factors. Curr. Cancer Drug Targets 10, 135-146. (2010)
DOI: 10.2174/156800910791054158
PMid:20088800

43. Genin EC, Caron N, Vandenbosch R, Nguyen L, Malgrange B Concise review: forkhead pathway in the control of adult neurogenesis. Stem Cells 32, 1398-1407. (2014)
DOI: 10.1002/stem.1673
PMid:24510844

44. Kaestner KH, Knochel W, Martinez DE Unified nomenclature for the winged helix/forkhead transcription factors. Genes Dev. 14, 142-146. (2000)

45. Hannenhalli S, Kaestner KH The

evolution of Fox genes and their role in development and disease. Nat. Rev. Genet. 10, 233-240. (2009)
DOI: 10.1038/nrg2523
PMid:19274050 PMCid:PMC2733165

46. Carter ME, Brunet A. FOXO transcription factors. Current Biology. Feb 20 17. (4):R113-4. (2007)
DOI: 10.1016/j.cub.2007.01.008
PMid:17307039

47. Biggs WH 3rd, Meisenhelder J, Hunter T, Cavenee WK, Arden KC Protein kinase B/Akt-mediated phosphorylation promotes nuclear exclusion of the winged helix transcription factor FKHR1. Proc. Natl Acad. Sci. USA 96, 7421-7426. (1999)
DOI: 10.1073/pnas.96.13.7421
PMid:10377430 PMCid:PMC22101

48. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, Arden KC, Blenis J, Greenberg ME Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell 96, 857-868. (1999)
DOI: 10.1016/S0092-8674(00)80595-4

49. Henderson ST, Johnson TE daf-16 integrates developmental and environmental inputs to mediate aging in the nematode Caenorhabditis elegans . Curr. Biol. 11, 1975-1980. (2001)
DOI: 10.1016/S0960-9822(01)00594-2

50. Lin K, Hsin H, Libina N, Kenyon C Regulation of the Caenorhabditis elegans longevity protein DAF-16 by insulin/IGF-1 and germline signaling. Nat. Genet. 28, 139-145. (2001)
DOI: 10.1038/88850
PMid:11381260

51. Calnan DR, Brunet A The FoxO code. Oncogene 27, 2276-2288. (2008)
DOI: 10.1038/onc.2008.21
PMid:18391970

52. Webb AE, Brunet A FOXO transcription factors: key regulators of cellular quality control. Trends Biochem. Sci. 39, 159-169. (2014)
DOI: 10.1016/j.tibs.2014.02.003
PMid:24630600 PMCid:PMC4021867

53. Furuyama T, Nakazawa T, Nakano I, Mori N. Identification of the differential distribution patterns of mRNAs and consensus binding sequences for mouse DAF-16 homologues. Biochem J. 349:629-634. (2000)
DOI: 10.1042/bj3490629
PMid:10880363 PMCid:PMC1221187

54. Guo S, Rena G, Cichy S, He X, Cohen P, Unterman T Phosphorylation of serine 256 by protein kinase B disrupts transactivation by FKHR and mediates effects of insulin on insulin-like growth factor-binding protein-1 promoter activity through a conserved insulin response sequence. J. Biol. Chem. 274, 17184-17192. (1999)
DOI: 10.1074/jbc.274.24.17184
PMid:10358076

55. Murphy CT, McCarroll SA, Bargmann CI, Fraser A, Kamath RS, Ahringer J, Li H, Kenyon C Genes that act downstream of DAF-16 to influence the lifespan of Caenorhabditis elegans . Nature 424, 277-283. (2003)
DOI: 10.1038/nature01789
PMid:12845331

56. Greer EL, Brunet A. Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in C. elegans. Aging cell. Apr 8. (2):113-27. (2009)
DOI: 10.1111/j.1474-9726.2009.00459.x

PMid:19239417 PMCid:PMC2680339

57. Lin K, Dorman JB, Rodan A, Kenyon C daf-16: an HNF-3/forkhead family member that can function to double the life-span of Caenorhabditis elegans . Science. (New York, NY) 278, 1319-1322. . (1997)
DOI: 10.1126/science.278.5341.1319
PMid:9360933

58. Ogg S, Paradis S, Gottlieb S, Patterson GI, Lee L,) HA, Ruvkun G The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in C. elegans . Nature 389, 994-999. . (1997)
DOI: 10.1038/40194
PMid:9353126

59. Willcox BJ, Willcox DC, He Q, Curb JD, Suzuki M Siblings of Okinawan centenarians share lifelong mortality advantages. J. Gerontol. A Biol. Sci. Med. Sci. 61, 345-354. (2006)
DOI: 10.1093/gerona/61.4.345
PMid:16611700

60. Anselmi CV, Malovini A, Roncarati R, Novelli V, Villa F, Condorelli G, Bellazzi R, Puca AA Association of the FOXO3A locus with extreme longevity in a southern Italian centenarian study. Rejuvenation Res. 12, 95-104. (2009)
DOI: 10.1089/rej.2008.0827
PMid:19415983

61. Flachsbart F, Caliebe A, Kleindorp R, Blanché H, von Eller-Eberstein H, Nikolaus S, Schreiber S, Nebel A Association of FOXO3A variation with human longevity confirmed in German centenarians. Proc. Natl Acad. Sci. USA 106, 2700-2705. (2009)
DOI: 10.1073/pnas.0809594106
PMid:19196970 PMCid:PMC2650329

62. Soerensen M, Dato S, Christensen K, McGue M, Stevnsner T, Bohr VA, Christiansen L Replication of an association of variation in the FOXO3A gene with human longevity using both case-control and longitudinal data. Aging Cell 9, 1010-1017. (2010)
DOI: 10.1111/j.1474-9726.2010.00627.x
PMid:20849522 PMCid:PMC2992870

63. Soerensen M, Nygaard M, Dato S, Stevnsner T, Bohr VA, Christensen K, Christiansen L Association study of FOXO3A SNPs and aging phenotypes in Danish oldest-old individuals. Aging Cell 14, 60-66. (2015)
DOI: 10.1111/acel.12295
PMid:25470651 PMCid:PMC4326903

64. Brooks-Wilson AR Genetics of healthy aging and longevity. Hum. Genet. 132, 1323-1338. (2013)
DOI: 10.1007/s00439-013-1342-z
PMid:23925498 PMCid:PMC3898394

65. Bao JM, Song XL, Hong YQ, Zhu HL, Li C, Zhang T, Chen W, Zhao SC, Chen Q Association between FOXO3A gene polymorphisms and human longevity: a meta-analysis. Asian J. Androl. 16, 446-452. (2014)
DOI: 10.4103/1008-682X.123673
PMid:24589462 PMCid:PMC4023376

66. Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T, Yu L, Arnold AM, Aspelund T, Benjamin EJ, De Jager PL, Eirkisdottir G, Evans DA, Garcia ME, Hofman A, Kaplan RC, Kardia SL, Kiel DP, Oostra BA, Orwoll ES, Parimi N, Psaty BM, Rivadeneira F, Rotter JI, Seshadri S, Singleton A, Tiemeier H, Uitterlinden AG, Zhao W, Bandinelli S, Bennett DA, Ferrucci L, Gudnason V, Harris TB, Karasik D,

Launer LJ, Perls TT, Slagboom PE, Tranah GJ, Weir DR, Newman AB, van Duijn CM, Murabito JM GWAS of longevity in CHARGE consortium confirms APOE and FOXO3 candidacy. J. Gerontol. A Biol. Sci. Med. Sci. 70, 110-118. (2015)
DOI: 10.1093/gerona/glu166
PMid:25199915 PMCid:PMC4296168

67. Zhao J, Brault JJ, Schild A, Cao P, Sandri M, Schiaffino S, Lecker SH, Goldberg AL FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. Cell Metab. 6, 472-483. (2007)
DOI: 10.1016/j.cmet.2007.11.004
PMid:18054316

68. Sengupta A, Molkentin JD, Yutzey KE FoxO transcription factors promote autophagy in cardiomyocytes. J. Biol. Chem. 284, 28319-28331. (2009)
DOI: 10.1074/jbc.M109.024406
PMid:19696026 PMCid:PMC2788882

69. Demontis F, Perrimon N FOXO/4E-BP signaling in Drosophila muscles regulates organism-wide proteostasis during aging. Cell 143, 813-825. (2010)
DOI: 10.1016/j.cell.2010.10.007
PMid:21111239 PMCid:PMC3066043

70. Puig O, Tjian R. Transcriptional feedback control of insulin receptor by dFOXO/FOXO1. Genes Dev. 19:2435-46. (2005)
DOI: 10.1101/gad.1340505
PMid:16230533 PMCid:PMC1257398

71. van der Horst A, Burgering BM. Stressing the role of FoxO proteins in lifespan and disease. Nat Rev Mol Cell Biol. 8:440-50. (2007)
DOI: 10.1038/nrm2190
PMid:17522590

72. Kops GJ, Dansen TB, Polderman PE, Saarloos I, Wirtz KW, Coffer PJ, Huang TT, Bos JL, Medema RH, Burgering BM Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. (2002)
DOI: 10.1038/nature01036
PMid:12239572

73. Storz P Forkhead homeobox type O transcription factors in the responses to oxidative stress. Antioxid. Redox Signal. 14, 593-60. (2011)
DOI: 10.1089/ars.2010.3405
PMid:20618067 PMCid:PMC3038124

74. Essers MA, Weijzen S, de Vries-Smits AM, Saarloos I, de Ruiter ND, Bos JL, Burgering BM FOXO transcription factor activation by oxidative stress mediated by the small GTPase Ral and JNK. EMBO J. 23, 4802-4812. (2004)
DOI: 10.1038/sj.emboj.7600476
PMid:15538382 PMCid:PMC535088

75. Eijkelenboom A, Burgering BM. FOXOs: signalling integrators for homeostasis maintenance. Nat. Rev. Mol. Cell Biol. 14, 83-97. (2013)
DOI: 10.1038/nrm3507
PMid:23325358

76. Putker M, Madl T, Vos HR, de Ruiter H, Visscher M, van den Berg MC, Kaplan M, Korswagen HC, Boelens R, Vermeulen M, Burgering BM, Dansen TB Redox-dependent control of FOXO/DAF-16 by transportin-1. Mol. Cell 49, 730-742. (2013)
DOI: 10.1016/j.molcel.2012.12.014
PMid:23333309

77. Nemoto S, Finkel T Redox regulation of forkhead proteins through a p66shc-

dependent signaling pathway. Science 295, 2450-2452. (2002)
DOI: 10.1126/science.1069004
PMid:11884717

78. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. Nature. 434:113-8. (2005)
DOI: 10.1038/nature03354
PMid:15744310

79. Tothova Z, Gilliland DG. (2007) FoxO transcription factors and stem cell homeostasis: insights from the hematopoietic system. Cell Stem Cell 1, 140-152. (2007)
DOI: 10.1016/j.stem.2007.07.017
PMid:18371346

80. Tsuchiya K, Westerterp M, Murphy AJ, Subramanian V, Ferrante AW Jr, Tall AR, Accili D Expanded granulocyte/monocyte compartment in myeloid-specific triple FoxO knockout increases oxidative stress and accelerates atherosclerosis in mice. Circ. Res. 112, 992-1003. (2013)
DOI: 10.1161/CIRCRESAHA.-112.300749
PMid:23420833 PMCid:PMC3736810

81. Nakae J., M. Oki, Y. Cao The FoxO transcription factors and metabolic regulation FEBS Lett., 582, 54-67. (2008)
DOI: 10.1016/j.febslet.2007.11.025
PMid:18022395

82. Peng S. L. Foxo in the immune system Oncogene, 27, 2337-2344. (2008)
DOI: 10.1038/onc.2008.26
PMid:18391975

83. Morley JF, Brignull HR, Weyers JJ, Morimoto RI The threshold for polyglutamine-expansion protein aggregation and cellular toxicity is dynamic and influenced by aging in Caenorhabditis elegans . Proc. Natl Acad. Sci. USA 99, 10417-10422. (2002)
DOI: 10.1073/pnas.152161099
PMid:12122205 PMCid:PMC124929

84. Hsu A-L, Murphy CT, Kenyon C Regulation of aging and age-related disease by DAF-16 and heat-shock factor. Science. (New York, NY) 300, 1142-1145. (2003)
DOI: 10.1126/science.1083701
PMid:12750521

85. Salminen A, Kaarniranta K. Insulin/IGF-1 paradox of aging: regulation via AKT/IKK/NF-kappaB signaling. Cell Signal. 22:573-7. (2010)
DOI: 10.1016/j.cellsig.2009.10.006
PMid:19861158

86. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441, 885-889. (2006)
DOI: 10.1038/nature04724
PMid:16625204

87. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J-I, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, Tanaka K. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 441, 880-884. (2006)
DOI: 10.1038/nature04723
PMid:16625205

88. Jung HS, Chung KW, Won Kim J, Kim J, Komatsu M, Tanaka K, Nguyen YH, Kang TM, Yoon K-H, Kim J-W, Jeong YT, Han MS, Lee M-K, Kim K-W, Shin J, Lee M-S. Loss of autophagy diminishes pancreatic

beta cell mass and function with resultant hyperglycemia. Cell Metab. 8, 318-324. (2008)
DOI: 10.1016/j.cmet.2008.08.013
PMid:18840362

89. Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, Wyss-Coray T. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. J. Clin. Invest. 118, 2190-2199. (2008)
DOI: 10.1172/JCI33585
PMid:18497889 PMCid:PMC2391284

90. Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, Metzger D, Reggiani C, Schiaffino S, Sandri M. Autophagy is required to maintain muscle mass. Cell Metab. 10, 507-515. (2009)
DOI: 10.1016/j.cmet.2009.10.008
PMid:19945408

91. Lee JH, Budanov AV, Park EJ, Birse R, Kim TE, Perkins GA, Ocorr K, Ellisman MH, Bodmer R, Bier E, Karin M. Sestrin as a feedback inhibitor of TOR that prevents age-related pathologies. Science. (New York, NY) 327, 1223-1228. (2010)
DOI: 10.1126/science.1182228
PMid:20203043 PMCid:PMC2866632

92. Lee JH, Budanov AV, Park EJ, Birse R, Kim TE, Perkins GA, Ocorr K, Ellisman MH, Bodmer R, Bier E, Karin M. Sestrin as a feedback inhibitor of TOR that prevents age-related pathologies. Science 327, 1223-1228. (2010)
DOI: 10.1126/science.1182228
PMid:20203043 PMCid:PMC2866632

93. Conconi M, Szweda LI, Levine RL, Stadtman ER, Friguet B. Age-related decline of rat liver multicatalytic proteinase activity and protection from oxidative inactivation by heat-shock protein 90. Arch. Biochem. Biophys. 331, 232-240. (1996)
DOI: 10.1006/abbi.1996.0303
PMid:8660703

94. Petropoulos I, Conconi M, Wang X, Hoenel B, Brégégère F, Milner Y, Friguet B. Increase of oxidatively modified protein is associated with a decrease of proteasome activity and content in aging epidermal cells. J. Gerontol. A Biol. Sci. Med. Sci. 55, B220-B22. (2000)
DOI: 10.1093/gerona/55.5.B220
PMid:10819308

95. Bulteau A-L, Szweda LI, Friguet B. Age-dependent declines in proteasome activity in the heart. Arch. Biochem. Biophys. 397, 298-304. (2002)
DOI: 10.1006/abbi.2001.2663
PMid:11795886

96. Husom AD, Peters EA, Kolling EA, Fugere NA, Thompson LV, Ferrington DA. Altered proteasome function and subunit composition in aged muscle. Arch. Biochem. Biophys. 421, 67-76. (2004)
DOI: 10.1016/j.abb.2003.10.010
PMid:14678786

97. Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, Poueymirou WT, Panaro FJ, Na E, Dharmarajan K, Pan ZQ, Valenzuela DM, DeChiara TM, Stitt TN, Yancopoulos GD, Glass DJ. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. (New York, NY) 294, 1704-1708. (2001)
DOI: 10.1126/science.1065874
PMid:11679633

98. Sandri M, Sandri C, Gilbert A, Skurk C, Calabria E, Picard A, Walsh K, Schiaffino S, Lecker SH, Goldberg AL. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. Cell 117, 399-412. (2004)
DOI: 10.1016/S0092-8674(04)00400-3

99. Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyva Y, Kline WO, Gonzalez M, Yancopoulos GD, Glass DJ. The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. Mol. Cell 14, 395-403. (2004)
DOI: 10.1016/S1097-2765(04)00211-4

100. Vilchez D, Boyer L, Morantte I, Lutz M, Merkwirth C, Joyce D, Spencer B, Page L, Masliah E, Berggren WT, Gage FH, Dillin A. Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature 489, 304-308. (2012)
DOI: 10.1038/nature11468
PMid:22972301 PMCid:PMC5215918

101. Salminen A, Kaarniranta K. AMP-activated protein kinase. (AMPK) controls the aging process via an integrated signaling network. Ageing research reviews. Apr 1 11. (2):230-41. (2012)
DOI: 10.1016/j.arr.2011.12.005
PMid:22186033

102. Miyamoto K, Araki KY, Naka K, Arai F, Takubo K, Yamazaki S, Matsuoka S, Miyamoto T, Ito K, Ohmura M, Chen C, Hosokawa K, Nakauchi H, Nakayama K, Nakayama KI, Harada M, Motoyama N, Suda T, Hirao A. Foxo3a is essential for maintenance of the hematopoietic stem cell pool. Cell Stem Cell 1, 101-112. (2007)
DOI: 10.1016/j.stem.2007.02.001
PMid:18371339

103. Zhang X, Yalcin S, Lee DF, Yeh TY, Lee SM, Su J, Mungamuri SK, Rimmele P, Kennedy M, Sellers R, Landthaler M, Tuschl T, Chi NW, Lemischka I, Keller G, Ghaffari S. FOXO1 is an essential regulator of pluripotency in human embryonic stem cells. Nat. Cell Biol. 13, 1092-1099. (2011)
DOI: 10.1038/ncb2293
PMid:21804543 PMCid:PMC4053529

104. Miller DL, Roth MB. Hydrogen sulfide increases thermotolerance and lifespan in Caenorhabditis elegans. Proc Natl Acad Sci U S A 104: 20618-20622. (2007)
DOI: 10.1073/pnas.0710191104
PMid:18077331 PMCid:PMC2154480

105. Lemos V, De Oliveira RM, Naia L, Szegö É, Ramos E, Pinho S, Magro F, Cavadas C, Rego AC, Costa V, Outeiro TF. The NAD+-dependent deacetylase SIRT2 attenuates oxidative stress and mitochondrial dysfunction and improves insulin sensitivity in hepatocytes. Human molecular genetics. Nov 1 26. (21):4105-17. (2017)
DOI: 10.1093/hmg/ddx298
PMid:28973648

106. Sanokawa-Akakura R, Akakura S, Tabibzadeh S. Replicative senescence in human fibroblasts is delayed by hydrogen sulfide in a NAMPT/SIRT1 dependent manner. PLoS One. Oct 12 11. (10):e0164710. (2016)
DOI: 10.1371/journal.pone.0164710
PMid:27732642 PMCid:PMC5061390

107. Guarente L. Sirtuins in aging and disease. Cold Spring Harb. Symp. Quant. Biol. 72:483-488. (2007)
DOI: 10.1101/sqb.2007.72.024
PMid:18419308

108. Vaquero A, Reinberg D. Calorie restriction and the exercise of chromatin. Genes Dev. 23:1849-1869. (2009)
DOI: 10.1101/gad.1807009
PMid:19608767 PMCid:PMC2725938

109. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. Annu Rev Pathol. 5:253-295. (2010)
DOI: 10.1146/annurev.pathol.-4.110807.092250
PMid:20078221 PMCid:PMC2866163

110. Baur JA, Ungvari Z, Minor RK, Le Couteur DG, De Cabo R. Are sirtuins viable targets for improving healthspan and lifespan?. Nature reviews Drug discovery. Jun 11. (6):443-61. (2012)
DOI: 10.1038/nrd3738
PMid:22653216 PMCid:PMC4684642

111. Michan S, Sinclair D. Sirtuins in mammals: insights into their biological function. Biochemical Journal. May 15 404. (1):1-3. (2007)
DOI: 10.1042/BJ20070140
PMid:17447894 PMCid:PMC2753453

112. Michishita E, Park JY, Burneskis JM, Barrett JC, Horikawa I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. Molecular biology of the cell. Oct 16. (10):4623-35. (2005)
DOI: 10.1091/mbc.e05-01-0033
PMid:16079181 PMCid:PMC1237069

113. Sinclair DA, Guarente L. Extrachromosomal rDNA circles-a cause of aging in yeast. Cell. 91:1033-1042. (1997)
DOI: 10.1016/S0092-8674(00)80493-6

114. Dang W, Steffen KK, Perry R, Dorsey JA, Johnson FB, Shilatifard A, Kaeberlein M, Kennedy BK, Berger SL. Histone H4 lysine 16 acetylation regulates cellular lifespan. Nature. 459:802-807. (2009)
DOI: 10.1038/nature08085
PMid:19516333 PMCid:PMC2702157

115. Haigis MC, Guarente LP. Mammalian sirtuins-emerging roles in physiology, aging, and calorie restriction. Genes & development. Nov 1 20. (21):2913-21. (2006)
DOI: 10.1101/gad.1467506
PMid:17079682

116. Haigis MC, Yankner BA. The aging stress response. Mol. Cell. 40:333-344. (2010)
DOI: 10.1016/j.molcel.2010.10.002
PMid:20965426 PMCid:PMC2987618

117. Ruderman NB, Xu XJ, Nelson L, Cacicedo JM, Saha AK, Lan F, Ido Y. AMPK and SIRT1: a long-standing partnership?. American Journal of Physiology-Endocrinology and Metabolism. Apr 1. (2010)
DOI: 10.1152/ajpendo.00745.2009
PMid:20103737 PMCid:PMC2853213

118. Lan F, Cacicedo JM, Ruderman N, Ido Y. SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1 possible role in AMP-activated protein kinase activation. Journal of Biological Chemistry. Oct 10 283. (41):27628-35. (2008)
DOI: 10.1074/jbc.M805711200
PMid:18687677 PMCid:PMC2562073

119. Oberdoerffer P, Michan S, McVay M, Mostoslavsky R, Vann J, Park SK, Hartlerode A, Stegmuller J, Hafner A, Loerch P, Wright SM. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. Cell. Nov 28 135. (5):907-18. (2008)
DOI: 10.1016/j.cell.2008.10.025

PMid:19041753 PMCid:PMC2853975

120. Le Bourg E. Hormesis, aging and longevity. Biochimica et Biophysica Acta. (BBA)-General Subjects. Oct 1 1790. (10):1030-9. (2009)
DOI: 10.1016/j.bbagen.2009.01.004
PMid:19463497

121. Mostoslavsky R, Chua KF, Lombard DB, Pang WW, Fischer MR, Gellon L, Liu P, Mostoslavsky G, Franco S, Murphy MM, Mills KD. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell. Jan 27 124. (2):315-29. (2006)
DOI: 10.1016/j.cell.2005.11.044
PMid:16439206

122. Kawahara TL, Michishita E, Adler AS, Damian M, Berber E, Lin M, McCord RA, Ongaigui KC, Boxer LD, Chang HY, Chua KF. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell. 136:62-74. (2009)
DOI: 10.1016/j.cell.2008.10.052
PMid:19135889 PMCid:PMC2757125

123. Kawahara TL, Rapicavoli NA, Wu AR, Qu K, Quake SR, Chang HY. Dynamic chromatin localization of Sirt6 shapes stress-and aging-related transcriptional networks. PLoS Genet. 2011 Jun 30;7(6):e1002153.PLoS Genet., 7. e1002153. (2011)
DOI: 10.1371/journal.pgen.1002153
PMid:21738489 PMCid:PMC3128103

124. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, Cheung P, Kusumoto R, Kawahara TL, Barrett JC, Chang HY. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature. Mar 452. (7186):492-6. (2008)
DOI: 10.1038/nature06736
PMid:18337721 PMCid:PMC2646112

125. Tennen RI, Chua KF. Chromatin regulation and genome maintenance by mammalian SIRT6. Trends Biochem. Sci. 36:39-46. (2011)
DOI: 10.1016/j.tibs.2010.07.009
PMid:20729089 PMCid:PMC2991557

126. Yang H, Lavu S, Sinclair DA. Nampt/PBEF/Visfatin: a regulator of mammalian health and longevity?. Experimental gerontology. Aug 1 41. (8):718-26. (2006)
DOI: 10.1016/j.exger.2006.06.003
PMid:16842957 PMCid:PMC3366689

127. Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Sinclair DA. Nicotinamide and Pnc1 govern lifespan extension by calorie restriction in S cerevisiae. Nature. 423:181-185. (2003)
DOI: 10.1038/nature01578
PMid:12736687 PMCid:PMC4802858

128. Gallo CM, Smith DL, Jr, Smith JS. Nicotinamide clearance by Pnc1 directly regulates Sir2-mediated silencing and longevity. Mol. Cell Biol. 24:1301-1312. (2004)
DOI: 10.1128/MCB.24.3.1301-1312.2004
PMid:14729974 PMCid:PMC321434

129. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. Jan 21 307. (5708):426-30. (2005)
DOI: 10.1126/science.1097243
PMid:15604363

130. Rongvaux A, Shea RJ, Mulks MH, Gigot

D, Urbain J, Leo O, Andris F. Pre-B-cell colony-enhancing factor, whose expression is up-regulated in activated lymphocytes, is a nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur. J. Immunol. 32:3225-3234. (2002)
DOI: 10.1002/1521-4141(200211)32:11<3225::AID-IMMU3225>3.0.CO;2-L

131. Brandl L, Kirstein N, Neumann J, Sendelhofert A, Vieth M, Kirchner T, Menssen A. The c-MYC/NAMPT/SIRT1 feedback loop is activated in early classical and serrated route colorectal cancer and represents a therapeutic target. Medical Oncology. Jan 1 36. (1):5. (2019)
DOI: 10.1007/s12032-018-1225-1
PMid:30460421

132. Esposito E, Impellizzeri D, Mazzon E, Fakhfouri G, Rahimian R, Travelli C, Tron GC, Genazzani AA, Cuzzocrea S. The NAMPT inhibitor FK866 reverts the damage in spinal cord injury. Journal of neuroinflammation. Dec 1 9. (1):66. (2012)
DOI: 10.1186/1742-2094-9-66
PMid:22490786 PMCid:PMC3353188

133. Imai SI. Nicotinamide phosphoribosyltransferase. (Nampt): a link between NAD biology, metabolism, and diseases. Current pharmaceutical design. Jan 1 15. (1):20-8. (2009)
DOI: 10.2174/138161209787185814
PMid:19149599 PMCid:PMC2734389

134. Aman Y, Qiu Y, Tao J, Fang EF. Therapeutic potential of boosting NAD+ in aging and age-related diseases. Translational Medicine of Aging. Jan 1 2:30-7. (2018)
DOI: 10.1016/j.tma.2018.08.003

135. van der Veer E, Ho C, O'Neil C, Barbosa N, Scott R, Cregan SP, Pickering JG. Extension of human cell lifespan by nicotinamide phosphoribosyltransferase. Journal of Biological Chemistry. Apr 13 282. (15):10841-5. (2007)
DOI: 10.1074/jbc.C700018200
PMid:17307730

136. Kuro-o M. Klotho and aging. Biochimica et Biophysica Acta. (BBA)-General Subjects. Oct 1 1790. (10):1049-58. (2009)
DOI: 10.1016/j.bbagen.2009.02.005
PMid:19230844 PMCid:PMC2743784

137. Kuro-o M. Klotho. Pflügers Archiv-European Journal of Physiology. Jan 1 459. (2):333-43. (2010)
DOI: 10.1007/s00424-009-0722-7
PMid:19730882

138. Rubinek T, Wolf I, Modan-Moses D. The longevity hormone klotho is a new player in the interacion of the growth hormone/insulin-like growth factor 1 axis. Pediatric endocrinology reviews: PER. Sep 1 14. (1):9-18. (2016)
DOI: 10.1016/bs.vh.2016.02.009
PMid:27125739

139. Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, McGuinness OP, Chikuda H, Yamaguchi M, Kawaguchi H, Shimomura I. Suppression of aging in mice by the hormone Klotho. Science. Sep 16;309(5742):1829-33. (2005)
DOI: 10.1126/science.1112766
PMid:16123266 PMCid:PMC2536606

140. Arking DE, Krebsova A, Macek M, Arking A, Mian IS, Fried L, Hamosh A, Dey S, McIntosh I, Dietz HC. Association of human aging with a functional variant of

klotho. Proceedings of the National Academy of Sciences. Jan 22 99. (2):856-61. (2002)
DOI: 10.1073/pnas.022484299
PMid:11792841 PMCid:PMC117395

141. Ogata N, Matsumura Y, Shiraki M, Kawano K, Koshizuka Y, Hosoi T, Nakamura K, Kuro-o M, Kawaguchi H. Association of klotho gene polymorphism with bone density and spondylosis of the lumbar spine in postmenopausal women. Bone. Jul 1 31. (1):37-42. (2002)
DOI: 10.1016/S8756-3282(02)00786-X

142. Kawano KI, Ogata N, Chiano M, Molloy H, Kleyn P, Spector TD, Uchida M, Hosoi T, Suzuki T, Orimo H, Inoue S. Klotho gene polymorphisms associated with bone density of aged postmenopausal women. Journal of Bone and Mineral Research. Oct 17. (10):1744-51. (2002)
DOI: 10.1359/jbmr.2002.17.10.1744
PMid:12369777

143. Yamada Y, Ando F, Niino N, Shimokata H. Association of polymorphisms of the androgen receptor and klotho genes with bone mineral density in Japanese women. Journal of molecular medicine. Jan 1 83. (1):50-7. (2005)
DOI: 10.1007/s00109-004-0578-4
PMid:15536520

144. Arking DE, Becker DM, Yanek LR, Fallin D, Judge DP, Moy TF, Becker LC, Dietz HC. KLOTHO allele status and the risk of early-onset occult coronary artery disease. The American Journal of Human Genetics. May 1 72. (5):1154-61. (2003)
DOI: 10.1086/375035
PMid:12669274 PMCid:PMC1180268

145. Arking DE, Atzmon G, Arking A, Barzilai N, Dietz HC. Association between a functional variant of the KLOTHO gene and high-density lipoprotein cholesterol, blood pressure, stroke, and longevity. Circulation research. Mar 4 96. (4):412-8. (2005)
DOI: 10.1161/01.RES.00001-57171.04054.30
PMid:15677572

146. Goetz R, Beenken A, Ibrahimi OA, Kalinina J, Olsen SK, Eliseenkova AV, Xu C, Neubert TA, Zhang F, Linhardt RJ, Yu X. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Molecular and cellular biology. May 1 27. (9):3417-28. (2007)
DOI: 10.1128/MCB.02249-06
PMid:17339340 PMCid:PMC1899957

147. Bartke A, Brown-Borg H. Life extension in the dwarf mouse. Handbook of models for the study of human aging. Jan 1:403-14. (2006)
DOI: 10.1016/B978-012369391-4/50035-7

148. Kliewer SA, Mangelsdorf DJ. Fibroblast growth factor 21: from pharmacology to physiology. The American journal of clinical nutrition. Jan 1 91. (1):254S-7S. (2010)
DOI: 10.3945/ajcn.2009.28449B
PMid:19906798 PMCid:PMC2793111

149. McBean GJ. The transsulfuration pathway: a source of cysteine for glutathione in astrocytes. Amino acids. Jan 1 42. (1):199-205. (2012)
DOI: 10.1007/s00726-011-0864-8
PMid:21369939

150. Kimura H. Hydrogen sulfide: from brain to gut. Antioxidants & redox signaling. May 1 12. (9):1111-23. (2010)
DOI: 10.1089/ars.2009.2919
PMid:19803743

151. Tabibzadeh S. Nature creates, adapts, protects and sustains life using hydrogen sulfide. Frontiers in bioscience. (Landmark edition). Jan 21:528-60. (2016)
DOI: 10.2741/4407
PMid:26709792

152. Lee M, Sparatore A, Del Soldato P, Mcgeer E, McGeer PL. Hydrogen sulfide-releasing NSAIDs attenuate neuroinflammation induced by microglial and astrocytic activation. Glia. Jan 1 58. (1):103-13. (2010)
DOI: 10.1002/glia.20905
PMid:19544392

153. Kimura H. Production and physiological effects of hydrogen sulfide. Antioxidants & redox signaling. Feb 10 20. (5):783-93. (2014)
DOI: 10.1089/ars.2013.5309
PMid:23581969 PMCid:PMC3910667

154. Kimura H. Hydrogen sulfide and polysulfides as biological mediators. Molecules. Oct 19. (10):16146-57. (2014)
DOI: 10.3390/molecules191016146
PMid:25302704 PMCid:PMC6270867

155. Calvert JW, Coetzee WA, Lefer DJ. Novel insights into hydrogen sulfide-mediated cytoprotection. Antioxidants & redox signaling. May 15 12. (10):1203-17. (2010)
DOI: 10.1089/ars.2009.2882
PMid:19769484 PMCid:PMC2864658

156. Hine C, Zhu Y, Hollenberg AN, Mitchell JR. Dietary and endocrine regulation of endogenous hydrogen sulfide production: implications for longevity. Antioxidants & redox signaling. Jun 1 28. (16):1483-502. (2018)
DOI: 10.1089/ars.2017.7434
PMid:29634343 PMCid:PMC5930795

157. Whiteman M, Winyard PG. Hydrogen sulfide and inflammation: the good, the bad, the ugly and the promising. Expert review of clinical pharmacology. Jan 1 4. (1):13-32. (2011)
DOI: 10.1586/ecp.10.134
PMid:22115346

158. Li L, Bhatia M, Zhu YZ, Zhu YC, Ramnath RD, Wang ZJ, Anuar FB, Whiteman M, Salto-Tellez M, and Moore PK. Hydrogen sulfide is a novel mediator of lipopolysaccharide-induced inflammation in the mouse. FASEB J 19: 1196-1198. (2005)
DOI: 10.1096/fj.04-3583fje
PMid:15863703

159. Szabo C. Roles of hydrogen sulfide in the pathogenesis of diabetes mellitus and its complications. Antioxid Redox Signal 17: 68-80. (2012)
DOI: 10.1089/ars.2011.4451
PMid:22149162 PMCid:PMC4701125

160. Liu Y, Yang R, Liu X, Zhou Y, Qu C, Kikuiri T, Wang S, Zandi E, Du J, Ambudkar IS, and Shi S. Hydrogen sulfide maintains mesenchymal stem cell function and bone homeostasis via regulation of Ca2+ channel sulfhydration. Cell Stem Cell 15: 66-78. (2014)
DOI: 10.1016/j.stem.2014.03.005
PMid:24726192 PMCid:PMC4082757

161. Paul BD, Sbodio JI, Xu R, Vandiver MS, Cha JY, Snowman AM, and Snyder SH. Cystathionine ?-lyase deficiency mediates neurodegeneration in Hunting-ton's disease. Nature 509: 96-100. (2014)
DOI: 10.1038/nature13136
PMid:24670645 PMCid:PMC4349202

162. Blackstone E, Morrison M, and Roth MB. H2S induces a suspended animation-like state in mice. Science 308: 518. (2005)

DOI: 10.1126/science.1108581
PMid:15845845

163. Zhao W, Zhang J, Lu Y, and Wang R. The vasorelaxant effect of H2S as a novel endogenous gaseous K. (ATP) channel opener. EMBO J 20: 6008-6016. (2001)
DOI: 10.1093/emboj/20.21.6008
PMid:11689441 PMCid:PMC125693

164. Elrod JW, Calvert JW, Morrison J, Doeller JE, Kraus DW, Tao L, Jiao X, Scalia R, Kiss L, Szabo C, Kimura H, Chow CW, and Lefer DJ. Hydrogen sulfide attenuates myocardial ischemia-reperfusion injury by preservation of mitochondrial function. Proc Natl Acad Sci U S A 104: 15560-15565. (2007)
DOI: 10.1073/pnas.0705891104
PMid:17878306 PMCid:PMC2000503

165. Jha S, Calvert JW, Duranski MR, Ramachandran A, and Lefer DJ. Hydrogen sulfide attenuates hepatic ischemia-reperfusion injury: role of antioxidant and antiapoptotic signaling. Am J Physiol Heart Circ Physiol 295: H801-H806. (2008)
DOI: 10.1152/ajpheart.00377.2008
PMid:18567706 PMCid:PMC2519205

166. Xue R, Hao DD, Sun JP, Li WW, Zhao MM, Li XH, Chen Y, Zhu JH, Ding YJ, Liu J, and Zhu YC. Hydrogen sulfide treatment promotes glucose uptake by increasing insulin receptor sensitivity and ameliorates kidney lesions in type 2 diabetes. Antioxid Redox Signal 19: 5-23, 201. (2013)
DOI: 10.1089/ars.2012.5024
PMid:23293908 PMCid:PMC3676664

167. Giuliani D, Ottani A, Zaffe D, Galantucci M, Strinati F, Lodi R, and Guarini S. Hydrogen sulfide slows down progression of experimental Alzheimer's disease by targeting multiple pathophysiological mechanisms. Neurobiol Learn Mem 104: 82-91. (2013)
DOI: 10.1016/j.nlm.2013.05.006
PMid:23726868

168. Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev 92: 791-896. (2012)
DOI: 10.1152/physrev.00017.2011
PMid:22535897

169. Miller DL. and Roth MB. Hydrogen sulfide increases thermotolerance and lifespan in Caenorhabditis elegans. Proc Natl Acad Sci U S A 104: 20618-20622. (2007)
DOI: 10.1073/pnas.0710191104
PMid:18077331 PMCid:PMC2154480

170. Qabazard B, Li L, Gruber J, Peh MT, Ng LF, Kumar SD, Rose P, Tan CH, Dymock BW, Wei F, Swain SC. Hydrogen sulfide is an endogenous regulator of aging in Caenorhabditis elegans. Antioxidants & redox signaling. Jun 1 20. (16):2621-30. (2014)
DOI: 10.1089/ars.2013.5448
PMid:24093496 PMCid:PMC4025568

171. Donehower LA. Using mice to examine p53 functions in cancer, aging, and longevity. Cold Spring Harbor Perspectives in Biology. Dec 1 1. (6):a001081. (2009)
DOI: 10.1101/cshperspect.a001081
PMid:20457560 PMCid:PMC2882127

172. de Keizer PL, Laberge RM, Campisi J. p53: Pro-aging or pro-longevity?. Aging. (Albany NY). Jul 2. (7):377. (2010)
DOI: 10.18632/aging.100178
PMid:20657035 PMCid:PMC2933881

173. Feng Z, Lin M, Wu R. The regulation of

aging and longevity: a new and complex role of p53. Genes & cancer. Apr 2. (4):443-52. (2011)
DOI: 10.1177/1947601911410223
PMid:21779512 PMCid:PMC3135645

174. Liu D, Xu Y. p53, oxidative stress, and aging. Antioxidants & redox signaling. Sep 15 15. (6):1669-78. (2011)
DOI: 10.1089/ars.2010.3644
PMid:21050134 PMCid:PMC3151427

175. Vousden KH, Ryan KM. p53 and metabolism. Nature Reviews Cancer. Oct 9. (10):691-700. (2009)
DOI: 10.1038/nrc2715
PMid:19759539

176. Balaburski GM, Hontz RD, Murphy ME. p53 and ARF: unexpected players in autophagy. Trends in cell biology. Jun 1 20. (6):363-9. (2010)
DOI: 10.1016/j.tcb.2010.02.007
PMid:20303758 PMCid:PMC2891045

177. Feng Z, Levine AJ. The regulation of energy metabolism and the IGF-1/mTOR pathways by the p53 protein. Trends in cell biology. Jul 1 20. (7):427-34. (2010)
DOI: 10.1016/j.tcb.2010.03.004
PMid:20399660 PMCid:PMC2921989

178. Vaseva AV, Moll UM. The mitochondrial p53 pathway. Biochimica et Biophysica Acta. (BBA)-Bioenergetics. May 1 1787. (5):414-20. (2009)
DOI: 10.1016/j.bbabio.2008.10.005
PMid:19007744 PMCid:PMC2819081

179. Saleem A, Adhihetty PJ, Hood DA. Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. Physiological genomics. Mar 37. (1):58-66. (2009)
DOI: 10.1152/physiolgenomics.-90346.2008
PMid:19106183

180. Kitamura N, Nakamura Y, Miyamoto Y, Miyamoto T, Kabu K, Yoshida M, Futamura M, Ichinose S, Arakawa H. Mieap, a p53-inducible protein, controls mitochondrial quality by repairing or eliminating unhealthy mitochondria. PloS one. Jan 17 6. (1):e16060. (2011)
DOI: 10.1371/journal.pone.0016060
PMid:21264228 PMCid:PMC3022033

181. Sablina AA, Budanov AV, Ilyinskaya GV, Agapova LS, Kravchenko JE, Chumakov PM. The antioxidant function of the p53 tumor suppressor. Nature medicine. Dec 11. (12):1306-13. (2005)
DOI: 10.1038/nm1320
PMid:16286925 PMCid:PMC2637821

182. Maclaine NJ, Hupp TR. The regulation of p53 by phosphorylation: a model for how distinct signals integrate into the p53 pathway. Aging. May 1. (5):490. (2009)
DOI: 10.18632/aging.100047
PMid:20157532 PMCid:PMC2806026

183. Feng Z, Hu W, Teresky AK, Hernando E, Cordon-Cardo C, Levine AJ. Declining p53 function in the aging process: a possible mechanism for the increased tumor incidence in older populations. Proceedings of the National Academy of Sciences. Oct 16 104. (42):16633-8. (2007)
DOI: 10.1073/pnas.0708043104
PMid:17921246 PMCid:PMC2034252

184. Kawauchi K, Araki K, Tobiume K, Tanaka N. Loss of p53 enhances catalytic activity of IKKß through O-linked ß-N-acetyl glucosamine modification. Proceedings of the National Academy of Sciences. Mar 3 106. (9):3431-6. (2009)
DOI: 10.1073/pnas.0813210106
PMid:19202066 PMCid:PMC2651314

185. Salminen A, Kaarniranta K. Control of

p53 and NF-kB signaling by WIP1 and MIF: role in cellular senescence and organismal aging. Cellular signalling. May 1 23. (5):747-52. (2011)
DOI: 10.1016/j.cellsig.2010.10.012
PMid:20940041

186. Kroemer G, Mariño G, Levine B. Autophagy and the integrated stress response. Molecular cell. Oct 22 40. (2):280-93. (2010)
DOI: 10.1016/j.molcel.2010.09.023
PMid:20965422 PMCid:PMC3127250

187. Jones RG, Plas DR, Kubek S, Buzzai M, Mu J, Xu Y, Birnbaum MJ, Thompson CB. AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. Molecular cell. Apr 29 18. (3):283-93. (2005)
DOI: 10.1016/j.molcel.2005.03.027
PMid:15866171

188. Okoshi R, Ozaki T, Yamamoto H, Ando K, Koida N, Ono S, Koda T, Kamijo T, Nakagawara A, Kizaki H. Activation of AMP-activated protein kinase induces p53-dependent apoptotic cell death in response to energetic stress. Journal of biological chemistry. Feb 15 283. (7):3979-87. (2008)
DOI: 10.1074/jbc.M705232200
PMid:18056705

189. Between Scylla and Charybdis: p53 links tumor suppression and aging. Mech. Ageing Dev. 123: 567-573. (2002)
DOI: 10.1016/S0047-6374(02)00006-4

190. Campisi J. Between Scylla and Charybdis: p53 links tumor suppression and aging. Mechanisms of ageing and development. 6. (123):567-73. (2002)
DOI: 10.1016/S0047-6374(02)00006-4

191. Wright WE, Shay JW. The two-stage mechanism controlling cellular senescence and immortalization. Experimental gerontology. Jul 1 27. (4):383-9. (1992)
DOI: 10.1016/0531-5565(92)90069-C

192. Maier B, Gluba W, Bernier B, Turner T, Mohammad K, Guise T, Sutherland A, Thorner M, Scrable H. Modulation of mammalian life span by the short isoform of p53. Genes Dev. 18:306-319. (2004)
DOI: 10.1101/gad.1162404
PMid:14871929 PMCid:PMC338283

193. Migliaccio E. The p66shc adaptor protein controls oxidative stress response and life-span in mammals. Nature. 402: 309-313. (1999)
DOI: 10.1038/46311
PMid:10580504

194. Matheu A, Maraver A, Klatt P, Flores I, Garcia-Cao I, Borras C, Flores JM, Viña J, Blasco MA, Serrano M. Delayed ageing through damage protection by the Arf/p53 pathway. Nature. Jul 448. (7151):375-9. (2007)
DOI: 10.1038/nature05949
PMid:17637672

195. Tavernarakis N, Pasparaki A, Tasdemir E, Maiuri MC, Kroemer G. The effects of p53 on whole organism longevity are mediated by autophagy. Autophagy. Oct 1 4. (7):870-3. (2008)
DOI: 10.4161/auto.6730
PMid:18728385

196. Feng Z, Lin M, Wu R. The regulation of aging and longevity: a new and complex role of p53. Genes & cancer. Apr;2(4):443-52. 2. (2011)
DOI: 10.1177/1947601911410223
PMid:21779512 PMCid:PMC3135645

197. Meijer AJ, Codogno P. Autophagy:

regulation and role in disease. Critical reviews in clinical laboratory sciences. Aug 1 46. (4):210-40. (2009)
DOI: 10.1080/10408360903044068
PMid:19552522

198. Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell. Sep 2 146. (5):682-95. (2011)
DOI: 10.1016/j.cell.2011.07.030
PMid:21884931

199. Galluzzi L, Kepp O, Kroemer G. TP53 and MTOR crosstalk to regulate cellular senescence. Aging. (Albany NY). Sep 2. (9):535. (2010)
DOI: 10.18632/aging.100202
PMid:20876940 PMCid:PMC2984599

200. Vigneron A, Vousden KH. p53, ROS and senescence in the control of aging. Aging. (Albany NY). Aug 2. (8):471. (2010)
DOI: 10.18632/aging.100189
PMid:20729567 PMCid:PMC2954038

201. Mayo LD, Donner DB. The PTEN, Mdm2, p53 tumor suppressor-oncoprotein network. Trends Biochem Sci. 27:462-467. (2001)
DOI: 10.1016/S0968-0004(02)02166-7

202. Tomás-Loba A, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borrás C, Matheu A, Klatt P, Flores JM, Viña J, Serrano M, Blasco MA. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell. 135:609-622. (2008)
DOI: 10.1016/j.cell.2008.09.034
PMid:19013273

203. Braendle C, Milloz J, Felix MA. Mechanisms and evolution of environmental responses in Caenorhabditis elegans. Curr Top Dev Biol. 80:171-207 (2008)
DOI: 10.1016/S0070-2153(07)80005-6

204. Klass M, Hirsh D. Non-ageing developmental variant of Caenorhabditis elegans. Nature. 260:523-5. (1976)
DOI: 10.1038/260523a0
PMid:1264206

205. Kimura KD,) HA, Liu Y, Ruvkun G. daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. Science. 277:942-6. (1997)
DOI: 10.1126/science.277.5328.942
PMid:9252323

206. Van Heemst D. Insulin, IGF-1 and longevity. Aging and disease. Oct 1. (2):147. (2010)

207. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 7:85-96. (2006)
DOI: 10.1038/nrm1837
PMid:16493415

208. Bluher M, Kahn BB, Kahn CR. Extended longevity in mice lacking the insulin receptor in adipose tissue. Science. 299:572-4. (2003)
DOI: 10.1126/science.1078223
PMid:12543978

209. Holzenberger M, Dupont J, Ducos B, Leneuve P, Geloen A, Even PC, Cervera P, Le Bouc Y. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature. 421:182-7. (2003)
DOI: 10.1038/nature01298
PMid:12483226

210. Brown-Borg HM, Borg KE, Meliska CJ, Bartke A. Dwarf mice and the ageing process. Nature. 384:33. (1996)

DOI: 10.1038/384033a0
PMid:8900272

211. Flurkey K, Papaconstantinou J, Miller RA, Harrison DE. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. Proc Natl Acad Sci U S A. 98:6736-41. (2001)
DOI: 10.1073/pnas.111158898
PMid:11371619 PMCid:PMC34422

212. Chandrashekar V, Bartke A, Coschigano KT, Kopchick JJ. Pituitary and testicular function in growth hormone receptor gene knockout mice. Endocrinology. 140:1082-8. (1999)
DOI: 10.1210/endo.140.3.6557
PMid:10067829

213. Bartke A. Insulin and aging. Cell Cycle. 7:3338-43. (2008)
DOI: 10.4161/cc.7.21.7012
PMid:18948730

214. Masternak MM, Panici JA, Bonkowski MS, Hughes LF, Bartke A. Insulin sensitivity as a key mediator of growth hormone actions on longevity. J Gerontol A Biol Sci Med Sci. 64:516-21. (2009)
DOI: 10.1093/gerona/glp024
PMid:19304940 PMCid:PMC2667133

215. Shevah O, Laron Z. Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. Growth Horm IGF Res. 17:54-7. (2007)
DOI: 10.1016/j.ghir.2006.10.007
PMid:17166755

216. Suh Y, Atzmon G, Cho MO, Hwang D, Liu B, Leahy DJ, Barzilai N, Cohen P. Functionally significant insulin-like growth factor I receptor mutations in centenarians. Proc Natl Acad Sci U S A. 105:3438-42. (2008)
DOI: 10.1073/pnas.0705467105
PMid:18316725 PMCid:PMC2265137

217. Engelman J. A., Luo J., Cantley L. C. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 7:606-619. (2006)
DOI: 10.1038/nrg1879
PMid:16847462

218. Arendt T. Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: The 'Dr. Jekyll and Mr. Hyde' concept of Alzheimer's disease or the yin and yang of neuroplasticity. Prog. Neurobiol. 71:83-248. (2003)
DOI: 10.1016/j.pneurobio.2003.09.007
PMid:14687983

219. Shin B. C., Suzuki M., Inukai K., Anai M., Asano T., Takata K. Multiple isoforms of the regulatory subunit for phosphatidylinositol 3-kinase. (PI3-kinase) are expressed in neurons in the rat brain. Biochem. Biophys. Res. Commun. 246:313-319. (1998)
DOI: 10.1006/bbrc.1998.8606
PMid:9610355

220. Trejo J. L., Pons S. Phosphatidylinositol-3-OH kinase regulatory subunits are differentially expressed during development of the rat cerebellum. J. Neurobiol. 47:39-50. (2001)
DOI: 10.1002/neu.1014
PMid:11257612

221. Kapeller R., Cantley L. C. Phosphatidylinositol 3-kinase. Bioessays. 16:565-576. (1994)
DOI: 10.1002/bies.950160810
PMid:8086005

222. King D, Yeomanson D, Bryant HE.

PI3King the lock: targeting the PI3K/Akt/mTOR pathway as a novel therapeutic strategy in neuroblastoma. Journal of pediatric hematology/-oncology. May 1 37. (4):245-51. (2015)
DOI: 10.1097/MPH.0000000000000329
PMid:25811750

223. Vanhaesebroeck B., Waterfield M. D. Signaling by distinct classes of phosphoinositide 3-kinases. Exp. Cell Res. 253:239-254. (1999)
DOI: 10.1006/excr.1999.4701
PMid:10579926

224. Wang X, McCullough KD, Franke TF, Holbrook NJ. Epidermal growth factor receptor-dependent Akt activation by oxidative stress enhances cell survival. Journal of Biological Chemistry. May 12 275. (19):14624-31. (2000)
DOI: 10.1074/jbc.275.19.14624
PMid:10799549

225. Yang Y, Gehrke S, Haque ME, Imai Y, Kosek J, Yang L, Beal MF, Nishimura I, Wakamatsu K, Ito S, Takahashi R. Inactivation of Drosophila DJ-1 leads to impairments of oxidative stress response and phosphatidylinositol 3-kinase/Akt signaling. Proceedings of the National Academy of Sciences. Sep 20 102. (38):13670-5. (2005)
DOI: 10.1073/pnas.0504610102
PMid:16155123 PMCid:PMC1224636

226. Crowder R.J., Freeman R.S. Phosphatidylinositol 3-kinase and AKT protein kinase are necessary and sufficient for the survival of nerve growth factor-dependent sympathetic neurons. J. Neurosci. 18:2933-2943 (1998)
DOI: 10.1523/JNEUROSCI.18-08-02933.1998
PMid:9526010 PMCid:PMC6792598

227. Kang J. Q., Chong Z. Z., Maiese K. Critical role for AKT1 in the modulation of apoptotic phosphatidylserine exposure and microglial activation. Mol. Pharmacol. 64:557-569. (2003)
DOI: 10.1124/mol.64.3.557
PMid:12920191

228. Kang J. Q., Chong Z. Z., Maiese K. AKT1 protects against inflammatory microglial activation through maintenance of membrane asymmetry and modulation of cysteine protease activity. J. Neurosci. Res. 74:37-51. (2003)
DOI: 10.1002/jnr.10740
PMid:13130504

229. Lu J., Wu D. M., Zheng Z. H., Zheng Y. L., Hu B., Zhang Z. F. Troxerutin protects against high cholesterol-induced cognitive deficits in mice. Brain. 134:783-797. (2011)
DOI: 10.1093/brain/awq376
PMid:21252113

230. Kenyon C. The plasticity of aging: Insights from long-lived mutants. Cell. 120:449-460. (2005)
DOI: 10.1016/j.cell.2005.02.002
PMid:15734678

231. Morris J. Z.,) H. A., Ruvkun G. A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in Caenorhabditis elegans. Nature. 382:536-539. (1996)
DOI: 10.1038/382536a0
PMid:8700226

232. Clancy D. J., Gems D., Harshman L. G., Oldham S., Stocker H., Hafen E., Leevers S. J., Partridge L. Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. Science. 292:104-106. (2001)

DOI: 10.1126/science.1057991
PMid:11292874

233. Sharp Z. D., Bartke A. Evidence for down-regulation of phosphoinositide 3-kinase/AKT/mammalian target of rapamycin. (PI3K/AKT/mTOR)-dependent translation regulatory signaling pathways in Ames dwarf mice. J. Gerontol. A Biol. Sci. Med. Sci. 60:293-300. (2005)
DOI: 10.1093/gerona/60.3.293
PMid:15860463

234. Mattson M. P. Calcium and neurodegeneration. Aging Cell. 6:337-350. (2007)
DOI: 10.1111/j.1474-9726.2007.00275.x
PMid:17328689

235. Davinelli S, Willcox DC, Scapagnini G. Extending healthy ageing: nutrient sensitive pathway and centenarian population. Immunity & Ageing. Dec 1;9(1):9. (2012)
DOI: 10.1186/1742-4933-9-9
PMid:22524452 PMCid:PMC3379947

236. Blagosklonny M. V. Aging and immortality: Quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle. 5:2087-2102. (2006)
DOI: 10.4161/cc.5.18.3288
PMid:17012837

237. Laplante M, Sabatini DM. mTOR signaling at a glance. Journal of cell science. Oct 15;122(20):3589-94. (2009)
DOI: 10.1242/jcs.051011
PMid:19812304 PMCid:PMC2758797

238. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. Mar 9 168. (6):960-76. (2017)
DOI: 10.1016/j.cell.2017.02.004
PMid:28283069 PMCid:PMC5394987

239. Iglesias-Bartolome R, Patel V, Cotrim A, Leelahavanichkul K, Molinolo AA, Mitchell JB, Gutkind JS. mTOR inhibition prevents epithelial stem cell senescence and protects from radiation-induced mucositis. Cell stem cell. Sep 7 11. (3):401-14. (2012)
DOI: 10.1016/j.stem.2012.06.007
PMid:22958932 PMCid:PMC3477550

240. Tuo Y, Xiang M. mTOR: A double-edged sword for diabetes. Journal of leukocyte biology. Aug 106. (2):385-95. (2019)
DOI: 10.1002/JLB.3MR0317-095RR
PMid:29578634

241. Fabrizio P, Pozza F, Pletcher SD, Gendron CM, Longo VD. Regulation of longevity and stress resistance by Sch9 in yeast. Science. 292. (5515):288-90. (2001)
DOI: 10.1126/science.1059497
PMid:11292860

242. Jia K, Chen D, Riddle DL: The TOR pathway interacts with the insulin signaling pathway to regulate C. elegans larval development, metabolism and life span. Development. 131. (16):3897-906. (2004)
DOI: 10.1242/dev.01255
PMid:15253933

243. Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, Müller F. Influence of TOR kinase on lifespan in C. elegans. Nature. Dec 426. (6967):620. (2003)
DOI: 10.1038/426620a
PMid:14668850

244. Papadopoli D, Boulay K, Kazak L, Pollak M, Mallette F, Topisirovic I, Hulea L. mTOR as a central regulator of lifespan and aging. F1000Research. 8. (2019)

DOI: 10.12688/f1000research.17196.1
PMid:31316753 PMCid:PMC6611156

245. McKiernan SH, Colman RJ, Lopez M, Beasley TM, Aiken JM, Anderson RM, Weindruch R. Caloric restriction delays aging-induced cellular phenotypes in rhesus monkey skeletal muscle. Experimental gerontology. Jan 1 46. (1):23-9. (2011)
DOI: 10.1016/j.exger.2010.09.011
PMid:20883771 PMCid:PMC2998549

246. Colman RJ, Beasley TM, Allison DB, Weindruch R. Attenuation of sarcopenia by dietary restriction in rhesus monkeys. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. Jun 1 63. (6):556-9. (2008)
DOI: 10.1093/gerona/63.6.556
PMid:18559628 PMCid:PMC2812805

247. Cava E, Fontana L. Will calorie restriction work in humans?. Aging. (Albany NY). Jul 5. (7):507. (2013)
DOI: 10.18632/aging.100581
PMid:23924667 PMCid:PMC3765579

248. Messaoudi I, Young JE, Colman RJ, Handy AM, Roth GS, Ingram DK, Mattison JA. Aging and the effect of calorie restriction in rhesus monkeys. InCalorie Restriction, Aging and Longevity 55-78. Springer, Dordrecht. (2010)
DOI: 10.1007/978-90-481-8556-6_4

249. Fontana L, Partridge L, Longo VD. Extending healthy life span-from yeast to humans. Science. 328:321-326. (2010)
DOI: 10.1126/science.1172539
PMid:20395504 PMCid:PMC3607354

250. Fielenbach N, Antebi A. C. elegans dauer formation and the molecular basis of plasticity. Genes Dev. 22:2149-2165. (2008)
DOI: 10.1101/gad.1701508
PMid:18708575 PMCid:PMC2735354

251. Sallon S, Solowey E, Cohen Y, Korchinsky R, Egli M, Woodhatch I, Simchoni O, Kislev M. Germination, genetics, and growth of an ancient date seed. Science. 320:1464. (2008)
DOI: 10.1126/science.1153600
PMid:18556553

252. Cano RJ, Borucki MK. Revival and identification of bacterial spores in 25- to 40-million-year-old Dominican amber. Science. 268:1060-1064. (1995)
DOI: 10.1126/science.7538699
PMid:7538699

253. McKnight GS. Differential expression of mRNAs for protein kinase inhibitor isoforms in mouse brain. Curr Opin Cell Biol. 3:213-217 (1991)

254. Brandon EP, Idzerda RL, McKnight GS. PKA isoforms, neural pathways, and behaviour: making the connection. Curr Opin Neurobiol. 7:397-403. (1997)
DOI: 10.1016/S0959-4388(97)80069-4

255. Niswender CM, Ishihara RW, Judge LM, Zhang C, Shokat KM, McKnight GS. Protein engineering of protein kinase A catalytic subunits results in the acquisition of novel inhibitor sensitivity. J Biol Chem. 277:28916-28922. (2002)
DOI: 10.1074/jbc.M203327200
PMid:12034735

256. Zhang J, Wang Y, Liu X, Dagda RK, Zhang Y. How AMPK and PKA interplay to regulate mitochondrial function and survival in models of ischemia and diabetes. Oxidative medicine and cellular longevity. Jan 1 2017. (2017)
DOI: 10.1155/2017/4353510

PMid:29391924 PMCid:PMC5748092

257. Rodriguez-Cuenca S, Carobbio S, Velagapudi VR, Barbarroja N, Moreno-Navarrete JM, Tinahones FJ, Fernandez-Real JM, Orešic M, Vidal-Puig A. Peroxisome proliferator-activated receptor ?-dependent regulation of lipolytic nodes and metabolic flexibility. Molecular and cellular biology. Apr 15 32. (8):1555-65. (2012)
DOI: 10.1128/MCB.06154-11
PMid:22310664 PMCid:PMC3318581

258. Marrades MP, Gonzalez-Muniesa P, Martinez JA, Moreno-Aliaga MJ. A dysregulation in CES1, APOE and other lipid metabolism-related genes is associated to cardiovascular risk factors linked to obesity. Obesity facts. 3. (5):312-8. (2010)
DOI: 10.1159/000321451
PMid:20975297 PMCid:PMC6452131

259. Kenyon CJ: The genetics of ageing. Nature. 464. (7288):504-12. (2010)
DOI: 10.1038/nature08980
PMid:20336132

260. Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S. Regulation of lifespan in Drosophila by modulation of genes in the TOR signaling pathway. Current Biology. May 25 14. (10):885-90. (2004)
DOI: 10.1016/j.cub.2004.03.059
PMid:15186745 PMCid:PMC2754830

261. Longo VD: Mutations in signal transduction proteins increase stress resistance and longevity in yeast, nematodes, fruit flies, and mammalian neuronal cells. Neurobiol Aging. 20. (5):479-86. (1999)
DOI: 10.1016/S0197-4580(99)00089-5

262. Slack C, Alic N, Foley A, Cabecinha M, Hoddinott MP, Partridge L. The Ras-Erk-ETS-signaling pathway is a drug target for longevity. Cell. Jul 2 162. (1):72-83. (2015)
DOI: 10.1016/j.cell.2015.06.023
PMid:26119340 PMCid:PMC4518474

263. Enns L, Morton J, Treuting P, Emond M, Wold N, McKnight GS, Rabinovitch P, Ladiges WC. Disruption of protein kinase A in mice enhances healthy aging. PLoS. Jun 18 4. (6):e5963. (2009)
DOI: 10.1371/journal.pone.0005963
PMid:19536287 PMCid:PMC2693670

264. Wei M, Fabrizio P, Hu J, Ge H, Cheng C, Li L, Longo VD. Life span extension by calorie restriction depends on Rim15 and transcription factors downstream of Ras/PKA, Tor, and Sch9. PLoS Genet. Jan 25 4. (1):e13. (2008)
DOI: 10.1371/journal.pgen.0040013
PMid:18225956 PMCid:PMC2213705

265. Roger F, Picazo C, Asami C, Reiter W, Hanzén S, Gao C, Lagniel G, Welkenhuysen N, Labarre J, Nyström T, Grøtli M. Peroxiredoxin promotes longevity and H2O2-resistance in yeast through redox-modification of PKA. bioRxiv. Jan 1:676270. (2019)
DOI: 10.1101/676270

266. Wang C, Skinner C, Easlon E, Lin SJ. Deleting the 14-3-3 protein Bmh1 extends life span in Saccharomyces cerevisiae by increasing stress response. Genetics. Dec 1 183. (4):1373-84. (2009)
DOI: 10.1534/genetics.109.107797
PMid:19805817 PMCid:PMC2787426

267. Deprez MA, Eskes E, Wilms T, Ludovico P, Winderickx J. pH homeostasis links the nutrient sensing PKA/TORC1/Sch9 ménage-à-trois to stress tolerance and longevity. Microbial cell. Mar 5 5. (3):119.

(2018)
DOI: 10.15698/mic2018.03.618
PMid:29487859 PMCid:PMC5826700

268. Cheng C, Fabrizio P, Ge H, Longo VD, Li LM. Inference of transcription modification in long-live yeast strains from their expression profiles. BMC genomics. Dec 1 8. (1):219. (2007)
DOI: 10.1186/1471-2164-8-219
PMid:17617911 PMCid:PMC1949827

269. Kang WK, Kim YH, Kang HA, Kwon KS, Kim JY. Sir2 phosphorylation through cAMP-PKA and CK2 signaling inhibits the lifespan extension activity of Sir2 in yeast. Elife. Sep 2 4:e09709. (2015)
DOI: 10.7554/eLife.09709
PMid:26329457 PMCid:PMC4586308

270. Longo VD. The Ras and Sch9 pathways regulate stress resistance and longevity. Experimental gerontology. Jul 1 38. (7):807-11. (2003)
DOI: 10.1016/S0531-5565(03)00113-X

271. Enns LC, Pettan-Brewer C, Ladiges W. Protein kinase A is a target for aging and the aging heart. Aging. (Albany NY). Apr 2. (4):238. (2010)
DOI: 10.18632/aging.100138
PMid:20448293 PMCid:PMC2881512

272. Zeisberg, E. & Zeisberg, M. A rationale for epigene c repurposing of hydralazine in chronic heart and kidney failure. J. Clin. Epigenetics 2, 5. (2016)

273. Goldberg AA, Richard VR, Kyryakov P, Bourque SD, Beach A, Burstein MT, Glebov A, Koupaki O, Boukh-Viner T, Gregg C, Juneau M. Chemical genetic screen identifies lithocholic acid as an anti-aging compound that extends yeast chronological life span in a TOR-independent manner, by modulating housekeeping longevity assurance processes. Aging. (Albany NY). Jul 2. (7):393. (2010)
DOI: 10.18632/aging.100168
PMid:20622262 PMCid:PMC2933888

274. Blokh D, Stambler I. Information theoretical analysis of aging as a risk factor for heart disease. Aging and Disease. 6. (3):196-207. (2015)
DOI: 10.14336/AD.2014.0623
PMid:26029478 PMCid:PMC4441402

275. Niccoli T, Partridge L. Ageing as a risk factor for disease. Current Biology. 22. (17):R741-52. (2012)
DOI: 10.1016/j.cub.2012.07.024
PMid:22975005

276. Pike CJ. Sex and the development of Alzheimer's disease. Journal of Neuroscience Research. 95. (1-2):671-80. (2017)
DOI: 10.1002/jnr.23827
PMid:27870425 PMCid:PMC5120614

277. van der Ende MY, Hartman MH, Hagemeijer Y, Meems LM, de Vries HS, Stolk RP, de Boer RA, Sijtsma A, van der Meer P, Rienstra M, van der Harst P. The LifeLines Cohort Study: prevalence and treatment of cardiovascular disease and risk factors. International journal of cardiology. Feb 1 228:495-500. (2017)
DOI: 10.1016/j.ijcard.2016.11.061
PMid:27875724

278. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: A potentially modifiable relationshiAmerican Journal of Preventive Medicine. S. 46:7-15. (2014)
DOI: 10.1016/j.amepre.2013.10.029
PMid:24512933 PMCid:PMC4544764

279. McKay MM, Morrison DK. Integrating

signals from RTKs to ERK/MAPK. Oncogene. 26. (22):3113-21. (2007)
DOI: 10.1038/sj.onc.1210394
PMid:17496910

280. Wittinghofer A, Nassar N. How Ras-related proteins talk to their effectors. Trends in Biochemical Sciences. 21. (12):488-91. (1996)
DOI: 10.1016/S0968-0004(96)10064-5

281. Mendoza MC, Er EE, Blenis J. The Ras-ERK and PI3K-mTOR pathways: Cross-talk and compensation. Trends in Biochemical Sciences. 36. (6):320-8. (2011)
DOI: 10.1016/j.tibs.2011.03.006
PMid:21531565 PMCid:PMC3112285

282. McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, Lehmann B, Terrian DM, Milella M, Tafuri A, Stivala F. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochimica et Biophysica Acta. (BBA)-Molecular Cell Research. Aug 1 1773. (8):1263-84. (2007)
DOI: 10.1016/j.bbamcr.2006.10.001
PMid:17126425 PMCid:PMC2696318

283. Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 103. (2):211-25. (2000)
DOI: 10.1016/S0092-8674(00)00114-8

284. Fabrizio P, Liou LL, Moy VN, Diaspro A, Valentine JS, Gralla EB, Longo VD. SOD2 functions downstream of Sch9 to extend longevity in yeast. Genetics. Jan 1 163. (1):35-46. (2003)

285. Goitre L, Trapani E, Trabalzini L, Retta SF. The Ras superfamily of small GTPases: The unlocked secrets. Methods in Molecular Biology. 1120:1-18. (2014)
DOI: 10.1007/978-1-62703-791-4_1
PMid:24470015

286. Rajalingam K, Schreck R, Rapp UR, Albert S. Ras oncogenes and their downstream targets. Biochimica et Biphysica Acta. 1773. (8):1177-95. (2007)
DOI: 10.1016/j.bbamcr.2007.01.012
PMid:17428555

287. Sun J, Kale SP, Childress AM, Pinswasdi C, Jazwinski SM. Divergent roles of RAS1 and RAS2 in yeast longevity. The Journal of Biological Chemistry. 269. (28):18638-45. (1994)

288. Jazwinski SM. The RAS genes: A homeostatic device in Saccharomyces cerevisiae longevity. Neurobiology of Aging. 20. (5):471-8. (1999)
DOI: 10.1016/S0197-4580(99)00095-0

289. Fabrizio P, Pletcher SD, Minois N, Vaupel JW, Longo VD. Chronological aging-independent replicative life span regulation by Msn2/Msn4 and Sod2 in Saccharomyces cerevisiae. FEBS Lett. 557. (1-3):136-42. (2004)
DOI: 10.1016/S0014-5793(03)01462-5

290. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science. 289. (5487):2126-8. (2000)
DOI: 10.1126/science.289.5487.2126
PMid:11000115

291. Medvedik O, Lamming DW, Kim KD, Sinclair DA. MSN2 and MSN4 link calorie restriction and TOR to sirtuin-mediated lifespan extension in Saccharomyces cerevisiae. PLoS Biology. 5. (10):e261. (2007)

DOI: 10.1371/journal.pbio.0050261
PMid:17914901 PMCid:PMC1994990

292. Slack C, Alic N, Foley A, Cabecinha M, Hoddinott MP, Partridge L. The Ras-ERK-ETS-signaling pathway is a drug target for longevity. Cell. 162. (1):72-83. (2015)
DOI: 10.1016/j.cell.2015.06.023
PMid:26119340 PMCid:PMC4518474

293. Alic N, Giannakou ME, Papatheodorou I, Hoddinott MP, Andrews TD, Bolukbasi E, Partridge L. Interplay of dFOXO and two ETS-family transcription factors determines lifespan in Drosophila melanogaster. PLoS Genet. Sep 18 10. (9):e1004619. (2014)
DOI: 10.1371/journal.pgen.1004619
PMid:25232726 PMCid:PMC4169242

294. Nanji M, Hopper NA, Gems D. LET-60 RAS modulates effects of insulin/IGF-1 signaling on development and aging in Caenorhabditis elegans. Aging Cell. 4. (5):235-45. (2005)
DOI: 10.1111/j.1474-9726.2005.00166.x
PMid:16164423

295. Borrás C, Monleón D, López-Grueso R, Gambini J, Orlando L, Pallardó FV, Santos E, Viña J, de Mora JF. RasGrf1 deficiency delays aging in mice. Aging. (Albany NY). Mar 3. (3):262. (2011)
DOI: 10.18632/aging.100279
PMid:21422498 PMCid:PMC3091520

296. Fernandez-Medarde A, Santos E. The RasGrf family of mammalian guanine nucleotide exchange factors. Biochimica et Biophysica Acta. 1815. (2):170-88. (2011)
DOI: 10.1016/j.bbcan.2010.11.001
PMid:21111786

297. Mirisola MG, Longo VD. Conserved role of Ras-GEFsin promoting aging: From yeast to mice. Aging. 3(4):340-3 (2011)
DOI: 10.18632/aging.100320
PMid:21732566 PMCid:PMC3117446

298. Jazwinski SM, Kim S, Dai J, Li L, Bi X, Jiang JC, Arnold J, Batzer MA, Walker JA, Welsh DA, Lefante CM. HRAS1 and LASS1 with APOE are associated with human longevity and healthy aging. Aging cell. Oct 9. (5):698-708. (2010)
DOI: 10.1111/j.1474-9726.2010.00600.x
PMid:20569235 PMCid:PMC2941558

299. Bonafe M, Barbi C, Olivieri F, Yashin A, Andreev KF, Vaupel JW, De Benedictis G, Rose G, Carrieri G, Jazwinski SM, Franceschi C. An allele of HRAS1 3' variable number of tandem repeats is a frailty allele: implication for an evolutionarily-conserved pathway involved in longevity. Gene. Mar 6 286. (1):121-6. (2002)
DOI: 10.1016/S0378-1119(01)00812-5

300. Rauen KA. HRAS and the Costello syndrome. Clinical Genetics. 71. (2):101-8. (2007)
DOI: 10.1111/j.1399-0004.2007.00743.x
PMid:17250658

301. Aliper AM, Csoka AB, Buzdin A, Jetka T, Roumiantsev S, Moskalev A and Zhavoronkov A. Signaling pathway activation drift during aging: Hutchinson-Gilford Progeria Syndrome fibroblasts are comparable to normal middle-age and old-age cells. Aging. 7. (1):26-37. (2015)
DOI: 10.18632/aging.100717
PMid:25587796 PMCid:PMC4350323

302. Altarejos JY, Montminy M. CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. Nature reviews Molecular cell biology. Mar 12.

(3):141-51. (2011)
DOI: 10.1038/nrm3072
PMid:21346730 PMCid:PMC4324555

303. Mair W, Morantte I, Rodrigues AP, Manning G, Montminy M, Shaw RJ, Dillin A. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. Nature. Feb 470. (7334):404-8. (2011)
DOI: 10.1038/nature09706
PMid:21331044 PMCid:PMC3098900

304. Takemori H, Kajimura J, Okamoto M. TORC-SIK cascade regulates CREB activity through the basic leucine zipper domain. The FEBS journal. Jul 1 274. (13):3202-9. (2007)
DOI: 10.1111/j.1742-4658.2007.05889.x
PMid:17565599

305. Yamazaki D, Horiuchi J, Miyashita T, Saitoe M. Acute inhibition of PKA activity at old ages ameliorates age-related memory impairment in Drosophila. Journal of Neuroscience. Nov 17 30. (46):15573-7. (2010)
DOI: 10.1523/JNEUROSCI.3229-10.2010
PMid:21084612 PMCid:PMC6633660

306. Foster TC, Sharrow KM, Masse JR, Norris CM, Kumar A. Calcineurin links Ca2+ dysregulation with brain aging. Journal of Neuroscience. Jun 1 21. (11):4066-73. (2001)
DOI: 10.1523/JNEUROSCI.21-11-04066.2001
PMid:11356894 PMCid:PMC1201477

307. Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, Landfield PW, Kraner SD. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. Journal of Neuroscience. May 4 25. (18):4649-58. (2005)
DOI: 10.1523/JNEUROSCI.0365-05.2005
PMid:15872113 PMCid:PMC1201418

308. Dwivedi M, Song HO, Ahnn J. Autophagy genes mediate the effect of calcineurin on life span in C. elegans. Autophagy. Jul 1 5. (5):604-7. (2009)
DOI: 10.4161/auto.5.5.8157
PMid:19279398

309. Screaton RA, Conkright MD, Katoh Y, Best JL, Canettieri G, Jeffries S, Guzman E, Niessen S, Yates III JR, Takemori H, Okamoto M. The CREB coactivator TORC2 functions as a calcium-and cAMP-sensitive coincidence detector. Cell. Oct 1 119. (1):61-74. (2004)
DOI: 10.1016/j.cell.2004.09.015
PMid:15454081

310. Koo SH, Flechner L, Qi L, Zhang X, Screaton RA, Jeffries S, Hedrick S, Xu W, Boussouar F, Brindle P, Takemori H. The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. Nature. Oct 437. (7062):1109-14. (2005)
DOI: 10.1038/nature03967
PMid:16148943

311. Wang B, Goode J, Best J, Meltzer J, Schilman PE, Chen J, Garza D, Thomas JB, Montminy M. The insulin-regulated CREB coactivator TORC promotes stress resistance in Drosophila. Cell metabolism. May 7 7. (5):434-44. (2008)
DOI: 10.1016/j.cmet.2008.02.010
PMid:18460334 PMCid:PMC3704161

312. Burkewitz K, Morantte I, Weir HJ, Yeo R, Zhang Y, Huynh FK, Ilkayeva OR, Hirschey MD, Grant AR, Mair WB. Neuronal CRTC-1 governs systemic mitochondrial metabolism and lifespan

via a catecholamine signal. Cell. Feb 26 160. (5):842-55. (2015)
DOI: 10.1016/j.cell.2015.02.004
PMid:25723162 PMCid:PMC4392909

313. Saura CA, Cardinaux JR. Emerging roles of CREB-regulated transcription coactivators in brain physiology and pathology. Trends in neurosciences. Dec 1 40. (12):720-33. (2017)
DOI: 10.1016/j.tins.2017.10.002
PMid:29097017

314. Escoubas CC, Silva-García CG, Mair WB. Deregulation of CRTCs in Aging and Age-Related Disease Risk:. (Trends in Genetics, 33, 303-321, 2017). Trends in Genetics. Apr 1 34. (4):326. (2018)
DOI: 10.1016/j.tig.2018.01.008
PMid:29398010

315. Parra-Damas A, Valero J, Chen M, Espana J, Martín E, Ferrer I, Rodríguez-Alvarez J, Saura CA. Crtc1 activates a transcriptional program deregulated at early Alzheimer's disease-related stages. Journal of Neuroscience. Apr 23 34. (17):5776-87. (2014)
DOI: 10.1523/JNEUROSCI.5288-13.2014
PMid:24760838 PMCid:PMC6608295

316. Chaturvedi RK, Hennessey T, Johri A, Tiwari SK, Mishra D, Agarwal S, Kim YS, Beal MF. Transducer of regulated CREB-binding proteins. (TORCs) transcription and function is impaired in Huntington's disease. Human molecular genetics. Aug 1 21. (15):3474-88. (2012)
DOI: 10.1093/hmg/dds178
PMid:22589249 PMCid:PMC3491961

317. Chen YC, Chen HJ, Tseng WC, Hsu JM, Huang TT, Chen CH, Pan CL. A C. elegans thermosensory circuit regulates longevity through crh-1/CREB-dependent flp-6 neuropeptide signaling. Developmental cell. Oct 24 39. (2):209-23. (2016)
DOI: 10.1016/j.devcel.2016.08.021
PMid:27720609

318. Chung HY, Kim HJ, Kim JW, Yu BP. The inflammation hypothesis of aging: molecular modulation by calorie restriction. Annals of the New York Academy of Sciences. Apr 928. (1):327-35. (2001)
DOI: 10.1111/j.1749-6632.2001.tb05662.x

319. Reed T, Dick DM, Uniacke SK, Foroud T, Nichols WC. Genome-wide scan for a healthy aging phenotype provides support for a locus near D4S1564 promoting healthy aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. Mar 1 59. (3):B227-32. (2004)
DOI: 10.1093/gerona/59.3.B227
PMid:15031306

320. Baker RG, Hayden MS, Ghosh S. NF-kB, inflammation, and metabolic disease. Cell metabolism. Jan 5 13. (1):11-22. (2011)
DOI: 10.1016/j.cmet.2010.12.008
PMid:21195345 PMCid:PMC3040418

321. Sung JY, Choi HC. Aspirin-induced AMP-activated protein kinase activation regulates the proliferation of vascular smooth muscle cells from spontaneously hypertensive rats. Biochemical and biophysical research communications. May 6 408. (2):312-7. (2011)
DOI: 10.1016/j.bbrc.2011.04.027
PMid:21514281

322. Chi Y, Li K, Yan Q, Koizumi S, Shi L, Takahashi S, Zhu Y, Matsue H, Takeda M, Kitamura M, Yao J. Nonsteroidal anti-

inflammatory drug flufenamic acid is a potent activator of AMP-activated protein kinase. Journal of Pharmacology and Experimental Therapeutics. Oct 1 339. (1):257-66. (2011)
DOI: 10.1124/jpet.111.183020
PMid:21765041

323. Helenius M, Hänninen M, Lehtinen SK, Salminen A. Changes associated with aging and replicative senescence in the regulation of transcription factor nuclear factor-?B. Biochemical Journal. Sep 1 318. (2):603-8. (1996)
DOI: 10.1042/bj3180603
PMid:8809053 PMCid:PMC1217663

324. Helenius M. Hanninen M, Lehtinen SK, Salminen A. Aging-induced up-regulation of nuclear binding activities of oxidative stress responsive NF-kB transcription factor in mouse cardiac muscle. J Mol Cell Cardiol. 28:487-98. (1996)
DOI: 10.1006/jmcc.1996.0045
PMid:9011632

325. Helenius M, Kyrylenko S, Vehviläinen P, Salminen A. Characterization of aging-associated up-regulation of constitutive nuclear factor-?B binding activity. Antioxidants and Redox Signaling. Feb 1 3. (1):147-56. (2001)
DOI: 10.1089/152308601750100669
PMid:11291593

326. Lin L, Hron JD, Peng SL. Regulation of NF-kB, Th activation, and auto-inflammation by the forkhead transcri-ption factor Foxo3a. Immunity. Aug 1 21. (2):203-13. (2004)
DOI: 10.1016/j.immuni.2004.06.016
PMid:15308101

327. Zhou W, Cao Q, Peng Y, Zhang QJ, Castrillon DH, DePinho RA, Liu ZP. FoxO4 inhibits NF-kB and protects mice against colonic injury and inflammation. Gastroenterology. Oct 1 137. (4):1403-14. (2009)
DOI: 10.1053/j.gastro.2009.06.049
PMid:19560465 PMCid:PMC2764529

328. Willcox BJ, Donlon TA, He Q, Chen R, Grove JS, Yano K, Masaki KH, Willcox DC, Rodriguez B, Curb JD. FOXO3A genotype is strongly associated with human longevity. Proceedings of the National Academy of Sciences. Sep 16 105. (37):13987-92. (2008)
DOI: 10.1073/pnas.0801030105
PMid:18765803 PMCid:PMC2544566

329. Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, Mayo MW. Modulation of NF-kB-dependent transcription and cell survival by the SIRT1 deacetylase. The EMBO journal. Jun 16 23. (12):2369-80. (2004)
DOI: 10.1038/sj.emboj.7600244
PMid:15152190 PMCid:PMC423286

330. Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2. (Nrf2) in inflammatory disorders. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. Aug 7 690. (1-2):12-23. (2010)
DOI: 10.1016/j.mrfmmm.2009.09.007
PMid:19799917

331. Yu M, Li H, Liu Q, Liu F, Tang L, Li C, Yuan Y, Zhan Y, Xu W, Li W, Chen H. Nuclear factor p65 interacts with Keap1 to repress the Nrf2-ARE pathway. Cellular signalling. May 1 23. (5):883-92. (2011)
DOI: 10.1016/j.cellsig.2011.01.014
PMid:21262351

332. Hiebert P, Wietecha MS, Cangkrama M, Haertel E, Mavrogonatou E, Stumpe M, Steenbock H, Grossi S, Beer HD, Angel

P, Brinckmann J. Nrf2-mediated fibroblast reprogramming drives cellular senescence by targeting the matrisome. Developmental cell. Jul 16 46. (2):145-61. (2018)
DOI: 10.1016/j.devcel.2018.06.012
PMid:30016619

333. Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of aging by continual NF-kB activity. Genes & development. Dec 15 21. (24):3244-57. (2007)
DOI: 10.1101/gad.1588507
PMid:18055696 PMCid:PMC2113026

334. Bernard D, Gosselin K, Monte D, Vercamer C, Bouali F, Pourtier A, Vandenbunder B, Abbadie C. Involvement of Rel/nuclear factor-?B transcription factors in keratinocyte senescence. Cancer research. Jan 15 64. (2):472-81. (2004)
DOI: 10.1158/0008-5472.CAN-03-0005
PMid:14744759

335. Hayden MS, Ghosh S. Signaling to NF-kB. Genes & development. Sep 15 18. (18):2195-224. (2004)
DOI: 10.1101/gad.1228704
PMid:15371334

336. Hardy K, Mansfield L, Mackay A, Benvenuti S, Ismail S, Arora P, O'Hare MJ, Jat PS. Transcriptional networks and cellular senescence in human mammary fibroblasts. Molecular biology of the cell. Feb 16. (2):943-53. (2005)
DOI: 10.1091/mbc.e04-05-0392
PMid:15574883 PMCid:PMC545924

337. Zhang JY, Tao S, Kimmel R, Khavari PA. CDK4 regulation by TNFR1 and JNK is required for NF-kB-mediated epidermal growth control. The Journal of cell biology. Feb 14 168. (4):561-6. (2005)
DOI: 10.1083/jcb.200411060
PMid:15699216 PMCid:PMC2171750

338. Cai D, Frantz JD, Tawa Jr NE, Melendez PA, Oh BC, Lidov HG, Hasselgren PO, Frontera WR, Lee J, Glass DJ, Shoelson SE. IKKß/NF-kB activation causes severe muscle wasting in mice. Cell. Oct 15 119. (2):285-98. (2004)
DOI: 10.1016/j.cell.2004.09.027
PMid:15479644

339. Chen J, Zhou Y, Mueller-Steiner S, Chen LF, Kwon H, Yi S, Mucke L, Gan L. SIRT1 protects against microglia-dependent amyloid-ß toxicity through inhibiting NF-kB signaling. Journal of Biological Chemistry. Dec 2 280. (48):40364-74. (2005)
DOI: 10.1074/jbc.M509329200
PMid:16183991

340. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, Karin M. IKK-ß links inflammation to obesity-induced insulin resistance. Nature medicine. Feb 11. (2):191-8. (2005)
DOI: 10.1038/nm1185
PMid:15685170

Abbreviations: Deoxyribonucleic acid (DNA), Ribonucleic acid (RNA), 5' AMP-activated protein kinase (AMPK), FOX (forkhead box), Nicotinamide phosphoribosyltransferase (NAm-PRTase or Nampt), Nicotinamide mono-nucleotide (NMN), Nicotinamide mononu-cleotide (NMN), Nicotinamide adenine dinucleotide (NAD^+), S-adenosylmethionine (SAM), Silent information regulator 1 (SIRT1), Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ), Transforming growth factor-β-activated kinase 1 (TAK1), Deoxy-ribonucleic acid (DNA), Protein phosphatases (PP), Peroxisome Proliferator-activated

receptor Gamma Coactivator 1α (PPGC-1α), Dietrary restriction (DR), calorie restriction (CR), Nicotinic acid (vitamin B3), Soluble form (sKlotho), Fibroblast growth factors (FGF), Hydrogen sulfide (H_2S), nitric oxide (NO), Carbon monoxide (CO), S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Sulfide quinone oxidoreductase (SQR), Glutathione persulfide (GSSH or GSS^-), Cysteine (Cys), 3-mercaptopyruvate sulfur-transferase (3MPST or 3MST), cystathionine-γ-lyase (CGL, also known as cystathionase, CTH, or CSE), Cystathionine β-synthase (CBS or CGL), D-amino-acid oxidase (DAO), Sulfide quinone oxidoreductase (SQR), Glutathione persulfide (GSSH or GSS^-), Electron transport chain (ETC), DNA-damage regulated autophagy modulator 1 (DRAM1), Insulin growth factor (IGF) , Growth hormone (GH), Insulin receptor substrate proteins (IRS1-4), Protein Kinase A (PKA), Dual-specificity A-kinase anchoring protein 1 (D-AKAP1), Casein kinase 2 (CK2), Cyclic AMP (cAMP, adaptable target of rapamycin (TOR), Mitogen-activated protein kinase (MAPK), E-twenty-six (ETS), Adenylyl cylase (AC), Extracellular signal-regulated kinase (ERK), GTPase activating proteins (GAPs), cAMP-response element binding protein (CREB), AMP-activated kinase-2 (AAK-2), cAMP-response element binding protein (CREB)-regulated transcription co-activators (CRTC), Kelch-like ECH-associated protein 1 (Keap1), Nuclear factor erythroid 2-related factor 2 (Nrf2), Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)

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