Impact papers on aging in 2009

Mikhail V. Blagosklonny 1, Judy Campisi 2, David A. Sinclair 3, Andrzej Bartke 4, Maria A. Blasco 5, William M. Bonner 6, Vilhelm A. Bohr 7, Robert M. Brosh Jr 7, Anne Brunet 8, Ronald A. DePinho 9, Lawrence A. Donehower 10, Caleb E. Finch 11, Toren Finkel 12, Myriam Gorospe 7, Andrei V. Gudkov 1, Michael N. Hall 13, Siegfried Hekimi 14, Stephen L. Helfand 15, Jan Karlseder 16, Cynthia Kenyon 17, Guido Kroemer 18, Valter Longo 11, Andre Nussenzweig 6, Heinz D. Osiewacz 19, Daniel S. Peep 20, Thomas A. Rando 8, K. Lenhard Rudolph 21, Paolo Sassone-Corsi 22, Manuel Serrano 5, Norman E. Sharpless 23, Vladimir P. Skulachev 24, Jonathan L. Til 25, John Tower 11, Eric Verdin 17, Jan Vijg 26

1 Roswell Park Cancer Institute, Buffalo, NY, USA, 2 Buck Institute for Age Research, Novato, CA, USA, 3 Harvard Medical School, Boston, MA, USA, 4 Southern Illinois University, Springfield, IL, USA, 5 Spanish National Cancer Center, Madrid, Spain, 6 National Cancer Institute, NIH, Bethesda, MD, USA, 7 National Institute on Aging, NIH, Baltimore, MD, USA, 8 Stanford University, Stanford, CA, USA, 9 Dana-Farber Cancer Institute, Boston, MA, USA, 10 Baylor College of Medicine, Houston, TX, USA, 11 University of Southern California, Los Angeles, CA, USA, 12 NHLBI, NIH, Bethesda, MD, USA, 13 University of Basel, Basel, Switzerland, 14 McGill University, Montreal, Canada, 15 Brown University, Providence, RI, USA, 16 The Salk Institute, La Jolla, CA, USA, 17 University of California, San Francisco, CA, USA, 18 INSERM, U848, Villejuif, France, 19 Goethe University Frankfurt, Frankfurt, Germany, 20 The Netherlands Cancer Institute, Amsterdam, Netherlands, 21 Medical School Hannover, Hannover, Germany, 22 University of California, Irvine, CA, USA, 23 University of North Carolina, Chapel Hill, NC, USA, 24 Moscow State University, Moscow, Russia, 25 Massachusetts General Hospital, Boston, MA, USA, 26 Albert Einstein College of Medicine, Bronx, USA

Running title: Impact papers on aging in 2009

Key words: aging, senescence, signal transduction, genes for longevity

Correspondence: Blagosklonny, MD/PhD, MD, PhD, Professor, Department of Cell Stress Biology, Roswell Park Cancer Institute, BLSC, L3-312, Elm and Carlton Streets, Buffalo, NY 14263, USA

Received: 03/2/10; accepted: 03/22/10; published on line: 03/23/10

E-mail: Blagosklonny@oncotarget.com

Copyright: © Blagosklonny et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Abstract

The editorial board of Aging reviews research papers published in 2009, which they believe have or will have a significant impact on aging research. Among many others, the topics include genes that accelerate aging or in contrast promote longevity in model organisms, DNA damage responses and telomeres, molecular mechanisms of life span extension by calorie restriction and pharmacologic interventions into aging. The emerging message in 2009 is that aging is not random but determined by a genetically-regulated longevity network and can be decelerated both genetically and pharmacologically.
Telomeres

The 2009 Nobel Prize in Physiology or Medicine was awarded to Elizabeth Blackburn, Carol Greider and Jack Szostak for their contributions to our understanding of how the ends of eukaryotic chromosomes, telomeres, are maintained by a specialized reverse transcriptase, telomerase. This award is the closest Nobel Prize to date related to aging. Of course, the major significance of the work relates to basic cell biology and cancer, rather than aging research. In fact, whereas telomere shortening explains the Hayflick limit (replicative senescence) in human cells, it cannot explain the difference in longevity between mice and men. But there may be other links between telomeres and aging. In 2009, several publications by Epel, Blackburn and co-workers provide a new link between telomere length and age-related diseases. As published in the first issue of Aging, the rate of telomere shortening in peripheral leukocytes predicts mortality from cardiovascular disease in elderly men [1]. Even more intriguingly, pessimism correlates with short leukocyte telomeres and elevated interleukin (IL)-6 in post-menopausal women [2]. The cause-and-effect relationship between telomere length and these physiological endpoints is unknown, but several non-mutually exclusive explanations can be proposed. Rapid telomere shortening may indicate a cellular hyper-activation, hyper-proliferation and/or hyper-secretory phenotypes often associated with cellular senescence, stem cell exhaustion and diseases of aging.

In agreement with these possibilities, telomere length was shown to regulate the expression of interferon-stimulated gene 15 (ISG15). Short-telomeres up-regulated ISG15 independent of DNA damage signaling. This finding demonstrated for the first time that an endogenous human gene can be regulated by telomere length prior to the onset of telomere dysfunction and DNA damage signals. It was suggested that the upregulation of ISG15 by telomere shortening may contribute to the chronic inflammation associated with human aging [3]. Pertinent to this idea, also in 2009, the secretion of inflammatory cytokines such as IL-6 and IL-8 by senescent cells, whether made senescent by dysfunctional telomeres or DNA damage, was shown to be suppressed by two micro-RNAs (miR-146a and 146b) [4]. It was proposed that these micro-RNAs modulate inflammatory responses by affecting signal transduction pathways that contribute to a larger senescence associated secretory phenotype. It will be of interest to know whether miR-146a/b also suppresses ISG15 expression, and if this effect is influenced by telomere status.

It was also demonstrated that dysfunction of a telomere-binding protein is sufficient to produce severe telomeric damage in the absence of telomere shortening, resulting in premature tissue degeneration and development of neoplastic lesions [5]. New insight has been gained in the understanding of how telomeres are maintained and how the processes of DNA repair occur in telomeres. For example, it appears that the guardians of the genome, the RecQ helicases, actively participate in this repair process [6].

Damaged telomeres were also found to be the major factor contributing to the wide variability in the amount of DNA damage signaling in human tumor cell lines, findings that may help clarify the relative contributions of non-telomeric DNA double-strand breaks and damaged telomeres to levels of genomic instability [7].

DNA damage response and aging

In 2009, it was demonstrated that the persistent (but not transient) DNA damage response (DDR) associated with senescent cells is essential for their ability to express and secrete inflammatory cytokines [8]. Cell surface-bound IL-1alpha is essential for the senescence-associated secretion of IL-6 and IL-8, 2 proinflammatory cytokines, reinforcing the senescence phenotype [9].

Both the initiation and maintenance of cytokine secretion required the DDR proteins ATM, NBS1 and CHK2, but not p53. ATM was also essential for IL-6 secretion during oncogene-induced senescence and by damaged cells that bypass senescence. It was proposed that this activity of the DDR allows senescent cells to communicate their compromised state to the surrounding tissue [8]. In addition, a DDR may occur in senescent cells even in the absence of detectable DNA damage [10]. This pseudo-DDR is a marker of cellular hyperactivation and is inhibited by rapamycin [10], a clinically approved drug that decelerates cellular senescence [11]. Thus, persistent DDR signaling, regardless of DNA damage, may be a part of the senescent phenotype.

It was shown that longevity extension mutations in the yeast SCH9, the yeast homolog of the conserved pro-aging gene S6K (Ribosomal Protein S6 Kinase), caused a major reduction in age-dependent DNA damage by lowering the activity of error-prone DNA repair genes [12].

Also, age-dependent deterioration of nuclear pore complexes causes an increase in nuclear permeability and the leaking of cytoplasmic proteins into the nucleus in postmitotic cells [13].

www.impactaging.com
The ability to respond to stress decreases with age. Stress-responding factors which regulate transcription can influence longevity. In 2009, Westerheide et al demonstrated that stress-induced regulation of heat shock factor 1 (HSF-1) by the deacetylase SIRT1 (sirtuin 1) may play a role in the regulation of life span [14]. Defining the targets of sirtuins may help to understand the importance of transcriptional regulation in age-related diseases.

An intriguing possibility is that the response of the cells to certain types of DNA damage (e.g. DNA breaks) results in epigenetic changes that alter gene expression [15]. These changes do occur in mammals and it will be interesting to test whether these epigenetic changes in response to DNA damage are associated with, or can actually cause aging.

**Mitochondria, oxidative stress and aging**

On the other hand, the free radical theory, which posits that aging is caused by an accumulation of oxidative damage, was critically questioned in 2009. First, overexpression of major antioxidant enzymes, which decrease free radicals, did not extend the lifespan of mice [16]. Second, deletion of mitochondrial superoxide dismutase (Sod-2) extended life span in Caenorhabditis elegans [17]. Third, life span extension by dietary restriction was not linked to protection against somatic DNA damage in Drosophila melanogaster [18]. Fourth, Sod-2 haploinsufficiency did not accelerate murine aging, even in mice with dysfunctional telomeres [19]. In addition it was demonstrated that the reduced energy metabolism and the increased oxidative stress in the mitochondria of young Mclk1+/− mice results in an almost complete protection from the age-dependent loss of mitochondrial function. Moreover, this altered mitochondrial condition is linked to a significant attenuation of the rate of development of oxidative biomarkers of aging. Thus, this study indicates that mitochondrial oxidative stress is not causal to aging [20]. It was reported that RNAi of five genes encoding components of mitochondrial respiratory complexes I, III, IV, and V leads to increased life span in flies. Long-lived flies with reduced expression of electron transport chain (ETC) genes do not consistently show reduced assembly of respiratory complexes or reduced ATP levels. In addition, extended longevity is not consistently correlated with increased resistance to the free-radical generator paraquat [21].

These results are in agreement with previous papers showing that antioxidants overexpression causes minor effects in life span extension in yeast, flies, and mice compared to those caused by mutations in signal transduction genes. It is likely that increase protection against superoxide must be accompanied by a number of other changes to be effective in life span extension. For instance, LON, a AAA protease located in the mitochondrial matrix, increases stress tolerance, mitochondrial oxygen consumption, while decreasing oxidative damage of proteins in the fungal aging model Podospora anserine [22]. In the same model organism, deletion of a gene encoding a O-methyltransferase, which decrease levels of reactive oxygen species, leads to a decreased lifespan [23].

**Calorie restriction (CR)**

Caloric restriction (CR) without malnutrition delays aging and extends life span in diverse species; however, its effect in primates had not been clearly established. In 2009, a 20-year longitudinal study of adult-onset CR in rhesus monkeys demonstrated that moderate CR lowered the incidence of aging-related deaths. At the time point reported, 50% of control animals had survived, compared with 80% of CR animals. CR delayed the onset of several age-associated pathologies such as diabetes, cancer, cardiovascular disease and brain atrophy [24]. The CR trial in primates raised hope that CR might be effective in humans.

In 2009, numerous studies continued to establish links between caloric restriction (CR) and longevity signaling pathways, including Sir2 (sirtuin) and p53 in D. melanogaster [25] and the E3 ubiquitin ligase WWP-1 in C. elegans [26] as well as upstream and downstream components of the TOR (Target of Rapamycin) pathway: RHEB-1 in C. elegans [27], Tor1 and Sch9 (a homolog of the mammalian kinases Akt and S6K) in yeast [28], and 4E-BP (Eukaryotic Translation Initiation Factor 4E Binding Protein) in Drosophila [29]. It was shown that glucose shortens the life span of C. elegans by downregulating DAF-16/FOXO activity and aquaporin gene expression [30]. In addition, the HIF (hypoxia inducible factor) pathway was implicated in aging and longevity in C. elegans [31, 32]. The different results of two studies have been in general reconciled [33]. In 2009, it has also been shown that in C. elegans CR is mediated by a network of independent, but overlapping pathways [34], suggesting a ‘CR network’. Notably, neuronal SIRT1 regulated endocrine and behavioral responses to CR [35].

It has been shown that disruption of growth hormone receptor (GHR) prevents calorie restriction from improving insulin action and longevity [36]. In normal mice, CR increased insulin sensitivity in liver and muscle. In GHRKO mice, intrinsic insulin-sensitivity
could be attributed to a reduction of inhibitory serine phosphorylation of IRS-1 (Insulin receptor substrate 1) in muscle. CR failed to further increase insulin signaling (insulin sensitivity) in GHRKO mice as compared to normal mice, likely explaining the absence of CR effects on longevity in these long-lived mice [36].

Finally, it was tested whether reallocation of nutrients from reproduction to somatic maintenance could explain the life extending effect of CR. If this were the case, long life under dietary restriction and high fecundity (reproduction) under full feeding would be mutually exclusive. Adding methionine alone to the dietary restriction condition was necessary and sufficient to increase fecundity as much as did full feeding, but without reducing lifespan. Reallocation of nutrients therefore does not explain the responses to dietary restriction. In contrast, reduced activity of the insulin/insulin-like growth factor signaling protected against the shortening of lifespan with full feeding [37].

Pharmacologic intervention

The ultimate goal of biomedical research is the development of therapeutic drugs. As shown previously, activation of mTOR (mammalian Target of Rapamycin) is required for acquiring senescent phenotype in p21-arrested human cells, whereas deactivation of mTOR converts senescence into quiescence. In 2009, it was further demonstrated that the inhibitor of mTOR rapamycin decelerated cellular senescence of p21-arrested human and mouse cells [11]. Similarly, inhibitors of PI-3K and MEK, LY-294002 and U0126, deactivated mTOR and suppressed cellular senescence (converting it into quiescence) [38], defining direct and indirect mTOR inhibitors as aging-suppressants or gerostressors.

The most striking event of the year was the demonstration that rapamycin, administrated to middle-aged (600 day old) mice, significantly extended their life span [39]. The effect was seen at three independent test sites in genetically heterogeneous mice, chosen to avoid genotype-specific effects on disease susceptibility [39]. Rapamycin also prolonged the life of 22-month old mice [40]. [Note: publications by Bjedov et al (Cell Metab 2010 Jan) and by Moskalev and Shaposhnikov (coming in print 2010) that rapamycin extends life span in Drosophila will be reviewed next year].

It was shown that clioquinol, a metal chelator that has beneficial effects in several models of neurodegenerative diseases, inhibits the activity of the mitochondrial enzyme CLK-1 in mammalian cells. Clioquinol-treated nematodes and mice presented a variety of phenotypes produced by mutational reduction of CLK-1. Given that reduction of CLK-1 slows down aging in these organisms, these results suggest that clioquinol (by inhibiting CLK-1) may slow down the aging process [41].

Finally, as a follow-up of the work on the anti-aging effects of mitochondria-targeted antioxidant SkQ1 [42], it was demonstrated that Sk inhibits age-dependent involution of the thymus in normal and senescence-prone mice [43].

Stem cells and aging

In 2009, several lines of evidence suggested that overactivation of signaling pathways might cause exhaustion of stem cells and that vice versa ‘longevity genes’ could prevent stem cell exhaustion. Thus, mTOR mediated Wnt-induced epidermal stem cell exhaustion and aging phenotypes in skin [44]. Further, hyper-activation of mTORC1 caused hyper-proliferation and subsequent exhaustion of hematopoietic stem cells. Pharmacological approaches showed that PTEN, TSC1 and PML regulate hematopoietic stem cell (HSC) maintenance through mTORC1 [45]. In addition, FOXO transcription factors were found to be necessary for adult neural stem cell homeostasis [46, 47]. Importantly, stem cell aging could be suppressed pharmacologically [40, 44]. The PI3K-AKT-FoxO pathway is integral to lifespan regulation in lower organisms plays a prominent role in neural stem/progenitor cell (NSC) proliferation and renewal. FoxO-deficient mice show initial increased brain size and proliferation of neural progenitor cells during early postnatal life, followed by precocious significant decline in the NSC pool and accompanying neurogenesis in adult brains [46].

In addition, functions of aging organs can be rejuvenated by young supporting stem cells. As published in the first issue of Aging, once-monthly infusions of bone marrow (BM)-derived cells from young adult female mice sustained the fertility of aging females long past their time of normal reproductive failure [48]. The fertility-promoting effects were observed regardless of whether the infusions were initiated in young adult or middle-aged females, and were specific for bone marrow harvested from female donors. This “rejuvenation” did not depend on the development of mature eggs from germline cells in the donor marrow, but from host germline cells sustained by the infusions [48, 49]. In fact, very recent studies showed that aged mouse ovaries lacking oocytes retain a rare population of germline stem cells that, when
transplanted into a young host ovarian environment, are able to generate immature oocytes contained within follicles [49]. Thus, reproductive failure with age may be due, at least in part, to deterioration of somatic microenvironments (niches) that support stem cell function.

**Nuclear reprogramming and senescence**

Much interest has also been devoted in the past year to nuclear reprogramming of differentiated cells into induced pluripotent stem (iPS) cells by using defined factors. Understanding which factors facilitate the reprogramming process is thought to give clues to the process of carcinogenesis. Inversely, nuclear reprogramming could be also envisioned as a “rejuvenation process”. In this regard, p53 and p16
^{INK4a} tumor suppressor proteins were shown to be important in limiting reprogramming [50-55]. Activation of p53 was suggested to be more important in murine cells, whereas activation of p16
^{INK4a} appeared the predominant barrier in human cells [50].

Of particular importance to the field of regenerative medicine, which will need patient-specific stem cells derived from older patients, is reprogramming efficiency in fibroblasts from aged humans versus young humans. There is an age-associated decline in reprogramming efficiency in fibroblasts from aged humans versus derived from older patients, is reprogramming efficiency, which is largely reversed by “rejuvenation process”. In this regard, p53 and p16
^{INK4a} tumors suppressor genes, whose expression is increased markedly with aging in several human and murine tissues [50, 55]. Along these lines, it was shown that the increased expression of p16
^{INK4a} with aging could be measured on human peripheral blood samples, and that an individual’s p16INK4a expression was a good biomarker of their “molecular age” [56]. The same group also provided further understanding of the observed linkage of SNPs near the CDKN2a/b locus (which encodes the p16
^{INK4a}, p15
^{INK4b} and ARF tumor suppressors) with human atherosclerotic disease [57]. Expression of CDKN2a/b transcripts is decreased in individuals harboring the risk alleles, suggesting that atherosclerotic disease may result from aberrant, unrestrained proliferation. In this regard, studies on mice overexpressing the CDKN2a/b locus were found to have delayed aging and extended longevity [58].

**Genetics of aging**

In 2009, numerous publications extended our knowledge on the role of sirtuins [35], TOR signaling [59, 60], and the stress response factors HSF-1 and DAF-16 [61] in aging. Of particular importance, it was shown that deletion of the gene encoding Ribosomal Protein S6 Kinase 1 (S6K1) and disruption of PKA extend the life span of mice [62, 63], whereas the gene encoding Eukaryotic Translation Initiation Factor 4E Binding Protein (4E-BP) was shown to be essential for life span extension by CR in Drosophila [29]. Moreover, 4E-BP was shown to act downstream of TOR to modulate cardiac aging in Drosophila [64]. Finally, SIRT6 was shown to play a critical role in DNA double-strand break repair [65].

In 2009, Kenyon and co-workers further uncovered mechanisms of their previous observations made in 1999 (Hsin and Kenyon, Nature, 1999, 399:362-6) that in C elegans and Drosophila the aging of the soma is influenced by the germline: namely, when germline-stem cells are removed, aging slows and lifespan is increased. In 2009, it was published that a predicted transcription elongation factor, TCER-1, plays a key role in this process [66]. When the germ cells are removed, the levels of TCER-1 rise in somatic tissues. This increase is sufficient to trigger key downstream events, as overexpression of tcer-1 extends the lifespan of normal animals that have an intact reproductive system. Intriguingly, TCER-1 specifically links the activity of a broadly deployed transcription factor, DAF-16/FOXO, to longevity signals from reproductive tissues [66]. In mice, Foxo1 integrates insulin signaling with mitochondrial function, and inhibition of Foxo1 can improve hepatic metabolism during insulin resistance and the metabolic syndrome [67].

A prior work by Willcox et al (PNAS 2008, 105: 13987) showed that genetic variation within the FOXO3A gene was strongly associated with human longevity. Long-lived men also presented several additional phenotypes linked to healthy aging, including lower prevalence of cancer and cardiovascular disease, and high physical and cognitive function. Long-lived men also exhibited greater insulin sensitivity associated with homozygosity for the FOXO3A GG genotype. In 2009, confirming the Wilcoxon observation, the flurry of papers showed the association between SNPs in the FoxO3A gene and extreme longevity in Japanese, German, American, Italian, and Chinese populations [68-71].

There were intriguing publications on the complex role of p53 in longevity. In Drosophila melanogaster, p53 exerted developmental stage-specific and sex-specific effects on adult life span, indicative of sexual antagonistic pleiotropy [72, 73]. Further, an association between single nucleotide polymorphisms (SNPs) in p53 pathway genes and human fertility suggested that p53 regulates the efficiency of human reproduction. These results provide a plausible explanation for
selective pressure to retain some alleles in the p53 pathway, and suggest that such alleles are a good example of antagonistic pleiotropy [74].

Interestingly, SNPs in the p21 gene correlated with longevity in an Italian population [75]. Several papers have highlighted an important role of p53 in tissue fitness through its impact in preventing mobilization of stem cells harboring persistent DNA damage (ie, dysfunctional telomeres) [76, 77]. However, the phenotypic outcome was tissue and context specific. In mouse epidermis deletion of p53 rescued organ maintenance and body fitness of neborn mice with dysfunctional telomeres [76]. In contrast, p53 deletion in the intestinal epithelium accelerated tissue dysfunction and shortened the lifespan of aging telomere dysfunctional mice [77]. The latter phenotype was associated with aberrant survival chromosomal instability and p53-independent apoptosis. The limitation of the survival of chromosomal unstable stem cells is likely to represent a key step in the known role of p53 as a tumor suppressor. Also it was shown that the p53 family member, TAp63, is essential for maintenance of epidermal and dermal precursors and that, in its absence, these precursors senesce and skin ages prematurely [78].

Model systems continue to be instrumental in understanding the genetics of longevity. The WRN gene defective in the premature aging disorder Werner syndrome encodes a protein with both helicase and exonuclease activities [79]. To dissect its genetic functions, human WRN was tested for its ability to rescue sgs1-related phenotypes. WRN was shown to genetically interact with topoisomerase 3 and restore the slow growth phenotype of sgs1 top3. WRN helicase but not exonuclease activity was genetically required for restoration of top3 growth phenotype, demonstrating separation of function of WRN catalytic activities. In a top3 mutant background, DNA unwinding by WRN helicase may be deleterious to cell growth and genome homeostasis [80].

In 2009, a few studies delved into the genetics of the insulin-producing pancreatic beta-cell aging in humans and mice [81-83]. A loss of beta-cell replication with aging is a contributor to age-related increase in the incidence of type II diabetes. Prior work had shown that p16INK4a tumor suppressor causes an age-dependent decline in beta-cell replication. In 2009, it was reported that loss of Polycomb (PcG) repression of p16INK4a mediated by the EZH2 histone methyltransferase occurred with aging in humans and mice [82]. In mice, somatic deletion of EZH2 led to loss of beta-cell replication and diabetes, and these effects could be rescued by concomitant deletion of p16INK4a and Arf.

This work linked alterations of chromatin architecture with aging to expression of anti-proliferative molecules. Bhushan and colleagues also reported a similar regulation of p16INK4a expression with aging by the Bmi-1 PcG protein, which functions in concert with EZH2 to repress p16INK4a expression [81]. Lastly, it was shown that p38MAPK activates p16INK4a with aging in beta-cells, suggesting a possible pharmacologic approach to regulating aging of this tissue [83].

**Autophagy**

In 2009, the simple dogma that autophagy is always associated with or causes senescence was challenged. Although autophagy remains a crucial anti-aging mechanism, the relationship is likely to be complex. Thus, autophagy was shown to be activated during cellular senescence, and activation correlated with negative feedback in the PI3K-mTOR pathway. A subset of autophagy-related genes was up-regulated during senescence: overexpression of one gene, ULK3, induced autophagy and senescence. Furthermore, inhibition of autophagy delayed the senescence phenotype, including senescence-associated secretion. These data suggest that autophagy, and its consequent protein turnover, may mediate acquisition of the senescence phenotype [84]. Inhibition of autophagy in adult *Drosophila* [85] or *C. elegans* [86] was found not to affect longevity, however autophagy was required for the increased life span caused by several pharmacologic and genetic manipulations in yeast, *Drosophila* and *C. elegans* [87-90], suggesting that autophagy may be limiting for life span under some conditions but not others. Interestingly, resveratrol-mediated inhibition of mammalian S6 kinase by resveratrol suppressed autophagy [91]. In 2009, several reports further demonstrated that the TOR signaling pathway targets the Atg1/Atg13 protein kinase complex to control autophagy [92-94]. Furthermore, TOR-mediated autophagy regulates cell death in Drosophila neurodegenerative disease [95].

The natural polyanion spermidine can extend the chronological and replicative life span in yeast and increase the median and maximal longevity of fruit flies and nematodes (*C. elegans*). Spermidine was found to act as a potent inducer of autophagy in all species tested, including yeast, *Drosophila, C. elegans* [96]. The antiaging effect of spermidine was abolished by the deletion or depletion of essential autophagy genes in yeast, *Drosophila* and *C. elegans* [96]. In mice, a dietary supplementation with polyanions (including
spermidine) also increases healthspan and lifespan [97], although the dependency of this phenomenon on autophagy has not been addressed yet. Spermidine likewise induces autophagy and longevity through its capacity to inhibit histone acetylases in yeast cells [96].

Sirtuin-1 and that of its C. elegans orthologue induce autophagy in human and nematode cells. Sirtuin-1 is also required for the induction of autophagy by its allosteric activator resveratrol (both in human cells and nematodes), culture in nutrient-free media (in human cells) and caloric restriction (in nematodes). In C. elegans, it was found that activation of Sirtuin-1 extended longevity in an autophagy-dependent fashion. Thus, the knockdown of the essential autophagy gene Beclin1/ATG6 abolished life span extension by Sirtuin-1 activation [87]. These results underscore the contribution autophagy to the regulation of longevity by pharmacological agents [98].

Post-transcriptional gene regulation and aging

In fact, 2009 saw an escalation in interest in microRNAs and other non-coding RNAs implicated in aging and replicative senescence. A prominent example of this regulation came studies of the mitogen-activated protein kinase (MAPK) signaling component MKK4 (MAPK kinase kinase 4). MKK4 levels were elevated in aging tissues and in senescent cells thanks to reductions in the abundance of four microRNAs (miR-15b, miR-24, miR-25, and miR-141) that interacted with the 5’- and 3’-untranslated regions of the MKK4 mRNA and repressed its translation [99].

The other major class of post-transcriptional regulatory factors, RNA-binding proteins (RBPs), were also the focus of important age-related studies in 2009. Several RBPs that affect the turnover and translation of proteins implicated in proliferation, survival, inflammation, neurodegeneration, and cancer (HuR, AUFB1, TIA-1, TTP) displayed elevated abundance in a broad array of human tissues and in all ages, suggesting that their influence extends throughout the human life span [100].

The RBP TTP (tristetraprolin) attracted especial attention because it triggered replicative senescence [101]; in keeping with the tumor-suppressive influence of replicative senescence, TTP was found to be eliminated in certain cancers [102].

Circadian clock

There is growing evidence for a link between circadian rhythm, signal-transduction genes, metabolism, cancer and aging [103, 104]. The circadian clock gene period extended the health span of aging in Drosophila melanogaster [105]. Further, circadian control of the NAD+ salvage pathway by CLOCK-SIRT1 was demonstrated [106]. Intriguingly, light was found to activate MAPK (mitogen activated pathway kinase) in zebrafish cells, and this light-dependent activation controlled DNA repair [107]. In rats, circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats [108]. In mice, it was reported that N-acetyl-L-cysteine (NAC), an antioxidant, ameliorated symptoms of premature aging associated with the deficiency of the circadian protein BMAL1 [109].

Cancer and aging

CR is known to slow aging and delay cancer. In 2009, it was reported that fasting abrogates side effects caused by chemotherapy in cancer patients. Importantly, for those patients in whom cancer progression could be assessed, fasting did not prevent chemotherapy-induced reduction of tumor volume or tumor markers [110]. The link between aging and cancer via p53 was shown to be complex in 2009. Thus, the ability of p53 to act as a defense against tumor progression was shown to be age-dependent [111]. Further, Levine and co-workers previously showed that p53 activity declines with age, and a recent study showed that p53 transcriptional activity is reduced in senescent cells [112]. Interestingly, SIRT1 knockout mice, which do not live longer when calorically restricted, were found to have normal rates of skin cancer but the ability of resveratrol, a SIRT1 activator, to protect the mice was greatly reduced [113], indicating that the anti-tumor activity of resveratrol is mediated at least in part by SIRT1.

Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. These changes of fatal neoplasms are similar to the effects observed with calorie restriction and therefore could possibly be a major contributing factor to the extended life span observed in the GHR/BP KO mice. [114]

Overall, 2009 was an exciting year for increasing our understanding of aging and its relationship to age-related disease, and developing promising strategies and candidates for pharmacological interventions into the aging process. Several approaches in combination with drugs and diet may slow aging, although not making it negligible [115].

ACKNOWLEDGMENTS AND ANNOUNCEMENTS

We apologize to the authors whose important publications were not discussed due to space limitations
or were simply overlooked. Here we referenced only papers published in the 2009 calendar year. That was not an easy task given that most of publications are the continuation of or based on previous research. We expect to make this a tradition to publish the year overview every year. The next year, the task will be easier, given that “Aging in 2010” will be the continuation of “Aging in 2009”.

Please e-mail your reprints to us in December 2010 (editors@impactaging.com) or, even better, please submit your best manuscripts for publication in Aging at papers@impactaging.com.

REFERENCES

1. Epel ES, Merkin SS, Cawthon R, Blackburn EH, Adler NE, M.J. P, Seeman TE. The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. Aging 2009, 1: 81-88.
2. O’Donovan A, Lin J, Dhabhar FS, Wolkwitz O, Tillie JM, Blackburn E, Epel E. Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in post-menopausal women. Brain Behav Immun 2009, 23: 446-449.
3. Lou Z, Wei J, Riethman H, Baur JA, Voglauer R, Shay JW, Wright WE. Telomere length regulates ISG15 expression in human cells. Aging 2009, 1: 608-621.
4. Bhaumik D, Scott GK, Schokprur S, Patil CK, Orjalo AV, Rodier F, Lithgow GJ, Campisi J. MicroRNAs miR-146a/b negatively modulate the senescence-associated inflammatory mediators IL-6 and IL-8. Aging 2009, 1: 402-411.
5. Martinez P, Thanasoula M, Munoz P, Liao C, Tejera A, McNees C, Flores JM, Fernandez-Capetillo O, Tarsounas M, Blasco MA. Increased telomere fragility and fusions resulting from TRF1 deficiency lead to degenerative pathologies and increased cancer in mice. Genes Dev 2009, 23: 2060-2075.
6. Ghosh A, Rossi ML, Aulds J, Croteau D, Bohr VA. Telomeric D-loops containing 8-oxo-2-deoxyguanosine are preferred substrates for Werner and Bloom syndrome helicases and are bound by POT1. J Biol Chem 2009, 284: 31074-31084.
7. Nakamura AJ, Redon CE, Bonner WM, Sedelnikova OA. Telomere-dependent and telomere-independent origins of endogenous DNA damage in tumor cells. Aging 2009, 1: 212-218.
8. Rodier F, Coppé JP, Patil CK, Hoiejmakers WA, Muñoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol. 2009, 11: 973-979.
9. Orjalo AV, Bhaumik D, Gengler BK, Scott GK, Campisi J. Cell surface-bound IL-1α is a upstream regulator of the senescence-associated IL-6/IL-8 cytokine network. Proc Natl Acad Sci U S A 2009, 106: 17031-17036.
10. Pospelova TV, Demidenk ZN, Bukeeva EI, Pospelov VA, Gudkov AV, Blagosklonny MV. Pseudo-DNA damage response in senescent cells. Cell Cycle 2009, 8: 4112-4118.
11. Demidenko ZN, Zubova SG, Bukeeva EI, Pospelov VA, Pospelova TV, Blagosklonny MV. Rapamycin decelerates cellular senescence. Cell Cycle 2009, 8: 1888-1895.
12. Madia F, Wei M, Yuan V, Hu J, Gattazzo C, Pham P, Goodman MF, Longo VD. Oncogene homologue Sch9 promotes age-dependent mutations by a superoxide and Rev1/Pol3eta-dependent mechanism. J Cell Biol 2009, 186: 509-523.
13. D’Angelo MA, Raices M, Panowski SH, Hetzer MW. Age-dependent deterioration of nuclear pore complexes causes a loss of nuclear integrity in postmitotic cells. Cell 2009, 136: 284-295.
14. Westerheide SD, Anckar J, Stevens SMJ, Sistonen L, Morimoto RI. Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. Science 2009, 323: 1063-1066.
15. Sinclair DA, Oberdoerffer P. The ageing epigenome: damaged beyond repair? Ageing Res Rev 2009, 8: 189-198.
16. Perez VI, Van Remmen H, Bokov A, Epstein CJ, Vijg J, Richardson A. The overexpression of major antioxidant enzymes does not extend the lifespan of mice. Aging Cell 2009, 8: 73-75.
17. Van Raamsdonk JM, Hekimi S. Deletion of the mitochondrial superoxide dismutase sod2 extends lifespan in Caenorhabditis elegans. PLoS Genet 2009, 5: e1000361.
18. Edman U, Garcia AM, Busuttil RA, Sorensen D, Lundell M, Kapahi P, Vijg J. Lifespan extension by dietary restriction is not linked to protection against somatic DNA damage in Drosophila melanogaster. Aging Cell 2009, 8: 331-338.
19. Guachalla LM, Ju Z, Koziel R, von Figura G, Song Z, Fusser M, Epe B, Jansen-Derr P, Rudolph KL. Sod2 haploinsufficiency does not accelerate aging of telomere dysfunctional mice. Aging 2009, 1: 303-315.
20. Lapointe J, Stepanyan Z, Bigras E, Hekimi S. Reversal of the mitochondrial phenotype and slow development of oxidative biomarkers of aging in long-lived Mck1+/− mice. J Biol Chem 2009, 284: 20364-20374.
21. Copeland JM, Cho J, Lo T, Jr., Hur JH, Bahadorani S, Arabyan T, Rabie J, Soh J, Walker DW. Extension of Drosophila life span by RNAi of the mitochondrial respiratory chain. Curr Biol 2009, 19: 1591-1598.
22. Luce K, Osiewacz HD. Increasing organisinal lifespan by enhancing mitochondrial protein quality control. Nat Cell Biol 2009, 11: 852-858.
23. Kunstmann B, Osiewacz HD. The S-adenosylmethionine dependent O-methyltransferase PaMTH1: a longevity assurance factor protecting Podospora anserina against oxidative stress. Aging 2009, 1: 328-334.
24. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Czucia C, Simmons HA, Kemnitz JW, Weindruch R. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009, 325: 201-204.
25. Bauer JH, Morris SN, Chang C, Flatt T, Wood JG, Helfand SL. Dsir2 and Dmp53 interact to mediate aspects of CR-dependent life span extension in D. melanogaster. Aging 2009, 1: 38-48.
26. Carrano AC, Liu Z, Dillin A, Hunter T. A conserved ubiquitination pathway determines longevity in response to diet restriction. Nature 2009, 460: 396-399.
27. Honjo S, Yamamoto T, Uno M, Nishida E. Signalling through RHEB-1 mediates intermittent fasting-induced longevity in C. elegans. Nature 2009, 457: 726-730.
28. Wei M, Fabrizio P, Madia F, Hu J, Ge H, Li LM, Longo VD. Tor1/Sch9-regulated carbon source substitution is as effective as calorie restriction in life span extension. PLoS Genet. 2009, 5: e1000467.
29. Zid BM, Rogers AN, Katewa SD, Vargas MA, Koliipski MC, Lu TA, Benzer S, Kapahi P. 4E-BP extends lifespan upon dietary...
restriction by enhancing mitochondrial activity in Drosophila. Cell 2009, 139: 149-160.

30. Lee SJ, Murphy CT, Kenyon C. Glucose shortens the life span of C. elegans by downregulating DAF-16/FOXO activity and aquaporin gene expression. Cell Metab 2009, 10: 379-391.

31. Chen D, Thomas EL, Kapahi P. HIF-1 modulates dietary restriction-mediated lifespan extension via IRE-1 in Caenorhabditis elegans. PLoS Genet 2009, 5: e1000486.

32. Mehta R, Steinkraus KA, Sutphin GL, Ramos FJ, Shamieh LS, Huh A, Davis C, Chandler-Brown D, Kaeberlein M. Proteasomal regulation of the hypoxic response modulates aging in C. elegans. Science 2009, 324: 1196-1198.

33. Kaeberlein M, Kapahi P. The hypoxic response and aging. Cell Cycle 2009, 8: 2324.

34. Greer EL, Brunet A. Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in C. elegans. Aging Cell 2009, 8: 113-127.

35. Cohen DE, Supinski AM, Bonkowski MS, Donnegg G, Guarente LP. Neuronal SIRT1 regulates endocrine and behavioral responses to calorie restriction. Genes Dev 2009, 23: 2812-2817.

36. Bonkowski MS, Dominici FP, Arum O, Rocha JS, Al Regaiey KA, Westbrook R, Spong A, Panici J, Masternak MM, Kopchick JJ, Bartke A. Disruption of growth hormone receptor prevents calorie restriction from improving insulin action and longevity. PLoS One 2009, 4: e5467.

37. Grandison RC, Piper MD, Partridge L. Amino-acid imbalance explains extension of lifespan by dietary restriction in Drosophila. Nature 2009, 462: 1061-1064.

38. Demidenko ZN, Shutman M, Blagosklonny MV. Pharmacologic inhibition of MEK and PI-3K converges on the mTOR/S6 pathway to decelerate cellular senescence. Cell Cycle 2009, 8: 1896-1900.

39. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogenous mice. Nature 2009, 460: 392-396.

40. Chen C, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Sci Signal 2009, 2: ra75.

41. Wang Y, Branicky R, Stepanyan Z, Carroll M, Guimond MP, Hihi A, Hayes S, McBride K, Hekimi S. The neurodegeneration drug cloquingol inhibits the aging-associated protein CLK-1. J Biol Chem 2009, 284: 314-323.

42. Skulachev VP, Anisimov VN, Antonenko YN, Bakeeva LE, Chernyak BV, Erichev VP, Filenko OF, Kalinina NI, Kapelko VI, Kolosova NG, Kopnin BP, Korshunova GA, Lichinster MR, Obukhova LA, Pasyukova EG, Pisarenko OI, Roginsky VA, Ruuge EK, Senin, II, Severina, II, Skulachev MV, Spivak IM, Tashlitsky VN, Tkachuk VA, Vyssokikh MY, Yaguzhinsky LS, Zorov DB. An attempt to prevent senescence: a mitochondrial approach. Biochim Biophys Acta 2009, 1787: 437-461.

43. Obukhova LA, Skulachev VP, Kolosova NG. Mitochondria-targeted antioxidant Skq1 inhibits age-dependent involution of the thymus in normal and senescence-prone rats. Aging 2009, 1: 389-401.

44. Castilho RM, Squarize CH, Chodosh LA, Williams BO, Gutkind JS. mTOR mediates Wnt-induced epidermal stem cell exhaustion and aging. Cell Stem Cell 2009, 5: 279-289.

45. Gan B, DePinho RA. mTORC1 signaling governs hematopoietic stem cell quiescence. Cell Cycle 2009, 8: 1003-1006.

46. Paik JH, Ding Z, Narurkar R, Ramkisson S, Muller F, Kamoun WS, Chae SS, Zheng H, Ying H, Mahoney J, Hiller D, Jiang S, Protopopov A, Wong WH, Chin L, Ligon KL, DePinho RA. FoxOs cooperatively regulate diverse pathways governing neural stem cell homeostasis. Cell Stem Cell 2009, 5: 540-553.

47. Renault VM, Rafalski VA, Morgan AA, Salih DA, Brett JO, Webb AE, Villeda SA, Thekkat PU, Guillerey C, Denko NC, Palmer TD, Butte AJ, Brunet A. FoxO3 regulates neural stem cell homeostasis. Cell Stem Cell 2009, 5: 527-539.

48. Selesniemi K, Lee HJ, Nikiura T, Tilly JL. Young adult donor bone marrow infusions into female mice postpone age-related reproductive failure and improve offspring survival. Aging 2009, 1: 49-57.

49. Nikiura Y, Nikiura T, Tilly JL. Aged mouse ovaries possess rare premeiotic germ cells that can generate oocytes following transplantation into a young host environment. Aging 2009, 1: 971-978.

50. Li H, Collado M, Villasante A, Strati K, Ortega S, Canamero M, Blasco MA, Serrano M. The Ink4a/Arf locus is a barrier for iPS cell reprogramming. Nature 2009, 460: 1136-1139.

51. Kawamura T, Suzuki J, Wang YV, Menendez S, Morera LB, Raya A, Wahl GM, Belmonte JC. Linking the p53 tumour suppressor pathway to somatic cell reprogramming. Nature 2009, 460: 1140-1144.

52. Utkal J, Polo JM, Stadtfeld M, Maherali N, Kulaert W, Walsh RM, Khalil A, Rheinwald JG, Hochedlinger K. Immortalization eliminates a blockroad during cellular reprogramming into iPS cells. Nature 2009, 460: 1145-1148.

53. Marion RM, Strati K, Li H, Murga M, Blanco R, Ortega S, Fernandez-Capetillo O, Serrano M, Blasco MA. A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity. Nature 2009, 460: 1149-1153.

54. Hanna J, Saha K, Pando B, van Zon J, Lengner CJ, Creighton MP, van Oudenaarden A, Jaenisch R. Direct cell reprogramming is a stochastic process amenable to acceleration. Nature 2009, 462: 595-601.

55. Banito A, Rashid ST, Acosta JC, Li S, Pereira CF, Geti I, Pinho S, Silva JC, Azuara V, Walsh M, Vallier L, Gil J. Senescence impairs successful reprogramming to pluripotent stem cells. Genes Dev 2009, 23: 2134-2139.

56. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, Thomas NE, Sharpless NE. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. Aging Cell 2009, 8: 439-448.

57. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Mohlke KL, Ibrahim JG, Thomas NE, Sharpless NE. INK4/ARF transcript expression is associated with chromosome 9p21 variants linked to atherosclerosis. PLoS One 2009, 4: e5027.

58. Matheu A, Maraver A, Collado M, Garcia-Cao I, Canamero M, Borras C, Flores JM, Klatt P, Vina J, Serrano M. Anti-aging activity of the Ink4/Arf locus. Aging Cell 2009, 8: 152-161.

59. Pan Y, Shadel GS. Extension of chronological life span by reduced TOR signaling requires down-regulation of Sch9p and involves increased mitochondrial OXPHOS complex density. Aging 2009, 1: 131-145.

60. Soukas AA, Kane EA, Carr CE, Melo JA, Ruvkun G. Rictor/TORC2 regulates fat metabolism, feeding, growth, and life span in Caenorhabditis elegans. Genes Dev 2009, 23: 496-511.
Anselmi Condorelli signaling study.

66. An elongation centenarians.

Waskar M, Landis GN, Shen J, Curtis C, Tozer K, Abdueva D, Skvortsov D, Tavare S, Tower J. Drosophila melanogaster p53 has developmental stage-specific and sex-specific effects on adult life span indicative of sexual antagonistic pleiotropy. Aging 2009, 1: 903-936.

30. Donehower LA. Longevity regulation in flies: a role for p53. Aging 2009, 1: 6-8.

Kang HJ, Feng Z, Sun Y, Atwal G, Murphy ME, Rebeck TR, Rosenwaks Z, Levine AJ, Hu W. Single-nucleotide polymorphisms in the p53 pathway regulate fertility in humans. Proc Natl Acad Sci U S A 2009, 106: 9761-9766.

Gravina S, Lescai F, Hurteau G, Brock GJ, Saramaki A, Salvioli S, Franceschi C, Roninson IB. Identification of single nucleotide polymorphisms in the p21 (CDKN1A) gene and correlations with longevity in the Italian population. Aging 2009, 1: 470.

Flores I, Blasco MA. A p53-dependent response limits epidermal stem cell functionality and organizational size in mice with short telomeres. PLoS One 2009, 4: e4934.

Begus-Nahrmann Y, Lechel A, Obenauf AC, Nalapareddy K, Peit E, Hoffmann E, Schlaurad F, Liss B, Schirmacher P, Kestler H, Danenberg E, Barker N, Clevers H, Speicher MR, Rudolph KL. p53 deletion impairs clearance of chromosomal-instable stem cells in aging telomere-dysfunctional mice. Nat Genet 2009, 41: 1138-1143.

Su X, Paris M, Gi YJ, Tsai KY, Cho MS, Lin YL, Biernaskie JA, Sinha S, Prives C, Pevny LH, Miller FD, Flores E. Tap63 prevents premature aging by promoting adult stem cell maintenance. Cell Stem Cell 2009, 5: 64-75.

Agarwal M,Brosh RM, Jr. Premature aging syndrome gene WRN genetically interacts with a topoisomerase. Cell Cycle 2009, 8: 2143.

Agarwal M,Brosh RM. WRN helicase defective in the premature aging disorder Werner syndrome genetically interacts with topoisomerase 3 and restores the top3 slow growth phenotype of sgs1 top3. Aging 2009, 1: 219-233.

Dhawan S, Tschen SI, Bhushan A. Bmi-1 regulates the Ink4a/Arf locus to control pancreatic beta-cell proliferation. Genes Dev 2009, 23: 906-911.

Chen H, Gu X, Su H, Bottino R, Contreras JL, Tarakhovsky A, Kim SK. Polycytop bacterial Ezh2 regulates pancreatic beta-cell Ink4a/Arf expression and regeneration in diabetes mellitus. Genes Dev 2009, 23: 975-985.

Wong ES, Le Guezenec X, Demidov ON, Marshall NT, Wang ST, Krishnamurthy J, Sharpless NE, Dunn NR, Bulavin DV. P38MAPK controls expression of multiple cell cycle inhibitors and islet proliferation with advancing age. Dev Cell 2009, 17: 142-149.

Young AR, Narita M, Ferreira M, Kirschner K, Sadaie M, Darot JF, Tavare S, Arakawa S, Shimizu S, Watt FM, Narita M. Autophagy mediates the mitotic senescence transition. Genes Dev. 2009, 23:798-803.

Ren C, Finkel SE, Tower J. Conditional inhibition of autophagy genes in adult Drosophila impair survival without compromising longevity. Exp Gerontol 2009, 44: 228-235.

Hansen M, Chandra A, Mitic LL, Onken B, Driscoll M, Kenyon C. A role for autophagy in the extension of lifespan by dietary restriction in C. elegans. PLoS Genet 2008, 4: e24.

Morselli E, Galluzzi L, Kepp O, Criollo A, Mairi MC, Tavernarakis N, Madeo F, Kroemer G. Autophagy mediates pharmacological lifespan extension by spermidine and resveratrol. Aging 2009, 1: 961-970.

Alvers AL, Wood MS, Hu D, Kaywell AC, Dunn WA Jr., Aris JP. Autophagy is required for extension of yeast chronological life span by rapamycin. Autophagy 2009, 5: 847-849.

Dwivedi M, Song HO, Ahnn J. Autophagy genes mediate the effect of calcineurin on life span in C. elegans. Autophagy 2009, 5: 604-607.

Tavernarakis N, Pasparaki A, Tasdemir E, Mairi MC, Kroemer G. The effects of p53 on whole organism longevity are mediated by autophagy. Autophagy 2008, 4: 870-873.
91. Armour SM, Joseph A. Baur, Sherry N. Hsieh SN, Land-Bracha A, Thomas SM, Sinclair DA. Inhibition of mammalian S6 kinase by resveratrol suppresses autophagy. Aging 2009, 1: 515-528.
92. Stephan JS, Yeh YY, Ramachandran V, Deminoff SJ, Herman PK. The Tor and PKA signaling pathways independently target the Atg1/Atg13 protein kinase complex to control autophagy. Proc Natl Acad Sci U S A 2009, 106: 17049-17054.
93. Chang YY, Neufeld TP. An Atg1/Atg13 complex with multiple roles in TOR-mediated autophagy regulation. Mol Biol Cell 2009, 20: 2004-2014.
94. Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, Kundu M, Kim DH. ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol Biol Cell 2009, 20: 1992-2003.
95. Wang T, Lao U, Edgar BA. TOR-mediated autophagy regulates cell death in Drosophila neurodegenerative disease. J Cell Biol 2009, 186: 703-711.
96. Eisenberg T, Knauer H, Schauer A, Buttnér S, Ruckenstuhl C, Carmona-Gutierrez D, Ring J, Schroeder S, Magnes C, Antonacci L, Fussi H, Desczcz L, Hartl R, Schraml E, Criollo A, Megalou E, Weiskopf D, Laun P, Heeren G, Breitenbach M, Grubeck-Loebenstein B, Herker E, Fahrenkrog B, Frohlich KU, Sinner F, Tavarianakis N, Minois N, Kroemer G, Madoe F. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol 2009, 11: 1305-1314.
97. Soda K, Dobashi Y, Kano Y, Tsujinaka S, Konishi F. Polyamine-rich food decreases age-associated pathology and mortality in aged mice. Exp Gerontol 2009, 44: 727-732.
98. Madoe F, Eisenberg T, Kroemer G. Autophagy for the avoidance of neurodegeneration. Genes Dev 2009, 23: 2253-2259.
99. Marasa BS, Srikanth S, Masuda K, Abdelmohsen K, Kuwano Y, Yang X, Martindale JL, Rinker-Schaeffer CW, Gorospe M. Increased MKK4 abundance with replicative senescence is linked to the joint reduction of multiple microRNAs. Sci Signal 2009, 2: ra69.
100. Masuda K, Marasa B, Martindale JL, Halushka MK, Gorospe M. Tissue- and age-dependent expression of RNA-binding proteins that influence mRNAs turnover and translation. Aging 2009, 1: 681-698.
101. Sanduja S, Kaza V, Dixon DA. The mRNA decay factor tristetraprolin (TTP) induces senescence in human papillomavirus-transformed cervical cancer cells by targeting E6-AP ubiquitin ligase. Aging 2009, 1: 803-817.
102. Brennan SE, Kuwano Y, Alkharouf N, Blackshear PJ, Gorospe M, Wilson GM. The mRNA destabilizing protein tristetraprolin is suppressed in many cancers, altering tumorigenic phenotypes and patient prognosis. Cancer Res 2009, 69: 5168-5176.
103. Kang TH, Sancar A. Circadian regulation of DNA excision repair: implications for chrono-chemotherapy. Cell 2009, 18: 1665-1667.
104. Sahar S, Sassone-Corsi P. Metabolism and cancer: the circadian clock connection. Nat Rev Cancer 2009, 9: 886-896.
105. Krishnan N, Kretzschmar D, Rakshit K, Chow E, Giebultowicz JM. The circadian clock gene period extends healthspan in aging Drosophila melanogaster. Aging 2009, 1: 937-948.
106. Nakahata Y, Sahar S, Astarita G, Kaluzova M, Sassone-Corsi P. Circadian control of the NAD+ salvage pathway by CLOCK:SIRT1. Science 2009, 324: 598-599.
107. Hirayama J, Miyamura N, Uchida Y, Asaoka Y, Honda R, Sawanobori K, Todo T, Yamamoto T, Sassone-Corsi P, Nishina H. Common light signaling pathways controlling DNA repair and circadian clock entrainment in zebrafish. Cell Cycle 2009, 8: 2794-2801.
108. Vinogradova IA, Anisimov VN, Bukalev AV, Semenchenko AV, Zabehzhinski MA. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. Aging 2009, 1: 855-865.
109. Kondratov RV, Vykhovanets O, Kondratova AA, Antoch MP. Antioxidant N-acetyl-L-cysteine ameliorates symptoms of premature aging associated with the deficiency of the circadian protein BMAL1. Aging 2009, 1: 979-987.
110. Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: a case series report. Aging 2009, 1: 988-1007.
111. Hinkal G, Parikh N, Donehower LA. Timed somatic deletion of p53 in mice reveals age-associated differences in tumor progression. PLoS One 2009, 4: e6654.
112. Huang B, Vassilev LT. Reduced transcriptional activity in the p53 pathway of senescent cells revealed by the MDM2 antagonist nutlin-3. Aging 2009, 1: 845-854.
113. Boily G, He XH, Pearce B, Jardine K, McBurney MW. SirT1-null mice develop tumors at normal rates but are poorly protected by resveratrol. Oncogene 2009, 28: 2882-2893.
114. Ikeno Y, Hubbard GB, Lee S, Cortez LA, Lew CM, Webb CR, Berryman DE, List EQ, Kopchick JJ, Bartke A. Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. J Gerontol A Biol Sci Med Sci 2009, 64: 522-529.
115. Finch CE. Update on slow aging and negligible senescence--a mini-review. Gerontology 2009, 55: 307-313.