

Meeting Report: American Aging Association 40th Annual Meeting, Raleigh, North Carolina, June 3–6, 2011

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Abstract

The focus of the 2011 American Aging Association meeting was emerging concepts in the mechanisms of aging. Many of the usual topics in aging were covered, such as dietary restriction (DR), inflammation, stress resistance, homeostasis and proteasome activity, sarcopenia, and neural degeneration. There was also discussion of newer methods, such as microRNAs and genome sequencing, that have been employed to investigate gene expression variance with aging and genetic signatures of longevity. Aging as a field continues to mature, including the following areas: Using a systems approach to tracing conserved pathways across organisms; sharpening definitions of sarcopenia, frailty, and health span; and distinguishing interventions by age tier (early-onset versus late-onset). A preconference session on late-onset intervention concluded that there are numerous benefits to deriving such interventions. Conference talks applied the biology of aging in a translational manner to intervention development. Using an individual's own stem cells to regenerate organs for transplantation and as a cell source for cellular therapies could be a powerful near-term solution to disease. Several proposed interventions were pharmaceutical, myostatin inhibition, losartan, Janus kinase (JAK) pathway inhibitors, and enalapril for frailty and sarcopenia, and metformin to promote the Nrf2 antiinflammation response. In DR, protein restriction was found to be better than general calorie restriction. Short-term fasting may be helpful in chemotherapy, surgery, and acute stress, simultaneously increasing the killing of cancer cells by chemotherapy, while improving the survival of normal cells. Immune system interventions remain elusive, although statins may help to improve cellular senescence promoted bacterial infection. Engineered enzymes may be useful in lysosomal catabolism. Dietary restriction mimetics, most promisingly involving target of rapamycin (TOR; TORC1 inhibition and rapamycin), may be more feasible than dietary restriction.

Introduction

THE 40TH ANNUAL MEETING OF THE American Aging Association was held in Raleigh, North Carolina on June 3–6, 2011. The focus of the meeting was emerging concepts in the mechanisms of aging, a nice complement to the topics covered during the 2010 and 2009 meetings, inflammation, and the endocrine aspects of aging. Major conference sessions highlighted microRNAs and the epigenetics of aging, the comparative biology of aging, stress resistance in aging and disease, translational aging research, the environment and aging, cardiovascular aging, and late-onset interventions against aging. The 200 or so attendees were on par with recent attendance levels. The number of submissions to the organization's journal *AGE* has been more than doubling annually in the last 2 years. This summary attempts to provide a general

overview of the meeting. The scope is necessarily limited and certain key findings may have been omitted. Research is more often grouped by topic rather than chronological order.

Late-Onset Intervention against Aging: Tools, Approaches, Impact

A preconference meeting investigated late-onset intervention against aging, finding that appropriate interventions may vary by age group. Even if late-onset interventions are challenging, time consuming, and expensive to develop, they are still desirable, given the substantial economic, political, and personal benefits.¹ A quantitative analysis considered a variety of life extension scenarios, and determined that overpopulation or other concerns would be unlikely to arise even in aggressive cases.²

MicroRNAs: Emerging Tool for Aging Process Elucidation and Intervention

MicroRNAs (miRNAs), an abundant class of approximately 22-nucleotide small regulatory RNAs, were discussed as an emerging tool for investigating aging-related gene expression and the dynamic systems processes of aging. Over 900 miRNA genes have been identified in the human genome. Expression may vary dramatically over the lifetime in different conditions of aging. miRNAs may also be used as a leading indicator of aging, predicting the onset of aging-related disease as their levels change before aging is apparent in other ways. For example, p16 (a tumor suppressor) miRNA increases 1.2-fold per decade, which is an average of a 16-fold increase over an eight-decade human life span. A second example is that miR-71 expression patterns in early adulthood have been found to correlate with life span in worms.³ It may be useful to target miRNAs in antiaging interventions, for example, through selective deletion. Adding to the complexity, miRNAs are themselves subject to a variety of complex posttranscriptional regulation processes.⁴

Norm Sharpless (University of North Carolina–Chapel Hill) showed data demonstrating the trade-offs in biological processes, that the expression of the p16(INK4a) tumor suppressor promotes aging but prevents cancer. Chemotherapy patients had the T-cell and p16 levels of those 2 years older than their chronological age. Further findings were that selective p16 deletion in mice helped to rescue age-related phenotypes, for example thymic involution and defects in naïve T-cell production.⁵

Frank Slack (Yale University) found that miRNAs impacted life span both positively and negatively and that mutations in several of the most upregulated miRNAs led to life span defects in worms that could be similarly involved in more complex organisms because these genes are in conserved pathways of aging.³

Two talks focused on miRNAs and p53, a key regulator of cell cycle and apoptosis. Izumi Horikawa (National Cancer Institute) reviewed the complex interactions of p53, cellular senescence, and stem cells in cancer and aging, noting that p53 influences related miRNAs and vice versa.⁶ Heidi Scoble (Mayo Clinic) looked at epigenetic modifiers in stem cells, finding that aging may begin as early as embryogenesis when insulin-like growth factor (IGF) switches cells from pluripotency to differentiation, in particular as levels of the protein IGF-1R decline and miR-675 is induced.⁷

Comparative Biology: Naked Mole Rats, Endocrine Aging, Telomere Length, and Oxidative Stress Resistance

The comparative biology of aging was a lens for the discussion of aging process characterization in the naked mole rat (NMR), reproductive aging and the benefits of dietary restriction (DR) in the rhesus macaque, how replicative aging and repressed telomerase may have evolved, and Nrf2 dysfunction as a causal factor in age-related oxidative stress.

Shelley Buffenstein (University of Texas) presented challenges in the application of comparative biology, including circadian rhythms (sleep cycles, feeding cycles, seasonality), antibody recognition and validation (most antibodies have been designed for mice and humans), and diverse species responses in cell culturing. Buffenstein's main focus was

characterizing the NMR with regard to aging. The NMR is the longest-living rodent, having an extremely long life span (30 years on average versus 2–5 years for normal rats, and five times longer than expected on the basis of body size), and maintaining good health throughout. Old animals (28 years) start to show pathologies of aging, like muscle loss and lipofuscin accumulation, but no tumorigenesis. The NMR's long life span is attributed to good health and cancer resistance. Surprisingly, NMRs have high levels of oxidative damage (e.g., isoprostane, protein carbonyl, and malondialdehyde) and relatively short telomeres, but are extremely resilient to stress. Stress management and cancer resistance may be related to high levels of certain markers in NMR cells, for example, p53 (460 times greater than in mouse; related to cell cycle surveillance and arrest and DNA repair) and high Nrf2 activity (related to inflammation and oxidative stress regulation) and high proteasome activity.⁸

Mary Ann Ottinger (University of Maryland) focused on endocrine aging, finding comparative biology to be a useful tool for elucidating the conserved mechanisms and environmental factors influencing reproductive aging.⁹ Another study investigated DR in male rhesus macaques, finding health and longevity benefits, with only a modest influence on pituitary and testicular gene expression and no detrimental effect on reproduction.¹⁰

Woodring Wright (University of Texas) discussed the broad context of mammalian telomeres, examining telomere length and telomerase in cultured cells from over 60 mammalian species as well as ancestral telomeres. The ancestral mammalian phenotype included short telomeres (less than 20 kb, the same as now seen in humans) and repressed telomerase. It is possible that repressed telomerase was an energy-saving response to a higher mutation load brought on by the evolution of homeothermy (it takes 10 times as much energy to maintain body temperature in warm-blooded organisms). Replicative aging (progressive telomere shortening from cell division, possibly for the purpose of conferring cancer protection) could have evolved from repressed telomerase.¹¹ Cancer, telomere length, and telomerase are connected: Short telomeres are present in almost all preneoplastic lesions, critically short telomeres are present in almost all tumors, telomerase is detected in 90% of human cancers, and the human telomerase reverse transcriptase (TERT) enzyme is expressed in cancer cells and some normal stem cells.

Zoltan Ungvari (University of Oklahoma) investigated the causality of oxidative stress, which is a potential precursor to cardiovascular disease. Support for the oxidative stress hypothesis of aging was found in comparing the long-lived ocean quahog *Arctica islandica* with a shorter-lived hard clam, *Mercenaria mercenaria*. The longer-living bivalves had greater oxidative stress resistance, which reduced both mortality and cell death. Interestingly, *A. islandica* did not exhibit greater antioxidant capacities, a more pronounced homeostatic antioxidant response, or protein recycling, just better oxidative stress resistance.¹² Other work looked at vascular oxidative stress in rats, and its link with Nrf2, a transcription factor present in all tissues that regulates the expression of genes involved in inflammation and oxidative stress, activated by reactive oxygen species (ROS). Aged rats exhibited decreased nuclear Nrf2 and Nrf2 target gene activity (NQO1, GCLC, and heme oxygenase-1), and increased

nuclear factor- κ B (NF- κ B) target gene (intercellular adhesion molecule-1 [ICAM-1] and interleukin-6 [IL-6]) activity. It was concluded that Nrf2 dysfunction is a causal factor in age-related oxidative stress.¹³

Stress Resistance: Fasting, Amino Acid Deprivation, TORC1 Inhibition and Rapamycin, and Nrf2 Activation

A number of stress resistance topics were discussed, including the benefits of fasting in chemotherapy and acute stress, that amino acid (e.g., protein) restriction may be more important than calorie restriction, how the mechanisms of TORC1 inhibition and rapamycin in the target of rapamycin (TOR) pathway act to extend life span, and Nrf2 anti-inflammation activation through metformin.

Valter Longo (University of Southern California) reviewed studies on fasting, DR, and cancer treatment. A key finding was that fasting simultaneously increased the killing of cancer cells by chemotherapy while improving the survival of normal cells.¹⁴ Fasting for up to 5 days followed by a normal diet was helpful in protecting patients against chemotherapy. James Mitchell (Harvard School of Public Health) extended previous research which found that short-term DR and fasting may be beneficial not only in longevity but also in acute stress reduction in mice.¹⁵ Amino acid sensing (which occurs through the GCN2 and TOR pathways) was found to be an important modulator of acute stress resistance. Protein versus calories was important in dietary restriction as essential amino acid deprivation (e.g., tryptophan, methionine, and leucine) increased stress resistance independent of caloric restriction.

Understanding specifically how the inhibition of the TOR kinase extends longevity in model organisms ranging from yeast to mice continues to be an important focus in aging research. Keith Blackwell (Harvard Medical School) showed that two methods, TORC1 inhibition and rapamycin, increased longevity and stress resistance in *Caenorhabditis elegans* by acting through the SKN-1(Nrf) and DAF-16(FOXO) transcription factors that induced the transcription of protective genes. Longevity through TORC1 inhibition required both transcription factors, whereas longevity through rapamycin only required SKN-1.¹⁶ Dudley Lamming (Massachusetts Institute of Technology) also looked at rapamycin and TORC1 inhibition. Although rapamycin is typically thought of as a TORC1-specific inhibitor, chronic rapamycin may disturb TORC2 function in tissues. Rapamycin was found to increase life span while decreasing glucose tolerance and insulin sensitivity in yeast. Decreased TORC1 activity also promoted yeast life span, interestingly via normally deleterious ROS generation.¹⁷

Rafael de Cabo (National Institute on Aging) examined Nrf2, which may become dysfunctional with aging, particularly in the vasculature.¹³ DR may help to activate Nrf2 as well as DR mimetics. Metformin, for example, a glucose-regulating type 2 diabetes drug, may serve as a DR mimetic and activate Nrf2.

Translational Aging Research: Remedy of Frailty and Sarcopenia

A translational aging research session focused on ameliorating frailty and sarcopenia. Sarcopenia is characterized mainly as an excessive reduction in skeletal muscle mass, but

also includes changes in adiposity. It is an 'undefined' condition in that it is not yet prescribable and does not have agreed-upon measurement parameters and cutoff points for intervention. One definitional approach could be measuring loss of function in physical performance, for example gait speed has been linked with survival in humans¹⁸ as well as falls and Timed Up and Go (TUG) capability.¹⁹ Frailty, on the other hand, is a diagnosable geriatric syndrome that is defined by one or more factors: A decline in strength and activity, an increase in inflammation, involuntary weight loss, exhaustion, slow walking speed, and reduced grip strength. Proposed interventions were pharmacological, including myostatin inhibition, losartan, Janus kinase (JAK) pathway inhibitors, and enalapril.

Nathan LeBrasseur (Mayo Clinic) investigated the signaling and transcriptional regulatory pathways involved in increasing muscle mass and glycolytic capacity.

The high degree of plasticity in skeletal muscle suggests the potential success of interventions such as resistance training, genetic alterations, and pharmaceuticals. Myostatin inhibition was examined for its potential to improve muscle mass, physical function, and metabolism in mice and humans.²⁰

Jeremy Walston (Johns Hopkins University) discussed how multiple physiological systems become dysregulated in frailty, breaking down under stress and the chronic activation of inflammation. Some candidate genes for frailty were identified—MTR, CASP8, FN1, CREB-BP, and GST, which are mostly related to inflammation and oxidative stress. Losartan, an angiotensin II receptor antagonist commonly used to treat high blood pressure, was found to have a beneficial impact on muscle remodeling in sarcopenic mice and might be explored for human muscle atrophy.²¹

James Kirkland (Mayo Clinic) discussed translating basic research advances to clinical application generally and two findings in particular that might be investigated for the treatment of frailty and sarcopenia. The first was JAK pathway inhibitors, which have been found to decrease the levels of circulating inflammatory cytokines in myelofibrosis (a type of chronic leukemia) and might be used in other situations to diminish inflammation.²² Pregnancy-associated plasma protein-A (PAPP-A) may also be of interest as a potential blood biomarker to identify and potentially treat unstable atherosclerotic plaques (PAPP-A is produced at sites of injury and cleaves insulin-like growth factor binding proteins [IGFBPs] to increase local IGF-1 availability).²³

Christy Carter (University of Florida) examined the renin-angiotensin system (RAS), which is important in regulating blood pressure and maintaining cardiopulmonary homeostasis. Two pharmaceutical interventions were studied for sarcopenia, enalapril (an angiotensin-converting enzyme [ACE] inhibitor) and losartan (as mentioned, an angiotensin receptor blocker) for potential benefits regarding body composition, physical performance, and muscle quality in aged rats. Both enalapril and losartan improved grip strength; however, only enalapril was effective in improving muscle strength, possibly by reducing skeletal muscle apoptosis.²⁴

Personalized Therapies: Organ Regeneration and Stem Cells

One of the most exciting, and possibly near-term, solutions for aging-related conditions is regenerative medicine—using

an individual's own stem cells to recreate organs for transplantation and as a cell source for cellular therapies. Regenerative medicine efforts are currently underway for 20–30 organs. There are also numerous uses for stem cell therapies. Approaches discussed here are improving neural stem cell genesis and treating neurodegenerative disease, and ameliorating telomere dysfunction present in both aging pathologies and disease states.

Shay Soker (Wake Forest University) presented an overview of Anthony Atala lab's wide range of preeminent regenerative medicine work. Existing progress has been made in the organ regeneration of bladders, urethras,²⁵ and tracheas, and additional work is underway in the liver, kidney, pancreas, intestine, and other organs. Making regenerated organs fully functional may involve several tricky steps. For example, in working with cardiomyocytes, experiments are being conducted to facilitate cell–cell communication by incorporating connexin 43, a protein that assembles to form gap junctions between cells and is important for the coordinated depolarization of cardiac muscle. A second example is working with urinary incontinence, where urine-holding muscles weaken. Research is looking at the injection of chondrocytes (cells found in cartilage that produce and maintain the cartilaginous matrix) into dog bladders.

Some of the key challenges in tissue engineering are cell sources, vascularization, optimal biomaterials, and scaffolding.²⁶ Vascularization solutions are a topic of extensive contemporary research in the regenerative medicine field. One technique under investigation is injecting muscle cells with vascular endothelial growth factor (VEGF), a signaling protein that stimulates vasculogenesis and angiogenesis. Some of the new research in biomaterials is investigating polyglycolic acid (PGA), a synthetically absorbable biodegradable, thermoplastic polymer used in sutures and other biomaterial applications. Scaffolding is another area of contemporary research, with a variety of synthetic, biomimetic, and biological solutions under development. One example is decellularization, which involves dissolving cells out of the extracellular matrix (ECM) in real tissue and using this matrix as a scaffold, as in reseeding a liver bioscaffold with hepatocytes and endothelial cells.

Walter Funk (BioTime) discussed two kinds of personalized medicine, induced pluripotent stem (iPS) cells, the “ultimate personal medicine,” and genome sequencing. There have been many recent iPS cell advances in disease modeling, drug toxicity screening and drug discovery, gene therapy, and cell replacement therapy.²⁷ Another emerging tool for personalized medicine is genome sequencing. The cost of whole human genome sequencing continues to fall, currently costing \$3,500 with Complete Genomics and \$4,000 with Illumina (order size of fifty).²⁸ One important application of personalized genomics, for example, is Alzheimer disease risk profiling.

Paula Bickford (University of South Florida) presented research on neural therapies designed to counter the decline in stem cell neurogenesis with aging. Stem cell therapies could be used to improve the environmental quality of neural stem cell niches and offer microglial neuroprotection. A cellular therapy in the form of a single intravenous injection of human umbilical cord blood mononuclear cells (UCBMCs) in aged rats was found to significantly improve the hippocampus microenvironment and rejuvenate neural

stem cells.²⁹ Also in neural aging, microglia may be exposed to pathogenic stimuli and become overactivated. Oxidative stress and inflammatory markers are released, which may damage dopaminergic neurons and lead to neurodegeneration. Two potential remedies were presented, a chemokine and a nutritional supplement. CX3CL1 is a fractalkine, a membrane-bound chemokine that is a suppressive signal between microglia and neurons. CX3CL1 was found to have a neuroprotective role in dopaminergic lesions and might be an effective therapeutic target for neurodegenerative diseases, including Parkinson disease and Alzheimer disease, where inflammation plays an important role.³⁰ A commercially available nutraceutical comprised of blueberry, green tea, carnosine, and vitamin D3 improved cognitive function in aged rats.³¹

Zhenyu Ju (Hangzhou Normal University) investigated dysfunctional telomeres and hematopoietic stem cells (HSCs). Earlier research found that patients developing cirrhosis as a consequence of chronic liver disease had telomerase gene mutations, suggesting the possibility of telomere shortening being a causal factor not only in aging but also in disease pathogenesis.³² A current study found that the transplantation of wild-type HSCs could possibly improve telomere dysfunction in the setting of ameliorated environmental defects.

Genetics and Aging

In genetics and aging, research was presented suggesting that centenarians, while having the same disease mutational profile as noncentenarians, have other aspects to their genetic profile that indicate a signature for exceptional longevity. Other work found 27 specific longevity single-nucleotide polymorphisms (SNPs) and demonstrated a means of measuring the rate of epigenetic mutations in aging.

Thomas Perls (Boston University) discussed the New England Centenarian Study, which has enrolled 2,500 centenarians and their offspring since 1995. He postulated that anyone may be able to add 8–10 years to their life span through lifestyle, including attitude, exercise, nutrition, and interests. Only 25% of the ability to reach the mid-80s may be attributable to heritability. On the other hand, the ability to achieve exceptional longevity may be heavily related to genetics. A high-profile paper published in *Science* in July, 2010,³³ has been revised per editorial concerns. Apparently errors were corrected, a more stringent quality control process was employed, and a clean dataset from an independent lab was developed. The new results feature nine SNP associations (versus two previously), and associate 281 SNPs with signatures for exceptional longevity (versus 180 SNPs). The overall conclusion did not change, that exceptional longevity may be determined by varied combinations of common and likely rare alleles. The study is notable in first looking for genetic profile similarities, and then seeing if the study population has phenotypic similarities (instead of vice versa as in other studies). An interesting finding was that the burden of disease alleles was the same in centenarians and noncentenarians.

Svetlana Ukraintseva (Duke University) extended earlier work suggesting that alleles with small individual effects on longevity may jointly influence life span.³⁴ A list of 27 longevity-specific SNPs was developed from an analysis of Framingham Heart Study data. The SNPs are in genes

functionally involved in cell growth and proliferation, apoptosis, cell adhesion, brain information processing, and inflammation, several of which are also involved in cancer. Anatoli Yashin (Duke University) used the same data to conclude that differences in the number of longevity genes (e.g., the number of favorable alleles possessed by an individual) may impact the dynamics of aging-related changes in stress resistance.

Jan Vijg (Albert Einstein College of Medicine) discussed genetic and epigenetic mutations as potential causal factors in aging. Epigenetics has been linked to cancer development, because hypermethylation may inactivate tumor suppressor genes. To assess methylation differences between cells, the team developed an approach using bisulfite conversion, whole genome amplification, and massively parallel sequencing. There was some success in measuring the rate of epimutations in aging in different organs and tissues.³⁵

DR and DR Mimetics

DR is a known technique for increasing longevity in model organisms. Because DR may not be feasible to implement in humans, DR mimetics that would produce the same prolongevity impact are sought. This would likely be in the form of pharmaceuticals that would target the same pathways and proteins (e.g., TOR, sirtuins, and adenosine monophosphate [AMP] kinases) involved in the biophysical response to DR. TOR is a strong candidate on the basis of its conserved pathway across organisms and successful experimental results in animals.

Matt Kaeberlein (University of Washington) discussed the aging field's progress in identifying conserved pathways of aging and DR across organisms, particularly TOR signaling, sirtuins, and molecular determinants. A variety of studies were summarized to conclude that TOR is a conserved longevity pathway in organisms ranging from yeast to rodents and an important part of the response to DR. Rapamycin has been found to extend life span in model organisms. On the other hand, sirtuins, specifically Sir2, are more problematic because the current consensus is that they are involved in life extension in flies but not in yeast and mice, when it would seem that these pathways should be conserved across organisms. Genotype too plays a key role in response to DR, as it is not universally beneficial.

David Sharp (University of Texas) presented a study finding that rapamycin fed late in life extended life span in mice (by 10% in males and 18% in females), possibly by downregulating the TOR complex 1, TORC1. Resveratrol and simvastatin did not show similar life-extending effects.³⁶ It was suggested that rapamycin is more technically an immunomodulator, not just an immunosuppressor, because it activates some processes and suppresses others. Additional work included recent preclinical results with rapamycin in humans, establishing a proof of concept that may be used for subsequent trials.³⁷

Michael Rae (SENS Foundation) looked at the biomedical case for late-life interventions in aging³⁸ and provided a review of existing DR studies in humans, particularly in late-onset intervention. The conclusion was that DR mimetics may be better than DR, particularly for late-onset populations, and that late-onset dietary restriction requires further study and likely adjustment before being applied.

Immune System and Infection

The decline of the immune system is a central problem in aging. Research was presented discussing immune system impairment being exacerbated by viral infection and how cellular senescence may promote bacterial infection in addition to aging.

Megan Smithey (University of Arizona) looked at the immunodeficiency that occurs with aging, characterizing CD8(+) populations in aged mice. It was found that defects in the functional maturation of CD8(+) cells rendered T cell populations insufficient in size and capability to effectively clear newly encountered pathogens. Viral infections (e.g., cytomegalovirus [CMV], herpes simplex virus [HSV], etc.) likely accelerate immune system impairment as cellular memory becomes increasingly replete over a lifetime. The ratio of naïve T cells to memory T cells shifts to diminish the number of naïve cells available to respond to new pathogens.³⁹

Carolos Orihuela (University of Texas) discussed how the secretory phenotype of cellular senescence (e.g., the release of proinflammatory cytokines) may be responsible for not only promoting tumor development and aging but also bacterial infection. Aged humans had elevated levels of the senescence markers p16, pRb, and mH2A in their lungs. This can facilitate the adhesion of bacteria to cells and increase the risk of pneumonia, the leading cause of infectious death in the elderly.⁴⁰ Statins were found to confer some protection against bacterial adhesion to cells.

Catabolism

Catabolism (waste removal) is a final topic of importance in aging research. Jacques Mathieu (Rice University) presented work on catabolism, investigating solutions for breaking down 7-ketocholesterol (7KC), a cytotoxic oxysterol that may form and accumulate in the lysosome, preventing enzymatic activity and weakening the lysosomal wall. Three kinds of interventions were tried on human fibroblasts: Engineered enzymes, overexpression of the lysosomal membrane protein LAMP1, and treatment with cyclodextrin. One of the engineered constructs, a lysosomally targeted cholesterol oxidase that lacked isomerization activity (pEGFP-COXL1) significantly increased cell viability. Overexpressing LAMP1 and cyclodextrin treatment also helped to decrease 7KC-mediated cell death.

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