Advances in Geroscience: Impact on Healthspan and Chronic Disease

ABSTRACTS

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Advances in Geroscience: Impact on Healthspan and Chronic Disease Index

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Advances in Geroscience: Impact on Healthspan and Chronic Disease

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
WELCOMING REMARKS

Session I: Keynote Presentations

Christopher J. L. Murray, M.D., D.Phil.
University of Washington
The Global Burden of Disease

The Global Burden of Disease (GBD) approach is a systematic, scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geography for specific points in time. It estimates premature death and disability due to 291 diseases and injuries, 1,160 sequelae, and 67 risk factors for 20 age groups and both sexes in 1990, 2005, and 2010 for 187 countries and 21 regions. GBD makes use of all available data that meet quality inclusion criteria, correcting for biases in the data, and providing uncertainty intervals for all estimates.

GBD found that as life expectancy has increased in the US, people are living more years with disability. Causes such as musculoskeletal disorders, chronic obstructive pulmonary disease (COPD), and diabetes were dominant drivers of disability among ages 65 to 74; musculoskeletal disorders, COPD, and dementia accounted for most years lived with disability among ages 75 to 79; and dementia, COPD, and low back pain were the leading causes of disability among ages 80 and older. GBD revealed that the US has made little to no progress in reducing rates of years lost from the leading causes of disability. While the US ranks better than most of its economic peer countries for years lived with disability, its lack of progress in this area underscores the need for additional investments in research to identify effective prevention strategies and treatments for disabling conditions. In terms of premature death, the major causes among ages 65 to 79 were ischemic heart disease, lung cancer, and COPD, while ischemic heart disease, dementia, and stroke were the leading causes among ages 80 and older. Relative to countries with similar income levels, the US has not enjoyed the same rate of decline for myriad causes of premature death.

Brian K. Kennedy, Ph.D.
Buck Institute for Research on Aging

Current Status on Basic Research on Aging

Aging research has made great strides in the last three decades. While there are many factors driving this progress, one major influence has come from the utility and exploitation of non-vertebrate animal models such as worms, flies and yeast. From studies in these organisms, we have established that (1) there are many genetic pathways modulating aging, and lifespan is highly modifiable, (2) at least some pathways controlling lifespan are conserved across species from yeast to mammals and very likely humans, and (3) the aging process appears to be a major cause of age-associated chronic disease states, since interventions that extend lifespan often protect against the onset of these diseases. Another way of saying it is that the major causes of morbidity and mortality in the United States (and increasingly worldwide) have one thing in common – aging.

Another sign that the aging field has matured is that disparate theories about aging are being found to intersect and involve similar sets of molecular pathways associated with lifespan. There is a growing sense that a holistic understanding of the mechanisms driving aging and enabling disease may be achievable in the not-too-distant future. This would represent a tremendous advance in our collective understanding of biology and afford many more opportunities to intervene in efforts to enhance human health. The TOR (target of rapamycin) pathway represents one such point of convergence and recent studies have shown that a clinically approved drug, rapamycin, extends lifespan and healthspan in mice. Many more small molecules and drugs are in the testing stage and more will be added to the list of anti-aging compounds in the near future. Here, rapamycin will be used to conceptualize how small molecules that extend healthspan might be developed to improve human health.

Addressing the question of how aging enables disease remains an underexplored area of biomedical research that offers great promise toward identifying novel therapeutic approaches to preventing and treating many disease indications as a whole. While challenges still remain the increasingly older demographic distributions in most of the world demand that we answer this question and exploit it if possible to keep people healthy longer.

Linda P. Fried, M.D., M.P.H.
Columbia University, Mailman School of Public Health

Frailty and Relationships to Disease in the Elderly

Mounting scientific evidence indicates interrelationships between physiologic changes associated with aging and the onset, severity and outcomes of age-related chronic diseases. One such dynamic pertains for the clinical syndrome of frailty. Frailty can be understood to be a clinical syndrome manifesting as a distinct phenotype which marks a subset of older adults who are vulnerable to adverse outcomes and demonstrate distinct pathophysiologic alterations of dysregulated physiologic and biologic systems underlying this vulnerability. This presentation considers the evidence to support this syndrome and the underlying biology that drives this, and then will describe the relationships that have been investigated between frailty and chronic diseases, particularly catabolic diseases. It is proposed that these relationships include shared etiology and joint contributions to distal outcomes, and both frailty and specific chronic diseases having causal relationships with each other, bidirectional. The implications of these causal relationships will be considered.

Session II: Inflammation

Claudio Franceschi, M.D.
Università di Bologna

INTRODUCTION

Aging is a ubiquitous complex phenomenon that results from environmental, stochastic, genetic and epigenetic events in different cell types and tissues and their interactions throughout life. A pervasive feature of aging tissues and most if not all age-related diseases is chronic inflammation. 'Inflammaging' describes the low-grade chronic inflammation in aging, and is a highly significant risk factor for both morbidity and mortality in the elderly.

Inflammaging can be triggered by a variety of "danger signals" which can be exogenous (viruses such as CMV or HIV, bacteria including the gut microbiota and its products) or endogenous (senescent and damaged cells, dysfunctional organelles such as mitochondria, cell debris, altered/modified proteins and N-glycans, mtDNA, ATP, ROS, AGE, ceramides). Thus, "garbage" disposal plays a major role in triggering inflammation and inflammaging. All these potential stimulants are physiologically produced even in young humans, and it is tempting to speculate that the health status is assured by a "physiological inflammatory tone" as an essential ingredient to maintain body homeostasis. Within this perspective, inflammaging would represent the progressive increase with age of such an inflammatory tone, fostered by:

- increasing exposure to exogenous "danger" agents (e.g. alteration of gut microbiota, persistent infections such as cmv)
- increased generation of endogenous danger signals (increased number of senescent cells and cell debris produced by dying cells, damaged/dysfunctional mitochondria and altered molecules such as aggregated proteins, mtdna, n-glycans, atp, ros, age, ceramides)
- decreased garbage disposal, including the decreased efficiency of ups/proteasomes, autophagy and mitophagy;
- increased activation of nf-kb and inflammasomes

Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remains largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people. The session on inflammation aims to define the important unanswered questions about inflammaging.

Luigi Ferrucci, M.D., Ph.D.
National Institute on Aging

How do inflammatory processes associated with chronic disease differ
from those due to acute insults/disease?

Aging is characterized by chronically elevated levels of circulating biomarkers that suggest chronic inflammation. This pro-inflammatory state, or "inflammaging", have negative consequences on all aspects of aging including increasing the risk of disability and death, hinting that inflammaging boosts

"accelerated" aging. Theories on mild-pro-inflammatory state of aging are rooted in the notion that inflammation acts as a defense and maintenance/repair mechanism through a chain of events that are tightly regulated in sequence, timing and local-versus systemic diffusion. Sequence, time and local versus systemic diffusion are, in fact, the landmarks that differentiate inflammaging from the physiologic inflammatory response.

An important step in the phylogenetic development from short-lived, monocellular organisms to long-lived multicellular organisms was the emergence of sophisticated mechanisms aimed at maintaining morphological and functional integrity of tissues in the face of long-term exposure to environmental challenges. The mammal immune system is the most advanced achievement of this evolutionary process. Inflammation is commonly described as a relatively stereotyped immune response aimed at fighting invaders while less frequently recognized is that inflammation also contributes to promoting repair and regeneration. The "defense" response is prominent in the initial stage of physical, chemical or biological aggression and characterized by polymorphonucleates, macrophages and chemotactic and pro-inflammatory mediators attempting to remove the stressor and "cleaning-up" the damaged areas. When the stressor is successfully removed the immune system shift to a repair mode with macrophages from a M1 to M2 phenotypes and production of anti-inflammatory cytokines, growth factors. A successful inflammatory response should ideally lead to a full "restitution ad integrum". When the stressor cannot be removed, inflammation persists and repair and growth are delayed leading to collagen deposition formation of cicatricial tissue. The systemic signature of local inflammation (high il-6 and later C-reactive protein) rapidly decline after the resolution.

The systemic generalization of inflammation affects a number of signaling pathways important for energetic metabolism and tissue maintenance, including down-regulation of IGF-1 production and signaling, diminished erythropoietin activity on the bone marrow and others. During the "defense" phase of inflammation tissue repair and maintenance come to a standstill, perhaps because they are considered to have low-priority at a time of emergency and can be easily delayed. However, when inflammation is sustained, the absence of maintenance and repair leads to tissue degeneration. Indeed, diseases characterized by over chronic inflammation are associated with a high risk of cancer, derangement of the energetic metabolism, accelerated atherosclerosis and, at the extreme range of the spectrum, even cachexia. Analogously, with inflammaging, it appears that the "defense" mode is always active and the time of "repair and maintenance" is permanently delayed. Though, it remains unclear whether the inability to exit from the "defense" mode is due to the chronic permanence of the stressful stimulus or rather is linked with an intrinsic defect of the immune system and, in particular, the mechanisms that switch off inflammation. Distinguishing between these two mechanisms has fundamental therapeutic implications.

James L. Kirkland, M.D., Ph.D.
Mayo Clinic and Arlene Kogod Center on Aging

How do local and systemic sources of chronic inflammation contribute to chronic disease processes?

Chronic diseases, including cancers, atherosclerosis, dementias, diabetes, arthritis, blindness, and kidney diseases, are the leading cause of morbidity and mortality and the major driver of health costs. Processes that contribute both to aging phenotypes as well as to the etiologies of these age-related chronic diseases include chronic, low-grade, "sterile" tissue inflammation, stem cell and progenitor dysfunction, and

accumulation of cytotoxic proteins, glycation endproducts, and lipids and metabolites. These processes can occur in combination and interact, with damaged molecules or cells, pro-inflammatory senescent cells, an altered microbiome, and immune system dysregulation being among stimuli that can initiate age- and chronic disease-related dysfunction. Consistent with a key role for inflammation in age-related pathologies, circulating pro-inflammatory molecules are predictors of morbidity, but are they the important drivers of many age-related diseases in humans? What are the roles of *local* vs. *systemic* production of pro-inflammatory cytokines in driving phenotypes and pathologies associated with aging? To what extent do distinct components of the inflammatory signatures of each stimulus affect phenotypic outcomes or age-related disease? Do stimulus-specific inflammatory mediators act primarily at a distance (systemically) or only locally? Is there an age-related decline in protective local or circulating factors that are present in younger individuals? Answers to these questions will be important to guide development of diagnostic methods and interventions to prevent or treat the range of age-related conditions as a group, instead of one at a time.

Jayakrishna Ambati, M.D.
University of Kentucky

What are the Commonalities and differences in inflammatory drivers of chronic diseases?

The four great diseases of aging – Alzheimer's disease, age-related macular degeneration, atherosclerosis, and degenerative arthritis – have multifaceted and unclear etiologies, yet immune dysfunction is a recurring theme in their pathogenesis. These various forms of age-associated tissue degeneration each can be described in terms of such signature pathologies, which is likely the result of cell or tissue-specific stresses or response to stress. The diverse microenvironments and unique biological flux experienced in these heterogeneous cell types make it difficult to assign common inciting stressors or stress responses – which are likely to be many and overlapping in effect – of these diseases. Yet all are characterized by age-dependent degenerative and destructive processes that result in a molecular hallmark: the accumulation and inadequate elimination of "self debris". These toxic accumulations often incite an inflammatory response that is initially beneficial and promotes longevity. Persistence of inflammation, however, becomes detrimental to the health of cells, which in most instances are not easily replaceable. Self debris can take the form of lipids, nucleic acids, polypeptides, or sugars; despite their apparent heterogeneity, however, these toxins are often redundant in that they can produce similar pathologic effects. It is an appealing concept that the persistence of cellular detritus represents a common node at which point myriad stressors converge. In this respect, most chronic diseases have many potential upstream causes or damage-inducing stimuli that funnel into downstream and less-redundant pathways. Therefore, any therapeutic intervention that addresses an isolated injurious mechanism is unlikely to counter the convergence of parallel conduits. The NLRP3 inflammasome has emerged as a common inflammatory platform that integrates various danger signals and transduces signals that initiate or potentiate cellular injury. It is therefore worth defining the potential therapeutic role of filtering the cellular milieu at the confluence, rather than the source, of the disease pathogenesis watershed. Looking toward the future of therapy, an emerging paradigm complements the conventional approach of preventing cellular dysfunction and death. Empowering tissue health in spite of injury by modulating or enhancing specific cellular and tissue coping mechanisms, is an intriguing conceptual scaffold on which to base future therapeutic developments.

Vishwa Deep Dixit, D.V.M., M.V.Sc., Ph.D.
Yale School of Medicine

Can age-associated chronic inflammation be adaptive or beneficial or is it always pathogenic?

Age is the greatest risk factor for chronic diseases. Data from several clinical studies suggest an association between increase in pro-inflammatory markers and emergence of age-related degenerative changes. If aging is a common trigger for multiple diseases and if inflammation is a major pathway causing morbidity and mortality, then identification of specific mechanism of inflammation that is triggered with age should delay the onset of multiple chronic diseases. Translation of such basic research discovery into practice would be a major advance in achieving the goal of extending human healthspan. However, it remains unclear whether downregulating inflammation, a critical protective response for host-defense and tissue remodeling, represents a viable therapeutic approach during aging process. For example, recent studies suggest that inflammasome mediated sensing of pathogens by macrophages is a critical signal for initiating a protective immune response that allows survival against infections. But uncontrolled inflammasome activation in response to persistent cellular stress signals or damage is also implicated in age-related diseases such as dementia, diabetes, bone loss, atherosclerosis, macular degeneration and gout. Given specific cytokines that produce local inflammation also controls tissue remodeling and regenerative responses, it raises the question if low-grade inflammation that emerges during aging is an adaptive repair mechanism? If so, is inflammatory signaling that link recruitment of progenitor cells and regenerative mechanism defective or exhausted during aging? Does chronic intake of calorie dense foods increase the generation of 'metabolic danger signals' that activate specific innate immune sensors? Is the regulatory loop between tissue-damage, inflammation and tissue regeneration impaired with age? Inflammation is a complex coordinated response that involves interplay between wide array of cytokines and chemokines that are derived from multiple innate and adaptive immune cell subpopulations. How controlling this inflammatory interplay will affect aging? The answers to these questions would hinge on continued investigation of basic mechanism of biology of aging. The new data that emerges from ongoing research will eventually guide the quest for developing appropriate strategies to extend human healthspan that balances the cost-benefit tradeoff equation of inflammation and health

Russell Tracy, Ph.D.
University of Vermont

Are there interventions that can alter the dynamics of inflammation and prevent/limit chronic disease?

Interventions that suppress, prevent or alter the dynamics of chronic inflammation hold great promise for treating or preventing multiple age-related pathologies, and possibly the aging process itself. Several clinical conditions have been declared as "accelerated aging," HIV infection among them. In examining HIV pathology, increased inflammation clearly plays a role through the acceleration of pathological processes such as atherosclerosis. Increased coagulation status – directly linked to inflammation – also appears to play a role. Both increased inflammation and coagulation are linked to loss of adaptive immunity and effects on the liver. Loss of adaptive immunity in Gut-Associated Lymphoid Tissue (GALT) yields increased microbial

translocation and a proinflammatory/procoagulant “micro-endotoxemia”. Among liver changes are increased fibrosis and altered protein synthesis including an altered “coagulome” which adds to the coagulopathy and proinflammatory state. These findings, and others, lead to a hypothetical model of chronic disease and aging that implicates increased inflammation and coagulation, and decreased adaptive immunity, working in a cycle of decline.

When considering interventions, a major concern is that the same system that causes ***pathophysiology*** is needed for ***normal physiology***. Therefore, there are several key issues to consider, including when to intervene (e.g., young people vs. old), whether one is attempting prevention or treatment, and how to intervene. One structure to help define “how” might focus on: a) behavior modification vs. pharmacotherapy to reduce proinflammatory risk factors, b) behavior modification vs. pharmacotherapies to reduce inflammatory response, and c) therapies to reduce the need for inflammation by improving adaptive immunity. Many therapeutic options are available and more are currently under development. In addition to common (e.g., aspirin, exercise) and novel (e.g., canakinumab for IL-1 inhibition) systemic inflammation, other approaches of interest include: reducing infectious burden; reducing microbial translocation; increasing adaptive immune function; decreasing fibrosis especially in lymphoid tissue and the liver; anticoagulation; decreasing cellular aging and the senescent cellular phenotype; and modulating metabolic pathways known to be associated with inflammation such as lipid metabolism (e.g., statins) and carbohydrate metabolism (e.g., metformin).

Judith Campisi, Ph.D.
Buck Institute for Research on Aging

DISCUSSION AND WRAP-UP

Session III: Adaptation to Stress

Elissa Epel, Ph.D.
University of California, San Francisco

INTRODUCTION

The rate of biological aging is "elastic," and modulated in part by genes interacting with stressor exposures. Basic research in simple laboratory animals has shown that exposure to acute or short term stress can strengthen cellular responses to stress. This 'hormetic stress' promotes multiplex stress resistance, which is characterized in part by enhanced activity of molecular chaperones and other defense mechanisms. In contrast, prolonged exposure to stress can overwhelm compensatory responses ("toxic stress") and can shorten lifespan. One key question is whether the stressors that are well understood in basic models of aging have any relationship to understanding psychological stressors and health in humans. The psychological stress response promotes some changes known to be important in aging, such as increases in circulating stress hormones, inflammation, oxidative stress, insulin and glucose. In adult humans, there are many descriptive examples of relationships between chronic psychological stress and both indices of cellular aging, as well as of organismal aging (early disease processes). The most dramatic examples in human cohort studies show that exposure to major stressors in childhood (abuse or neglect) are followed by inflammation and accelerated telomere shortening, and earlier onset of diseases of aging. It is important to understand the mechanisms by which stress affects human aging, and what we might learn from basic science on stress and aging. We need to address fundamental questions, such as understanding the types of stressors and stress responses in humans that promote stress resistance (vs. damage), and how stress resistance might retard aging in humans. We also need to understand how different types of stress modulate aging pathways such as gene expression, telomere shortening, and pathways rarely studied in humans, such as mitochondrial health and metabolic sensing. Lastly, how might exercise and other salutary interventions be used as a model to address these questions? Can successful coping with manageable challenges in humans follow similar pathways? How can we translate what we have learned from simple animals to humans, that resistance of cells to damage slows the rate of aging and late life disease? This will include an examination of pathways along a continuum from cellular to psychological levels of stress, and will require interdisciplinary novel approaches that hold much promise for understanding and intervening in human chronic disease.

Firdaus Dhabhar, Ph.D.
Stanford University)

Under what conditions is stress linked to disease processes?

Mother Nature gave us the fight-or-flight stress response to help us survive, not to kill us. However, stress is known to suppress immune function, accelerate biological aging, and have numerous deleterious effects on brain and body. These seemingly paradoxical effects of stress are better understood by considering the duration of the biological stress response: Chronic stress

(months to years) has been shown to have harmful effects on health and healing. In contrast, short-term stress (minutes to hours) can have protective, immuno-enhancing effects.

Short-term stress experienced at the time of immune activation enhances neutrophil, macrophage, and lymphocyte trafficking and function, and has been shown to augment innate and adaptive immunity in preclinical and clinical studies. In contrast, chronic stress accelerates biological aging, suppresses and innate and adaptive immune responses, dysregulates the Type 1-Type 2 cytokine balance, induces chronic inflammation, and suppresses numbers, trafficking, and function of immuno-protective cells. For example, chronic stress accelerates cancer progression by suppressing Type 1 cytokines and protective T and NK cells, increasing regulatory/suppressor T cell function, and enhancing tumor angiogenic and metastatic mechanisms.

It is important to recognize that Mother Nature gave us the physiological stress response in order to promote survival. Stress-related neurotransmitters, hormones, and factors, act as biological alarm signals that prepare the immune and other physiological systems for potential challenges (e.g. wounding or infection) perceived by the brain (e.g. detection of an attacker). However, this defense mechanism may inadvertently exacerbate immuno-pathology if the enhanced immune response is directed against innocuous or self-antigens, or if the system is chronically activated as seen during long-term stress. In view of the ubiquitous nature of stress and its significant effects on immuno-protection and immuno-pathology, it is important to further elucidate the mechanisms mediating both, the salubrious as well as harmful effects of stress, and to meaningfully translate findings from bench to bedside.

Gretchen Darlington, Ph.D.
Baylor College of Medicine

What experimental models may be useful in defining the impact of stress at a molecular and cellular level?

Two paradigms of extended longevity have provided novel molecular information about the extension of healthspan as well as lifespan in several model organisms. Caloric or nutrient restriction has been well documented to extend lifespan in rodents and a second model, that of growth hormone/insulin/IGF1 signaling (GH/IIS) deficiency has now been shown to be a promising subject for decoding the genetic basis of aging. Importantly, both nutrient restriction and GH/IIS deficiency also lead to a delay in the onset of age-related disorders including the incidence of cancer and kidney disease, common causes of morbidity and mortality in mice. Reduction in food intake and insulin/IGF1 signaling (IIS) in several lower organisms have a similar extending effect on longevity and genetic screens have informed the genetic analyses that has been carried out in mice. Detailed analysis of the biochemical events that are impacted by food restriction and GH/IIS deficiency has revealed a relatively small (albeit complex) number of interacting pathways involved in energy metabolism that are major regulators of the aging process. In general, the life extending properties of these pathways appear to come from reducing overall energy metabolism. Attempts to examine the effect of nutrient restriction in non-human primates and humans are beginning to suggest that the evolutionary conservation of the aging process will allow dietary modifications that similarly delay important age-associated conditions such as cardiovascular disease, cancer incidence and diabetes. While many of the human mutations in GH/IIS signaling result in severe medical conditions that are often

incompatible with life, studies of genetic isolates with rare alleles in the GH/IIS pathway suggest beneficial effects of these genes. Such findings give hope that molecular/drug interventions can be found to reduce the susceptibility of humans to age-related decrements in function and increased disease susceptibility by interfering with the GH/IIS signaling activity and/or downstream molecular targets.

Richard A. Miller, M.D., Ph.D.
University of Michigan

Cellular Stress Resistance: Clues to (Real) Anti-Aging Medicines?

Key concepts: (1) There are now many ways to extend lifespan in mice, some of which have already been shown to extend healthy lifespan. At least some of these slow aging, and thus prevent, in parallel, most or all of the major diseases and disabilities of aging. (2) The availability of such experimental systems allows us to test molecular and cellular hypotheses about pathways that might be shared by different sorts of slow-aging mice, providing pointers to potentially druggable targets. (3) The hypothesis that increased cellular resistance to stress is the key mechanism by which mutations slow aging in worms can now be tested in mice. (4) Drugs, diets and mutations can increase rodent lifespan by 25% - 40% or more. If similar results could be obtained, by drugs, in humans, then the effect on healthy active life would be about 3-fold larger than the effect of a complete cure for both cancer and heart attacks.

Nathan K. LeBrasseur, Ph.D.
Mayo Clinic

How does exercise affect stress and stress-related diseases?

More than 60% of older adults are insufficiently active or overtly inactive and 35% are obese. While aging is the primary risk factor for most chronic diseases, a sedentary lifestyle and excess energy intake are powerful contributors that lead to premature mortality. Conversely, there is a wealth of data that underscores the positive effects of physical activity on health- and lifespan. Indeed, higher levels of physical activity are associated with a lower incidence of musculoskeletal, cardiovascular, metabolic, neurodegenerative and hyperproliferative conditions. In addition, structured exercise training interventions improve resiliency, or reduce sensitivity, to physical and psychological stress. While the benefits of exercise are incontrovertible, multiple questions remain. For example, how do physical inactivity and exercise influence underlying mechanisms of aging? How does exercise mediate systemic effects? Is exercise equally adept at preventing and reversing aging? Are there optimal modes, frequencies, intensities or durations of exercise interventions? How can exercise be utilized to improve physical and psychological resiliency in later life? Can the multifactorial effects of exercise (mechanical, metabolic, neural, hormonal, etc.) be replicated in a pill? The objective of this presentation is to set the stage for a lively discussion of these fascinating topics.

Steven Cole, Ph.D.
UCLA School of Medicine

How does the human genome's response to stress regulate aging?

Aging-related biological dynamics are driven in part by systematic changes in gene expression that alter cell function, tissue structure, and ultimately, systems-level organismic function. Environmental factors also play a significant role in structuring gene expression, and recent research has illuminated a striking overlap between the gene transcriptional programs that are activated in response to adverse social environmental conditions (e.g., poverty, isolation, and social instability) and those involved in aging and the pathogenesis of chronic diseases (e.g., cardiovascular, metabolic, and neoplastic). This talk will review some of the emerging themes regarding which specific types of genes are regulated by psychological stress and social adversity, which "social signal transduction pathways" mediate these effects, how those "social genomic" programs evolved, and what role they now play in the pathogenesis of age-related disease.

Gordon Lithgow, Ph.D.
Buck Institute for Research on Aging

DISCUSSION AND WRAP-UP

SESSION IV: EPIGENETICS AND REGULATORY RNA

Shelley L. Berger, Ph.D.
University of Pennsylvania, Perelman School of Medicine

INTRODUCTION

Aging is associated with a wide range of disorders, including cancer, diabetes, cardiovascular, and neurodegenerative diseases, and age is the prime risk factor for these diseases. A fundamental question is whether aging is just an inexorable road toward decline and diseases, or in contrast, whether there is plasticity to the aging process. Such plasticity could be used to approach age-related diseases from a novel perspective. In fact, findings over the past two decades have revealed that aging is not an inevitable downhill path, and, amazingly, that aging can be slowed or even reversed by genetic or environmental alterations. While initial studies focused on the genes that impact aging, the non-genetic regulation of aging is gaining increasing attention. A main appeal to the understanding of the non-genetic regulation of aging is that it opens avenues for actionable interventions that should benefit the diseases of age. Examples of non-genetic interventions that can delay age-dependent onset of diseases in most organisms include dietary restriction – the restriction in food intake without malnutrition (*1*). Arguably, one of the most intriguing aspects of the non-genetic control of aging is the possibility of aging *reversal* (*2*). For example, hallmarks of aging in muscle, brain, and heart, can be reversed by parabiosis – the fusion of the blood circulation between an old animal and a young animal (*3*). The changes to aging imparted by non-genetic factors appear to be relatively long-lasting, suggesting that certain epigenetic mechanisms, which are relatively stable in nature, are a pivotal component of this regulation.

David A. Sinclair, Ph.D.
Harvard Medical School

Do epigenetic changes cause aging and disease, and are these changes reversible?

A first key area for our Session is the tantalizing link between genome stability and epigenetic changes that may underlie common diseases of aging, which will be discussed by **David Sinclair (Harvard Medical School)**. For example, the sirtuin family of protein deacylases protect from diseases of aging and extend lifespan. Sirtuins can deacetylate many substrates, including histones, and their activity is enhanced when the ratio between [NAD^+] and [NADH] is high, thereby linking chromatin regulation to food intake and exercise. Recent evidence suggests that relocalization of chromatin modifiers in response to DNA damage (the RCM Hypothesis) may drive epigenetic changes during aging. Sirtuins can be targeted by small molecule activators (e.g. 'STACs') and by molecules that raise NAD levels (e.g. CD38 inhibitors, NAD precursors). These represent an epigenetic interventional path to preventing and treating diseases of aging, thereby extending healthspan in humans. New concepts and technologies relevant to the aging field will also be discussed including the potential to reverse aspects of aging, the metabolic

similarity between aging and cancer, nuclear mitochondrial communication breakdown, genome editing, and utilizing the incoming deluge of bioinformation.

Stuart Kim, Ph.D.
Stanford University

Is there an underlying epigenetic clock that determines the rate of normal aging?

We are studying the normal process of aging in *C. elegans* (which age in two weeks) and humans. Is there an underlying intrinsic clock for aging that determines our lifespan during normal aging? What are the regulatory factors that control our rate of aging and specify our lifespan?

To understand mechanisms of aging in *C. elegans*, we first identified genes that are differentially-expressed in old versus young animals. Next, we identified GATA transcription factors (ELT-2 and ELT-3) that bind upstream of the age-related genes and are responsible for their expression changes in old age. Both transcription factors decline with age. Resetting the GATA transcription factors in old worms to the young state (by overexpression) rejuvenates the aging transcriptome and increases lifespan. Conversely, resetting the GATA transcription factors in young worms to the old state (by RNAi inhibition) results in a transcriptome with premature aging and decreases lifespan.

We are also studying aging of the kidney in humans. We have found that a key driver of kidney aging is the STAT3 transcription factor, which becomes more active in old age and results in a steady increase in target gene expression. These results identify novel transcriptional circuits that drive the aging processes in *C. elegans* and human kidneys. Aging may be driven by drift of epigenetic pathways in addition to accumulation of damage.
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Li-Huei Tsai, Ph.D.
Massachusetts Institute of Technology

Epigenetics in cognitive aging and neurodegeneration: a slope or a switch?

Alzheimer's disease (AD) is the most common cause of age-related dementia. Due to an incomplete understanding of the molecular basis of AD pathogenesis, as well as an aging global population, AD represents a looming health and economic crisis. One prominent feature of AD neuropathology is a chronic decrease in neuronal activity that is closely associated with cognitive decline. Accordingly, recent large-scale genome-wide analyses reveal that genes associated with synaptic plasticity are selectively reduced in the AD brain, while the expression of immune response and inflammation genes is significantly upregulated. We found that transcriptional dysregulation of synaptic plasticity and immune response gene networks is recapitulated in a mouse model of progressive neural dysfunction and neurodegeneration. Moreover, these

transcriptional alterations predict subsequent locus-specific epigenetic changes that correlate with impaired synaptic plasticity. Our data suggest a model wherein neurodegeneration is associated with targeted transcriptional dysfunction that corresponds to gradual locus-specific chromatin alterations that permanently impair synaptic plasticity. Nonetheless, the restoration of the locus specific changes in chromatin dynamics using existing small-molecule compounds may reverse the cognitive and pathological phenotypes of AD.

Peter D. Adams, Ph.D.
University of Glasgow

Why does the incidence of cancer increase with age?

The incidence of many cancers increase strikingly with age, particularly after 50 years of age. Indeed, age is the biggest single risk factor for most cancers. Other lines of evidence point to the tight association between aging and cancer; for example, genetic and dietary interventions that extend lifespan also tend to suppress cancer. However, the reasons for this tight association between aging and cancer are largely unknown. For decades, there has tended to be an assumption within the cancer field that cancers increase with age because a neoplasm takes decades to accumulate the requisite number of cancer-causing genetic and epigenetic alterations and also to grow to a size where it can be detected and/or causes symptoms. Typically, these acquired genetic and epigenetic alterations are considered as simple "digital" events, i.e. wild type or mutant, expressed or silenced. Peter Adams (Beatson Institute for Cancer Research) will re-assess the evidence underlying this idea, propose that it is an insufficient explanation for age-associated increase in cancer and propose alternative models. Specifically, Dr. Adams will propose that more progressive and graded age-associated changes in dynamic and “plastic” cell and tissue features, including chromatin, metabolic networks and tissue composition and organization, also predisposes to cancer with age. A better understanding of these areas is likely to be important for risk assessment, early detection and chemoprevention of cancer.

Juan Carlos Izpisua-Belmonte, Ph.D.
Salk Institute

Can stem cell models provide new insights on the mechanisms of human aging?

Epigenetic reprogramming allows for the dedifferentiation of somatic cells to an induced pluripotent stem cell state (iPSC Whereas most reprogramming approaches have focused on the use of iPSCs to model genetic diseases, the analogies between dedifferentiation and rejuvenation and, inversely, differentiation and aging, provides new opportunities for the study of human longevity. The derivation of iPSCs from patients with Hutchinson-Gilford progeria syndrome demonstrated that aging phenotypes could be recapitulated in a dish and highlighted the role of the nuclear envelope in chromatin remodeling. More recently, generation of Parkinson’s disease iPSCs indicated the importance of gene-edited isogenic lines for the discovery of previously unknown cellular phenotypes and poised iPSCs for the study of degenerative disorders. This talk will will discuss these and the most recent findings in the application of stem cell technologies

for aging studies and their implications in the development of novel therapeutics. Using Werner Syndrome iPSCs, his group has recently observed a correlation between aberrant epigenetic signatures (5-hmC) and aging phenotypes. Unraveling the role of reprogramming in cellular rejuvenation and, inversely, the epigenetic factors contributing to recapitulation of aging phenotypes upon differentiation may allow for the development of fundamental models for the study of human aging as well as provide models for the development of novel therapeutics targeting human longevity.

Anne Brunet, Ph.D.
Stanford University

DISCUSSION AND WRAP-UP

Session V: Metabolism

Christopher B. Newgard, Ph.D.
Duke University Medical Center

INTRODUCTION

Many sessions in this Summit address several aspects of cellular degeneration that underlay susceptibility to chronic aging-associated diseases, morbidity and mortality. In particular, this session on Metabolism focuses on the interrelationship between signal transduction, intermediary metabolism, and metabolic products and byproducts that contribute to pathophysiologic phenotypes and detrimental effects that occur during the aging process, thus leading to susceptibility to disease. Although its well established that many metabolic pathways (i.e.: oxidative phosphorylation, insulin-stimulated glucose uptake) decline with age, it often remains uncertain if these are a cause or consequence of the aging process. Moreover, the mechanisms accounting for the decline in metabolic function remain enigmatic. Recently, several novel and unexpected concepts are emerging that help define the roles of altered metabolic control in the degenerative mechanisms of aging.

Morris J. Birnbaum, M.D., Ph.D.
University of Pennsylvania

How do signaling pathways that regulate growth and metabolism contribute to aging?

The long recognized life-extending effects of calorie restriction have suggested an inverse relationship between organismal anabolism and ageing. Genetic studies involving modulation of the action of insulin, the major anabolic hormone, support this notion. The mechanistic target of rapamycin (mTOR) complexes serve as phylogenetically conserved sensors and integrators of growth signals from hormones and nutrients. Pharmacological and genetic studies implicate mTOR as a major regulator of generalized ageing as well as age related disease, most notably cancer. Much of the evidence to support this idea derives from studies using rapamycin, a pharmacological inhibitor of the mTORC1 complex, but also a drug exerting complex, multi-organ secondary effects. In particular, the effects of rapamycin overlap with but are clearly not identical to calorie restriction. Genetic studies also support the notion that reduced mTORC1 and possibly mTORC2 signaling extend both average and maximal lifespan. However, the specific cell types and mechanisms responsible have yet to be resolved.

William J. Evans, Ph.D.
GlaxoSmithKline and Duke University
Implications of age-associated increased nutrient requirements and decreased energy needs

A substantial age associated reduction in daily energy needs is a result of loss of skeletal muscle mass (sarcopenia) that decreases basal metabolic rate and a reduction in level of physical activity. At the same time, the dietary needs for protein are increased. This increase in the need for protein may result from "anabolic resistance" where essential amino acids (EAA) have a diminished affect on stimulating muscle protein synthesis. Because of the resistance of muscle to the stimulatory effects of EAA consumption of the current Recommended Dietary Allowance for protein by elderly people is insufficient to maintain muscle mass. The diminished energy needs and intake of the elderly often results inadequate dietary protein. This effect is exacerbated by reduced energy intake and/or periods of reductions in physical activity such as bed rest.

Deborah M. Muoio, Ph.D.
Duke University
Fueling healthspan through futile metabolic cycles

Evidence from studies of dietary restriction and lifelong physical activity suggests that minimizing caloric excess and curtailing whole body energy reserves can have a profound, positive impact on longevity and healthspan. This talk will examine the prospect of targeting futile metabolic cycles as an alternative approach to optimizing energy balance and metabolic control. A futile substrate cycle is defined as a set of opposing, non-equilibrium reactions catalyzed by different enzymes that act simultaneously, with at least one of the reactions driven by ATP hydrolysis. These cycles can consume ATP and generate heat without a net change in the cellular ratio of substrate-to-product. The metabolic control theory of substrate cycling posits a role for these reactions in enhancing cellular sensitivity to regulatory cues, thereby permitting rapid and robust shifts in net flux. Many of these cycles are activated by caloric restriction and/or exercise and have the potential to generate signals linked to health and longevity. The question of whether futile cycles can be exploited for therapeutic gain will be considered.

Dongsheng Cai, M.D., Ph.D.
Albert Einstein College of Medicine
Hypothalamic neurodegeneration: a common link between
metabolic disease and aging

In this talk, I will discuss the role of hypothalamic neural stem cells and related neurodegeneration in obesity-related metabolic syndrome as well as aging development. First, I will provide an overview on the involvement of hypothalamic pro-inflammatory IKK-beta and NF-kappaB pathway in development of metabolic syndrome and aging. Second, I will describe the identification of hypothalamic neural stem cells and their vulnerability to inflammatory stress arising from overnutrition or aging. Finally, I will present the importance of hypothalamic neural stem cells in physiology, the disruption of these cells by neuroinflammation, and the disease consequences in terms of metabolic syndrome and aging. Altogether, inflammation-induced

hypothalamic degeneration may represent a common causal link between aging and related metabolic diseases.

Roman Kondratov, Ph.D.
Cleveland State University

Circadian desynchronization: chronic metabolic diseases of aging

In order to answer the question in the title, I think, two main questions must be answered: 1. How does clock change with age? Does aging of the clock affect clock dependent synchronization of metabolic processes in the organism, namely synchronization in the tissue, synchronization between different tissues, and synchronization of organism with environment? What is the effect of aging on molecular clock? 2. How does clock disruption contribute to age associated diseases? Is the desynchronization of metabolic processes the only mechanism? Emerging data suggest that circadian clock proteins have clock independent functions, how does clock disruption affect these functions? There is some evidence that clock functions are changed with age, which raises the possibility of contribution of clock aging to age associated pathologies, but data are sporadic and more systemic analysis of molecular clockworks in age tissues is necessary.

Jeffrey Pessin, Ph.D.
Albert Einstein College of Medicine

DISCUSSION AND WRAP-UP

Session VI: Macromolecular Damage

Arlan Richardson, Ph.D.
University of Texas Health Science Center San Antonio

INTRODUCTION

Although several decades of research have shown that macromolecular damage increases with age and that macromolecular damage appear to be important factors in specific age-related diseases, it is currently unclear whether damage to macromolecules is a key molecular component to the actual process(es) of aging. Discoveries in the 1970s and 80 showed that damage to lipid, protein and DNA increased with age, which was widely hailed by the aging community as support for the popular Free Radical (or Oxidative Stress) Theory of Aging, a theory that argued aging was a consequence of stochastic damage accumulation. The strongest evidence that macromolecular damage is a causative factor in aging comes from studies showing that manipulations in both rodents and invertebrates that increase lifespan are correlated reduced damage to macromolecules and increased resistance to stress. While it is intuitively appealing to assume that macromolecular damage plays a causative role in aging and the onset of age-associated diseases, data from several recent studies suggest that alterations in macromolecular damage does not alter lifespan/aging. For example, transgenic mice that overexpress one or more antioxidant enzymes, as well as mice in which these same enzymes have been reduced/eliminated, have shown a striking lack of correlation between longevity and macromolecular damage. In addition, the long-lived naked mole-rat shows increased macromolecular damage, not reduced damage. This session will focus on whether macromolecular damage plays a role in aging, and if so, how damage to protein or DNA would lead to the phenotypes observed with aging.

Jan Vijg, Ph.D.
Albert Einstein College of Medicine)

Do DNA damage or mutations ever reach high enough levels to cause functional decline?

DNA damage and mutations have been implicated as causal factors in age-related cellular degeneration and death since the 1950s when the first evidence emerged that low doses of ionizing radiation led to accelerated aging. DNA damage as a driver of aging is an attractive hypothesis for two main reasons. First, since DNA is the primary informational macromolecule, loss or alteration of its sequence is essentially irreversible, which is generally not true for damage in other macromolecules. Second, heritable mutations in multiple genes involved in genome maintenance in both humans and mice have been found associated with segmental progeria. There is virtually no evidence that the same is true for other gene families thought to be involved in longevity, including antioxidant defense systems and autophagy. However, to prove that persistent DNA damage and/or mutations, including large genome rearrangements and chromosomal aneuploidy, are causally contributing to aging has proved difficult. First, in view of

its rare and stochastic nature, DNA damage and mutations are difficult to quantitate and characterize. However, recently, using novel assays, it has been conclusively demonstrated that a diverse array of mutations accumulate in both the nuclear and mitochondrial genome of different tissues and organisms. The second key problem, and the topic of this presentation, is how to conclusively show that DNA damage and/or mutations collectively contribute, at least in part, to age-related cell and tissue degeneration and disease. I will discuss one possible way of doing that by using single-cell genomics and epigenomics in combination with computational modeling.

William M. Bonner, Ph.D.
National Cancer Institute

Are chromatin changes a result of aging, a cause of aging, or both?

Chromatin is a complex molecular machine which controls the timing and level of gene expression. It is composed of the chromosomal DNA, histones, a variety of nucleoplasmic proteins, and many types of RNA species. Interphase chromatin resides in nuclei bounded by nuclear lamia and membranes containing pores which regulate the exchange of molecules with the cytoplasm. In addition, other structures have been identified in the nucleoplasm including the nucleoli and a variety of complexes, speckles and bodies, many with poorly understood functions. Epigenetic markers are found on the DNA, the histones, and perhaps other proteins. These markers include covalently bound small molecules to DNA bases and protein amino acid residues, as well as a variety of small RNA species.

As the cell ages, chromatin undergoes several changes which are not damage in the chemical sense of aberrant structures but which correlate with cellular and organismal aging. Identified changes include decreased levels of 5MeC and histone ADP-ribosylation, as well as increased levels of tri-Me H4 K20 and heterochromatin. As the rate of DNA repair slows with age, various chromatin aberrations appear including senescence-associated heterochromic foci (SAHF).
The best known age-related chromatin components are the telomeres, special structures on the end of chromosomes which prevent the DNA double-stranded ends from activating the DNA DSB repair response. However, DNA polymerase cannot replicate the DNA at the ends of the double-helices, and a specific enzyme telomerase is needed to maintain their lengths. Generally telomerase is not present in adult cells causing telomeres to shorten with each cell division until they begin to lose their capacity to protect the DNA ends, at which time cells enter a state named replicative senescence. This cessation of replication was once considered an explanation for the Hayflick limit. In addition, there is evidence that telomeres may lengthen in adult humans.

There are many genetic diseases affecting chromatin and its associated complexes which lead to accelerated mortality and aging. Defects in telomeric factors may lead to telopathies such as dyskeratosis congenita while defects in DNA repair factors lead to a variety of progeria-like diseases. In addition, defects in lamin A lead to HGPS (progeria). These diseases often exhibit several but not all of the symptoms of aging and thus have been named segmental progerias. Thus further research is needed to clarify what processes define aging as opposed to other degenerative phenomena.

Rod Levine, M.D., Ph.D.
National Heart, Lung and Blood Institute
Can oxidized proteins be repaired?

The steady-state levels of oxidized macromolecules increase during aging of most species, and they rise particularly rapidly during the last third of lifespan. This observation spawned the reasonable hypothesis that the oxidatively modified molecules disrupt normal cellular function. While the fraction of modified DNA is relatively small, even in very old animals, the level or carbonylated proteins often reaches 30%. This means that average, at least 3 of every 10 proteins carry an oxidative modification. Oxidation has been shown to impair enzymatic function and to hobble the function of structural proteins. Thus, the accumulation of dysfunctional proteins may be causal of the changes observed during aging. Whether it is causal or correlative has not yet been rigorously tested by experiment.

With the exception of a few oxidative modifications such as disulfide formation, it is commonly assumed that oxidatively modified proteins cannot be repaired. They can only be disposed of by degradation. While oxidatively modified proteins are generally more susceptible to proteolytic degradation, the possibility of repair has not been seriously considered. In particular, oxidation of arginine or lysine to produce carbonylated proteins is almost always assumed to be irreversible. But that may not be the case. If repair is possible, does efficiency vary with age? If repair is possible, can efficiency be modulated either by the cell or externally?

Dean P. Jones, M.D.
Emory University
What therapeutic strategies prevent or remedy changes in redox potential?

Measures of human plasma thiol/disulfide redox potential show that both GSH/GSSG and cysteine/cystine become oxidized with age. Decreased GSH is linked to a decline in maintenance of protein thiol systems, and an increase in cystine activates pro-inflammatory and pro-fibrotic signaling. These processes are beginning to be understood in terms of the organizational structure of the redox proteome. The “redox proteome” is a collective term for components of the proteome that undergo reversible redox reactions and those modified irreversibly by reactive species during oxidative stress. Cysteine, methionine and selenocysteine (Sec) are amino acids that undergo reversible oxidation in biologic systems, while many amino acids and the peptide backbone can be irreversibly modified by free radical mechanisms. Reversible cysteine oxidation provides a central sulfur switching mechanism in proteins, linking redox changes to protein structure, activity, interaction and trafficking. Emerging knowledge of the organizational structure indicates that central oxidative and reductive hubs control functional protein networks. Relatively little is known about the spatiotemporal changes in the redox network structure with aging, but one can speculate that either oxidative or reductive hubs could provide suitable therapeutic targets. In principle, control of dietary sulfur amino acids (Met + Cys), zinc and selenium could also provide therapeutic strategies as each of these impacts central redox hubs.

Michael B. Yaffe, M.D., Ph.D.
Massachusetts Institute of Technology

How does signaling in the surrounding microenvironment affect
the response of cells to macromolecular damage?

In this talk, I will discuss the role of chronic inflammation in age-related diseases, particularly the connection between cytokine production and genotoxic stress. Inflammatory and stress-related signal transduction events within the stromal microenvironment modulates the response of epithelial cells to various types of DNA damage. The source of the cytokines includes neutrophils and macrophages, fibroblasts, and endothelial cells, in addition to the epithelial cells themselves. Cytokine production and release appears to be heavily regulated at the post-transcriptional level, largely through modulation of RNA-binding proteins through the MAP kinase and NF-kB pathways. Together with age-related decreases in innate immune function, this cytokine-genotoxin interaction may contribute to poor tissue self-renewal, increased risk of malignancy, and a poorer response to anti-tumor therapies.

Eric E. Schadt, Ph.D.
Icahn School of Medicine at Mount Sinai

DISCUSSION AND WRAP-UP

SESSION VII: PROTEOSTASIS

Richard Morimoto, Ph.D.
Northwestern University

INTRODUCTION

Maintenance of the cellular proteome is essential to preserve cell functionality and the ability to respond and adapt to the changing environment. A dedicated set of molecular components, known as the proteostasis network, is in place in all cells to assure protein homeostasis and thus prevent the toxicity associated with protein misfolding and subsequent accumulation of toxic aggregates in different cellular compartments. The efficiency of the proteostasis network decreases with age and this gradual failure in protein homeostasis has been proposed to underlie the basis of common age-related human disorders. The current advances in the understanding of the mechanisms and regulation of proteostasis and of the different types of digressions in this process in aging, has turned the attention toward the therapeutic opportunities that restoration of proteostasis could offer. Experts in this field discuss here key unresolved questions on proteostasis that need to be addressed to succeed in the extension of healthspan through modulation of the proteostasis network.

Alfred L. Goldberg, Ph.D.
Harvard Medical School

Aging and the selective degradation of abnormal proteins

The Ubiquitin Proteasome System (UPS) is the major site for protein degradation in mammalian cells. It catalyzes the selective breakdown of misfolded or damaged proteins, short-lived regulatory proteins, and the slower degradation of the most cell proteins. Most proteins are targeted for degradation by attachment of a chain of ubiquitin molecules, which leads to their rapid degradation by the 26S proteasome. However, the mechanisms involved in recognizing and selectively degrading misfolded proteins are still unclear. In the best-characterized example, the ubiquitin ligases (e.g. CHIP) utilize molecular chaperones (Hsp70 and Hsp90) to recognize misfolded proteins, including several involved in human disease. Systems exist for the elimination of misfolded proteins in the secretory pathway (ERAD), nucleus, cytosol, and on the ribosome. Ubiquitination also serves to target membrane and endocytosed proteins to the lysosome in the ESCRT pathway and protein aggregates and damaged mitochondria to autophagic vacuoles.

The 26S proteasome is a 60-subunit ATP-dependent proteolytic complex that binds selectively ubiquitinated proteins, disassembles their ubiquitin chains, unfolds the polypeptide, and digests it into small peptides. Recent studies have clarified how this multistep machine functions. Surprisingly, many ubiquitinated proteins bind to the proteasome and are simply deubiquitinated and not degraded. Moreover, proteasomal function can be regulated pharmacologically. Proteasome inhibitors are widely used to treat certain cancers, and recently, mechanisms have

been identified that activate proteasomes and are promising approaches to eliminate toxic proteins.

Many studies suggest a loss of proteasome function in brain in the major neurodegenerative diseases and with aging. However, the effects of aging on UPS function in different tissues are not clear, largely because rigorous methods have only recently become available to evaluate its diverse activities.

Roberta Gottlieb, M.D.
Cedars Sinai Medical Center

Mitophagy: impact of organelle quality control in Proteostasis

Protein quality control is not limited to *de novo* generated proteins but it is also essential for functioning of organelles. Dedicate systems contribute to maintain organelle homeostasis. For example quality control of mitochondria is regulated by autophagy and by the mitochondrial unfolding protein response (mtUPR). Factors that impair global autophagy or the selective clearance of mitochondria (mitophagy), such as aging, overnutrition, high cholesterol, metabolic syndrome, and diabetes, have a negative impact in mitochondrial homeostasis. Because mitophagy and mitochondrial biogenesis are functionally linked, failure to clear dysfunctional mitochondria via autophagy will result in their accumulation and will prevent their replacement with more functional components. Impaired mitochondrial turnover is a feature of numerous diseases including Parkinson disease, Crohn's IBD, and the damage associated with myocardial ischemia/reperfusion injury. An imbalance between nuclear encoded and mitochondrial encoded proteins elicits mtUPR. Recent work has linked longevity to the mitochondrial unfolded protein response. As the same agents (fasting, rapamycin, chloramphenicol, sirtuins) that activate mtUPR also induce mitophagy, it is not clear whether it is the mtUPR or mitophagy that contributes to lifespan.

Judith Frydman, Ph.D.
Stanford University)

Consequences of the aging-associated decline in cellular protein homeostasis: the chaperone network

Chaperones help proteins fold or send them to degradation, but they also regulate conformational protein cycles, protein-protein interactions, transcriptional programs, and buffer the many mutations present in the proteomes of individuals and cells in both normal and diseased states. The emerging understanding of protein homeostasis as an extraordinarily complex, multifaceted and nuanced actor in cellular regulation, calls for a better consideration of the machinery responsible for it, how it works under normal conditions, how it is regulated and how its impairment leads to disease. This can only occur through the integration of mechanistic, cell biological and genetic data with physiological studies of disease states. It is well-established that an impairment of protein homeostasis during aging underlies the onset of a whole set of neurodegenerative misfolding diseases. Thus, upregulation of these pathways could have a tremendous impact in our treatment of late-onset devastating diseases. Similarly, cancer cells and

viruses upregulate chaperones to cope with their high protein production levels and exploit their buffering capacity to allow the elevated mutation rates that enable them to escape most drugs. In these cases decreasing chaperone capacity would deprive these highly plastic diseases from one of their major protective mechanisms. The tremendous therapeutic promise of protein homeostasis regulation calls for a better understanding of basic mechanisms and pathways and their regulation in disease, infection and aging.

Randal J. Kaufman, Ph.D.
Sanford-Burnham Medical Research Institute
The unfolding protein response at the organismal level

Proteins are handled in very different ways depending on the cellular compartment where they localize. For example, protein folding in the endoplasmic reticulum (ER) is fundamentally different to protein folding in the cytosol, as it depends on several variables that are affected by aging and disease, such as redox status, Ca^{2+} concentration, oligosaccharide assembly, etc. Excessive protein synthesis leads to oxidative stress that can disrupt productive folding in the ER, which in-turn can disrupt mitochondrial function to reduce oxidative phosphorylation. Such a consequence could lead to a metabolic crisis that has potential to be transmitted across all cell membranes. Likewise, inflammation and metabolic stress, associated with aging, impact protein folding in the ER with misfolding leading to further inflammatory stress and inflammatory cytokine stimulation in hepatocytes. In addition, a metabolic surplus, as in high-fat diet, challenges all cell types to increase protein synthesis rates/folding to exceed folding requirements within the ER. Accumulation of lipids in the hepatocyte is a contributing factor to hepatic inflammation, fibrosis and hepatocellular carcinoma. One of the fundamental questions for future modern medicine is how life style impacts inflammatory responses, metabolism and the protein folding environment in different cell types. Interactions between these components contribute to organismal pathology and degenerative diseases associated with aging.

Jeffery Kelly, Ph.D.
Scripps Institute
Novel therapeutic strategies against proteotoxicity

The growing number of connections between dysfunction of the proteostasis network and age-related disorders has provided momentum to explore the therapeutic opportunities that manipulation of this process may offer in the retardation or alleviation of severe age-related diseases. The proteostasis network can be manipulated through novel small molecules that target specific arms of the unfolded protein response (UPR) alleviate gain-of-toxic-function diseases where excessive secretion or accumulation of misfolding and aggregation of proteins leads to amyloid diseases. In addition, small molecule kinetic stabilizers are employed to halt the progression of peripheral neuropathy in the human disease familial amyloid polyneuropathy linked to transthyretin amyloidosis. These efforts have provided the first pharmacologic evidence supporting the amyloid hypothesis, the notion that protein aggregation causes degeneration of the heart and the nervous system. In addition the transthyretin stabilizing compounds indroduced into the clinic are providing insights about the etiology of protein conformational diseases vis-à-vis a successful clinical trial and longer-term patient assessments.

Ana Maria Cuervo, M.D., Ph.D.
Albert Einstein College of Medicine

DISCUSSION AND WRAP-UP

SESSION VIII: STEM CELLS AND REGENERATION

Thomas A. Rando, M.D., Ph.D.
Stanford University

INTRODUCTION

Aging is associated with a marked decline in the functionalities ofadult stem cells, namely tissue homeostasis, repair, and.The remarkable advances in the biology of stem cells has shed new light on the cellular and molecular mechanisms by which somatic stems cells generate new differentiated cells throughout the life of an organism and, simultaneously, maintain a pool of stem cells through self-renewal. However, many questions within this field, remain to be addressed particularly with respect to the relationship and contribution of the stem cell compartment to the structure and function of adult tissue. Since there is vast diversity among mammalian tissue types, the role of the stem cell compartment within specific tissue types is highly variable.

Some mammalian tissues, such as cells of the blood and epithelia of the skin and intestines, engage in constant turnover throughout life, attesting to the essential role of stem and progenitor cells in those tissues for the maintenance of organismal viability. Other tissues, such as the vasculature and skeletal muscle, exhibit far less turnover in the absence of injury or disease but have remarkable regenerative potential when the tissue is damaged. In those tissues, the stem cells are more like reserve cells. The liver represents an organ of endodermal origin with high regenerative potential that appears to be stem cell-independent, whereas pancreas also is derived from endoderm and has little regenerative potential and appears to be essentially devoid of stem cells. The central nervous system is highly stable with little regenerative capacity, properties that contribute to the devastating consequences of strokes and spinal cord injury, but has restricted areas of active stem cell function throughout life giving hope for the potential for stem cell therapeutics. Finally, there are tissues such as kidney and heart which also have extremely limited regenerative potential and in which the very existence of somatic stem cells in those tissues remains a matter of scientific debate. In the face of this diversity, questions arising from the roles of stem cells in tissue homeostasis and repair intersect directly with the critical issues of the biology of aging.

In this session, the fundamental relationships between stem cell function and tissue aging will be explored. Like age-related changes themselves, it is paramount to understand how stem cells either contribute to or fend off age-related diseases. Likewise, the promise of stem cell therapeutics, already a fundamental basis for the efficacy of bone marrow transplantation and skin grafting, has entered into the discussion of the future of virtually every age-related disease. Throughout the discussion, the importance of stem cell biology for healthspan will be a central focus, relating to each of the questions, as presented below, that will form the starting point of this critical topic.

Danica Chen, Ph.D.
University of California Berkeley
How do stem cells change intrinsically with age and what are the implications for stem cell based therapeutics?

With age, the capacity of stem cells to self-renew and to differentiate becomes dysregulated. These declines in stem cell function are consistent with degeneration and dysfunction in aging regenerative tissues. Thus, aging-related changes in the function of stem cells are likely to contribute significantly to diseases of aging, particularly in regenerative tissues. Recent development in the mechanistic understanding of stem cell aging reveals that stem cell aging is due to cumulative cellular and genomic damage, resulting in permanent cell cycle arrest, apoptosis, or senescence. Regulators of organismal aging also underlie the aging of stem cells, consistent with the notion that stem cells play a pivotal role in organismal aging and diseases of aging. Intriguingly, some regulators of organismal aging are particularly enriched in the stem cell compartment, lending further support to the stem cell theory of aging. Stem cell aging is also regulated by gate-keeping tumor suppressors, suggesting that stem cell aging is an evolved mechanism to oppose the increased incidence of cancer during aging. Thus, ideal stem cell based therapies should aim to reduce the accumulation of cellular damage in order to prevent both stem cell aging and cancer. Finally, although stem cell aging is thought to be determined by the passive accumulation of various forms of cellular damage over time, evidence is emerging to show that the buildup of insults in aging stem cells is more regulated than previously thought, providing the basis to rejuvenate aged stem cells in order to combat aging-associated degenerative diseases.

Hartmut Geiger, Ph.D.
Cincinnati Children's Hospital Medical Center
How does aging alter the local stem cell niche and does this contribute to chronic disease progression?

The cellular and non-cellular environment influencing stem cells is referred to as the niche. Niche aging impacts aging of stem cells. Aging of niches might thus contribute to tissue wasting as well as chronic, aging associated diseases of for example the hematopoietic system like chromic inflammation as well as types of chronic leukemia or chronic diseases in other stem cell driven tissues.

Emmanuelle Passegué, Ph.D.
University of California, San Francisco
How does DNA damage affect aging and function of stem cells?

DNA damage is among the most dangerous threats to life. If improperly repaired DNA damage can lead to genomic instability, which enables genetic deregulation and results in the accumulation of damaging or transforming mutations. Genomic instability is particularly dangerous for stem cells as they are long-lived cells from which all tissues arise and regenerate

over time. Mutations occurring in stem cells can directly affect stem cell activity and be passed along to their progeny to alter tissue function, both acutely or later in life. Maintenance of genomic stability in stem cells is therefore paramount for the proper development, maintenance and regeneration of tissues, and for preventing organ failure or cancer development. Here, we will describe the DNA-damaging insults that can affect stem cell function, and the mechanisms that are employed by stem cells to prevent, survive, and repair DNA lesions. We will also review the consequences of DNA damage for stem cell aging using the blood-forming hematopoietic stem cells as a paradigm.

Richard T. Lee, M.D.
Harvard Medical School

How do you repair whole organs in an aging system?

To physicians, patients, and even many scientists, the idea of regenerating diseased organs like limbs, hearts and brains may seem closer to science fiction than science. However, the distance between organ regeneration and organ failure may not be as great as it appears. For example, mice will regenerate their hearts at birth, but lose that potential in the first week of life. Axolotl salamanders can completely regenerate their limbs, throughout their life of 9 years or more. Armed with new understanding of regenerative biology, including when stem cells are required and when stem cells are not required, we are closing in on understanding how organ regeneration occurs in many species. This will allow us to define, for many organs, why regeneration fails in humans. A key factor in regenerating diseased organs will be defining the requirements to regenerate tissues in diseased environments, particularly the aged human environment. By combining our insights from aging biology, regenerative biology and stem cell science, we have the potential to stimulate regeneration in humans.

Irina Conboy, Ph.D.
University of California, Berkeley

Is stem cell rejuvenation a likely candidate for therapeutics against chronic disease?

Progressive decline in organ function with age erodes the quality of life for virtually everyone and is projected to cost trillions of dollars in the coming years. Our goal is to identify and reverse-engineer the molecular composition of the pro-regenerative soluble niche to enhance and rejuvenate tissue maintenance and repair, attenuate cellular senescence and increase healthy life span. As model systems we study the regeneration of skeletal muscle and of hippocampal neurogenesis as well as the neuroprotection of mature neurons in a model of Alzheimer's disease and the enhancement of tissue repair in cases of diabetes. Our work is likely to contribute to a broad understanding of how the efficiency of tissue regeneration is regulated by the soluble niches generated by embryonic, young and old cells. Extensive data demonstrate that when the extrinsic niches of organ stem cells are biochemically rejuvenated, stem cells residing in the old organism engage in productive tissue regeneration. Our goal is to determine the key factors and molecular mechanisms that are responsible for this phenomenon and reverse engineer an optimal

soluble niche for the efficient age-independent regeneration and maintenance of multiple organ systems.

Tony Wyss-Coray, Ph.D.
Stanford University

DISCUSSION AND WRAP-UP

Richard J. Hodes, M.D.
Director, National Institutes on Aging

CONCLUDING REMARKS