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Mechanisms of Age-Related Cognitive Change and Targets for Intervention: Epigenetics

Kenneth S. Kosik,[1] Peter R. Rapp,[2] Naftali Raz,[3] Scott A. Small,[4] J. David Sweatt,[5] and Li-Huei Tsai[6,7]

[1]Neuroscience Research Institute and Department of Molecular, Cellular and Developmental Biology, University of California, Santa Barbara.
[2]Laboratory of Experimental Gerontology, National Institute on Aging, Baltimore, Maryland.
[3]Institute of Gerontology and Department of Psychology, Wayne State University, Detroit, Michigan.
[4]Department of Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, New York.
[5]Evelyn F. McKnight Brain Institute, Department of Neurobiology, University of Alabama at Birmingham.
[6]Stanley Center for Psychiatric Research, Broad Institute of Harvard University, Cambridge, Massachusetts.
[7]Howard Hughes Medical Institute, Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge.

Address correspondence to Peter R. Rapp, PhD, Laboratory of Experimental Gerontology, National Institute on Aging, 251 Bayview Blvd, Suite 100, Baltimore, MD 21224. Email: rappp@mail.nih.gov

Epigenetic regulation of gene expression plays an important role in learning and memory, mediating the influence of experience on critical mechanisms of plasticity. Speakers in the opening session of the Summit reviewed research on epigenetic contributions to age-related cognitive decline and discussed strategies for the development of interventions targeting epigenetic mechanisms. The presentations focused on experience-dependent DNA methylation, the regulatory role of microRNAs, histone deacetylases as potential therapeutic targets, and strategies for exploring epigenetic contributions to the aging of brain and cognition. This session established useful mileposts for gaging progress in this rapidly advancing area of research.

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AGING is accompanied by changes in cognitive function and alterations in brain anatomy, physiology, and neurochemistry. The rate and magnitude of change, however, varies substantially across individuals, brain regions, and functional domains (1,2). Moreover, the brain is a dynamic system, exquisitely sensitive to environmental and organismic influences, and individual trajectories of aging are shaped by a wide array of factors that affect brain structure and function throughout the life span. Mounting evidence indicates that epigenetic mechanisms—potent regulators of gene expression that are unrelated to changes in DNA sequence—play a significant role in shaping environmental influences on brain and behavior. The emerging field of "cognitive neuroepigenetics" has begun to yield insights in many areas of neuroscience, including research on psychiatric illness, addiction, and neurodegenerative disease.

Research exploring potential epigenetic contributions to age-related cognitive change has only recently emerged, and the opening session of the Cognitive Aging Summit II provided a timely overview of this nascent area of inquiry. A seminal contributor to the field, J.D.S. (University of Alabama, Birmingham), opened the session with a survey of advances in research on the role of DNA methylation and other epigenetic mechanisms in learning and memory, including recent progress in studies on cognitive epigenetics of aging. K.S.K. (University of California, Santa Barbara) focused on another level of gene regulation involving microRNA's (miRNAs) that are capable of affecting large-scale protein networks implicated in fundamental aging processes. L.-H.T. (Broad Institute and the Massachusetts Institute of Technology) reviewed the development of preclinical strategies in mouse models targeting the regulation of histone acetylation with the aim of overcoming the repression of transcription and translation responsible for reduced synaptic plasticity in the aged brain. S.A.S. (Columbia University) extended the discussion to a consideration of human cognitive aging and the significance of regional vulnerability within the component circuitry of the hippocampus in relation to age-related effects on mediators of

histone acetylation. The session ended with concluding comments from two discussants, N.R. (Wayne State University) and P.R.R. (National Institute on Aging), touching on major themes, future directions, and challenges to progress.

Epigenetic Mechanisms in Memory Formation—J.D.S.

Age-related memory decline is manifest prominently in declarative/episodic and working memory, memory modalities anatomically based largely in the hippocampus and prefrontal cortex, respectively. The neurobiological underpinnings of age-related memory deficits include aberrant changes in gene transcription that ultimately affect the ability of the aged brain to be "plastic" (3). Memory and synaptic plasticity processes are associated with transcription of immediate-early genes (IEGs), including Arc (activity-regulated cytoskeletal gene), Zif268 (also known as nerve growth factor inducible-A, and early growth response gene [Egr-1]), and BDNF (brain-derived neurotrophic factor; [4–6]). Blocking the expression of these genes in adult animals prevents the consolidation of memory (4,5,7), and decreased immediate-early gene expression is seen in some models of memory disorders (8,9) and as a result of normal aging (3).

The molecular mechanisms underlying these aging-related changes in gene transcription are not currently known, but recent work points to a novel possibility involving the dysregulation of epigenetic control. The relevant epigenetic mechanisms include histone posttranslational modifications and DNA methylation, mechanisms that have recently been discovered to control hippocampal synaptic plasticity and long-term memory formation (10). These epigenetic changes involve the covalent chemical modification of histones by histone acetyltransferases and histone deacetylases (HDACs) and also covalent modification of DNA by DNA methyltransferases. Epigenetic mechanisms are powerful controllers of memory-associated gene transcription, typically resulting in transcriptional silencing and loss of gene function in the case of DNA methylation and transcriptional activation with histone acetylation. Although numerous other modifications and effects are also possible, it is now known that DNA methylation plays a key role in dynamically regulating gene transcription in the adult central nervous system (11,12), and in concert with histone acetylation (13,14), that these processes are involved in long-term memory formation. What is less clear is whether alterations in these mechanisms also contribute to age-related changes in gene transcription and memory decline.

This background has led us to hypothesize that the dysregulation of epigenetic control mechanisms and accumulation of aberrant epigenetic marks are drivers of aging-related cognitive dysfunction. Specifically, given that the transcription of key memory–promoting genes is known to decline during aging (3), we propose that these changes arise from abnormal epigenetic marks and control mechanisms within brain regions particularly vulnerable to the aging process (ie, hippocampus and prefrontal cortex), together resulting in age-related cognitive impairment.

In collaboration with Carol Barnes' research group, we have undertaken an assessment of memory formation–associated DNA methylation in the aged rat hippocampus, in order to begin to determine if aging is associated with a disruption of epigenomic signaling (15). Animals in this study (9 months old, $n = 6$; 24 months old, $n = 6$) were first screened using a spatial version of the Morris swim task, confirming that the aged animals exhibited impaired memory. One week later, the rats explored a novel environment for 5 minutes, that is, a treatment that results in both new memory formation for the novel spatial environment and active transcription of Arc in the hippocampus. After training, animals rested in their home cage for 25 minutes, followed by decapitation under deep isoflurane anesthesia. The hippocampus was extracted and dissected into CA1 and dentate gyrus samples. DNA extracted from these samples was processed for bisulfite modification, and methylation state was determined for the Arc gene via sequencing of control and bisulfite-treated DNA. A second group of rats sacrificed directly from the home cage ($n = 6$ per age group) was used to determine resting levels of DNA methylation of the Arc gene in hippocampus, providing a baseline for quantitating the relative change in methylation associated with spatial navigation.

These studies revealed a distinct pattern of methylation of the Arc gene within the aged hippocampus (15). In area CA1, young adult and aged rats showed significant and comparable demethylation of Arc DNA at the transcription start site promoter in response to spatial exploration. In the dentate gyrus, by comparison, aged rats showed not only less DNA methylation under basal conditions than adult rats but also significantly *increased* methylation of the Arc gene following spatial learning. To our knowledge, these results are the first to demonstrate that aging is accompanied by significant alterations in epigenomic signaling, including changes specifically targeting the memory-promoting gene Arc.

miRNAs Hold the Potential to Reveal a Genetic Architecture of Aging—K.S.K.

Biological aging is largely determined by two components: the internal biological clock and accumulation of insults to the organism. Whereas the life span of a species is closely tied to biological aging, individual longevity is related both to specific environmental circumstances, that is, accumulated insults, and individual differences in the settings of the biological age clock. These two facets of aging operate at every level of the biological hierarchy—genes, proteins, cells, organs, and organisms. Thus, aging as a multifaceted problem, poses the difficulty of finding an entry point that comprehensively captures the issues.

Progress on the complex problem of aging has come from a genetic approach. The first of the relevant genetic pathways was discovered in 1993, when Cynthia Kenyon found that a single-gene mutation in daf-2 could double the life span of *Caenorhabditis elegans* and that this could be reversed by a second mutation in daf-16m. Using the same model system, Victor Ambrose discovered a novel class of

posttranscriptional gene regulators called miRNAs. These miRNAs are ~21 nucleotide noncoding transcripts capable of partially silencing the translation of target messenger RNAs by forming an RNA–RNA duplex housed in a protein structure called the RNA-induced silencing complex. A single miRNA targets multiple messenger RNAs. Recent findings demonstrate the power of miRNAs to reveal insights into the aging process, suggesting that their exquisite tissue specificity may open a door to the problem of cognitive aging. Although several studies indicate that miRNA profiles change with age, the precise association of specific miRNAs with specific aging models is unclear. By ascertaining the miRNAs that change across several aging models, a coherent set of pathways related to aging will likely emerge. Because miRNA levels can be exogenously manipulated—both upregulated by delivery of precursor miRNAs and downregulated by delivery of locked nucleic acid antisense sequences—it will be possible to probe these models of aging for ameliorative outcomes.

The emerging biology of miRNAs has demonstrated that sets of miRNA targets are often functionally related. We have demonstrated this property in cancer by showing sets of messenger RNA targets that are all related to the p53 pathway in the case of the onco-miR, miR-21 (16). We have also found that miR-128 is a tumor suppressor miRNA that targets the functionally related genes within tyrosine kinase receptor pathways. The power of this approach rests on the role of miRNAs in modulating entire networks in a distributed and robust manner by making small changes in protein levels among many components of the network. Thus, an miRNA approach to modulating function differs radically from a classic pharmacological approach in which a single key gene product in a pathway, such as a kinase, is targeted by a small molecule. The flaw in the pharmaceutical approach is that pathways are highly redundant and inhibiting any single component results in compensatory responses elsewhere. By identifying and manipulating miRNAs that target multiple messenger RNAs, which are all functionally related to aging, it may be possible to modulate some facets of the aging process.

Among genes related to aging at a cellular level are tumor suppressor genes (17). This class of genes is a frequent miRNA target, and their derepression, associated with a reduced level of specific miRNAs, can accelerate an aging phenotype. For example, when genes at the *Ink4*/*Arf* locus are activated, the capacity for proliferation is reduced, and thus, an anticancer mechanism may contribute to the attrition of stem cells with aging. The chromatin-associated protein HMGA2 plays an age-related role in the self-renewal of mouse neural stem cells, particularly from late embryos, and regulates *Ink4a*/*Arf*. This pathway is directly linked to the miRNA, *let-7b*, which collaborates with Lin-28 to suppress HMGA2 (18). More generally, miRNAs have important roles in stem cells (19) particularly as pluripotent cells pass through stages of increasingly restricted potential until they reach terminal differentiation. If one loosely considers stem cells as immortal, then biological aging begins the moment cells exit from pluripotency. The pathway from pluripotency to terminal differentiation can be tracked by a set of miRNA changes (20), and each discrete stage in a cell's lineage is marked by a defining miRNA profile. Thus, unraveling the complex targeting networks of miRNAs could offer important new insights into the aging process.

Histone Acetylation and Histone Deacetylases in Mouse Models of Neurodegeneration—L.-H.T.

Alzheimer's disease (AD) is an age-related neurodegenerative disorder associated with severe memory impairment. A prominent feature of AD is the progressive loss of forebrain neurons and deterioration of learning and memory (21). There are currently no significantly effective treatments for AD (22). Recent drug trials have been disappointing, and the development of alternative therapeutic approaches is an absolute necessity.

Epigenetics can be defined as the study of changes in gene expression that are mediated by mechanisms other than changes in the sequence of the DNA. One example of this is chromatin remodeling, by which patterns of gene expression are modulated via the alteration of chromatin structure. Increased histone acetylation leads to a more relaxed chromatin structure and correlates with increased gene expression. Histone acetylation is regulated by the opposing activities of two groups of enzymes: the histone acetyltransferases, which transfer acetyl groups to histone tail lysines, and the HDACs (23), which remove acetyl groups.

Class I HDACs, in particular HDAC 1, 2, and 3, are primarily found within the nucleus, where they regulate histone acetylation and suppress gene expression. They are recruited to the promoter/enhancer regions of genes via transcriptional repressor and corepressor proteins (24). Recent work implicates histone acetylation as having an important role during learning and memory processes. Rodents display a transient increase in histone acetylation after exposure to various learning paradigms (25–28), and synaptic plasticity and memory formation are facilitated in wild-type mice and rats after treatment with HDAC inhibitors (HDACis), suggesting that increased histone acetylation facilitates cognitive function (25–27).

Our work with the CK-p25 mouse model has shown that treatment with the nonselective HDACi sodium butyrate significantly improves cognitive performance in mice, even after severe neurodegeneration has occurred (26). The HDACis suberoylanilide hydroxamic acid and phenylbutyrate have also been shown to reinstate learning behavior in a mouse model of AD (29,30). These mice displayed elevated H4 acetylation accompanied by an increased production of proteins implicated in synaptic function (30). Treatment with various HDACis has thus emerged as a promising new strategy for therapeutic intervention in neurodegenerative disease (31,32).

The overexpression of HDAC2 in mouse neurons results in a striking impairment of memory formation and synaptic plasticity, which are not observed in HDAC1-overexpressing mice (33). These mice also exhibit reduced hippocampal H4K12 and H4K5 acetylation, while other marks, such as AcH3K14, are not affected (33). HDAC2 knockout mice, but not HDAC1 knockout mice, likewise exhibit increased H4K12 and H4K5 acetylation, enhanced learning and memory and synaptic plasticity, and serve as a rare model of cognitive enhancement. Thus, HDAC2 seems to play a major role in learning and memory and synaptic plasticity, as well as in the regulation of H4K12, whose dysregulation is causatively implicated in age-associated memory impairment (34).

Chromatin immunoprecipitation revealed HDAC2 to be enriched on the promoters of genes that are implicated in synaptic remodeling and plasticity or that are regulated by neuronal activity such as *CREB*, NMDA receptor subunits, AMPA receptor subunits, *Bdnf*, and *Egr1*, among many others. Administration of suberoylanilide hydroxamic acid fails to further increase synaptic plasticity in HDAC2 knockout mice. Therefore, HDAC2 appears to be the major target of HDAC inhibitors in eliciting memory enhancement. This is in agreement with data demonstrating a role for HDAC2, but not HDAC1, in synaptic plasticity in adult hippocampal neurons (33,35).

Based on these observations, we propose that a dysregulation of chromatin remodeling may contribute to the cognitive impairments observed in neurodegenerative diseases of aging, such as AD. Either via the dysfunction of HDAC or histone acetyltransferase enzymes, chronic abnormalities in histone acetylation may lead to the aberrant expression of genes involved in learning and memory, synaptic plasticity, and synaptogenesis. Such dysregulation would effectively keep the brain in a "locked" or a frozen state, in which the probability of the activity-dependent expression of plasticity genes is reduced. These changes would explain the phenotype of cognitive impairment observed in neurodegenerative pathologies.

The Dentate Gyrus in Cognitive Aging: Is Histone Acetylation the Molecular Link?—S.A.S.

With age-related memory decline emerging as a cognitive epidemic, isolating underlying molecular mechanisms has become an urgent goal. Based on a broad series of findings, we hypothesize that "histone acetylation" is a molecular pathway mechanistically relevant to cognitive aging.

The Dentate Gyrus and Cognitive Aging

The frontal cortex and the hippocampal formation are two brain areas strongly implicated in age-related memory decline. Both are made up of distinct subregions, and pinpointing subregions differentially affected by aging can offer clues into the underlying pathogenic mechanisms of dysfunction. The hippocampal formation is made up of functionally distinct subregions—the entorhinal cortex, the dentate gyrus, the CA1 and CA3 pyramidal cell fields, and the subiculum. Recent studies have shown that each hippocampal subregion expresses a unique molecular profile, and this molecular anatomy can account for why individual subregions are differentially vulnerable to disease. Age-related hippocampal dysfunction is notable for an absence of neuron loss or other pathognomonic histological features. Because of this, in vivo techniques that assess the functional integrity of multiple hippocampal subregions are better suited for documenting differences in regional vulnerability to aging. Results from three in vivo techniques have implicated the dentate gyrus in cognitive aging: (a) high resolution functional magnetic resonance imaging studies applied to aging humans, rhesus monkeys, and rodents (36–38); (b) cognitive studies that have applied tasks differentially sensitive to CA3/dentate gyrus function (39,40); and (c) structural magnetic resonance imaging studies that have mapped the volume of multiple hippocampal subregions in aging humans (41,42).

The Aging Dentate Gyrus and Histone Acetylation

Histone acetylation epigenetically regulates transcription, and a number of studies suggest that the dentate gyrus differentially engages this pathway (43,44). We propose that "embryologic imprinting" might account for this observation. Specifically, available evidence indicates that regionally selective gene expression profiles in the adult brain are "imprinted" during embryogenesis (45), reflecting factors that regulate expression during periods of early brain development. One of the unique features of the dentate gyrus is that it supports neurogenesis late into development, even into the postnatal period (46). Histone acetylation is a molecular pathway critical for neuronal differentiation, and we hypothesize that the reason the adult dentate gyrus differentially engages this pathway is that it is imprinted early on, reflective of its neurogenic abilities. Taken together with recent evidence implicating histone acetylation in cognitive aging, we hypothesize that age-related defects in the histone acetylation pathway play an important role in age-related dentate gyrus dysfunction. This proposal suggests the following predictions and therapeutic implications:

Gene expression profiling.—According to the hypothesis, the aging dentate gyrus will manifest age-related changes in molecules that regulate histone acetylation. Future gene expression studies that harvest the aging dentate gyrus and other hippocampal subregions from postmortem human brain will be able to confirm or refute this hypothesis.

Therapeutic interventions.—According to the hypothesis, interventions that are known to ameliorate age-related hippocampal dysfunction will improve the function of the dentate gyrus and will do so by via the histone acetylation pathway. To date, there are two known interventions that

ameliorate age-related hippocampal dysfunction and have been shown by functional magnetic resonance imaging to differentially improve dentate gyrus function: physical exercise (47) and improving glucose control in diabetes mellitus (48). Future molecular studies will determine whether the improvement in dentate gyrus function is mediated by changes in the histone acetylation pathway.

Concluding Comments

Cognitive aging is a multifarious phenomenon, and its course is marked by significant individual differences. It seems improbable that this diversity arises from a small set of factors, and it is more likely that myriads of minor alterations in gene expression through modification of histones or miRNA regulation produce sizeable cumulative effects. Regionally and individually specific epigenetic tweaking on a normal genome by external stressors and pathogens could make the difference between a cognitively sound centenarian and a 60-year-old struggling with basic activities of daily living. The challenge is to identify the epigenetic pathways that enable cognitive vulnerability and to design individualized interventions that might undo or alleviate the damage. Alternatively, research aimed at understanding the basis of resilience in aging may reveal adaptive epigenetic strategies that can be exploited to promote optimally successful cognitive outcomes. At a minimum, identifying modifiable environmental triggers that alter chromatin configuration or miRNA activity may go a long way toward understanding age-related cognitive decline and designing remedial interventions. Expansion of epigenetic knowledge buttresses the understanding that decline does not begin at some magic senior moment but may stem from processes set in motion as early as the first step is taken away from cellular pluripotency toward specialization. Similarly, efforts aimed at stemming age-related deficits in cognition should not wait for overt clinical expressions of decline.

Research on epigenetic mechanisms of cognitive aging faces a number of obstacles. Key challenges are to identify the precise epigenetic changes linked to specific trajectories of cognitive decline, to determine the time scale of their influence, and to define how epigenetic mechanisms achieve specificity in the coordination of experience-dependent gene expression profile.

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