Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 June;69(S1):S17–S20
doi:10.1093/gerona/glu042

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Perspective

Epigenetics of Aging and Aging-related Disease

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Aging is associated with a wide range of human disorders, including cancer, diabetes, cardiovascular, and neurodegenerative diseases. Long thought to be an inexorable road toward decline and diseases, aging is in fact remarkably plastic. Such plasticity could be harnessed to approach age-related diseases from a novel perspective. Although many studies have focused on the genes that impact aging, the nongenetic regulation of aging is gaining increasing attention. Specifically, aging is associated with profound epigenetic changes, resulting in alterations of gene expression and disturbances in broad genome architecture and the epigenomic landscape. The potential reversibility of these epigenetic changes that occur as a hallmark of aging offers exciting opportunities to alter the trajectory of age-related diseases. This short review highlights key epigenetic players in the regulation of aging, as well as both future goals and challenges to the utilization of epigenetic strategies to delay and reverse the main diseases of aging.

Key Words: Epigenetic changes—Reversibility.

Received January 9, 2014; Accepted February 21, 2014

Decision Editor: Rafael de Cabo, PhD

THE main appeal of understanding the environmental nongenetic regulation of aging is to open new avenues for actionable interventions that could benefit the diseases of age. An example of nongenetic intervention that can delay age-dependent onset of diseases in most organisms is dietary restriction—the restriction in food intake without malnutrition (1). Arguably, one of the most intriguing aspects of the nongenetic control of aging is the possibility of aging "reversal" (2). For example, hallmarks of aging in muscle, brain, and heart can be reversed by heterochronic parabiosis (fusion of the blood circulation between an old animal and a young animal) (3). The changes to aging imparted by nongenetic factors appear to be relatively long lasting, suggesting that certain epigenetic mechanisms, which can be relatively stable in nature, are a pivotal component of this regulation.

Here, we define epigenetics liberally as "changes to the genome that do not involve changes in DNA sequence." These include chromatin, transcriptional networks, and noncoding RNAs (4). Hints and evidence for the epigenetic regulation of aging abound. For example, eusocial species, such as ants, honey bees, and naked mole rats, encompass "queens" and female "workers" that have nearly identical genomes, yet live very distinct life spans—with up to 10-fold difference in longevity. In humans, studies on identical twins who share the same genome yet have different life spans, exemplify this nongenetic component of human life span. In recent years, studies in many organisms have more directly implicated epigenetic changes in aging. First, aging is accompanied by changes in chromatin (eg, DNA methylation and histone modifications) and changes to coding and noncoding RNA profiles (5–11). Some of these epigenetic changes can be delayed by environmental factors known to influence aging. Importantly, studies in model organisms (eg, yeast, worms, and flies) have revealed the causative importance in life span of chromatin modifiers of histones and DNA, histones themselves, chromatin remodelers, transcriptional networks, and noncoding RNAs (12–17). Thus, aging is associated with profound changes in the epigenome, resulting in alterations of the gene expression, epigenetic landscape, and genome architecture. This review highlights how key epigenetic mechanisms affect aging and in turn impinge on the main diseases of aging: diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer.

Are Epigenetic Changes During Aging and Metabolic Diseases Preventable?

Epigenetic changes can affect genomic stability, which in turn underlies several common age-related diseases. David Sinclair (Harvard Medical School) discussed the link between epigenetic modifications and genomic

stability. A great example is the Sirtuin family of protein deacylases, which protects from several age-related diseases and extends the disease-free portion of life. Sirtuins deacetylate many substrates, including histones, and their activity is enhanced when the ratio between nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide dehydrogenase is high, thereby linking chromatin regulation to reduced food intake (dietary restriction) and exercise (18), two environmental interventions that delay aging. Recent evidence suggests that relocalization of Sirtuins in response to DNA damage may drive epigenetic changes and genomic instability during aging. Moreover, Sirtuins can be activated by small molecule activators (19–21) and by molecules that raise nicotinamide adenine dinucleotide levels (eg, nicotinamide adenine dinucleotide precursors). Some of these compounds mimic the effect of dietary restriction on genome-wide gene expression. These compounds represent an epigenetic interventional path to prevent and treat diseases of aging, thereby extending healthspan in humans (22).

Is There an Underlying Epigenetic Clock That Determines the Rate of Aging?

Age-dependent dysfunction in organs and tissues is particularly detrimental for vital organs such as heart and kidney. Stuart Kim (Stanford University) discussed how transcriptional networks become dysregulated during aging, using the worm *Caenorhabditis elegans* as a model system and human kidney as a test case for age-dependent organ failure. A key question regards the regulatory factors that control the rate of aging. Genome-wide expression studies have highlighted dramatic changes in gene expression that occur during aging (6,7,23,24). Coupled with the recent advent of ultra-high throughput sequencing technology, this work has enabled the identification of key transcription factors that can drive age-related transcriptional changes (25,26). An example is the GATA transcription factor family, whose expression declines with age. Resetting these transcription factors by overexpression remodels old worms to the young state, rejuvenates the aging transcriptome, and increases life span. In the kidney, some of these transcription factors are involved in inflammation and could represent a pivotal link between aging, inflammation, and age-dependent organ failure. These results identify novel transcriptional circuits that drive the aging processes in *C elegans* and human kidneys. Reversing the age-related changes of these key transcription factor networks could help "rejuvenate" the transcriptome of cells or tissues.

Cognitive Aging and Neurodegeneration: A Slope or an Epigenetic Switch?

As the population becomes older worldwide, a major social and economic problem is the striking exponential increase in the onset of neurodegenerative diseases. 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. Li-Huei Tsai (Massachusetts Institute of Technology) reviewed the impact of epigenetic factors on neurodegenerative diseases. Recent large-scale genome-wide analyses reveal that genes associated with synaptic plasticity are selectively reduced in the AD brain, whereas the expression of immune response and inflammation genes are significantly upregulated. Interestingly, 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. Thus, neurodegeneration is associated with targeted transcriptional dysfunction that corresponds to gradual locus-specific chromatin alterations that permanently impair synaptic plasticity. Provocatively, mouse models for neurodegeneration can recover lost memories when treated with inhibitors of histone deacetylases (27,28). Hence, these inhibitors are potential epigenetic therapies in the treatment of AD and may even be restorative for lost memories. Moreover, the histone deacetylase SIRT1 can prevent neurodegeneration, in particular in response to dietary restriction (29), cementing a burgeoning connection between AD and metabolic health. The restoration of locus-specific changes in chromatin dynamics using existing small molecule compounds may reverse the cognitive and pathological phenotypes of AD.

Could Age-dependent Chromatin Changes Be Responsible for the Age-dependency of Cancer?

The incidence of many cancers increases 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 life span also tend to suppress cancer. However, the reasons for this tight association between aging and cancer are largely unknown. For decades, an underlying assumption within the cancer field was 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, that is, wild type or mutant, expressed

or silenced. Peter Adams (Beatson Institute for Cancer Research) assessed the evidence in support of this idea and proposed that it is an insufficient explanation for age-associated increase in cancer. Dr. Adams proposed alternative models, in particular the possibility 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 (11,30). A better understanding of these areas is likely to be important for risk assessment, early detection, and chemoprevention of cancer.

Epigenetic Changes in Cellular Models for Progeroid Syndromes

Could cellular reprogramming to embryonic-like stem cells shed new light on the epigenetics of aging and diseases? The advent of reprogramming technology has allowed the generation of induced pluripotent stem cells (iPCs) from differentiated cells. This breakthrough has provided an exceptional opportunity for personalized regenerative medicine, which would be particularly impactful for diseases of age (31,32). Juan Carlos Izpisua Belmonte (Salk Institute) discussed the use of iPCs and embryonic stem cells to model progeroid syndromes such as Hutchinson–Gilford progeria and Werner syndrome. The derivation of iPCs from patients with Hutchinson–Gilford progeria syndrome has revealed that these cells show defects when redifferentiated into endothelial cells and the vasculature (33). iPC models for progeroid syndromes exhibit profound changes in the epigenome that may give insight into epigenetic changes that occur during normal aging. Importantly, these iPC models can in turn be used to screen for epigenetic therapeutics to improve the epigenomic and cellular defects associated with premature aging.

Conclusion

There needs to be a revolution in the way we treat age-related diseases. A central concept is that approaching the diseases of age through the lens of the aging clock rather than as disease-specific symptoms and phenotypes will provide fresh avenues for preventing and treating these diseases. The reversibility of epigenetic changes that occur as a hallmark of aging offers exciting opportunities for age-related diseases.

An important goal for the future will be to identify epigenetic drugs to reverse the epigenetic changes that occur as a hallmark of aging and diseases of aging. Several specific compounds that target enzymes responsible for epigenetic changes have been developed and are in the clinic or in clinical trials to be tested for several diseases of age, including cancer. A key challenge in this approach will be to develop additional drugs that specifically impact epigenetic pathways and test existing drugs in older animal models. A central question is whether these epigenetic drugs will have an effect on a constellation of age-related diseases that tend to cluster in older individuals. Thus, it will be important to test epigenetic drugs in several diseases of age.

In paving the way for epigenetic therapies, several challenges will need to be carefully considered. Given how many cellular processes are affected by epigenetic changes, one issue will be the specificity of targeting of epigenetic therapies by cell type or genomic loci. Another important consideration will be the balance between "rejuvenation" and tumor development in epigenetic therapies, as antidegenerative therapies could have pro-tumorigenic potential, and conversely, anticancer therapies may have degenerative effects on healthy cells.

A second goal will be to develop methods and technologies in which epigenetic changes can be used as accurate signatures for physiological age. Although the search for biomarkers of aging has been largely inconclusive, the breakthrough development of genome-wide ultra-high throughput parallel sequencing methods has in fact revealed that gene expression and chromatin signatures represent very accurate measurements of physiological age. Hence, a systematic examination is needed to fully assess the relationship between genome-wide epigenomics and aging in animal models and in human tissues. Such epigenetic signatures can then be exploited to test whether aging has been delayed and whether rejuvenation has occurred in response to therapeutics.

A key challenge will be to understand what aspect of these epigenomic signatures makes them most accurate to detect physiological versus chronological age, and, as mentioned previously, how they differ between tissues and cell types. Another crucial challenge will be to determine if certain signatures can be used in a more predictive manner than others.

Our broad perspective is that epigenetic changes are a fundamental response of the organism to short-term and long-term challenges. However, we fully appreciate that a major question in the aging field is the hierarchy of causality, as many cellular, tissue, and whole organism phenotypes are simultaneously altered during aging. Hence, a third future opportunity and challenge will be to understand how epigenetic alterations have long-range effects on age-related diseases and how they interact with other key pathways that play a fundamental role in the regulation of aging, including proteostasis and inflammation.

Funding

This study was funded by National Institutes of Health (National Institute on Aging; P01 AG036695 to A.B. and P01 AG031862 to S.L.B).

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