Is this environment making you older? Molecular biomarkers and new approaches to investigate the influences of environmental chemicals through aging

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ABSTRACT
Aging is characterized by a gradual and progressive decline in system integrity that occurs with advancing chronological age. Although it is a physiological process, aging is associated with a myriad of age-related diseases (ARDs), including frailty, sarcopenia, chronic obstructive pulmonary disease, cardiovascular disease, cancer, and neurodegenerative diseases. While not exclusively ARDs, many of these diseases lead to death, a lesser quality of life, and increased healthcare costs for individuals and systems. ARDs share several underlying molecular mechanisms, such as cellular damage, inflammation, DNA methylation changes, stem cells exhaustion, and DNA mutations, which have been outlined as hallmarks of aging. Evidence suggests that environmental exposures, including but not limited to metals, air pollution, endocrine-disrupting chemicals, and noise, may accelerate biological aging. Over the past few years, aging research has identified new molecular biomarkers of the aging process. When applied to investigate environmental influences, these biomarkers can help identify individuals who are particularly susceptible to the influences of environmental exposures on aging processes and therefore guide in implementing possible preventive measures.

INTRODUCTION
Aging is characterized by a gradual and progressive decline in system integrity that occurs with advancing chronological age (1, 2). The physiological changes that occur with aging contribute to a myriad of age-related syndromes including frailty and sarcopenia, and diseases (ARDs) such as chronic obstructive pulmonary, cardiovascular, cancer, and neurodegenerative diseases (3). These conditions account for a substantial population burden of disability and premature mortality. ARDs share several molecular mechanisms, including cellular damage (4), inflammation (5), epigenetic alterations (6), stem cells exhaustion (7), and DNA mutations (8), outlined as hallmarks of aging (9). Environmental exposures, including metals, air pollution, endocrine-disrupting chemicals, and noise, may affect these hallmarks, accelerating biological processes and leading to a reduction in lifespan, a
phenomenon called ‘age acceleration.’ While aging hallmarks themselves are challenging to measure in-vivo, researchers have recently identified several biomarkers thought to reflect the accumulation of changes in the hallmarks. These biomarkers measure the process of biological aging and can be applied to investigate the impacts of environmental exposures. Key applications include the detection of harmful effects, identifying individuals who are most susceptible or most severely affected, and evaluating the effectiveness of mitigation efforts, and therefore, guiding the implementation of possible preventive measures.

**Environment and Aging**

Available evidence suggests that all these hallmarks of aging are interrelated. External factors such as exposures to environmental chemicals, as well as behaviors (e.g., unhealthy diet and smoking), modify these molecular mechanisms, accelerate aging, and predispose to ARDs (10). It has been estimated that environmental causes impact up to 90% of human diseases (11). Air pollution is one of the most pervasive of these causes and accelerate ARDs such as cardiovascular and lung disease, bone damage (12, 13), cognitive decline (14), and cancer (15). Air pollution exposure modeling, which integrates data from different sources, including stationary air pollution monitors, point sources, traffic data, and satellite measures of aerosol optical density (e.g., MODerate resolution Imaging Spectroradiometer, MODIS) (16), has been applied to facilitate the determination of exposure in populations at risk. These technologies have helped us to refine effect estimates on human health. In a nationwide analysis of the United States between 1980 and 2010, hybrid approaches (i.e., land-use regression, traffic indicators, and Bayesian maximum entropy interpolation of land-use regression space-time residuals) were used to determine the levels of particulate matter $< 2.5 \, \mu m$ (PM$_{2.5}$) in 28 million adults from 3,034 counties, as well as the effect of the exposure and other common factors on exceptional aging (defined as reaching 85 years of age). We found that communities with the most exceptional aging showed low ambient air pollution and low rates of smoking, poverty, and obesity (17). These findings suggest several avenues of study to explore mechanisms by which environmentally-related factors may modify underlying biological mechanisms of aging, as well as the potential for this information to be used to reduce ARDs and promote healthy aging. To realize this potential, biomarkers are needed that can identify individuals with accelerated biological aging attributable to environmental exposures.

**Epigenetics as a Target and a Biomarker of Environmental-Related Damage**

Our team has been working with epigenetic modifications as an interface between the environment and human health. DNA methylation (DNAm) is one of the most well-studied epigenetic markers. It plays a critical role in several cellular processes, including gene regulation, imprinting, X-chromosome and retrotransposon silencing, and chromosome stability (18). DNAm is a chemical modification that occurs at carbon five in the CpG context (cytosine-phosphate-guanine) in mammalian organisms. Using some of the platforms showed in **Box 1**, we have demonstrated that air pollution may modify peripheral blood DNA methylation, affecting, among others, genes involved in mitochondrial oxidative energy metabolism (19), inflammation (i.e., ICAM-1) (20), and mitogen-activated protein kinase (MAPK) network (21). However, air pollution is not the only environmental exposure that may affect DNA methylation. Other studies have shown that pesticides (22), metals (23) and several other environmental toxicants may modify the epigenome (24). Machine learning methods now make it possible to use whole-genome DNAm data to model and measure exposure to environmental

**Box 1.** Epigenome-wide approaches to study DNA methylation in human population studies:

1. Illumina’s Infinium BeadChips (450K/850K methylation CpG sites).
2. Targeted methylation sequencing (3.3/5.5M methylation CpG sites).
3. Whole-genome bisulfite sequencing (28M methylation CpG sites).
toxicants. Our group recently used this approach to develop a fingerprint biomarker of chronic lead exposure (23). We have also constructed a minimally invasive lead biomarker based on 59 and 138 peripheral blood CpG sites, which could be used to reconstruct decades' worth of individual cumulative lead exposure. Remarkably, this same approach can be expanded to other environmental exposures. Ultimately, these DNAm models of toxicant exposure can catalyze development a new generation of environmental risk assessments. Because these models are all based on the same platform, a single assay will enable measurement of exposure to multiple different toxicants.

**Environmentally induced damage and acceleration of biological aging**

Human (and in general mammalian) chronological aging brings with biological changes that drive decline in system integrity, increasing risk for disease, disability, and mortality (25). Measures that quantify processes of biological aging—sometimes called biological clocks—include telomere length (26), transcriptomic age (27, 28) glycan age (29), among others (30), can detect differences in aging-related risks among individuals who are the same chronological age (31), suggesting that chronological age does not accurately reflect biological age, which may proceed at a different rate (32). The accurate determination of biological age and age acceleration using biological clocks offers the opportunity for early prevention of onset and progression of chronic diseases. Among these measures, DNA methylation clocks, particularly those described separately by Hannum (33) and Horvath (34), are among the most studied at present. These clocks are derived from machine learning analysis applied to epigenome-wide DNA methylation data. Clock-ages that are older than chronological ones indicate advanced biological aging and have been linked with increased risk for morbidity and mortality (35). Our team has recently demonstrated that clock ages are advanced in individuals with higher levels of exposure to environmental toxicants, as we found with exposure to particulate air pollution which resulted associated with age acceleration—measured through telomere shortening or accelerated DNA methylation age—in peripheral blood in older adults (36-38). We have also found that this difference between chronological age and DNA methylation age ($\Delta_{age}$) may predict mortality by any cause in older individuals (39), suggesting that individuals with higher levels of age acceleration will show early aging and early death (39). Additionally, we have reported that air pollution, in particular long-term PM$_{2.5}$, sulfate, and ammonium, are linked with particular changes in DNA methylation age (particularly sulfate and ammonium) (40). Evidence surrounding the role of other environmental factors that modify biological age and induce age acceleration is also available for metals (e.g., cadmium) and pesticides (e.g., organochlorides) (41).

DNA methylation changes can also be used to predict future risk of ARDs. A seminal work from our group evaluated more than 11,000+ individuals from longitudinal studies and found that methylation levels at 52 CpG sites are associated with two established ARDs: incident coronary heart disease (CHD) and myocardial infarction (42). These CpGs are related to calcium regulation ($\text{ATP2B2, CASR, GUCA1B, HPCAL1}$), serum calcium (CASR), serum calcium-related risk of CHD (CASR), coronary artery calcified plaque ($\text{PTPRN2}$), and kidney function ($\text{CDH23, HPCAL1}$), among others. These data suggest the possibility that blood DNA methylation may contribute to build-up predictive tools that forecast future development of ARDs (42). DNA methylation has also been associated with several other ARDs and age-related risk factors, including cancer, frailty, Parkinson's disease, and mortality (41).

**Other biological markers of environment-induced age acceleration and new directions**

An intensively growing area of current research is epitranscriptomics. While epigenetics corresponds to the study of chemical modifications to DNA, epitranscriptomics focuses on chemical changes to RNA (43). One of the most studied epitranscriptomic marks is N6-methyladenosine (m$^6$A), which is critical for gene regulation and is modulated by cellular stressors. This mark seems to be the most common epitranscriptomic modification on mRNA, with a presence in 0.1 to 0.4% of all adenines and 20-25%
Figure 1: Environmental exposures affect individuals during all life periods and are linked to changes in DNA sequence, epigenetics, and epitranscriptomics, creating exposure fingerprints. These lead to age acceleration and to an increased risk of age-related diseases.
of all transcripts. (44). In a recently published study, our team found that smoking may impact m^6A levels. We found that smoking was associated with a 10.7% reduction in m^6A in peripheral blood, compared with non-smokers (45). Black carbon, a marker of traffic-related air pollution, was associated with higher m^6A levels. Therefore, environmental exposures might generate several molecular changes that can be objectively measured in tissues DNA sequence, regulation, and expression, specifically affecting aging-related processes. Collectively, these molecular signs may help to detect risk of ARDs in time for preventive intervention.

Somatic mutations may also occur in response to environmental-related damage (46). These mutations accumulate in somatic cells during aging, and are referred to as a 'mutation burden' (47). Recent genomic analyses have revealed that the mutation burden in somatic tissues is directly linked with aging (48). Other studies have suggested that environmental exposures are major drivers of mutation load in somatic tissues, particularly in the lungs, suggesting that mutations and age acceleration might be associated with external exposures (49, 50). In fact, extensive evidence is available on the role of air pollutant-derived carcinogens (e.g., polycyclic aromatic hydrocarbons) in the generation of genetic mutations (51). Thus, the mutation burden in somatic cells could also be a strong predictor of biological aging and environmentally-induced cumulative damage in somatic tissues.

CONCLUSIONS

Environmental exposures modify our molecules in different ways that have the potential to be used as biomarkers of effect and early predictors of ARDs, including mutations, changes to DNA methylation, the epitranscriptome, and other molecules. These complex relationships between common environmental exposures, molecular changes, and age-related outcomes are shown in Figure 1. Current evidence suggests that at least some of these molecular changes can serve as novel biomarkers of cumulative, lifetime exogenous exposure, help capture environmentally-induced age-acceleration, and predict ARDs many years before their diagnosis. Blood-based DNA methylation fingerprinting of exogenous exposures can help identify priority areas for environmental interventions for individual persons. Precise information of age acceleration using molecular biomarkers could aid public health and clinical efforts to reduce effects of toxicants, particularly on ARDs. Additionally, the effect of potential age decelerators (e.g., physical activity, healthy diet, folates, etc.) could also be determined using environmentally-related molecular biomarkers. Molecular measures of accelerated aging may also provide surrogate endpoints to test effectiveness of interventions that aim to extend healthy lifespan by slowing biological processes of aging (52). Such measures could aid in efforts to mitigate health damage from environmental toxicants, serving as surrogate endpoints in studies evaluating impacts of programs and policies to mitigate environmental toxicant burden. More studies incorporating individuals from all life stages, in utero to old age, are needed to study molecular biomarkers and their potential interaction with aging and ARDs.

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