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Environmental Exposures, the Epigenome, and African American Women's Health

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Abstract Stress is a common feature of modern life, but both the extent of exposure to stressors and the downstream effects of these stress exposures can vary considerably among individuals, communities, and populations. When individuals are exposed to repeated or chronic stress, wear and tear on the body can accumulate and manifest in many ways. The term "allostatic load" represents the physiological consequences of repeated or chronic exposure to environmental stressors and is linked to fluctuating and/or heightened neural or neuroendocrine responses. African American women are one population subgroup that has been identified as potentially having both an elevated allostatic load and an enhanced resilience to external factors. One mechanism by which environmental stressors may impact human health is via epigenetic remodeling of the genome. This review will focus on what is known about how different types of environmental stressors may affect the epigenome and explore links between epigenetic reprogramming and altered allostatic load and resilience as it pertains to African American women's health.

Keywords Allostatic load · Epigenetics · Stress

Allostatic Load, Allostasis, and Resilience

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In 1993, the term allostatic load was defined as "the wear and tear on the body" that may accumulate for any given individual in response to repeated or chronic stress [1]. The concept of allostatic load emphasizes that there is often a hidden cost to the body when individuals experience prolonged periods of chronic stress, particularly with respect to the immune and cardiovascular systems. These costs are coupled with fluctuating physiologic and pathophysiologic processes in the body in response to stressors and can be modulated by the individual's behavioral responses to environmental challenges. Both the nervous system and the endocrine system play a key role in these responses, and the body can help to mediate the effects of the allostatic load by building up resilience to these exposures. Whereas the term homeostasis refers to the tendency of an individual or system to maintain a relatively stable equilibrium between interdependent elements, allostasis represents the process of adaptation that the body must undergo in order to maintain the equilibrium of the complex physiological responses to physical, psychosocial, and environmental challenges or stress. Maintaining allostasis is a complex process in the body with significant long-term implications. For example, the primary downstream hormones produced as a result of a stress response are cortisol and epinephrine (adrenaline). These are normal hormones in the body that are required for a wide range of normal physiological processes and which have beneficial effects on the body when carefully regulated. Unfortunately, for individuals and populations with a hyperactive stress response, allostasis is disrupted and the result in an overexertion of these

physiological systems. Stressors such as exposure to violence or trauma, poverty, war, hypoxia, or low socio-economic status, racism, and discrimination may all be associated with a hyperactive stress response, and with prolonged, elevated activation, both cortisol and epinephrine can have detrimental effects on the body such as promoting increased blood pressure and elevated heart rate.

The physiological responses involved in the stress response are widely considered to be adaptive, and this allows for the possibility that there are strategies individuals and populations can implement to enhance resilience and improve health outcomes in the face of a harmful allostatic load [2]. Resilience represents the ability of an individual to successfully maintain allostasis and effectively respond to both acute and chronic threats to survival across many species.

Environmental exposures and genetic predispositions begin in utero, and an additional research focused on regulatory mechanisms of specific changes in neural, neuroendocrine, and immune systems is needed to understand the relationship between allostatic load and human disease later in life. Successful research in allostatic load requires a reliable way to quantitate the cumulative effects of these external stressors. This work generally relies of a composite index of measures of cumulative strain on several key organs and tissues and commonly measures biomarkers associated with the relative health of the neuroendocrine, cardiovascular, nervous, immune, and metabolic systems [3]. Many of these measures are described in more detail throughout other manuscripts in this special issue. One challenge of this research is the diversity of biomarkers, both in terms of which biomarkers are used and the methodology by which they are assessed, resulting in different methods of assembling an allostatic load index. One of the most exciting new areas of research searching for potential biomarkers of allostatic load is the field of environmental epigenetics.

Environmental Epigenetics

Each cell in the human body contains approximately three billion base pairs of DNA (deoxyribonucleic acid). While the sequence of the human genome is inherited from parent to offspring and is identical in nearly every cell in the human body, the way that each cell interprets that chemical message varies widely, not only from cell to cell, but also within any given cell over time and in response to external stimuli. The term "epigenetics" translates as "above the genome" and refers to heritable chemical modifications to DNA that regulate the activity or expression of each gene within the genome. Like genetic changes, epigenetic changes can be passed down from cell to cell and from parent to offspring, and the sum total of these epigenetic modifications is referred to as the epigenome. Epigenetic changes are an essential component of normal development and are responsible for the differentiation of cells and tissues. The epigenome also changes as a part of normal aging, but abnormal changes to the epigenome can be key components of many human diseases including cancer and neurodegeneration. The epigenome can also be substantially changed in response to factors in the environment with both positive and negative consequences. Extensive research is being directed as part of the Roadmap Epigenomics Program, a trans-NIH program administered by the National Institute of Environmental Health Sciences (NIEHS) and other NIH Institutes and Centers. The goal is to understand how the epigenome responds to a wide range of different environmental exposures, the extent to which these changes may be directly linked to the initiation and progression of human disease, and to elucidate the mechanisms by which these changes can be passed down to future generations.

As mentioned above, epigenetics involves the study of heritable, reversible modifications that control gene function. Epigenetic changes generally fall into three main groups: (1) gain or loss of DNA methylation, (2) alterations in covalent histone modifications, and (3) alterations to RNA including changes in expression of microRNA (miRNA) and long non-coding RNA (lncRNA). Each of these epigenetic changes is described in more detail below.

DNA methylation is a common epigenetic modification in which a methyl group is added to the 5′ carbon in cytosine bases of DNA. DNA methylation most commonly occurs in the context of cytosine guanine dinucleotides (CpG), and this relatively stable mark was historically considered to be both heritable and generally permanent [4]. CpG dinucleotides are underrepresented across the mammalian genome, but are often found in dense regions of CpG dinucleotides called CpG Islands. CpG islands are generally defined as regions of DNA which are 200 base pairs in length or greater, contain a G/C content in excess of 55%, and have an observed/

expected ratio over 0.6. CpG islands are frequently found in non-coding repetitive elements throughout the genome and, in some cases, concentrated in the regulatory regions in the proximal promoter regions of protein-coding genes, 5′ to the transcription start site (TSS) [5]. In this context, they have been shown to have a regulatory function, facilitating the recruitment of transcriptional regulatory complexes and regulating RNA polymerase pausing. DNA methylation changes are frequently tissue-specific and are associated with normal development. For example, neural progenitor cells exhibit a strong correlation between DNA methylation and changes in histone modifications during neuronal differentiation [6]. While DNA methylation has long been acknowledged to be a normal feature of genomic organization, the disease-related importance of DNA methylation in the context of CpG islands first emerged within the context of cancer with the observation that hypermethylation of CpG island proximal promoter regions can lead to inactivation of tumor suppressor genes [7–10]. Gene expression is also affected by the absence or presence of DNA methylation at or adjacent to binding sites of transcription factors regardless of the presence of a CpG island and within regions up to 2000 or 4000 base pairs in CpG "shore" and "shelf" regions respectively [11–13]. These areas can be found both up and downstream of CpG islands.

DNA methylation is dynamic in the context of a single cell. Ten-eleven translocation (TET) enzymes hydroxylate the methyl group, ultimately leading to demethylation [14]. As part of the demethylation reaction, 5-methylcytosine (5-MC) is hydroxylated to form 5-hydroxymethylcytosine (5-HMC) and subsequently converted to a number of other intermediaries before being replaced with an un-methylated cytosine via base excision repair [15]. 5-HMC is by itself an important epigenetic modification associated with increased gene expression [16, 17]. 5-HMC levels are measurable and fluctuate in the brain during development and normal aging [18, 19]. Research is now beginning to assess the effect of environmental exposures/influences on changes in DNA methylation, including both 5-MC and 5-HMC, using molecular mechanisms that are relevant in terms of stress exposures, though these data remain somewhat limited. For example, researchers have demonstrated that restraining rodents in a physical restraint for a period of 30 min leads to both increases and decreases in 5-HMC in regions of the genome in the adult hippocampus [20].

DNA is packaged in a cell by winding around nucleosomes; protein octamers comprised of histones proteins. Histones have been shown to have highly modifiable tails that are subject to a range of covalent modifications including methylation, acetylation, ubiquitination, phosphorylation, and other modifications [21]. *Histone modifications* regulate nucleosome occupancy and define regions of chromatin as being either open, accessible euchromatin or closed, inaccessible heterochromatin. Histone modifications such as those on the lysine at position 4 of histone 3 (H3K4) have been extensively studied in terms of gene expression and are known to play an important role in differentiation, including in the developing brain. For example, dimethylation of H3K4 (H3K4me2) differentially and dynamically marks tissue-specific genes during the differentiation of progenitor cells in the mouse brain [22–24]. Histone tail modifications are dynamic regulators of gene transcription and can be altered in response to environmental cues or stressors.

Micro-RNAs (miRNA) are a subset of short noncoding RNA which bind target sequences in messenger RNA (mRNA) and inhibit translation of mRNA into protein. The production of miRNA involves a multistep enzymatic process and translocation from the nucleus [25]. The study of miRNAs is a growing field, and the details of how miRNAs regulate gene expression are continuing to emerge, but it is clear that miRNAs play a crucial role during development [26]. Similar to the other epigenetic modifications described above, environmental exposures have been shown to contribute to differential miRNA expression. For example, miRNAs have been shown to control neurobehavioral development and function in ethanol-exposed zebrafish [27].

Epigenetic Dysregulation and Chronic Stress

There is only a limited discussion of epigenetic dysregulation and allostatic load in the scientific literature. In 2015, Ramey et.al. published a model of preconception stress and resiliency pathways which emphasized the emerging evidence supporting the clinical importance of the preconception period in influencing pregnancy outcomes and child health [28]. This multi-level, transdisciplinary framework on maternal, paternal, and child health disparities was primarily derived using community-based participatory research conducted by

the NIH Community Child Health Network (CCHN) and highlighted major themes of stress and resilience within the context of families and communities. By building on what is known about the origins of lifelong health, epigenetics, and neighborhood and community influences on pregnancy outcome and family functioning, CCHN was able to overlay novel elements of the preconception/inter-conception period, role of fathers and the parental relationship, maternal allostatic load, resilience resources of parents, and local neighborhood and community level influences (e.g., employment, housing, education, healthcare, and stability of basic necessities) to consider new ways of thinking about how to improve health outcomes for future generations. While this model does contain some limitations with regard to the complexity and emphasizes the challenges of developing precise and sensitive biomarkers of resilience, it does provide a theoretical framework for future studies and highlights key areas of emphasis including a focus on epigenetic remodeling in the intrapartum period, an area of active interest of our group and others [29].

The importance of epigenetics and environmental exposures has been more closely tied to allostatic load in a conceptual model published in 2014 by Saban et.al. This model suggests that relationships among social context, early-life adversity, psychological stress, inflammation, adaptation, and epigenetic signature may contribute to the development of coronary heart disease (CHD) and ischemic stroke [30]. This research highlights the observation that African Americans (AA) experience greater social stressors than non-Hispanic Whites (NHW) including early-life adversity and traumatic early-life experiences and cumulative social stressors such as poverty, perceived discrimination, inadequate access to healthcare, neighborhood violence, subjective social status, and socioeconomic status [30, 31]. They hypothesize that these stressors directly contribute to known disparities in incidence and outcome for both CHD and stroke by inducing gene-specific epigenetic modifications that confer a pro-inflammatory epigenetic signature and mediate an enhanced pro-inflammatory state [30]. Biopsychosocial and other forms of environmental stress may incorporate hormonal changes and specifically disrupt normal signaling of the hypothalamic-pituitary-adrenal axis and immune system responsiveness and induce metabolic and neurodevelopmental maladaptation [32].

It is only within the last few years that we have had adequate tools to begin to assay for epigenetic changes in population-based, genome-wide studies in response to environmental stressors such as allostatic load. One of these tools, an epigenetic clock which utilizes DNA methylation changes to estimate the age of human tissues and cell types, was published by Horvath in 2013 [33]. This multi-tissue predictor of age was developed using 8000 samples from 82 Illumina DNA methylation array datasets, encompassing 51 healthy tissues and cell types, and has been used to estimate that cancer samples demonstrate significant age acceleration, particularly for tumors with mutations in steroid hormone receptors [33]. Interestingly, using this same methodology to determine epigenetic aging across ethnic groups, epigenetic aging rates were shown to be significantly associated with sex, race/ethnicity, and to a lesser extent CHD risk factors. African Americans were shown to have lower extrinsic epigenetic aging rates than Caucasians and Hispanics, but no differences were found for intrinsic measures [34]. This suggests that considering the differences in allostatic load predicted between these populations, African Americans may have a higher level of resilience and an enhanced ability to maintain allostasis. Additional studies from the same research team suggest that more recent evolutions of these epigenetic biomarkers of aging are useful predictors for a variety of human diseases including all-cause mortality, cancers, physical functioning, and Alzheimer's disease [35]. They find that epigenetic age biomarker signatures are informative regardless of cell or tissue type and are associated with increased activation of pro-inflammatory and interferon pathways and decreased activation of transcriptional/translational machinery, DNA damage response pathways, and mitochondrial signatures [35]. These links to inflammatory pathways, in particular, suggest that epigenetic age may also be a useful predictor of allostatic load, and the first studies directly testing this hypothesis in the context of racial disparities have now been published [36–38].

A 2016 study by Chen et.al. was designed to investigate potential relationships between cellular epigenetic aging and health disparities, macro-economic conditions, allostatic load, and self-reported health in African Americans [36]. This study, focused on the Great Recession of the late 2000s, comprised of a sample of 330 African American adolescents in Georgia who were followed from pre-recession (2007, M age = 16.6) to post-recession (2010, M age = 19.3). Study participants

were subdivided into three groups in order to represent economic trajectories across the period of the Great Recession (stable low economic hardship, downward mobility, and stable high economic hardship). Epigenetic aging was measured using Horvath's DNA methylation signature in white blood cells. The allostatic load was estimated based on a composite assay of blood pressure, C-reactive protein, cortisol, epinephrine, norepinephrine, and body mass index. Health outcomes were self-reported. The researchers concluded that the more time adolescents spent under economic hardship, the greater the extent of their epigenetic aging [estimate = 1.421, SE = 0.466, $p = .002$], allostatic load [estimate = 1.151, SE = 0.375, $p = .002$] scores, and the worse their self-report of health [estimate = 4.957, SE = 1.800, $p = .006$] [36]. Furthermore, when specific groups were compared, the results suggested that adolescents in the downward mobility group had higher levels of the allostatic load than adolescents in the stable low hardship group [$p < .05$]. While this is a relatively small population-based study, and the changes in health outcomes are self-reported and modest, this is the first study done specifically in African American youths that suggests that macro-economic conditions may induce measurable epigenetic changes early in life.

Additional data is beginning to emerge which may directly link alterations in key elements of allostatic load to modest changes in DNA methylation in African American individuals. In 2017, researchers showed that differential maternal DNA methylation is associated with higher levels of parenting stress in individuals with African ancestry [39]. This study focused on 74 mother-child dyads and identified 95 CpG sited which showed a statistically significant variation in maternal DNA methylation that could be linked to parenting stress. No significant differences were identified in child DNA methylation, but of the genes with differential DNA methylation in the mothers, poly (ADP-ribose) polymerase-1 (PARP-1) was highlighted due to its known role in the regulation of stress signaling. More recently, researchers have identified differential methylation that may be linked to perceived racial discrimination [40]. This data relies on a study of African American Women as part of the Intergenerational Impact of Genetic and Psychological Factors on Blood Pressure (InterGEN) study and explores potential links between experiences of racial discrimination and poor health outcomes. This study relies on measures of the Major Life Discrimination (MLD) and the Race-Related Events (RES) scales and utilized the 850K EPIC Illumina BeadChip to look for changes in DNA methylation. While no differential methylation was associated with changes on the RES scale, the investigators did identify 9 CpG dinucleotides which were differentially methylated based on measures on the MLD scale after controlling for age, smoking status, and cell composition (false discovery rate [FDR]-corrected $p < .05$) [40]. Genes with differential methylation have been shown to be associated with human disease (e.g., schizophrenia, bipolar disorder, and asthma), and the authors conclude that future studies are needed to understand potential links between epigenetic changes and health disparities in high-risk populations with high levels of psychosocial stress.

Interestingly, there is some data to suggest that a supportive family environment may be able to partially ameliorate the link between racial discrimination and epigenetic aging [41]. In a recent study of two independent cohorts of African American youth from rural Georgia, researchers measured perceived racial discrimination, supportive family environments, and confounding variables and measured these against patterns of DNA methylation in the peripheral blood measured as epigenetic aging. Results showed that among youth in supportive family environments, exposure to higher levels of racial discrimination did not forecast greater epigenetic aging, but exposure to higher levels of racial discrimination did forecast greater epigenetic aging for youths that were raised in less supportive family environments.

It should be noted that these are all very small population-based studies, and the DNA methylation changes that were identified are both limited and modest. They do provide, however, an experimental framework to justify larger population-based studies of allostatic load. Additional research is needed to extend these studies to larger populations and to investigate the underlying molecular mechanisms driving racial differences, ideally revealing the extent to which epigenetic remodeling may link the psychosocial environment to inflammation and disease risk and identifying novel biomarkers that can be used to assess risk, development, and progression of CHD/stroke and inform therapeutic strategies for vulnerable populations. This data is particularly intriguing considering that epigenetic changes have also been linked to health disparities and triple-negative breast cancer (TNBC) [37] and pre-term birth [38] in African American women.

Conclusion

With dramatic advances in technology to measure changes in the epigenome in recent years, we are on the cusp of an explosion in omics-level data designed to increase our understanding of the role that epigenetic remodeling plays in linking environmental stressors to human disease. These technological advances are well timed to allow us to extend these studies to address important questions regarding the molecular mechanisms responsible for mediating allostatic load and resilience in vulnerable populations, with an ultimate goal of developing effective intervention strategies to address health disparities and improve outcomes related to urban health.

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