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Epigenetics and Health Disparities

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Abstract

Purpose of review—African Americans disproportionately suffer from leading causes of morbidity and mortality including cardiovascular disease (CVD), cancer, and preterm birth. Disparities can arise from multiple social and environmental exposures, but how the human body responds to these exposures to result in pathophysiologic states is incompletely understood.

Recent findings—Epigenetic mechanisms, particularly DNA methylation, can be altered in response to exposures such as air pollution, psychosocial stress, and smoking. Each of these exposures has been linked to the above health states (CVD, cancer, and preterm birth) with striking racial disparities in exposure levels. DNA methylation patterns have also been shown to be associated with each of these health outcomes.

Summary—Whether DNA methylation mediates exposure-disease relationships and can help explain racial disparities in health is not known. However, because many environmental and adverse social exposures disproportionately affect minorities, understanding the role that epigenetics plays in the human response to these exposures that often result in disease, is critical to reducing disparities in morbidity and mortality.

Keywords

racial health disparities; epigenetics; epigenomics; DNA methylation; preterm birth; cardiovascular disease; breast cancer

Introduction

In the United States, health disparities continue to affect minority and disadvantaged groups leading to large inequities in morbidity and mortality. Despite improvements in health care

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Conflict of Interest

Alexis D. Vick and Heather H. Burris each declare no potential conflicts of interest.

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access,¹ African-Americans consistently have significantly worse health outcomes than white Americans (Table 1). Cardiovascular disease, hypertension, and death attributable to cardiovascular disease are all significantly more prevalent among African Americans compared to whites.² Cancer, the second leading cause of mortality of all Americans, is also marked by disparities. For example, African American women have both significantly higher risk of early-onset diagnoses (<50 years of age)³ and significantly higher mortality rates from breast cancer.⁴ Regarding pediatric health, disparities in preterm birth and low birthweight remain striking, with black infants having an almost 50% increased risk compared to white infants.⁵ Disparities in birth outcomes lead to a doubling of infant mortality in black vs. white infants.⁶ At birth, life expectancy is nearly four years shorter for African Americans compared to white Americans (75.2 years vs. 78.8 years, respectively).²

Common explanations for disparities in health include differences in socioeconomic status,⁷ education,⁸ stress and exposure to racism,^{9,10} as well as health behaviors including diet¹¹ and smoking.⁹ Environmental exposures including endocrine disrupting chemical exposures have also been put forth as contributing to disparities in health, particularly reproductive outcomes.¹² Recent studies have also explored whether differences in other toxic exposures such as air pollution may contribute to disparities.¹³ Although these studies highlight that exposures might contribute to disparities in health, *how* these exposures translate into differences in phenotype remains incompletely understood.

One potential mechanism by which differences in exposures, or differences in responses to exposures, lead to racial disparities in health is epigenetics. Epigenetics refers to differences in gene expression, in the absence of DNA sequence variation, resulting in varying phenotypes.¹⁴ Several epigenetic mechanisms have been described including modifications in transcription and translation by long non-coding RNAs, microRNAs, and histone modifications, but the best-studied in humans is DNA methylation. One of the reasons DNA methylation has been the focus of human epidemiologic studies is that DNA is more stable than RNA and chromatin. This makes collection, storage, and subsequent analysis more feasible on a large scale.¹⁵ DNA methylation can affect gene expression by adding a methyl group to a CpG site or a cytosine followed by a guanine (separated by a phosphate). Methylation typically results in obstruction of transcription of DNA into messenger RNA.¹⁴ DNA methylation does not always lead to down-regulation of transcription because methylation interacts with other regulatory mechanisms. However, if localized to a promoter region, DNA methylation is often associated with down-regulation of gene expression and can affect cellular function. If environmental factors affect DNA methylation, it follows that this may be one of the mechanisms by which the environment affects gene expression and then subsequent health and potentially its associated disparities.¹⁶

A few of the current, largest, unexplained health disparities in the United States include cardiovascular disease, breast cancer, and preterm birth. While distinct pathophysiologic states, these conditions share attributes that support the hypothesis that DNA methylation may mediate health disparities. First, within each of these disease states, African Americans have either a higher incidence or more severe disease presentation than whites (Table 1). Second, DNA methylation has been shown to be both associated with risk factors linked with each of these conditions as well as the health outcomes themselves. Therefore, it may

be inferred that a link exists between epigenetics and disparities in health. Many risk factors for adverse health outcomes differ between socioeconomic and racial/ethnic groups such as diet and exercise patterns¹⁷, exposure to stressors such as discrimination and violence¹⁸. In addition to environmental exposures, these factors may affect epigenetic regulation of gene expression^{19–21}, which may in-turn make disadvantaged groups more susceptible to the impact of environmental exposures. Because many environmental exposures disproportionately affect minorities, understanding how humans respond to these exposures, in addition to other exposures that often result in disease, is critical to preventing disparities in morbidity and mortality.

Differential exposures and DNA methylation

Air Pollution

Air pollution results from the combination of traffic and industrial emissions from fossil fuel combustion, as well as natural emissions, such as those from volcanoes and windstorms, that result in a mixture of gases and particulates that can effect health²². The gases known to adversely affect health include ozone, sulfur dioxide, nitrogen dioxide. Particulate matter refers to solid and liquid masses that are suspended in the air. Those that are less than 10 microns in diameter (PM₁₀) can penetrate the lower airways when inhaled and those less than 2.5 microns (PM_{2.5}) can cross penetrate the gas exchange respiratory epithelium.

Air pollution is associated with higher risks of not only asthma²³ and other upper airway diseases, but also CVD,²⁴ breast cancer,²⁵ and preterm birth.²⁶ African Americans typically are exposed to higher levels of ambient air pollution than whites, as they are more likely to be of low socioeconomic status and to live in dense urban centers.^{27–32} Higher exposure to air pollution has consistently been shown to be associated with DNA methylation changes.^{24,30,33,34} For example, Wang et al reported that per interquartile range increase (26.78µg/m³) in 24-hour exposure to fine particulate matter (PM_{2.5}), angiotensin-converting enzyme DNA methylation (%5mC) was 1.12% lower.²⁴ Breton et al recently found that first trimester prenatal exposure to multiple pollutants was associated with lower DNA methylation of a retrotransposon repetitive element found throughout the genome (long-interspersed nuclear element 1 [LINE1]) and that O₃ exposure later on in pregnancy was associated with higher LINE1 methylation levels.³³

Psychosocial Stress

Psychosocial stress can result from exposure to violence, discrimination, trauma and other negative life events.³⁵ Psychosocial stress has been shown to be a risk factor for many adverse health outcomes including hypertension,³⁶ breast cancer,³⁷ and preterm birth.³⁸ African-Americans often endure more psychosocial stress than whites due to circumstances such as life adversity, lower socioeconomic status, discrimination, neighborhood violence, and traumatic events such as abuse or family member incarceration.^{39,40} Psychosocial stress has been associated with DNA methylation as well.^{38,41} Associations between both pre- and post-natal psychosocial stress and DNA methylation have been observed. For example, Oberlander et al found an association between infants born to mothers that were depressed and/or anxious during their third trimester, and increased methylation of the glucocorticoid

receptor gene, *NR3C1*, and the nerve growth factor inducible protein-A (*NGFI-A*) binding site.²⁰ Increased *NR3C1* methylation was later associated with increased salivary cortisol responses at 3 months in the infants.²⁰ Furthermore, a few years later, DNA methylation of one particular CpG site of *NR3C1* to be significantly associated with prenatal stress as well.³⁸ Post-birth, psychosocial stress has also been shown to be associated with DNA methylation. Weaver et al researched the effects of stress on animal health. They found that nurturing maternal behaviors, such as licking and grooming, influence the development of offspring hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor expression via both increased histone acetylation and DNA methylation by transcription factor NGFI-A and increased hippocampal serotonergic tone.⁴² Cross-fostering experiments demonstrated that the maternal behaviors, as opposed to genetic factors, were responsible for DNA methylation changes in the offspring, suggesting that DNA methylation is modified by the social environment.³²

Smoking

Smoking causes a number of adverse health outcomes, including those with the highest disparities in morbidity and mortality rates in the US such as cardiovascular disease, cancer, and preterm birth. Although African Americans currently begin smoking at a later age and have similar rates of smoking (16.6% in non-Hispanic blacks vs. 16.8% in whites⁴³), African American smokers consistently have worse smoking-related disease outcomes (Table 1).⁴⁴ This is often referred to in the literature as the “African American smoking paradox.”⁴⁴ Epigenetic modifications, such as DNA methylation, may lead to a better understanding of this paradox.

Several studies have shown that smoking induces changes in DNA methylation patterns.^{45–47} Steenaard et. al measured methylation in the whole blood of 724 Dutch Caucasian adults and found 15 CpG sites significantly associated with coronary artery disease (CAD) genes.⁴⁵ Of these 15 sites, 12 had 1.2–2.4% decreased methylation and 3 had 1.2–1.8% increased methylation in smokers compared to subjects who had never smoked.⁴⁵ Joubert et al analyzed cord blood DNA methylation among infants born to mothers who smoked and found statistically significant associations between smoking and methylation of the aryl hydrocarbon receptor repressor (*AHRR*).⁴⁸ In adults, Philibert et. al studied 22 year old African American male smokers and found significant DNA demethylation at two distinct loci of *AHRR* that was not present in non-smokers.⁴⁹ Three years later, Philibert investigated the effects of DNA methylation in smoking cessation and found that those who were able to quit averaged a greater increase in DNA methylation (5.9% vs 2.8%) at *AHRR* than those who were unable to quit.⁴⁷ Of note the CpG that was most significantly altered was the same CpG site within *AHRR* that Joubert et al demonstrated to be differentially methylated among infants born to smoking vs. non-smoking mothers. A recent meta-analysis combining 13 birth cohorts the a total of 6,685 newborns, identified 6,073 CpGs with FDR significance, 568 of which also met the strict Bonferroni threshold for statistical significance with multiple comparisons (p value $< 1.08 \times 10^{-7}$). The top finding from this study was the same CpG site identified in the aforementioned studies, *AHRR* (MIM: 606517) cg05575921 (p value = 1.64×10^{-193})⁴⁸.

Health outcomes & DNA methylation

Cardiovascular Disease

The leading cause of death in the United States, heart disease,⁵⁰ along with hypertension, are both more common in African-Americans compared to whites. Cardiovascular disease has also been shown to be associated with differences in DNA methylation. Guarrera et al found differential methylation of the zinc finger and Broad complex, Tramtrak, Bric à brac (BTB) domain-containing protein 12 (*ZBTB12*) gene body and LINE-1 hypo-methylation in 291 cases of myocardial infarction vs. 292 controls from a large Italian European Prospective Investigation in to Cancer and Nutrition Study (EPICOR).⁵¹ Replication in a second cohort, demonstrated that including DNA methylation profile with other traditional CVD risk factors may improve risk prediction.⁵¹ CVD has also been associated with DNA methylation changes in response to a number of environmental factors, including air pollution. Recently, Zhong et. al analyzed the association between short-term fine particle (PM_{2.5}) exposure and adverse cardiac outcomes in 573 elderly men in the Boston-area repeatedly over 11 years.³⁴ They found that subjects who had higher *TLR2* methylation were more susceptible to the adverse cardiac autonomic effects caused by PM_{2.5} exposure.³⁴ Breton et. al utilized newborn bloodspots of 459 subjects of the Children's Health study to analyze the effects of prenatal pollutant exposure on LINE1 and another repetitive element, ALuYb8, DNA methylation levels, carotid intima-media thickness, and blood pressure.³³ They found that in-utero exposure to NO₂ in the third trimester of pregnancy was associated with higher systolic blood pressure at age 11 and O₃. Additionally, they reported that the air pollution-cardiovascular outcome associations were significantly modified by single nucleotide polymorphisms (SNPs) of two DNA methyltransferase enzyme genes (DNMT 1 and DNMT3b).³³ DNA methyltransferases are enzymes that methylate DNA. These findings suggest that DNA methylation may affect CVD risk and may explain differential risk to environmental risk factors for CVD.

Breast Cancer

The second leading cause of death in the United States is cancer and except for some types of skin cancer, breast cancer is the most common cancer among women.⁵⁰ African American women consistently have both significantly higher rates of early-onset diagnoses of breast cancer (<50 years of age) and significantly higher breast cancer mortality rates⁵² (Table 1). Differential methylation has been repeatedly established between cancerous and benign tissue.^{53,54} In a study of 65 breast tumor samples from the University of Maryland Medical Center and the Baltimore Veterans Administration, Wang et al demonstrated that women with early-onset disease had significant hypermethylation of the tumor suppressor gene, *CDH13*.⁵³ *CDH13* when inactivated, is associated with early onset breast cancer.⁵³ Grandin et al analyzed breast cancer samples provided by The Cancer Genome Atlas to discover that a substantial portion of human breast tumors demonstrate concurrent DNA methylation-dependent loss of expression of *NTN1* and the serine threonine kinase, *DAPK1*, which transduces the netrin-1 dependence receptor pro-apoptotic pathway.⁵⁵

Preterm Birth

A leading cause of infant mortality is preterm birth and its complications.⁵⁶ African Americans have an almost 50% increased risk of preterm birth compared to whites (Table 1). Recently, DNA methylation has been shown to be associated with preterm birth and gestational age. Several cross-sectional studies have demonstrated that neonatal DNA methylation is associated with gestational age at birth.^{57,58} Schroeder et al took samples from 259 neonates born to women with histories of neuropsychiatric disorders and 194 neonates of unaffected mothers.⁵⁹ They found an association between gestational age and CpG sites in 39 genes, of which were previously implicated in labor and delivery (e.g., *AVP*, *OXT*, *CRHBP* and *ESR1*). In a prospective birth cohort, Burris et al also demonstrated that maternal peripheral blood LINE-1 DNA methylation in the first trimester was negatively associated with the risk of preterm delivery.⁵⁷ In addition, in a target tissue more directly related to preterm birth, the cervix, Burris et al found an increase of 3.3 days in gestations for each interquartile range of the prostaglandin receptor 2 gene (*PTGER2*) DNA methylation.⁶⁰ They also reported shorter gestations were associated with increased methylation of LINE1.⁶⁰ These findings suggest that maternal DNA methylation status may predict the length of gestation.

Connecting DNA methylation to racial disparities in health

A limited number of studies have examined epigenetics as a potential link between differences in environmental exposures and health disparities. However, a few research teams have reported intriguing findings. Wang et al. found that women with early-onset breast cancer had significant hyper-methylation of the tumor suppressor gene, *CDH13*.⁵³ Moreover, they found other cancer-associated genes, *HIN-1*, *Twist*, *Cyclin D2*, *RASSF1A*, *RAR(Beta)2*, were also associated with increased mortality from breast cancer and *all* were more highly methylated in tumors of black women compared to those of white women.^{53,61} Additionally, Song et. al conducted a study of 61 white women and 22 black women and compared healthy breast tissue between the two groups.⁶² After analyzing methylation patterns of known promotor-related CpGs of cancer-associated genes, they found that 52% were hyper-methylated in white women compared to 27% in black women.⁵³ This evidence indicates that the increased risk of cancer among black women may be associated with epigenetics and its effects on transcription and translation. Furthermore, African Americans may be programmed early in life to have increased disease risk as they are born with significantly higher DNA methylation levels at loci involved in known cancer pathways compared to whites (13.7% vs. 2%).⁶³ Recently, Salihu et al. studied umbilical cord blood DNA methylation of several genes implicated in preterm birth from 22 black neonates and 69 non-black neonates and found differential DNA methylation among black vs. non-black infants in 2 of the 20 genes analyzed. In addition, the identified three CpG sites on 2 distinct genes (*TNF-α* and *PON1*) that were differentially methylated between black and non-black infants.⁶⁴

In contrast, many studies link epigenetics to exposures or outcomes, but do not focus on differences in DNA methylation by race in the analyses. For example, in the aforementioned study, Zhong et al studied 575 men over 60 years of age and found that after higher short-

term fine particle (PM_{2.5}) exposure, men had reduced heart rate variability.³⁴ Within their results, they reported that non-white participants were both more highly exposed to PM_{2.5} (0.2 µg/m³ higher mean exposure) and had lower *TLR2* methylation (2.8 vs. 3.0 %5mC), but differences by race/ethnicity were not explored in the discussion.

Often epigenetics is cited as a potential mediator between exposure and outcomes but is not formally explored. For example, Hu et al reported that of all the female breast cancer cases (255,128) in the California Surveillance Epidemiology and End Results Cancer data, adults exposed to higher levels of PM₁₀ and PM_{2.5} had a significantly shorter survival from breast cancer than those living in lower exposure areas.⁶⁵ Their findings also revealed blacks had higher PM_{2.5} exposure (>15.04ug/m³) compared to whites (41.9% vs. 33.1%) as did those who lived in highly urbanized areas (51.7%) compared to lower urbanized areas (30.65%).⁶⁵ Furthermore, black females had nearly double the unadjusted hazard ratio (HR) for death due to breast cancer compared to white females (HR 1.9, 95% CI 1.8–2.0)). Even after adjustment for confounding variables and air pollution exposure, black women still higher death rates from breast cancer (adjusted HR 1.6, 95% CI 1.5, 1.7).⁶⁵ The extent to which air pollution may have mediated disparities in breast cancer death rate disparities was not quantified. The authors also mention that DNA methylation may also play a role, but it was not measured in this study.⁶⁵ These important studies lay the foundation for work to be done linking the environment, epigenetics and racial disparities in health.

There is at least one study that simultaneously addressed all three topics of race, DNA methylation, and environmental exposures.⁶⁶ Sun et al. studied smoking-associated DNA methylation in African Americans and whites and found that DNA methylation sites most associated with smoking were similar between the two groups.⁶⁶ Whether other exposures will have similar associations with DNA methylation between groups has not been explored. Furthermore, with higher levels of adverse social and environmental exposures among African Americans, DNA methylation may still mediate, if not moderate, differences in health by race.

In conclusion, the literature thus far suggests that prospective, adequately powered studies are warranted to discover the role that epigenetics plays in contributing to the currently intractable racial disparities in morbidity and mortality in the United States. This has become a priority for the National Institutes of Health and specifically the National Institute of Minority Health and Health Disparities (NIMHD), which recently released a social epigenomics Funding Opportunity Announcement to do just that (PAR-16-355 and PAR-16-356, http://grants.nih.gov/grants/guide/pa-files/PAR-16-355.html?utm_medium=email&utm_source=govdelivery). Understanding mechanisms underlying racial disparities in health and disease can help to validate the science underlying disparities in health that may come from more than simply personal life-style choices. The recognition that society at large is at least partially responsible for disparities in health may lead to the prioritization of programs and policies focused specifically on reducing toxic exposures in disadvantaged groups.

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Table 1

Black-white health disparities in the United States

Outcome	Black	White
Life expectancy (years) ⁵⁰	75.6	79.0
Cardiovascular disease (%) ⁶⁷	47.2	34.1
Hypertension prevalence (%) ⁶⁷	42.1	28.0
Breast cancer (age-adjusted rate per 100,000) ⁵²	122.9	124.4
Breast cancer mortality (age-adjusted rate per 100,000) ⁵²	28.2	20.3
Preterm birth rate (%) ⁵	13.2	8.9
Low birth weight (%) ⁵	13.2	7.0
Infant mortality rate (per 1,000) ⁶	11.1	5.1