COMMENTARIES

COMMENTARY: RACE AND PRETERM BIRTH-THE CASE FOR EPIGENETIC INQUIRY

Heather H. Burris, MD, MPH; James W. Collins, Jr, MD, MPH

Preterm birth and infant mortality disproportionately affect African American families compared to White families. More than 18% of African American infants are born preterm (<37 weeks' gestation) compared to just less than 12% of White infants. Consequently, African American infants are twice as likely to die in their first year of life as White infants. Differences in socioeconomic status, prenatal care usage, and behavioral characteristics fail to explain the disparity in preterm birth between African Americans and Whites. Epidemiologic data support a life-course conceptual model for African American women's pregnancy disadvantage. Life-course factors influence pregnancy outcomes through two proposed mechanisms: early-life (fetal) programming of reproductive potential and cumulative wear and tear (weathering). The biologic mechanisms behind this theory are poorly understood. In this commentary, we argue that epigenetic inquiry represents the next frontier in investigating the mechanisms underlying racial disparities in birth outcome. We propose this with the hope that these discoveries will lead to opportunities for interventions and ultimate improvements in birth outcomes. (*Ethn Dis*. 2010;20:296–299)

Key Words: Race, Preterm birth, Epigenetic Processes, DNA methylation, Ethnicity, Infant Mortality, Minority Health

From the Department of Neonatology, Beth Israel Deaconess Medical Center, Division of Newborn Medicine, Harvard Medical School (HHB); Department of Neonatology, Children's Memorial Hospital, Northwestern University's Feinberg School of Medicine (JWC).

Address correspondence to Heather H. Burris, MD, MPH; 330 Brookline Avenue RO 318; Boston, MA 02215; 617-667-3276; 617-667-7040; heburris@bidmc.harvard.edu

INTRODUCTION

In the United States, preterm birth and infant mortality disproportionately affect African American families compared to White families. In 2006, 18.5% of African American infants were born preterm (<37 weeks) vs just 11.7% of White infants.[1] In 2005, the infant mortality rate for African American infants was 13.6/1,000 live-births compared to just 5.8/1,000 for White infants.[2] These racial disparities remain independent of maternal education attainment,[3] adequacy of prenatal care utilization,[4,5] and behavioral characteristics.[6] An extensive epidemiologic literature strongly suggests that genetic factors also fail to explain the racial disparity in birth outcomes.[7,8] In an attempt to encapsulate all of the known risk factors for preterm birth, the life-course hypothesis proposes that the accumulation of events over a woman's lifetime affects birth outcomes.[9] Consistent with this hypothesis, an expanding literature shows that African American women's life-time exposure to interpersonal racial discrimination and neighborhood poverty are risk factors for preterm birth.[10–12] The biological mechanisms underlying these associations remain poorly understood.

Since race is a social construct strongly associated with birth outcomes, the different rates of gene expression as opposed to variation in genotype is likely to explain reproductive health disparities.[7,13] Cultural phenomena such as residential and educational segregation can lead to differential social and environmental exposures, dietary practices, and physical activities that may lead to changes in gene expression resulting in different rates of preterm birth between the races. In this paper, we argue that epigenetic (ie, gene-environment interactions) mechanisms will improve our understanding of racial disparities in the rate of preterm birth and consequent infant mortality, and propose that now is the time to translate what has been learned from the laboratory and the agouti mouse, into the realm of human cohort studies.

In 2006, 18.5% of African American infants were born preterm (<37 weeks) vs just 11.7% of White infants.[1]

EPIGENETICS

Epigenetics is the study of changes in phenotype or gene expression caused by mechanisms other than alterations in the underlying nucleotide sequence.[14] Histone modifications and micro-RNA variations are two of the three primary mechanisms by which epigenetic variation affect gene express. However, DNA methlyation is the best-studied and best-understood mechanism and for this reason it will serve as a model of epigenetics for the remainder of this paper. DNA methylation involves adding methyl groups, or a carbon and three hydrogens, to DNA through a chemical bond. These connections occur in areas of the DNA rich in "CpG" islands where there are many cytosines followed by guanines linked by a phosphodiester bond.[15] CpG islands reside in the promoter region of some genes and when the promoter is highly methylated, gen-

erally there is a decreased rate of gene transcription, decreased subsequent translation, and a decreased production of the resultant protein. In other words, highly methylated promoter regions serve as gene silencers. Conversely, hypomethylated promoter regions typically precede actively transcribed genes resulting in more of the specific protein coded for by that gene. This variation occurs in the absence of alteration of the gene sequence. The degree of methylation simply affects how easily the enzymes that transcribe the genes can do their job.

Determining the factors that affect methylation, subsequent gene transcription and downstream phenotype could help explain why individuals with similar genotype can have such different biological outcomes. If some of the well-known social determinants of health (socioeconomic status, race/ethnicity, education, violence, experiences of racism, health behaviors including dietary practices, environmental exposures, etc.), which are notoriously difficult to capture completely in epidemiologic inquiries, are found to affect the degree of DNA methylation and differences in phenotype, then one of the mysteries of the gene-environment interactions could be solved.

THE AGOUTI MOUSE

Dietary differences represent the most direct way that behaviors might affect DNA methylation. The agouti mouse model provides a compelling case for how this might work.[16] The agouti mouse (A^{vy}/a) litters vary in coat color distribution depending on the degree of DNA methylation occurring in the promoter region of a particular allele in the genome called the A^{vy} allele. If the promoter is highly methylated, then the mouse is brown, lean, and more resistant to cancer.[17] If the promoter region is less methylated, then the mice tend to have coats that are more yellow, to be obese and more susceptible to cancer. If the dams (mothers) are supplemented with methyl-donors such as folic acid in the periconceptional period and throughout pregnancy and lactation, the phenotypic distribution of the litter becomes shifted toward the healthier brown mice that live longer, healthier lives compared to their yellow littermates. All of this variation occurs in mice that are genotypically identical.

Additional exciting work has shown that susceptibility to environmental toxins can be affected by availability of methyl-donors.[14] For example, adequate dietary supplementation with folic acid has been shown in the laboratory to negate the negative impact of bisphenol-A (BPA).[18] BPA is an endocrine disrupter that, when given to the same agouti dams described above, causes hypomethylation of the promoter region of the A^{vy} allele in the offspring and shifts the coat color distribution toward yellow and results in more mice with increased adiposity, insulin resistance, and prone to tumors. If these same dams are exposed to both BPA and adequate methyl-donors (folic acid), the same promoter region is more highly methylated, shifting the coat color distribution and phenotype toward the brown, healthier mice.

FOLIC ACID DISPARITIES

Whether intrauterine exposures to both toxins and beneficial dietary supplements can alter phenotypes through epigenetic mechanisms has not yet been explored in human cohorts. However, there is some indirect evidence that DNA methylation may play a role in the disparities seen in preterm birth. First, in the United States, it is has been shown that Black women take periconceptional folic acid and multivitamin supplements less often than their White counterparts.[19,20] Furthermore, based on data from the US National Health and Nutrition Examinations Surveys (NHANES), overall dietary intake of folic acid is lower in Black non-pregnant women of childbearing age (147 mcg) compared to White women (253 mcg).[21] Furthermore, even in the post-fortification era of folic acid in our food supply, folic acid levels in red blood cells remain lower in African American subjects than in White subjects.[22] Lastly, it has been shown in observational work that folic acid and multivitamin supplementation may decrease the risk of preterm birth and lower the risk of poor fetal growth,[23–25] especially in Black infants.[20] This evidence suggests that it is plausible that the lower availability of dietary methyl donors (folic acid) may play a role in racial disparities in preterm birth through differential DNA methylation.

TRANSGENERATIONAL EFFECTS

Transgenerational effects epitomize epigenetic mechanisms. The ''epigenome'' or pattern of DNA methylation is laid down during early fetal life and may determine later health status.[26] One later health outcome is the development of preterm labor. Preterm birth can result because of fetal or maternal factors. Thus, if preterm birth is caused at all by epigenetics, the pregnant mother's own in-utero environment, when she was a fetus decades prior to her pregnancy, might have set her epigenetic profile. Unidentified genes might have been activated or deactivated by epigenetic mechanisms during a woman's own fetal life that later contribute to the development of preterm labor when she, herself, is pregnant. If this were the case, then a grandmother's experiences during pregnancy would affect her daughter's physiology when she is pregnant with a grandchild. The Barker hypothesis states that much of an adult's health is programmed during his or her experience as a fetus and in early childhood.[27] This phenomenon has been demonstrated in a three generation linked dataset of African Americans in Illinois.[28] Rates of low birthweight were

associated with worsening maternal grandmothers' residential environments during her pregnancy with her daughter that years later delivered a low birthweight neonate. This association was independent of the living conditions of the daughter during her pregnancy with the infant with low birthweight. This transgenerational effect supports the notion that epigenetic mechanisms are likely to play a role in the pathophysiology of preterm labor.

DISCUSSION

With complex disease processes like preterm birth, it is unlikely that any one particular gene or promoter region of a gene would be analogous the A^{vy} locus of the agouti mouse model. However, it is possible that a group of genes could be affected by methyl-donor status and that a mother's diet, toxin exposures, stress, and other factors could be altering gene expression and subsequent proteins that could make the mother more or less susceptible to known triggers of preterm birth. Infection is one of those triggers. While it is known that bacterial vaginosis is a risk factor for preterm birth, not every pregnant women who is exposed to bacterial vaginosis delivers early.[29] It is possible that epigenetic mechanisms will explain differences in physiologic responses to infectious agents, leading to some women becoming colonized with certain pathogens while also explaining why, among women who become colonized, some develop preterm labor and others do not.

…it is possible that a group of genes could be affected by methyl-donor status and that a mother's diet, toxin exposures, stress, and other factors could be altering gene expression and subsequent proteins that could make the mother more or less susceptible to known triggers of preterm birth.

Investigation into epigenetic mechanisms may improve our understanding of African American women's pregnancy outcome disadvantage. The agouti mouse model demonstrates that maternal dietary intake of methyl donors, such as folic acid, affect the coat color and subsequent health status of her offspring. The phenotypic shift from yellow, obese, insulin resistant, and tumor prone mice toward brown, healthier mice in genetically identical offspring through increased DNA methylation represents an exciting model for how genetically similar individuals can differ from one another based on different environmental exposures. While there is an abundance of evidence that there is no genetic basis of the racial disparities in preterm birth, examining this model begs the question of whether the different life events, stressors, environmental exposures, and socially patterned behaviors that are all linked to preterm birth may work through differential DNA methylation or through other epigenetic mechanisms. The time has come to begin this line of investigation.

ACKNOWLEDGMENTS

Many thanks to the Harvard Pediatric Health Services Fellowship Program; the AHRQ T32 HS000063 training grant; the Harvard Neonatal-Perinatal Medicine Fellowship Program, and the Beth Israel Deaconess Medical Center Department of Neonatology. Funding for this research was supported by a grant from the March of Dimes (12-FY04-45 and 12-FY09-159).

REFERENCES

1. Martin JA HB, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Matthews TJ. Births: final data for 2006. *National Vital Statistics Reports*. 2009;57(7).
2. Centers for Disease Control and Prevention and the National Center for Health Statistics. http://205.207.175.93/VitalStats/TableViewer/tableView.aspx. Accessed May 8, 2009.
3. Schoendorf KC, Hogue CJ, Kleinman JC, Rowley D. Mortality among infants of black as compared with white college-educated parents. *N Engl J Med*. 1992;326(23): 1522–1526.
4. Barfield WD, Wise PH, Rust FP, Rust KJ, Gould JB, Gortmaker SL. Racial disparities in outcomes of military and civilian births in California. *Arch Pediatr Adolesc Med*. 1996; 150(10):1062–1067.
5. Murray JL, Bernfield M. The differential effect of prenatal care on the incidence of low birth weight among blacks and whites in a prepaid health care plan. *N Engl J Med*. 1988;319(21): 1385–1391.
6. Colen CG, Geronimus AT, Bound J, James SA. Maternal upward socioeconomic mobility and black-white disparities in infant birthweight. *Am J Public Health*. 2006;96(11): 2032–2039.
7. David R, Collins J, Jr. Disparities in infant mortality: what's genetics got to do with it? *Am J Public Health*. 2007;97(7):1191–1197.
8. David RJ, Collins JW, Jr. Differing birth weight among infants of U.S.-born blacks, African-born blacks, and U.S.-born whites. *N Engl J Med*. 1997;337(17):1209–1214.
9. Lu MC, Halfon N. Racial and ethnic disparities in birth outcomes: a life-course perspective. *Matern Child Health J*. 2003;7(1): 13–30.
10. Rich-Edwards J, Krieger N, Majzoub J, Zierler S, Lieberman E, Gillman M. Maternal experiences of racism and violence as predictors of preterm birth: rationale and study design. *Paediatr Perinat Epidemiol*. 2001;15 Suppl 2:124–135.
11. Collins JW, Jr., David RJ, Handler A, Wall S, Andes S. Very low birthweight in African American infants: the role of maternal exposure to interpersonal racial discrimination. *Am J Public Health*. 2004;94(12): 2132–2138.
12. Collins JW, Jr., Wambach J, David RJ, Rankin KM. Women's lifelong exposure to neighborhood poverty and low birth weight: a population-based study. *Matern Child Health J*. 2009;13(3):326–333.
13. Goodman AH. Why genes don't count (for racial differences in health). *Am J Public Health*. 2000;90(11):1699–1702.
14. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr*. 2009;21(2):243–251.
15. Kuzawa CW, Sweet E. Epigenetics and the embodiment of race: developmental

origins of US racial disparities in cardiovascular health. *Am J Hum Biol*. 2009;21(1): 2–15.

16. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol*. 2003;23(15):5293–5300.
17. Dolinoy DC. The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. *Nutr Rev*. 2008;66 Suppl 1:S7–11.
18. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci U S A*. 2007; 104(32):13056–13061.
19. Vahratian A, Siega-Riz AM, Savitz DA, Thorp JM, Jr. Multivitamin use and the risk of preterm birth. *Am J Epidemiol*. 2004;160(9): 886–892.
20. Burris HH, Mitchell AA, Werler MM. Periconceptional multivitamin use and infant birth weight disparities. *Ann Epidemiol*, 20(3): 233–240.
21. Yang QH, Carter HK, Mulinare J, Berry RJ, Friedman JM, Erickson JD. Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: findings from the National Health and Nutrition Examination Survey, 2001–2002. *Am J Clin Nutr*. 2007;85(5): 1409–1416.
22. Dowd JB, Aiello AE. Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? *Int J Epidemiol*. 2008;37(5):1059–1066.
23. Petrou S, Sach T, Davidson L. The long-term costs of preterm birth and low birth weight: results of a systematic review. *Child Care Health Dev*. 2001;27(2):97–115.
24. Scholl TO, Hediger ML, Schall JI, Khoo CS, Fischer RL. Dietary and serum folate: their influence on the outcome of pregnancy. *Am J Clin Nutr*. 1996;63(4):520–525.
25. Catov JM, Bodnar LM, Ness RB, Markovic N, Roberts JM. Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. *Am J Epidemiol*. 2007;166(3):296–303.
26. Waterland RA. Early environmental effects on epigenetic regulation in humans. *Epigenetics*. 2009;4(8):523–525.
27. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*. 1986;1(8489):1077–1081.
28. Collins JW, Jr., David RJ, Rankin KM, Desireddi JR. Transgenerational effect of neighborhood poverty on low birth weight among African Americans in Cook County, Illinois. *Am J Epidemiol*. 2009;169(6): 712–717.
29. Hitti J, Nugent R, Boutain D, Gardella C, Hillier SL, Eschenbach DA. Racial disparity in risk of preterm birth associated with lower genital tract infection. *Paediatr Perinat Epidemiol*. 2007;21(4):330–337.