The Hispanic Paradox Unraveled?

How wonderful that we have met with a paradox. Now we have some hope of making progress.—Niels Bohr

Chronic obstructive pulmonary disease (COPD) has recently risen to the third leading cause of death in the United States (1). While a wealth of important studies work to identify populations at risk for the development and progression of COPD, current research falls short in evaluating a group that is potentially *protected* from development of COPD: the U.S. Hispanic population. Hispanics, the fastest growing minority in the United States (2), have a heterogeneous ethnic ancestry comprised of American Indian, European, and African origin. Despite being the largest U.S. minority, Hispanics have traditionally fallen outside the scope of COPD clinical trials because of the relatively low prevalence of COPD and challenges of recruitment in this population. Ironically, it is these exclusions that may have delayed the understanding of genetic factors associated with protection against COPD development and progression, a key step in our understanding of the underlying susceptibility to COPD.

As early as 1969, it was recognized that U.S. Hispanics were using psychiatric resources at rates much lower than other minority groups (3). After reviewing additional clinical outcomes, including infant mortality and cardiovascular disease, Markides and Coreil codified the term “Hispanic paradox” to characterize the observation that health outcomes in U.S. Hispanics were more comparable to non-Hispanic whites than to African Americans, despite lower socioeconomic indices (4). The Hispanic paradox has been shown to apply to COPD. Samet and colleagues demonstrated that New Mexico Hispanics have reduced risk of physician-diagnosed COPD and chronic airflow obstruction compared with non-Hispanic whites (5). In addition, while the age-adjusted mortality for COPD increased in Hispanics from 1958 to 1982, the annual rates of death were lower than those for non-Hispanic whites for each year studied (6). Recently, the PLATINO study evaluated the prevalence of COPD in five Latin cities, finding the lowest prevalence in Mexico City, consistent with the Hispanic paradox (7). Theories explaining the better clinical outcomes in Hispanics include differential smoking habits (5), the effects of altitude on lung growth (7), a healthy immigrant effect (disproportionate migration of individuals with good health), and the “salmon bias” (less healthy Hispanics may return home where they die) (8). Although the etiology and validity of the Hispanic paradox remains unclear, the epidemiological literature suggests that Hispanics have improved COPD outcomes.

In this issue of the *Journal*, Bruse and colleagues (pp. 1254–1260) expand our understanding of the ethnic and genetic factors related to COPD prevalence and disease progression in Hispanic smokers (9). They accomplish this by examining nearly 2,000 participants of the Lovelace Smokers’ Cohort, a community-based longitudinal cohort of former and current smokers in Albuquerque, New Mexico. With these data, the risk of spirometry-defined COPD and risk of rapid decline in the forced expiratory volume in one second (FEV₁) is compared between Hispanic and non-Hispanic white smokers. Importantly, the authors use ancestry informative markers in addition to self-reported ethnicity to determine the relative effect of Native American ancestry on spirometric outcomes. At baseline, Hispanics were slightly younger and less likely to have a high school education than non-Hispanic whites. Smoking habits also differed between the ethnic groups, with Hispanics having more current smokers (77 versus 54%; $P < 0.001$), lower cumulative

pack-years (34 versus 41; $P < 0.001$), and fewer packs smoked per day (1.10 versus 1.24; $P < 0.001$). After adjustment for relevant covariates, self-reported Hispanic ethnicity was associated with a 51% reduction in the odds of COPD compared with non-Hispanic whites (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.35–0.71). Hispanic ethnicity was also associated with a reduction in the odds of rapid ($> 3\%$ per year) decline in FEV₁ (OR, 0.48; 95% CI, 0.30–0.78). These findings persisted in models that adjusted for various measures of smoking intensity and duration. When exploring ancestry informative markers to define ethnicity, Hispanics in this cohort were composed of nearly 2/3 European markers and 1/3 American Indian markers. Higher American Indian ancestry was associated with a reduced odds of COPD (OR, 0.47; 95% CI, 0.33–0.69; $P < 0.001$) and rapid decline in FEV₁ (OR, 0.51; 95% CI, 0.32–0.83).

So how do these data contribute to unraveling the Hispanic paradox? First, the protective effect of Hispanic ethnicity does not appear to be solely related to smoking behavior in this cohort. The authors are to be commended for their multiple efforts to adjust for the effects of smoking. While it is always impossible to adjust for all potential confounders, it is reassuring that the reduced association between Hispanic ethnicity and COPD outcomes was resilient to several different models of smoking. Second, by defining ethnicity with ancestry informative markers, the authors have provided a more rigorous characterization of the relationship between COPD outcomes and specific genetic ancestry in Hispanics. The authors’ approach successfully quantifies the inherently qualitative and complicated concept of ethnicity. Finally, this report highlights the need to consider other populations of study in COPD. The Hispanic population is particularly understudied in COPD trials. To understand the factors related to disease susceptibility, populations protected from the disease should be evaluated just as rigorously as those known to be vulnerable to the disease. It is important that future population-based studies evaluating the genetic basis of COPD include Hispanics, as protective alleles may be more readily identified in this population. Ultimately, studies of the Hispanic paradox like this one may help to clarify our understanding of the paradoxes of COPD. Fortunately, we have some hope of making progress.

Author disclosures are available with the text of this article at www.atsjournals.org.

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DOI: 10.1164/rccm.201109-1684ED

Endotoxemia before and after Surgical Repair for Congenital Heart Disease

In this issue of the *Journal*, Pathan and colleagues (pp. 1261–1269) report the frequency of biochemical evidence of intestinal injury and systemic endotoxemia in 61 children undergoing surgery for congenital heart disease (1). They serially measured a newly described biomarker for intestinal injury known as intestinal fatty acid-binding protein (IFABP) and lipopolysaccharide (LPS) levels in plasma using a rapid chemiluminescence method, the endotoxin activity assay (2, 3).

Both IFABP and endotoxin levels were significantly higher pre-operatively in children with duct-dependent (requiring a patent ductus arteriosus to maintain systemic or pulmonary circulation) compared with children without duct-dependent cardiac lesions. Elevated postoperative LPS levels, but not IFABP levels, were significantly associated with prolonged ICU stays, greater frequency and duration of organ dysfunction, elevated inflammatory markers, and a longer need for inotropic support.

Gene microarray profiles from circulating blood compared the transcriptome immediately before and then 24 hours after cardiac surgery. They found 512 genes to be differentially expressed, with about half (54.7%) being up-regulated and 45.3% down-regulated. Gene pathway analysis revealed that a large number of affected gene transcripts belonged to cell activation, host defense, inflammatory, and antigen-processing pathways (1). Toll-like receptor (TLR) signaling and other pattern recognition receptor pathways were differentially expressed before and after surgery. Some of these changes were verified by flow cytometry of circulating leukocytes, in which TLR4 and HLADR expression were markedly diminished in the immediate post-operative period. The transcriptome response in these children is remarkably similar to the microarray findings in normal human volunteers after a signal dose of bacterial LPS (4).

Bacterial LPS (also known as endotoxin) is the major structural component of the outer membrane of gram-negative bacteria and is the quintessential pathogen-associated molecular pattern (PAMP) substance (5, 6). LPS is detectable by innate immune cells at minute (picomolar) concentrations, and this ligand alerts the host to a potential microbial threat. The molecular details of LPS signaling are now well understood and necessitate the assembly of a number of cell surface receptors including CD14, MD-2, and TLR4 to activate two major intracellular signaling pathways, the myeloid differentiation factor-88 (MyD88) and TLR adapter-inducing interferon- β (TRIF) pathways (6, 7).

While the MD2:TLR4 complex is the primary LPS receptor, other endogenous host-derived molecules, collectively referred to as “alarmins,” are capable of alerting the host of danger after tissue trauma or necrosis via signaling through TLR4 (5, 6). Alarmins come in two forms. One class is a group of highly conserved intracellular or intranuclear components released upon necrotic cell death, and the other class is the structural elements of the extracellular matrix that can be solubilized by

tissue injury. Examples of the former are High Mobility Group Box-1, histone protein, heme, and mitochondrial DNA, and the latter include heparan, fibronectin, biglycans, and hyaluronate (8–10).

Perhaps not surprisingly, as both alarmins and LPS can activate the acute inflammatory response through the same TLR4-signaling pathways, the clinical and laboratory findings following sterile inflammation from necrosis is similar to the initial host response to LPS either with or without actual infection with gram-negative bacterial pathogens (10). Sterile inflammation is a well-known concomitant of gut ischemia as a result of splanchnic hypoperfusion from surgical interventions that necessitate proximal vascular clamping of the aorta. This problem is anticipated in high-risk surgery in adults undergoing thoraco-abdominal repair for large aortic aneurysms (11). These surgical procedures induce a marked inflammatory cytokine and chemokine response in the systemic and mesenteric circulation, despite the absence of bacteremia or evidence of circulating bacterial DNA (11). The children with complex congenital heart defects studied by Pathan and coworkers likely have a comparable hemodynamic process with systemic vascular insufficiency with limited splanchnic circulation punctuated by acute hypoperfusion to the gut epithelium during cardiac surgery (1).

Gut hypoperfusion impairs mucosal barrier function and increases uptake of LPS and perhaps other PAMPs or even host tissue-derived alarmins in the mesenteric circulation. TLR4 is normally expressed on enterocytes, particularly on the basilar surface, and appears to play a functional role in maintaining local immune defense (12, 13). Small amounts of LPS within the microenvironment of the gastrointestinal tract probably act under physiologic conditions to preserve host antimicrobial defenses (14). The LPS-resistant C3H/HeJ mouse carries a point mutation in the coding sequence (P712H) for the intracellular signaling domain of TLR4. These mice are highly resistant to LPS but rapidly succumb to a variety of bacterial infections readily tolerated by wild-type mice. This finding attests to the fact that while high levels of LPS are detrimental to survival, the capacity to detect and respond to smaller amounts of LPS is likely advantageous to the host (14).

The host immune response to LPS is further complicated by the phenomenon of “endotoxin tolerance,” or more correctly endotoxin reprogramming, wherein immune cells of the innate and acquired immune systems reprogram their inflammatory responses and antimicrobial defense programs after their initial interactions with LPS. This reprogramming response can either be advantageous or deleterious depending on the overall pathophysiologic status of the host. Down-regulation of pattern receptors and attenuation of inflammatory mediators can reestablish control over excessive inflammation; however, reduced adaptive immune functions can render the host at increased risk for secondary infection (15). The evidence of diminished expression