CD36 Provides Host Protection Against *Klebsiella pneumoniae* Intrapulmonary Infection by Enhancing Lipopolysaccharide Responsiveness and Macrophage Phagocytosis

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*Klebsiella pneumoniae* remains an important cause of intrapulmonary infection and invasive disease worldwide. *K. pneumoniae* can evade serum killing and phagocytosis primarily through the expression of a polysaccharide capsule, but its pathogenicity is also influenced by host factors. We examined whether CD36, a scavenger receptor that recognizes pathogen and modified self ligands, is a host determinant of *K. pneumoniae* pathogenicity. Despite differences in serum sensitivity and virulence of 3 distinct *K. pneumoniae* (hypermucoviscous K1, research K2, and carbapenemase-producing ST258) strains, the absence of CD36 significantly increased host susceptibility to acute intrapulmonary infection by *K. pneumoniae*, regardless of strain. We demonstrate that CD36 enhances LPS responsiveness to *K. pneumoniae* to increase downstream cytokine production and macrophage phagocytosis that is independent of polysaccharide capsular antigen. Our study provides new insights into host determinants of *K. pneumoniae* pathogenicity and raises the possibility that functional mutations in CD36 may predispose individuals to *K. pneumoniae* syndromes.

**Keywords.** CD36; *Klebsiella pneumoniae*; macrophage; host defense; multi-drug resistant *K. pneumoniae*; pneumonia; hypermucoviscous strains.

Bacterial pneumonia is a major cause of morbidity and mortality [1], and *Klebsiella pneumoniae* remains an important causative agent of gram-negative bacterial pneumonia [2]. The global emergence and nosocomial dissemination of multi-drug-resistant, carbapenemase-producing strains of *K. pneumoniae* (KPC) have been associated with increased costs, length of hospitalization, and significant morbidity and mortality but are generally observed in critically ill patients [3, 4]. On the other hand, *K. pneumoniae* causes a distinct severe community-acquired invasive syndrome prevalent in parts of Asia and Africa but uncommon in North America, Europe, and Australia [5]. This invasive syndrome is characterized by the presence of necrotizing pneumonia, hepatic abscesses, bacteremia, endophthalmitis, and meningitis and is attributed to *K. pneumoniae* strains expressing the K1 or K2 capsular antigen [6]. K1/K2 serotype *K. pneumoniae* strains are especially virulent due to the presence of mucoviscosity-associated gene A (*magA*), the regulator of mucoid phenotype A gene (*rmpA*), and the capsular antigens K1 and K2, which promote resistance to phagocytosis by neutrophils and macrophages, promote evasion of killing by serum components, and enable disease in presumably healthy hosts [5, 6].

The early innate immune response to intrapulmonary *K. pneumoniae* infection involves phagocytosis and clearance of foreign pathogens with inflammation. Disruption of any part of this normal host response to infection can result in adverse outcomes, but specific host factors that influence susceptibility to *K. pneumoniae* infection are less known. Scavenger receptors play a key role in maintaining homeostasis through recognition and removal of foreign substances from the body. Initially identified as receptors for oxidized low-density lipoprotein (oxLDL) [7], scavenger receptors recognize a diverse range of ligands, including both modified endogenous molecules or danger-associated molecular patterns and exogenous pathogen-associated molecular patterns [8, 9]. Eight classes of scavenger receptors have been defined (classes A–H) and are distinguished from each other by their unique structural characteristics [10]. Class B, which includes scavenger receptor class B1, lysosomal integral membrane protein II, and CD36 (also known as glycoprotein IV), is structurally defined by possessing 2 transmembrane regions. CD36 is predominantly expressed by...
components of oxLDL and amyloid β indicate that lipopolysaccharide (LPS) and the gram-negative bacteria are highly virulent in mice and humans (hereafter, the K. pneumoniae K1 strain) in the lungs and extrapulmonary bacterial dissemination to distant organ sites. In addition, we show that CD36 mediates recognition of LPS, enhances phagocytosis of K. pneumoniae by alveolar macrophages, and enhances JNK activation for optimal cytokine production in the lung. Collectively, our findings demonstrate a host-protective role for CD36 and implicate CD36 as a host determinant of K. pneumoniae pathogenicity.

**METHODS**

**Animals**

A total of 8–12-week-old age- and sex-matched C57Bl/6J mice were purchased from the Jackson Laboratory (Bar Harbor, ME). Cd36−/− (B6.129S1-Cd36tm1Mfe/l) mice that were backcrossed to the C57Bl/6J mice for 11 generations were obtained from the Jackson Laboratory. These Cd36−/− mice were subsequently crossed to Cd36−/− mice (also backcrossed to the C57Bl/6J mice for 11 generations) from the Blood Research Institute (Blood Center of Wisconsin, Milwaukee, WI) to establish a founder colony at the University of Pittsburgh. C57Bl/6J control mice were also bred and housed in specific-pathogen-free conditions with free access to food and water within the same animal care facility at the University of Pittsburgh. For in vivo pneumonia studies with predetermined time points of harvest, a group size of 8 per group was determined a priori to achieve a power of 0.83 for a 2-tailed test using an α of 0.05. Mice were randomly assigned, and a skilled technician who was blinded to the biological hypothesis performed the inoculations, monitoring, and harvest. Male and female mice aged 8–12 weeks were used for experiments. Survival study was conducted separately from pneumonia studies. The mice were monitored carefully and euthanized when they met predefined criteria for euthanasia. All procedures were performed with approval of the Institutional Animal Care and Use Committee at the University of Pittsburgh (protocol numbers 14013145 and 15086456).

**K. pneumoniae Inoculation**

*K. pneumoniae* strains were grown overnight in tryptic soy broth (TSB) for 18 hours at 37°C. A 1:100 dilution of bacteria in TSB was then incubated again at 37°C for 1.5 hours. Initial studies indicated that the *K. pneumoniae* K2 strain grown to early logarithmic phase but not at the late logarithmic phase induced a reproducible pathogenic phenotype in the lungs of wild-type (WT) mice, and subsequent studies used an OD600 nm of 0.2 to prepare the bacterial inoculum. We have previously described a detailed method of intratracheal administration of bacteria by direct visualization [21, 23].

**Bronchoalveolar Lavage**

We have also previously described a detailed method of bronchoalveolar lavage [24].

**Cytokine Enzyme-Linked Immunosorbent Assays (ELISAs)**

ELISA Duo-sets for interleukin 6 (IL-6), interleukin 10 (IL-10), interferon γ (IFN-γ), monocye chemoattractant protein 1 (MCP-1), interleukin 12p70 (IL-12p70), interleukin 17A (IL-17A), interleukin 1β (IL-1β), and TNF-α were purchased from R&D Systems (Minneapolis, Minnesota).
Serum from healthy volunteers was obtained from peripheral whole blood following collection of a 20-mL blood sample by venipuncture. All subjects underwent venipuncture after providing informed written consent, and ethnicities and sex were identified by self-reporting. Following collection, serum was processed from whole blood and used in the in vitro study in a deidentified manner. The Institutional Review Board of the University of Pittsburgh approved the study (protocol number IRB0410173). Overnight cultures of *K. pneumoniae* strains were diluted 100-fold in TSB and incubated at 37°C until reaching an OD<sub>600</sub> of 0.2. A total of 10<sup>6</sup> bacterial cells in early logarithmic phase, 5% sterile TSB, and 85% nonimmune human serum were incubated at 37°C. Bacterial growth in nonimmune human serum was determined by measurement at OD<sub>600</sub> and, in select experiments, confirmed by determining colony-forming units (CFU) via bacterial serial plating.

**Statistical Analysis**
A Student *t* test was performed for comparisons between 2 groups. For data that were not normally distributed, a 2-tailed Mann–Whitney *U* test was used, and differences were considered significant for *P* values of < .05. Statistical analysis was performed using Graph Pad Prism 6 software (La Jolla, California).

**Additional Assays**
Detailed descriptions of bacterial strains, Western blot analysis, ex vivo stimulation of macrophages, cytotoxicity detection, and phagocytosis are provided in the Supplementary Materials.

**RESULTS**

**Cd36<sup>−/−</sup> Mice Show Higher Lung Bacterial Burden and Greater Extrapulmonary Dissemination Following Intrapulmonary Infection With the K2 Strain**

CD36 is a scavenger receptor that binds various polyanionic ligands and recognizes lipid signatures expressed by pathogen and modified self-ligand. We sought to determine the contribution of this receptor to pulmonary host defense against the K2 strain, which is a well-known ATCC research strain that is pathogenic in mice [21]. At 24 and 48 hours following bacterial inoculation of 2 × 10<sup>3</sup> CFU, *Cd36<sup>−/−</sup>* mice showed a higher bacterial burden in the lungs, compared with WT mice (Figure 1A). By 48 hours, *Cd36<sup>−/−</sup>* mice showed greater bacterial dissemination to the spleen, liver, and blood (Figure 1A). An inability to optimally control the bacterial load in *Cd36<sup>−/−</sup>* mice was reflected by a higher level of lung myeloperoxidase, a marker of neutrophilic inflammation following infection (Figure 1B). Impaired host defense led us to examine the effects of CD36 on mortality during intrapulmonary *K. pneumoniae* infection. At an inoculum of 7 × 10<sup>3</sup> CFU, *Cd36<sup>−/−</sup>* mice showed greater susceptibility to *K. pneumoniae* (Figure 1C). By 72 hours, 79% of *Cd36<sup>−/−</sup>* mice were dead following intratracheal instillation, in contrast to 44% of WT mice, with a few WT mice surviving the virulent *K. pneumoniae* infection for up to 20 days when the study was terminated (*P* = .01 by the log-rank test; Figure 1C).

**Cd36<sup>−/−</sup> Mice Have a Higher Lung Bacterial Burden and Greater Extrapulmonary Dissemination Following Intrapulmonary Infection With the K1 Strain**

The K1 strain causes liver abscesses and disseminated disease in humans [25–27]. Indeed, *K. pneumoniae* virulence is associated with capsular serotypes K1 and K2 in mice and humans [28, 29], but host factors that contribute to aggressive disease remain largely unknown. Thus, we tested the responses of WT and *Cd36<sup>−/−</sup>* mice to the K1 strain. At an inoculum of 1 × 10<sup>5</sup> CFU, *Cd36<sup>−/−</sup>* mice showed a higher bacterial burden in the lungs, early liver dissemination, increased neutrophilic inflammation, and greater weight loss as compared to WT mice (Figure 2A–C). Taken together, these findings indicate that CD36 is required for optimal control of virulent *K. pneumoniae* in the lung to prevent extrapulmonary dissemination and mitigate systemic toxicity.

**KPC-Producing *K. pneumoniae* ST258 Is Susceptible to Serum Killing but Shows Enhanced Pathogenicity in *Cd36<sup>−/−</sup>* Mice Following Acute Intrapulmonary Infection**

*K. pneumoniae* virulence determinants include the ability to evade complement-mediated killing and phagocytosis that is dictated primarily by the polysaccharide capsular structure [30] and lipopolysaccharide (LPS) [31]. Both factors contribute to bacteremia and lethality in murine models of experimental pneumonia [30, 32]. In contrast, KPC-producing strains generally lack virulence determinants such as K1 and K2 capsular serotypes and do not induce lethality in mouse septicemia models [33, 34]. We examined the ability of nonimmune serum obtained from healthy volunteers to inhibit the growth of various *K. pneumoniae* strains and determined their relative virulence in vitro. Although all strains showed similar growth curves in culture broth, K1 and K2 strains exhibited continued growth in human serum, as measured by OD<sub>600</sub>, whereas human serum from healthy subjects inhibited growth of all KPC strains tested (Figure 3A). The subject demographic characteristics are shown in Figure 3B. Representative data examining CFU indicated KPC-producing strains were susceptible to human serum killing, whereas K1 and K2 strains escaped human serum killing (Figure 3C). Inactivation of heat-labile serum factors abrogated the susceptibility of KPC-producing strains and enabled growth in human serum (Figure 3C). As these findings highlight the role of soluble factors in providing defense to control growth of KPC-producing strains in blood, we sought to determine whether CD36 contributes to host defense against KPC-producing strains in the lung, where the pathogen is initially encountered.

When compared with WT mice, *Cd36<sup>−/−</sup>* mice showed impaired bacterial burden and increased extrapulmonary dissemination to the spleen and liver following intrapulmonary infection with KPC (Figure 4A). Moreover, bronchoalveolar lavage (BAL) concentrations of the cytokines IFN-γ, IL-1β, IL-6, IL-10, IL-12p70, IL-17A, MCP-1, and TNF-α were significantly
reduced in Cd36−/− mice as compared to WT mice during infection (Figure 4B). For a similar inoculum given, it was notable that the bacterial burden in the lungs of WT mice following infection by KPC-producing strains was substantially less than that observed with virulent K. pneumoniae strains (Figures 1A, 2A, and 4A). Despite the muted virulence of KPC-producing strains relative to the virulence of K1 and K2 strains, the absence of CD36 enhanced host susceptibility to acute infection by KPC-producing K. pneumoniae and impaired lung cytokine production.
**Cd36**−/− Macrophages Show Blunted Cytokine Production in Response to *K. pneumoniae* LPS That Is Independent of Capsular Serotype

Given the impaired cytokine response observed in the airspaces of *Cd36*−/− mice following infection, we next examined whether CD36 expressed by macrophages is involved in the recognition of *K. pneumoniae*. As the capsular polysaccharide and LPS are secreted [35], we exposed WT and *Cd36*−/− macrophages to cell-free supernatants obtained from K2 and K41 strains following a culture for 18 hours in TSB. We measured cytokine production as a readout to test CD36 function as a pattern-recognition...
receptor. Incubation in TSB alone failed to induce cytokine production by WT and Cd36−/− macrophages (Figure 5A). In contrast, cell-free supernatants from K2 and K41 strains induced IL-10 and IL-6 production in WT macrophages, but this response was notably attenuated in Cd36−/− macrophages (Figure 5A). Similarly, K1, K2, and K41 supernatants induced TNF-α production in WT macrophages, and the response was attenuated in Cd36−/− macrophages (Figure 5A). Residual cytokine release in the absence of CD36 is due to TLR4 (Supplementary Figure 1) [36]. Reduction of capsular polysaccharide synthesis by sodium salicylate [37] did not alter K. pneumoniae–induced TNF-α production in WT and Cd36−/− macrophages, indicating an alternative bacterial component recognized by macrophages (Figure 5A). Bacterial cell lysates obtained from K1, K2, and K41 recapitulated IL-10 and IL-6 responses in WT macrophages observed with cell-free supernatants, and cytokine production was blunted in Cd36−/− macrophages (Figure 5B). At neutral pH, polylysine exhibits a high affinity for LPS (K_D = 1.1 × 10^{-11} M) [38]. Removal of LPS by treatment of K2 and K41 cell lysates by spinning in a polylysine column resulted in negligible endotoxin levels (<8 endotoxin units/mL by the Limulus amebocyte lysate test; data not shown) and abrogated macrophage cytokine production (Figure 5B). Moreover, incubation with purified LPS from K2 and K41 strains recapitulated macrophage cytokine response observed with K. pneumoniae supernatant in WT but not in Cd36−/− macrophages (Figure 5C). The attenuated cytokine response in Cd36−/− macrophages was not due to appreciable differences in cytotoxicity, as measured by lactate dehydrogenase release (Figure 5D). Collectively, these findings indicate CD36
mediates LPS responsiveness and macrophage cytokine production that is independent of the capsular polysaccharide antigen.

**Cd36**<sup>−/−</sup> Macrophages Show Impaired Phagocytosis and JNK Activation

A main virulence mechanism of extracellular *K. pneumoniae* is related to the ability to evade phagocytosis [39]. To further examine CD36-mediated host protection, we evaluated CD36 involvement in *K. pneumoniae* phagocytosis and the downstream signaling pathway. We isolated alveolar macrophages from WT and *Cd36*<sup>−/−</sup> mice and exposed them to a tdTomato plasmid–expressing *K. pneumoniae* clinical strain to visualize internalization within F4/80-positive macrophages by quantitative confocal microscopy. To ensure an unbiased approach, the 4 corners of each cover slip were imaged and analyzed by a binary region of interest function within Nikon Instrument digital software. Compared with WT macrophages, *Cd36*<sup>−/−</sup> macrophages showed significant reduction in the uptake of *K. pneumoniae* (Figure 6A), indicating that CD36 is involved in the recognition and phagocytosis of *K. pneumoniae* [20]. We next determined whether impaired recognition results in impaired signaling. Macrophages isolated from *Cd36*<sup>−/−</sup> mice previously showed reduced activation of JNK but not p38 in response to oxLDL [40], and CD36-overexpressing HEK293 cells showed higher levels of JNK phosphorylation following treatment with LPS or *E. coli* in vitro [20]. JNK signaling is tightly linked to cytokine production [41, 42], and inhibition of JNK activity in macrophages impairs cytokine production following...
K. pneumoniae stimulation (Supplementary Figure 2). It remains unclear, however, whether CD36-dependent JNK activation occurs in primary alveolar macrophages ex vivo and in the lung in vivo following stimulation with a gram-negative pathogen. We isolated and pooled alveolar macrophages from BAL fluid of WT and Cd36−/− mice and exposed them to K. pneumoniae (multiplicity of infection, 10) in vitro. Under basal conditions, both WT and Cd36−/− alveolar macrophages showed minimal JNK phosphorylation (Figure 6B). Following exposure to K. pneumoniae ex vivo, Cd36−/− macrophages showed impaired JNK activation as compared to WT macrophages (Figure 6B). In contrast, there were no significant differences observed in phosphorylated or total p38 between WT and Cd36−/− alveolar macrophages at various multiplicities of infection (Figure 6C). We next examined JNK activation in the lung tissues of WT and Cd36−/− mice following infection with K. pneumoniae in vivo. Cd36−/− lungs showed reduced levels of p-JNK when compared to WT lungs (Figure 6D).

There were no differences in levels of total JNK levels between the 2 groups (Figure 6D), suggesting that although JNK is detectable, CD36 is required for optimal activation of JNK in response to K. pneumoniae.

DISCUSSION

We investigated the role of the scavenger receptor CD36 in the innate immune response to Klebsiella pneumoniae using 3 different strains (K2, K1, and K41) in an acute bacterial pneumonia model. Mice defective in CD36 showed impaired ability to clear the K2 strain from the lungs and displayed increased dissemination into extrapulmonary sites such as the blood, liver, and spleen. Inability to adequately contain the infection within the lung was associated with increased mortality. A similar finding was observed following intrapulmonary infection with the K1 strain, where Cd36−/− mice showed higher bacterial burden in the lungs, increased liver dissemination and systemic toxicity compared to WT mice. Importantly, the K41 strain showed...
enhanced pathogenicity in mice defective in CD36 that is associated with impaired lung cytokine production. Our findings further indicate that CD36 functions to enhance LPS responsiveness and increase phagocytosis and macrophage cytokine production, which play crucial roles in eliminating the extracellular bacteria *K. pneumoniae* from the lung. These findings are independent of the capsular serotype and strongly support the contention that CD36 is a host determinant of *K. pneumoniae* pathogenicity.

CD36 is involved in many critical aspects of innate immunity, including the recognition and clearance of pathogen-derived phospholipids, modified host-derived lipoproteins, and apoptotic cells to maintain cellular homeostasis [10]. Depending on the ligand stimulus, the cell type, and the binding partners that CD36 engages, CD36 has the ability to influence the course of inflammation [10, 11]. For example, CD36 mediates endocytosis of oxLDL and amyloid-β into lysosomes [43] and regulates TLR4/TLR6 complex formation to potentiate nuclear factor κB activity in response to oxLDL and amyloid-β in HEK293 cells [19]. However, CD36 can also facilitate recognition and clearance of apoptotic cells, with resolution of inflammation through production of the antiinflammatory cytokine IL-10 [44, 45]. Following stimulation with oxLDL, the carboxyl terminal domain of CD36 containing the CXCX5K motif interacts with a signaling complex containing Lyn kinase and MEKK2 with downstream JNK 1/2 activation in macrophages [40].

**Figure 6.** Cd36−/− macrophages show impaired uptake of *Klebsiella pneumoniae*, and Cd36−/− mice show impaired JNK activation following *K. pneumoniae* infection. A, Alveolar macrophages pooled from wild-type (WT) mice (n = 6) and Cd36−/− mice (n = 6) were stimulated with tdTomato plasmid–expressing *K. pneumoniae* clinical strain 883 (multiplicity of infection [MOI], 50) for 1 hour. Cells were washed and subsequently fixed. Left, The middle slice of each z-stack confocal image was analyzed to determined the mean *K. pneumoniae* intensity per cell. Dots and squares represent individual cells (WT, 87 cells; Cd36−/−, 85 cells). Lines indicate median values. ****P < .0001, by the 2-tailed Mann–Whitney U test. Right, Representative slices of z-stack confocal images are shown from WT and Cd36−/− macrophages following stimulation with tdTomato plasmid–expressing *K. pneumoniae*. Green, F4/80-positive macrophages; red, tdTomato plasmid–expressing *K. pneumoniae*. B, p-JNK, total JNK, and α-tubulin expression in alveolar macrophages pooled from naive WT (n = 16) or Cd36−/− mouse lungs (n = 12) stimulated ex vivo in the presence or absence of *K. pneumoniae* (MOI, 10) for 1 hour. Data in the bar graph indicate the relative density of p-JNK (normalized to total JNK) in pooled alveolar macrophages exposed to *K. pneumoniae* (MOI, 10) for 1 hour. C, p-p38, total p38, and α-tubulin expression in alveolar macrophages pooled from naive WT (n = 16) or Cd36−/− mouse lungs (n = 12) stimulated ex vivo with *K. pneumoniae* (MOI, 0, 2, and 10) for 1 hour. The graph indicates the relative density of p-p38 (normalized to total p38) in pooled alveolar macrophages exposed to *K. pneumoniae* (MOI, 10) for 1 hour. D, p-JNK, total JNK, and α-tubulin expression in WT and Cd36−/− lungs following intratracheal instillation of *K. pneumoniae*. Lung tissue homogenates were obtained from perfused WT and Cd36−/− lungs harvested 0.5 hours following intratracheal instillation of *K. pneumoniae* (1 × 10⁸ CFU). Each lane indicates lung tissue homogenate from an individual mouse. Dots and squares represent lungs of individual mice. Lines indicate median values. *P < .05, by the 2-tailed Student t test. Abbreviation: RFU, relative fluorescence units.
Moreover, CD36 has been shown to enhance recognition of LPS and gram-negative bacteria in HEla and HEK293 cells and to mediate cytokine signaling through JNK 1/2 activation that is independent of TLR4 [20, 46]. The evidence thus far indicates that JNK2 phosphorylation is an important signaling pathway that triggers CD36-dependent proinflammatory cytokine responses in macrophages [40]. In this study, we show that CD36 contributes to JNK but not p38 activation in alveolar macrophages ex vivo and in lung in vivo following K. pneumoniae challenge. A pattern-recognition receptor for components of microbial pathogens such as Plasmodium falciparum erythrocyte membrane protein 1 and certain microbial-derived diacylglycerides [11, 15, 18], CD36 promotes diverse responses depending on the type of pathogen the host encounters. Although CD36 activates the TLR2 signaling pathway through recognition of S. aureus and lipoteichoic acid to enhance inflammatory cytokine responses [15], others have shown that CD36 suppresses inflammation induced by S. pneumoniae by binding to phosphocholine residues of lipoteichoic acid [16]. These studies suggest a pathogen-specific interaction with host CD36 during infection that dictates the subsequent inflammatory response and, in some cases, host outcome following infection. These findings also highlight the need for in vivo studies using relevant models to properly ascertain the biology of CD36. Herein, our findings indicate that, in response to a live gram-negative pathogen, K. pneumoniae, CD36 contributes to an effective host defense strategy following intrapulmonary infection. Our data also indicate that CD36 enhances LPS signaling by macrophages, phagocytosis, and subsequent cytokine production. Approximately 3%–11% of Asians, 2.4% of African Americans, and 7%–8% of sub-Saharan Africans lack platelet CD36 (type II deficiency) [12, 47–49], a deficiency originally identified as the Nak phenotype that is associated with refractoriness to HLA-matched platelet transfusions [50]. Of those individuals with the Nak phenotype, 10% presumably lack CD36 in all cells (type I deficiency) [12, 47]. It remains to be seen whether type I or type II deficiency in CD36 contributes to host-pathogen interactions that explain geographic differences in K. pneumoniae–associated severe community-acquired pneumonia and invasive syndromes of endophthalmitis, meningitis, or liver abscesses occurring almost exclusively in portions of Asia and Africa [5].

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**Supplementary Data**

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

**Financial support.** This work was supported by the Howard Hughes Medical Institute (research fellow award to T. F. O.), the National Institutes of Health (grants R01 HL086884 [to J. S. L.], R21 AI119042 [to J. S. L.], and PO1 HL114453 [to R. K. M. and P. R.]), the Flight Attendant Medical Research Institute (to J. S. L.), the Vascular Medicine Institute, the Hemophilia Center of Western Pennsylvania, and the Institute for Transfusion Medicine (J. S. L.).
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