Greater attention should be paid to enhance our understanding of these disparities and to identify actionable solutions to address them.

The inclusion of $PM_{2.5}$-CKD as an environmental health risk-outcome pair in future iterations of the GBD study will be an important future milestone. Realizing this goal hinges on the availability of more high-quality longitudinal studies representing different geographic areas. GBD will then produce global and national estimates of the burden of kidney disease attributable to air pollution on an ongoing basis. GBD estimates are widely used by governments to set policy priorities and allocate budget. These estimates will not only provide a more comprehensive accounting of the health effects of air pollution but will also further elevate the stature of kidney disease as an important global health problem. We must all synergize our effort to realize this important goal and to ensure that evidence generated by our scientific inquiries is serving the greater public good.

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See related article, "Long-Term Exposure to Ambient $PM_{2.5}$ and Increased Risk of CKD Prevalence in China," on pages 448–458.

Missing Self and DSA—Synergy of Two NK Cell Activation Pathways in Kidney Transplantation

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Antibody-mediated rejection (ABMR) remains one of the leading causes of allograft dysfunction and kidney transplant failure. The diagnosis of ABMR relies on donor-specific antibodies (DSAs) detected in the recipient's blood, along with histopathologic features of active or chronic antibody-mediated damage evident in the graft microvasculature.[1] The prototypical lesions of ABMR are those of microvascular inflammation (MVI). Gene expression characteristics of endothelial activation and capillary deposition of complement breakdown product C4d are also regularly observed and are evident of immune attack on graft endothelial cells. Overall, the morphologic phenotype of ABMR indicates that DSA binds onto targets

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(most commonly HLA molecules) and facilitates the direct engagement of mononuclear cells on graft endothelium.

Although DSA is the critical component that initiates the ABMR process, we now realize that circulating DSA is not a strong predictor for the development of ABMR or graft loss, despite having strong associations with both.[2] Multifactorial heterogeneity exists between the appearance of DSA, progression to clinically evident ABMR, and graft loss as a result of ABMR.[3] There are multiple DSA properties that dictate their potential to incur damage, and these may account for some of the heterogeneity. For example, various studies suggest that the ability of DSA to fix complement portends a higher probability to develop ABMR and progression to graft loss.[4] However, complement activation by DSA has yet to be demonstrated as a true effector responsible for endothelial damage in ABMR.

The cells recruited to the microvasculature in ABMR are innate immune cells, natural killer (NK) cells and monocytes, which express Fc gamma (γ) (Fcγ) receptors that allow for the recognition of DSA on the endothelial surface. Some of the activating Fcγ receptors are polymorphic and display cell-selective expression. NK cells almost exclusively express Fc gamma receptor (FcγR) IIIA (FcγRIIIA), more commonly known as CD16. When examined in kidney transplantation, patients expressing high-affinity variants of FcγRIIIA demonstrate more robust ABMR responses.[5] Clinical associations with FcγRIIIA polymorphisms have also been described in heart and lung transplantation.[6,7] NK cells, therefore, seem to instigate the cellular response component of ABMR using their primary Fcγ receptor FcγRIIIA, and FcγRIIIA polymorphism adds to the heterogeneity in the evolution of ABMR.

MVI in a transplanted organ pertains to a poor prognosis. The current assumption when MVI is identified by histopathology is that it is caused by the presence of antibody capable of recognizing endothelium on the donor organ. This assumption was recently challenged by Koenig *et al.*,[8] who showed that when graft endothelial cells fail to provide an inhibitory signal through expression of HLA class 1 molecules used to educate recipient NK cells, NK cells are activated, leading to chronic vascular rejection. This is an antibody-independent mechanism of NK cell activation, a process known as "missing self" (MS). These studies add a new dimension to the way we think about ABMR and MVI and center the focus on NK cells as primary architects of MVI, which may occur in the presence of DSA or MS—both of which are independently detrimental to allograft survival.

In this issue of *JASN*, Koenig *et al.*[9] continue their studies on NK cell activation through MS and report a synergy between MS and DSA-mediated NK cell activation that negatively contributes to ABMR outcomes. The study focuses on 135 patients with renal transplants, selected from a total cohort of 1682 patients, with a diagnosis of ABMR on their biopsy. DSA strength was defined by the complement-fixing ability as determined using a Luminex-based C3d binding assay. Recipient killer cell Ig-like receptor genotyping was performed and combined with donor HLA class 1 typing to predict MS. Comparisons were then made between three groups: MVI+/DSA+/C3d−/MS+, MVI+/DSA+/C3d−/MS−, and MVI+/DSA+/C3d+. As expected, the worse graft outcomes were observed in patients with complement-fixing DSA. However, a novel finding in this study is that in the presence of noncomplement-fixing DSA, the presence of MS shows a higher risk for graft loss when compared with patients predicted to be MS negative with their organ. This key result confirms that MS can synergize with weak DSA-mediated NK cell activation and translate into increased graft damage that accelerates the development of chronic lesions (interstitial fibrosis and tubular atrophy).

The results of this report from Koenig *et al.*[9] have multiple implications to the interpretation of HLA antibody and transplant immunology testing in organ transplants. The identification of MS is now an additional task that will be required to more accurately predict the immunologic risk pertaining to DSAs identified post-transplant and possibly, pretransplant. We can envision recipient killer cell Ig-like receptor typing soon becoming the norm to allow for the prediction of MS between recipient NK cells and donor endothelium. The interpretation of DSA mean fluorescent intensity values has always been semiquantitative at best, and incorporation of the MS dimension may further confound DSA interpretation. However, DSA interpretation along with MS prediction does offer the potential to improve the identification of pathogenic DSAs. Although not addressed by the authors' current or previous studies, it is possible that roles of other inhibitory and activating receptors on human NK cells exist in organ transplant outcomes.

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See related article, "Missing Self-Induced Activation of NK Cells Combines with Non-Complement-Fixing Donor-Specific Antibodies to Accelerate Kidney Transplant Loss in Chronic Antibody-Mediated Rejection," on pages 479–494.