conducted during very brief periods (only 2 h of respiratory electro dialysis), and that further complications may arise when performing the technique over clinically meaningful periods. Moreover, the technical setup is complex and will need to be as safe as possible before it can be deployed in human trials.

Conclusions

During the last decades, we have learned that the iatrogenic effects of invasive mechanical ventilation may negatively influence outcomes. Minimally invasive extracorporeal lung assist devices markedly reducing the need for alveolar ventilation would or could play a pivotal role in mitigating these negative influences.

The innovative approach of Zanella and colleagues opens the possibility of ensuring sufficient CO₂ removal with a less-invasive way of using positive pressure ventilation than the current standard, or by eliminating invasive mechanical ventilation altogether. Doubling the amount of extracorporeal CO₂ removal would allow a considerable decrease in invasiveness by enabling lower flow rates and vascular access with smaller cannulae. Moreover, it offers the opportunity to widely apply and evaluate the concept of ultraprotective ventilation to reduce VILI, as well as a potential alternative to invasive mechanical ventilation for the support of hypercapnic respiratory failure. If the technique of Zanella and colleagues could be successfully transferred to the clinical setting, it might mark a quantum jump in the treatment of respiratory failure of different etiologies. ■

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Solving the Conundrum: Immunogenetics of Sarcoidosis

Despite decades of research, sarcoidosis is still among the most enigmatic lung diseases, with poorly understood etiology, course, and outcome. Recent clinical and genetic observations have significantly highlighted the importance of immune mediators and

immunogenetics in determining the phenotypic behavior of the disease, and potentially of its pathogenesis. In the context of the paper in this issue of the *Journal* by Fischer and colleagues (pp. 727–736) (1), the association of the major histocompatibility

complex class II allele DRB1*03 with decreased risk for persistent disease in patients with sarcoidosis who are of European and African descent (2, 3); the associations of declines in CD4⁺, CD8⁺, and B cell counts with severe sarcoidosis phenotypes (4); and the peripheral blood expression changes in T-cell receptor signaling, Janus kinase–signal transducer and activator of transcription signaling and cytokine–cytokine receptor signaling pathways (5, 6) are of most relevance. These clinical and genomic observations suggest that although sarcoidosis pathogenesis may be related to aberrant patterns of immune activation, it is unlikely to be caused by a single major gene or molecular pathway but, more likely, to a complex interaction of multiple genes/pathways with contributing environmental factors that determine not only the presence of the disease but also its unique phenotypic manifestations.

Aiming to address this complex interaction, Fischer and colleagues (1) use an approach applied successfully in other inflammatory disorders. Building on findings from previous genome-wide association studies that most consistently identified loci in *BTNL2*, *ANXA11*, and *HLA* genes as disease susceptibility genes, but also suggested overlap with other autoimmune and inflammatory disorders, they applied the Illumina Immunochip Single Nucleotide Polymorphism (SNP) array, designed for genotyping and fine mapping of gene variants known to associate with immune diseases, to a European cohort of 1,726 patients with sarcoidosis and 5,482 healthy controls. They replicated their results in multiple additional cohorts that included several European cohorts and one African American cohort, using other methods. Overall, they analyzed more than 19,000 individuals, making this the largest sarcoidosis case control study ever performed. This unique design allowed the authors to identify new disease susceptibility loci while fine-mapping previously identified loci. For example, in addition to confirming the association of the *BTNL2* region with a predisposition to sarcoidosis, they now delineate that the most strongly associated variants in the promoter region are predicted to reside in transcription factor binding sites, a finding with significant functional implications. Similarly, in addition to finding associations with the known *HLA* variants, they identify an independent variant located in the 3' untranslated region of *HLA-DPB1*, suggesting an effect on microRNA binding.

The novel disease susceptibility loci the authors identified are near inflammatory regulators or cytokines such as 12q24.12 (*ATXN2/SH2B3*), 5q33.3 (near *IL12B*), 4q24 (*MANBA/NFKB1*), 2q33.2 (*FAM117B*), and 1p31.3 (*IL23R*). In fact, some overlap with known loci for psoriasis and inflammatory bowel disease (7–9), findings consistent with the finding of multiple aberrations in adaptive immunity in patients with sarcoidosis (10–12). Others have previously demonstrated the significance of reduced levels of nuclear factor- κ B (NF- κ B)/P65 to sarcoidosis disease severity (12), as well as dysregulation within IL-12 and IL-23 pathways within cutaneous sarcoidosis specimens, using microarray analysis (13). Reversal of global CD4⁺ subset dysfunction is present during spontaneous clinical resolution of pulmonary sarcoidosis. Anergic T-cell responses correlate with diminished expression of NF- κ B and sarcoidosis disease progression (14). It is currently unknown whether any of these patients carry the risk variants identified in the current study.

One of the obvious limitations of this study is inherent with the use of Immunochip assays. For example, the authors identified no significant SNP associated with patients with sarcoidosis of African descent, despite inclusion of a large cohort. Immunochip assays were designed on the basis of SNPs identified in individuals of European origin; variation present in non-European-origin populations is underrepresented (9). Moreover, although the chip has dense coverage of the major histocompatibility complex and killer immunoglobulin-like receptor loci, it still misses new loci. Also, those identified after the February 2010 release of the early 1,000 Genomes Pilot data are not densely covered.

However, to the authors of this editorial, it is possible that results would not have been much more impressive, even if the authors performed whole-genome sequencing on their cohorts. The reason for that lies in the intriguing results of the cumulative heritability the authors performed. Their results point to the most significant challenge when trying to assess the risk for sarcoidosis: the interaction between genetic predisposition and environmental exposures. Using sophisticated analyses, the authors define 11 independent sarcoidosis risk variants; however, when they assess their cumulative heritability, they come up with a dismal number of less than 3%, which is a very low number for a very large study. Considering that none of these risk variants was replicated in African Americans, the heritability may be even lower for the general global population of subjects with sarcoidosis, and especially those expressing some of the more severe and life-threatening forms of the disease. Thus, application of rare allele polymorphisms in well-defined phenotypes and clarification of environmental factors, such as in fire fighters, health care workers, or agricultural exposure, or on changes in the microbiome may provide important context regarding gene–environment interactions. The authors' identification of an independent variant located in the 3' untranslated region of *HLA-DPB1* suggests epigenetic modifications may contribute to sarcoidosis clinical outcomes and may point toward mechanisms influencing relevant gene–environment interactions.

Does this mean genetic variants do not play a major role in sarcoidosis? Our answer is that we believe they do; however, the data to date have not revealed significant global regulators of disease predisposition. Considering the clinical variability of the sarcoidosis, this should not come as a surprise. We should not be looking for genetic variants predisposing to a disease that is so variable in presentation, course, and outcome. We should look for variants explaining distinct phenotypic aspects of the disease. If this is true, one would argue that before more investigations of sarcoidosis genetics are performed, better phenotyping of patients should be conducted, using not only clinical characterizations but also advanced immunophenotyping technologies that could provide functional context to the clinical findings.

Thus, we believe, there is critical importance of a multidisciplinary teams in studying sarcoidosis: clinicians, geneticists, immunologists, microbiome experts, as well as environmental and occupational medicine, should work together to redefine the disease and identify the genetic variants that underlie the molecular underpinning of the disease. The impressive results reported by Fischer and colleagues in this issue of the *Journal* should encourage funding agencies and the research community to undertake such an effort, because based

on these results, we can state that solving the sarcoidosis conundrum is possible. ■

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Noninvasive Quantitative Imaging–based Biomarkers and Lung Cancer Screening

Lung cancer is the leading cause of cancer-related death among men and women globally and in the United States (1, 2). Despite improvements in patient survival in recent years for many other cancer types, there have been few improvements in non-small cell lung cancer patient survival, mainly because by the time a diagnosis is made, the tumor is often well advanced and treatment options are limited. Approximately 57% of all lung cancers are diagnosed at a distant stage, for which 5-year survival is 4% (1). Because of the large number of affected individuals and poor outcomes, screening and early detection could have a significant effect on increasing patient survival, as by identifying the cancer at an earlier stage, patients have a better possibility of a surgical cure. Until recently, however, no screening method has been shown to decrease mortality rates for non-small cell lung cancer. The National Lung Screening Trial (NLST) compared

low-dose computed tomography (LDCT) and standard chest radiography for three annual screens and found a 20% reduction in lung cancer mortality for CT compared with standard chest radiography (3). On the basis of the findings from the NLST, in December 2013 the U.S. Preventive Services Task Force (4) issued a recommendation for annual screening for lung cancer with LDCT, and in February 2015, the Centers for Medicare & Medicaid Services made the determination that LDCT is appropriate for eligible beneficiaries (5).

Although the NLST demonstrated a clear benefit for lung cancer and all-cause mortality reduction, LDCT screening also identifies large numbers of false positives and indeterminate pulmonary nodules, of which only a fraction actually develop into cancer. Further, LDCT screening detects indolent neoplasms, which are generally adenocarcinoma, that may not otherwise cause