Leveraging Omics to Predict Chronic Obstructive Pulmonary Disease Exacerbations: The "Immunome"

The face of chronic obstructive pulmonary disease (COPD) is rapidly evolving. Rather than a superficial view of a self-inflicted disease of elderly smokers, COPD has now been recognized as a complex condition with multiple etiotypes (1). Ultimately, the development of new therapies, however, relies on the discovery of endotypes that reflect varied pathobiological manifestations. Such COPD endotypes are currently being investigated, leveraging the numerous omics tools that are increasingly available (2). Indeed, the use of omics is driving the effort toward a "personalized," "precision," and "individualized" approach to COPD, which relies on genetic, biomarker, phenotypic, and psychosocial characteristics to distinguish between patients who all have airflow obstruction that defines the disease. Combined, this information could potentially help us anticipate the disease course and individual patient responses to therapies. Ultimately, it is hoped that an omics-based approach could help circumvent the current trial and error required to find effective therapies for individual patients living with COPD (3).

One of the major unmet needs in the identification of targetable COPD pheno/endotypes is the lack of blood biomarkers that can function as reliable surrogates of the pathobiological manifestations occurring in the COPD lung. The search for these biomarkers has recently been revolutionized by high-throughput sequencing techniques and multiplex platforms that can measure thousands of gene transcripts, proteins, or metabolites (4). Additionally, the development of several well-phenotyped longitudinal COPD cohorts with blood sampling has facilitated the identification of blood biomarkers of COPD (5).

Although most of the studies of blood biomarkers have focused on large-scale measurement of omics data types, including DNA, RNA, proteins, and metabolites, the circulating immune compartment in COPD has not been well explored, despite evidence that COPD is associated with profound alterations in immune cells (6). Novel, cell-type deconvolution approaches accurately infer the relative proportions of immune cell types from genome-wide blood gene expression data. Thus, cell-type deconvolution is a potentially powerful approach to enable the simultaneous study of many different cell types in large cohorts of participants (7) with available blood gene expression. This link between blood biomarkers and the identification of a circulating immune signature, or what one might term an "immunome," could be a powerful tool to predict COPD onset, progression, and therapeutic targets.

In this issue of the *Journal,* Ryu and colleagues (pp. 247–255) looked at the relationship between blood-based molecular and cellular phenotypes with COPD exacerbations using three complementary datasets: blood RNA-sequencing data from the COPDGene study, blood microarray data from the ECLIPSE study for validation, and blood flow cytometry data from SPIROMICS (8–11).

The COPDGene study identified over 3,500 unique genes in the blood transcriptome that were associated with a history of exacerbation, persistent exacerbations, and/or prospective exacerbation rate. These data extend the findings of previous works associating frequent exacerbations to gene expression in the ECLIPSE study (10) and the authors' previous analysis of the Treatment of Emphysema with a γ-Selective Retinoid Agonist study (12). However, whereas individual genes or even pathways may explain only a minority of the variance in clinical phenotypes, combinations of multiple biomarkers can explain a more extended variance for some COPD phenotypes. Thus, the authors took the next step to deconvolute the circulating cell-type composition to derive a blood immune signature, or "immunome," associated with the risk of future exacerbations. It is interesting that, in the COPDgene study, the number of prospective exacerbations in subjects with COPD was inversely associated with the numbers of circulating $CD8^+$ T cells, $CD4^+$ T cells, and resting natural killer cells. The inverse association with naive $CD4^+$ T cells was replicated in the ECLIPSE study. In the flow cytometry study, an increase in the immune checkpoint CTLA4 on $CD4^+$ T cells, indicating an inhibition of the $CD4^+$ T cell activity, was positively associated with acute exacerbations of COPD (AECOPDs).

Altogether, these data point to a blunted adaptive immune response, involving both the T helper and cytotoxic component, contributing to AECOPDs, either directly or indirectly by means of an off-targeted stimulation of the B cell compartment. In fact, the decrease in naive and resting memory $CD4^+$ T cell populations was associated with increases in the plasma cell population in the frequent exacerbators. The involvement of activated antibody-producing B cells was confirmed by KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis and led the authors to put forth the compelling hypothesis that autoimmune-like responses may predispose patients with COPD to future exacerbations. Previous data have shown that patients with COPD—in particular, those with emphysema-predominant COPD—have upregulated B cell responses with autoimmune features (13, 14). To clarify whether this is also occurring in AECOPDs, a logical next step would be to assess whether the circulating plasma cell signature is enriched in frequent exacerbators with a greater extent of emphysema as defined by means of a computed tomography scan.

Furthermore, the exact role of the adaptive immune compartment in determining AECOPDs remains unclear, given the limitations of these observational cohorts. Whether these blood-based immunologic signatures reflect specific signatures in the COPD lung is hard to determine and opens interesting research avenues. The systemic inflammation may reflect a "spillover" of inflammatory
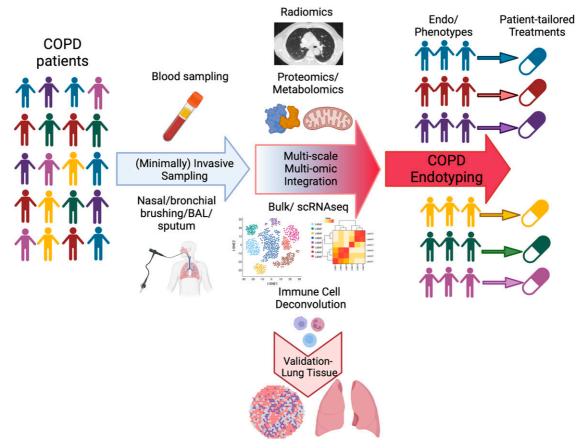
Figure 1. Leveraging omic endotyping to enable personalized medicine in chronic obstructive pulmonary disease (COPD). Individuals with COPD share many clinical traits that allow a common disease diagnosis, yet this shared phenotype accounts for different types of pathobiology (i.e., endotypes). Important steps in patient endotyping are *1*) minimally invasive sampling of patient diseased tissue; *2*) molecular and cellular characterization of diseased samples with analyses of bulk and or scRNAseq, metabolomic and proteomic processes, and radiological features to identify pathobiological mechanisms in the disease group (ultimately, this step will require validation of the findings in lung tissue from independent cohorts); *3*) integration of multiscale, multi-omic data with machine-learning approaches; and *4*) separation of patients into endotype groups on the basis of the presence and/or level of one or more of these pathobiology types. The endotype of the patient with COPD forms the basis for personalized clinical disease management. scRNAseq = single-cell RNA sequencing.

processes within the lung, primary alterations in the extrapulmonary immune response, or a combination of both (7). It would be compelling to determine whether any of these immune cell populations deconvoluted in the blood can be confirmed longitudinally in the same compartment and/or in airway samples (e.g., bronchial brushing) using bulk and/or single-cell RNA sequencing. Also, it is important to determine whether, in other independent cohorts, the same features of the circulating immunome identified here can be found in lung tissue from frequent exacerbators versus nonexacerbators, although that would require a cross-sectional analysis of the COPD lung because of the obvious limitations in sampling lung tissue longitudinally (Figure 1).

To conclude, this study from Ryu and colleagues highlights the need of shifting toward multi-omics panels as opposed to relying on singular markers in the stratification of patients with COPD. As we navigate this multi-omics era (Figure 1), machine-learning approaches have emerged as effective methods for mining and integrating large-scale, heterogeneous medical data for clinical practice. Rather than oversimplifying subjects into broad categories that are based on clinical phenotyping alone, large-scale, data-driven

analyses could integrate select biomarker subsets, thus allowing better identification of patients who are susceptible to COPD exacerbation and enabling more nuanced and effective stratification of patients with COPD. ∎

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Enhancing the Efficacy of Mesenchymal Stromal Cells in COVID-19–related Acute Respiratory Distress Syndrome

Mesenchymal stromal cells (MSCs) have garnered considerable attention as a potential therapeutic option for patients with acute respiratory distress syndrome (ARDS) because of their capacity to modulate inflammation and promote tissue repair (1, 2). In this editorial, we summarize the noteworthy findings of a study published in this issue of the *Journal* by Gorman and colleagues (pp. 256–269) on patients with coronavirus disease (COVID-19)-related ARDS (3). We discuss the implications of this study for the field and propose a potential strategy to enhance the likelihood of MSCs fulfilling their promise to improve outcomes in patients with ARDS.

The Study by Gorman and Colleagues

Gorman and colleagues conducted a multicenter, randomized, double-blind, placebo-controlled trial to investigate the safety and efficacy of a single dose of 400×10^6 cells (ORBCEL-C), a CD362-enriched, umbilical cord–derived MSC product, in 60 patients with moderate-to-severe COVID-19–related ARDS. The primary outcomes assessed were the incidence of serious adverse events (safety) and the oxygenation index (efficacy) at Day 7. Secondary outcomes included respiratory compliance, driving pressure, Pa_{O_2}/FI_{O_2} ratio, and Sequential Organ Failure Assessment score, as well as clinical outcomes such as ventilation duration, length of ICU and hospital stays, mortality, and long-term follow-up measures.

The study yielded encouraging results regarding the safety profile of ORBCEL-C, demonstrating no significant difference in the incidence of serious adverse events compared with placebo. In addition, transcriptomic analysis of peripheral blood samples provided evidence that the ORBCEL-C was active in modulating the peripheral blood transcriptome. However, despite the administration of a very large single dose of MSCs, there were no significant differences in the Day 7 oxygenation index, most secondary outcomes (including surrogate markers of pulmonary dysfunction), and mortality rates at various time points up to 2 years.

Dosing, Sex Disparity, and Subgroup Analysis

A key question is why this study was negative, considering the substantial body of basic science evidence suggesting the efficacy of MSCs in acute lung injury. Several potential explanations exist—aside from the possibility that MSCs simply lack efficacy in COVID-19 ARDS. First, it is possible that the specific dose of ORBCEL-C used, although large, was still insufficient to exert significant therapeutic effects in this patient population. The heterogeneity of the baseline characteristics, biology, physiology, and pathology among patients with ARDS may lead to variability in treatment response, necessitating individualized dosing strategies (4, 5). Second, the