Cleaving the Acute Respiratory Distress Syndrome into Treatable Traits

A Role for Caspase 1?

Acute respiratory distress syndrome (ARDS) is characterized by acute-onset, protein-rich pulmonary edema and is a frequent cause for acute respiratory failure (1). Rather than being a single disease with a specific cause, ARDS is a heterogeneous syndrome with several pathophysiological processes that drive increased pulmonary vascular permeability and subsequent pulmonary edema. The biological heterogeneity that is encountered in ARDS is one plausible explanation for the disappointing results of randomized controlled trials that studied the effects of pharmacological interventions in an unselected population (2). One of the major advances in the last decade has been the notion that there are multiple ARDS subphenotypes and that trials require predictive enrichment: inclusion of only those subgroups of patients who are likely to benefit from the intervention (2, 3). What the field needs now is a deeper understanding of the biological underpinnings of ARDS subphenotypes so that targeted, personalized therapeutic approaches can be tested.

In this issue of the *Journal*, Peukert and colleagues (pp. 53–63) beautifully illustrate this reverse-translational approach and show that subgroups of patients with ARDS differ substantially in the levels of inflammasome-derived cytokines (IL-1β and IL-18) in the airspace (4). They take this important observation back to the laboratory and show that inhibition of caspase 1, a key initiator of inflammasome activation, with tetracycline prevents lung injury in two animal models of direct acute lung injury induced by inhaled LPS and influenza virus. To close the translational loop, they take this new mechanistic insight back to humans and show that tetracycline inhibits IL-1β and IL-18 release from human ARDS alveolar macrophages. These findings allow them to propose that inclusion of patients with direct causes of ARDS might be one method of enrichment in future clinical trials (4).

A pessimist might argue that we have cured acute lung injury in rodents many times before (5), so what makes this study novel and exciting? Many other pharmacological treatments have been used in preclinical studies and showed improved survival and decreased lung injury only to fail completely in clinical trials. However, this study is unique in its translational precision approach. Peukert and colleagues started with the identification of a subset of patients with ARDS who showed biological evidence for activation of caspase 1 in the pulmonary compartment. They went on to use not one, but two animal models with a similar mechanism of lung injury development and were able to prove a causal relationship between caspase 1 activity and outcomes in these models. To bring these findings back to the bedside, they reexamined the subtype of patients with ARDS that were identified earlier and were able to confirm that tetracycline would limit caspase 1 activity of pulmonary leukocytes.

The combination of precision medicine and translation from bed to bench and back is novel to ARDS research and is the major strength of the study. Our colleagues who study and treat patients with asthma are way ahead of us in this regard. The development of IL-5 inhibition in hypereosinophilic asthma is a beautiful example of the bedside to bench to bedside approach (6). It is tempting to criticize the ARDS field for lagging behind in their approach to personalized medicine and putting the proverbial cart before the horse by studying the same treatment in all patients with ARDS without a good understanding of biologic heterogeneity. It is important to keep in mind that the "one size fits all" approach has led to major breakthroughs in the field and has saved countless lives because of the application of protective lung ventilation and other process-of-care measures. Some might argue that we have reached the limits of process-of-care improvements. Whether in agreement with this or not, it is clearly time for us to change our approach to studying ARDS and to learn some lessons about biologically relevant subphenotypes from our asthma colleagues.

This study also has some limitations. First, although two different animal models were used, they do not fully represent the complexity of most patients with ARDS. The models lacked invasive mechanical ventilation, were limited to a single hit, and were limited to C57BL/6J mice only. Second, the authors assumed that patients with a "direct" cause for lung injury were enriched for pulmonary caspase 1 activity. However, this conclusion was based on an average concentration of the biomarker within a clinical subphenotype, and the observed values varied wildly. A more direct measurement of pulmonary caspase 1 activity may be more appropriate for future patient selection. In addition, the concept of "direct" lung injury has existed as a clinically recognizable subphenotype, but this has not translated into clinically important differences between "direct" and "indirect" causes of ARDS. Thus, using this distinction in patients as a starting point for the study might not have been the most clinically relevant approach. It would be quite interesting to see if there are differences in inflammasome-derived cytokines in the well-described ARDS subphenotypes by Calfee and colleagues (7, 8), although a recent study suggests otherwise (9).

So, what can we learn from this study, and how can that inform future research approaches? Caspase 1 activity by alveolar leukocytes can be decreased with tetracycline, and it seems biologically plausible that this would decrease pulmonary injury in the subset of patients with ARDS with high BAL concentrations of IL-1β and IL-18. This study provides a clear path toward a phase 2 randomized controlled trial that employs predictive enrichment to include the right patients who may benefit from the intervention. The most obvious logistic hurdle for such a study would be the rapid and reliable quantification of the cytokines of interest in BAL fluid, and precisely that challenge shows entanglement of

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diagnostics and therapeutics in the application of precision medicine in ARDS. These challenges are currently being tackled by others (https://clinicaltrials.gov/ct2/show/NCT04009330), and it is possible that we will have rapid diagnostics in the not-so-distant future. The best lesson, one that we can act on starting today, is that the bedside to bench to bedside approach is a powerful method for understanding clinically relevant biology. This illustrates that the path toward clinical application of personalized interventions in ARDS requires synchronized research by multiple groups with complementary expertise. If these steps are taken in the coming years, the field may look back at this study as a pioneering step toward a treatable trait approach for ARDS (10). ■

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CFTR Modulators to the Rescue of Individuals with Cystic Fibrosis and Advanced Lung Disease

The development of CFTR modulators has been one of the most remarkable stories in respiratory medicine. Defining the genetic, molecular, and cellular biology of cystic fibrosis (CF) mutations enabled high-throughput screening to identify compounds that partially restore CFTR function. The first highly effective CFTR modulator became available in 2012 when the U.S. Food and Drug Administration approved ivacaftor (Kalydeco, IVA) for individuals with the G551D CFTR mutation. IVA substantially decreased sweat chloride, increased respiratory function, promoted weight gain, reduced exacerbation frequency, and improved the quality of life for patients with an FEV_1 40–90% predicted (1). Since that time, IVA was approved for several other gating mutations such that by early 2020, ∼20% of individuals with CF had access to an efficacious disease-modifying oral medication. Several studies have examined the effect of IVA on patients with advanced lung disease and demonstrated similar improvements to what was observed in patients with modest lung disease (2–5). More recently, the second highly effective CFTR modulator therapy, elexacaftor–tezacaftor–IVA (Trikafta, ETI) was approved for individuals with the F508del CFTR mutation. ETI also dramatically improves sweat chloride, FEV_1 (by ∼14% absolute predicted), nutritional status, exacerbation frequency, and quality of life for individuals with an FEV_1 40–90% predicted (6–8). Because F508del is the most common CFTR mutation, now ∼90% of individuals with CF have access to an efficacious disease-modifying therapy. Although the transformative effects of ETI have been extensively studied in

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