in the context of this work and other respiratory diseases (10)? Graham Hall and Charlie Irvin recently challenged the profession by asking, "As health professionals, do we have an obligation to reflect on what the actual pathophysiology for a specific lung disease is and considering this, look at different physiological outcomes beyond FEV_1?" (15). Indeed, within the realm of lung transplantation, should we call time on our obedience to a test that is "too little, too late"? Being cognizant of the devastating potential consequences for the transplanted patient, we need to embrace and incorporate a more physiologically relevant and structurally accurate noninvasive test to detect the site of pathology early, to finally unleash the noise of the silent zone. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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suPAR Surprises as a Biomarker of Invasive Outcomes in Pleural Infection

Pleural infection is a major healthcare burden worldwide. Adhesions and loculations, often present in pleural infection, have fascinated pulmonologists for centuries. Their pathogenesis and best management are still debated.

The fibrinolytic pathway has been the subject of active research, and derangements of the local fibrinolytic system can influence the pathogenesis of pleural organization and fibrotic repair, as reviewed elsewhere (1). The suPAR (soluble urokinase-type plasminogen activator receptor) represents a potential clinical application of the cumulative knowledge gained to date. In this issue of the *Journal* (p. 1545–1553), Arnold and colleagues (2) explore the measurement of suPAR as a new biomarker in pleural infection. Their findings merit further investigation.

suPAR occurs in biologic fluids, including plasma, urine, and pleural fluids, and is proteolytically cleaved from the surface of cells bearing the uPAR (urokinase-type plasminogen activator receptor), which regulates cellular proteolysis, viability, movement, and proliferation (3). It is also possible that an alternatively spliced variant of suPAR may contribute to the suPAR concentrations seen in pleural fluids, as has previously been demonstrated in cancer cell lines (4). suPAR concentrations increase in

Originally Published in Press as DOI: 10.1164/rccm.202003-0525ED on March 16, 2020

inflammatory conditions, including bacterial, viral, and mycobacterial infections and cancer (3). Pleural fluid suPAR concentrations have been shown to discriminate between effusions attributable to congestive heart failure of inflammatory or malignant causes (5, 6). Traditional biomarkers such as pleural fluid pH, glucose, and lactate dehydrogenase often influence decisions on chest tube placement in the setting of pleural infection, but they do not predict the need for intrapleural fibrinolytic therapy or surgery.

Arnold and colleagues found that pleural fluid suPAR concentrations were increased in 37 patients with pleural infections versus 47 control subjects who had either transudative effusions or malignancy (2). The pleural fluids were removed at presentation and archived, after which suPAR concentrations were measured using a commercially available assay. The assay detects suPAR (consisting of domains I–III) and the suPAR (or uPAR) domains II and III, so that the readout of the assay reflects intact suPAR and a fragment that may be present in solution. In addition, the assay may also detect the membrane-bound cell receptor uPAR because microvesicles or cellular fragments may be present in pleural fluids.

Pleural fluid suPAR concentrations were significantly elevated in pleural fluids obtained from patients with loculated pleural infection versus those with infection who did not have progression to loculation. Although traditional biomarker trends were similar, pleural fluid suPAR concentrations predicted subsequent chest tube insertion more accurately than did pleural fluid pH. Pleural fluid suPAR also more accurately predicted the need for more invasive management, as assessed by referral for intrapleural fibrinolytic therapy or thoracic surgery.

Clinician behavior in deciding on chest tube drainage, and more so in employing fibrinolytic therapy and surgery, is notoriously variable among or even within medical centers. It is therefore most intriguing that pleural fluid suPAR concentrations are able to predict these rather difficult clinical decisions. Can this be chance, or is suPAR causally related to more severe (or worsening of) parapneumonic effusions? To make a firm statement about the clinical relevance of suPAR will require a prospective validation cohort from different healthcare systems with assessment against clinical data relating to patient progress (e.g., ongoing fever, leukocyte counts, and C-reactive protein) and predetermined criteria for intrapleural fibrinolytic therapy and/or surgery.

Is it possible that suPAR is a marker of pleural loculation not specific to pleural infection? Pleural loculation is usually an indirect reflection of the degree of inflammation and not solely found in parapneumonic effusions. The authors provide data showing that similar results were found within an albeit small malignant effusion cohort, supporting this hypothesis. The findings suggest that high-grade inflammation that progresses to intrapleural organization results in elevations in pleural fluid suPAR that in turn can predict the need for interventions to expedite drainage in patients with pleural infection.

Loculations, however, are not good predictors of ability to drain pleural effusions; they are often (but not necessarily correctly) the reason why chest tubes are inserted and intrapleural therapy and/or surgery is initiated. Currently, there is no consensus about the definition of "loculation," let alone a validated quantification method of loculation in the literature. In daily practice, a loculated effusion can range from a few septations to extensive "honeycombing." In the study by Arnold and colleagues, loculation was graded as "yes" or "no" without a preset definition, often by junior staff. This highlights the need for a way to evaluate the severity of loculation within the pleural cavity, and suPAR may serve such a role. If so, the next step will be to determine what outcome suPAR (or degree of loculation) accurately predicts various pleural diseases extending beyond infection.

The results of the work of Arnold and colleagues add credence to the possibility that suPAR may contribute to the regulation of pleural loculation in addition to its role as a biomarker. suPAR is known to bind scuPA (single-chain urokinase plasminogen activator), which increases its ability to exhibit plasminogen activator activity (7). suPAR can also bind the more active two-chain urokinase (tcuPA) that derives from plasmin-mediated cleavage of scuPA and thus could localize plasminogen activator activity within pleural fluids. These effects could support fibrinolysis in the presence of low concentrations of PAI-1 (plasminogen activator inhibitor) that may occur after intrapleural administration of fibrinolysins, as occurs when scuPA is administered intrapleurally (8). However, suPAR-bound single- or two-chain uPA is susceptible to PAI-1, and increments of PAI-1 are generally seen in pleural loculation in pleural infection (1, 9). Thus, the role of suPAR in the regulation of intrapleural fibrinolytic therapy remains unclear and is worthy of further investigation.

Apart from suPAR, other new inflammation- and fibrinolysis-related biomarkers of the outcomes of pleural infection may soon emerge. For instance, PAI-1 and its activity have likewise been strongly implicated in the pathogenesis of pleural injury outcomes (1, 10). The ability of baseline pleural fluids to support fibrinolytic activity, called the "fibrinolytic potential," is another candidate biomarker (11). The clinical implication of these markers as predictors of treatment or prognosis provides a new and exciting area of pleural disease research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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