Thinking small, but with big league consequences: procoagulant microparticles in the alveolar space

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PULMONARY EDEMA FLUID is not just water but is instead a complex biological medium. The daedal nature and variability of its makeup are particularly apparent when samples of alveolar edema or bronchoalveolar lavage fluid from patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) are examined compared with those from subjects with hydrostatic (“cardiogenic”) pulmonary edema (5). In their recent article, Bastarache and colleagues (2) describe a previously unrecognized element in the complex composition of alveolar edema from subjects with ALI/ARDS: procoagulant microparticles (MPs) that contribute tissue factor (TF) activity and may be critically involved in deposition of fibrin on the injured alveolar surface. Because fibrin deposition may be a key factor in persistence and progression of ALI/ARDS and in lethal complications such as multiple organ failure (5, 12), focusing small, in this case, on cellular MPs that have at times been dismissed as biologically irrelevant detritus, may yield big league insights into dysregulated pathophysiological mechanisms in the injured lung.

Using differential sedimentation and centrifugation protocols and a MP capture assay, the authors found evidence that the alveolar edema fluid from patients with ALI/ARDS is enriched in MPs compared with hydrostatic edema fluid. Spherical particles of a size and configuration consistent with MPs were also detected by electron microscopy. Of note, vesicles of size and structure suggestive of MPs can be seen in the alveolar space in electron micrographs in the classic descriptions of the histology of human ALI/ARDS by Bachofen and Weibel (1) and in later accounts (11). Bastarache et al. (2) also reported that MPs were enriched in a sucrose gradient fraction that contained the highest concentrations of TF, and that this fraction was distinct from those containing the highest concentrations of total protein; furthermore, procoagulant activity measured by a clot time acceleration assay was greater in the MP- and TF-rich fraction of edema fluid from ALI/ARDS subjects than in other fractions. The MP-rich fraction from ALI/ARDS samples had increased procoagulant activity compared with the same fraction of hydrostatic edema fluid samples, consistent with earlier analysis of TF and procoagulant activity in these two forms of lung edema (3). Together, these findings suggested to the authors that intra-alveolar MPs containing high levels of TF likely contribute to intra-alveolar coagulation and fibrin deposition, since MPs have been shown to influence clot propagation in the intravascular space (reviewed in Ref. 6; 10). Bastarache et al. also suggest that formation of procoagulant MPs may be a novel target for therapeutic intervention in ALI/ARDS.

This study reports the first evidence for procoagulant MPs in the alveolar space of the injured lung, but what, in fact, are MPs? Circulating intravascular procoagulant MPs have been defined as membrane fragments that range in size from 0.1 to 1 µm and that display on their surfaces negatively charged phospholipids that can initiate and accelerate coagulation, chiefly phosphatidylinerine (6, 10). Although originally thought to be inert and randomly produced membrane fragments of injured and dying cells, this view has changed for many investigators and physicians. There is evidence that intravascular MPs have activities that can both positively and negatively modify hemostasis, inflammation, immune responses, and angiogenesis depending on the question asked and conditions of the experiment, and that MPs are generated in regulated fashion by parent cells (4, 6, 7). There is also considerable evidence, although controversial in some aspects, that intravascular MPs can deliver TF to sites of vascular injury and thrombosis and that circulating MPs can target to evolving thrombi via mechanisms that involve P-selectin/P-selectin glycoprotein-1 and other molecular interactions, depending on the cellular source of MPs and the experimental or pathological conditions (reviewed in Ref. 6; 10). Clinical studies suggest that circulating MPs are effectors and modulators of a variety of thrombotic, inflammatory, and immune diseases (6). The report by Bastarache et al. (2) extends questions related to the pathological activities of MPs to the alveolar space, and identifies ALI/ARDS as a human syndrome in which MPs may contribute to cellular pathobiology. As a corollary, deposition and activities of MPs in the vasculature of the injured lung remain to be explored.

Where do MPs come from? Bastarache et al. (2) suggest that injured alveolar epithelial cells are sources of MPs in edema fluid from subjects with ALI/ARDS, based on higher levels of receptor for advanced glycation end products (RAGE) associated with MPs in ALI/ARDS edema fluid. In addition, they found release of procoagulant activity, TF, and MPs from the A549 epithelial cell line activated with cytokines in vitro. The authors cautiously and correctly point out, however, that there are several possible sources of intra-alveolar MPs in ALI/ARDS. Activated platelets, myeloid leukocytes, and endothelial cells are key “parent” sources for circulating MPs, as are erythrocytes and tumor cells depending on the experimental model and/or clinical condition (reviewed in Ref. 6; 10). There is evidence that many of these cell types have access to the alveolar space in ALI/ARDS (1, 5, 11) and could be parent cells for intra-alveolar MPs. Under conditions of fibrin deposition and inflammation, platelets and monocytes may be particularly important sources of MPs that bear TF, which can be deposited on their surfaces by synthesis by the
parent cell and/or by intercellular transfer (4, 6, 8, 9a). Complete characterization of MPs requires demonstration of at least one antigenic marker distinctive for the parent cell (10). The marker used by Bastarache et al. (2), RAGE, is not unique to alveolar epithelial cells and is basally expressed and/or induced on other cell types (9). Thus, additional analysis to dissect the sources of intra-alveolar MPs in ALI/ARDS is indicated.

Small and seemingly simple forms in nature sometimes are taken as evidence for trivial or inconsequential function and biological impact. This may have been true for MPs in the past, but the report by Bastarache et al. (2) and observations in a significant body of literature, only some of which is cited here, argue otherwise. If MPs are indeed found to be therapeutic targets that can influence fibrin deposition and its sequelae in the injured lung, then size of the effector does not matter in this instance, and it is substance, potentially, uniquely packaged, and delivered procoagulant activity in this case, that counts.

REFERENCES