Editorial

Hyaluronan in acute respiratory distress syndrome (ARDS): simply a biomarker or a deeper insight into ARDS mechanisms?

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Acute respiratory distress syndrome (ARDS) affects a large number of patients admitted to the intensive care unit, it's usually associated with multiple organ dysfunctions and mortality rate is very high (≈40%) (1).

Identifying the ARDS cause while providing organs support and protection represents the mainstay of ARDS treatment and mechanical ventilation is mandatory to maintain viable oxygenation and assure carbon dioxide removal during ARDS. Major research effort for the past 50 years focused on understanding which ventilator strategy would allow lung repair while minimizing further harm. This clinical approach was paralleled by digging into ARDS pathophysiology to identify specific molecular targets and improve the care of ARDS patients (2-4).

Unbalanced lung inflammation in response to a *noxious stimulus* represents the initiating and perpetrating molecular mechanism at the basis of ARDS pathogenesis. It results in disruption of alveolar-capillary membrane integrity, increased lung permeability and non-cardiogenic alveolar flooding (5). Unfortunately, all pharmacological therapies aimed to reduce deregulated lung inflammatory response in ARDS showed promising results in pre-clinical tests but failed to improve patients outcome (6-8).

On a bio-molecular level, the acute phase of ARDS is characterized by inflammation, damage and apoptosis of cells composing the alveolar-capillary barrier. These events are often followed (or even co-exist) by a fibro-proliferative phase, during which proliferation of pneumocytes, fibroblasts, and myofibroblasts as well as deregulated deposition of extracellular matrix occur. This phenomenon might ultimately lead to pulmonary fibrosis, which significantly contribute to impaired respiratory mechanics, prolonged weaning from mechanical ventilation and worse outcome of ARDS patients (9). The processes through which the lungs of ARDS patients either recover their structure and mechanical properties or progress to develop lung fibrosis have not been clarified yet.

In the light of the above mentioned molecular and clinical scenario, we read with interest the study from Esposito and colleagues, recently published on the journal *Critical Care* (10). The authors performed a retrospective analysis of prospectively collected data from patients previously enrolled in the Phase II Randomized Trial of Fish Oil in Patients with Acute Lung Injury (NCT00351533) at five North American medical centers (11). The original randomized trial did not show a reduction in lung inflammation, measured as interleukin (IL)-8 concentration in broncho-alveolar lavage fluid (BALF), among ARDS patients receiving enteral fish oil supplementation. However, in the present study, the researchers shifted their focus on profibrotic inflammation mechanisms and measured hyaluronan (HA) concentration in serum and BALF collected from 86 patients diagnosed with ARDS according to the 1994 American-European Consensus Conference. Samples were collected at enrollment (within 48 hours from ARDS diagnosis) and on study day 4 and 8.

The rationale for the study is based on the evidence that HA is an important component of the lung

extracellular matrix and, besides structural function such as tissue hydration, lubrication and support for cells, this glycosaminoglycan plays an essential role in lung tissue homeostasis (12). It has been widely showed that, based on their chain length, HA molecules exert different biological activities: high-molecular-weight (HMW) HA helps maintaining lung tissue properties promoting homeostasis and repair; whereas low-molecular-weight (LMW) HA is a lung tissue damage sensor taking crucial part into activation of the acute phase inflammatory response (13). In the context of ARDS, LMW-HA fragments have been reported to promote inflammation by translating "danger signals" to infiltrating leukocytes through activation and maturation of dendritic cells and the increased release of pro-inflammatory cytokines such as IL-1ß, Tumor Necrosis Factor (TNF)-α, IL-6, and IL-12 by multiple cell types (14). Of note, accumulation of LMW-HA molecules in the small airways not only stimulates macrophages to release chemokines, cytokines, and growth factors, but also promotes fluid retention in the extracellular space, thereby contributing to interstitial and alveolar edema (15). HA oligos with molecular weight <10 kDa have also been associated with unbalanced tissue remodeling, which, depending on the severity of tissue damage, contributes to extracellular matrix deposition and increased risk of lung fibrosis (13). By contrast, HMW-HA mostly exerts anti-inflammatory properties by interaction with CD44, the most important cell-surface HA-binding transmembrane glycoprotein, widely expressed on the membrane of both immune and structural cells. HMW-HA to CD44 cross-linking modulates epithelial cells toll-like receptor (TLR) 2 and 4 signaling at multiple points, preventing type II cell apoptosis (15) and inhibiting inflammation, thereby contributing to maintain tissue integrity. In a pre-clinical model of sterile lung inflammation CD44 was shown to play a critical role in the resolution of tissue inflammation by promoting removal of HA fragments (16). *In-vitro* data, further confirmed in an *in-vivo* model of LPS-induced inflammatory lung injury with increased vascular permeability, suggest that HMW-HA, via a CD44-mediated pathway, exerts a protective effect on restoring the integrity of the endothelial-epithelial barrier, potentially indicating that heavy-chain HA might represents a therapeutic target for syndromes characterized by increased vascular permeability (17). In summary, high and low molecular weight HA fragments and the HA receptors expressed by epithelial and immune cells constitute an integrated system that allow to sense/detect the presence of intact or fragmented extracellular matrix, starting a pro- and anti-inflammatory response aimed at eliminating the *noxa* while restoring lung tissue integrity. The fine-tuning of these mechanisms activated from the recognition of tissue fragments is crucial for determining the phenotype of inflammatory response either toward inflammation propagation and fibrosis or tissue repair.

Furthermore, HA is a major component of the endothelial glycocalyx (18), a negatively charged mesh of membrane glycoproteins, proteoglycans and glycosaminoglycans located on the luminal side of the vessels endothelium. Endothelial glycocalyx is believed to have important biological functions, including regulation of vascular permeability, modulation of leukocyte rolling and adhesion, transduction of shear stress leading to nitric oxide release and inhibition of coagulation. Having the lungs the largest vascular surface in the body, they contains extremely large amount of HA.

It has been demonstrated that the application of either sterile or infectious injurious stimuli to the lungs induces HA degradation and release of HA fragments in alveolar fluids and blood. Gao and colleagues described that increased levels of oxidants in the lung lead to an increase in LMW-HA (19). Lung ischemia induced an increase in LMW-HA in mice lungs subject to ischemic injury through fragmentation and *de novo* synthesis (20). Moriondo *et al.* described that by applying progressively increasing levels of mechanical stress on the lung parenchyma, as a model of ventilator induced lung injury, glycosaminoglycan fragmentation occurred even in the presence of previously healthy rats' lungs (21). Further evidence of the role of LMW-HA in experimental ARDS comes from *in vitro* data where stretch-induced LMW-HA from fibroblasts increased production of IL-8 from lung epithelial cells (22). In the clinical setting, a previous exploratory study from Hällgren *et al.* (23) reported increased HA concentration in BALF from twelve ARDS patients, compared to control subjects. Since BALF HA levels could not be completely explained by passive leakage from the bloodstream, active release of HA has been hypothesized secondary to HA fragmentation or *de novo* synthesis. Furthermore, the concentration of HA in the alveolar and extracellular space has been suggested to contribute to water retention within the lung parenchyma, as shown by the correlation between HA BALF levels and worsening of gas exchange (23).

In the present study, the researchers correlated the HA serum and BALF concentration with scores of pulmonary injury [Lung Injury Score (LIS)] and systemic severity [Sequential Organ Failure Assessment score (SOFA score)]. The authors reported a positive correlation between day

0 serum and BALF levels of HA and the values of LIS, specifically through the association between HA levels and the degree of hypoxemia and set positive end-expiratory pressure level. By investigating the association between HA levels and SOFA score as index of systemic involvement, Esposito and colleagues described that, while HA levels in BALF showed only a positive correlation with the respiratory component of SOFA score, serum HA levels were increased in patients with worsen respiratory, coagulation, hepatic, cardiovascular and renal failures, based on evaluation by the SOFA. The study did not identify any correlation between serum and BALF HA levels and clinical relevant outcomes such as mortality and ventilator free days. The authors attributed this result to low numerosity, to an unexpected low mortality rate among the cohort of ARDS patients enrolled in the trial and to the confounders that might interfere with mortality and duration of mechanical ventilation in ICU patients with ARDS. Main finding of the study is that serum and BALF HA levels, coming from structural alterations affecting the lung, are related to the severity of lung disease and to the severity of multiple distal organs dysfunction. The study is a retrospective analysis of prospectively collected data and thus, for its nature, should be considered only as hypothesis generating. Moreover, the study is affected by some limitations. Firstly, even if matching a posteriori the Berlin Criteria for ARDS diagnosis (24), patients were enrolled based on the previous definition of ARDS (25), this leading to include mild to moderate ARDS patients. Second, the patients included in the analysis were selected from both arms of the Fish Oil in Patients with Acute Lung Injury Randomized Clinical Trial. The authors tried to correct this potential bias by including treatment group as covariate in the multiple regression analysis. Third, concerning the HA measurement, the authors did not differentiate between HA fragments of different molecular weight, while measuring the differential release of both low and high molecular weight HA might represent a crucial information to clarify the biological role of HA. Fourth, by study methodology, it is not possible to identify which source of HA was predominant between the lung extracellular matrix and the endothelial surface, which, instead, could have shed light on progressive steps involved in development of lung injury.

Nonetheless, the strong bio-molecular rationale and the correlation between the severity of the disease and the HA levels in biological fluids disclosed by this study, pose the basis for further pre-clinical and clinical investigations on the role of HA molecules in lung injury and lung healing.

We might speculate that, in the perspective of developing more precisely tailored medicine, a thorough study of the differential HA concentrations based on the molecules size, better description of the source of HA (either from fragmentation and/or *de novo* production) and, further investigation on the pathway activated by HA could provide useful information into ARDS pathogenesis. Given the relevance of minimizing long-term lung fibrosis development throughout the clinical course of the disease, we deem necessary to consider HA as potential marker of increased risk and target for therapeutic interventions in ARDS patients.

In conclusion, the study from Esposito and coworkers provides interesting new experimental evidence on the association between HA and loss of lung tissue integrity as well as with clinically relevant scores of systemic involvement during ARDS. Looking at the present report in the light of data from previous literature, the role of HA in ARDS pathogenesis, recovery and development of fibrosis deserves further scrutiny.

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Footnote

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