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Sugarcoating Lung Injury: A Novel Role for High-Molecular-Weight Hyaluronan in Pneumonia

Despite many decades of active research and several clinical treatment trials, acute lung injury (ALI)/acute respiratory distress syndrome remains a severe complication of pneumonia and severe sepsis, and pharmacological treatment is still lacking (1). The traditional treatment of pneumonia (and infections in general) has been to focus on the microbial component and treat patients with antibiotics. In recent years, increased attention has been given to the host response and ways to ameliorate the dysregulated inflammatory response and tissue injury occurring after infection.

In this issue of the *Journal*, Liu and colleagues (pp. 1234–1245) provide an important contribution to the literature (2) by using translationally relevant human ALI and pneumonia models to demonstrate the utility of high-molecular-weight hyaluronan (HMWHA) in ALI in infection. There is increased awareness that extracellular vesicles (EVs) play an important role in the initiation and propagation of acute lung injury (3). The authors demonstrate that EVs are released after the administration of *Escherichia coli* in *ex vivo* perfused human lungs, predominantly by endothelial cells and circulating platelets. These EVs then promote an inflammatory response, leading to lung injury. Addition of HMWHA in the perfusate after EV administration improved alveolar fluid clearance, which would decrease alveolar edema, and decreased TNFα (tumor necrosis factor α) and IL-6 levels in the lung lavage fluid. Interestingly, a decrease in cytokine levels was noted after HMWHA treatment, even though total white blood cell and neutrophil counts did not significantly change, suggesting that HMWHA reduced inflammatory cell activation. Interestingly, in spite of its very large size (molecular weight $>$ 1,000 kD), HMWHA added in the perfusate was detected in the alveolar after *E. coli* instillation. *Ex vivo*, HMWHA improved bacterial clearance by phagocytes, and this was mirrored by decreased colony-forming units in the pneumonia model. Furthermore, HMWHA decreased EV uptake by monocytes in a (at least partially) CD44 (cluster of differentiation 44)-dependent manner and reduced inflammatory cytokine release after EV exposure. In aggregate, these findings support that HMWHA may be of therapeutic utility in ALI and pneumonia.

What is the relevance of these exciting findings? Hyaluronic acid (HA) is a deceptively simple molecule present in all extracellular matrices, consisting of repeating disaccharides made of N-acetylglucosamine and glucuronic acid, and does not undergo further modification after its expression by HA synthases. Reactive oxygen species (e.g., HOCl) released by activated inflammatory cells, as well as exposures such as ozone and halogens, degrade HMWHA to low-molecular-weight fragments (LMWHA) of 0.1–500 kD (4, 5). Although HMWHA and LMWHA bind to the same receptors, they exert opposite effects (4). LMWHA activates innate and adaptive immunity and increases permeability and airway resistance by activating RhoA (ras homolog gene family, member A) and ROCK2 (rho-associated coiled-coil containing protein kinase 2), whereas HMWHA has strong antiinflammatory and prohomeostasis functions (4). The reason for this difference may be differences in receptor engagement or cell uptake depending on size, but ultimately remains elusive. Recent work suggests that HMWHA may create a transmembrane "picket fence" barrier, tethered on CD44 and the cellular cytoskeleton, that prevents ligands from reaching and activating their respective receptors, an effect that as abolished after HA degradation (6). HMWHA also binds several extracellular proteins with strong antiinflammatory potential, such as inter-α-inhibitor, which is associated with decreased endothelial injury (7) and organ dysfunction (8, 9) in sepsis, and pentraxin-3, which contributes to host defense, including prevention against aspergillosis in stem cell transplant recipients (10). Furthermore, HMWHA is a recently recognized crucial constituent of the endothelial glycocalyx, and HA homeostasis is central to the maintenance of a healthy endothelial barrier and the avoidance of tissue injury (11). Finally, HA has well-described antimicrobial properties, inhibiting bacterial adhesion and promoting phagocytosis (4). Thus, HMWHA acts along with its binding partners in the cell, the circulation, and the interstitium and on pathogens to reduce inflammation and promote antibacterial properties of the host.

A major theoretical concern, whenever antiinflammatory applications of HMWHA are being discussed, is its potential degradation into smaller, proinflammatory fragments. It is interesting to note, however, that in this study, HMWHA retained its large molecular weight despite being several hours in a

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presumably prodegradation environment. This agrees with existing literature on the use of HMWHA in lung inflammation (12) and suggests that pharmacologically dosed HMWHA either overwhelms or somehow escapes the degrading activity of the inflammatory milieu and therefore is safe to use in this setting. It should be noted that the therapeutic potential of HMWHA in lung disease is very strong. Inhaled HMWHA is already in clinical use as an ancillary treatment in cystic fibrosis (12) and sinusitis (13) with an excellent safety profile and is being evaluated in chronic obstructive pulmonary disease (14). Experimental evidence further suggests the utility of HMWHA as a treatment modality in asthma (15, 16), acid aspiration lung injury (17), halogen lung injury (5), and chronic lung allograft dysfunction (18). The common thread here is the antiinflammatory and cell-protective action of HMWHA, which can be applied to any disease in which inflammation and tissue injury are prominent. Thus, there are tangible translational implications to this paper.

We should note several limitations in this study, which will need to be taken into consideration when discussing the implications. The experimental setup was somewhat artificial, using isolated and perfused lungs as opposed to a living organism with intact anatomy and immunology. Furthermore, HMWHA was given in fairly high doses, and when given intrabronchially, it was apparently instilled and not nebulized (as would be the likely therapeutic delivery mode). It is therefore unclear whether HMWHA would be equally effective in clinically used doses. It is also unclear how a large molecule such as HMWHA translocates from the vascular space to the airway. Furthermore, the authors studied very early stages of lung infection (i.e., within hours of bacterial seeding). Thus, the conclusions may not be entirely translatable to a pneumonia setting in which lung consolidation (with associated ventilation and perfusion defects) is prevalent. In fact (and as a corollary), it may be prudent to consider HMWHA as ancillary prophylaxis for reducing the incidence of acute respiratory distress syndrome in septic shock, where translocation of gut bacteria into the circulation is a prominent feature. Other suitable applications may include lung allograft preservation and primary graft dysfunction. Thus, far from limiting possibilities, this paper supports exciting new avenues for HMWHA as a treatment modality in lung injury settings. ■

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Stavros Garantziotis, M.D.
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

Sadis Matalon, Ph.D.
University of Alabama in Birmingham
Birmingham, Alabama

ORCID ID: 0000-0003-4007-375X (S.G.).

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