Hyaluronan: Local Climate Change in Asthma?

The extracellular matrix (ECM) in the lung is most commonly characterized in terms of its fundamental fibrillar composition: type I collagen and elastic fibers. These elegant structural proteins give the lungs their remarkable physiologic characteristics that have provided selective advantages for vertebrate life forms, and their study has provided gainful employment for research and clinical professionals who deal with their involvement in a variety of diseases. Their functional impacts are readily measurable, and highly useful for defining normal versus abnormal health status. A fuller understanding of other components of the ECM's composition and functionality has finally begun to emerge, and with it has come an appreciation for the complex intricacies of their contributions to biological microenvironments and relationships with cells, both fixed and migratory.

Clearly, what can be physically and microscopically visualized and quantified has commanded the attention of basic and clinical scientists alike, and rightfully so. Much of what goes wrong in the lung ultimately affects collagen and elastic fiber integrity and function, as manifested in chronic obstructive pulmonary disease, interstitial lung disease, bronchopulmonary displasia, and related diseases. The significant quantities of so-called "ground substance," which includes the glycosaminoglycans chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate, heparin, and hyaluronan (HA; also known as hyaluronate or hyaluronic acid), were presumed to function primarily to hold water and thought of simply as an interstitial filler, adding volume and texture. Early work on tissue regeneration, however, demonstrated that this "filler" could be very important biologically. Studies in newt limbs were the first to show that proliferation occurred in HA-rich tissues, and differentiation was closely linked with chondroitin sulfate (1). These and numerous subsequent studies led to the conclusion that the production or removal of specific nonfibrillar ECM components necessarily preceded temporally organized, critical events that control cellular attachment, migration, differentiation, survival, and/or senescence, as well as tissue expansion and maturation. Importantly, this conceptually changed how ECMs fit into the context of the biological activities of a tissue and/or organ, and codified them as true biological response modifiers.

HA has been studied in a wide variety of biological systems and pathologies. It is a critical regulator of inflammation (2) and has a distinct role in airway diseases such as rhinosinusitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, and primary ciliary dyskinesia (3, 4). More specifically, HA has been shown to orchestrate TGF-β–dependent maintenance of the myofibroblast phenotype (5) and control the deposition of fibronectin and collagen, as well as TGF-β induction of lung myofibroblasts (6). Relatedly, HA synthase 2 (HAS2), a membrane-bound enzyme that is responsible for the production of HA, regulates fibroblast senescence in pulmonary fibrosis (7). In this issue of the *Journal*, Walker and colleagues (pp. 702–710) hypothesize that peribronchiolar accumulation of HA contributes to airway inflammation, remodeling, and hyperresponsiveness in asthma (8). To examine its role(s) in this context, they challenged mice with targeted overexpression of HAS2 to stimulate production of HA. They then examined its overexpression in myofibroblasts and smooth muscle cells expressing the α-smooth muscle actin (α-SMA) promoter in a chronic model of allergic airway disease using aerosolized ovalbumin (OVA). Predictably, the results demonstrated significantly increased peribronchial HA in OVA-challenged α-SMA–HAS^{+} mice, with an accompanying increase in collagen (trichrome staining) compared with α-SMA–HAS^{-} and naive α-SMA–HAS^{+} mice. One of the major unexpected findings, however, was that these same animals displayed significantly reduced airway responsiveness to methacholine compared with α-SMA–$HAS2^{-}$ mice. This was attributed to the observed peribronchial fibrosis and resulting stiffness of the proximal airways, as evidenced by measured airway resistance. Interestingly, unchallenged α-SMA–HAS^{+} mice had peribronchial HA levels comparable to those observed in the OVA-challenged α-SMA–HAS^{-} mice, which did not correlate with α-SMA and collagen levels, suggesting that overexpression of *HAS* alone does not drive the tissue response. However, previous studies have shown that HA from myofibroblasts can promote collagen synthesis and deposition (9, 10), and the authors argue in favor of the notion that *HAS* overexpression contributes to myofibroblast and smooth muscle cell–mediated increased collagen deposition, leading to stiffer airways. This argument might have been strengthened by measurements of total lung collagen (hydroxyproline) and/or gene expression of Col1a1 and/or fibronectin (11). Nevertheless, similar increases in HA, *HAS2*, and *HAS*3 have been observed in a cockroach antigen–induced model of allergic asthma in mice, and increased expression of *HAS2 a*nd *HAS3* was found in primary isolated bronchial epithelial cells from asthmatic children compared with those from healthy children (12). Collectively, this and previous studies suggest important roles for *HAS* expression and HA production by airway fibroblasts in tissue remodeling and alterations in airway responsiveness in allergic asthma. It is hoped that in this will define the role that HA fragments play in the described model, as they have previously been shown to be important mediators in human asthma (13). These studies provide new insights into components of the ECM as important biological response modifiers in the lung, and provide a new and expanding context for basic and clinical pulmonary research. ■

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