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Role of hyaluronan and hyaluronan-binding proteins in lung pathobiology

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Lennon FE, Singleton PA. Role of hyaluronan and hyaluronan-binding proteins in lung pathobiology. *Am J Physiol Lung Cell Mol Physiol* 301: L137–L147, 2011. First published May 13, 2011; doi:10.1152/ajplung.00071.2010.—Hyaluronan (HA) has diverse functions in normal lung homeostasis and pulmonary disease. HA constitutes the major glycosaminoglycan in lung tissue, with HA degradation products, produced by hyaluronidase enzymes and reactive oxygen species, being implicated in several lung diseases, including acute lung injury, asthma, chronic obstructive pulmonary disease, and pulmonary hypertension. The differential activities of HA and its degradation products are due, in part, to regulation of multiple HA-binding proteins, including cluster of differentiation 44 (CD44), Toll-like receptor 4 (TLR4), HA-binding protein 2 (HABP2), and receptor for HA-mediated motility (RHAMM). Recent research indicates that exogenous administration of high-molecular-weight HA can serve as a novel therapeutic intervention for lung diseases, including lipopolysaccharide (LPS)-induced acute lung injury, sepsis/ventilator-induced lung injury, and airway hyperreactivity. This review focuses on the regulatory role of HA and HA-binding proteins in lung pathology and discusses the capacity of HA to augment and inhibit various lung diseases.

lung disease; therapy

HYALURONAN (HA), the major nonsulfated glycosaminoglycan (GAG) in the lung, is a dynamic molecule that can differentially promote or inhibit lung pathology on the basis of its molecular weight and accessibility to various HA-binding proteins. HA comprises a linear repeat of disaccharide units consisting of D-glucuronic acid and *N*-acetylglucosamine (1, 61, 102, 149) (Fig. 1). The prevalent form of HA in vivo is high-molecular-weight ($>1 \times 10^6$) HA (HMW-HA) (1, 61, 102). Structurally, HMW-HA exhibits a random coil structure that can expand in aqueous solutions (117, 141). Aqueous HMW-HA is highly viscous and elastic, properties that contribute to its space-filling and filtering functions (39, 117). In the lungs, HA is mainly located in the peribronchial and interalveolar/perialveolar tissue (62).

Proinflammatory cytokines, including TNFα, IL-1β, and LPS, induce HA production in vitro by various cell types, including endothelial (91), dendritic (8), and fibroblast (153) cells. Increased HA and its degradation products are observed in animal models of chronic obstructive pulmonary disease (COPD) and bleomycin-induced lung injury (31, 101, 160). Furthermore, increased HA levels are observed in bronchoalveolar lavage (BAL) fluid and/or plasma from patients with lung disorders such as pulmonary fibrosis (7), COPD (31), allergic alveolitis (128), asthma (115, 161), interstitial lung disease (14), sarcoidosis (89), and idiopathic pulmonary arterial hypertension (106). An increase in HA production has also been reported in airway epithelial cells in response to tunicamycin-induced endoplasmic reticulum stress (70). The levels of HA are regulated, in part, by the opposing activities of HA synthases and hyaluronidases (18, 141). HA can directly influence cell behavior through binding cell surface receptors. It has long been known that molecular weight is an important factor in regulation of HA's signaling activities. HMW-HA can induce cyclooxygenase-2 expression in endothelial cells via cluster of differentiation 44 (CD44) (94), mediate epithelial-mesenchymal transition during heart valve formation via ErbB2 (13), and enhance endothelial cell barrier function in the lung via CD44, the sphingosine 1-phosphate (S1P1) receptor, Akt, and Rac signaling (124, 125). Low-molecular-weight HA (LMW-HA), on the other hand, has been shown to decrease endothelial cell barrier function (124, 125), stimulate angiogenesis (30), and induce expression of a host of inflammatory mediators in alveolar macrophages, including macrophage inflammatory protein-1α (MIP-1α), regulated upon activation, normal T cell expressed and secreted (RANTES), Mig, IFN-γ-induced protein 10, and plasminogen activator inhibitor 1, via CD44 and Toll-like receptor (TLR) 2 and TLR4 (57, 58, 60, 86). Therefore, the effects of HA are wide-ranging and are dependent not only on its molecular weight, but also on the specific receptors expressed and the cell type involved.

HA Synthases and Lung Disease

HA is synthesized by at least three HA synthases (HAS1, HAS2, and HAS3), which are well conserved evolutionally, despite being located on separate chromosomes (27). The synthases comprise seven membrane-spanning regions (which are hypothesized to form a channel) and a large cytoplasmic loop (the putative substrate-binding domain). The mode of HA synthesis is unusual, in that it is synthesized at the inner face of the plasma membrane, and not inside the Golgi, as is usual for

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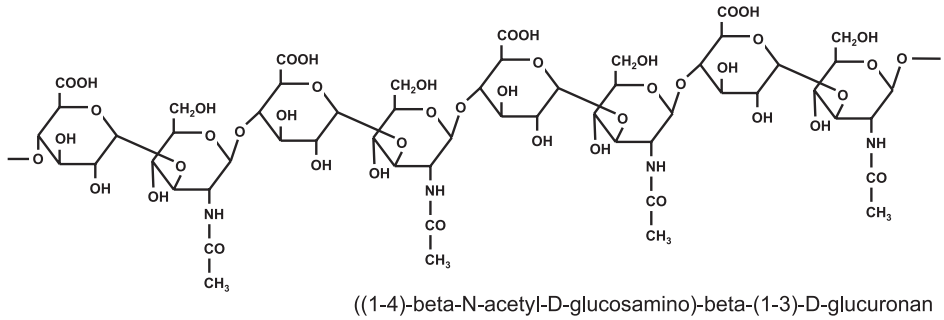

Fig. 1. Structure of hyaluronan (HA). HA is composed of a linear repeat of disaccharide units consisting of D-glucuronic acid and *N*-acetylglucosamine. Molecular weight of HA is $>1 \times 10^6$ in vivo (140, 141).

other GAGs. The growing HA molecule is extended at the reducing, rather than the nonreducing, terminus, and as the polymer grows, it is extruded into the extracellular space via the membrane-spanning domains of the HA synthase (98, 140). Although HA synthases catalyze the same reaction, the three enzymes differ in a number of ways: *1*) K_m values for their substrates (D-glucuronic acid and *N*-acetylglucosamine), leading to differential rates of HA synthesis (59) and *2*) production of $>5 \times 10^5$ molecular weight (M_r) HA by HAS1 and HAS2 and $<5 \times 10^5$ M_r HA by HAS3 (152). These differences are believed to contribute to the multiple types of HA matrix secreted by different cell types (24, 59). Studies utilizing HA synthase gene knockout mice indicate that only HAS2 is required for viability, with HAS2 deletion resulting in lethal defects in cardiac development and vascular abnormalities that are rescued by addition of exogenous 7.5×10^5 M_r HA (12, 13).

HA synthase expression is altered in a number of lung pathologies. HAS2 expression is increased in an animal model of monocrotaline-induced pulmonary hypertension, leading to increased total lung HA concentration (105). In addition, increased HAS1 and decreased HAS2 levels are observed in pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension, where total lung HA concentration was also increased (106). In a murine model of asthma, expression of HAS1 and HAS2 is increased in lung tissue (22). Furthermore, an increase in HA accumulation is associated with lung airways, blood vessels, and alveolar interstitium (22). In contrast, HAS1 and HAS2 are decreased in primary airway smooth muscle cells from asthma patients, resulting in secretion of lower levels of HA into the cell culture medium (67). HAS3 levels are increased in the lungs of mice in a cigarette smoke model of COPD (11). These mice also show increased HA deposition in the alveolar walls and peribronchial regions. Further characterization of the HA deposits by electrophoresis indicates that its molecular weight is lower (7×10^4) than that of HA from control lungs (5×10^5). Bai et al. (5) utilized a HA synthase knockout mouse to study the role of HAS3 and LMW-HA in ventilator-induced lung injury (VILI). While they observed an increase in LMW-HA and neutrophil infiltration in control animals at high-ventilation tidal volumes, no increase in LMW-HA was detected in the HAS3 knockout animals, and neutrophil infiltration was decreased (5). Lauer et al. (70) also showed that HA synthesis may be regulated by endoplasmic reticulum stress, as they observed an increase in the HA matrix secreted by airway epithelial cells following treatment with tunicamycin. This matrix stimulated the binding of a macrophage precursor cell line, U937, to the epithelial cell layer (70). Unfortunately, Lauer et al. did not examine the expression of HA synthase in these cells or its activity following tunicamycin treatment. These studies and others indicate that HA synthesis has a role in many lung pathologies (5). HA synthase levels are variable, depending on the pulmonary cell type and disease state. In most of these studies, an increase or a decrease in HA synthase expression is accompanied by the expected increase or decrease in HA deposition in the lung. Although HA synthesis and total HA concentration are important in regulating lung function, we must also consider that HA degradation products can alter downstream signaling pathways and directly affect lung function.

Hyaluronans and Lung Disease

HA is degraded by hyaluronidases to produce lower-molecular-weight ($<5 \times 10^5$) fragments (47). Six hyaluronidase genes encode HYAL-1, -2, -3, and -4, PHYAL1 (a pseudogene), and PH-20 (27, 130–132). A recent study by Hofinger et al. (54) revealed that HA degradation by hyaluronidase enzymes may be pH-dependent. HYAL-1 was found to have maximal and complete HA-degrading activity at pH 3.5–4.0, which is consistent with its role as a HA-degrading enzyme within the lysosome. PH-20 continuously degrades HMW-HA to small oligosaccharides at pH 4.5; at pH 5.5, HA is degraded to larger fragments (54). Unfortunately, the other hyaluronidase proteins were not examined in this study, but the authors speculate that the pH dependence of these enzymes could lead to different biological responses based on the production of different-sized HA fragments at the site of action. Extracellular acidosis is often observed in the airways of smokers and patients suffering from COPD and asthma (92). HA fragments are implicated in the progression of lung diseases (131). HYAL-1 expression is increased in a rat model of monocrotaline-induced pulmonary hypertension, leading to increased fragmentation of native HMW-HA and increased hyaluronidase activity in lung lysates (105). In addition, HYAL-1 is increased in primary airway smooth muscle cells from asthma and COPD patients, and these cells were found to degrade HMW-HA into 2.5×10^5 M_r fragments compared with 7×10^5 M_r fragments for control cells (67). Dentener and colleagues (31) found that HYAL-2 expression was also increased in the lungs of patients with COPD, while HAS2 was decreased. In contrast, HYAL-1 levels were decreased in the lungs of patients with idiopathic pulmonary arterial hypertension (106). However, hyaluronidases are not the only HA-degrading moiety in the lung, and other factors, including

reactive oxygen species (ROS) production, can account for the presence and potential regulating activity of lower-molecular-weight HA.

Reactive Oxygen Species and Hyaluronan

In addition to the enzymatic activity of hyaluronidases, HA can be degraded to LMW species by ROS (92, 129, 132). ROS is increased in the lungs with many types of pulmonary diseases (107). Excess lung ROS can be generated from a variety of exogenous (particulate air pollution, cigarette smoke) and endogenous (activation of phagocytes, stimuli-induced NADPH oxidase, mitochondrial electron transport chain, xanthine oxidase, lipid peroxidation) sources (21, 25, 35, 112, 121, 144). Cigarette smoke-generated ROS can degrade HA (20, 28, 85). Recently, Monzon at al. (92) reported that ROS can regulate the expression of HYAL-2 in primary airway epithelial cells. This combination of ROS and HYAL-2 expression stimulates the appearance of $\sim 7.5 \times 10^4$ M_r HA fragments in lung secretions. Monzon at al. speculate that ROS exposure leads to an initial direct effect on HA degradation by ROS followed by sustained effects through the upregulation of hyaluronidase enzymes. Furthermore, in human airway epithelial cells exposed to xanthine/xanthine oxidase, HA fragment accumulation is blocked by addition of SOD or catalase (82). In addition, LMW-HA in the lung is increased in the extracellular SOD knockout mouse compared with wild-type controls (41). Intratracheal crocidolite asbestos exposure increases the appearance of $<2.5 \times 10^5$ M_r lung HA, with exacerbation of asbestos-induced increases in lung HA production in the extracellular SOD knockout mouse. In addition to endogenous lung hyaluronidase production, many infectious microbes express HA lyases on their surface or secrete the protein. It is considered a virulence factor allowing for degradation of the host organism's extracellular matrix (ECM), thereby increasing permeability and facilitating invasion by the pathogen. Bacteria that express HA lyases responsible for human disease include *Streptococcus, Staphylococcus*, and *Clostridium* (48, 113).

Hyaluronic Acid-Binding Proteins in Lung Disease

HA and its degradation products bind to a variety of HA-binding proteins that exist in diverse locales, including the blood, ECM, cell plasma membrane, cytosol, and nucleus (29, 143). Many HA-binding proteins contain Link modules consisting of conserved clusters of positively charged amino acids that bind to HA (29, 99). The differential activities of HA are regulated in the lung, in part, through interactions with HA-binding proteins, including CD44, TLR4, HA-binding protein 2 (HABP2), and receptor for HA-mediated motility (RHAMM). The role of these proteins in lung disease is discussed below (also see Table 1).

CD44. CD44 is a type 1 transmembrane glycoprotein expressed in a variety of lung cell types, including pulmonary epithelial, fibroblast, endothelial, and hematopoietic cells (122, 123). Its expression can be regulated in response to inflammatory stimuli such as LPS and cytokines, including IL-1β and TNFα, and growth factors, such as basic fibroblast growth factor and VEGF (34, 37, 46, 50). Several CD44 isoforms result from alternative exon splicing (52, 77), often occurring between exons 5 and 15, leading to a tandem insertion of one or more variant exons (v1–v10, or exon 6–exon 14) within the membrane proximal region of the extracellular domain (10, 45). It has been reported that CD44 can be expressed in an "active" form, capable of binding HA, or an "inducible" form, capable of binding HA following treatment with a CD44-activating antibody or PMA (72). The exact mechanism by which CD44 may be activated or induced to bind HA is unclear but may involve clustering of the receptor or alterations in glycosylation state. CD44 is modified by extensive *N*- and *O*-glycosylations and GAG additions (10, 143). The extracellular domain of CD44 contains clusters of conserved basic residues that are part of a HA-binding Link module common to HA-binding proteins (99, 143). The cytoplasmic domain of CD44 functions to recruit regulatory proteins to the cell membrane and initiate HA-mediated intracellular signaling (10, 143). Some examples of signaling pathways and molecules activated by HA binding of CD44 include Rac activation, leading to lamellipodia formation (103); ERM and merlin proteins (93); Src (124); and Rho kinase (ROCK) (123, 124). The importance of CD44 in the lung has been demonstrated through the use of the CD44 knockout mouse in multiple models of lung disease, including inflammation, vascular leak syndromes, and noninfectious lung diseases, which are discussed below (45, 56, 111, 139, 145, 147).

CD44 AND LPS-INDUCED LUNG INJURY. LPS is a potent endotoxin from gram-negative bacteria that, when administered intratracheally, produces an inflammatory reaction characterized by disruption of epithelial/endothelial barriers and leakage of fluid, protein, and immune cells into lung air spaces (6). Recently, our laboratory and others have demonstrated increased BAL protein and HA concentration and exaggerated inflammatory cell recruitment of macrophages and neutrophils with LPS-induced lung injury in CD44 knockout mice (56, 126). Increased NF-κB nuclear translocation and cytokine production have also been reported in CD44 knockout mice (56). In this model of intratracheal administration of LPS, it appears that CD44 acts as a negative regulator to limit the in vivo response to LPS and prevent excessive tissue damage.

Table 1. *HA-binding proteins and their associated lung diseases*

HA-Binding Protein	Associated Lung Disease
CD44	LPS-induced lung injury (56, 125), noninfectious lung injury (134, 138), asthma (49), pneumonia (145, 150), tuberculosis (71, 73), pulmonary vascular leakiness (125, 126), hyperoxia (146)
TLR4	LPS-induced lung injury (74), noninfectious lung injury (60, 159), VILI (127), ozone-induced lung injury (43), hyperoxia (110)
HABP2	LPS-induced lung injury (81), VILI (81), ARDS (155), pulmonary vascular leakiness (81)
RHAMM	Noninfectious lung injury (158)

HA, hyaluronan; CD44, cluster of differentiation 44; TLR4, Toll-like receptor 4; HABP2, HA-binding protein 2; RHAMM, receptor for HA-mediated motility; VILI, ventilator-induced lung injury; ARDS, acute respiratory distress syndrome. Reference numbers are shown in parentheses.

However, Hollingsworth et al. (56) observed decreased macrophage infiltration and chemokine secretion in their model of aerosolized LPS-induced inflammation. These differences are likely accounted for by the different modes of delivery (intratracheal vs. aerosolized) and lower LPS concentration, leading to a milder inflammatory response and faster resolution. One common finding in all these studies is the increased concentration of HA in the BAL fluid of CD44 knockout mice (56, 75, 125).

CD44 AND PNEUMONIA. Pneumonia, a disease characterized by inflammation of the parenchyma of the lung and alveolar edema, is the sixth-leading cause of death in America (133, 151). In animal models of pneumonia using live *Escherichia coli* and *Streptococcus pneumoniae*, CD44-deficient mice exhibited increased expression of the neutrophil chemoattractant proteins KC and MIP-2 (150). However, CD44-deficient mice exhibited increased neutrophil migration and edema formation only in the *E. coli* model of pneumonia (150). Katoh et al. (65) reported increased levels of HA and soluble CD44 in BAL fluid and increased numbers of CD44-expressing eosinophils in BAL of patients with eosinophilic pneumonia. The increase in CD44 is reported to be due to a local increase in IL-5 production in the lung. Unfortunately, Katoh et al. did not examine the size of HA in the BAL or its effect on other cell types such as neutrophils or macrophages.

CD44 AND TUBERCULOSIS. Tuberculosis (TB) is a serious lung disease caused by *Mycobacteria* infection. It is estimated that up to one-third of the world's population has been exposed to *Mycobacterium tuberculosis*, although only 5–10% of those exposed will develop TB and become infectious (136). CD44 knockout mice were used in two similar studies of TB infection. Both studies report increased neutrophil infiltration and increased lung lesion burden as the infection progressed in the CD44 knockout mice compared with control (66, 71). However, only Leemans et al. (71) reported a decrease in macrophage infiltration into the lung in the early stages of infection and increased bacterial load in the lungs and liver. They also observed increased mortality in the CD44 knockout mice. Kipnis et al. (66) did not observe significant differences in macrophage numbers. This could be due to the lower doses of bacilli used for initial infection than in the study of Leemans et al. Similarly, these lower doses may explain the differences in bacterial load in both studies. Given these results, it would appear that CD44 is necessary for successful control of TB infection at low and high doses. Recently, Hirayama et al. (53) reported that addition of HA to the culture medium of A549 cells infected with *M. tuberculosis* or *Mycobacterium bovis bacillus* (Calmette-Guerin) enhanced the growth rate of both bacterial strains. They reported that TB bacilli can use HA as a carbon source and that the *Mycobacteria* possess hyaluronidase activity (53). Furthermore, they found that mycobacterial growth could be reduced in vivo through the use of the hyaluronidase inhibitor Vcpal (53). One could also speculate that the action of mycobacterial hyaluronidase can also lead to an increase in LMW-HA fragments in the lungs of infected patients, leading to altered HA signaling and pathogenesis.

CD44 AND NONINFECTIOUS LUNG INJURY. A prevalent animal model for noninfectious lung injury is intratracheal administration of bleomycin, which causes an acute pulmonary epithelial cell injury and an inflammatory response that later subsides and develops into lung fibrosis (83). Lung CD44 expression is increased in the initial inflammatory response, along with a transient increase in HA concentration in the lung interstitium (138). In the CD44 knockout mouse, the bleomycin-induced acute inflammatory response persists, leading to excess immune cell recruitment to the lungs, excess inflammatory cytokine production, decreased transforming growth factor-β activation, progressive HA fragment ($<5 \times 10^5$ M_r) accumulation, and, ultimately, death (139). In humans, CD44 is upregulated in the lungs of patients with acute lung injury (ALI) (134). Treatment of lung mesenchymal cells isolated from these patients with anti-CD44 antibody attenuated migration and invasion into a fibrin matrix (134). This study did not examine HA localization, concentration, or molecular weight in the lungs of these patients. As the principal ligand for CD44, any alterations in HA size or concentration could greatly influence CD44 signaling.

CD44 AND ASTHMA. Asthma is an increasingly common lung disease characterized by bronchial hyperresponsiveness and airway thickening due to scarring and inflammation (32, 135). CD44 is overexpressed in the lungs of rats with experimental asthma (73). In addition, CD44 variant 6 (CD44v6) is upregulated in bronchial smooth muscle of asthma patients (49). Antibody blockage of CD44 decreased mast cell adhesion to human bronchial smooth muscle cells in vitro (49), a process associated with airway hyperresponsiveness and remodeling. Klagas et al. (67) reported a decrease in HA secretion by airway smooth muscle cells from asthma patients. Also the molecular weight of the HA was lower than that of the HA secreted by airway smooth muscle cells from healthy volunteers. Klagas et al. reported that CD44 expression is also decreased on airway smooth muscle cells from asthma patients, although the decrease was only significant following 24 h of in vitro culturing.

CD44 AND HYPEROXIA. Recently, van der Windt et al. (146) reported that CD44 has a protective role in hyperoxia-induced lung injury. Hyperoxia is often used as a treatment to increase tissue oxygenation during ALI or respiratory distress syndrome but can also lead to further lung damage, even in healthy tissue (2). van der Windt et al. reported that CD44 knockout mice have increased mortality compared with wild-type animals and exhibit higher levels of necrosis in their lungs, particularly, in the bronchiolar tissue. Although both groups of mice have increased numbers of neutrophils in BAL fluid after 24 h of hyperoxia, CD44 knockout mice have significantly higher numbers of neutrophils than control mice. CD44 knockout mice also have increased levels of HA in BAL fluid, but, unfortunately, the size of this HA was not determined. No changes were observed in the levels of osteopontin, another CD44 ligand. These data suggest that CD44 protects the lung epithelium during hyperoxia by limiting the neutrophil response and preventing HA buildup in the lung. The role of other HA-binding protein receptors, such as TLR4, which may modulate the functions of CD44 in the lung, should also be considered in this context, considering that TLR4 knockout mice are more susceptible to hyperoxia injury (159). In addition, hyperoxia-mediated pulmonary apoptosis is reduced in the inducible transgenic mouse with the human TLR4 signaling domain expressed in airways (110).

CD44 AND PULMONARY VASCULAR LEAKINESS. Endothelial cells make up ~30% of lung tissue and function as a semiselective cellular barrier to regulate the interface between the circulating

blood and the vessel wall (26, 80, 108). Disruption of the endothelial cell barrier is a critical feature of inflammation, as well as an important contributing factor to ALI, an inflammatory condition that is a major cause of morbidity and mortality in critically ill patients, because it results in leakage of fluid, protein, and cells into lung air spaces. We have demonstrated that human pulmonary endothelial cells express the CD44 isoforms CD44s (standard form) and CD44v10 (124). In vitro models of pulmonary endothelial cell barrier function indicate that HMW-HA ($\sim 1 \times 10^6$) activates CD44s signaling and promotes barrier enhancement through its interaction with the S1P1 receptor and activation of Rac1 signaling, leading to cytoskeletal reorganization, while HA fragments ($\sim 2.5 \times 10^6$) activate CD44v10 signaling and induce barrier disruption via S1P3 and Rho signaling (124) (Fig. 2). In addition, we have demonstrated that targeted deletion of CD44 in the mouse pulmonary vasculature increases basal leakiness in the lungs (125). In contrast, pulmonary vascular leak caused by intraperitoneal administration of IL-2 is attenuated in CD44 knockout mice and by CD44 antibody blockage (51, 95, 111).

TLR4. TLRs sense exogenous and endogenous danger-associated molecular motifs and produce inflammatory responses (104). Structurally, TLRs contain an extracellular leucine-rich repeat domain and a cytosolic Toll/IL-1 receptor homology domain (44). TLR4 is the major receptor for LPS and can also bind HA, high-mobility-group protein B1, oxidized lipoproteins, and oxidized phospholipids, since these molecules contain features of "pathogen-associated molecular patterns" (104). Interestingly, CD44 and TLR4 have been shown to be physically associated in a signaling complex following exposure to HA (137).

TLR4 AND LPS-INDUCED LUNG INJURY. Intratracheal administration of gram-negative bacteria endotoxin, LPS, induces a lung inflammatory reaction (6, 142). Inhibition of TLR4 in animal models protects against LPS-induced lung injury (38, 79, 127). TLR4 knockout animals show decreased neutrophil infiltration and have decreased levels of TNFα, IL-1β, and IL-6 (55). A TLR4-blocking antibody has been reported to decrease lung inflammation in a rabbit model of LPS-induced injury in mechanically ventilated animals (127). In humans, TLR4 loss-of-function mutations attenuate inhaled LPS-induced lung injury (4, 87). Interestingly, CD44-deficient mice have decreased expression of negative regulators of TLR, including IL-1 receptor-associated kinase M, Toll-interacting protein, and TNFα-induced protein 3 (A20) (74). Muto et al. (96) go one step further in their model of the septic response to LPS by showing that pretreatment with HMW-HA ($<5 \times 10^5$) is protective against LPS-induced shock. CD44 knockout mice are not protected in this model (96). This indicates that CD44 plays an active role in regulating TLR4 signaling events. Alveolar macrophages isolated from control treated and CD44 knockout mice have differences in TNFα and IL-6 expression, with HA-pretreated control macrophages showing decreased expression following LPS exposure. Also, expression of the TLR4-negative regulator TNFα-induced protein 3/A20 is increased in HA-treated macrophages (96).

TLR4 AND NONINFECTIOUS LUNG INJURY. Intratracheal bleomycin treatment in the double TLR2/TLR4 knockout mouse causes enhanced pulmonary epithelial cell apoptosis, exaggerated lung injury, and impaired inflammatory cell migration, results similar to blocking HA with the Pep-1 peptide in bleomycin-treated wild-type mice (60). In addition, inflammatory cytokine expression by HA fragments ($\sim 1.35 \times 10^5$ M_r) is completely blocked in double TLR2/TLR4 knockout mouse peritoneal macrophages and reduced in the TLR4 knockout mouse (60). Using a model of lung inflammation induced by LMW-HA (2×10^5) administered directly to the trachea, Zhao et al. (159) reported that TLR4 acts as a negative regulator. They found an increase in neutrophilic infiltration and red blood cells in BAL fluid of TLR4 knockout animals (159). They reported that TLR deficiency essentially increases LMW-HA-induced lung injury due to an imbalance in the ratio of pro- to anti-inflammatory mediators in the lungs of TLR4 knockout animals. In TLR4 knockout animals, IL-1β, MIP-2, TNFα, and IL-6 levels in BAL fluid are increased following LMW-HA administration and can be rescued by pretreatment with IL-1RA (159). These results are somewhat at odds with the findings of Jiang et al. (60), who reported that TLR4 knockout reduced MIP-2 expression by peritoneal macrophages. This difference may be accounted for by the cell-specific effects of TLR4 and HA. Scheibner et al. (116) reported that TLR2, but not TLR3 or TLR5 (TLR4 was not examined), is required for peritoneal macrophage activation and MIP-1α expression by LMW-HA (2×10^5), which can be blocked by HMW-HA (6×10^6) (116).

TLR4 AND AIRWAY HYPERREACTIVITY. Ozone-exposed mice develop airway hyperreactivity and accumulate HA fragments ($<2 \times 10^5$ M_r) in BAL fluid (42). CD44 and TLR4 knockout mice, as well as mice treated with a HA-binding peptide, are protected from ozone- and HA fragment ($2–4 \times 10^5$ M_r)-induced airway hyperreactivity (42, 43). The effects of LMW-HA in airway hyperreactivity may be mediated through alveolar macrophages. Garantziotis et al. (43) reported that while there was no TLR4/HA colocalization on airway epithelial cells in their

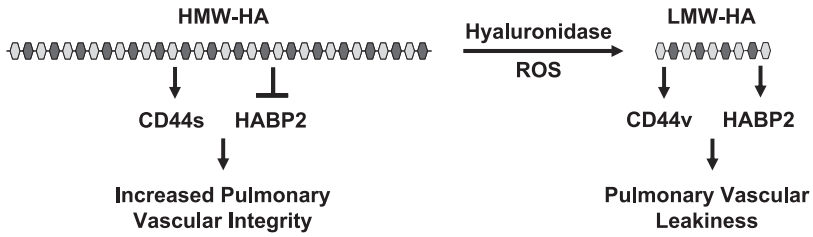

Fig. 2. HA regulation of pulmonary vascular function. High-molecular-weight HA (HMW-HA) can be degraded to low-molecular-weight fragments (LMW-HA) by hyaluronidases and/or reactive oxygen species (ROS) production with lung disease (129–132). HMW-HA activates the standard form of cluster of differentiation 44 (CD44s) signaling in pulmonary endothelial cells and inhibits HA-binding protein 2 (HABP2) protease activity (81, 124). These events promote increased pulmonary vascular integrity. LMW-HA activates cluster of differentiation 44 variant (CD44v) signaling and induces HABP2 protease activity (81, 124), events that lead to pulmonary vascular leakiness, which is a prominent feature of acute lung injury.

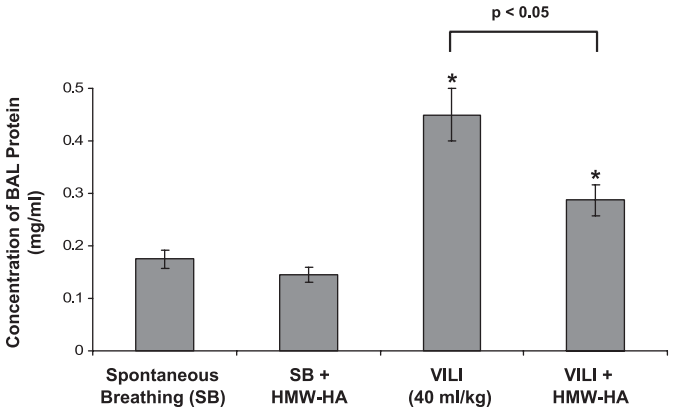

Fig. 3. HMW-HA protects against ventilator-induced lung injury. Male C57BL/6J wild-type mice (8–10 wk old; Jackson Laboratories, Bar Harbor, ME) were anesthetized with an intraperitoneal injection of ketamine (150 mg/kg) and acetylpromazine (15 mg/kg); then the right internal jugular vein was exposed via neck incision. Mice were allowed to spontaneously breathe or were ventilated (40 ml/kg tidal volume) for 4 h. After 1 h of ventilation, mice received HMW-HA (1.5 mg/kg) or saline control through the internal jugular vein. Mice were killed after 4 h of ventilator-induced lung injury (VILI), and bronchoalveolar lavage protein was analyzed ($n = 5$ mice per group). *Statistically significant difference ($P < 0.05$) from spontaneously breathing (SB) group. There is also a statistically significant difference ($P < 0.05$) between VILI alone and HMW-HA + VILI.

model of airway hyperresponsive, there were significant increases in HA and TLR4 staining on alveolar macrophages following ozone exposure.

HABP2. HABP2, also called factor VII-activating protease, is a HA-binding extracellular serine protease involved in the extrinsic pathway of blood coagulation via activation of factor VII and fibrinolysis via activation of pro-urokinase-type plasminogen activator (23, 33, 64, 114). It is expressed as a single amino acid chain proenzyme that undergoes autocatalytic cleavage upon binding of a ligand (63). The mature enzyme consists of a trypsin-like catalytic domain, linked via a disulfide bond to the kringle domain, and three epidermal growth factor-like domains (64, 114). The second and third epidermal growth factor-like domains form the polyanion-binding domain (3).

HABP2 AND ACUTE RESPIRATORY DISTRESS SYNDROME. HABP2 levels and activity are increased in the BAL fluid of mechanically ventilated patients with early acute respiratory distress syndrome (ARDS) compared with patients with cardiogenic pulmonary edema or healthy controls (155). In patients who died from ARDS, immunohistochemical analysis of excised lungs revealed increased HABP2 levels in alveolar macrophages and bronchial epithelial and pulmonary endothelial cells (155). This suggests a role for HABP2 in the pathogenesis of ARDS.

HABP2 AND LUNG INJURY WITH PULMONARY VASCULAR LEAKINESS. As stated previously, intratracheal LPS administration produces an inflammatory reaction characterized by disruption of epithelial and endothelial cellular barriers, with leakage of fluid, protein, and immune cells into lung air spaces (6, 142). Although HABP2 is mainly produced in the liver, we and others have demonstrated that the pulmonary endothelium expresses HABP2, which is upregulated with lung injury (81, 155). HABP2 promotes LPS- and HA fragment ($\sim 2.5 \times 10^6$ M_r)-mediated human pulmonary endothelial cell barrier disruption through a mechanism that involves protease-activated receptors and inhibits HMW-HA-mediated endothelial barrier protection in vitro (81) (Fig. 2). We determined the contribution of vascular HABP2 to lung injury in mice by inhibiting HABP2 through intravenous administration of HABP2 small interfering RNA and observed attenuation of LPS-induced ALI (81). In addition, vascular inhibition of HABP2 expression attenuates another mouse model of lung injury with pulmonary vascular hyperpermeability, VILI, demonstrating an important role of HABP2 in the development of lung disease (81).

RHAMM. RHAMM is found in diverse cellular locales, including the cell surface, cytosol, mitochondria, and nucleus (143). RHAMM activates ERK1/2 and regulates mitotic-spindle integrity (84). RHAMM is alternatively spliced, similar to CD44, and these two HA-binding proteins are often coexpressed in pulmonary cells (78, 143). In some cases, RHAMM can compensate for CD44 function (100).

RHAMM AND NONINFECTIOUS LUNG INJURY. As stated previously, one common animal model for noninfectious lung injury is intratracheal administration of bleomycin (83). RHAMM expression is increased in lung macrophages with bleomycin treatment (158). Intraperitoneal injection of anti-RHAMM antibody attenuates bleomycin-induced lung macrophage recruitment and reduction of alveolar septae thickening and early indications of lung fibrosis (158).

RHAMM AND AIRWAY CILIARY FUNCTION AND MUCOSAL HOST DEFENSE. HA binding to RHAMM in ciliated airway epithelial cells stimulates ciliary beat frequency, suggesting a role for HA and RHAMM in airway mucosal host defense (36). In

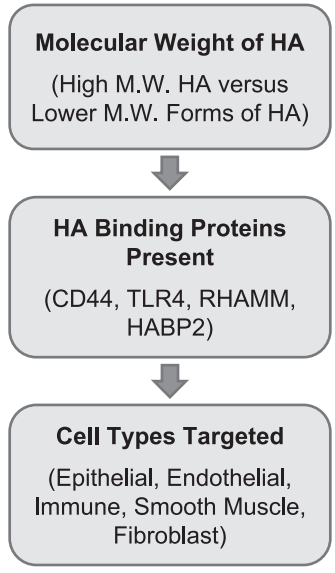

Fig. 4. Schematic diagram of factors that regulate HA-mediated lung pathobiology. HA mainly exists as HMW-HA in normal lung. Total HMW-HA levels can change in lung pathology due, in part, to the levels and activity of HA synthases. In several lung diseases, HMW-HA is degraded to lower-molecular-weight HA by hyaluronidase enzymes and ROS. HMW-HA and LMW-HA can differentially bind to and have opposing effects on various HA-binding proteins that exist extracellularly (HABP2) on the cell surface (CD44 and Toll-like receptor 4), as well as in other cellular locales (receptor for HA-mediated motility). Therefore, the type of HA-binding protein(s) upregulated in various lung diseases can often determine the functional effects of HA. Furthermore, cell types (e.g., epithelial, endothelial, immune, smooth muscle, fibroblast) targeted by HMW-HA and LWM-HA will have a distinct impact on lung disease progression.

addition, RHAMM antibody blockage attenuates xanthine/xanthine oxidase-mediated increase in human airway epithelial ciliary beat frequency (82).

Protective Effects of Exogenous Administration of HMW-HA

Although HMW-HA ($>1 \times 10^6$) is produced endogenously and is an integral component of the ECM, synovial fluid, and vitreous humor, recent attention has been focused on the use of exogenously administered HMW-HA in a variety of diseases, including lung disease (15, 40, 68, 156). In vitro, exogenous administration of HMW-HA inhibits ROS, nitrotyrosine, and inflammatory cytokine production and also promotes immune tolerance (9, 88, 157). In addition, excess production of endogenous HMW-HA in mice overexpressing HAS2 in airway epithelia protects against bleomycin-induced lung injury and ozone-induced airway hyperresponsiveness (42, 60).

Exogenous HMW-HA and LPS-induced lung injury. We recently demonstrated that intravenous administration of HMW-HA ($\sim 1 \times 10^6$) 4 h after intratracheal administration of LPS protects against lung injury in mice (125, 126). This finding is consistent with results from the study of Nadkarni et al. (97), who demonstrated that pretreatment of hamsters with aerosolized HMW-HA protects against endotoxin-induced lung injury. Interestingly, these authors noted that treatment with aerosolized HMW-HA after endotoxin treatment actually enhanced lung inflammation, indicating that the timing and route of administration are important determinants of HMW-HA's effectiveness.

Exogenous HMW-HA and sepsis/VILI. Intraperitoneal administration of HMW-HA (1.6×10^6) 18 h before mechanical ventilation with a low tidal volume (7 ml/kg) and carotid artery administration of LPS (to induce sepsis) protects rats from lung injury (76). In these same studies, simultaneous intravenous administration of HMW-HA and initiation of ventilation also protected from lung injury (76). Interestingly, the use of 3.5×10^4 M_r HA showed partial protection in these models, but to a lesser extent than HMW-HA (76). Our laboratory had demonstrated that intravenous administration of HMW-HA protects from VILI in mice (Fig. 3).

Exogenous HMW-HA and airway hyperreactivity. Aerosolized HMW-HA reduces neutrophil elastase- and pancreatic elastase-induced bronchoconstriction in sheep (16, 118–120). In addition, oropharyngeal administration of exogenous HMW-HA before or after ozone exposure significantly attenuates airway hyperreactivity in mice (42). Furthermore, pretreatment of aerosolized HMW-HA protects asthma patients from exercise-induced bronchoconstriction (109).

Exogenous HA and experimental emphysema. Aerosolized 1.5×10^5 M_r HA given to mice 1 h before a model of cigarette smoke-induced pulmonary emphysema protected against lung injury (17, 19). Although this LMW-HA provides protection, it would be prudent to examine whether HMW-HA offers greater protection, as observed in the sepsis/VILI model (see above).

Exogenous HMW-HA and chronic bronchitis. In patients with chronic bronchitis, subcutaneous administration of HMW-HA for 6 mo protects against acute exacerbations and results in less consumption of antibiotics (148).

Given the numerous animal and patient studies indicating that HMW-HA protects against a variety of lung diseases, the therapeutic potential of exogenously administered HMW-HA warrants further study. It should be noted, however, that intraperitoneal injection of IL-2, which causes systemic vascular leak, is attenuated in CD44 knockout mice and with intraperitoneal injection of human umbilical cord HA, anti-CD44 (9F3) mouse antibody or the HA-specific binding peptide Pep-1 (51, 95, 111). Whether intravenous (vs. intraperitoneal) administration of HMW-HA protects from IL-2-induced vascular leak syndrome remains to be determined. These studies by Mustafa et al. (95) with IL-2 use HA that is not purified to remove LMW-HA. We previously reported that LMW-HA induces human endothelial cell barrier disruption in vitro (124). The IL-2 model involves intraperitoneal injection three times a day for 3 days followed by a single dose on *day 4* (51, 95, 111, 126). Therefore, the targeting of injury (lung vs. systemic model), the IL-2 receptor expression level of the pulmonary endothelium, the molecular weight of HA, and the route of HA delivery (intravenous vs. intraperitoneal) can be important factors in the effectiveness of HMW-HA.

Concluding Remarks

HA, its degradation products, and its target binding proteins are important regulators of a multitude of lung diseases. They are also involved in lung cancer oncogenic function, which is beyond the scope of this review. The effects of HA are complex and dependent on its concentration in the lung and molecular weight. Different-sized HA species are regulated by the opposing actions of HA synthases, hyaluronidases, and ROS production. The LMW-HA produced in pathological conditions of the lung can selectively bind to HA-binding proteins upregulated in specific pulmonary cell types in various disease states (81, 124, 125) (Fig. 4). Future areas of investigation will include elucidating the exact mechanisms by which HA and HA fragments can differentially regulate HA-binding protein function. Furthermore, although this review focused on four HA-binding proteins, several others, including versican, TNFα-induced protein-6, and stabilin (69, 90, 99, 154), could potentially regulate lung pathology. Although many HA-binding proteins can be expressed by the same cell type in the lung, certain HA-binding proteins, including HABP2 and CD44v10, are overexpressed in lung pathology and can account for the differential effects of HMW-HA vs. LMW-HA (81, 124, 125). Understanding the complexities of HA in lung disease will allow for future therapeutic exploration.

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DISCLOSURES

F. E. Lennon has no conflict of interest. P. A. Singleton holds a provisional patent involving applications of hyaluronan with the University of Chicago and has received no financial gain.

REFERENCES

1. **Almond A.** Hyaluronan. *Cell Mol Life Sci* 64: 1591–1596, 2007.
2. **Altemeier WA, Sinclair SE.** Hyperoxia in the intensive care unit: why more is not always better. *Curr Opin Crit Care* 13: 73–78, 2007.
3. **Altincicek B, Shibamiya A, Trusheim H, Tzima E, Niepmann M, Linder D, Preissner KT, Kanse SM.** A positively charged cluster in the epidermal growth factor-like domain of factor VII-activating protease

(FSAP) is essential for polyanion binding. *Biochem J* 394: 687–692, 2006.

4. **Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, Frees K, Watt JL, Schwartz DA.** TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. *Nat Genet* 25: 187–191, 2000.
5. **Bai KJ, Spicer AP, Mascarenhas MM, Yu L, Ochoa CD, Garg HG, Quinn DA.** The role of hyaluronan synthase 3 in ventilator-induced lung injury. *Am J Respir Crit Care Med* 172: 92–98, 2005.
6. **Bannerman DD, Goldblum SE.** Direct effects of endotoxin on the endothelium: barrier function and injury. *Lab Invest* 79: 1181–1199, 1999.
7. **Bensadoun ES, Burke AK, Hogg JC, Roberts CR.** Proteoglycan deposition in pulmonary fibrosis. *Am J Respir Crit Care Med* 154: 1819–1828, 1996.
8. **Bollyky PL, Evanko SP, Wu RP, Potter-Perigo S, Long SA, Kinsella B, Reijonen H, Guebtner K, Teng B, Chan CK, Braun KR, Gebe JA, Nepom GT, Wight TN.** Th1 cytokines promote T-cell binding to antigen-presenting cells via enhanced hyaluronan production and accumulation at the immune synapse. *Cell Mol Immunol* 7: 211–220, 2010.
9. **Bollyky PL, Falk BA, Wu RP, Buckner JH, Wight TN, Nepom GT.** Intact extracellular matrix and the maintenance of immune tolerance: high molecular weight hyaluronan promotes persistence of induced $CD4^+CD25^+$ regulatory T cells. *J Leukoc Biol* 86: 567–572, 2009.
10. **Bourguignon LY, Zhu D, Zhu H.** CD44 isoform-cytoskeleton interaction in oncogenic signaling and tumor progression. *Front Biosci* 3: d637–d649, 1998.
11. **Bracke KR, Dentener MA, Papakonstantinou E, Vernooy JH, Demoor T, Pauwels NS, Cleutjens J, van Suylen R, Joos GF, Brusselle GG, Wouters EF.** Enhanced deposition of low weight hyaluronan in lungs of cigarette smoke-exposed mice. *Am J Respir Cell Mol Biol*. In press.
12. **Camenisch TD, Schroeder JA, Bradley J, Klewer SE, McDonald JA.** Heart-valve mesenchyme formation is dependent on hyaluronan-augmented activation of ErbB2-ErbB3 receptors. *Nat Med* 8: 850–855, 2002.
13. **Camenisch TD, Spicer AP, Brehm-Gibson T, Biesterfeldt J, Augustine ML, Calabro A Jr, Kubalak S, Klewer SE, McDonald JA.** Disruption of hyaluronan synthase-2 abrogates normal cardiac morphogenesis and hyaluronan-mediated transformation of epithelium to mesenchyme. *J Clin Invest* 106: 349–360, 2000.
14. **Cantin AM, Larivee P, Martel M, Begin R.** Hyaluronan (hyaluronic acid) in lung lavage of asbestos-exposed humans and sheep. *Lung* 170: 211–220, 1992.
15. **Cantor JO.** Potential therapeutic applications of hyaluronan in the lung. *Int J Chron Obstruct Pulmon Dis* 2: 283–288, 2007.
16. **Cantor JO, Cerreta JM, Armand G, Turino GM.** Aerosolized hyaluronic acid decreases alveolar injury induced by human neutrophil elastase. *Proc Soc Exp Biol Med* 217: 471–475, 1998.
17. **Cantor JO, Cerreta JM, Ochoa M, Ma S, Chow T, Grunig G, Turino GM.** Aerosolized hyaluronan limits airspace enlargement in a mouse model of cigarette smoke-induced pulmonary emphysema. *Exp Lung Res* 31: 417–430, 2005.
18. **Cantor JO, Nadkarni PP.** Hyaluronan: the Jekyll and Hyde molecule. *Inflamm Allergy Drug Targets* 5: 257–260, 2006.
19. **Cantor JO, Turino GM.** Can exogenously administered hyaluronan improve respiratory function in patients with pulmonary emphysema? *Chest* 125: 288–292, 2004.
20. **Casalino-Matsuda SM, Monzon ME, Day AJ, Forteza RM.** Hyaluronan fragments/CD44 mediate oxidative stress-induced MUC5B up-regulation in airway epithelium. *Am J Respir Cell Mol Biol* 40: 277–285, 2009.
21. **Cave AC, Brewer AC, Narayanapanicker A, Ray R, Grieve DJ, Walker S, Shah AM.** NADPH oxidases in cardiovascular health and disease. *Antioxid Redox Signal* 8: 691–728, 2006.
22. **Cheng G, Swaidani S, Sharma M, Lauer ME, Hascall VC, Aronica MA.** Hyaluronan deposition and correlation with inflammation in a murine ovalbumin model of asthma. *Matrix Biol* 30: 126–134, 2011.
23. **Choi-Miura NH, Tobe T, Sumiya J, Nakano Y, Sano Y, Mazda T, Tomita M.** Purification and characterization of a novel hyaluronan-binding protein (PHBP) from human plasma: it has three EGF, a kringle and a serine protease domain, similar to hepatocyte growth factor activator. *J Biochem (Tokyo)* 119: 1157–1165, 1996.
24. **Chow G, Tauler J, Mulshine JL.** Cytokines and growth factors stimulate hyaluronan production: role of hyaluronan in epithelial to mesenchymal-like transition in non-small cell lung cancer. *J Biomed Biotechnol* 2010: 485468, 2010.
25. **Circu ML, Aw TY.** Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med* 48: 749–762, 2010.
26. **Crapo JD, Barry BE, Gehr P, Bachofen M, Weibel ER.** Cell number and cell characteristics of the normal human lung. *Am Rev Respir Dis* 125: 740–745, 1982.
27. **Csoka AB, Frost GI, Stern R.** The six hyaluronidase-like genes in the human and mouse genomes. *Matrix Biol* 20: 499–508, 2001.
28. **Dabrowski R, Maslinski C.** Collagen, glycosaminoglycans and histamine in lungs of guinea pigs exposed chronically to cigarette smoke. *Bull Acad Pol Sci Biol* 23: 125–128, 1975.
29. **Day AJ, Prestwich GD.** Hyaluronan-binding proteins: tying up the giant. *J Biol Chem* 277: 4585–4588, 2002.
30. **Deed R, Rooney P, Kumar P, Norton JD, Smith J, Freemont AJ, Kumar S.** Early-response gene signalling is induced by angiogenic oligosaccharides of hyaluronan in endothelial cells. Inhibition by non-angiogenic, high-molecular-weight hyaluronan. *Int J Cancer* 71: 251–256, 1997.
31. **Dentener MA, Vernooy JH, Hendriks S, Wouters EF.** Enhanced levels of hyaluronan in lungs of patients with COPD: relationship with lung function and local inflammation. *Thorax* 60: 114–119, 2005.
32. **Duan QL, Tantisira KG.** Pharmacogenetics of asthma therapy. *Curr Pharm Des* 15: 3742–3753, 2009.
33. **Etscheid M, Kress J, Seitz R, Dodt J.** The hyaluronic acid-binding protease: a novel vascular and inflammatory mediator? *Int Immunopharmacol* 8: 166–170, 2008.
34. **Fitzgerald KA, O'Neill LA.** Characterization of CD44 induction by IL-1: a critical role for Egr-1. *J Immunol* 162: 4920–4927, 1999.
35. **Forman HJ, Maiorino M, Ursini F.** Signaling functions of reactive oxygen species. *Biochemistry* 49: 835–842, 2010.
36. **Forteza R, Lieb T, Aoki T, Savani RC, Conner GE, Salathe M.** Hyaluronan serves a novel role in airway mucosal host defense. *FASEB J* 15: 2179–2186, 2001.
37. **Foster LC, Arkonac BM, Sibinga NE, Shi C, Perrella MA, Haber E.** Regulation of CD44 gene expression by the proinflammatory cytokine interleukin-1β in vascular smooth muscle cells. *J Biol Chem* 273: 20341–20346, 1998.
38. **Freudenberg MA, Tchaptchet S, Keck S, Fejer G, Huber M, Schutze N, Beutler B, Galanos C.** Lipopolysaccharide sensing an important factor in the innate immune response to Gram-negative bacterial infections: benefits and hazards of LPS hypersensitivity. *Immunobiology* 213: 193–203, 2008.
39. **Furlan S, La Penna G, Perico A, Cesaro A.** Hyaluronan chain conformation and dynamics. *Carbohydr Res* 340: 959–970, 2005.
40. **Gaffney J, Matou-Nasri S, Grau-Olivares M, Slevin M.** Therapeutic applications of hyaluronan. *Mol Biosyst* 6: 437–443, 2010.
41. **Gao F, Koenitzer JR, Tobolewski JM, Jiang D, Liang J, Noble PW, Oury TD.** Extracellular superoxide dismutase inhibits inflammation by preventing oxidative fragmentation of hyaluronan. *J Biol Chem* 283: 6058–6066, 2008.
42. **Garantziotis S, Li Z, Potts EN, Kimata K, Zhuo L, Morgan DL, Savani RC, Noble PW, Foster WM, Schwartz DA, Hollingsworth JW.** Hyaluronan mediates ozone-induced airway hyperresponsiveness in mice. *J Biol Chem* 284: 11309–11317, 2009.
43. **Garantziotis S, Li Z, Potts EN, Lindsey JY, Stober VP, Polosukhin VV, Blackwell TS, Schwartz DA, Foster WM, Hollingsworth JW.** TLR4 is necessary for hyaluronan-mediated airway hyperresponsiveness after ozone inhalation. *Am J Respir Crit Care Med* 181: 666–675, 2010.
44. **Gay NJ, Gangloff M.** Structure and function of Toll receptors and their ligands. *Annu Rev Biochem* 76: 141–165, 2007.
45. **Gee K, Kryworuchko M, Kumar A.** Recent advances in the regulation of CD44 expression and its role in inflammation and autoimmune diseases. *Arch Immunol Ther Exp (Warsz)* 52: 13–26, 2004.
46. **Gee K, Lim W, Ma W, Nandan D, Diaz-Mitoma F, Kozlowski M, Kumar A.** Differential regulation of CD44 expression by lipopolysaccharide (LPS) and TNF-α in human monocytic cells: distinct involvement of c-Jun N-terminal kinase in LPS-induced CD44 expression. *J Immunol* 169: 5660–5672, 2002.
47. **Girish KS, Kemparaju K.** The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. *Life Sci* 80: 1921–1943, 2007.
48. **Girish KS, Kemparaju K, Nagaraju S, Vishwanath BS.** Hyaluronidase inhibitors: a biological and therapeutic perspective. *Curr Med Chem* 16: 2261–2288, 2009.

49. **Girodet PO, Ozier A, Trian T, Begueret H, Ousova O, Vernejoux JM, Chanez P, Marthan R, Berger P, Tunon de Lara JM.** Mast cell adhesion to bronchial smooth muscle in asthma specifically depends on CD51 and CD44 variant 6. *Allergy* 65: 1004–1012, 2010.
50. **Griffioen AW, Coenen MJ, Damen CA, Hellwig SM, van Weering DH, Vooys W, Blijham GH, Groenewegen G.** CD44 is involved in tumor angiogenesis: an activation antigen on human endothelial cells. *Blood* 90: 1150–1159, 1997.
51. **Guan H, Nagarkatti PS, Nagarkatti M.** Blockade of hyaluronan inhibits IL-2-induced vascular leak syndrome and maintains effectiveness of IL-2 treatment for metastatic melanoma. *J Immunol* 179: 3715–3723, 2007.
52. **Hirano H, Screaton GR, Bell MV, Jackson DG, Bell JI, Hodes RJ.** CD44 isoform expression mediated by alternative splicing: tissue-specific regulation in mice. *Int Immunol* 6: 49–59, 1994.
53. **Hirayama Y, Yoshimura M, Ozeki Y, Sugawara I, Udagawa T, Mizuno S, Itano N, Kimata K, Tamaru A, Ogura H, Kobayashi K, Matsumoto S.** *Mycobacteria* exploit host hyaluronan for efficient extracellular replication. *PLoS Pathog* 5: e1000643, 2009.
54. **Hofinger ES, Hoechstetter J, Oettl M, Bernhardt G, Buschauer A.** Isoenzyme-specific differences in the degradation of hyaluronic acid by mammalian-type hyaluronidases. *Glycoconj J* 25: 101–109, 2008.
55. **Hollingsworth JW 2nd, Cook DN, Brass DM, Walker JK, Morgan DL, Foster WM, Schwartz DA.** The role of Toll-like receptor 4 in environmental airway injury in mice. *Am J Respir Crit Care Med* 170: 126–132, 2004.
56. **Hollingsworth JW, Li Z, Brass DM, Garantziotis S, Timberlake SH, Kim A, Hossain I, Savani RC, Schwartz DA.** CD44 regulates macrophage recruitment to the lung in lipopolysaccharide-induced airway disease. *Am J Respir Cell Mol Biol* 37: 248–253, 2007.
57. **Horton MR, McKee CM, Bao C, Liao F, Farber JM, Hodge-DuFour J, Pure E, Oliver BL, Wright TM, Noble PW.** Hyaluronan fragments synergize with interferon-γ to induce the C-X-C chemokines mig and interferon-inducible protein-10 in mouse macrophages. *J Biol Chem* 273: 35088–35094, 1998.
58. **Horton MR, Olman MA, Bao C, White KE, Choi AM, Chin BY, Noble PW, Lowenstein CJ.** Regulation of plasminogen activator inhibitor-1 and urokinase by hyaluronan fragments in mouse macrophages. *Am J Physiol Lung Cell Mol Physiol* 279: L707–L715, 2000.
59. **Itano N, Kimata K.** Mammalian hyaluronan synthases. *IUBMB Life* 54: 195–199, 2002.
60. **Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, Prestwich GD, Mascarenhas MM, Garg HG, Quinn DA, Homer RJ, Goldstein DR, Bucala R, Lee PJ, Medzhitov R, Noble PW.** Regulation of lung injury and repair by Toll-like receptors and hyaluronan. *Nat Med* 11: 1173–1179, 2005.
61. **Jiang D, Liang J, Noble PW.** Hyaluronan in tissue injury and repair. *Annu Rev Cell Dev Biol* 23: 435–461, 2007.
62. **Jiang D, Liang J, Noble PW.** Regulation of non-infectious lung injury, inflammation, and repair by the extracellular matrix glycosaminoglycan hyaluronan. *Anat Rec (Hoboken)* 293: 982–985, 2010.
63. **Kannemeier C, Feussner A, Stohr HA, Weisse J, Preissner KT, Romisch J.** Factor VII and single-chain plasminogen activator-activating protease: activation and autoactivation of the proenzyme. *Eur J Biochem* 268: 3789–3796, 2001.
64. **Kanse SM, Parahuleva M, Muhl L, Kemkes-Matthes B, Sedding D, Preissner KT.** Factor VII-activating protease (FSAP): vascular functions and role in atherosclerosis. *Thromb Haemost* 99: 286–289, 2008.
65. **Katoh S, Taniguchi H, Matsubara Y, Matsumoto N, Fukushima K, Kadota J, Matsukura S, Kohno S.** Overexpression of CD44 on alveolar eosinophils with high concentrations of soluble CD44 in bronchoalveolar lavage fluid in patients with eosinophilic pneumonia. *Allergy* 54: 1286–1292, 1999.
66. **Kipnis A, Basaraba RJ, Turner J, Orme IM.** Increased neutrophil influx but no impairment of protective immunity to tuberculosis in mice lacking the CD44 molecule. *J Leukoc Biol* 74: 992–997, 2003.
67. **Klagas I, Goulet S, Karakiulakis G, Zhong J, Baraket M, Black JL, Papakonstantinou E, Roth M.** Decreased hyaluronan in airway smooth muscle cells from patients with asthma and COPD. *Eur Respir J* 34: 616–628, 2009.
68. **Kogan G, Soltes L, Stern R, Gemeiner P.** Hyaluronic acid: a natural biopolymer with a broad range of biomedical and industrial applications. *Biotechnol Lett* 29: 17–25, 2007.
69. **Kzhyshkowska J, Gratchev A, Goerdt S.** Stabilin-1, a homeostatic scavenger receptor with multiple functions. *J Cell Mol Med* 10: 635–649, 2006.
70. **Lauer ME, Erzurum SC, Mukhopadhyay D, Vasanji A, Drazba J, Wang A, Fulop C, Hascall VC.** Differentiated murine airway epithelial cells synthesize a leukocyte-adhesive hyaluronan matrix in response to endoplasmic reticulum stress. *J Biol Chem* 283: 26283–26296, 2008.
71. **Leemans JC, Florquin S, Heikens M, Pals ST, van der Neut R, Van Der Poll T.** CD44 is a macrophage binding site for *Mycobacterium tuberculosis* that mediates macrophage recruitment and protective immunity against tuberculosis. *J Clin Invest* 111: 681–689, 2003.
72. **Lesley J, Hascall VC, Tammi M, Hyman R.** Hyaluronan binding by cell surface CD44. *J Biol Chem* 275: 26967–26975, 2000.
73. **Li L, Yang L, Tang H, Jin R.** [Role of CD44 on airway inflammatory response in rats with asthma]. *Zhongguo Dang Dai Er Ke Za Zhi* 11: 142–145, 2009.
74. **Liang J, Jiang D, Griffith J, Yu S, Fan J, Zhao X, Bucala R, Noble PW.** CD44 is a negative regulator of acute pulmonary inflammation and lipopolysaccharide-TLR signaling in mouse macrophages. *J Immunol* 178: 2469–2475, 2007.
75. **Liao YH, Jones SA, Forbes B, Martin GP, Brown MB.** Hyaluronan: pharmaceutical characterization and drug delivery. *Drug Deliv* 12: 327–342, 2005.
76. **Liu YY, Lee CH, Dedaj R, Zhao H, Mrabat H, Sheidlin A, Syrkina O, Huang PM, Garg HG, Hales CA, Quinn DA.** High-molecular-weight hyaluronan—a possible new treatment for sepsis-induced lung injury: a preclinical study in mechanically ventilated rats. *Crit Care* 12: R102, 2008.
77. **Lokeshwar VB, Iida N, Bourguignon LY.** The cell adhesion molecule, GP116, is a new CD44 variant (ex14/v10) involved in hyaluronic acid binding and endothelial cell proliferation. *J Biol Chem* 271: 23853–23864, 1996.
78. **Lokeshwar VB, Selzer MG.** Differences in hyaluronic acid-mediated functions and signaling in arterial, microvessel, and vein-derived human endothelial cells. *J Biol Chem* 275: 27641–27649, 2000.
79. **Lu YC, Yeh WC, Ohashi PS.** LPS/TLR4 signal transduction pathway. *Cytokine* 42: 145–151, 2008.
80. **Luscher TF, Barton M.** Biology of the endothelium. *Clin Cardiol* 20: II-3–II-10, 1997.
81. **Mambetsariev N, Mirzapoiazova T, Mambetsariev B, Sammani S, Lennon FE, Garcia JG, Singleton PA.** Hyaluronic acid binding protein 2 is a novel regulator of vascular integrity. *Arterioscler Thromb Vasc Biol* 30: 483–490, 2010.
82. **Manzanares D, Monzon ME, Savani RC, Salathe M.** Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. *Am J Respir Cell Mol Biol* 37: 160–168, 2007.
83. **Matute-Bello G, Frevert CW, Martin TR.** Animal models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 295: L379–L399, 2008.
84. **Maxwell CA, McCarthy J, Turley E.** Cell-surface and mitotic-spindle RHAMM: moonlighting or dual oncogenic functions? *J Cell Sci* 121: 925–932, 2008.
85. **McDevitt CA, Beck GJ, Ciunga MJ, O'Brien J.** Cigarette smoke degrades hyaluronic acid. *Lung* 167: 237–245, 1989.
86. **McKee CM, Penno MB, Cowman M, Burdick MD, Strieter RM, Bao C, Noble PW.** Hyaluronan (HA) fragments induce chemokine gene expression in alveolar macrophages. The role of HA size and CD44. *J Clin Invest* 98: 2403–2413, 1996.
87. **Michel O, LeVan TD, Stern D, Dentener M, Thorn J, Gnat D, Beijer ML, Cochaux P, Holt PG, Martinez FD, Rylander R.** Systemic responsiveness to lipopolysaccharide and polymorphisms in the toll-like receptor 4 gene in human beings. *J Allergy Clin Immunol* 112: 923–929, 2003.
88. **Miki Y, Teramura T, Tomiyama T, Onodera Y, Matsuoka T, Fukuda K, Hamanishi C.** Hyaluronan reversed proteoglycan synthesis inhibited by mechanical stress: possible involvement of antioxidant effect. *Inflamm Res* 59: 471–477, 2010.
89. **Milman N, Kristensen MS, Bentsen K, Grode G, Frederiksen J.** Hyaluronan and procollagen type III amino terminal peptide in serum and bronchoalveolar lavage fluid in patients with pulmonary sarcoidosis. *Sarcoidosis* 12: 38–41, 1995.
90. **Milner CM, Higman VA, Day AJ.** TSG-6: a pluripotent inflammatory mediator? *Biochem Soc Trans* 34: 446–450, 2006.

91. **Mohamadzadeh M, DeGrendele H, Arizpe H, Estess P, Siegelman M.** Proinflammatory stimuli regulate endothelial hyaluronan expression and CD44/HA-dependent primary adhesion. *J Clin Invest* 101: 97–108, 1998.
92. **Monzon ME, Fregien N, Schmid N, Falcon NS, Campos M, Casalino-Matsuda SM, Forteza RM.** Reactive oxygen species and hyaluronidase 2 regulate airway epithelial hyaluronan fragmentation. *J Biol Chem* 285: 26126–26134, 2010.
93. **Morrison H, Sherman LS, Legg J, Banine F, Isacke C, Haipek CA, Gutmann DH, Ponta H, Herrlich P.** The NF2 tumor suppressor gene product, merlin, mediates contact inhibition of growth through interactions with CD44. *Genes Dev* 15: 968–980, 2001.
94. **Murphy JF, Lennon F, Steele C, Kelleher D, Fitzgerald D, Long AC.** Engagement of CD44 modulates cyclooxygenase induction, VEGF generation, and proliferation in human vascular endothelial cells. *FASEB J* 19: 446–448, 2005.
95. **Mustafa A, McKallip RJ, Fisher M, Duncan R, Nagarkatti PS, Nagarkatti M.** Regulation of interleukin-2-induced vascular leak syndrome by targeting CD44 using hyaluronic acid and anti-CD44 antibodies. *J Immunother* 25: 476–488, 2002.
96. **Muto J, Yamasaki K, Taylor KR, Gallo RL.** Engagement of CD44 by hyaluronan suppresses TLR4 signaling and the septic response to LPS. *Mol Immunol* 47: 449–456, 2009.
97. **Nadkarni PP, Kulkarni GS, Cerreta JM, Ma S, Cantor JO.** Dichotomous effect of aerosolized hyaluronan in a hamster model of endotoxin-induced lung injury. *Exp Lung Res* 31: 807–818, 2005.
98. **Nandi A, Estess P, Siegelman MH.** Hyaluronan anchoring and regulation on the surface of vascular endothelial cells is mediated through the functionally active form of CD44. *J Biol Chem* 275: 14939–14948, 2000.
99. **Neame PJ, Barry FP.** The link proteins. *Experientia* 49: 393–402, 1993.
100. **Nedvetzki S, Gonen E, Assayag N, Reich R, Williams RO, Thurmond RL, Huang JF, Neudecker BA, Wang FS, Turley EA, Naor D.** RHAMM, a receptor for hyaluronan-mediated motility, compensates for CD44 in inflamed CD44-knockout mice: a different interpretation of redundancy. *Proc Natl Acad Sci USA* 101: 18081–18086, 2004.
101. **Nettelbladt O, Hallgren R.** Hyaluronan (hyaluronic acid) in bronchoalveolar lavage fluid during the development of bleomycin-induced alveolitis in the rat. *Am Rev Respir Dis* 140: 1028–1032, 1989.
102. **Olczyk P, Komosinska-Vassev K, Winsz-Szczotka K, Kuznik-Trocha K, Olczyk K.** [Hyaluronan: structure, metabolism, functions, and role in wound healing]. *Postepy Hig Med Dosw* 62: 651–659, 2008.
103. **Oliferenko S, Kaverina I, Small JV, Huber LA.** Hyaluronic acid (HA) binding to CD44 activates Rac1 and induces lamellipodia outgrowth. *J Cell Biol* 148: 1159–1164, 2000.
104. **Opitz B, van Laak V, Eitel J, Suttorp N.** Innate immune recognition in infectious and non-infectious diseases of the lung. *Am J Respir Crit Care Med* 181: 1294–1309, 2010.
105. **Ormiston ML, Slaughter GR, Deng Y, Stewart DJ, Courtman DW.** The enzymatic degradation of hyaluronan is associated with disease progression in experimental pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 298: L148–L157, 2010.
106. **Papakonstantinou E, Kouri FM, Karakiulakis G, Klagas I, Eickelberg O.** Increased hyaluronic acid content in idiopathic pulmonary arterial hypertension. *Eur Respir J* 32: 1504–1512, 2008.
107. **Park HS, Kim SR, Lee YC.** Impact of oxidative stress on lung diseases. *Respirology* 14: 27–38, 2009.
108. **Pearson JD.** Endothelial cell biology. *Radiology* 179: 9–14, 1991.
109. **Petrigni G, Allegra L.** Aerosolised hyaluronic acid prevents exercise-induced bronchoconstriction, suggesting novel hypotheses on the correction of matrix defects in asthma. *Pulm Pharmacol Ther* 19: 166–171, 2006.
110. **Qureshi ST, Zhang X, Aberg E, Bousette N, Giaid A, Shan P, Medzhitov RM, Lee PJ.** Inducible activation of TLR4 confers resistance to hyperoxia-induced pulmonary apoptosis. *J Immunol* 176: 4950–4958, 2006.
111. **Rafi-Janajreh AQ, Chen D, Schmits R, Mak TW, Grayson RL, Sponenberg DP, Nagarkatti M, Nagarkatti PS.** Evidence for the involvement of CD44 in endothelial cell injury and induction of vascular leak syndrome by IL-2. *J Immunol* 163: 1619–1627, 1999.
112. **Ray R, Shah AM.** NADPH oxidase and endothelial cell function. *Clin Sci (Lond)* 109: 217–226, 2005.
113. **Rigden DJ, Littlejohn JE, Joshi HV, de Groot BL, Jedrzejas MJ.** Alternate structural conformations of *Streptococcus pneumoniae* hyaluronan lyase: insights into enzyme flexibility and underlying molecular mechanism of action. *J Mol Biol* 358: 1165–1178, 2006.
114. **Romisch J.** Factor VII activating protease (FSAP): a novel protease in hemostasis. *Biol Chem* 383: 1119–1124, 2002.
115. **Sahu S, Lynn WS.** Hyaluronic acid in the pulmonary secretions of patients with asthma. *Biochem J* 173: 565–568, 1978.
116. **Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR.** Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. *J Immunol* 177: 1272–1281, 2006.
117. **Scott JE, Heatley F.** Biological properties of hyaluronan in aqueous solution are controlled and sequestered by reversible tertiary structures, defined by NMR spectroscopy. *Biomacromolecules* 3: 547–553, 2002.
118. **Scuri M, Abraham WM.** Hyaluronan blocks human neutrophil elastase (HNE)-induced airway responses in sheep. *Pulm Pharmacol Ther* 16: 335–340, 2003.
119. **Scuri M, Abraham WM, Botvinnikova Y, Forteza R.** Hyaluronic acid blocks porcine pancreatic elastase (PPE)-induced bronchoconstriction in sheep. *Am J Respir Crit Care Med* 164: 1855–1859, 2001.
120. **Scuri M, Sabater JR, Abraham WM.** Hyaluronan blocks porcine pancreatic elastase-induced mucociliary dysfunction in allergic sheep. *J Appl Physiol* 102: 2324–2331, 2007.
121. **Selemidis S, Sobey CG, Wingler K, Schmidt HH, Drummond GR.** NADPH oxidases in the vasculature: molecular features, roles in disease and pharmacological inhibition. *Pharmacol Ther* 120: 254–291, 2008.
122. **Singleton PA, Bourguignon LY.** CD44 interaction with ankyrin and IP_3 receptor in lipid rafts promotes hyaluronan-mediated Ca^{2+} signaling leading to nitric oxide production and endothelial cell adhesion and proliferation. *Exp Cell Res* 295: 102–118, 2004.
123. **Singleton PA, Bourguignon LY.** CD44v10 interaction with Rho-kinase (ROK) activates inositol 1,4,5-triphosphate (IP_3) receptor-mediated Ca^{2+} signaling during hyaluronan (HA)-induced endothelial cell migration. *Cell Motil Cytoskeleton* 53: 293–316, 2002.
124. **Singleton PA, Dudek SM, Ma SF, Garcia JG.** Transactivation of sphingosine 1-phosphate receptors is essential for vascular barrier regulation. Novel role for hyaluronan and CD44 receptor family. *J Biol Chem* 281: 34381–34393, 2006.
125. **Singleton PA, Mirzapoiazova T, Guo Y, Sammani S, Mambetsariev N, Lennon FE, Moreno-Vinasco L, Garcia JG.** High-molecular-weight hyaluronan is a novel inhibitor of pulmonary vascular leakiness. *Am J Physiol Lung Cell Mol Physiol* 299: L639–L651, 2010.
126. **Singleton PA, Salgia R, Moreno-Vinasco L, Moitra J, Sammani S, Mirzapoiazova T, Garcia JG.** CD44 regulates hepatocyte growth factor-mediated vascular integrity. Role of c-Met, Tiam1/Rac1, dynamin 2, and cortactin. *J Biol Chem* 282: 30643–30657, 2007.
127. **Smith LS, Kajikawa O, Elson G, Wick M, Mongovin S, Kosco-Vilbois M, Martin TR, Frevert CW.** Effect of Toll-like receptor 4 blockade on pulmonary inflammation caused by mechanical ventilation and bacterial endotoxin. *Exp Lung Res* 34: 225–243, 2008.
128. **Soderberg M, Bjermer L, Hallgren R, Lundgren R.** Increased hyaluronan (hyaluronic acid) levels in bronchoalveolar lavage fluid after histamine inhalation. *Int Arch Allergy Appl Immunol* 88: 373–376, 1989.
129. **Soltes L, Mendichi R, Kogan G, Schiller J, Stankovska M, Arnhold J.** Degradative action of reactive oxygen species on hyaluronan. *Biomacromolecules* 7: 659–668, 2006.
130. **Stern R.** Devising a pathway for hyaluronan catabolism: are we there yet? *Glycobiology* 13: 105R–115R, 2003.
131. **Stern R, Asari AA, Sugahara KN.** Hyaluronan fragments: an information-rich system. *Eur J Cell Biol* 85: 699–715, 2006.
132. **Stern R, Kogan G, Jedrzejas MJ, Soltes L.** The many ways to cleave hyaluronan. *Biotechnol Adv* 25: 537–557, 2007.
133. **Summah H, Qu JM.** Biomarkers: a definite plus in pneumonia. *Mediators Inflamm* 2009: 675753, 2009.
134. **Svee K, White J, Vaillant P, Jessurun J, Roongta U, Krumwiede M, Johnson D, Henke C.** Acute lung injury fibroblast migration and invasion of a fibrin matrix is mediated by CD44. *J Clin Invest* 98: 1713–1727, 1996.
135. **Szekely JI, Pataki A.** Recent findings on the pathogenesis of bronchial asthma. *Acta Physiol Hung* 96: 385–405, 2009.
136. **Tabbara KF.** Tuberculosis. *Curr Opin Ophthalmol* 18: 493–501, 2007.
137. **Taylor KR, Yamasaki K, Radek KA, Di Nardo A, Goodarzi H, Golenbock D, Beutler B, Gallo RL.** Recognition of hyaluronan released in sterile injury involves a unique receptor complex dependent on Toll-like receptor 4, CD44, and MD-2. *J Biol Chem* 282: 18265–18275, 2007.

138. **Teder P, Heldin P.** Mechanism of impaired local hyaluronan turnover in bleomycin-induced lung injury in rat. *Am J Respir Cell Mol Biol* 17: 376–385, 1997.
139. **Teder P, Vandivier RW, Jiang D, Liang J, Cohn L, Pure E, Henson PM, Noble PW.** Resolution of lung inflammation by CD44. *Science* 296: 155–158, 2002.
140. **Toole BP.** Hyaluronan is not just a goo! *J Clin Invest* 106: 335–336, 2000.
141. **Toole BP.** Hyaluronan: from extracellular glue to pericellular cue. *Nat Rev Cancer* 4: 528–539, 2004.
142. **Trent MS, Stead CM, Tran AX, Hankins JV.** Diversity of endotoxin and its impact on pathogenesis. *J Endotoxin Res* 12: 205–223, 2006.
143. **Turley EA, Noble PW, Bourguignon LY.** Signaling properties of hyaluronan receptors. *J Biol Chem* 277: 4589–4592, 2002.
144. **Ushio-Fukai M.** Localizing NADPH oxidase-derived ROS. *Sci STKE* 2006: re8, 2006.
145. **van der Windt GJ, Hoogendijk AJ, de Vos AF, Kerver ME, Florquin S, van der Poll T.** The role of CD44 in the acute and resolution phase of the host response during pneumococcal pneumonia. *Lab Invest* 91: 588–597, 2011.
146. **van der Windt GJ, Schouten M, Zeerleder S, Florquin S, Poll T.** CD44 is protective during hyperoxia-induced lung injury. *Am J Respir Cell Mol Biol* 44: 377–383, 2010.
147. **van der Windt GJ, van 't Veer C, Florquin S, van der Poll T.** CD44 deficiency is associated with enhanced *Escherichia coli*-induced proinflammatory cytokine and chemokine release by peritoneal macrophages. *Infect Immun* 78: 115–124, 2010.
148. **Venge P, Pedersen B, Hakansson L, Hallgren R, Lindblad G, Dahl R.** Subcutaneous administration of hyaluronan reduces the number of infectious exacerbations in patients with chronic bronchitis. *Am J Respir Crit Care Med* 153: 312–316, 1996.
149. **Wang A, de la Motte C, Lauer M, Hascall V.** Hyaluronan matrices in pathobiological processes. *FEBS J*. In press.
150. **Wang Q, Teder P, Judd NP, Noble PW, Doerschuk CM.** CD44 deficiency leads to enhanced neutrophil migration and lung injury in *Escherichia coli* pneumonia in mice. *Am J Pathol* 161: 2219–2228, 2002.
151. **Ware LB.** Clinical year in review. I. Interstitial lung disease, pulmonary vascular disease, pulmonary infections, and cardiopulmonary exercise testing and pulmonary rehabilitation. *Proc Am Thorac Soc* 6: 487–493, 2009.
152. **Weigel PH, DeAngelis PL.** Hyaluronan synthases: a decade-plus of novel glycosyltransferases. *J Biol Chem* 282: 36777–36781, 2007.
153. **Wilkinson TS, Potter-Perigo S, Tsoi C, Altman LC, Wight TN.** Pro- and anti-inflammatory factors cooperate to control hyaluronan synthesis in lung fibroblasts. *Am J Respir Cell Mol Biol* 31: 92–99, 2004.
154. **Wu YJ, La Pierre DP, Wu J, Yee AJ, Yang BB.** The interaction of versican with its binding partners. *Cell Res* 15: 483–494, 2005.
155. **Wygrecka M, Markart P, Fink L, Guenther A, Preissner KT.** Raised protein levels and altered cellular expression of factor VII activating protease (FSAP) in the lungs of patients with acute respiratory distress syndrome (ARDS). *Thorax* 62: 880–888, 2007.
156. **Yadav AK, Mishra P, Agrawal GP.** An insight on hyaluronic acid in drug targeting and drug delivery. *J Drug Target* 16: 91–107, 2008.
157. **Yasuda T.** Hyaluronan inhibits cytokine production by lipopolysaccharide-stimulated U937 macrophages through down-regulation of NF-κB via ICAM-1. *Inflamm Res* 56: 246–253, 2007.
158. **Zaman A, Cui Z, Foley JP, Zhao H, Grimm PC, Delisser HM, Savani RC.** Expression and role of the hyaluronan receptor RHAMM in inflammation after bleomycin injury. *Am J Respir Cell Mol Biol* 33: 447–454, 2005.
159. **Zhao H, Leu SW, Shi L, Dedaj R, Zhao G, Garg HG, Shen L, Lien E, Fitzgerald KA, Shiedlin A, Shen H, Quinn DA, Hales CA.** TLR4 is a negative regulator in noninfectious lung inflammation. *J Immunol* 184: 5308–5314, 2010.
160. **Zhao HW, Lu CJ, Yu RJ, Hou XM.** An increase in hyaluronan by lung fibroblasts: a biomarker for intensity and activity of interstitial pulmonary fibrosis? *Respirology* 4: 131–138, 1999.
161. **Zhu Z, Lee CG, Zheng T, Chupp G, Wang J, Homer RJ, Noble PW, Hamid Q, Elias JA.** Airway inflammation and remodeling in asthma. Lessons from interleukin 11 and interleukin 13 transgenic mice. *Am J Respir Crit Care Med* 164: S67–S70, 2001.