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Modulators of Inflammation in Bronchopulmonary Dysplasia

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Abstract

Over 50 years after its first description, Bronchopulmonary Dysplasia (BPD) remains a devastating pulmonary complication in preterm infants with respiratory failure and develops in 30–50% of infants less than 1000-gram birth weight. It is thought to involve ventilator- and oxygen-induced damage to an immature lung that results in an inflammatory response and ends in aberrant lung development with dysregulated angiogenesis and alveolarization. Significant morbidity and mortality are associated with this most common chronic lung disease of childhood. Thus, any therapies that decrease the incidence or severity of this condition would have significant impact on morbidity, mortality, human costs, and healthcare expenditure. It is clear that an inflammatory response and the elaboration of growth factors and cytokines are associated with the development of BPD. Numerous approaches to control the inflammatory process leading to the development of BPD have been attempted. This review will examine the anti-inflammatory approaches that are established or hold promise for the prevention or treatment of BPD.

Bronchopulmonary Dysplasia is a complex condition that has a multifactorial pathogenesis. Key contributors include oxygen toxicity, ventilator-induced lung injury, inflammation and an arrest of lung vascular development.^{1,2} Inflammation, an accumulation of neutrophils and macrophages into the injured preterm lung, results in the elaboration of pro-inflammatory and pro-fibrotic growth factors, an imbalance of the proteolytic activity in the lung and increased vascular permeability.³ Neutrophil and macrophage accumulation commences early in the first week of life and counts remain elevated in infants that develop BPD.⁴ Coordinated development of the distal epithelial and vascular compartments is a necessity for the final ability to conduct adequate gas exchange. Lung microvascular development is critical to normal secondary septation leading to alveolar formation. Multiple animal models and examination of autopsy samples of infants with BPD have confirmed an arrest of vascular development and a simplification of the distal lung architecture as a result of preterm birth and associated lung injury.⁵ Indeed, alveolar septation can be preserved in animal models by decreasing the effects of contributors to BPD pathogenesis, including

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inflammation, oxygen and mechanical ventilation.⁶ The pathogenesis of BPD involves the effects of these multiple pathologic mechanisms on lung development.

A number of models of BPD have been developed. Two large animal models, the sheep and baboon preterm birth and ventilation models, recapitulate the essential features of the human condition, including preterm birth, oxygen exposure, mechanical ventilation, inflammation and arrested lung development.⁷ However, these models do not support genetic studies to identify the molecular determinants of BPD. Therefore, rodent models of newborn lung injury, that involve either hyperoxia or hypoxia exposure for up to 14 days and result in pathology that mimics BPD, were established.^{8–10} Further, a model in which bleomycin, administered intra-peritoneally to neonatal rodents, also recapitulates the features of BPD.¹¹ While these rodent models do not involve preterm birth or ventilation, several groups have confirmed changes in inflammation, cytokines, oxidative stress, and vascular defects in association with alveolar simplification that validate the use of these models in the study of BPD.^{8–11} The fact that alveolar development is entirely a postnatal event occurring in the first 2–3 weeks of life in rodents, provides an appropriate window to examine the effects of injury on the alveolar phase of the developing lung. More recently, the use of high oxygen exposures during the first 14 days of life has been questioned since human preterm infants are exposed to these conditions only during the sacular phase of lung development.^{12,13} Thus, more appropriate oxygen exposure in the first four to five days of life in rodents have been developed and also demonstrate inflammatory changes and alveolar defects.^{14,15}

The recruitment of inflammatory cells to the injured lung requires activation of bone marrow-derived cells, circulating leukocytes and the endothelium. Initiation of injury results in initial rolling, then firm adhesion of inflammatory cells to the activated endothelium. This is followed by transmigration of leukocytes through the endothelium and their accumulation in areas of injury. Initially recruited neutrophils undergo apoptosis and alveolar macrophages engulf these cells. This process results in the production of active transforming growth factor beta (TGF β) which promotes fibrosis. A number of key molecules have been identified in the process of inflammatory cell recruitment and include selectins, integrins, cytokines and growth factors, the innate immune system including Toll-Like Receptors (TLRs), Surfactant Protein A (SPA) and SPD, as well as components of the extracellular matrix.^{16,17}

Macrophage subsets demonstrating differential functions have been identified. Classically activated macrophages (CAMs), also called M1 macrophages, result from TLR stimulation, bacterial infection and interferon-gamma stimulation. Alternatively activated macrophages (AAMs), also called M2 macrophages, result from Th2 cytokine (e.g. interleukin or IL4 and IL13) stimulation.¹⁸ Specific markers for M1 and M2 macrophages have emerged. For instance, M1 macrophages can be identified by the expression of inducible nitric oxide synthase (iNOS) and CD11c, whereas M2 macrophages can be identified by the expression of Arginase 1 or YM1 (also known as chitinase-like 3 or Chil3).^{19,20} While M1 macrophages have potent microbicidal properties and promote Th1 responses, M2 macrophages play a role in the resolution of inflammation, with high endocytic clearance capacity and reduced pro-inflammatory cytokine secretion. Given the large predominance of inflammation in the pathogenesis of BPD, considerable efforts have been made to develop anti-inflammatory strategies, ranging from glucocorticoids to newer more novel therapeutic

targeting of components of the innate immune system. The pathogenesis of BPD and the multiple anti-inflammatory strategies discussed in this review are summarized in Figure 1.

Non-invasive respiratory support

The contribution of intubation and mechanical ventilation to inflammation and the incidence and severity of BPD has been established in animal models and in human preterm infants.^{21,22} Mouse and lamb models show that mechanical ventilation alone without hyperoxia or lipopolysaccharide (LPS) exposure is sufficient for the development of lung inflammation, as well as altered alveolarization and lung function.^{23,24} Indeed, respiratory management with continuous positive airway pressure (CPAP) in baboons and mice, or high frequency, non-invasive ventilation in lambs is associated with less inflammation and better alveolarization.^{25–27} In large clinical trials, the incidence of BPD in infants randomized to either non-invasive respiratory support or selective intubation and surfactant therapy were found to be equivalent, findings that have pushed changes in neonatal practice significantly in favor of non-invasive approaches to respiratory management.^{28–30}

Corticosteroids

First described in sheep in 1969³¹ and in a human trial in 1972, antenatal glucocorticoid therapy to enhance fetal lung maturity was associated with decreased incidence of Respiratory Distress Syndrome (RDS) and death.³² Indeed, this therapy is also associated with decreased intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and early sepsis.³³ Given the early descriptions of inflammation in infants with BPD, postnatal glucocorticoid therapy to decrease or abrogate the inflammatory response, improve lung function and increase the likelihood of extubation failure has been examined since the early 1970's. While benefits of early (in the first week of life) corticosteroid therapy in preterm infants at risk of developing BPD include decreased incidence of BPD at 28 days and at 36 weeks postmenstrual age (PMA), decreased rates of failure of extubation and decreased incidence of patent ductus arteriosus (PDA) and retinopathy of prematurity (ROP), significant adverse events have been noted including hyperglycemia, hypertension, hypertrophic cardiomyopathy, growth failure, intestinal perforation and bleeding, as well as an increased incidence of cerebral palsy.^{34,35} The use of postnatal steroids in infants that remain intubated past 7–14 days of life has also been reviewed recently.³⁶ Similar benefits with respect to decreased rates of death or BPD at 28 days and 36 weeks PMA and adverse outcomes including hyperglycemia and hypertension were found, but longer term cerebral palsy or neurodevelopmental complications were not significantly different from those of controls.³⁵ However, given the considerable adverse effects described, the current recommendations are for judicious use of postnatal corticosteroid therapy. Further, although difficult to demonstrate in preterm infants, dexamethasone treatment of newborn rodents is associated with an arrest of alveolarization that persists into adulthood.^{37–39}

Caffeine

The methylxanthines caffeine, aminophylline and theophylline bind to adenosine receptors and act as non-selective adenosine antagonists.⁴⁰ Caffeine also inhibits phosphodiesterases

leading to the accumulation of cAMP and cGMP.⁴¹ These two mechanisms likely explain the different neurologic and respiratory effects of caffeine respectively.⁴⁰ Despite reports of potential harmful effects of caffeine including tachycardia, growth failure, neurologic energy failure and long-term behavioral problems,⁴² this drug was widely used to stimulate the respiratory center of preterm infants in the treatment of apnea of prematurity. The Caffeine for Apnea of Prematurity or CAP Trial established, in a randomized controlled manner, that caffeine therapy in preterm infants 500–1250 grams birth weight was associated with a decrease in the incidence of BPD and PDA, and although a lower weight gain was noted in treated infants at two weeks of age, this was not sustained and there were no differences in mortality, head ultrasound findings of injury or NEC.⁴³ Indeed, long-term follow up of caffeine-treated infants in this trial has demonstrated a reduced incidence of motor impairment and no effect on academic or behavioral outcomes at 11 years of age.⁴⁴

While an increased respiratory drive most likely contributed to the favorable outcomes in caffeine-treated infants, other mechanisms for the effects of caffeine have been proposed. Thus, caffeine can increase diaphragmatic contractility,⁴⁵ has a diuretic effect,⁴⁶ can protect neuronal injury,^{47,48} and can even transcriptionally induce SP-B.^{49,50} Interestingly, however, caffeine has anti-inflammatory effects in newborn animals. Thus, hyperoxia exposure of six-day old rat pups induced cytokine and inflammatory cell recruitment, both of which were inhibited by administration of caffeine.⁵¹ Additionally, premature rabbits exposed to hyperoxia and treated with caffeine had less inflammation and improved alveolarization compared to hyperoxia-exposed controls.⁵² Indeed, postnatal inflammation driven by LPS-induced amnionitis was also abrogated by caffeine treatment, although alveolar simplification was not.⁵³ Thus, caffeine has significant anti-inflammatory effects though the mechanisms of these effects are unclear to date.

Nitric oxide (NO)

NO, generated by nitric oxide synthases (neuronal or nNOS, endothelial or eNOS and iNOS) upon the conversion of L-arginine to L-citrulline, plays a key role in developmental and physiological processes in the lung.^{54,55} Studies in the mature airway indicate that the epithelium is the primary source of NO⁵⁶ and that NO mediates neurotransmission, smooth muscle relaxation, bacteriostasis, ciliary motility, mucin secretion, and plasma exudation.^{54,55,57} Elegant *in vitro* studies from the Shaul/Mineo laboratories implicate NO in anti-inflammatory processes such as inhibition of monocyte adhesion to activated endothelium and platelet aggregation.^{58,59} Indeed, inhaled NO (iNO) attenuates pulmonary inflammation in a neonatal rat hyperoxia model.⁶⁰

NO plays an important role in pulmonary vascularization, alveolarization, and airway branching.^{61–66} NO also has a well-recognized role in mediating pulmonary vasomotor tone around the time of birth.⁶⁷ In studies of lungs from fetal baboons, pulmonary NOS expression is upregulated during normal fetal development. However, in the baboon model of BPD, expression of nNOS and eNOS was significantly decreased, and iNO given at 5ppm improved pulmonary artery pressures, pulmonary mechanics, lung elastin deposition and was associated with modest increases in secondary septation.⁶⁸ Based on these and other animal and early stage human studies,^{22,64,69,70} multiple trials of iNO therapy have been

performed in human preterm infants to prevent BPD^{71–74}. These have yielded mixed results and the use of iNO is not currently recommended for the prevention of BPD.

Vitamin D

Vitamin D or cholecalciferol is a fat-soluble vitamin that is synthesized from 7-dehydrocholesterol in the skin after ultraviolet B exposure or absorbed from the diet. Vitamin D is converted to 25-hydroxy-vitamin D in the liver and to the biologically active 1,25-hydroxy-vitamin D or calcitriol in the kidney. The effects of 1,25-OH-vitamin D are mediated by a nuclear receptor, the vitamin D receptor (VDR) that binds to Vitamin D-responsive elements to regulate the transcription of a wide number of genes. Vitamin D deficiency is highly prevalent, particularly in pregnancy and has been associated with a number of adverse outcomes such as poor maternal weight gain, preeclampsia, increased rates of operative delivery and shorter gestation.⁷⁵ In addition, the impact of vitamin D deficiency on lung development and health is evident in VDR knockout mice that have an imbalance of matrix metalloproteinases and develop emphysema and inflammation.^{76,77}

More recently, direct demonstration of the importance of Vitamin D in pregnancy and BPD has been obtained from experiments in which antenatal Vitamin D supplementation was associated with improved placental vascularization and fetal growth.⁷⁸ Postnatal Vitamin D supplementation was associated with an improvement in alveolarization in rats that were exposed to intra-amniotic LPS,⁷⁹ and Vitamin D induced downregulation of TLR4 and therefore decreased downstream cytokines such as IL1 β in neonatal rats exposed to hyperoxia.⁸⁰ The effects of Vitamin D on the activation of eNOS likely contribute to the beneficial observations with Vitamin D both on the placenta and postnatal vascular and alveolar growth.⁸¹ Interestingly, a recent report demonstrated beneficial effects of nebulized Vitamin D to enhance lung maturation.⁸²

Peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists

PPAR- γ is a key anti-inflammatory nuclear hormone receptor that regulates a wide array of downstream effects.⁸³ When ligands bind PPAR- γ , the receptor dimerizes with retinoid X receptors (RXRs) and this heterodimer translocates to the nucleus, binding to PPAR response elements of target genes that stimulate the transcription of genes regulating key pathways, including lipid metabolism, glucose homeostasis and cell differentiation. A number of ligands for PPAR- γ have been described and include nitrated fatty acids and anti-diabetic glitazones.^{84,85} Importantly, PPAR- γ ligands inhibit transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) and signal transducer and activator of transcription 1 (STAT1), and decrease the induction of pro-inflammatory molecules such as iNOS.^{86,87} Thus, a key feature of PPAR- γ signaling is the inactivation of macrophages. Proof of concept that PPAR- γ agonists are useful therapeutic agents in models of neonatal lung injury include prevention of aberrant TGF β and Wnt signaling, dampening of inflammation and improvement of secondary septation changes in models of hyperoxia-mediated neonatal lung injury.^{88,89} Indeed, antenatally administered and postnatally nebulized PPAR- γ agonists have also shown promise in preventing the changes seen in hyperoxia-induced neonatal lung injury.^{90–92}

Curcumin

Curcumin or diferuloylmethane, a yellow pigment found in turmeric that is obtained from the turmeric plant *Curcuma longa*, is a dietary spice used in Indian curry and in Ayurvedic medicine.⁹³ Curcumin has been evaluated in a wide range of pulmonary diseases including chronic obstructive pulmonary disease (COPD), acute lung injury and fibrosis.^{94–96} A wide range of molecular actions have been ascribed to curcumin but, in the case of lung inflammatory diseases, they largely fall into three categories. First, it blocks activation of NFκB, a key transcription factor that activates inflammatory pathways,⁹⁷ it acts as an antioxidant targeting superoxide among others,⁹⁸ and inhibits key growth factors such as TGFβ that contribute to fibrosis.⁹⁹ Another proposed mechanism, that curcumin acts as a PPAR-γ agonist, remains controversial.^{100,101}

Curcumin has been evaluated in neonatal hyperoxia models of BPD.^{102–104} Neonatal hyperoxia in rodents is associated with increased expression of pro-inflammatory cytokines and growth factors, an inflammatory response, increased myofibroblasts and decreased alveolarization. Curcumin effectively reverses these observations and promotes improved lung architecture.^{102–104} The major issue with the development of curcumin as a drug is its poor solubility, poor bioavailability and rapid metabolism.¹⁰⁵ A number of alternate approaches have been explored, including co-administration of piperine to enhance bioavailability, and the development of nanoparticle delivery devices.^{106,107}

Club Cell Protein 16 (CC16; Clara Cell or CC10)

CC10, also known as uteroglobin, is a 10kDa homodimeric secretory protein produced by Clara cells in the airways and in the urogenital tract. This protein possesses a number of *in vitro* anti-inflammatory properties including blocking of N-Formyl-methionyl-leucyl—phenylalanine (fLMP)-stimulated neutrophil and monocyte chemotaxis,¹⁰⁸ inhibition of phospholipase A₂ (PLA₂),¹⁰⁹ inhibition of platelet aggregation,¹¹⁰ and suppression of IL2-stimulated production of tumor necrosis factor alpha (TNFα), IL1β and interferon (IFN)γ in lymphocytes.¹¹¹ CC10 knockout mice exposed to hyperoxia,^{112,113} or ozone,¹¹⁴ demonstrate an increased inflammatory response consisting of an exaggerated pro-inflammatory cytokine profile including IL1β and an accumulation of inflammatory cells.

Given the low concentrations of CC10 that are found in tracheal aspirate samples obtained from premature infants born at 28 to 32 weeks, its anti-inflammatory properties, and its ability to inhibit PLA₂, an enzyme that inactivates surfactant, it was natural to propose recombinant human CC10 (rhCC10) as a potential therapeutic agent to limit the incidence and severity of BPD.¹¹⁵ Safety of rhCC10 was demonstrated in several animal models of lung injury, including neonatal pigs¹¹⁶, rabbits¹¹⁷ and lambs.^{118,119} Intratracheal administration of rhCC10 in a Phase I trial demonstrated that, while endogenous CC10 concentrations did not rise in tracheal aspirate samples of control infants until 72 hours of life, rhCC10 increased the concentration in tracheal aspirates as early as 12 hours of life and showed systemic absorption and urinary excretion at 6–12 hours of life. Treatment with rhCC10 was associated with a lower neutrophil count, lower protein concentration and lower

IL6 concentrations.¹¹⁵ These encouraging results in 22 infants have prompted a larger study involving over 80 patients, but the results have yet to be published.

Insulin-like Growth Factor 1 (IGF-1) / IGF-binding protein 3 (IGFBP3)

IGF-1 is an important contributor to fetal growth and development and low serum concentrations of IGF-1 have been reported in premature infants in association with ROP,¹²⁰ IVH,¹²¹ NEC¹²² and BPD.¹²³ In fact, IGF-1 has a number of properties that define it as a reparative growth factor. For example, IGF-1 promotes the endothelial survival signaling of vascular endothelial growth factor (VEGF),¹²⁴ and regulates glucose metabolism in the brain.¹²⁵ Interestingly, IGF-1 suppresses neonatal immune responses to phorbol ester stimulation in cord blood monocytes in association with decreased DNA binding of NF κ B, suggesting profound anti-inflammatory properties.¹²⁶ Collectively, these findings suggest that IGF-1 replacement in preterm neonates could hold benefit in a number of diseases, but most likely in ROP and BPD.

Indeed, following pharmacokinetic studies of continuous rhIGF-1 and its binding partner rhIGFBP3,^{127,128,129} a drug called SHP607 (Shire Pharmaceuticals), a Phase I/IIa trial was conducted to decrease the incidence and/or severity of ROP. The results of this trial have been announced as a press release. While this trial did not meet this goal, substantial decreases in the severity of BPD and severe IVH were noted. Further confirmation of these findings is currently being pursued.

Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome blockade

IL1 β , a key initiator of inflammation, has a complex two-step activation system, and has been implicated in inflammatory disorders in humans. In the first step, endogenous danger-associated molecular patterns (DAMPs) stimulate pattern recognition receptors (PRR) such as Toll-Like Receptors (TLRs) to activate NF κ B, resulting in transcriptional increases the expression of pro-IL1 β .¹³⁰ Further elucidation of this pathway revealed the existence of a family of exclusively intracellular proteins called NLRs that also bind to DAMPs.¹³¹ One such NLR, NLRP3, forms a protein complex with the adaptor molecule *Apoptosis-associated Speck-like protein containing a CARD* (ASC) and pro-caspase1 to form the *NLRP3 inflammasome*.^{132,133} Thus, the second signal is the activation of the purinergic receptor P2X7 by extracellular ATP that results in the formation of the NLRP3 inflammasome,^{134,135} a response that has been demonstrated after hyperoxia exposure in adult mice¹³⁵ and in our studies of neonatal mice exposed to hyperoxia.¹³⁶ Activation of this complex cleaves pro-caspase1 to caspase1 (p20), which in turn proteolytically cleaves pro-IL1 β to produce mature IL1 β . This cytokine is released and interacts with its receptor, IL1R, to signal inflammatory pathways. Importantly, interleukin 1 receptor antagonist (IL1ra) is an endogenous blocker of IL1R, and its recombinant form, rIL1ra is used in monogenic disorders with elevated IL1 β as well as several rheumatologic disorders.^{137,138}

Elevated concentrations of IL1 β in amniotic fluid¹³⁹ and postnatally⁴ have been associated with the development of BPD. Indeed, in preterm infants at risk of BPD, there is a balance

of mature IL1 β to IL1 α in the first few days of life, but the ratio of IL1 β to IL1 α is increased by days 5–7 in infants that subsequently developed BPD.¹⁴⁰ Further, in fetal and neonatal mice, conditional transgenic overexpression of IL1 β in Clara cells, even in the absence of hyperoxia, results in inflammation, airway remodeling and distal alveolar simplification, changes reminiscent of BPD.^{141,142}

A number of reports have now demonstrated at least partial efficacy of rIL1 α treatment in neonatal rodent models of BPD. Thus, rIL1 α treatment of neonatal rats exposed to 60% O₂ resulted in decreased inflammation, improved alveolarization, and partially restored vessel density.¹⁴³ Nold et al., using a model of *in utero* LPS exposure followed by postnatal O₂ exposure, showed that rIL1 α treatment up to 28 days of life rescued inflammation and alveolarization at least at lower concentrations, and less so at high concentrations of O₂.¹⁴⁴ Our own studies show that the NLRP3 inflammasome is critically involved in the neonatal hyperoxia model of BPD, and that the NLRP3 inflammasome is activated in the preterm baboon model of BPD. Importantly, tracheal aspirate IL1 β concentrations in the first three days of life are independently associated with death or BPD at 36 weeks PMA in preterm infants with respiratory failure.¹³⁶ Further development of this strategy holds promise for the ability to block the effects of the NLRP3 inflammasome (Figure 2).

Hyaluronan Binding Peptides

Hyaluronan (hyaluronic acid, HA), a glycosaminoglycan component of the extracellular matrix, is a polymer made up of repeating disaccharide units of glucuronic acid and N-acetyl glucosamine, and is an early and important mediator of inflammation.^{145,146} HA regulation of inflammation is both dose- and molecular size-dependent. HA, at doses of 1 mg/ml or greater and in high molecular weight (HMW) form, inhibits inflammatory cell chemotaxis,^{147,148} phagocytosis,¹⁴⁹ elastase release,¹⁵⁰ and respiratory burst activity.¹⁴⁹ On the other hand, at lower concentrations and at lower molecular weights, fragmented HA (LMW HA) promotes monocyte maturation into macrophages as measured by production of IGF-1¹⁵¹ and IL1 β .^{152,153}

An increased recovery of HA in bronchoalveolar lavage (BAL) has been found in various disease states such as sarcoidosis,¹⁵⁴ occupational disorders¹⁵⁵ and acute RDS (ARDS),¹⁵⁶ and after acute lung injury induced by intratracheal bleomycin instillation in rodents.^{157–159} Further, the increased recovery of HA temporally correlates with an influx of inflammatory cells.¹⁶⁰ We have previously demonstrated that alveolar macrophages from bleomycin-injured animals are more motile than those from control animals and that an HA-binding peptide (HABP) is able to completely inhibit this increased motility.¹⁶¹ Further, systemic administration of this HABP to animals prior to injury resulted in decreased macrophage accumulation and fibrosis.¹⁶¹ These data suggest that HA is upstream of and critical for the inflammatory response to lung injury.

Preterm infants destined to develop BPD have increased superoxide and peroxynitrite levels early in their postnatal course.^{162,163} Both superoxide and peroxynitrite cause chemical fragmentation of HA to generate HA fragments (LMW HA) that act as endogenous danger signals that interact with HA and TLRs to activate the innate immune system.^{164–168}

Interestingly, we and others have demonstrated that HA fragments are able to activate the NLRP3 inflammasome,^{152,153} thereby providing direct rationale to study the effects of HA-binding peptides in models of BPD, and eventually in preterm infants at risk of developing BPD. These concepts are depicted in Figure 2.

HA interacts with specific cell-associated receptors including CD44 and Receptor for HA-Mediated Motility (RHAMM, CD168). Both of these ubiquitously expressed proteins have been implicated in acute lung injury¹⁴⁵. CD44 expression is increased after bleomycin injury,^{169,170} and acute lung injury in CD44 knockout (KO) mice results in the accumulation of inflammatory cells and excess HA accumulation, suggesting that CD44 is necessary for the resolution of inflammation.¹⁷¹ RHAMM is expressed at the cell surface, in the cytoplasm and in the nucleus, and regulates cell locomotion and proliferation.^{172–174} RHAMM expression is increased in macrophages,¹⁴⁶ fibroblasts,¹⁷⁵ epithelial cells,¹⁶⁷ and smooth muscle cells¹⁷⁴ responding to injury. After intratracheal bleomycin-induced acute lung injury, RHAMM expression is increased in macrophages responding to injury, and the increased motility of these cells is entirely dependent on RHAMM.^{161,176} Interestingly, antibody blockade of RHAMM *in vivo* decreases the accumulation of macrophages into the bleomycin-injured lung, suggesting that RHAMM-HA interactions are crucial for the recruitment of these cells to the site of injury.^{161,176} In order to examine the role of RHAMM in acute lung injury using genetic models, we recently studied the response to intratracheal bleomycin in RHAMM KO mice and in mice that had transgenic overexpression of RHAMM specifically in macrophages.¹⁷⁷ As expected, RHAMM KO mice had less respiratory distress, decreased inflammatory cell accumulation and less fibrosis than littermate controls. On the other hand, bleomycin injury of mice with transgenic overexpression of RHAMM in macrophages resulted in worse respiratory distress, increased inflammation and severe fibrosis compared to littermate wild type animals injured with bleomycin.¹⁷⁷ Therefore, RHAMM is a potential novel therapeutic target to control inflammation after lung injury. We propose that LMW HA uses RHAMM and CD44 as a complex to allow signaling to activate the NLRP3 inflammasome (Figure 2).

SUMMARY

Despite over 50 years of efforts that have resulted in significant improvements in the care of premature infants, including antenatal glucocorticoid treatment, exogenous surfactant administration, gentler ventilation techniques, judicious use of fluids, prevention of infections and improved nutrition, the incidence of BPD has remained essentially unchanged. Given its importance in the pathogenesis of BPD, there continues to be an intense focus on the mechanisms of inflammation in this disorder. Significant progress has been made with the use of animal models with promising therapies emerging. Translational of these promising avenues into clinical use that will decrease the incidence and/or severity of BPD will be challenging and will require careful investigation and substantial support from public, private and commercial sources.

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The author is mindful that this review is not intended to be all encompassing and any omission of work that would be relevant to the topic of this review is not intentional. The author is a co-founder of Eravon Therapeutics, Inc. that

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Figure 1: Pathogenesis of BPD and anti-inflammatory Interventions

Lung development occurs in five distinct but overlapping phases. Several antenatal factors can adversely influence lung development and include intrauterine growth restriction (IUGR), prolonged preterm rupture of membranes (PPROM) and chorioamnionitis. These factors all appear to activate the innate immune system and increase the expression of cytokines that result in inflammation. Among a multitude of effects, antenatal corticosteroid therapy accelerates lung development, in particular, the surfactant system. Preterm birth is often associated with initiation of ventilation and exposure to oxygen and an increased incidence of infections, all of which also result in the activation of the innate immune system and the elaboration of cytokines that drive inflammation. Lung development now has to occur ex-utero, is influenced by this inflammatory milieu, and results in an inhibition of alveolar and vascular development recognized as BPD. A number of strategies and approaches have been investigated to abrogate or dampen the inflammatory response. These are indicated in bold boxes in the figure and are discussed in the review. For additional abbreviations, please see the text.

Figure 2: Activation of the NLRP3 inflammasome and the utility of its blockade in the prevention of BPD

Interleukin 1 beta (IL1 β) is a master regulator of inflammation. Endogenous danger associated molecular patterns (DAMPs) activate the innate immune system to elaborate IL1 β . One such DAMP is low molecular weight hyaluronan (LMW HA), which is formed by the fragmentation of HMW HA by oxidative stress. Acting through the HA receptors RHAMM and CD44, LMW HA activates the transcription factor NF κ B to transcriptionally upregulate pro-IL1 β . At the same time, the NLRP3 inflammasome is also activated which results in the formation of active caspase 1 which cleaves pro-IL1 β to IL1 β to initiate inflammation. The development of HA-binding peptides holds promise in interfering with the LMW HA-RHAMM-CD44 complex to prevent activation of the NLRP3 inflammasome system, which would be predicted to prevent the formation of IL1 β . Recombinant IL1 receptor antagonist will block the effects of IL1 β to also prevent its downstream actions. For additional abbreviations, please see the text.