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Mini Reviews

Hyaluronan in the pathogenesis of acute and post-acute COVID-19 infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recently emerged as the cause of a global pandemic. Infection with SARS-CoV-2 can result in COVID-19 with both acute and chronic disease manifestations that continue to impact many patients long after the resolution of viral replication. There is therefore great interest in understanding the host factors that contribute to COVID-19 pathogenesis. In this review, we address the role of hyaluronan (HA), an extracellular matrix polymer with roles in inflammation and cellular metabolism, in COVID-19 and critically evaluate the hypothesis that HA promotes COVID-19 pathogenesis. We first provide a brief overview of COVID-19 infection. Then we briefly summarize the known roles of HA in airway inflammation and immunity. We then address what is known about HA and the pathogenesis of COVID-19 acute respiratory distress syndrome (COVID-19 ARDS). Next, we examine potential roles for HA in post-acute SARS-CoV-2 infection (PASC), also known as "long COVID" as well as in COVID-associated fibrosis. Finally, we discuss the potential therapeutics that target HA as a means to treat COVID-19, including the repurposed drug hymecromone (4-methylumbelliferone). We conclude that HA is a promising potential therapeutic target for the treatment of COVID-19.

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Introduction

In late 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new and highly pathogenic strain of coronavirus, was identified in China [1]. It soon became clear that infection with SARS-CoV-2 can lead to coronavirus disease (COVID-19), including potentially severe respiratory tract disease [2,3]. By February of 2020, Chinese healthcare workers encountered an average of 3000 new cases per day, and on March 11, 2020, the World Health Organization (WHO) officially categorized the worldwide outbreak of COVID-19 a pandemic [1,3]. The virus has caused a worldwide health crisis causing nearly 604 million confirmed cases and 6.5 million deaths as of September 2022 [1,4–7].

Three years after it emerged and despite the development of effective vaccines, the COVID-19 pandemic continues to spread. Moreover, many individuals suffer persistent, debilitating post-acute sequelae of SARS-CoV-2 infection (PASC), also known as "long COVID" [8–10]. Therefore, there is great interest in identifying additional inflammatory factors and pathways that contribute to COVID-19, in the hope that these might lead to novel therapeutic targets and biomarkers.

The purpose of this article is to review the existing data on one such factor, the extracellular matrix polymer hyaluronan (HA), in COVID-19 disease and

to critically evaluate the hypothesis that HA drives COVID-19 pathogenesis. We first provide a short overview of HA in inflammation and cellular metabolism, particularly in the context of pulmonary disease. We then briefly review the literature on COVID-19 acute respiratory syndrome (ARDS) and PASC. Next, we address what is known about HA in acute-COVID and PASC. Finally, we discuss potential therapeutics for COVID-19 that target HA. This review provides a foundation for understanding the role of HA in the pathogenesis and treatment of COVID-19.

HA is elevated in airway inflammation, lung infection, and chronic fibrotic diseases of the lung

HA is a glycosaminoglycan with important roles in inflammation and cellular metabolism [11]. HA is a polysaccharide comprised of a repeating disaccharide that plays important roles in healthy tissues. Unlike other glycosaminoglycans, it is not linked to a protein core and instead exists as elongated, highly charged strands [12]. HA is extremely hygroscopic and is able to absorb water over 1000 times its own molecular weight [13,14]. In healthy tissues its high molecular weight and flexible polymer chain structure allow it to form viscoelastic barriers. In healthy tissues, HA provides structural support to skin, joints, and other tissues [12]. Within the lung, HA is a crucial component of bronchial basement membranes, bronchiolar epithelium, alveolar tissues, and the endothelial glycocalyx. In addition, HA is found at the surface of alveolar macrophages and Type II alveolar epithelial cells [15].

At these sites, HA is typically bound to a diverse group of HA binding proteins, called hyaladherins. These HA–hyaladherin macromolecular complexes interact with a variety of cell-surface proteins, growth factors, chemokines, and proteases to modulate the adhesive properties and activation state of inflammatory cells [16–18]. Examples of hyaladherins include inter-α-trypsin-inhibitor (IαI) and TNF-stimulated gene-6 (TSG-6) [19–23].

TSG-6 catalyzes the covalent transfer of heavy chains (HCs)(also known as HA-associated protein SHAP) from IαI to HA [24]. This results in the formation of the HC—HA complex, a form of HA that promotes the adhesion of leukocytes to HA-rich matrices and thereby influences the inflammatory response [21,25,26]. Elements of IαI and versican, including the heavy chains (HC) of IαI, can interact with HA, forming a new HC—HA complex called HA cables. These HC—HA complexes promote the binding of leukocytes to the ECM and monocytes to the cell membrane, contributing to tissue destruction [21,25] can also be potently anti-inflammatory (for example, in amniotic membrane where it polarizes macrophages to M2 phenotype [27]. There is evidence that TSG-6 drives pathology in a number of lung conditions (e.g., ozone-induced airway hyperresponsiveness), whereas it can be protective in others (e.g., LPS-induced lung injury), as recently reviewed [28]. In these and other ways, hyaladherins modulate interactions between ECM and the innate immune system.

At sites of tissue injury and infection, both HA production and catabolism are greatly upregulated leading to the accumulation of HA fragments. In this context, HA promotes leukocyte migration and activation within inflamed tissues [29,30]. The capacity of HA to absorb water drives edema and swelling in ways that increase leukocyte extravasation and tissue stiffness [31].

The biological function of HA is influenced by its size. High-molecular weight HA (HMW-HA); $\sim 2 \times 10^5$ - 7×10^6 Da, predominates in most tissues under healthy conditions and dampens inflammation [32–36]. In contrast, fragmented low-molecular weight HA (LMW-HA); $<$120 kDa, has been reported to be pro-inflammatory and predominates at sites of active inflammation [37]. Recent work suggests LMW-HA octa-saccharides prove effective monovalent competitors HMW-HA receptor interactions, potentially abrogating the anti-inflammatory effects of HMW-HA [38]. Moreover, LMW-HA is reported to function as an endogenous danger-associated molecular pattern molecule (DAMPs) that triggers inflammatory responses through TLR4 [39–41]. In this way, LMW-HA fragments may promote inflammatory cell recruitment and release of inflammatory cytokines [42,43]. Alternatively, HA may also distinctly activate a complex of TLR4/MD2/CD44 receptors [44].

However, this body of literature is complicated by publications which suggest that bacterial contaminants as well as DNA may have played a role in some of these pro-inflammatory effects [15,45,46]. Direct data demonstrating binding between HA and TLR4 are also absent. There is clearly a need to learn more about the role of HA in the host's response to pathogens. Several excellent reviews summarize the current state of knowledge regarding the role of HA size in inflammatory responses and a detailed investigation of the receptors involved in this biology [42,47–49].

The amount and size of HA polymers are regulated both at the level of HA synthesis and HA catabolism. HA is synthesized by three membrane-bound synthase enzymes (HAS1, HAS2, HAS3), found on the inner surface of the plasma membrane, which extrude HA as a polymer of repeating disaccharide units of N-acetylglucosamine and glucuronic acid [50]. The HA synthases generate HA polymers of distinct lengths [51] in response to inflammatory cytokines (i.e. TNF and interferons [52]), including in

viral respiratory infections [53]. HA is degraded in part by the activity of hyaluronidases [30,54,55] which catalyze the cleavage of HMW-HA strands into smaller, LMW-HA fragments generally of <120 kDa [30,56]. Mechanical force, injury, infection, and oxidative stress also contribute to HA catabolism and result in LMW-HA [57,58]. The biology of HA synthesis and catabolism has been addressed in excellent reviews elsewhere [42].

There is an abundance of data implicating HA in inflammatory diseases of the lung. Research has found heightened HA levels in cases of chronic obstructive pulmonary disease (COPD) [59,60], asthma, and pulmonary hypertension (pH) [61]. HA is also associated with fibrotic diseases in the lung, including IPF [62–64], a disease characterized by progressive lung scarring, chronic respiratory failure, and severe hypoxemia [65]. While the causes of IPF remain unknown, HA has been shown to be important for regulating disease progression and HA-based treatments have shown efficacy in treating chronic inflammation and collagen deposition in IPF [66–69]. Enhanced expression of HA through overexpression of HAS2 has been demonstrated to exacerbate fibrotic injury of the lung [70]. Similarly, in models of pulmonary hypertension, increased HA has been detected [71–74], and its role in promoting vascular remodeling has been identified using gain and loss of function approaches targeting HAS2 [72]. Herein, HAS2 deletion protected mice from developing pH yet overexpression of HAS in smooth muscle cells led to worsening pH.

In line with these studies, inhibition of HA synthesis ameliorates disease in many of these settings [71,75–77]. While HA is increased in many diseases featuring airway injury or inflammation, the degree of accumulation and localization within the tissue parenchyma [15] can vary greatly. However, a more nuanced view of HA in these contexts is needed as in some settings HA can be anti-fibrotic while in others it can be pro-fibrotic [62,78].

HA is also implicated in ARDS [79,80]. Ventilator-induced lung injury promotes the synthesis of LMW-HA via HAS3 upregulation in fibroblasts, leading to increased inflammatory cell infiltration, vascular leak, and both interstitial and alveolar edema [81]. In combination with alveolar collapse, this contributes to the ventilation-perfusion mismatch, hypoxia, and respiratory failure seen in ARDS. HA levels in bronchoalveolar lavage fluid are associated with organ failure in ARDS [79] and there is an inverse correlation between the concentration of HA (BAL and serum) and the pulmonary oxygenation index in patients with ARDS [82,83]. Using experimental models of ARDS, investigators have demonstrated that inhibition of HA reduced markers of cell injury [84,85].

The role of HA in lung inflammation is a large and complex subject and the sections above only provide a short overview of this biology. For further information, we refer the reader to several excellent reviews [15,30,51,59].

COVID-19 infection is associated with both acute disease as well as long-term sequalae post-infection

Following transmission via respiratory droplets, SARS-CoV2 binds to multiple cell types, including epithelial cells, alveolar epithelial cells, vascular endothelial cells, fibroblasts and macrophages via the angiotensin-converting enzyme 2 (ACE2). The molecular mechanisms involved in SARS-CoV2 infection and the pathophysiology of COVID-19 infection have been addressed in depth elsewhere [86, 91, 87, 88] However, in brief, upon infection, host cells undergo necrosis, pyroptosis and necroptosis as a result of direct viral toxicity. Cellular debris and viral components then trigger innate immune pathogen recognition receptors. They similarly activate pathways downstream of the ACE2 receptors which SARS-CoV-2 uses for host entry [89–91]. Induction of cytokine “storm” and endothelial dysfunction, topics addressed later in this review, drive the inflammatory cascade that underlies acute COVID-19 [92,93]. This pathophysiology can impact nearly every organ system, including the lungs, heart [94], neurologic tissues [95], and gastrointestinal tract [96].

There is substantial heterogeneity in the patterns of disease associated with COVID-19 [97,98]. Mild cases of acute COVID-19 often display symptoms typical of upper respiratory tract infections, including fever, fatigue, and sore throat [2]. Older populations and patients with risk factors (e.g. diabetes, immune suppression, etc.) are prone to develop more severe respiratory symptoms [3,99]. Mortality is linked to risk factors including age, diabetes, underlying immune suppression, and host ethnic background and genetics [100–103].

Severe cases of COVID-19 can manifest as ARDS [104,105], a respiratory syndrome characterized by widespread pulmonary inflammation, airway edema, and poor oxygenation [50] which often necessitates prolonged, challenging mechanical ventilation. Many computed tomographic images of patients with severe COVID-19 disease revealed “ground glass opacities”, often associated with areas of airway edema, in the patient’s lungs. Consistent with ARDS, dense hyaline material was found in the lungs of autopsy cases [106,107]. Thick, respiratory secretions are also a prominent feature of severe COVID-19 respiratory disease [105,108].

In addition to acute COVID-19 respiratory disease, many individuals suffer persistent, debilitating symptoms of PASC [8–10]. PASC cases vary in

severity and duration and can present symptoms ranging from respiratory difficulty and fatigue to neurological issues [109]. While acute COVID-19 lasts for 1–4 weeks, PASC symptoms can persist for months [8,98,110,111]. Approximately a third of patients developing PASC experienced asymptomatic acute COVID, suggesting that PASC is possible regardless of the severity of the acute COVID infection [112]. One study on Italian Healthcare Workers found obesity significantly predisposes participants to PASC [113]. Other metabolic and autoimmune diseases have been implicated [113,114]. In light of the ongoing COVID-19 pandemic and the uncertain pathogenesis of PASC, many countries are implementing programs dedicated to understanding PASC and similar post-infection syndromes [99].

One of the most severe, long-term manifestations of COVID-19 is lung fibrosis [115,116]. This can be highly debilitating, requiring long-term oxygen therapy [117]. There are indications that up to a third of patients who recover from COVID-19 ARDS develop fibrotic abnormalities [118]. The severity of ARDS and the duration of illness seem to be important predictors of pulmonary fibrosis in COVID-19 [119,120]. For a subset of these patients, lung transplantation is the only treatment option [121]. In these patients, extensive fibrotic lung injury presents on average 79 days from the time of the first COVID-19 symptoms or first positive test for SARS-CoV-2 [122,123]. COVID-19 pulmonary fibrosis appears to be distinct from idiopathic pulmonary fibrosis (IPF) and other fibrotic lung diseases that can take decades to develop [124–127]. However, only a handful of studies have probed into the mechanisms that lead to fulminant lung fibrosis in patients with COVID-19 [122,128,129].

In addition to lung fibrosis, SARS-CoV-2 has been demonstrated to induce profound effects in the vasculature including intussusceptive angiogenesis, endothelial cell injury, vascular remodeling and changes in vascular tone. These changes have been summarized in a pair of articles [130,131]**.** The effects of SARS-CoV2 in the pulmonary circulation are significant since not only were they impacted by thrombotic process in the early stages of SARS-CoV2 infection, but pulmonary vascular sequelae following COVID-19 is increasingly recognized as a potential public health problem [132].

For further information, we refer the reader to several excellent reviews summarizing the clinical features and epidemiology of PASC [133–135].

HA is abundant in acute COVID-19 ARDS

HA is increased in the lungs of individuals with COVID-19. This was first demonstrated by Hellman et al., who showed HA staining in cadaveric histologic lung tissue sections from deceased COVID-19 patients [14]. Similar findings were reported in preprints or speculated upon earlier in the pandemic [13,136]. In these and other studies, significant HA staining was found in intra-alveolar spaces, particularly in areas of necrosis and inflammation, together with diffuse hemorrhage and hyaline membranes [137,138]. Consistent with this, genes involved in HA metabolism were over-represented in bronchoalveolar cells infected by SARS-CoV-2 [139]. HA synthases expression (HAS1–3) is likewise significantly upregulated in lung tissue of COVID-19 patients [140].

HA is abundant in the respiratory secretions of patients with severe COVID-19 compared to healthy patients [14,136]. A recent study observed greatly increased HA content (predominantly LMW-HA) in sputum from recently intubated patients along with increased DNA from dead or dying cells [137]. Treatment with hyaluronidase and DNase demonstrated that these two polymers contribute to the thick, tenacious respiratory secretions seen in COVID-19 ARDS [137]. The increase in the amount of HA may contribute to the respiratory pathophysiology of COVID-19 ARDS, including fluid accumulation, airway plugging, and reduction of oxygen exchange in the lung, leading to respiratory failure [141]. This LMW-HA may drive further inflammatory responses. Alternatively, it may be that the accumulation of HA fragments is not "an accumulation of pro-inflammatory HA fragments" but rather removing the anti-inflammatory HMW-HA via a competitive inhibitor mechanism [38]. More research is needed to tease these relationships apart.

Along with HA, hyaladherins levels are also altered in the lung. Increased versican and diminished TSG-6 were observed in lung sections from deceased patients with COVID-19 ARDS compared to other ARDS cases [137]. However, as discussed above, the impact of TSG-6 on HA in the lung is complex and the impact of TSG-6 levels on COVID-19 pathophysiology is unclear.

Serum HA is likewise associated with the pathogenesis of severe COVID-19. This is supported by Queisser et al., who reported that circulating HA fragments and serum hyaluronidase were strongly associated with organ failure and increased inflammatory cytokine levels in patients with COVID-19 [55]. Furthermore, serum HA has been identified as a predictor of COVID-19 disease severity [138]. Plasma HA levels during early infection and admission to healthcare facilities may similarly distinguish severely ill patients with COVID-19 [14,142]. Gene expression studies of cells in BAL fluid from COVID-19 patients further implicated HA in a “bradykinin-storm” signature associated with severe disease [140]. It has further been proposed based on transcriptomic and metabolomic studies that glutamine deficiency and overproduced HA is the central metabolic characteristic of severe, acute COVID-19

[143]. Together, these reports support a pathological role for HA in humans with COVID-19 disease.

Several factors may contribute to HA production during acute COVID-19. As noted above, SARS-CoV-2 infection triggers a "storm" of pro-inflammatory cytokines [144], leading to pronounced airway inflammation and systemic lymphocytopenia [145–149]. This includes injury to the endothelial glycocalyx, a pericellular structure which contains hyaluronan [150–152]. At an early stage, the infected cells also release inflammatory cytokines and chemokines such as IL-1β, IL-8, IL-18 [104], IL6, Type I interferon, and TNF-α [153]. Increased levels of the inflammatory cytokine IL-6 correspond to a greater need for mechanical ventilation [14]. Type 1 interferon production has likewise been associated with acute respiratory disease [154,155]. Along with driving HA production, these factors further promote immune activation and neutrophil degranulation, leading to the release of reactive oxygen species, proteases, and other factors that perpetuate the inflammatory cascade [156].

Several of these cytokines, including IL-6, IFNy, and TNFα, are known to drive HA production in other contexts [52]. These include in-vitro experiments observing the effect of pro-inflammatory cytokines on HA synthesis in human umbilical cord endothelial cells [157] and orbital fibroblasts [158].

In a mouse model of COVID-19 infection, HA production in the lung could be triggered by IL-13 administration and reduced by blockade of IL-13 in conjunction with less HAS1 expression, suggesting that this cytokine could contribute to HA levels in COVID-19. Consistent with this, IL-13 was increased in serum samples from a cohort of 178 COVID-19 patients [159] and in a second study of 138 COVID-19 patients [160]. However, in another study of 82 patients with severe COVID-19, IL-13 was decreased [159]. IL-13 was also not increased in a small study of human respiratory secretions from 22 patients [137]. Similarly, IL-13 was not found to be elevated in cadaveric lung tissues from a small cohort of 6 COVID-19 patients compared to controls with influenza [161].

Along with these conflicting data on IL-13 levels, the data on IL-13 contributions to COVID-19 pathophysiology are also unclear. Blockade of IL-4/IL-13 signaling with dupilumab led to significantly reduced ventilation and death in COVID-19 patients already on this drug. [162]. However, IL-13 was found to be protective against SARS-CoV-2 infection in vitro [163,164]. Further study and data from additional cohorts are needed to resolve the role of IL-13 and the value of targeting this cytokine therapeutically in COVID-19.

The hypoxic conditions in the COVID-19 lung can also trigger the hypoxic adenosinergic response [130]**.** This results in elevated expression of the adenosine A2B receptor [165], which has been shown to mediate HAS2 expression and subsequently lead to production of HA from macrophages and smooth muscle cells [74,166].

The cells that produce HA in acute COVID-19 infection are likewise unclear. HA is produced by many cell types in the lung, as reviewed elsewhere [59,167], including many of the same epithelial cells, endothelial cells, fibroblasts and macrophages that can be infected by SARS-CoV-2. However, we find that cell types that can be infected with SARS-CoV-2, including respiratory tract epithelial cells in air-liquid-interface (ALI) cultures and lung organoids, produce minimal amounts of HA upon viral culture (unpublished observations). This suggests that bystander cells, and not primary infected cells are likely to produce HA in response to COVID-19 infection. Ravindra N, et al. observed increased interferon-stimulated gene (ISG) induction in bystander and some infected cells in response to interferons released by specific infected cells [168]. While both bystander and infected cells experience heightened ISG activity, differentiated gene and cytokine expression found by the study between the two cell states support a unique role for bystander cells.

Together, based on this report we propose that SARS-CoV-2 infection triggers HA production by bystander cells as part of an anti-viral inflammatory response (Fig.1) and suggest that inhibition of HA could be a therapeutic target in severe COVID-19 ARDS. Additional work is needed to implement this idea and understand how HA shapes the inflammatory microenvironment. dummy citation Fig.2

HA in "long" COVID (PASC)

PASC is both common and devastating [169,170]. In one UK-based study of 1.1 million patients with PASC, the duration of symptoms was over 12 weeks for 65%, and over 20% experienced "persistent COVID-19″ disabling symptoms [171]. Chronic shortness of breath or dyspnea is a particularly common and debilitating symptom of PASC and is thought to reflect post-infectious sequalae in the lung [172]. A recent meta-analysis found that up to 80% of patients display one or more post-acute COVID-19 symptoms, with fatigue and shortness of breath (dyspnea) being among the most common [173]. Some groups have reported that over 18–25% of PASC patients have structural lung abnormalities and dyspnea [169,170,174].

The pathophysiology underlying these phenotypes is unclear. Moreover, it is unknown whether the same disease mechanisms are involved across the entire spectrum of PASC. This uncertainty, together with the increasing relevance of PASC in healthcare, highlight the need to develop biomarkers and therapeutic strategies to identify, prevent, and treat lung disease in PASC.

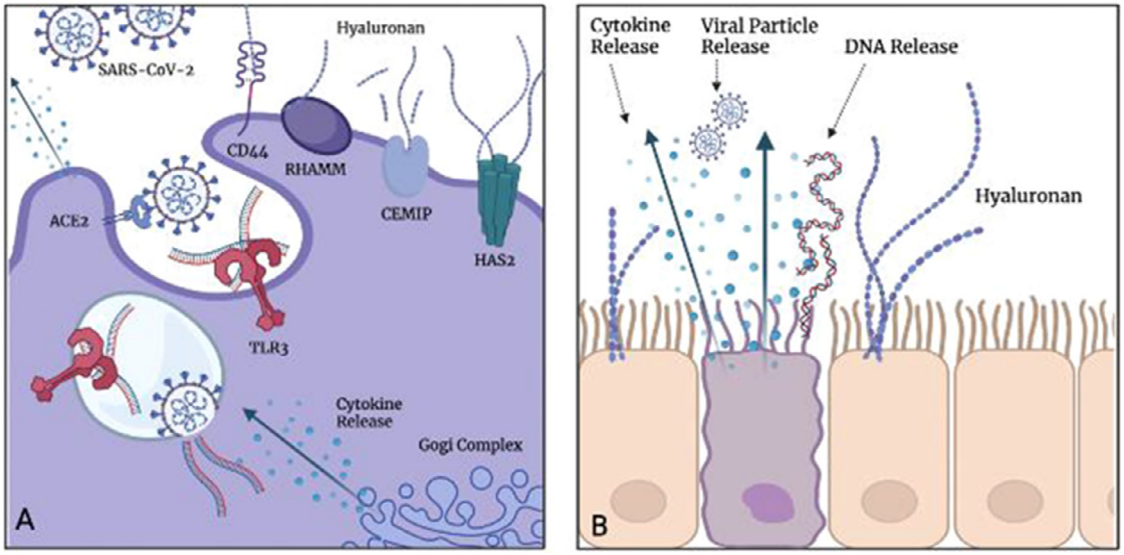

Fig. 1. A model for HA production in the COID-19 infected lung. **A.** HA production by airway cells in response to viral triggers. Inflammatory cytokines and viral PAMPs, including dsRNA, trigger HA production by respiratory epithelial cells. This HA production is mediated by HA synthases, most notably HAS2. The accumulation of HA fragments may perpetuate the inflammatory casecade associated with infection. **B.** While dying cells infected with SARS-CoV-2 make minimal HA, infection drives robust HA production by respiratory epithelial cells. This, together with DNA released from dead cells, results in thick, tenacious airway secretions in COVID-19 acute lung infections.

While several independent reports have documented increased serum and sputum HA levels in patients with acute COVID-19, there are very little data on HA levels in PASC. A recent report indicated that perivascular HA levels were increased in lung tissue samples of patients with COVID-19 and non-resolvable COVID-19 (NR-COVID-19) [175]. Interestingly, this was not associated with increased in HAS1–2 expression levels but rather reduced levels of CD44, potentially implicating impaired HA clearance in these effects. A study of post-COVID-19 liver fibrosis likewise reported that serum HA was elevated in individuals with this condition and that HA levels were associated with liver stiffness and elevated liver enzymes [176]. However, while reports of post-COVID-19 lung fibrosis are beginning to appear in the literature [177], much remains unknown about this devastating condition.

Despite the lack of published data, a role for HA in PASC would be consistent with the abundance of HA in acute COVID-19 and the well-established role of HA in other chronic inflammatory and fibrotic diseases [69,78,178–186], a role for HA in long-COVID is worthy of further study. We propose that robust HA production in the lungs and peripheral tissues

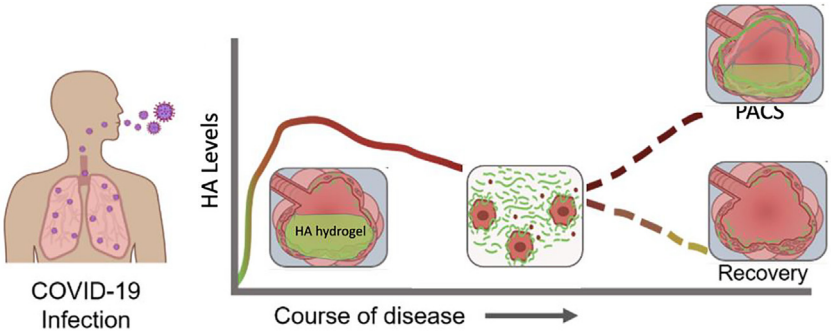

Fig. 2. A model for how HA might contribute to PASC pathophysiology. Thick, HA-rich hyaline material fills lung alveolae in response to acute SARS-CoV-2 infection. In severe acute COVID-19 infection, this can lead to thick respiratoty secretions, edema, and impaired gas exchange typical of ARDS. This HA is catabolized over time into LMW-HA, which drives further inflammation. Most individuals clear this HA via hyaladherin-mediated cellular uptake. However, when hyaladherin levels or function are impaired, HA persists and promotes fibrosis and poor gas exchange (respiratory PACS).

contributes to the pathogenesis of severe acute COVID-19 and a subsequent inability to clear these HA fragments contributes to post-COVID-19 fibrotic syndromes and to the chronic inflammatory and metabolic derangements associated with long COVID-19.

Taken together, these data support that HA is abundant in COVID-19 PASC, and inhibition of HA could be a therapeutic target with the potential to significantly improve clinical outcomes for patients with severe COVID-19 PASC.

HA is a novel therapeutic target in COVID-19

Existing therapies to treat COVID-19 infection which target viral replication (e.g. Remdesivir) or systemic inflammation (e.g. Dexamethasone) are not indicated as treatments for post-COVID-19 fibrosis. Similarly, anti-fibrotic agents such as Nintedanib and Pirfenidone [115,187,188] have shown modest effects in COVID-19 induced fibrosis [115,189–191]. This highlights the need to develop strategies to identify, prevent, and treat lung fibrosis in COVID-19 patients. The data presented in this review suggest that it may be beneficial to target HA in COVID-19, as was originally suggested by Shi et al., early in the pandemic. Potential options include targeting the production of HA during infection, post-production HA degradation via hyaluronidases, and using HMW-HA as an anti-inflammatory therapy.

Dupilumab, an IL-13 antagonist and an already approved therapy, is another potential therapeutic option to block HA production [162]. In a recent clinical trial of 19 patients who received dupilumab and 21 controls, there were no differences in the proportion of patients on mechanical ventilation at either 28 or 60 days. There was a difference of 2 deaths in the dupilumab group (2/19; 10.5%) versus 5 deaths in the control group (5/21; 23.8%) at 60 days but this difference was not significant (Unadjusted HR: 0.40 (0.08–2.05)) until the data were adjusted for sex and mechanical ventilation as a time-varying predictor (Adjusted HR: 0.05 (0.004–.72)) [162]. Larger, better controlled studies are needed to explore dupilumab as a potential therapy in COVID-19.

One molecule known to inhibit HA synthesis is 4-methylumbelliferone (4-MU), also known as hymecromone [192–196]. 4-MU is a competitive substrate for UDP-glucuronyl transferases (UGTs), depleting one of the HA precursors, UDP-glucuronic acid [197]. 4-MU also indirectly reduces the expression of mRNA transcripts involved in HA synthesis [192,198]. The main metabolite of 4-MU, 4-methylumbelliferyl glucuronide (4-MUG), has also been shown to be bioactive [199]. In the lung, 4-MU reduces HA and ameliorates disease in mouse models of lung infection [85,200,201], lung metastases [202], pulmonary hypertension [71], and pulmonary fibrosis [203]. Work from our lab and others has shown that the immunosuppressive effect of 4-MU is mediated in large part through inhibition of antigen presentation and the induction of anti-inflammatory Foxp3+ Tregs [204–206].

Tantalizingly, 4-MU is already an approved drug in Europe, currently used to treat biliary spasm [207–210]. It is given orally and is safe and well-tolerated [192,197,208–217]. A Stage 1 clinical trial of 4-MU in healthy human volunteers was recently completed and demonstrated inhibition of sputum HA levels at drug dosages currently approved in Europe. This suggests that it may be possible to repurpose 4-MU to inhibit HA production and prevent fibrosis in COVID-19 and other conditions. [75].

In pursuit of this goal, a single-center, randomized, placebo-controlled, double-blind clinical trial is currently exploring this at Shanghai Zhongshan Hospital (NCT05386420). This follows on the heels of an earlier trial that was performed in China that yielded tantalizing results that were unfortunately difficult to interpret due to issues with study design [218].

Dupilumab, hyaluronidase and 4-MU have all been clinically approved for other indications and could be repurposed to treat COVID-19. HAdases such as PH20 have been used to enhance the absorption and dispersion of injected drugs, for subcutaneous fluid administration for hypodermoclysis, and for subcutaneous urography to improve absorption of radiopaque agents. PH20 could be repurposed to treat COVID-19. Thinning of the fluid to improve lung clearance is a common goal across a range of diseases with respiratory inflammation [219–222]. Indeed, intranasal administration of exogenous HAdase was reported to sufficiently reduce the level of lung HA content, thereby restoring the lung function in the influenza mouse model [53]. In vitro treatment of acute COVID-19 respiratory secretions with HAdase decreased the flow resistance of thick samples [137].

A number of studies have shown encouraging results in treating inflammatory lung diseases with aerosolized HMW-HA [63,179,223], including in patients with bronchial asthma [224], cystic fibrosis [225,226], in children with recurrent upper respiratory infections [227], and in patients with COPD [228,229]. A feasibility and outcomes trial for the use of HMW-HA in patients with severe COVID-19 to prevent late-stage COVID-19-associated cytokine storm is currently underway (NCT04830020). Specifically, this trial aims to determine whether inhaled HMW-HA protects against progression of COVID-19-induced respiratory failure and promotes recovery from COVID-19 lung disease in hospitalized patients. Further investigation is warranted to identify whether HMW-HA treatment will improve

COVID-19 severe outcomes, optimal administration methods, and dosing regimens that effectively ameliorate disease.

Conclusions and outstanding questions

The data reviewed here implicate HA in the pathogenesis of severe, acute COVID-19. In particular, HA appears to be linked to COVID-19 respiratory secretions and to ARDS. The available studies further suggest that serum HA could serve as a biomarker for severe acute COVID-19 disease. These associations require further validation in larger, independent cohorts.

It is not known whether HA levels are sustained or increased in PASC. This is an exciting avenue of investigation that requires additional research. If an association with HA is demonstrated in COVID-19, it may be possible to use sputum and/or serum levels to identify patients at risk of developing lung fibrosis.

Numerous other questions remain. It is unclear how HA accumulates and persists in COVID-19 ARDS. A more nuanced understanding of the cells and stimuli that drive HA production in COVID-19 will be essential to define mechanisms of HA accumulation.

The receptors and pathways involved in HA contributions to COVID-19 pathophysiology are unknown [230,231]. There are limited data on the role of CD44 in COVID-19. Donlan et al. [138], demonstrated that blocking of CD44 in mice infected with SARS-CoV-2 reduced clinical scores (an observational metric which includes data on eye rubs, weight loss, activity, and posture) but no survival benefit. Further complicating interpretation of these data, anti-CD44 antibodies are known to trigger neutropenia, platelet depletion, and impaired leukocyte migration [232] and could impact this model and SARS-CoV-2 susceptibility in non-specific ways. Studies with CD44-/- mice have not been performed. Further investigation is needed on this topic.

More generally, we need to learn more about how HA shapes selective pro- and anti-inflammatory microenvironments in the lungs to develop effective treatments that protect against the development of a pathological HA matrix while maintaining an anti-inflammatory or pro-resolving matrix.

More studies that determine how HA promotes pro-fibrotic responses in COVID-19 and the pathways implicated are needed. Nonetheless, HA is a promising potential target and biomarker in this terrible disease.

Data availability

No data was used for the research described in the article.

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Abbreviations:
ARDS, : Acute respiratory distress syndrome; BAL, : Bronchoalveolar lavage; ECM, : Extracellular matrix; HA, : Hyaluronan; HMW-HA, : High molecular weight hyaluronan; LMW-HA, : Low molecular weight hyaluronan

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References

[1] B. Hu, H. Guo, P. Zhou, Z.-.L. Shi, Characteristics of SARS-CoV-2 and COVID-19, Nat. Rev. Microbiol. 19 (2021) 141–154, doi: 10.1038/s41579-020-00459-7.
[2] K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: a review, Clin. Immunol. 215 (2020) 108427, doi: 10.1016/j.clim.2020.108427.
[3] D. Cucinotta, M. Vanelli, WHO declares COVID-19 a pandemic, Acta Bio. Medica Atenei Parmensis 91 (2020) 157–160, doi: 10.23750/abm.v91i1.9397.
[4] Y. Jin, H. Yang, W. Ji, W. Wu, S. Chen, W. Zhang, G. Duan, Virology, epidemiology, pathogenesis, and control of COVID-19, Viruses 12 (2020) 372, doi: 10.3390/v12040372.
[5] Y.-.R. Guo, Q.-.D. Cao, Z.-.S. Hong, Y.-.Y. Tan, S.-.D. Chen, H.-.J. Jin, K.-.S. Tan, D.-.Y. Wang, Y. Yan, The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak − an update on the status, Mil Med. Res. 7 (2020) 11, doi: 10.1186/s40779-020-00240-0.
[6] S. Platto, Y. Wang, J. Zhou, E. Carafoli, History of the COVID-19 pandemic: origin, explosion, worldwide spreading, Biochem. Biophys. Res. Commun. 538 (2021) 14–23, doi: 10.1016/j.bbrc.2020.10.087.
[7] C. del Rio, S.B. Omer, P.N. Malani, Winter of omicron—the evolving COVID-19 pandemic, JAMA 327 (2022) 319, doi: 10.1001/jama.2021.24315.
[8] A. v Raveendran, R. Jayadevan, S. Sashidharan, Long C. O.V.I.D.: an overview, Diabet. Metabol. Syndrome 15 (2021) 869–875, doi: 10.1016/j.dsx.2021.04.007.

[9] S.J. Yong, Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments, Infect. Dis. 53 (2021) 737–754, doi: 10.1080/23744235.2021.1924397.
[10] M. Dani, A. Dirksen, P. Taraborrelli, M. Torocastro, D. Panagopoulos, R. Sutton, P.B. Lim, Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies, Clin. Med. 21 (2021) e63–e67, doi: 10.7861/clinmed.2020-0896.
[11] B.P. Toole, Hyaluronan: from extracellular glue to pericellular cue, Nat. Rev. Cancer 4 (2004) 528–539, doi: 10.1038/nrc1391.
[12] T.C. Laurent, U.B. Laurent, J.R.E. Fraser, The structure and function of hyaluronan: an overview, Immunol. Cell Biol. 74 (1996) a1–a7, doi: 10.1038/icb.1996.32.
[13] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito, G. Melino, COVID-19 infection: the perspectives on immune responses, Cell Death Differ. 27 (2020) 1451–1454, doi: 10.1038/s41418-020-0530-3.
[14] U. Hellman, M.G. Karlsson, A. Engström-Laurent, S. Cajander, L. Dorofte, C. Ahlm, C. Laurent, A. Blomberg, Presence of hyaluronan in lung alveoli in severe Covid-19: an opening for new treatment options? J. Biol. Chem. 295 (2020) 15418–15422, doi: 10.1074/jbc.AC120.015967.
[15] P. Johnson, A.A. Arif, S.S.M. Lee-Sayer, Y. Dong, Hyaluronan and its interactions with immune cells in the healthy and inflamed lung, Front. Immunol. 9 (2018) 2787, doi: 10.3389/fimmu.2018.02787.
[16] A.J. Day, G.D. Prestwich, Hyaluronan-binding proteins: tying up the giant, J. Biol. Chem. 277 (2002) 4585–4588, doi: 10.1074/jbc.R100036200.
[17] Hyaluronan cross-linking: a protective mechanism in inflammation? Trends Immunol. 26 (2005) 637–643, doi: 10.1016/j.it.2005.09.009.
[18] A. Abbadi, M. Lauer, S. Swaidani, A. Wang, V. Hascall, Hyaluronan rafts on airway epithelial cells, J. Biol. Chem. 291 (2016) 1448–1455, doi: 10.1074/jbc.M115.704288.
[19] C.A. de la Motte, V.C. Hascall, J. Drazba, S.K. Bandyopadhyay, S.A. Strong, Mononuclear leukocytes bind to specific hyaluronan structures on colon mucosal smooth muscle cells treated with polyinosinic acid: polycytidylic acid, Am. J. Pathol. 163 (2003) 121–133, doi: 10.1016/S0002-9440(10)63636-X.
[20] M.E. Lauer, M. Aytekin, S.A. Comhair, J. Loftis, L. Tian, C.F. Farver, V.C. Hascall, R.A. Dweik, Modification of hyaluronan by heavy chains of inter-α-inhibitor in idiopathic pulmonary arterial hypertension, J. Biol. Chem. 289 (2014) 6791–6798, doi: 10.1074/jbc.M113.512491.
[21] A.C. Petrey, C.A. de la Motte, Thrombin cleavage of inter-α-inhibitor heavy chain 1 regulates leukocyte binding to an inflammatory hyaluronan matrix, J. Biol. Chem. 291 (2016) 24324–24334, doi: 10.1074/jbc.M116.755660.
[22] Y. Ogawa, H. He, S. Mukai, T. Imada, S. Nakamura, C.-.W. Su, M. Mahabole, S.C.G. Tseng, K. Tsubota, Heavy chain-hyaluronan/pentraxin 3 from amniotic membrane suppresses inflammation and scarring in murine lacrimal gland and conjunctiva of chronic graft-versus-host disease, Sci. Rep. 7 (2017) 42195, doi: 10.1038/srep42195.
[23] M.S. Lord, J. Melrose, A.J. Day, J.M. Whitelock, The inter-α-trypsin inhibitor family: versatile molecules in biology and pathology, J. Histochem. Cytochem. 68 (2020) 907–927, doi: 10.1369/0022155420940067.
[24] M.S. Rugg, A.C. Willis, D. Mukhopadhyay, V.C. Hascall, E. Fries, C. Fülöp, C.M. Milner, A.J. Day, Characterization of complexes formed between TSG-6 and inter-α-inhibitor that act as intermediates in the covalent transfer of heavy chains onto hyaluronan, J. Biol. Chem. 280 (2005) 25674–25686, doi: 10.1074/jbc.M501332200.
[25] W. Selbi, C.A. de la Motte, V.C. Hascall, A.J. Day, T. Bowen, A.O. Phillips, Characterization of hyaluronan cable structure and function in renal proximal tubular epithelial cells, Kidney Int. 70 (2006) 1287–1295, doi: 10.1038/sj.ki.5001760.
[26] S.P. Evanko, S. Potter-Perigo, P.Y. Johnson, T.N. Wight, Organization of hyaluronan and versican in the extracellular matrix of human fibroblasts treated with the viral mimetic poly I:C, J. Histochem. Cytochem. 57 (2009) 1041–1060, doi: 10.1369/jhc.2009.953802.
[27] H. He, S. Zhang, S. Tighe, J. Son, S.C.G. Tseng, Immobilized Heavy Chain-Hyaluronic Acid Polarizes Lipopolysaccharide-activated Macrophages toward M2 Phenotype, J. Biol. Chem. 288 (2013) 25792–25803, doi: 10.1074/jbc.M113.479584.
[28] A.J. Day, C.M. Milner, TSG-6: a multifunctional protein with anti-inflammatory and tissue-protective properties, Matrix Biol. 78−79 (2019) 60–83, doi: 10.1016/j.matbio.2018.01.011.
[29] H.F. Kuipers, M. Rieck, I. Gurevich, N. Nagy, M.J. Butte, R.S. Negrin, T.N. Wight, L. Steinman, P.L. Bollyky, Hyaluronan synthesis is necessary for autoreactive T-cell trafficking, activation, and Th1 polarization, Proc. Nat. Acad. Sci. 113 (2016) 1339–1344, doi: 10.1073/pnas.1525086113.
[30] D. Jiang, J. Liang, P.W. Noble, Hyaluronan as an immune regulator in human diseases, Physiol. Rev. 91 (2011) 221–264, doi: 10.1152/physrev.00052.2009.
[31] N. Nagy, A. de la Zerda, G. Kaber, P.Y. Johnson, K.H. Hu, M.J. Kratochvil, K. Yadava, W. Zhao, Y. Cui, G. Navarro, J.P. Annes, T.N. Wight, S.C. Heilshorn, P.L. Bollyky, M.J. Butte, Hyaluronan content governs tissue stiffness in pancreatic islet inflammation, J. Biol. Chem. 293 (2018) 567–578, doi: 10.1074/jbc.RA117.000148.
[32] P.L. Bollyky, B.A. Falk, R.P. Wu, J.H. Buckner, T.N. Wight, G.T. Nepom, 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 (2009) 567–572, doi: 10.1189/jlb.0109001.
[33] P.L. Bollyky, J.D. Lord, S.A. Masewicz, S.P. Evanko, J.H. Buckner, T.N. Wight, G.T. Nepom, Cutting edge: high molecular weight hyaluronan promotes the suppressive effects of $CD4^+CD25^+$ regulatory T cells, J. Immunol. 179 (2007) 744–747, doi: 10.4049/jimmunol.179.2.744.
[34] T. Ooki, N. Murata-Kamiya, A. Takahashi-Kanemitsu, W. Wu, M. Hatakeyama, High-molecular-weight hyaluronan is a hippo pathway ligand directing cell density-dependent growth inhibition via PAR1b, Dev. Cell 49 (2019) 590–604.e9, doi: 10.1016/j.devcel.2019.04.018.
[35] M.M. Temple-Wong, S. Ren, P. Quach, B.C. Hansen, A.C. Chen, A. Hasegawa, D.D. D'Lima, J. Koziol, K. Masuda, M.K. Lotz, R.L. Sah, Hyaluronan concentration and size distribution in human knee synovial fluid: variations with age and cartilage degeneration, Arthritis Res. Ther. 18 (2016) 18, doi: 10.1186/s13075-016-0922-4.
[36] S.M. Ruppert, T.R. Hawn, A. Arrigoni, T.N. Wight, P.L. Bollyky, Tissue integrity signals communicated by high-molecular weight hyaluronan and the resolution of

inflammation, Immunol. Res. 58 (2014) 186–192, doi: 10.1007/s12026-014-8495-2.
[37] J. Liang, D. Jiang, Y. Jung, T. Xie, J. Ingram, T. Church, S. Degan, M. Leonard, M. Kraft, P.W. Noble, Role of hyaluronan and hyaluronan-binding proteins in human asthma, J. Allergy Clin. Immunol. 128 (2011) 403–411.e3, doi: 10.1016/j.jaci.2011.04.006.
[38] T. Curk, G. v Dubacheva, A.R. Brisson, R.P. Richter, Controlling superselectivity of multivalent interactions with cofactors and competitors, J. Am. Chem. Soc. 144 (2022) 17346–17350, doi: 10.1021/jacs.2c06942.
[39] N. Nagy, H.F. Kuipers, P.L. Marshall, E. Wang, G. Kaber, P.L. Bollyky, Hyaluronan in immune dysregulation and autoimmune diseases, Matrix Biol. 78−79 (2019) 292–313, doi: 10.1016/j.matbio.2018.03.022.
[40] K.R. Taylor, J.M. Trowbridge, J.A. Rudisill, C.C. Termeer, J.C. Simon, R.L. Gallo, Hyaluronan fragments stimulate endothelial recognition of injury through TLR4 *, J. Biol. Chem. 279 (2004) 17079–17084, doi: 10.1074/jbc.M310859200.
[41] P. Teder, R.W. Vandivier, D. Jiang, J. Liang, L. Cohn, E. Puré, P.M. Henson, P.W. Noble, Resolution of lung inflammation by CD44, Science 296 (2002) (1979) 155–158, doi: 10.1126/science.1069659.
[42] R. Stern, A.A. Asari, K.N. Sugahara, Hyaluronan fragments: an information-rich system, Eur. J. Cell Biol. 85 (2006) 699–715, doi: 10.1016/j.ejcb.2006.05.009.
[43] D. Jiang, J. Liang, P.W. Noble, Hyaluronan in tissue injury and repair, Annu. Rev. Cell Dev. Biol. 23 (2007) 435–461, doi: 10.1146/annurev.cellbio.23.090506.123337.
[44] K.R. Taylor, K. Yamasaki, K.A. Radek, A. di Nardo, H. Goodarzi, D. Golenbock, B. Beutler, R.L. Gallo, 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 (2007) 18265–18275, doi: 10.1074/jbc.M606352200.
[45] Y. Dong, A. Arif, M. Olsson, V. Cali, B. Hardman, M. Dosanjh, M. Lauer, R.J. Midura, V.C. Hascall, K.L. Brown, P. Johnson, Endotoxin free hyaluronan and hyaluronan fragments do not stimulate TNF-α, interleukin-12 or upregulate co-stimulatory molecules in dendritic cells or macrophages, Sci. Rep. 6 (2016) 36928, doi: 10.1038/srep36928.
[46] M.C. Filion, N.C. Phillips, Pro-inflammatory activity of contaminating DNA in hyaluronic acid preparations, J. Pharm. Pharmacol. 53 (2001) 555–561, doi: 10.1211/0022357011775677.
[47] S. Misra, V.C. Hascall, R.R. Markwald, S. Ghatak, Interactions between hyaluronan and its receptors (CD44, RHAMM) regulate the activities of inflammation and cancer, Front. Immunol. 6 (2015), doi: 10.3389/fimmu.2015.00201.
[48] A.G. Tavianatou, I. Caon, M. Franchi, Z. Piperigkou, D. Galesso, N.K. Karamanos, Hyaluronan: molecular size-dependent signaling and biological functions in inflammation and cancer, FEBS J. 286 (2019) 2883–2908, doi: 10.1111/febs.14777.
[49] M. Litwiniuk, A. Krejner, M.S. Speyrer, A.R. Gauto, T. Grzela, Hyaluronic acid in inflammation and tissue regeneration, Wounds 28 (2016) 78–88.
[50] N. Albtoush, A.C. Petrey, The role of hyaluronan synthesis and degradation in the critical respiratory illness COVID-19, Am. J. Physiol.-Cell Physiol. 322 (2022) C1037–C1046, doi: 10.1152/ajpcell.00071.2022.
[51] M.E. Lauer, R.A. Dweik, S. Garantziotis, M.A. Aronica, The rise and fall of hyaluronan in respiratory diseases, Int. J. Cell Biol. 2015 (2015) 1–15, doi: 10.1155/2015/712507.
[52] P.L. Bollyky, S.P. Evanko, R.P. Wu, S. Potter-Perigo, S.A. Long, B. Kinsella, H. Reijonen, K. Guebtner, B. Teng, C.K. Chan, K.R. Braun, J.A. Gebe, G.T. Nepom, T.N. Wight, Th1 cytokines promote T-cell binding to antigen-presenting cells via enhanced hyaluronan production and accumulation at the immune synapse, Cell Mol. Immunol. 7 (2010) 211–220, doi: 10.1038/cmi.2010.9.
[53] T.J. Bell, O.J. Brand, D.J. Morgan, S. Salek-Ardakani, C. Jagger, T. Fujimori, L. Cholewa, V. Tilakaratna, J. Östling, M. Thomas, A.J. Day, R.J. Snelgrove, T. Hussell, Defective lung function following influenza virus is due to prolonged, reversible hyaluronan synthesis, Matrix Biol. 80 (2019) 14–28, doi: 10.1016/j.matbio.2018.06.006.
[54] A.B. Csoka, G.I. Frost, R. Stern, The six hyaluronidase-like genes in the human and mouse genomes, Matrix Biol. 20 (2001) 499–508, doi: 10.1016/S0945-053X(01)00172-X.
[55] K.A. Queisser, R.A. Mellema, E.A. Middleton, I. Portier, B.K. Manne, F. Denorme, E.J. Beswick, M.T. Rondina, R.A. Campbell, A.C. Petrey, COVID-19 generates hyaluronan fragments that directly induce endothelial barrier dysfunction, JCI Insight 6 (2021) 147472, doi: 10.1172/jci.insight.147472.
[56] A. Hoarau, M. Polette, C. Coraux, Lung Hyaluronasome, Involvement of low molecular weight Ha (Lmw-Ha) in innate immunity, Biomolecules 12 (2022) 658, doi: 10.3390/biom12050658.
[57] S. Garantziotis, R.C. Savani, Hyaluronan biology: a complex balancing act of structure, function, location and context, Matrix Biol. 78−79 (2019) 1–10, doi: 10.1016/j.matbio.2019.02.002.
[58] M.I. Tammi, A.J. Day, E.A. Turley, Hyaluronan and Homeostasis: a Balancing Act *, J. Biol. Chem. 277 (2002) 4581–4584, doi: 10.1074/jbc.R100037200.
[59] F.E. Lennon, P.A. Singleton, Role of hyaluronan and hyaluronan-binding proteins in lung pathobiology, Am. J. Physiol.-Lung Cellular Mol. Physiol. 301 (2011) L137–L147, doi: 10.1152/ajplung.00071.2010.
[60] M.A. Dentener, Enhanced levels of hyaluronan in lungs of patients with COPD: relationship with lung function and local inflammation, Thorax 60 (2005) 114–119, doi: 10.1136/thx.2003.020842.
[61] M.L. Ormiston, G.R.D. Slaughter, Y. Deng, D.J. Stewart, D.W. Courtman, The enzymatic degradation of hyaluronan is associated with disease progression in experimental pulmonary hypertension, Am. J. Physiol.-Lung Cellular Mol. Physiol. 298 (2010) L148–L157, doi: 10.1152/ajplung.00097.2009.
[62] J. Liang, Y. Zhang, T. Xie, N. Liu, H. Chen, Y. Geng, A. Kurkciyan, J.M. Mena, B.R. Stripp, D. Jiang, P.W. Noble, Hyaluronan and TLR4 promote surfactant-protein-C-positive alveolar progenitor cell renewal and prevent severe pulmonary fibrosis in mice, Nat. Med. 22 (2016) 1285–1293, doi: 10.1038/nm.4192.
[63] J. Liang, D. Jiang, P.W. Noble, Hyaluronan as a therapeutic target in human diseases, Adv. Drug. Deliv. Rev. 97 (2016) 186–203, doi: 10.1016/j.addr.2015.10.017.
[64] H. Xia, J. Herrera, K. Smith, L. Yang, A. Gilbertsen, A. Benyumov, E. Racila, P.B. Bitterman, C.A. Henke, Hyaluronan/CD44 axis regulates S100A4-mediated mesenchymal progenitor cell fibrogenicity in idiopathic pulmonary

fibrosis, Am. J. Physiol. Lung Cell. Mol. Physiol. 320 (2021) L926–L941, doi: 10.1152/ajplung.00456.2020.

[65] A. Kekevian, M.E. Gershwin, C. Chang, Diagnosis and classification of idiopathic pulmonary fibrosis, Autoimmun. Rev. 13 (2014) 508–512, doi: 10.1016/j.autrev.2014.01.037.

[66] P. Spagnolo, J.A. Kropski, M.G. Jones, J.S. Lee, G. Rossi, T. Karampitsakos, T.M. Maher, A. Tzouvelekis, C.J. Ryerson, Idiopathic pulmonary fibrosis: disease mechanisms and drug development, Pharmacol. Ther. 222 (2021) 107798, doi: 10.1016/j.pharmthera.2020.107798.

[67] M. Gharaee-Kermani, S.H. Phan, Molecular Mechanisms of and Possible Treatment Strategies for Idiopathic Pulmonary Fibrosis, Curr. Pharm. Des. 11 (2005) 3943–3971, doi: 10.2174/138161205774580561.

[68] Antifibrotic therapy for the treatment of pulmonary fibrosis, Am. J. Med. Sci. 322 (2001) 213–221, doi: 10.1097/00000441-200110000-00012.

[69] L. Bjermer, R. Lundgren, R. Hällgren, Hyaluronan and type III procollagen peptide concentrations in bronchoalveolar lavage fluid in idiopathic pulmonary fibrosis, Thorax 44 (1989) 126–131, doi: 10.1136/thx.44.2.126.

[70] Y. Li, D. Jiang, J. Liang, E.B. Meltzer, A. Gray, R. Miura, L. Wogensen, Y. Yamaguchi, P.W. Noble, Severe lung fibrosis requires an invasive fibroblast phenotype regulated by hyaluronan and CD44, J. Exp. Med. 208 (2011) 1459–1471, doi: 10.1084/jem.20102510.

[71] S.D. Collum, N.-.Y. Chen, A.M. Hernandez, A. Hanmandlu, H. Sweeney, T.C.J. Mertens, T. Weng, F. Luo, J.G. Molina, J. Davies, I.P. Horan, N.W. Morrell, J. Amione-Guerra, O. Al-Jabbari, K. Youker, W. Sun, J. Rajadas, P.L. Bollyky, B.H. Akkanti, S. Jyothula, N. Sinha, A. Guha, H. Karmouty-Quintana, Inhibition of hyaluronan synthesis attenuates pulmonary hypertension associated with lung fibrosis, Br. J. Pharmacol. 174 (2017) 3284–3301, doi: 10.1111/bph.13947.

[72] V. Tseng, S.D. Collum, A. Allawzi, K. Crotty, S. Yeligar, A. Trammell, M. Ryan Smith, B.-.Y. Kang, R.L. Sutliff, J.L. Ingram, S.S.S.K. Jyothula, R.A. Thandavarayan, H.J. Huang, E.S. Nozik, E.J. Wagner, C. Michael Hart, H. Karmouty-Quintana, 3'UTR shortening of HAS2 promotes hyaluronan hyper-synthesis and bioenergetic dysfunction in pulmonary hypertension, Matrix Biol. 111 (2022) 53–75, doi: 10.1016/j.matbio.2022.06.001.

[73] S.D. Collum, J.G. Molina, A. Hanmandlu, W. Bi, M. Pedroza, T.C.J. Mertens, N. Wareing, W. Wei, C. Wilson, W. Sun, J. Rajadas, P.L. Bollyky, K.M. Philip, D. Ren, R.A. Thandavarayan, B.A. Bruckner, Y. Xia, M.R. Blackburn, H. Karmouty-Quintana, Adenosine and hyaluronan promote lung fibrosis and pulmonary hypertension in combined pulmonary fibrosis and emphysema, Dis. Model Mech. 12 (2019), doi: 10.1242/dmm.038711.

[74] T.C.J. Mertens, A. Hanmandlu, L. Tu, C. Phan, S.D. Collum, N.-.Y. Chen, T. Weng, J. Davies, C. Liu, H.K. Eltzschig, S.S.K. Jyothula, K. Rajagopal, Y. Xia, A. Guha, B.A. Bruckner, M.R. Blackburn, C. Guignabert, H. Karmouty-Quintana, Switching-Off Adora2b in vascular smooth muscle cells halts the development of pulmonary hypertension, Front. Physiol. 9 (2018) 555, doi: 10.3389/fphys.2018.00555.

[75] S. Yang, Y. Ling, F. Zhao, W.W. Li, Z. Song, L. Wang, Q. Li, M. Liu, Y. Tong, L. Chen, D. Ru, T. Zhang, K. Zhou, B. Zhang, P. Xu, Z. Yang, W.W. Li, Y. Song, J. Xu, T. Zhu, F. Shan, W. Yu, H. Lu, Hymecromone: a clinical prescription hyaluronan inhibitor for efficiently blocking COVID-19 progression, Signal Transduct. Target Ther. 7 (2022) 1–10, doi: 10.1038/s41392-022-00952-w.

[76] H.F. Kuipers, N. Nagy, S.M. Ruppert, V.G. Sunkari, P.L. Marshall, J.A. Gebe, H.D. Ishak, S.G. Keswani, J. Bollyky, A.R. Frymoyer, T.N. Wight, L. Steinman, P.L. Bollyky, The pharmacokinetics and dosing of oral 4-methylumbelliferone for inhibition of hyaluronan synthesis in mice, Clin. Exp. Immunol. 185 (2016) 372–381, doi: 10.1111/cei.12815.

[77] J.I. Rosser, N. Nagy, R. Goel, G. Kaber, S. Demirdjian, J. Saxena, J.B. Bollyky, A.R. Frymoyer, A.E. Pacheco-Navarro, E.B. Burgener, J. Rajadas, Z. Wang, O. Arbach, C.E. Dunn, A. Kalinowski, C.E. Milla, P.L. Bollyky, Oral hymecromone decreases hyaluronan in human study participants, J. Clin. Investigat. 132 (2022) e157983, doi: 10.1172/JCI157983.

[78] J. Liang, N. Liu, X. Liu, J.M. Mena, T. Xie, Y. Geng, C. Huan, Y. Zhang, F. Taghavifar, G. Huang, A. Kurkciyan, V. Barron, D. Jiang, P.W. Noble, Mitogen-activated protein kinase−activated protein kinase 2 inhibition attenuates fibroblast invasion and severe lung fibrosis, Am. J. Respir. Cell Mol. Biol. 60 (2019) 41–48, doi: 10.1165/rcmb.2018-0033OC.

[79] A.J. Esposito, P.K. Bhatraju, R.D. Stapleton, M.M. Wurfel, C. Mikacenic, Hyaluronic acid is associated with organ dysfunction in acute respiratory distress syndrome, Crit. Care 21 (2017) 304, doi: 10.1186/s13054-017-1895-7.

[80] C. Lonati, J. Fumagalli, A. Zanella, E. Spinelli, T. Mauri, Hyaluronan in acute respiratory distress syndrome (ARDS): simply a biomarker or a deeper insight into ARDS mechanisms? J. Lab Precis. Med. 3 (2018) 49−49, doi: 10.21037/jlpm.2018.05.03.

[81] K.-.J. Bai, A.P. Spicer, M.M. Mascarenhas, L. Yu, C.D. Ochoa, H.G. Garg, D.A. Quinn, The role of hyaluronan synthase 3 in ventilator-induced lung injury, Am. J. Respir. Crit. Care Med. 172 (2005) 92–98, doi: 10.1164/rccm.200405-652OC.

[82] R. Hällgren, T. Samuelsson, T.C. Laurent, J. Modig, Accumulation of hyaluronan (hyaluronic acid) in the lung in adult respiratory distress syndrome, Am. Rev. Respiratory Dis. (2012), doi: 10.1164/ajrccm/139.3.682.

[83] J. Modig, R. Hällgren, Increased hyaluronic acid production in lung — a possible important factor in interstitial and alveolar edema during general anesthesia and in adult respiratory distress syndrome, Resuscitation 17 (1989) 223–231, doi: 10.1016/0300-9572(89)90038-5.

[84] R.J. McKallip, H.F. Hagele, O.N. Uchakina, Treatment with the hyaluronic acid synthesis inhibitor 4-methylumbelliferone suppresses SEB-induced lung inflammation, Toxins (Basel) 5 (2013) 1814–1826, doi: 10.3390/toxins5101814.

[85] R.J. McKallip, H. Ban, O.N. Uchakina, Treatment with the Hyaluronic Acid Synthesis Inhibitor 4-Methylumbelliferone Suppresses LPS-Induced Lung Inflammation, Inflammation 38 (2015) 1250–1259, doi: 10.1007/s10753-014-0092-y.

[86] S.H. Nile, A. Nile, J. Qiu, L. Li, X. Jia, G. Kai, COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons, Cytokine Growth Factor Rev. 53 (2020) 66–70, doi: 10.1016/j.cytogfr.2020.05.002.

[87] S.B. Polak, I.C. van Gool, D. Cohen, J.H. von der Thüsen, J. van Paassen, A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression, Modern Pathol. 33 (2020) 2128–2138, doi: 10.1038/s41379-020-0603-3.

[88] M. So, H. Kabata, K. Fukunaga, H. Takagi, T. Kuno, Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis, BMC Pulm. Med. 21 (2021) 97, doi: 10.1186/s12890-021-01463-0.
[89] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (2020) 363–374, doi: 10.1038/s41577-020-0311-8.
[90] H. Jia, E. Neptune, H. Cui, Targeting ACE2 for COVID-19 Therapy: opportunities and Challenges, Am. J. Respir. Cell Mol. Biol. 64 (2021) 416–425, doi: 10.1165/rcmb.2020-0322PS.
[91] T. Behl, I. Kaur, S. Bungau, A. Kumar, M.S. Uddin, C. Kumar, G. Pal, K. Shrivastava, G. Zengin, S. Arora, The dual impact of ACE2 in COVID-19 and ironical actions in geriatrics and pediatrics with possible therapeutic solutions, Life Sci. 257 (2020) 118075, doi: 10.1016/j.lfs.2020.118075.
[92] A.F. Rendeiro, H. Ravichandran, Y. Bram, V. Chandar, J. Kim, C. Meydan, J. Park, J. Foox, T. Hether, S. Warren, Y. Kim, J. Reeves, S. Salvatore, C.E. Mason, E.C. Swanson, A.C. Borczuk, O. Elemento, R.E. Schwartz, The spatial landscape of lung pathology during COVID-19 progression, Nature 593 (2021) 564–569, doi: 10.1038/s41586-021-03475-6.
[93] S.S. Batah, A.T. Fabro, Pulmonary pathology of ARDS in COVID-19: a pathological review for clinicians, Respir. Med. 176 (2021) 106239, doi: 10.1016/j.rmed.2020.106239.
[94] R.O. Bonow, G.C. Fonarow, P.T. O'Gara, C.W. Yancy, Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality, JAMA Cardiol. 5 (2020) 751, doi: 10.1001/jamacardio.2020.1105.
[95] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China, JAMA Neurol. 77 (2020) 683, doi: 10.1001/jamaneurol.2020.1127.
[96] C. Han, C. Duan, S. Zhang, B. Spiegel, H. Shi, W. Wang, L. Zhang, R. Lin, J. Liu, Z. Ding, X. Hou, Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes, Am. J. Gastroenterol. 115 (2020) 916–923, doi: 10.14309/ajg.0000000000000664.
[97] Q. Ma, J. Liu, Q. Liu, L. Kang, R. Liu, W. Jing, Y. Wu, M. Liu, Global percentage of asymptomatic SARS-CoV-2 infections among the tested population and individuals with confirmed COVID-19 diagnosis, JAMA Netw. Open. 4 (2021) e2137257, doi: 10.1001/jamanetworkopen.2021.37257.
[98] A. Nalbandian, K. Sehgal, A. Gupta, M. v Madhavan, C. McGroder, J.S. Stevens, J.R. Cook, A.S. Nordvig, D. Shalev, T.S. Sehrawat, N. Ahluwalia, B. Bikdeli, D. Dietz, C. Der-Nigoghossian, N. Liyanage-Don, G.F. Rosner, E.J. Bernstein, S. Mohan, A.A. Beckley, D.S. Seres, T.K. Choueiri, N. Uriel, J.C. Ausiello, D. Accili, D.E. Freedberg, M. Baldwin, A. Schwartz, D. Brodie, C.K. Garcia, M.S. v Elkind, J.M. Connors, J.P. Bilezikian, D.W. Landry, E.Y. Wan, Post-acute COVID-19 syndrome, Nat. Med. 27 (2021) 601–615, doi: 10.1038/s41591-021-01283-z.
[99] M.J. Peluso, S.G. Deeks, Early clues regarding the pathogenesis of long-COVID, Trends Immunol. 43 (2022) 268–270, doi: 10.1016/j.it.2022.02.008.
[100] L.A. Callender, M. Curran, S.M. Bates, M. Mairesse, J. Weigandt, C.J. Betts, The impact of pre-existing comorbidities and therapeutic interventions on COVID-19, Front. Immunol. 11 (2020), doi: 10.3389/fimmu.2020.01991.
[101] I.G. Ovsyannikova, I.H. Haralambieva, S.N. Crooke, G.A. Poland, R.B. Kennedy, The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity, Immunol. Rev. 296 (2020) 205–219, doi: 10.1111/imr.12897.
[102] C.P. Gross, U.R. Essien, S. Pasha, J.R. Gross, S. Wang, M. Nunez-Smith, Racial and ethnic disparities in population-level covid-19 mortality, J. Gen. Intern. Med. 35 (2020) 3097–3099, doi: 10.1007/s11606-020-06081-w.
[103] A. Booth, A.B. Reed, S. Ponzo, A. Yassaee, M. Aral, D. Plans, A. Labrique, D. Mohan, Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis, PLoS One 16 (2021) e0247461, doi: 10.1371/journal.pone.0247461.
[104] J.J. Marini, L. Gattinoni, Management of COVID-19 respiratory distress, JAMA 323 (2020) 2329–2330, doi: 10.1001/jama.2020.6825.
[105] M.J. Kratochvil, G. Kaber, S. Demirdjian, P.C. Cai, E.B. Burgener, N. Nagy, G.L. Barlow, M. Popescu, M.R. Nicolls, M.G. Ozawa, D.P. Regula, A.E. Pacheco-Navarro, S. Yang, V.A. de Jesus Perez, H. Karmouty-Quintana, A.M. Peters, B. Zhao, M.L. Buja, P.Y. Johnson, R.B. Vernon, T.N. Wight, C.E. Milla, A.J. Rogers, A.J. Spakowitz, S.C. Heilshorn, P.L. Bollyky, Biochemical, biophysical, and immunological characterization of respiratory secretions in severe SARS-CoV-2 infections, JCI Insight 7 (2022), doi: 10.1172/jci.insight.152629.
[106] Y. Wang, C. Dong, Y. Hu, C. Li, Q. Ren, X. Zhang, H. Shi, M. Zhou, Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: a Longitudinal Study, Radiology 296 (2020) E55–E64, doi: 10.1148/radiol.2020200843.
[107] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.-.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (2020) 420–422, doi: 10.1016/S2213-2600(20)30076-X.
[108] G.W. Williams, N.K. Berg, A. Reskallah, X. Yuan, H.K. Eltzschig, Acute respiratory distress syndrome, Anesthesiology 134 (2021) 270–282, doi: 10.1097/ALN.0000000000003571.
[109] A.D. Proal, M.B. VanElzakker, Long COVID or Post-acute Sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms, Front. Microbiol. 12 (2021), doi: 10.3389/fmicb.2021.698169.
[110] H. Crook, S. Raza, J. Nowell, M. Young, P. Edison, Long covid—Mechanisms, risk factors, and management, BMJ (2021) n1648, doi: 10.1136/bmj.n1648.
[111] S.R. Stein, SARS-CoV-2 infection and persistence in the human body and brain at autopsy, Nature 612 (2022) 758–763, doi: 10.1038/s41586-022-05542-y.
[112] L. Tabacof, J. Tosto-Mancuso, J. Wood, M. Cortes, A. Kontorovich, D. McCarthy, D. Rizk, N. Mohammadi, E. Breyman, L. Nasr, C. Kellner, D. Putrino, Post-acute COVID-19 syndrome negatively impacts health and well-being despite less severe acute infection, Rehab. Med. Phys. Therapy (2020) http://medrxiv.org/lookup/doi/10.1101/2020.11.04.20226126 .

[113] P.E. Scherer, J.P. Kirwan, C.J. Rosen, Post-acute sequelae of COVID-19: a metabolic perspective, Elife 11 (2022) e78200, doi: 10.7554/eLife.78200.
[114] T.D. Müller, B. Finan, S.R. Bloom, D. D'Alessio, D.J. Drucker, P.R. Flatt, A. Fritsche, F. Gribble, H.J. Grill, J.F. Habener, J.J. Holst, W. Langhans, J.J. Meier, M.A. Nauck, D. Perez-Tilve, A. Pocai, F. Reimann, D.A. Sandoval, T.W. Schwartz, R.J. Seeley, K. Stemmer, M. Tang-Christensen, S.C. Woods, R.D. DiMarchi, M.H. Tschöp, Glucagon-like peptide 1 (GLP-1), Mol Metab. 30 (2019) 72–130, doi: 10.1016/j.molmet.2019.09.010.
[115] E. Bazdyrev, P. Rusina, M. Panova, F. Novikov, I. Grishagin, V. Nebolsin, Lung fibrosis after COVID-19: treatment prospects, Pharmaceuticals 14 (2021) 807, doi: 10.3390/ph14080807.
[116] L.T. McDonald, Healing after COVID-19: are survivors at risk for pulmonary fibrosis? Am. J. Physiol.-Lung Cellular Mol. Physiol. 320 (2021) L257–L265, doi: 10.1152/ajplung.00238.2020.
[117] B. Malik, B. Abdelazeem, A. Ghatol, Pulmonary fibrosis after COVID-19 pneumonia, Cureus (2021) 13, doi: 10.7759/cureus.13923.
[118] E. Vasarmidi, E. Tsitoura, D.A. Spandidos, N. Tzanakis, K.M. Antoniou, Pulmonary fibrosis in the aftermath of the Covid-19 era (Review), Exp. Ther. Med. 20 (2020) 2557–2560, doi: 10.3892/etm.2020.8980.
[119] P.M. George, A.U. Wells, R.G. Jenkins, Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy, Lancet Respir. Med. 8 (2020) 807–815, doi: 10.1016/S2213-2600(20)30225-3.
[120] S.R. Ambardar, S.L. Hightower, N.A. Huprikar, K.K. Chung, A. Singhal, J.F. Collen, Post-COVID-19 pulmonary fibrosis: novel sequelae of the current pandemic, J. Clin. Med. 10 (2021) 2452, doi: 10.3390/jcm10112452.
[121] H. Javaid, M. Nigo, B. Zhao, D.O. Trujillo, R. Hasbun, L. Ostrosky-Zeichner, M. Patel, S. Jyothula, Post-lung transplantation outcomes and ex vivo histopathological findings in severe post-Covid-19 pulmonary disease-a single-center experience, Open Forum Infect. Dis. 9 (2022) ofac425, doi: 10.1093/ofid/ofac425.
[122] A. Bharat, M. Querrey, N.S. Markov, S. Kim, C. Kurihara, R. Garza-Castillon, A. Manerikar, A. Shilatifard, R. Tomic, Y. Politanska, H. Abdala-Valencia, A. v Yeldandi, J.W. Lomasney, A. v Misharin, G.R.S. Budinger, Lung transplantation for patients with severe COVID-19, Sci. Transl. Med. 12 (2020) eabe4282, doi: 10.1126/scitranslmed.abe4282.
[123] A. Bharat, T.N. Machuca, M. Querrey, C. Kurihara, R. Garza-Castillon, S. Kim, A. Manerikar, A. Pelaez, M. Pipkin, A. Shahmohammadi, M. Rackauskas, S.R. KG, K.R. Balakrishnan, A. Jindal, L. Schaheen, S. Hashimi, B. Buddhdev, A. Arjuna, L. Rosso, A. Palleschi, C. Lang, P. Jaksch, G.R.S. Budinger, M. Nosotti, K. Hoetzenecker, Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries, Lancet Respir. Med. 9 (2021) 487–497, doi: 10.1016/S2213-2600(21)00077-1.
[124] M. Kolb, K. Borensztajn, B. Crestani, M. Kolb, Idiopathic pulmonary fibrosis: from epithelial injury to biomarkers - insights from the bench side, Respiration 86 (2013) 441–452, doi: 10.1159/000357598.
[125] T.E. King, A. Pardo, M. Selman, Idiopathic pulmonary fibrosis, Lancet 378 (2011) 1949–1961, doi: 10.1016/S0140-6736(11)60052-4.
[126] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T. v Colby, J.-F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King, Y. Kondoh, J. Myers, N.L. Müller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schünemann, An Official ATS/ERS/JRS/ALAT Statement, Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am. J. Respir. Crit. Care Med. 183 (2011) 788–824, doi: 10.1164/rccm.2009-040GL.
[127] M. Selman, A. Pardo, Alveolar epithelial cell disintegrity and subsequent activation, Am. J. Respir. Crit. Care Med. 186 (2012) 119–121, doi: 10.1164/rccm.201206-0997ED.
[128] M. Cypel, S. Keshavjee, When to consider lung transplantation for COVID-19, Lancet Respir. Med. 8 (2020) 944–946, doi: 10.1016/S2213-2600(20)30393-3.
[129] C. Giacomelli, R. Piccarducci, L. Marchetti, C. Romei, C. Martini, Pulmonary fibrosis from molecular mechanisms to therapeutic interventions: lessons from post-COVID-19 patients, Biochem. Pharmacol. 193 (2021) 114812, doi: 10.1016/j.bcp.2021.114812.
[130] H. Karmouty-Quintana, R.A. Thandavarayan, S.P. Keller, S. Sahay, L.M. Pandit, B. Akkanti, Emerging mechanisms of pulmonary vasoconstriction in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) and potential therapeutic targets, Int. J. Mol. Sci. 21 (2020), doi: 10.3390/ijms21218081.
[131] F. Potus, V. Mai, M. Lebret, S. Malenfant, E. Breton-Gagnon, A.C. Lajoie, O. Boucherat, S. Bonnet, S. Provencher, Novel insights on the pulmonary vascular consequences of COVID-19, Am. J. Physiol. Lung Cell. Mol. Physiol. 319 (2020) L277–L288, doi: 10.1152/ajplung.00195.2020.
[132] R.T. Dhawan, D. Gopalan, L. Howard, A. Vicente, M. Park, K. Manalan, I. Wallner, P. Marsden, S. Dave, H. Branley, G. Russell, N. Dharmarajah, O.M. Kon, Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19, Lancet Respir. Med. 9 (2021) 107–116, doi: 10.1016/S2213-2600(20)30407-0.
[133] A. Nalbandian, K. Sehgal, A. Gupta, M. v. Madhavan, C. McGroder, J.S. Stevens, J.R. Cook, A.S. Nordvig, D. Shalev, T.S. Sehrawat, N. Ahluwalia, B. Bikdeli, D. Dietz, C. Der-Nigoghossian, N. Liyanage-Don, G.F. Rosner, E.J. Bernstein, S. Mohan, A.A. Beckley, D.S. Seres, T.K. Choueiri, N. Uriel, J.C. Ausiello, D. Accili, D.E. Freedberg, M. Baldwin, A. Schwartz, D. Brodie, C.K. Garcia, M.S. v. Elkind, J.M. Connors, J.P. Bilezikian, D.W. Landry, E.Y. Wan, Post-acute COVID-19 syndrome, Nat. Med. 27 (2021) 601–615, doi: 10.1038/s41591-021-01283-z.
[134] B. Oronsky, C. Larson, T.C. Hammond, A. Oronsky, S. Kesari, M. Lybeck, T.R. Reid, A review of persistent post-COVID syndrome (PPCS), Clin. Rev. Allergy Immunol. (2021), doi: 10.1007/s12016-021-08848-3.
[135] F. Wang, R.M. Kream, G.B. Stefano, Long-term respiratory and neurological sequelae of COVID-19, Med. Sci. Monitor 26 (2020), doi: 10.12659/MSM.928996.
[136] M.J. Kratochvil, G. Kaber, P.C. Cai, E.B. Burgener, G.L. Barlow, M.R. Nicolls, M.G. Ozawa, D.P. Regula, A.E. Pacheco-Navarro, C.E. Milla, N. Nagy, S. Yang, A.J. Rogers, A.J. Spakowitz, S.C. Heilshorn, P.L. Bollyky, Biochemical and Biophysical Characterization of Respiratory Secretions in Severe SARS-CoV-2 (COVID-19) Infections,

Infectious Diseases (except HIV/AIDS), 2020. http://medrxiv.org/lookup/doi/10.1101/2020.09.11.20191692.
[137] M.J. Kratochvil, G. Kaber, S. Demirdjian, P.C. Cai, E.B. Burgener, N. Nagy, G.L. Barlow, M. Popescu, M.R. Nicolls, M. G. Ozawa, D.P. Regula, A.E. Pacheco-Navarro, S. Yang, V.A. de Jesus Perez, H. Karmouty-Quintana, A.M. Peters, B. Zhao, M.L. Buja, P.Y. Johnson, R.B. Vernon, T.N. Wight, C.E. Milla, A.J. Rogers, A.J. Spakowitz, S.C. Heilshorn, P. L. Bollyky, Biochemical, Biophysical, and Immunological Characterization of Respiratory Secretions in Severe SARS-CoV-2 (COVID-19) Infections, Infectious Diseases (except HIV/AIDS), 2022. http://medrxiv.org/lookup/doi/10.1101/2022.03.28.22272848.
[138] A.N. Donlan, T.E. Sutherland, C. Marie, S. Preissner, B.T. Bradley, R.M. Carpenter, J.M. Sturek, J.Z. Ma, G.B. Moreau, J.R. Donowitz, G.A. Buck, M.G. Serrano, S.L. Burgess, M.M. Abhyankar, C. Mura, P.E. Bourne, R. Preissner, M.K. Young, G.R. Lyons, J.J. Loomba, S.J. Ratcliffe, M.D. Poulter, A.J. Mathers, A.J. Day, B.J. Mann, J.E. Allen, W.A. Petri, Jr., IL-13 is a driver of COVID-19 severity, JCI Insight (2021), doi: 10.1172/jci.insight.150107.
[139] S. Andonegui-Elguera, K. Taniguchi-Ponciano, C.R. Gonzalez-Bonilla, J. Torres, H. Mayani, L.A. Herrera, E. Peña-Martínez, G. Silva-Román, S. Vela-Patiño, A. Ferreira-Hermosillo, C. Ramirez-Renteria, R. Carvente-Garcia, C. Mata-Lozano, D. Marrero-Rodríguez, M. Mercado, Molecular alterations prompted by SARS-CoV-2 infection: induction of hyaluronan, glycosaminoglycan and mucopolysaccharide metabolism, Arch. Med. Res. 51 (2020) 645–653, doi: 10.1016/j.arcmed.2020.06.011.
[140] M.R. Garvin, C. Alvarez, J.I. Miller, E.T. Prates, A.M. Walker, B.K. Amos, A.E. Mast, A. Justice, B. Aronow, D. Jacobson, A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm, Elife 9 (2020) e59177, doi: 10.7554/eLife.59177.
[141] L.E. Gralinski, V.D. Menachery, Return of the coronavirus: 2019-nCoV, Viruses 12 (2020) 135, doi: 10.3390/v12020135.
[142] M. Ding, Q. Zhang, Q. Li, T. Wu, Y. Huang, Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19, Respir. Med. 167 (2020), doi: 10.1016/j.rmed.2020.105981.
[143] T. Matsuyama, S.K. Yoshinaga, K. Shibue, T.W. Mak, Comorbidity-associated glutamine deficiency is a predisposition to severe COVID-19, Cell Death Differ. 28 (2021) 3199–3213, doi: 10.1038/s41418-021-00892-y.
[144] B. Hu, S. Huang, L. Yin, The cytokine storm and COVID-19, J. Med. Virol. 93 (2021) 250–256, doi: 10.1002/jmv.26232.
[145] N. Xiao, M. Nie, H. Pang, B. Wang, J. Hu, X. Meng, K. Li, X. Ran, Q. Long, H. Deng, N. Chen, S. Li, N. Tang, A. Huang, Z. Hu, Integrated cytokine and metabolite analysis reveals immunometabolic reprogramming in COVID-19 patients with therapeutic implications, Nat. Commun. 12 (2021) 1618, doi: 10.1038/s41467-021-21907-9.
[146] J.L. Schultze, A.C. Aschenbrenner, COVID-19 and the human innate immune system, Cell 184 (2021) 1671–1692, doi: 10.1016/j.cell.2021.02.029.
[147] J.G. Wilson, L.J. Simpson, A.-.M. Ferreira, A. Rustagi, J. Roque, A. Asuni, T. Ranganath, P.M. Grant, A. Subramanian, Y. Rosenberg-Hasson, H.T. Maecker, S.P. Holmes, J.E. Levitt, C.A. Blish, A.J. Rogers, Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis, JCI Insight 5 (2020) e140289, doi: 10.1172/jci.insight.140289.
[148] K.E. Huntington, A.D. Louie, C.G. Lee, J.A. Elias, E.A. Ross, W.S. El-Deiry, Cytokine ranking via mutual information algorithm correlates cytokine profiles with presenting disease severity in patients infected with SARS-CoV-2, Elife. 10 (2021) e64958. https://doi.org/10.7554/eLife.64958.
[149] D.D. Fraser, G. Cepinskas, M. Slessarev, C. Martin, M. Daley, M.R. Miller, D.B. O'Gorman, S.E. Gill, E.K. Patterson, C.C. dos Santos, Inflammation profiling of critically ill coronavirus disease 2019 patients, Crit. Care Explor. 2 (2020) e0144, doi: 10.1097/CCE.0000000000000144.
[150] R. Uchimido, E.P. Schmidt, N.I. Shapiro, The glycocalyx: a novel diagnostic and therapeutic target in sepsis, Crit. Care 23 (2019) 16, doi: 10.1186/s13054-018-2292-6.
[151] S.N. Goonewardena, O.G. Grushko, J. Wells, L. Herty, R.S. Rosenson, J.M. Haus, S.L. Hummel, Immune-mediated glycocalyx remodeling in hospitalized COVID-19 patients, Cardiovasc. Drugs Ther. (2021), doi: 10.1007/s10557-021-07288-7.
[152] K.A. Queisser, R.A. Mellema, E.A. Middleton, I. Portier, B.K. Manne, F. Denorme, E.J. Beswick, M.T. Rondina, R.A. Campbell, A.C. Petrey, COVID-19 generates hyaluronan fragments that directly induce endothelial barrier dysfunction, JCI Insight. 6 (2021), doi: 10.1172/jci.insight.147472.
[153] X. Sun, T. Wang, D. Cai, Z. Hu, J. Chen, H. Liao, L. Zhi, H. Wei, Z. Zhang, Y. Qiu, J. Wang, A. Wang, Cytokine storm intervention in the early stages of COVID-19 pneumonia, Cytokine Growth Factor Rev. 53 (2020) 38–42, doi: 10.1016/j.cytogfr.2020.04.002.
[154] S. Khanmohammadi, N. Rezaei, Role of Toll-like receptors in the pathogenesis of COVID-19, J. Med. Virol. 93 (2021) 2735–2739, doi: 10.1002/jmv.26826.
[155] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the `Cytokine Storm' in COVID-19, J. Infect. 80 (2020) 607–613, doi: 10.1016/j.jinf.2020.03.037.
[156] P. Ontong, V. Prachayasittikul, Unraveled roles of hyaluronan in severe COVID-19, EXCLI J 20 (2021) 117–125, doi: 10.17179/excli2020-3215.
[157] D. Vigetti, A. Genasetti, E. Karousou, M. Viola, P. Moretto, M. Clerici, S. Deleonibus, G. de Luca, V.C. Hascall, A. Passi, Proinflammatory cytokines induce hyaluronan synthesis and monocyte adhesion in human endothelial cells through hyaluronan synthase 2 (HAS2) and the Nuclear Factor-κB (NF-κB) Pathway, J. Biol. Chem. 285 (2010) 24639–24645, doi: 10.1074/jbc.M110.134536.
[158] H.J. Cao, H.-.S. Wang, Y. Zhang, H.-.Y. Lin, R.P. Phipps, T.J. Smith, Activation of Human Orbital Fibroblasts through CD40 engagement results in a dramatic induction of hyaluronan synthesis and prostaglandin endoperoxide H Synthase-2 Expression, J. Biol. Chem. 273 (1998) 29615–29625, doi: 10.1074/jbc.273.45.29615.
[159] G.P. Jardim-Santos, H.L. Schulte, P.S. Kurizky, C.M. Gomes, O.T. Nóbrega, E.T. de Gois, M.R.M. de Carvalho, F.P. Martins, A.M. Nicola, C.P. de Albuquerque, L.S. Espindola, L.A. Naves, A.A. de S.M. Soares, P. Albuquerque, W. Fontes, L.R. do Amaral, M. de S. Gomes, P.L.L. Bertarini, J.P. Brito-de-Sousa, A.C. Campi-Azevedo, V. Peruhype-Magalhães, A. Teixeira-Carvalho, V. Valim, O.A. Martins-Filho, L.M.H. da Mota, Unbalanced networks and disturbed kinetics of serum soluble mediators associated with distinct disease outcomes in severe COVID-19

patients, Front. Immunol. 13 (2022), doi: 10.3389/fimmu.2022.1004023.

[160] O.E. Amer, S. Sabico, E. Sheshah, N.H. Alotaibi, D.A. Aldisi, M.A. Enani, N.J. Aljohani, N. Alshingetti, S.Y. Alomar, S.D. Hussain, A.M. Alnaami, M.A. Elsaid, N.M. Al-Daghri, Evaluation of 34 cytokines and vitamin D status reveal a sexually-dimorphic active immune response to SARS-CoV-2, Healthcare 10 (2022) 2571, doi: 10.3390/healthcare10122571.

[161] C.B. Vaz de Paula, M.L.V. de Azevedo, S. Nagashima, A.P.C. Martins, M.A.S. Malaquias, A.F.R. dos S. Miggiolaro, J. da Silva Motta Júnior, G. Avelino, L.A.P. do Carmo, L.B. Carstens, L. de Noronha, IL-4/IL-13 remodeling pathway of COVID-19 lung injury, Sci. Rep. 10 (2020) 18689, doi: 10.1038/s41598-020-75659-5.

[162] J. Sasson, A.N. Donlan, J.Z. Ma, H.M. Haughey, R. Coleman, U. Nayak, A.J. Mathers, S. Laverdure, R. Dewar, P.E.H. Jackson, S.K. Heysell, J.M. Sturek, W.A. Petri, Safety and efficacy of dupilumab for the treatment of hospitalized patients with moderate to severe coronavirus disease 2019: a phase 2a trial, Open Forum. Infect. Dis. 9 (2022) ofac343, doi: 10.1093/ofid/ofac343.

[163] L.R. Bonser, W.L. Eckalbar, L. Rodriguez, J. Shen, K.D. Koh, K. Ghias, L.T. Zlock, S. Christenson, P.G. Woodruff, W.E. Finkbeiner, D.J. Erle, The type 2 asthma mediator IL-13 inhibits severe acute respiratory syndrome coronavirus 2 infection of bronchial epithelium, Am. J. Respir. Cell Mol. Biol. 66 (2022) 391–401, doi: 10.1165/rcmb.2021-0364OC.

[164] C.B. Morrison, C.E. Edwards, K.M. Shaffer, K.C. Araba, J.A. Wykoff, D.R. Williams, T. Asakura, H. Dang, L.C. Morton, R.C. Gilmore, W.K. O'Neal, R.C. Boucher, R.S. Baric, C. Ehre, SARS-CoV-2 infection of airway cells causes intense viral and cell shedding, two spreading mechanisms affected by IL-13, Proc. Nat. Acad. Sci. 119 (2022), doi: 10.1073/pnas.2119680119.

[165] H. Karmouty-Quintana, Y. Xia, M.R. Blackburn, Adenosine signaling during acute and chronic disease states, J. Mol. Med. (Berl) 91 (2013) 173–181, doi: 10.1007/s00109-013-0997-1.

[166] H. Karmouty-Quintana, K. Philip, L.F. Acero, N.-.Y. Chen, T. Weng, J.G. Molina, F. Luo, J. Davies, N.-.B. Le, I. Bunge, K.A. Volcik, T.-T.T. Le, R.A. Johnston, Y. Xia, H.K. Eltzschig, M.R. Blackburn, Deletion of ADORA2B from myeloid cells dampens lung fibrosis and pulmonary hypertension, FASEB J. 29 (2015) 50–60, doi: 10.1096/fj.14-260182.

[167] R.M. Tighe, S. Garantziotis, Hyaluronan interactions with innate immunity in lung biology, Matrix Biol. 78−79 (2019) 84–99, doi: 10.1016/j.matbio.2018.01.027.

[168] N.G. Ravindra, M.M. Alfajaro, V. Gasque, V. Habet, J. Wei, R.B. Filler, N.C. Huston, H. Wan, K. Szigeti-Buck, B. Wang, G. Wang, R.R. Montgomery, S.C. Eisenbarth, A. Williams, A.M. Pyle, A. Iwasaki, T.L. Horvath, E.F. Foxman, R.W. Pierce, D. van Dijk, C.B. Wilen, Single-cell longitudinal analysis of SARS-CoV-2 infection in human airway epithelium, Biorxiv (2020), doi: 10.1101/2020.05.06.081695.

[169] H.E. Davis, G.S. Assaf, L. McCorkell, H. Wei, R.J. Low, Y. Re'em, S. Redfield, J.P. Austin, A. Akrami, Characterizing long COVID in an international cohort: 7 months of symptoms and their impact, EClin. Med. 38 (2021) 101019, doi: 10.1016/j.eclinm.2021.101019.

[170] M. Taquet, Q. Dercon, S. Luciano, J.R. Geddes, M. Husain, P.J. Harrison, Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19, PLoS Med. 18 (2021) e1003773, doi: 10.1371/journal.pmed.1003773.

[171] F.J. Carod Artal, Síndrome post-COVID-19: epidemiología, criterios diagnósticos y mecanismos patogénicos implicados, Rev. Neurol. 72 (2021) 384, doi: 10.33588/rn.7211.2021230.

[172] A.M. Parker, E. Brigham, B. Connolly, J. McPeake, A. v Agranovich, M.T. Kenes, K. Casey, C. Reynolds, K.F.R. Schmidt, S.Y. Kim, A. Kaplin, C.M. Sevin, M.B. Brodsky, A.E. Turnbull, Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care, Lancet Respir. Med. 9 (2021) 1328–1341, doi: 10.1016/S2213-2600(21)00385-4.

[173] S. Lopez-Leon, T. Wegman-Ostrosky, C. Perelman, R. Sepulveda, P. Rebolledo, A. Cuapio, S. Villapol, More than 50 long-term effects of COVID-19: a systematic review and meta-analysis, Res Sq. (2021), doi: 10.21203/rs.3.rs-266574/v1.

[174] A. Carfì, R. Bernabei, F. Landi, Persistent symptoms in patients after acute COVID-19, JAMA 324 (2020) 603, doi: 10.1001/jama.2020.12603.

[175] A. Peters, S. Collum, X. Yuan, B. Zhao, P. Shivshankar, W. Bi, L.M. Buja, R. Thandavarayan, H. Huang, H. Eltzschig, I. Rosas, F.P. de Frias, B. Akkanti, S. Jyothula, N. Wareing, H. Karmouty-Quintana, Hyaluronan (HA) accumulation following SARS-CoV-2 infection and in non-resolvable COVID-19 fibrosis, ERJ Open Res. 8 (2022), doi: 10.1183/23120541.LSC-2022.175.

[176] O. Kolesova, I. Vanaga, S. Laivacuma, A. Derovs, A. Kolesovs, M. Radzina, A. Platkajis, J. Eglite, E. Hagina, S. Arutjunana, D.S. Putrins, J. Storozenko, B. Rozentale, L. Viksna, Intriguing findings of liver fibrosis following COVID-19, BMC Gastroenterol. 21 (2021) 370, doi: 10.1186/s12876-021-01939-7.

[177] C.B. Vaz de Paula, S. Nagashima, V. Liberalesso, M. Collete, F.P.G. da Silva, A.G.G. Oricil, G.S. Barbosa, G.V.C. da Silva, D.B. Wiedmer, F. da Silva Dezidério, L. Noronha, COVID-19: immunohistochemical analysis of TGF-β signaling pathways in pulmonary fibrosis, Int. J. Mol. Sci. 23 (2021), doi: 10.3390/ijms23010168.

[178] S.P. Evanko, S. Potter-Perigo, L.J. Petty, G.A. Workman, T.N. Wight, Hyaluronan controls the deposition of fibronectin and collagen and modulates TGF-β1 induction of lung myofibroblasts, Matrix Biol. 42 (2015) 74–92, doi: 10.1016/j.matbio.2014.12.001.

[179] S. Garantziotis, M. Brezina, P. Castelnuovo, L. Drago, The role of hyaluronan in the pathobiology and treatment of respiratory disease, Am. J. Physiol.-Lung Cellular Mol. Physiol. 310 (2016) L785–L795, doi: 10.1152/ajplung.00168.2015.

[180] S. Li, C. Li, Y. Zhang, X. He, X. Chen, X. Zeng, F. Liu, Y. Chen, J. Chen, Targeting mechanics-induced fibroblast activation through CD44-RhoA-YAP pathway ameliorates crystalline silica-induced silicosis, Theranostics 9 (2019) 4993–5008, doi: 10.7150/thno.35665.

[181] Y. Li, D. Jiang, J. Liang, E.B. Meltzer, A. Gray, R. Miura, L. Wogensen, Y. Yamaguchi, P.W. Noble, Severe lung fibrosis requires an invasive fibroblast phenotype regulated by hyaluronan and CD44, J. Experiment. Med. 208 (2011) 1459–1471, doi: 10.1084/jem.20102510.

[182] Y. Li, J. Liang, T. Yang, J. Monterrosa Mena, C. Huan, T. Xie, A. Kurkciyan, N. Liu, D. Jiang, P.W. Noble,

Hyaluronan synthase 2 regulates fibroblast senescence in pulmonary fibrosis, Matrix Biol. 55 (2016) 35–48, doi: 10.1016/j.matbio.2016.03.004.
[183] H.-.W. Zhao, C.-.J. Lu, R.-.J. Yu, X.-.M. Hou, An increase in hyaluronan by lung fibroblasts: a biomarker for intensity and activity of interstitial pulmonary fibrosis? Respirology 4 (1999) 131–138, doi: 10.1046/j.1440-1843.1999.00164.x.
[184] Y.M. Yang, M. Noureddin, C. Liu, K. Ohashi, S.Y. Kim, D. Ramnath, E.E. Powell, M.J. Sweet, Y.S. Roh, I.-.F. Hsin, N. Deng, Z. Liu, J. Liang, E. Mena, D. Shouhed, R.F. Schwabe, D. Jiang, S.C. Lu, P.W. Noble, E. Seki, Hyaluronan synthase 2−mediated hyaluronan production mediates Notch1 activation and liver fibrosis, Sci. Transl. Med. 11 (2019), doi: 10.1126/scitranslmed.aat9284.
[185] S.D. Collum, J.G. Molina, A. Hanmandlu, W. Bi, M. Pedroza, T.C.J. Mertens, N. Wareing, W. Wei, C. Wilson, W. Sun, J. Rajadas, P.L. Bollyky, K.M. Philip, D. Ren, R.A. Thandavarayan, B.A. Bruckner, Y. Xia, M.R. Blackburn, H. Karmouty-Quintana, Adenosine and hyaluronan modulate lung fibrosis and pulmonary hypertension in combined pulmonary fibrosis and emphysema (CPFE), Dis. Model. Mech. 12 (2019) dmm.038711, doi: 10.1242/dmm.038711.
[186] S.C. Sahu, Hyaluronic acid, Inflammation 4 (1980) 107–112, doi: 10.1007/BF00914107.
[187] F. Ferrara, G. Granata, C. Pelliccia, R. la Porta, A. Vitiello, The added value of pirfenidone to fight inflammation and fibrotic state induced by SARS-CoV-2, Eur. J. Clin. Pharmacol. 76 (2020) 1615–1618, doi: 10.1007/s00228-020-02947-4.
[188] S. Seifirad, Pirfenidone: a novel hypothetical treatment for COVID-19, Med. Hypotheses 144 (2020) 110005, doi: 10.1016/j.mehy.2020.110005.
[189] H. Ogata, T. Nakagawa, S. Sakoda, A. Ishimatsu, K. Taguchi, M. Kadowaki, A. Moriwaki, M. Yoshida, Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019, Respirol. Case Rep. 9 (2021), doi: 10.1002/rcr2.744.
[190] H. Shen, N. Zhang, Y. Liu, X. Yang, Y. He, Q. Li, X. Shen, Y. Zhu, Y. Yang, The interaction between pulmonary fibrosis and COVID-19 and the application of related anti-fibrotic drugs, Front. Pharmacol. 12 (2022) 805535, doi: 10.3389/fphar.2021.805535.
[191] Y. Umemura, Y. Mitsuyama, K. Minami, T. Nishida, A. Watanabe, N. Okada, K. Yamakawa, K. Nochioka, S. Fujimi, Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: an interventional study, Int. J. Infect. Dis. 108 (2021) 454–460, doi: 10.1016/j.ijid.2021.05.055.
[192] A. Kultti, S. Pasonen-Seppänen, M. Jauhiainen, K.J. Rilla, R. Kärnä, E. Pyöriä, R.H. Tammi, M.I. Tammi, 4-Methylumbelliferone inhibits hyaluronan synthesis by depletion of cellular UDP-glucuronic acid and downregulation of hyaluronan synthase 2 and 3, Exp. Cell. Res. 315 (2009) 1914–1923, doi: 10.1016/j.yexcr.2009.03.002.
[193] C.L. Mahaffey, M.E. Mummert, Hyaluronan synthesis is required for IL-2-mediated T cell proliferation, J. Immunol. 179 (2007) 8191–8199, doi: 10.4049/jimmunol.179.12.8191.
[194] N. Nagy, T. Freudenberger, A. Melchior-Becker, K. Röck, M. ter Braak, H. Jastrow, M. Kinzig, S. Lucke, T. Suvorava, G. Kojda, A.A. Weber, F. Sörgel, B. Levkau, S. Ergün, J.W. Fischer, Inhibition of Hyaluronan Synthesis Accelerates Murine Atherosclerosis, Circulation 122 (2010) 2313–2322, doi: 10.1161/CIRCULATIONAHA.110.972653.
[195] H. Ponta, L. Sherman, P.A. Herrlich, CD44: from adhesion molecules to signalling regulators, Nat. Rev. Mol. Cell Biol. 4 (2003) 33–45, doi: 10.1038/nrm1004.
[196] W. Huber, V.J. Carey, S. Davis, K.D. Hansen, M. Morgan, The Bioconductor channel in F1000Research, F1000Res (2016) https://f1000research.com/articles/4-217 .
[197] I. Kakizaki, K. Kojima, K. Takagaki, M. Endo, R. Kannagi, M. Ito, Y. Maruo, H. Sato, T. Yasuda, S. Mita, K. Kimata, N. Itano, A Novel Mechanism for the Inhibition of Hyaluronan Biosynthesis by 4-Methylumbelliferone, J. Biol. Chem. 279 (2004) 33281–33289, doi: 10.1074/jbc.M405918200.
[198] D. Vigetti, M. Rizzi, M. Viola, E. Karousou, A. Genasetti, M. Clerici, B. Bartolini, V.C. Hascall, G. de Luca, A. Passi, The effects of 4-methylumbelliferone on hyaluronan synthesis, MMP2 activity, proliferation, and motility of human aortic smooth muscle cells, Glycobiology 19 (2009) 537–546, doi: 10.1093/glycob/cwp022.
[199] N. Nagy, I. Gurevich, H.F. Kuipers, S.M. Ruppert, P.L. Marshall, B.J. Xie, W. Sun, A. v Malkovskiy, J. Rajadas, M. Grandoch, J.W. Fischer, A.R. Frymoyer, G. Kaber, P.L. Bollyky, 4-Methylumbelliferyl glucuronide contributes to hyaluronan synthesis inhibition, J. Biol. Chem. 294 (2019) 7864–7877, doi: 10.1074/jbc.RA118.006166.
[200] R. McKallip, H. Hagele, O. Uchakina, Treatment with the hyaluronic acid synthesis inhibitor 4-methylumbelliferone suppresses SEB-induced lung inflammation, Toxins (Basel) 5 (2013) 1814–1826, doi: 10.3390/toxins5101814.
[201] S.R. Reeves, K.A. Barrow, L.M. Rich, M.P. White, N.J. Shubin, C.K. Chan, I. Kang, S.F. Ziegler, A.M. Piliponsky, T.N. Wight, J.S. Debley, Respiratory syncytial virus infection of human lung fibroblasts induces a hyaluronan-enriched extracellular matrix that binds mast cells and enhances expression of mast cell proteases, Front. Immunol. 10 (2020) 3159, doi: 10.3389/fimmu.2019.03159.
[202] E. Arai, Y. Nishida, J. Wasa, H. Urakawa, L. Zhuo, K. Kimata, E. Kozawa, N. Futamura, N. Ishiguro, Inhibition of hyaluronan retention by 4-methylumbelliferone suppresses osteosarcoma cells in vitro and lung metastasis in vivo, Br. J. Cancer 105 (2011) 1839–1849, doi: 10.1038/bjc.2011.459.
[203] S.D. Collum, J.G. Molina, A. Hanmandlu, W. Bi, M. Pedroza, T.C.J. Mertens, N. Wareing, W. Wei, C. Wilson, W. Sun, J. Rajadas, P.L. Bollyky, K.M. Philip, D. Ren, R.A. Thandavarayan, B.A. Bruckner, Y. Xia, M.R. Blackburn, H. Karmouty-Quintana, Adenosine and hyaluronan modulate lung fibrosis and pulmonary hypertension in combined pulmonary fibrosis and emphysema (CPFE), Dis. Model Mech. (2019), doi: 10.1242/dmm.038711.
[204] N. Nagy, H.F. Kuipers, A.R. Frymoyer, H.D. Ishak, J.B. Bollyky, T.N. Wight, P.L. Bollyky, 4-Methylumbelliferone treatment and hyaluronan inhibition as a therapeutic strategy in inflammation, autoimmunity, and cancer, Front. Immunol. 6 (2015) https://www.frontiersin.org/articles/10.3389/fimmu.2015.00123 .
[205] N. Nagy, G. Kaber, P.Y. Johnson, J.A. Gebe, A. Preisinger, B.A. Falk, V.G. Sunkari, M.D. Gooden, R.B. Vernon, M. Bogdani, H.F. Kuipers, A.J. Day, D.J. Campbell, T.N. Wight, P.L. Bollyky, Inhibition of hyaluronan synthesis

restores immune tolerance during autoimmune insulitis, J. Clin. Investigat. 125 (2015) 3928–3940, doi: 10.1172/JCI79271.

[206] P.L. Marshall, N. Nagy, G. Kaber, G.L. Barlow, A. Ramesh, B.J. Xie, M.H. Linde, N.L. Haddock, C.A. Lester, Q.-.L. Tran, C.R. de Vries, A. Hargil, A. v Malkovskiy, I. Gurevich, H.A. Martinez, H.F. Kuipers, K. Yadava, X. Zhang, S.P. Evanko, J.A. Gebe, X. Wang, R.B. Vernon, C. de la Motte, T.N. Wight, E.G. Engleman, S.M. Krams, E.H. Meyer, P.L. Bollyky, Hyaluronan synthesis inhibition impairs antigen presentation and delays transplantation rejection, Matrix Biol. 96 (2021) 69–86, doi: 10.1016/j.matbio.2020.12.001.

[207] Y. Yoshioka, E. Kozawa, H. Urakawa, E. Arai, N. Futamura, L. Zhuo, K. Kimata, N. Ishiguro, Y. Nishida, Suppression of Hyaluronan Synthesis Alleviates Inflammatory Responses in Murine Arthritis and in Human Rheumatoid Synovial Fibroblasts, Arthritis Rheum. 65 (2013) 1160–1170, doi: 10.1002/art.37861.

[208] P. Walter, W. Seidel, [Studies on the effect of 4-methylumbelliferon (Hymecromone) in patients following surgical revision of the biliary pathways], Chirurg 50 (1979) 436–440.

[209] S. Quaranta, S. Rossetti, E. Camarri, [Double-blind clinical study on hymecromone and placebo in motor disorders of the bile ducts after cholecystectomy], Clin. Ter. 108 (1984) 513–517.

[210] E. Camarri, G. Marchettini, [Hymecromone in the treatment of symptoms following surgery of the bile ducts], Recenti Prog. Med. 79 (1988) 198–202.

[211] R.M. Hoffmann, G. Schwarz, C. Pohl, D.J. Ziegenhagen, W. Kruis, [Bile acid-independent effect of hymecromone on bile secretion and common bile duct motility], Dtsch. Med. Wochenschr. 130 (2005) 1938–1943, doi: 10.1055/s-2005-872606.

[212] E. Trabucchi, C. Baratti, A. Centemero, M. Zuin, E. Rizzitelli, R. Colombo, Controlled study of the effects of tiropramide on biliary dyskinesia, Pharmatherapeutica 4 (1986) 541–550.

[213] H.W. Krawzak, H.P. Heistermann, K. Andrejewski, G. Hohlbach, Postprandial bile-duct kinetics under the influence of 4-methylumbelliferone (hymecromone), Int. J. Clin. Pharmacol. Ther. 33 (1995) 569–572.

[214] S. Takeda, M. Aburada, The choleretic mechanism of coumarin compounds and phenolic compounds, J. Pharmacobiodyn. 4 (1981) 724–734, doi: 10.1248/bpb1978.4.724.

[215] E.R. Garretta, J. Venitz, Comparisons of Detections, Stabilities, and Kinetics of Degradation of Hymecromone and Its Glucuronide and Sulfate Metabolites, J. Pharm. Sci. 83 (1994) 115–116, doi: 10.1002/jps.2600830128.

[216] E.R. Garrett, J. Venitz, K. Eberst, J.J. Cerda, Pharmacokinetics and bioavailabilities of hymecromone in human volunteers, Biopharm. Drug Dispos. 14 (1993) 13–39, doi: 10.1002/bdd.2510140103.

[217] A. Abate, V. Dimartino, P. Spina, P.L. Costa, C. Lombardo, A. Santini, M. del Piano, P. Alimonti, Hymecromone in the treatment of motor disorders of the bile ducts: a multicenter, double-blind, placebo-controlled clinical study, Drugs Exp. Clin. Res. 27 (2001) 223–231.

[218] S. Yang, Y. Ling, F. Zhao, W. Li, Z. Song, L. Wang, Q. Li, M. Liu, Y. Tong, L. Chen, D. Ru, T. Zhang, K. Zhou, B. Zhang, P. Xu, Z. Yang, W. Li, Y. Song, J. Xu, T. Zhu, F. Shan, W. Yu, H. Lu, Hymecromone: a clinical prescription hyaluronan inhibitor for efficiently blocking COVID-19 progression, Signal Transduct. Target Ther. 7 (2022) 91, doi: 10.1038/s41392-022-00952-w.

[219] B.K. Rubin, Expectorants Mucolytics, Mucokinetic Medications, Respir. Care 52 (2007) 859–865 https://rc.rcjournal.com/content/52/7/859 .

[220] M. Wilkinson, K. Sugumar, S.J. Milan, A. Hart, A. Crockett, I. Crossingham, Mucolytics for bronchiectasis, Cochrane Database Syst. Rev. 2018 (2014), doi: 10.1002/14651858.CD001289.pub2.

[221] M.O. Henke, F. Ratjen, Mucolytics in cystic fibrosis, Paediatr. Respir. Rev. 8 (2007) 24–29, doi: 10.1016/j.prrv.2007.02.009.

[222] D.F. Rogers, Mucoactive agents for airway mucus hypersecretory diseases, Respir. Care 52 (2007) 1176–1197 https://rc.rcjournal.com/content/52/9/1176 .

[223] L. Máiz Carro, M.A. Martínez-García, Use of Hyaluronic Acid (HA) in chronic airway diseases, Cells 9 (2020) 2210, doi: 10.3390/cells9102210.

[224] G. Petrigni, L. Allegra, Aerosolised hyaluronic acid prevents exercise-induced bronchoconstriction, suggesting novel hypotheses on the correction of matrix defects in asthma, Pulm. Pharmacol. Ther. 19 (2006) 166–171, doi: 10.1016/j.pupt.2005.03.002.

[225] M.L. Furnari, L. Termini, G. Traverso, S. Barrale, M.R. Bonaccorso, G. Damiani, C. lo Piparo, M. Collura, Nebulized hypertonic saline containing hyaluronic acid improves tolerability in patients with cystic fibrosis and lung disease compared with nebulized hypertonic saline alone: a prospective, randomized, double-blind, controlled study, Ther. Adv. Respir. Dis. 6 (2012) 315–322, doi: 10.1177/1753465812458984.

[226] M. Ros, R. Casciaro, F. Lucca, P. Troiani, E. Salonini, F. Favilli, S. Quattrucci, D. Sher, B.M. Assael, Hyaluronic acid improves the tolerability of hypertonic saline in the chronic treatment of cystic fibrosis patients: a multicenter, randomized, controlled clinical trial, J. Aerosol. Med. Pulm. Drug Deliv. 27 (2014) 133–137, doi: 10.1089/jamp.2012.1034.

[227] A. Macchi, P. Castelnuovo, P. Terranova, E. Digilio, Effects of sodium hyaluronate in children with recurrent upper respiratory tract infections: results of a randomised controlled study, Int. J. Immunopathol. Pharmacol. 26 (2013) 127–135, doi: 10.1177/039463201302600112.

[228] J. Cantor, S. Ma, G. Turino, A pilot clinical trial to determine the safety and efficacy of aerosolized hyaluronan as a treatment for COPD, Int. J. Chron. Obstruct. Pulmon. Dis. 12 (2017) 2747–2752, doi: 10.2147/COPD.S142156.

[229] F. Galdi, C. Pedone, C.A. McGee, M. George, A.B. Rice, S.S. Hussain, K. Vijaykumar, E.R. Boitet, G.J. Tearney, J.A. McGrath, A.R. Brown, S.M. Rowe, R.A. Incalzi, S. Garantziotis, Inhaled high molecular weight hyaluronan ameliorates respiratory failure in acute COPD exacerbation: a pilot study, Respir. Res. 22 (2021) 30, doi: 10.1186/s12931-020-01610-x.

[230] Z. Cui, J. Liao, N. Cheong, C. Longoria, G. Cao, H.M. DeLisser, R.C. Savani, The Receptor for Hyaluronan-Mediated Motility (CD168) promotes inflammation and fibrosis after acute lung injury, Matrix Biol. 78−79 (2019) 255–271, doi: 10.1016/j.matbio.2018.08.002.

[231] A. Zaman, Z. Cui, J.P. Foley, H. Zhao, P.C. Grimm, H.M. DeLisser, R.C. Savani, Expression and role of the hyaluronan receptor RHAMM in inflammation after bleomycin injury, Am. J. Respir. Cell Mol. Biol. 33 (2005) 447–454, doi: 10.1165/rcmb.2004-0333OC.

[232] G. Hutás, É. Bajnok, I. Gál, A. Finnegan, T.T. Glant, K. Mikecz, CD44-specific antibody treatment and CD44 deficiency exert distinct effects on leukocyte recruitment in experimental arthritis, Blood 112 (2008) 4999–5006, doi: 10.1182/blood-2008-04-150383.