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GALECTIN-3 AND SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Selected Research*

On the comprehensive approach and use of modified citrus pectin in the setting of Coronavirus Disease 2019.

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ABSTRACT

Coronavirus disease 2019 (COVID-19), the global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has resulted thus far in greater than 1 million deaths worldwide. The disease pathogenesis remains unclear, and treatment options currently are very limited. One underreported factor that may be very relevant to COVID-19 prevention or treatment is the carbohydrate-binding protein Galectin-3 (Gal-3). This lectin plays deleterious roles in at least three major stages of the COVID-19 disease process. First, a key domain in the spike protein of SARS-CoV2 has been shown to bind *N*-acetylneuraminic acid (Neu5Ac), a process that may be necessary to cell entry by the virus. This Neu5Ac-binding domain shares striking morphological, sequence, and functional similarities with human Gal-3. Second, the major cause of death in COVID-19, referred to as the "Cytokine Storm Syndrome" (CSS), is a direct result of dysregulated immune activation following SARS-CoV2 infection and results in excess release of inflammatory cytokines, including interleukin (IL)-1, tumor necrosis factor α (TNF-α), and IL-6, by macrophages, monocytes, and dendritic cells. Single cell analysis has also shown significantly elevated levels of Gal-3 in macrophages, monocytes, and dendritic cells in patients with severe COVID-19 as compared to mild disease. Also, anti-Gal-3 therapy attenuates the secretion of IL-1, IL-6, and TNF-α from macrophages *in vitro*. Third, Gal-3 inhibition reduces transforming growth factor ß (TGF-ß) mediated pulmonary fibrosis, a likely long-term consequence for survivors of severe COVID-19. As a result, modified citrus pectin (MCP) which is a classical Gal-3 inhibitor that has well-documented anti-inflammatory and anti-fibrotic effects, may be a reasonable therapeutic strategy in the setting of COVID-19.

INTRODUCTION

Galectin 3 (Gal-3) is a carbohydrate-binding protein that regulates basic cellular functions such as cell-cell and cell-matrix interactions, growth, proliferation, differentiation, and inflammation.[1-3] It is highly expressed in myeloid cells (monocytes, macrophages, dendritic cells, neutrophils, *etc.*) and fibroblasts, as well as in epithelial and endothelial cells.[4] Once exported, Gal-3 and other galectins act as pattern recognition receptors (PRRs), as well as immunomodulators (or cytokine-like modulators) in the innate response to some infectious diseases.[5]

The roles of Gal-3 in viral infections are now beginning to become understood.[6] In human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV), Gal-3 functions as an attachment factor that facilitates viral entry into T-cells.[6] HIV infection also induces additional Gal-3 expression by activating nuclear factor kappa beta (NF-κB) dependent pathways.[7] Secreted Gal-3 then promotes a number of harmful effects. In particular, Gal-3 has been shown during infection to affect the JAK/STAT1, ERK, and AKT signaling pathways and thereby alter the pro-inflammatory cytokine profile, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1ß, and IL-6, as well as other cytokines.[8] Both toll-like receptor 4 (TLR4) and NF-κB dependent pathways are activated by Gal-3,[9, 10] which is especially relevant in inflammation caused by infection.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is a deadly illness that has already claimed over 1 million lives. In severe COVID-19, patients display highly elevated levels of Gal-3, TNF-α, IL-1ß, and IL-6 compared to those with moderate disease.[11, 12] Inhibition of Gal-3 significantly reduces the levels of these cytokines, implying that it may be able to lower the inflammatory sequelae associated with COVID-19.[12-14]

Currently there is no effective standard of care for treatment of COVID-19, and thus there is immediate need to find effective therapies. This white paper highlights three mechanisms by which Gal-3 inhibition may be a therapeutic target in COVID-19: namely, protection against viral adhesion, cytokine storm syndrome (CSS), and pulmonary fibrosis. As a corollary, this suggests that the classical Gal-3 inhibitor, modified citrus pectin[15] (MCP, PectaSol-C, ecoNugenics, Santa Rosa, CA), would be a reasonable therapeutic strategy in the setting of COVID-19.

SARS-CoV2: host cell attachment and entry

A crucial step before viral infection is the entry of the virus into host cells, which in SARS-CoV2 is mediated by the S1 subunit of the spike protein.[16] Within coronaviridae, the S1 protein consists of two distinct regions: the C-terminal domain (CTD) and N-terminal domain (NTD).[17] Typically, the CTD binds peptide receptors and the NTD binds sugar receptors.[17] Examination of the main entry mechanism of SARS-CoV2 has focused on the CTD binding to angiotensin converting enzyme 2 (ACE2) receptors,[18] and until recently, little attention has been paid to the role of the NTD. However, novel *in vitro* research indicates that SARS-CoV2 also binds *N*-acetylneuraminic acid (Neu5Ac), and this interaction is mediated by the NTD of the S1 subunit.[19] This finding supports previous *in silico* studies which have hypothesized that a Neu5Ac binding site exists.[20] Multiple coronaviruses that are infectious to humans, particularly those of the bovine coronavirus family, gain entry by way of binding of sialic acids by the NTD.[21] In addition, middle eastern respiratory syndrome coronavirus (MERS-CoV), which holds many similarities to SARS-CoV2, also exhibits dual attachment functionality, where the CTD binds a peptide receptor and the NTD binds sialic acids.[22] Depletion of cell surface sialic acids by neuraminidase inhibitors prevented MERS-CoV entry of Calu-3 human airway cells.[22] Also, SARS-CoV2 cell entry was completely inhibited by a neutralizing antibody against the S1-NTD.[23] This demonstrates that the NTD region is necessary for viral entry and a promising therapeutic target.[23] The dual mechanism by which SARS-CoV2 may enter host cells is seen in Figure 1.

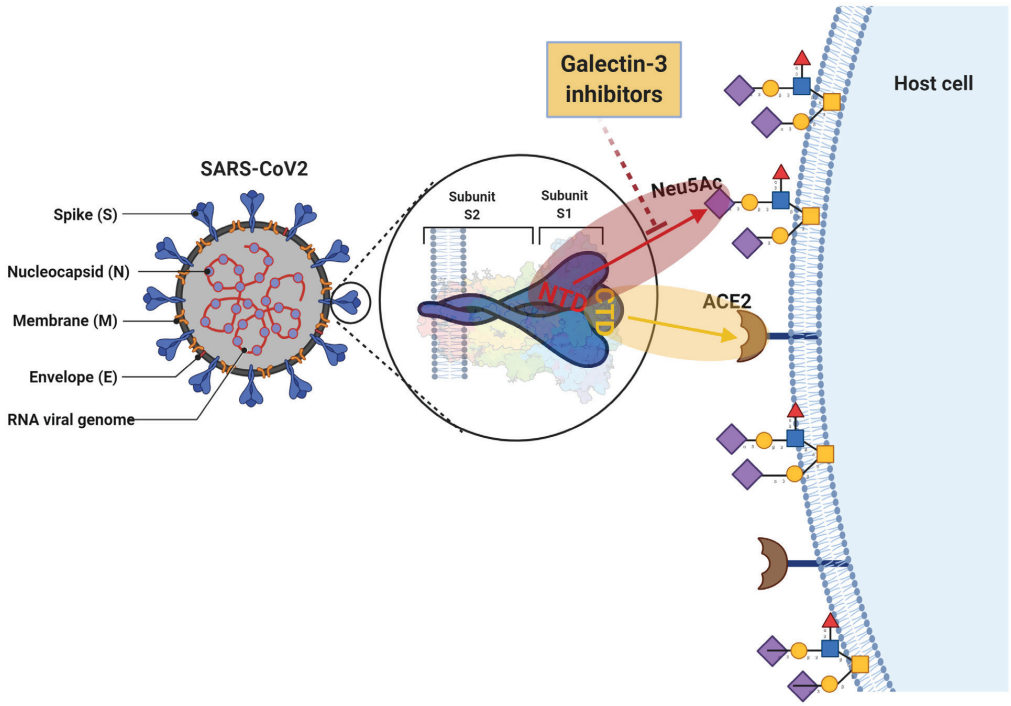

Figure 1. A dual attachment model for SARS-CoV2. Evidence has shown that a pocket in the NTD of SARS-CoV2 is capable of binding Neu5Ac. This strongly supports a dual attachment model for SARS-CoV2, where NTD-Neu5Ac interactions facilitate initial host cell recognition by the virus and stabilize its entry via ACE2 receptors.

The binding of Neu5Ac may also account for the greater communicability of SARS-CoV2 in relation to SARS-CoV.[24] Although the CTD of SARS-CoV2 has a higher affinity for ACE2 receptors compared to that of SARS-CoV, this cannot entirely explain the large difference in transmissibility.[25] THE NTD of SARS-CoV2 and the NTD of other coronaviruses have been compared to each other and also to human galectins.[20] Even though SARS-CoV2 and SARS-CoV have 74.8% similarity in the CTD, the similarity in the NTD region is just 52.7%.[20] Moreover, although SARS-CoV2 can bind Neu5Ac *in vitro*, the same domain on SARS-CoV does not have this ability;[19] *in silico* studies have noted similar results.[20] The high communicability of SARS-CoV2 may be understood by the much greater abundance of Neu5Ac in the human body as compared to ACE2 receptors, especially at common viral entry points such as the nasopharynx and oral mucosa.[26]

Research has identified a "galectin fold" present on the NTD of coronaviruses.[17, 20, 22, 27-29] Indeed, the structures of Gal-3 and the S1-NTD of betacoronaviridae are so similar that it is hypothesized that coronaviruses incorporated a host galectin gene into their genome (and then the NTD) at some point in their evolution.[21, 30] The structural similarity between the SARS-CoV2 NTD and Gal-3 is very high, with a *Z*-score of 6 ($p < 0.00001$).[20] Considering both sequence and structure, human Gal-3 is as similar to the SARS-CoV2 NTD as the NTD of NL63-CoV and infectious bronchitis coronavirus.[20] A possible inference is that the classical Gal-3 inhibitor MCP[15] could possess dual-binding capabilities. This would help to reduce viral entry into host cells.[31]

Gal-3 in severe infection: promoting immunologic sequelae of COVID-19

The primary cause of death in SARS-CoV and MERS-CoV infection was CSS,[32] and it is likely to be the case for COVID-19 as well.[33] CSS is the result of a hyper-activated state of macrophages, monocytes, and dendritic cells, which are stimulated to secrete multiple inflammatory mediators including IL-1, IL-6, and TNF-α. Systemic organ dysfunction then follows, which can result in death.[34] An evaluation of roughly 4000 patients observed that circulating levels of IL-1, IL-6, and TNF-α were significantly elevated in the sera of patients with severe COVID-19 as compared to those with mild disease.[11] In another cohort of over 1500 COVID-19 patients, serum IL-6 and TNF-α were independent predictors of disease severity and mortality.[35] Thus there is immediate need to find therapeutics that can lower the incidence and severity of CSS.

Gal-3 inhibition is likely to be an excellent anti-CSS therapy, particularly because of its ability to treat or prevent acute respiratory distress syndrome (ARDS). CSS can often evolve to ARDS, which may result in respiratory failure even when proactive measures such as mechanical ventilation and intubation are employed.[36] Higher levels of Gal-3 are significantly associated with disease severity and worse outcomes in ARDS patients.[37] Moreover, patients with severe COVID-19 have higher circulating levels of Gal-3 in relation to those with mild disease.[12] Additionally, Gal-3 was most elevated in immune cells during severe COVID-19.[13] Infected macrophages, monocytes, and dendritic cells, which are the cells that trigger CSS, had the highest levels of Gal-3.[14] A pathway through which Gal-3 may contribute to the development of CSS is described in Figure 2.

The effects of Gal-3 inhibition on cytokine release are well documented.[9, 38-40] Gal-3 silencing lowers the secretion of IL-1, IL-6, and TNF-α secretion by dendritic cells.[38] In models of traumatic brain injury and spinal cord injury, treatment with a Gal-3 inhibitor or with anti-Gal-3 antibodies both significantly lower circulating levels of IL-1, IL-6, and TNF-α.[9, 40] Furthermore, Gal-3 knockout (KO) reduces both NF-κB activation and HIV viral replication in infected cells.[7] Finally, in mice infected with H5N1 virus, Gal-3 KO increases survival rate and reduces IL-1ß secretion by macrophages.[39] These results can be explained by Gal-3's role as an alarmin of the innate immune system, responding to infection or other inflammatory insults by initiating the secretion of inflammatory cytokines, such as TNF-α and IL-6, from monocyte-derived cells.[9, 41] Both TLR4 and NF-κB dependent pathways probably mediate this augmented release of cytokines. In summary, anti-Gal-3 therapy is expected to lower the incidence and symptoms of CSS.

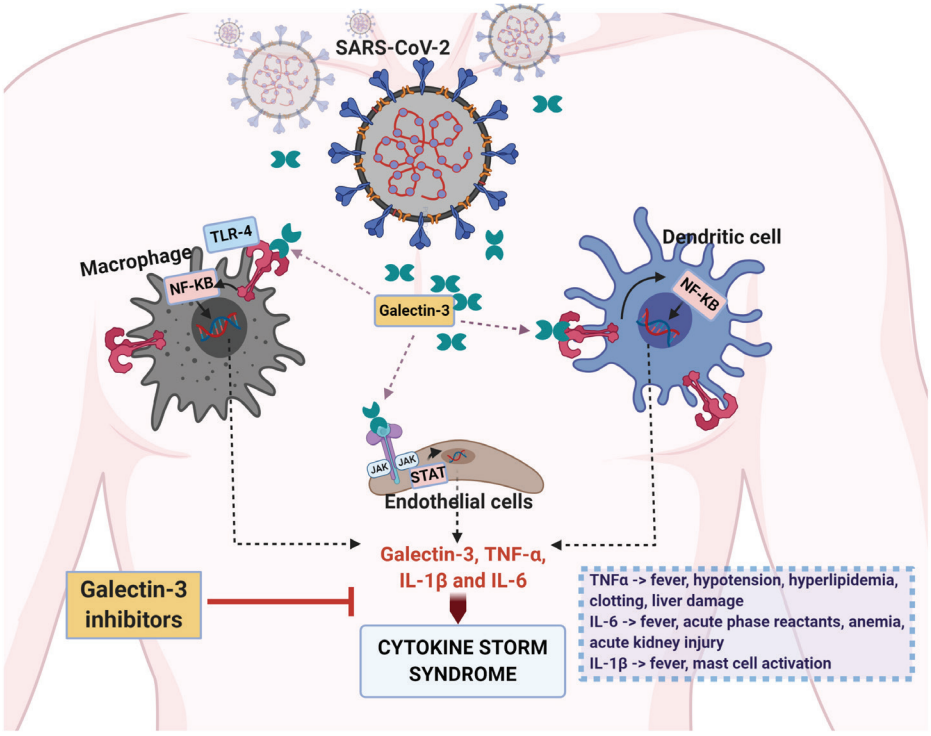

Figure 2. Gal-3 may amplify the cytokine storm associated with severe COVID-19. During severe SARS-CoV2 infection, increased plasma concentrations of Gal-3 are observed in circulating macrophages, monocytes, and dendritic cells. When secreted, Gal-3 can then agonize toll-like receptor 4 (TLR4) on its surface and induce the release of inflammatory cytokines such as IL-1, IL-6, and TNF-α. This process also results in the secretion of further Gal-3, resulting in a positive feedback loop that may contribute to the development of CSS.

Gal-3 post infection: pathologic fibrosis

Even in patients who have appeared to recover from COVID 19, serious long-term symptoms may persist. In one study, 20% of individuals tested positive for SARS-CoV-2 via reverse transcriptase polymerase chain reaction (RT-PCR) more than one month after symptom onset, and 10% of the patients did not have a negative test until after 33 days had passed.[42] Also, a study of patients who had recovered from COVID-19 found that 87.4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea, at an average of 60.3 days post infection.[43] For some, chronic post-viral inflammation could lead to deleterious changes such as pulmonary fibrosis.[44] Indeed, viral infection generally increases the risk of idiopathic pulmonary fibrosis.[45] Thus, some experts have suggested that anti-fibrotic therapy would be beneficial for patients with COVID-19.[46]

In prolonged SARS-CoV infection, marked pulmonary fibrosis was observed, especially in those with comorbid ARDS.[47] Although long-term outcomes are not available at the moment for COVID-19, similar changes in the acute phase have been shown in lung tissue: after a 24 hour SARS-CoV2 infection, human airway cells showed increased mRNA of ACE2, vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF), fibronectin (FN), and transforming growth factor ß (TGF-ß).[48] These changes were also found in lung tissues from lung fibrosis patients. It is hypothesized that many patients suffering from COVID-19 will eventually develop pulmonary fibrosis, and this will be mediated by several cytokines including TGF-ß, IL-1, IL-6, and TNF-α.[49]

Gal-3 has long been studied as a causal factor in lung fibrosis ever since its levels were found to be elevated in alveolar macrophages following lung injury.[50,51] Elevated Gal-3 is now associated with restrictive lung disease and interstitial lung abnormalities.[52] After cellular stress, Gal-3 is released from macrophages and upregulates TGF-ß receptors on fibroblasts and myofibroblasts.[53] The newly activated cells then begin the formation of granulation tissue (via collagen deposition) that is eventually remodeled to a fibrous scar.[53,54] This pathway exists throughout the body and is indispensable to fibrotic alterations in the liver, kidneys, and heart as well.[55] Gal-3 mediated fibrosis often has undesirable effects. For example, pathologic scar formation is the

likely cause of the increased mortality and heart failure that are observed post-myocardial infarction.[56] The mechanism by which Gal-3 may contribute to post-infectious pulmonary fibrosis in COVID-19 can be seen in Figure 3.

Anti-Gal-3 therapy could be effective in attenuating fibrotic change following lung injury. In a model of adenovirus induced lung injury, genetic deletion of Gal-3 lowered lung fibrosis via interruption of TGF-ß signaling.[54] In addition, pharmacologic inhibition of Gal-3 attenuated bleomycin-induced pulmonary fibrosis.[54] MCP, a natural polysaccharide extracted from citrus plants, is a classical Gal-3 inhibitor[15] that has been used safely for over 20 years. Although MCP has not yet been studied in lung fibrosis, it has shown tremendous effect in fibrosis of the heart,[57] kidney,[58] liver,[59] and adipose tissue.[60]

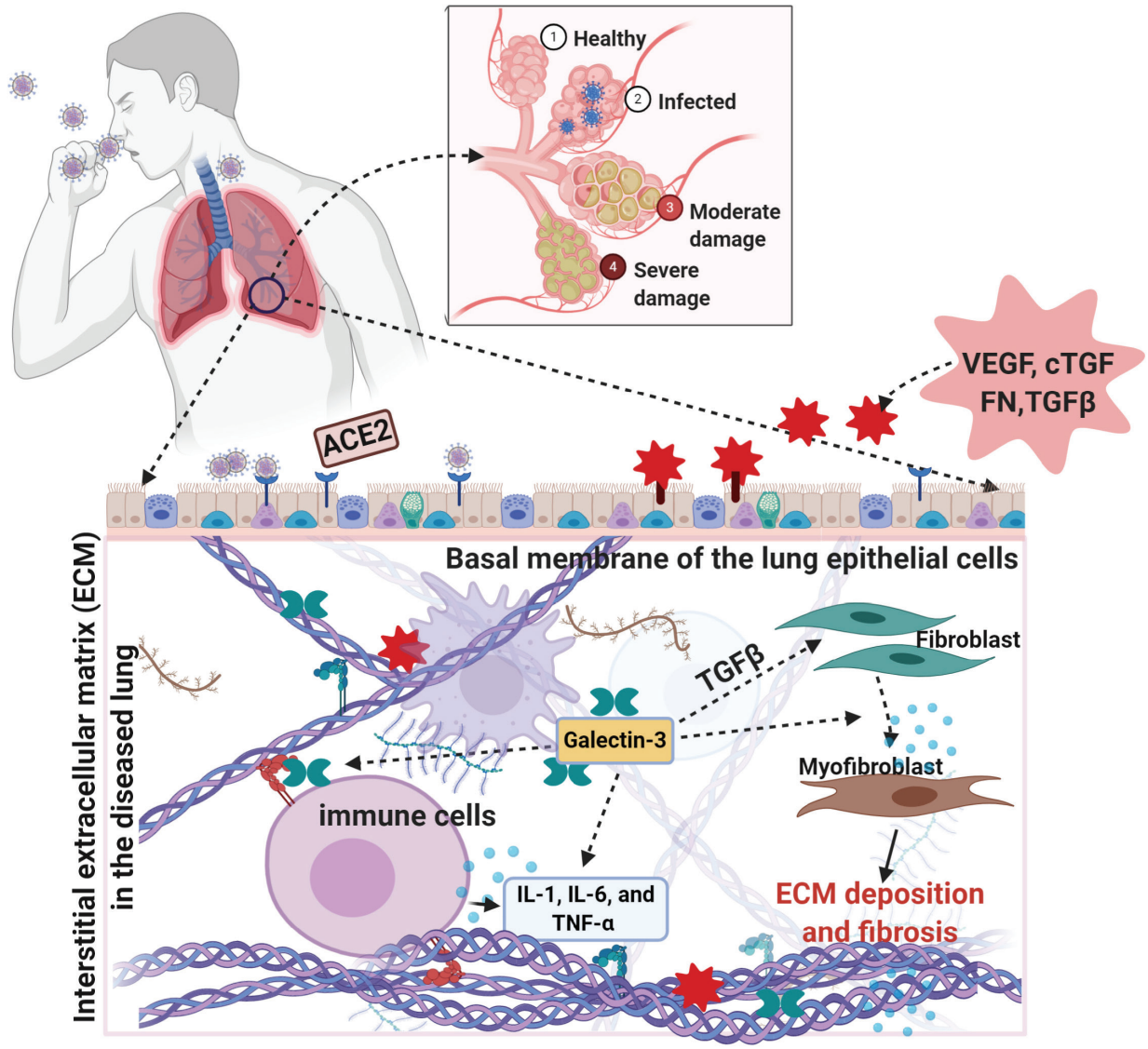

Figure 3. Gal-3 contributes to a pro-fibrotic microenvironment in COVID-19. During SARS-CoV2 infection, transcriptional upregulation of VEGF, TGF-ß, and FN is seen in the pulmonary epithelium, creating a pro-fibrotic microenvironment. Secretion of Gal-3 by macrophages contributes to fibrosis by increasing the expression of TGF-ß receptors on the surface of fibroblasts. The fibroblasts and myofibroblasts are then activated by TGF-ß mediated signaling, stimulating the deposition of extracellular matrix and collagen that leads to fibrotic damage. Cytokines induced by Gal-3 expression such as IL-1, IL-6, and TNF-α further accelerate this process.

SUMMARY

In summary, Gal-3 is a lectin that has multifaceted roles in both the short- and long-term consequences of infection and inflammation. New research demonstrates that Gal-3 is upregulated in COVID-19 patients.[12-14] A key domain in the spike protein of SARS-CoV2 has a great degree of morphological and sequence similarity to human Gal-3.[20] This NTD has been demonstrated to bind Neu5Ac *in vitro*, suggesting that it may be necessary for cell entry.[19, 24, 26] Gal-3 inhibitors that target regions of structural overlap with the NTD may exhibit dual binding capabilities, which would be a novel mechanism for preventing viral entry.[31]

On a cellular level, Gal-3 is most highly expressed in monocytes, macrophages, and dendritic cells during severe COVID-19 infection.[14] The main cause of death in COVID-19 is CSS with comorbid ARDS,[16, 33, 48] and elevated circulating Gal-3 level is directly associated with worse outcomes and lower survival in ARDS patients.[37] CSS is principally caused by the secretion of IL-1, IL-6, and TNF-α from macrophages, monocytes, and dendritic cells.[33] Anti-Gal-3 therapy lowers the secretion of these cytokines from immune cells.[9, 38, 40]

Finally, it is expected that longer-term research will reveal cytokine-mediated pulmonary fibrosis to be a major complication of survivors of COVID-19.[47, 49, 61] Among the cytokines, TGF-ß is anticipated to play a major role in this pathological process.[48] In response to injury, Gal-3 released by macrophages upregulates TGF-ß receptors, resulting in fibroblast activation and collagen deposition.[49] Gal-3 inhibition has been demonstrated to attenuate adenovirus-induced lung fibrosis.[54]

Given that Gal-3 plays deleterious roles in several stages of the COVID-19 disease process, the ideal Gal-3 inhibitor would be expected to exhibit pleiotropic effects. This is undoubtedly the case for MCP.[15] Clinical studies and preclinical research on the use of MCP have noted wide-ranging benefits. Based on its anti-inflammatory and anti-fibrotic properties related to Gal-3 blockade,[15] as well as its long track record of safe use, a growing number of researcher and health practitioners are highlighting MCP as a dietary supplement that has serious potential for aiding the prevention or treatment of COVID-19.[62]

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