

Hypothesis

Not peer-reviewed version

The Extracellular Matrix is Potentially a Key Regulator in Long COVID, Hypermobility Disorders, and Related Conditions

[Rosita Dangmann](#)^{*} and [Robert Schleip](#)^{*}

Posted Date: 20 October 2026

doi: 10.20944/preprints202610.1775.v1

Keywords: extracellular matrix; long COVID; hypermobility disorders; inflammation; hypothesis



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC, OpenAlex.

Copyright: This open access article is published under a [Creative Commons CC BY 4.0 license](#), which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Hypothesis

The Extracellular Matrix is Potentially a Key Regulator in Long COVID, Hypermobility Disorders, and Related Conditions

Rosita Dangmann ^{1,*} and Robert Schleip ^{2,3,*}

¹ Ennigerloh, Germany

² Conservative and Rehabilitative Orthopaedics, TUM School of Medicine and Health, Technical University of Munich, Munich, Germany; robert.schleip@tum.de

³ Department for Medical Professions, Diploma University of Applied Sciences, Bad Sooden-Allendorf, Germany

* Correspondence: rositadangmann@googlemail.com (R.D.); robert.schleip@tum.d (R.S.); Tel.: +49-172-2314785 (R.D.)

Abstract

Long coronavirus disease (long COVID) and hypermobility disorders (e.g., hypermobile Ehlers-Danlos syndrome) often share comorbidities, including mast cell activation syndrome, small fiber neuropathy, and myalgic encephalomyelitis/chronic fatigue syndrome. The relationship between long COVID and hypermobility disorders, as well as the extracellular matrix (ECM), has been reported, with evidence suggesting that ECM alterations may underlie these associations. The current hypothesis posits that ECM alterations may become partly self-perpetuating, with the severe acute respiratory syndrome coronavirus 2 spike protein as a possible initial trigger. The proposed mechanism involves interactions among the spike protein, integrins, latent transforming growth factor β , mast cells, interleukin-6, and matrix metalloproteinase-9 (MMP-9). Possible feedback loops, such as those between latent transforming growth factor β and a stiffened ECM, increased sympathetic activity and a pro-inflammatory state, insulin resistance and a pro-inflammatory state, inflammation and mast cell migration, and increased blood–brain barrier permeability via MMP-9 and inflammation, are highlighted. The impact of the modified ECM on the nervous system, as described through PIEZO and N-methyl-D-aspartate receptors, is also discussed, alongside evidence for increased differentiation of T-helper 17 cells and their potentially disruptive effects on efferocytosis. This new hypothesis may have important implications for clinical practice and future research.

Keywords: extracellular matrix; long COVID; hypermobility disorders; inflammation; hypothesis

1. Introduction

Long coronavirus disease (long COVID) and hypermobility disorders share overlapping features and potential underlying mechanisms. Both present complex clinical pictures that require multimodal treatment approaches; thus, identifying and understanding these underlying pathological mechanisms are important. Numerous studies on long COVID and hypermobility disorders link both conditions through the extracellular matrix (ECM) [1–3]. Comorbidities associated with hypermobility disorders can overlap with those of long COVID, including musculoskeletal pain, dysautonomia with or without small fiber neuropathy (SFN), cognitive disorders, myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), and mast cell activation syndrome (MCAS). Furthermore, hypermobility spectrum disorders (HSDs) and hypermobile Ehlers-Danlos syndrome (hEDS), the most common hypermobility conditions, as well as long COVID, can present with symptoms resembling fibromyalgia, which is characterized by chronic

musculoskeletal and myofascial pain, sleep disturbances, fatigue, and neuropsychiatric disorders (e.g., anxiety and depression) [1,4]. Similarly, HSD, hEDS, and long COVID may present with post-exertional malaise; fatigue; musculoskeletal, cardiovascular (e.g., postural orthostatic tachycardia syndrome [POTS]), gastrointestinal, urogenital, immunological, pulmonary, otolaryngologic, dermatologic, reproductive, and neuropsychiatric symptoms; and multiorgan systemic dysfunction [1–3]. Logarbo et al. [3] indicated that hEDS/HSD should be considered in cases of persistent long COVID, as they observed the co-occurrence of these conditions in some cases.

HSD and hEDS are hereditary disorders that can substantially impair quality of life. However, their complex multisystemic manifestations often lead to delayed or missed diagnosis. Unlike HSD, hEDS is diagnosed according to specific criteria, including a positive Beighton score, characteristic systemic features and/or a positive family history, and chronic musculoskeletal pain and/or joint instability. Increasing evidence suggests that HSD and hEDS may not represent distinct entities, but rather lie along a phenotypic continuum and share a similar underlying pathophysiology [5]. Historically, HSD and hEDS have been considered connective tissue disorders characterized by joint hypermobility and/or instability, among other features. These characteristics highlight the potential role of the fascial system ECM in the pathogenesis of these conditions [5]. Dysregulation of fibroblast-to-myofibroblast transformation has been reported in HSD and hEDS, with a marked increase in myofibroblasts in the deep fascia. This dysregulation may contribute to persistent ECM densification and dysfunction in patients with hEDS/HSD. ECM densification is accompanied by increased matrix viscosity, reduced interfascial glide, and impaired force transmission, potentially resulting in the irritation of free nerve endings [5].

Fascial myofibroblasts have been proposed to play a mechanistic role in long COVID [1]. Fascial myofibroblasts and the ECM form a dynamic network that regulates structural tissue integrity, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can interact with the ECM [6]. Furthermore, the SARS-CoV-2 spike (S) glycoprotein triggers a transcriptional response associated with ECM reorganization and latent transforming growth factor β (TGF- β) signaling, which could lead to barrier dysfunction and vascular leak [6]. In addition, the receptor-binding domain of the S protein within its S1 region (S1-RBD) binds to recombinant human $\alpha v \beta 3$ and $\alpha v \beta 6$ integrins. Thus, S1-RBD functions as an αv -selective integrin agonist and can dysregulate the ECM [7]. Enhanced $\alpha v \beta 3$ engagement can stimulate fibroblast contractility, thereby increasing the stiffness of the soft, nonlinear elastic ECM [8]. Similarly, integrin $\alpha v \beta 6$ has been shown to bind and activate latent TGF- $\beta 1$ [9].

Serum matrix metalloproteinase-9 (MMP-9) levels are elevated in patients with long COVID, and cultured human microglia stimulated with the spike protein exhibit significantly increased MMP-9 release [10]. Increased MMP-9 levels can promote vascular inflammation and increase blood–brain barrier (BBB) permeability. MMP-9 can also influence tight junctions and disrupt neuronal connectivity, playing a vital role in neurodegenerative disorders [10]. In patients with long COVID, elevated MMP-9 levels are associated with worse disease severity [10]. MMP-9 levels in skin fibroblasts are also elevated in vitro in patients with hEDS/HSD [11]. Furthermore, elevated MMP-9 levels may be associated with autism [12,13]. The possibility of co-occurring autism should also be considered in individuals with fibromyalgia [14]. Additionally, individuals with higher sensory reactivity scores on the Ritvo Autism & Asperger Diagnostic Scale are more likely to experience long COVID symptoms lasting longer than 12 weeks [15]. Moreover, autism can be a comorbidity of hEDS/HSD [16]. In one study, in the hEDS/HSD group, autistic individuals were more likely to have co-occurring physical and mental health conditions, including attention-deficit/hyperactivity disorder, depression, anxiety, dysautonomia/POTS, ME/CFS, and MCAS, than non-autistic individuals [17].

Taken together, these findings suggest that an ECM-based model may provide a plausible explanation for the overlapping pathophysiological features commonly observed in long COVID, hypermobility disorders, and related conditions. This paper outlines a new integrated model that

explains how these conditions and their comorbidities might be interconnected. Additionally, the model uncovers potential pathological mechanisms to inform future research.

2. Hypothesis

This section is divided into three subsections. The first subsection focuses on how SARS-CoV-2 can alter the ECM (Part 1a) and on how the ECM is altered in patients with hEDS/HSD (Part 1b) (Figure 1). The second subsection integrates the potentially important roles of mast cells and MMP-9 into the hypothesis (Figure 2). The third subsection discusses the possible roles of the N-methyl-D-aspartate receptor (NMDAR), PIEZO1, PIEZO2, insulin, and vitamin D (Figure 3).

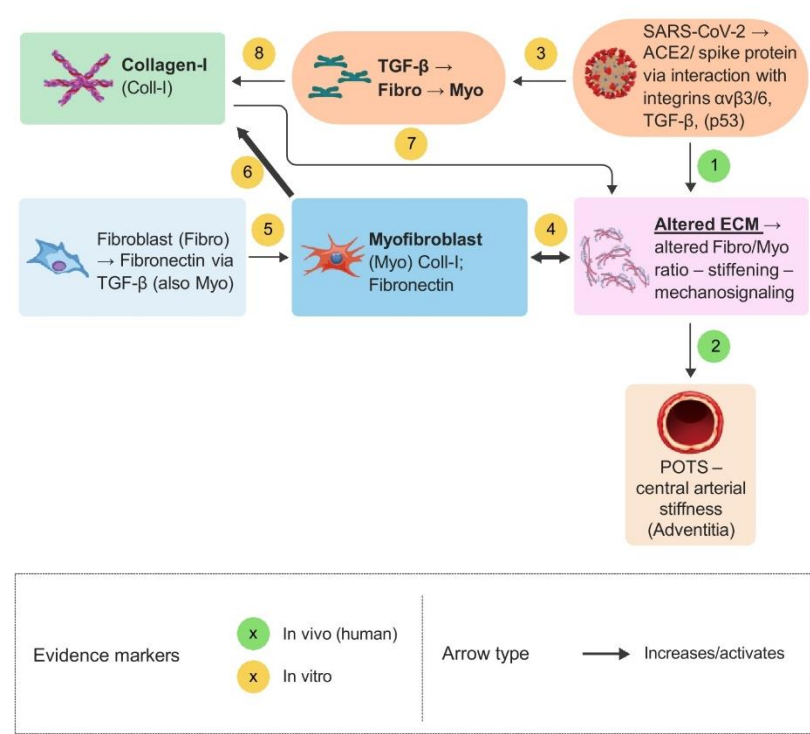


Figure 1. Illustration of the mechanisms through which SARS-CoV-2 may alter the extracellular matrix (ECM), the ECM changes observed in patients with hEDS/HSD, and potential structural links to postural orthostatic tachycardia syndrome (POTS). Latent transforming growth factor β (TGF- β) promotes fibroblast (Fibro) differentiation into myofibroblasts (Myo) and collagen type I (Coll-I) production. Both activated fibroblasts and myofibroblasts produce fibronectin in response to TGF- β . A possible positive feedback loop between an altered ECM (stiffened local areas, especially in inflamed regions) and enhanced TGF- β activation is shown (arrow 4). Arrows represent different types of interactions and are distinguished by color, line style, and shape, as indicated in the figure key. The numbers assigned to the arrows correspond to the respective descriptions and references in the main text.

2.1. Role of ECM in the Pathophysiology of SARS-CoV-2 and hEDS/HSD

2.1.1. Part 1a: SARS-CoV-2 Influences the ECM Through Multiple Pathways

Long COVID affects a broad spectrum of patients, including those with mild initial symptoms. The persistence of SARS-CoV-2 and its viral fragments has been suggested as a potential contributor to long COVID [18,19]. A 2020 bioinformatic study identified potential links between SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) and the integration of ACE2 into a molecular network involving TGF- β and connective tissue growth factor. Specifically, mRNA levels of TGF- β and connective tissue growth factor are elevated in lung epithelial cells following SARS-CoV-2 infection [20]. The ACE2 receptor facilitates SARS-CoV-2 entry into host cells and plays a role in the pulmonary fibrosis following COVID-19 [20]. ACE2 mRNA is also expressed at relatively high levels

in the normal, uninfected small intestine, suggesting that the small intestine may be susceptible to SARS-CoV-2 infection [20].

A 2022 *in vitro* study [6] using transcriptomic profiling of human pulmonary microvascular endothelial cells treated with soluble trimeric SARS-CoV-2 spike protein identified an upregulation of the TGF- β signaling pathway. Furthermore, the authors noted that the TGF- β signaling axis was required for spike protein-mediated dysfunction of endothelial and epithelial barriers. TGF- β is a mediator of cellular proliferation, differentiation (e.g., myofibroblast differentiation), and migration, and plays an important role in regulating vascular permeability and inflammatory responses [6,21]. TGF- β signaling may also promote tissue fibrosis, contributing to the vascular fibrosis and stiffness observed in long COVID [21,22]. This vascular stiffness may, in turn, contribute to the co-occurrence of POTS in patients with long COVID and hEDS, as increased central arterial stiffness is a feature of POTS (Figure 1, arrow 2) [23].

Norris et al. [7] demonstrated that the adhesive Arg-Gly-Asp (RGD) motif of the S1-RBD region binds to recombinant human integrins $\alpha\beta6$ and $\alpha\beta3$, offering a possible mechanism by which SARS-CoV-2 can upregulate the TGF- β pathway. Integrin $\alpha\beta6$ antibodies reduce fibrosis and TGF- β activity [24]. Notably, integrin $\alpha\beta6$ is expressed only in epithelial tissue. Upon activation of TGF- $\beta1$ and TGF- $\beta3$ by integrin $\alpha\beta6$, TGF- β may directly signal myofibroblasts to promote further ECM production (Figure 1, arrows 3 and 4) [24]. Integrin $\alpha\beta3$ can activate TGF- $\beta1$ and is involved in cardiac and skin fibrosis, as well as in aortic atherosclerosis [24–26]. Integrin $\alpha\beta3$ is typically expressed at low levels in most normal tissues, such as intestinal, vascular, and smooth muscle tissues [26]. High integrin $\alpha\beta3$ expression is mainly observed in bone, mid-cycle endometrium, placenta, sites of inflammation, and invasive tumors [26]. High integrin $\alpha\beta3$ levels can also be found in mature osteoclasts, activated macrophages, a small subset of neutrophils, angiogenic endothelial cells, and migrating smooth muscle cells [26].

Angiogenic stimuli, such as tumor necrosis factor alpha (TNF- α) and vascular endothelial growth factor (VEGF), produced by endothelial cells, induce integrin $\alpha\beta3$ expression on sprouting endothelial buds and promote the formation of new blood vessels [26]. TGF- $\beta1$ was previously shown to induce dose-dependent fibronectin synthesis during the early phase of cultured intestinal fibroblast-to-myofibroblast transformation, with peak production at 2 days in the fibroblast phase and continued production in the myofibroblast phase (Figure 1, arrow 5) [27]. A similar pattern was observed in cultured lung fibroblasts, with fibronectin production peaking at 2 days [28]. However, this experiment lasted only 2 days. Collectively, these results indicate that in long COVID, TGF- β activation, and subsequent fibroblast-to-myofibroblast differentiation and myofibroblast maintenance, may lead to changes in the ECM of certain tissues, resulting in increased stiffness (Figure 1, arrows 4 and 5) [29].

Importantly, a stiff ECM may promote TGF- β activation, thereby creating a positive feedback loop (Figure 1, arrow 4) [29] that can perpetuate inflammation and fibrosis. Mechanotransduction pathway enzymes/proteins (e.g., integrins, focal adhesion kinase, Rho-associated kinase, and Yes-associated protein) play a key role in these processes. Integrins are transmembrane receptors that serve as mechanosensors [30]. Integrins (e.g., $\alpha\beta6$) can bind to the RGD motif within the latency-associated protein (LAP) and, upon mechanical force transmission, promote the activation of TGF- β from its latent complex. Latent TGF- β binding protein (LTBP) binds to matrix proteins, such as fibrillin, proteoglycans, and fibronectin [21,29]. An extremely acidic environment may facilitate the activation of latent TGF- β [21].

A 2026 myotonometry study of four women with long COVID identified a reduction in creep (i.e., the reduced magnitude of fascial deformation over time under a constant load) in the superficial and deep fascia (Figure 1, arrow 1) [31]. The time-dependent viscoelasticity of the ECM characterizes creep behavior [32]. Fibrotic tissue is characterized by an altered ECM and a buildup of components such as fibrillar collagen type I, mediated by myofibroblasts (Figure 1, arrows 6–8) [33,34]. ECM stiffness can increase in fibrotic tissue, thereby reducing creep [35]. Regarding COVID and an altered ECM, one study reported that bleomycin-induced lung injury in mice led to perivascular fibrosis and

ECM densification (i.e., increased ECM viscosity and changes in gliding) [36]. Similar to ECM stiffness, ECM densification influences creep.

Notably, an *in silico* study suggested that the S2 subunit of SARS-CoV-2 interacts with tumor suppressor protein p53 [37], a protein implicated in fibrosis [38].

2.1.2. Part 1b: Altered ECM in hEDS/HSD Patients

Several studies of patients with hEDS/HSD have reported fascial thickening, reduced interfascial glide, altered viscoelasticity, and densification of the deep fascia, particularly in the sternocleidomastoid muscle, iliotibial tract, thoracolumbar fascia, and fascia iliaca [5,39,40]. In general, higher ECM stiffness is not commonly observed in patients with hEDS/HSD. By contrast, their tendons exhibit reduced stiffness and excessive elongation [5]. In one study, the strain index in regions with myofascial pain was higher in patients with non-hEDS than in patients with hEDS and pain or in patients with non-hEDS without back or knee pain [39]. This indicated greater fascial softening with relative muscle stiffening in patients with non-hEDS. Typically, myofascial pain involves softening of the fascia along with stiffening of the underlying muscles. However, this pattern does not apply to hEDS, where fascial stiffness in relation to muscle occurs in regions of myofascial pain instead [39]. Despite being preliminary, these data emphasize significant fascial features in hEDS [39]. Tissue-level alterations, such as excessive tendon elongation, can impair force transmission and increase the risk of subluxation and/or dislocation, leading to repetitive microtrauma [5].

Alterations in molecular pathways in hEDS/HSD include activation of Wnt/ β -catenin signaling; upregulation of miR-224, miR-378-3p, and the prolactin receptor; reduction of NR4A nuclear receptor expression; and downregulation of miR-23a, which is associated with increased Wnt/ β -catenin pathway activation [5]. Activation of canonical Wnt signaling is required for TGF- β -mediated fibrosis [41]. These changes can contribute to an inflammatory state and myofibroblast persistence, thereby leading to ECM alterations (Figure 1, arrow 4) [5]. At the cellular level, pathological dysregulation of fibroblast-to-myofibroblast transformation in hEDS/HSD, as mediated by upregulation of integrin $\alpha\beta$ 3, has been reported (Figure 1, arrow 5). The $\alpha\beta$ 3 integrin-ILK complexes and the Snail1/Slug transcription factors are involved in this fibroblast-to-myofibroblast transition in hEDS/HSD (Figure 1, arrow 5) [11].

In post-COVID-19 conditions, increased Snail expression is required for pulmonary fibrosis [42]. The spike protein can trigger an integrin $\alpha\beta$ 3 response, which can lead to Snail upregulation through various signaling pathways [7,42]. Snail can promote the expression of α -smooth muscle actin (α -SMA) with or without prior TGF- β activation, driving the transformation of fibroblasts into myofibroblasts. In patients with hEDS/HSD, 60–80% of fibroblasts express α -SMA, indicating a shift toward a pro-fibrotic ECM [5]. Furthermore, TGF- β , interleukin (IL)-6, ECM-derived danger-associated molecular patterns, fragmented fibronectin, collagen type I, and tenascin are upregulated [5]. Elastin is mislocalized to the cytoplasm rather than the ECM, potentially impairing elastogenesis [5]. Overall, a disorganized ECM is observed in hEDS/HSD. A unique fragment pattern consisting of 52 kDa fibronectin and 45 kDa collagen type I fragments was recently identified in the plasma of patients with hEDS/HSD, offering hope for a diagnostic blood test for hEDS/HSD [43].

The ECM can be divided into different structural entities, including (i) deep fascia that contains densely packed collagen bundles and elastin and (ii) thin gliding layers of loose connective tissue between individual layers of deep fascia [44]. The lamina propria is a loose connective tissue layer in direct proximity to the epithelial structures of the digestive tract and surrounding blood and lymph vessels. This loose connective tissue contains cells, such as fibroblasts and myofibroblasts, that can influence the structure and, consequently, the mechanical properties of the ECM [45]. These layers are of special interest to the hypothesis regarding hEDS/HSD, as they may be sites where densification and/or increased stiffness resulting from trauma and/or inflammation occur. The observed tendon elongation and reduced stiffness in hEDS/HSD fascia can increase the risk of traumatic injury and subsequent inflammation; this can then affect the mechanical properties of this loose connective tissue layer and help explain the observed reduced interfascial glide in hEDS/HSD.

Collectively, these findings indicate an altered ECM with potentially increased stiffness in localized areas, especially those affected by inflammation, as observed in long COVID. This altered ECM may create a positive feedback loop, as increased tissue stiffness can enhance TGF- β activation (Figure 1, arrows 4–8). A 2015 review of eight studies found elevated TGF- β levels in CFS in five (63%) studies [46]. Patients with long COVID, as well as patients with hEDS/HSD, frequently experience CFS.

2.2. Part 2: Incorporating the Potentially Important Roles of Mast Cells and MMP-9 into the Hypothesis

Mast cells are a type of white blood cell that plays a critical role in immune responses, including inflammation and allergic reactions (Figure 2, arrow 9). Mature mast cells are distributed throughout the collagenous connective tissue, between collagen bundles and elastic fibers, and near blood vessels and nerves. Mast cells are also detected in the superficial fascia, where they play modulatory roles in thermoregulation, exteroception, and pain modulation [47]. They recognize appropriate chemotactic stimuli, such as TGF- β 1–3 and TNF- α , and respond by migrating. Activated mast cells can produce chemoattractants, leading to the accumulation of mast cells and other hematopoietic cells at sites of inflammation [48]. This can result in a positive feedback loop between inflammation and mast cell migration.

MCAS is observed in both patients with hEDS/HSD and long COVID [49,50]. MCAS is associated with an increased number of mast cells, which may form clusters due to reduced cell death. This can affect multiple organs and lead to clinical symptoms, including flushing, hypotension, urticaria, angioedema, headache, vomiting, diarrhea, and anaphylaxis [49]. Common triggers in MCAS include weather changes, heat, pressure, rubbing, exercise, stress, and dietary factors (e.g., certain medications, including opiates) [50].

Furthermore, mast cells can express integrin $\alpha\text{v}\beta 3$ on their surface, which can interact with fibrin and platelet endothelial cell adhesion molecule on endothelial cells [51]. SARS-CoV-2 interacts with recombinant human $\alpha\text{v}\beta 3$ and $\alpha\text{v}\beta 6$ integrins via its S1-RBD. Consequently, SARS-CoV-2 may directly interact with mast cells via these integrins. Integrin $\alpha\text{v}\beta 3$ on the mast cell membrane functions as a true mechanosensor and can respond to stiffness [52]. Mast cells use integrin-mediated pathways to sense mechanical properties, guiding them toward regions of varying stiffness. Mechanical stimuli can alter the microscopic structure of collagen fibers, muscle bundles, nerve fibers, and vascular tracts within the ECM, enabling these structures to bind to integrins on the mast cell membrane (Figure 2, arrow 10) [53,54]. Under mechanical stimulation, integrins can transition from a bent to an extended conformation, thereby enhancing their interaction with ECM ligands (Figure 2, arrow 11) [54].

Mechanical stimulation has been shown to increase both mast cell density and degranulation rates in humans and various disease models (Figure 2, arrow 12a+b) [54,55]. Mast cell responses to mechanical signals promote fibrosis, and mechanical stretch-induced mast cell degranulation and TGF- β activation are attenuated by sodium cromoglycate, a mast cell stabilizer (Figure 2, arrow 13a+b) [54,56]. Mechanoreceptors on mast cell membranes include transient receptor potential vanilloid channel 2 (TRPV2) and adhesion G protein-coupled receptor E2 (ADGRE2). TRPV2 is highly sensitive to physical stimuli, including mechanical stress, shear forces, and thermal changes [54]. Loratadine, an antihistamine, has been shown to reduce calcium influx triggered by TRPV2. Meanwhile, ADGRE2 is activated by vibration; in human skin mast cells, this activation results in rapid histamine release (Figure 2, arrow 12b) [54].

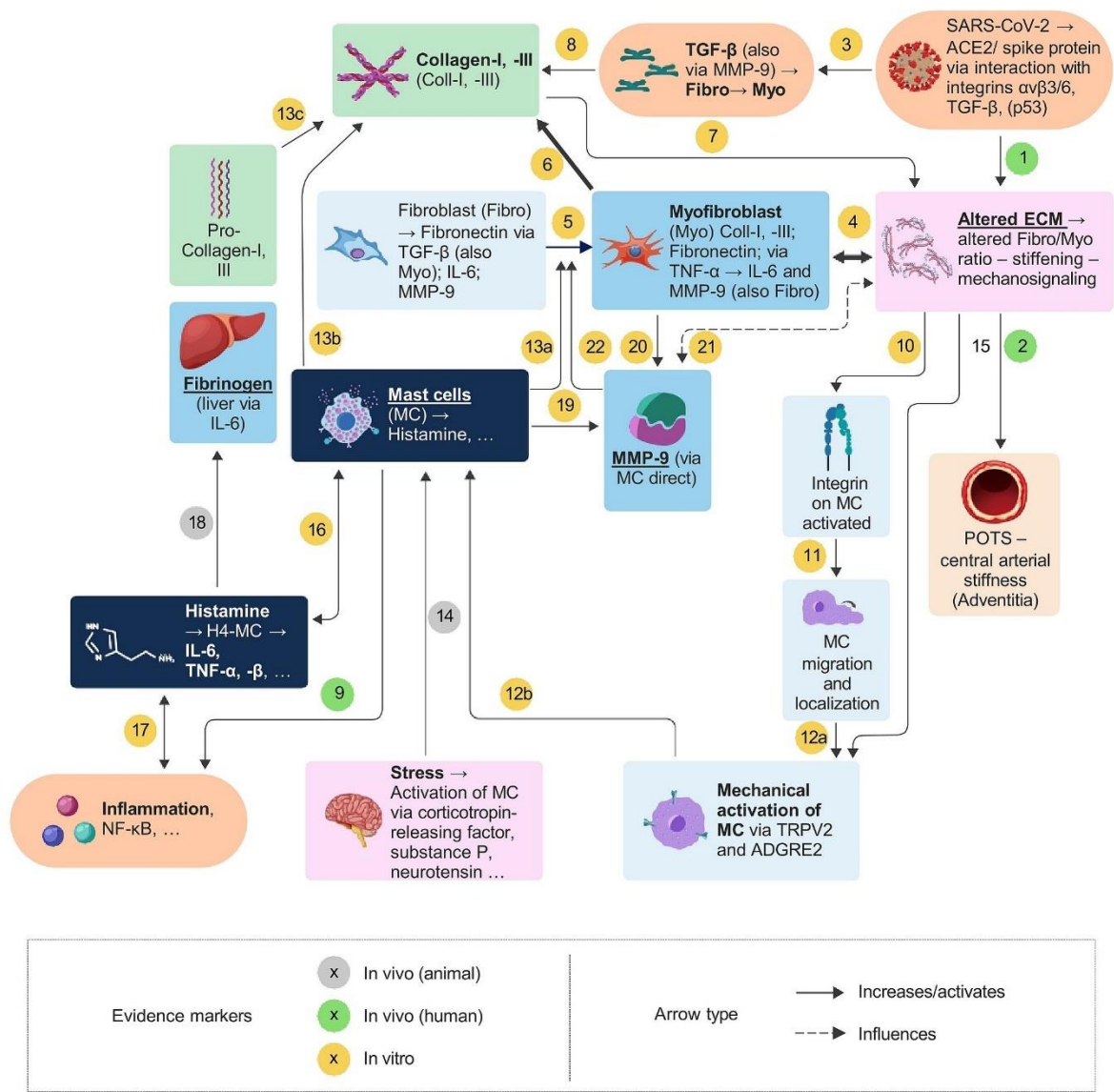


Figure 2. Influence of the altered ECM on the potentially important roles of mast cells (MCs) and matrix metalloproteinase 9 (MMP-9) within the hypothesis. Possible feedback loops involving activated mast cells and inflammation (arrows 16 and 17) are shown. The influence of mast cell mediators (e.g., interleukin-6 (IL-6) and MMP-9) on the ECM is also shown. This can form a major feedback loop, especially since the mast cell mediator tumor necrosis factor α (TNF- α) can also induce IL-6 and MMP-9 production in fibroblasts and myofibroblasts. Arrows represent different types of interactions and are distinguished by color, line style, and shape, as indicated in the figure key. The numbers assigned to the arrows correspond to the respective descriptions and references in the main text.

The mast cell Mas-related G-protein-coupled receptor member X2 (MRGPRX2) is mainly expressed by chymase⁺ cells, a specific subtype of human mast cells in connective tissues [54]. MRGPRX2 activation by substance P from mechanosensitive neurons can result in immunoglobulin E (IgE)-independent pseudo-allergic reactions (Figure2, arrow 14) [54,57,58]. In addition, activation of the mast cell receptor MRGPRX2 can result in the secretion of tryptase and chymase, among other substances. Tryptase can promote the transformation of fibroblasts into myofibroblasts, and chymase can contribute to the synthesis and secretion of collagen types I and III (Figure 2, arrow 13a, b, c) [54,56]. In an altered ECM, as in patients with long COVID and/or hEDS/HSD, mechanical stimulation of mast cells may occur more quickly and frequently (Figure 2, arrow 15).

Mast cells themselves can respond to histamine via their H4 receptor and then release inflammatory proteins, including TGF- β , TNF- α , tumor necrosis factor beta (TNF- β), IL-6, and IL-8

(Figure 2, arrows 16 and 17) [59]. IL-6 is also synthesized by macrophages and monocytes in response to other inflammatory cytokines, including TNF- β and IL-11 [60]. Increased IL-6 expression may contribute to pain in SFN when cutaneous nociceptors are damaged. In one study, incubation of murine sensory dorsal root ganglion neurons, cultured for 1 day as a model of SFN, increased action potential firing rates in response to IL-6 exposure [61]. The study also showed higher IL-6 and IL-8 expression in fibroblasts of patients with SFN, and their keratinocytes had higher netrin-1 expression. This is of interest because SFN is a comorbidity in both long COVID and hEDS/HSD.

IL-6, which is produced rapidly and transiently in response to infection and tissue injury, can trigger rapid induction of various acute-phase proteins mainly in the liver, including C-reactive protein, serum amyloid A, fibrinogen, haptoglobin, and α 1-antichymotrypsin (Figure 2, arrow 18) [60,62]. Plasma fibrinogen and haptoglobin have been identified as promising biomarkers for assessing disease severity and mortality risk in long COVID [63]. Fibrinogen is cleaved by thrombin, forming fibrin. Fibrin binds to the SARS-CoV-2 spike protein, forming pro-inflammatory blood clots that drive systemic thromboinflammation and neuropathology in COVID-19 [64]. After infection, fibrin promotes neuroinflammation and neuronal loss, suppresses natural killer cells, and activates macrophages in the lungs [64]. Furthermore, fibrin(ogen) can contribute to matrix stiffness through its deposition, cross-linking, and interactions with other ECM components [65].

IL-6, together with TGF- β , can induce the differentiation of T helper 17 (Th17) cells [66]. Although Th17 cells mainly play protective roles, dysregulated Th17 cells can lead to inappropriate inflammatory responses, resulting in autoimmune diseases (e.g., inflammatory bowel disease) [67]. An enhanced Th17-associated immune response has been reported in both long COVID and hypermobility disorders [68,69]. IL-17A signaling was shown to inhibit efferocytosis in synovial macrophages via a STAT3/ADAM17/MERTK-mediated pathway in a rat model of rheumatoid arthritis [70]. Impaired efferocytosis appears to be associated with the pathogenesis of various inflammatory diseases [71].

Mast cells, as well as myofibroblasts and fibroblasts, can produce MMP-9 when stimulated by TNF- α or other stimuli, and MMP-9 is involved in inflammation and tissue remodeling and repair (Figure 2, arrows 19 and 20) [72,73]. MMP-9 cleaves a wide range of ECM substrates, including collagen and gelatin (Figure 2, arrow 21) [73]. It can cause vascular inflammation and increase BBB permeability, thereby disrupting neural connectivity [10]. MMP-9 plays a crucial role in the onset and progression of central nervous system disorders, including neuropathic pain [74], not only through an inflammatory feedback loop that worsens pain, but also through its influence on neuron–glia interactions [74]. For example, nerve growth factor released by glial cells can be degraded by MMP-9 [74].

Pregabalin, a gamma-aminobutyric acid analog used to treat neuropathic pain, epilepsy, and generalized anxiety disorder, has been shown to reduce VEGF and MMP-9 levels in vitro [75]. Furthermore, in vitro studies have demonstrated that recruiting MMP-9 to the fibroblast surface can activate latent TGF- β and trigger fibroblast transformation into myofibroblasts (Figure 2, arrow 22) [76]. There may also be an interplay between TGF- β and MMP-9; this may involve a bidirectional positive feedback loop that varies by tissue type and context, as observed in idiopathic pulmonary fibrosis [73]. MMP-9 levels are elevated in long COVID and hEDS/HSD [5,10]. In long COVID, increased serum levels of MMP-9 are associated with disease severity [10]. Elevated MMP-9 levels may also contribute to autism, a comorbidity of hEDS/HSD. A relationship between autism and long COVID has also been reported [12,13,15].

2.3. Part 3: Potential Roles of NMDAR, PIEZO1, PIEZO2, Insulin, and Vitamin D in the Hypothesis

MMP-9 is a physiological regulator of NMDARs. NMDARs function as glutamate-gated Ca²⁺-permeable channels and require glycine as a co-agonist. Synaptic plasticity and memory are NMDAR-dependent. In vitro, MMP-9 enzymatic activity in hippocampal cells increases lateral diffusion and, consequently, the surface mobility of the NR1 subunit of NMDARs via an integrin- β 1-

dependent signaling pathway (Figure 3, arrow 23) [77]. Additionally, NMDARs have been shown to function as mechanosensitive receptors [78]. Therefore, they could theoretically respond to changes in the ECM, such as increased stiffness or densification (Figure 3, arrow 24). In fibromyalgia, NMDARs exhibit increased activity [79]. This finding suggests a potential role for NMDARs in the pathophysiology of hEDS/HSD and long COVID, as both conditions can resemble fibromyalgia. In addition, NMDAR dysfunction has been proposed in autism [80,81].

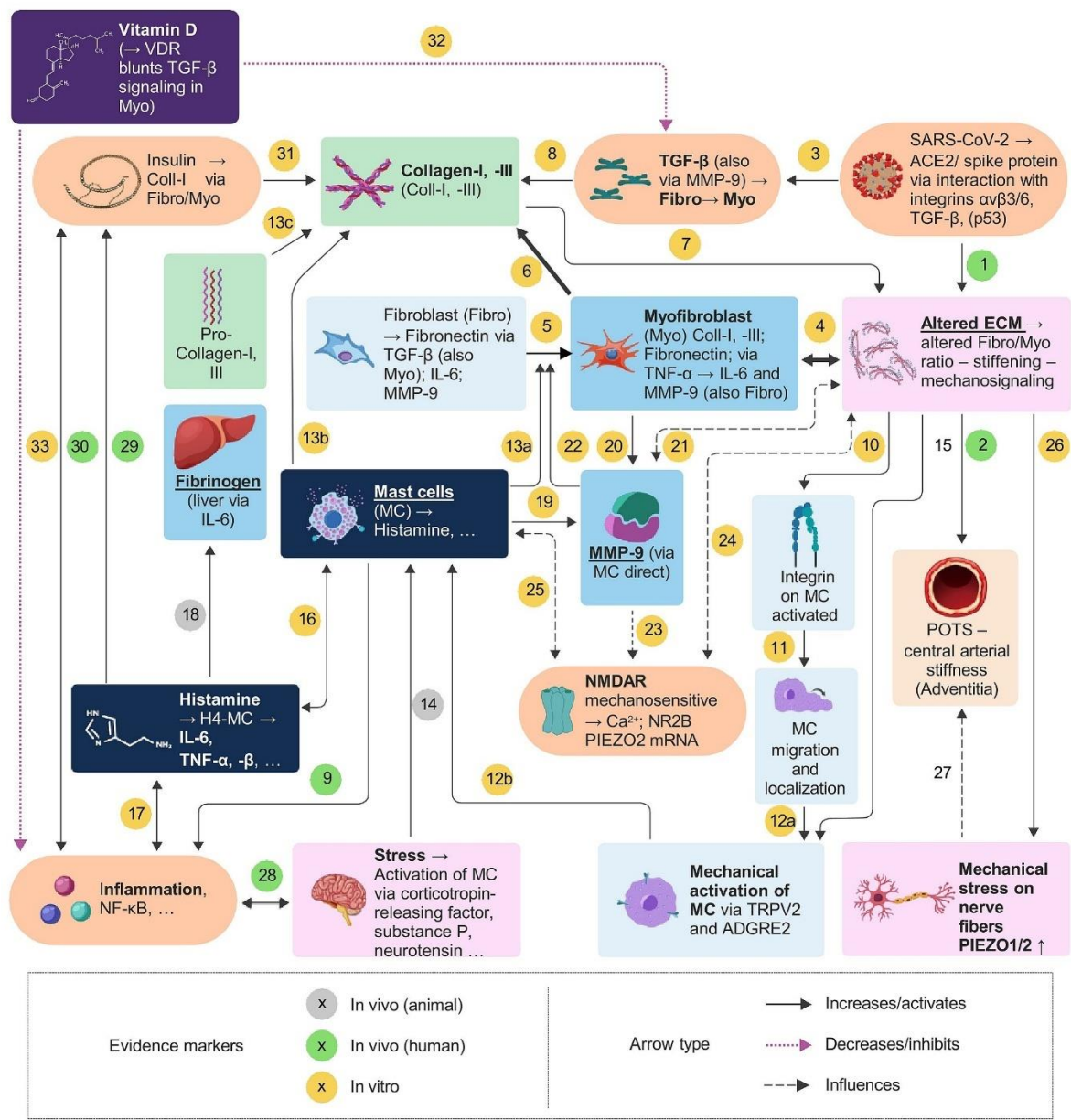


Figure 3. Integration of the nervous system, including the N-methyl-D-aspartate receptor (NMDAR), PIEZO1, PIEZO2, as well as stress and insulin, within the hypothesis and its possible interactions with vitamin D. The possible positive feedback loops between chronic stress and inflammation and between inflammation and insulin resistance are shown (arrows 28 and 30). Arrows represent different types of interactions and are distinguished by color, line style, and shape, as indicated in the figure key. The numbers assigned to the arrows correspond to the respective descriptions and references in the main text.

Homocysteine, a sulfur-containing amino acid and a product of methionine metabolism, is a recognized NMDAR agonist and contributes to neurotoxicity [82]. Polymorphisms of the *MTHFR* gene (e.g., C677T) in relation to autism, hEDS, and long COVID have also been proposed [83–85].

Recent studies have shown that NMDARs are not only present in the central nervous system, but also in peripheral tissues. Their role in atherosclerosis development has also been investigated

[86]. Furthermore, evidence suggests that NMDAR blockers attenuate bleomycin-induced pulmonary fibrosis in mice, possibly by inhibiting NMDAR-mediated senescence of bone marrow mesenchymal stem cells through the Wnt/ β -catenin signaling pathway [87].

In murine mast cells, glutamate induces upregulation of glutamate receptors, including ionotropic (NMDAR1, NMDAR2A, and NMDAR2B) and metabotropic (mGluR2 and mGluR7) types, at both the mRNA and protein levels (Figure 3, arrow 25) [88]. Glutamate also induces gene expression in mast cells, including upregulation of proinflammatory components (e.g., IL-6 and chemokine (C-C motif) ligand 2) [88]. These findings suggest functional glutamate-glutamate receptor signaling in mast cells [88]. However, the direct effects of homocysteine on human mast cells have not been sufficiently studied to date. Nevertheless, the expression of functional NMDARs on mast cells suggests that homocysteine could act directly on these cells via NMDAR-mediated signaling pathways.

Unlike NMDARs, whose role as mechanosensitive channels has only recently been recognized, piezo-type mechanosensitive ion channel components 1 and 2 (PIEZO1 and PIEZO2) are classic mechanosensitive channels involved in mechanotransduction (Figure 3, arrow 26). PIEZO1 is involved in regulating development and maintaining functional homeostasis. It is activated by poking, stretching, shear stress, local membrane tension, and myosin II-mediated traction force. PIEZO1 is expressed in various cell types, including epithelial cells, endothelial cells, microglia, astrocytes, musculoskeletal cells, and lymphatic and immune cells. Meanwhile, PIEZO2 primarily mediates mechanosensation for touch, tactile pain, proprioception, and sensing of mechanical states in internal organs. It is mainly activated by poking [89]. Both PIEZO1 and PIEZO2 are nonselective cation channels that slightly favor Ca^{2+} over Na^{2+} [89]. A 2024 study in rats showed that PIEZO1 detected substrate stiffness at the growth cone and regulated axon regrowth by activating the downstream Ca^{2+} -CaMKII-focal adhesion kinase-actin signaling cascade [90]. PIEZO1 knockdown in adult rat DRG neurons promoted axon regeneration and accelerated the recovery of sensory function after sciatic nerve injury. Furthermore, PIEZO1 inhibition enhanced growth on relatively soft substrates, whereas PIEZO1 activation impaired growth on relatively stiff substrates.

This presents an intriguing research approach, particularly in SFN and dysautonomia, which can occur in both long COVID and hEDS/HSD. One study proposed PIEZO1 as a potential therapeutic target for COVID-19 and long COVID, particularly for endothelial dysfunction [91]. PIEZO1 inhibition may prevent the disruption of intracellular calcium homeostasis in endothelial cells. PIEZO1 and PIEZO2 are also involved in arterial baroreceptor activity and in the acute regulation of blood pressure [92]. Therefore, they may also influence the pathophysiology of POTS, a potential comorbidity of long COVID and hEDS/HSD (Figure 3, arrow 27). Clinically, POTS manifests as orthostatic tachycardia without substantial orthostatic hypotension, with symptoms worsening in the upright position and improving in the recumbent position. Cardiovascular baroreflex function is altered in POTS, although this study has not found significant changes in cerebral autoregulation [93]. Notably, there may be a connection between NMDAR subunit 2B (NR2B), which is associated with nociceptive signaling, and PIEZO2 upregulation [94].

Chronic inflammatory processes, such as those seen in long COVID and hEDS/HSD, can affect neuronal stress networks through inflammatory signaling, thereby contributing to sustained elevation of sympathetic activity [5,95,96]. Increased sympathetic activity can, in turn, lead to a pro-inflammatory state via nuclear factor kappa-light-chain-enhancer of activated B-cell (NF- κ B) activation and other mechanisms, creating a bidirectional positive feedback loop that can maintain this state (Figure 3, arrow 28) [96]. Stress mediators include corticotropin-releasing factor and the neuropeptides neurotensin and substance P [96,97]. These mediators can contribute to mast cell degranulation (Figure 2 and 3, arrow 14) and cause microvascular inflammation and injury [97]. This inflammation and tissue injury can then manifest as cardiovascular diseases and BBB dysfunction [97]. A dysfunction of the blood-brain barrier is discussed in connection with the development of cerebrospinal fluid (CSF) leaks as a clinical symptom of hEDS [98]. Spontaneous CSF leakage can manifest as positional headache, nausea, vertigo, neck stiffness/pain, tinnitus, visual disturbances,

fatigue, cognitive changes, orthostatic hypotension, CSF otorrhea and rhinorrhea, metallic taste, extreme weakness, and pain [98].

Inflammation can mediate insulin resistance via NF- κ B, which is activated by TNF- α and IL-6 (Figure 3, arrow 29) [99,100]. Insulin resistance can also promote inflammation, thus creating a potential positive feedback loop between insulin resistance and inflammation (Figure 3, arrow 30) [99–101]. A 2022 study found that patients with POTS had reduced insulin sensitivity and signs of increased sympathetic activity, particularly during orthostatic stress [102]. Insulin has been shown to increase collagen production in cultured human embryonic lung fibroblasts, particularly collagen types I and III (Figure 3, arrow 31) [103]. Importantly, a prospective observational study identified a link between long COVID and insulin resistance [104].

The active vitamin D metabolite 1,25-dihydroxyvitamin D3 (hereinafter referred to as vitamin D) can act as an anti-fibrotic agent by inhibiting NF- κ B activation and TGF- β /SMAD signaling in myofibroblasts via the vitamin D receptor (VDR) (Figure 3, arrows 32 and 33) [105,106]. The TGF- β /SMAD pathway is the canonical TGF- β signaling pathway and is involved in fibrotic diseases [21]. Vitamin D may contribute to mast cell stabilization, and its deficiency may promote their activation and possibly cause increased degranulation [107]. A 2023 study found that low vitamin D levels were more prevalent among patients with long COVID than among the general population, though there was no correlation between vitamin D levels and symptom prevalence or severity [108]. It should be noted that a normal vitamin D level does not necessarily indicate normal function. For example, single-nucleotide polymorphisms can alter vitamin D receptors, thereby impairing normal signal transduction. A 2025 study found that vitamin D deficiency was significantly associated with overall long COVID signs and symptoms [109].

Vitamin D supplementation can lead to a significant reduction in ME/CFS symptoms among patients with vitamin D deficiency or insufficiency in cases where ME/CFS is caused by post-vaccination syndrome or post-acute sequelae of SARS-CoV-2 infection [110]. In a mouse model of experimental autoimmune encephalomyelitis, vitamin D, acting through VDR, ameliorated symptoms by suppressing Th17 cytokines and reducing the expression of IL-17 and IL-17F [111]. IL-17F expression is increased in patients with long COVID [68]. Vitamin D exerts regulatory effects through the widespread expression of VDR in key brain regions, profoundly influencing the complex physiological processes underlying sleep regulation and potential interactions with melatonin secretion pathways [112]. Individuals with vitamin D insufficiency (<20 ng/mL) exhibit prolonged sleep latency and reduced sleep efficiency [112]. VDR directly regulates the transcriptional activity of arylalkylamine N-acetyltransferase, a rate-limiting enzyme in melatonin synthesis [112].

3. Discussion

Although this hypothesis captures only a fraction of biological functions and relationships, it may help explain the pathological mechanisms underlying long COVID, hEDS/HSD, and their comorbidities in certain subgroups. Given the feedback loops described above, the disease process can theoretically persist even after the original trigger has been removed, particularly when underlying conditions are pre-existing or sufficiently severe. One possible pathway would begin with infection by SARS-CoV-2, which interacts with integrins α v β 6 and α v β 3 via the spike protein. This leads in part to a direct interaction with the ECM, particularly in endothelial and epithelial tissues (Figure 3, arrow 1), and the upregulation of active TGF- β (Figure 3, arrow 3), resulting in the conversion of fibroblasts into myofibroblasts (Figure 3, arrow 5). This is followed by myofibroblast-mediated remodeling of the ECM, including the production of collagen types I and III (Figure 3, arrow 6), driving increased stiffness (Figure 3, arrow 4), which in turn can activate additional TGF- β (Figure 3, arrow 4; feedback loop 1). A stiffer ECM can trigger mast cell migration via integrins (Figure 3, arrows 10 and 11) and mechanoreceptors, leading to mast cell activation and histamine release (Figure 3, arrows 12 and 13). This can then lead to the release of IL-6, IL-8, TNF- α , TNF- β , and TGF- β 1 by mast cells via the H4 receptor (Figure 3, arrows 13a+b and 16). TGF- β 1–3 and TNF- α act as

chemotactic stimuli for mast cells, prompting further migration (Figure 3, arrows 16 and 17; feedback loop 2).

In theory, this feedback loop can contribute to the development of MCAS. Mast cell activation can result in an inflammatory response (Figure 3, arrow 17). The resulting inflammation can activate the sympathetic nervous system, thereby inducing stress (Figure 3, arrow 28) and triggering the release of substance P, which is also secreted by mechanosensitive neurons. Activation of the mast cell receptor MRGPRX2 via substance P can in turn trigger the release of tryptase and chymase. Tryptase can promote the conversion of fibroblasts into myofibroblasts (Figure 3, arrow 13a), while chymase can contribute to the synthesis and secretion of collagen types I and III (Figure 3, arrow 13b, c). What has been described so far could constitute a major feedback loop in and of itself and can thus be self-perpetuating, with the altered mechanical properties of the ECM serving as a key element.

Inflammation and stress can reinforce each other in both directions (Figure 3, arrow 28, feedback loop 3). Inflammation, which is primarily systemic in this context, can promote insulin resistance and vice versa (Figure 3, arrow 30, feedback loop 4). Meanwhile, insulin can promote collagen production, particularly collagen types I and III (Figure 3, arrow 31). Activated mast cells, fibroblasts, and myofibroblasts can produce MMP-9 when stimulated by TNF- α and other factors (Figure 3, arrows 19 and 20). Elevated levels of MMP-9 and fibrinogen have been observed in patients with long COVID. Elevated MMP-9 levels are also observed in patients with hEDS/HSD and autism. IL-6 is secreted by mast cells and other inflammatory cells, stimulating the liver to increase fibrinogen synthesis and release (Figure 3, arrow 18). In addition to its ECM-modulating properties, MMP-9 can promote vascular inflammation and increase BBB permeability, thereby disrupting neural connections and contributing to neuropathic pain.

Furthermore, changes in the ECM can influence the properties of the mechanosensitive channels PIEZO1 and PIEZO2 (Figure 3, arrow 26), which in turn can affect nerve regeneration, SFN, and dysautonomia. PIEZO1 and PIEZO2 are also involved in arterial baroreceptor activity and, in addition to central arterial stiffening (Figure 3, arrow 2), may contribute to the development of POTS. Notably, there may be a partially reciprocal interaction between NMDARs and the structures described above, including an altered ECM, MMP-9, and mast cells (Figure 3, arrows 23–25). This is particularly relevant given that homocysteine is an NMDAR agonist and that a predisposition due to MTHFR mutations has been suggested for long COVID, hEDS, and autism. Severe damage, such as infection, disrupted efferocytosis, or pre-existing harm, may amplify one or more of these feedback loops, resulting in the persistence of the pathological system, either partially or entirely.

Preliminary data suggest that, in hEDS myofascial pain is associated with higher fascial stiffness (in relation to muscle) than in non-hEDS myofascial pain. One hypothetical explanation is that, in hEDS, the already altered ECM structure may lead to a more pronounced inflammatory response as a result of repetitive trauma. This triggers the cascade described above for long COVID, including its feedback loops. This may explain why hEDS/HSD can co-occur with long COVID, given that the tissue is pre-damaged. An initial means to test this hypothesis would be to analyze the mechanical properties of the ECM. A myotonometric study of long COVID patients has provided preliminary evidence of reduced creep in the superficial and deep fascia. For example, magnetic resonance elastography of the small intestine combined with a biopsy of the corresponding tissue and histopathological examination would be a feasible first approach in long COVID patients with gastrointestinal involvement. Furthermore, histopathological examination of the loose connective tissue layer between fascial layers, as well as the lamina propria, in patients with hEDS/HSD can provide additional insights into the pathophysiological mechanisms underlying this hypothesis.

This hypothesis has limitations. Each arrow in the figures represents one or more published studies and synthesizes evidence from different experimental models (in vivo, in vitro, and in silico). Further studies are needed to refine this hypothesis and to assess the proposed effects appropriately.

Author Contributions: Conceptualization, R.D. and R.S.; writing—original draft preparation, R.D.; writing—review and editing, R.D.; visualization, R.D.; funding acquisition, R.S. Both authors have read and agreed to the published version of the manuscript.

Funding: The open access publication fees for this article will be covered by the Technical University of Munich upon acceptance.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No datasets were generated or analyzed.

Acknowledgments: The authors used Grammarly solely for language editing. All scientific content, interpretations, and conclusions were developed and verified by the authors. The authors gratefully acknowledge Editage for English language editing and assistance with the preparation of the graphical abstract and illustrations.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACE2	angiotensin-converting enzyme 2
ADGRE2	adhesion G protein-coupled receptor E2
α-SMA	alpha-smooth muscle actin
BBB	blood–brain barrier
CFS	chronic fatigue syndrome
COVID	coronavirus disease
CSF	cerebrospinal fluid
ECM	extracellular matrix
hEDS	hypermobile Ehlers-Danlos syndrome
HSDs	hypermobility spectrum disorders
IgE	immunoglobulin E
IL	interleukin
LAP	latency-associated protein
LTBP	latent TGF-β binding protein
MCAS	mast cell activation syndrome
ME	myalgic encephalomyelitis
MMP-9	matrix metalloproteinase-9
MRGPRX2	Mas-related G-protein-coupled receptor member X2
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B-cell
NMDAR	N-methyl-D-aspartate receptor
PIEZO1/2	piezo-type mechanosensitive ion channel components 1 and 2
POTS	postural orthostatic tachycardia syndrome
RBD	receptor-binding domain
RGD	arginine–glycine–aspartic acid
S1-RBD	receptor-binding domain of the viral spike (S) protein within its S1 region
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SFN	small fiber neuropathy
TRPV2	transient receptor potential vanilloid channel 2
TGF-β	transforming growth factor β
TNF-α	tumor necrosis factor alpha
TNF-β	tumor necrosis factor beta
VEGF	vascular endothelial growth factor
VDR	vitamin D receptor

References

1. Plaut, S. "Long COVID-19" and Viral "Fibromyalgia-Ness": Suggesting a Mechanistic Role for Fascial Myofibroblasts (Nineveh, the Shadow Is in the Fascia). *Front. Med.* **2023**, *10*, 952278, doi:10.3389/fmed.2023.952278.
2. Ganesh, R.; Munipalli, B. Long COVID and Hypermobility Spectrum Disorders Have Shared Pathophysiology. *Front. Neurol.* **2024**, *15*, 1455498, doi:10.3389/fneur.2024.1455498.
3. Logarbo, B.P.; Yang, M.; Longo, M.T.; Kingry, C.; Courseault, J. Long COVID and the Diagnosis of Underlying Hypermobile EHLERS-DANLOS Syndrome and Hypermobility Spectrum Disorders. *PM&R* **2024**, *16*, 935–937, doi:10.1002/pmrj.13120.
4. Fairweather, D.; Bruno, K.A.; Darakjian, A.A.; Bruce, B.K.; Gehin, J.M.; Kotha, A.; Jain, A.; Peng, Z.; Hodge, D.O.; Rozen, T.D.; et al. High Overlap in Patients Diagnosed with Hypermobile Ehlers-Danlos Syndrome or Hypermobility Spectrum Disorders with Fibromyalgia and 40 Self-Reported Symptoms and Comorbidities. *Front. Med.* **2023**, *10*, 1096180, doi:10.3389/fmed.2023.1096180.
5. Wang, T.J.; Stecco, A.; Hakim, A.J.; Schleip, R. Fascial Pathophysiology in Hypermobility Spectrum Disorders and Hypermobile Ehlers–Danlos Syndrome: A Review of Emerging Evidence. *IJMS* **2025**, *26*, 5587, doi:10.3390/ijms26125587.
6. Biering, S.B.; Gomes de Sousa, F.T.; Tjang, L.V.; Pahmeier, F.; Zhu, C.; Ruan, R.; Blanc, S.F.; Patel, T.S.; Worthington, C.M.; Glasner, D.R.; et al. SARS-CoV-2 Spike Triggers Barrier Dysfunction and Vascular Leak via Integrins and TGF- β Signaling. *Nat Commun* **2022**, *13*, 7630, doi:10.1038/s41467-022-34910-5.
7. Norris, E.G.; Pan, X.S.; Hocking, D.C. Receptor-Binding Domain of SARS-CoV-2 Is a Functional Av-Integrin Agonist. *Journal of Biological Chemistry* **2023**, *299*, 102922, doi:10.1016/j.jbc.2023.102922.
8. Fiore, V.F.; Wong, S.S.; Tran, C.; Tan, C.; Xu, W.; Sulchek, T.; White, E.S.; Hagood, J.S.; Barker, T.H. Av β 3 Integrin Drives Fibroblast Contraction and Strain Stiffening of Soft Provisional Matrix during Progressive Fibrosis. *JCI Insight* **2018**, *3*, e97597, doi:10.1172/jci.insight.97597.
9. Munger, J.S.; Huang, X.; Kawakatsu, H.; Griffiths, M.J.; Dalton, S.L.; Wu, J.; Pittet, J.F.; Kaminski, N.; Garat, C.; Matthay, M.A.; et al. The Integrin Alpha v Beta 6 Binds and Activates Latent TGF Beta 1: A Mechanism for Regulating Pulmonary Inflammation and Fibrosis. *Cell* **1999**, *96*, 319–328, doi:10.1016/s0092-8674(00)80545-0.
10. Kempuraj, D.; Tsilioni, I.; Aenlle, K.K.; Klimas, N.G.; Theoharides, T.C. Long COVID Elevated MMP-9 and Release from Microglia by SARS-CoV-2 Spike Protein. *Translational Neuroscience* **2024**, *15*, 20220352, doi:10.1515/tnsci-2022-0352.
11. Zoppi, N.; Chiarelli, N.; Binetti, S.; Ritelli, M.; Colombi, M. Dermal Fibroblast-to-Myofibroblast Transition Sustained by Av β 3 Integrin-ILK-Snail1/Slug Signaling Is a Common Feature for Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease* **2018**, *1864*, 1010–1023, doi:10.1016/j.bbadis.2018.01.005.
12. Lord, J.R.; Mashayekhi, F.; Salehi, Z. How Matrix Metalloproteinase (MMP)-9 (Rs3918242) Polymorphism Affects MMP-9 Serum Concentration and Associates with Autism Spectrum Disorders: A Case-Control Study in Iranian Population. *Dev Psychopathol* **2022**, *34*, 882–888, doi:10.1017/S0954579420002102.
13. Hu, C.; Li, H.; Cui, J.; Li, Y.; Zhang, F.; Li, H.; Luo, X.; Hao, Y. Integrative Analysis Identifies IL-6/JUN/MMP-9 Pathway Destroyed Blood-Brain-Barrier in Autism Mice via Machine Learning and Bioinformatic Analysis. *Transl Psychiatry* **2025**, *15*, 239, doi:10.1038/s41398-025-03452-x.
14. Johnston, H.; Bacon, A.M. Autistic Traits in Fibromyalgia Are Associated with Hypersensitivity and Central Sensitisation. *Psychology, Health & Medicine* **2025**, 1–17, doi:10.1080/13548506.2025.2519237.
15. Raw, R.K.; Rees, J.; Pearson, A.; Chadwick, D.R. Neurodivergence as a Risk Factor for Post-Covid-19 Syndrome 2023.
16. Casanova, E.L.; Baeza-Velasco, C.; Buchanan, C.B.; Casanova, M.F. The Relationship between Autism and Ehlers-Danlos Syndromes/Hypermobility Spectrum Disorders. *JPM* **2020**, *10*, 260, doi:10.3390/jpm10040260.
17. Crompton, C.J.; Efthimiou, T.N.; Dockrell, D.M.; Berg, K.M. Health Experiences and Outcomes of Autistic and Non-Autistic Adults with Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorder. *BMC Med* **2026**, *24*, 193, doi:10.1186/s12916-026-04713-2.

18. Liu, S.; Guo, Y.; Wang, F.-S. Viral Persistence in Long COVID: Research Advances and Treatment Strategies. *Infectious Diseases & Immunity* **2025**, *5*, 272–288, doi:10.1097/ID9.0000000000000163.
19. Rong, Z.; Mai, H.; Ebert, G.; Kapoor, S.; Puellas, V.G.; Czogalla, J.; Hu, S.; Su, J.; Prtvar, D.; Singh, I.; et al. Persistence of Spike Protein at the Skull-Meninges-Brain Axis May Contribute to the Neurological Sequelae of COVID-19. *Cell Host & Microbe* **2024**, *32*, 2112–2130.e10, doi:10.1016/j.chom.2024.11.007.
20. Xu, J.; Xu, X.; Jiang, L.; Dua, K.; Hansbro, P.M.; Liu, G. SARS-CoV-2 Induces Transcriptional Signatures in Human Lung Epithelial Cells That Promote Lung Fibrosis. *Respir Res* **2020**, *21*, 182, doi:10.1186/s12931-020-01445-6.
21. Deng, Z.; Fan, T.; Xiao, C.; Tian, H.; Zheng, Y.; Li, C.; He, J. TGF- β Signaling in Health, Disease and Therapeutics. *Sig Transduct Target Ther* **2024**, *9*, 61, doi:10.1038/s41392-024-01764-w.
22. Kamdar, A.; Sykes, R.; Thomson, C.R.; Mangion, K.; Ang, D.; Lee, M.A.; Van Agtmael, T.; Berry, C. Vascular Fibrosis and Extracellular Matrix Remodelling in Post-COVID 19 Conditions. *Infectious Medicine* **2024**, *3*, 100147, doi:10.1016/j.imj.2024.100147.
23. Pugh, G.E.; Thomas, K.N.; Fan, J.-L.; Fisher, J.P. Central Arterial Stiffness, Flow-Mediated Dilation, and Venous Function in Postural Orthostatic Tachycardia Syndrome. *American Journal of Physiology-Heart and Circulatory Physiology* **2026**, *330*, H89–H99, doi:10.1152/ajpheart.00590.2025.
24. Conroy, K.P.; Kitto, L.J.; Henderson, N.C. Av Integrins: Key Regulators of Tissue Fibrosis. *Cell Tissue Res* **2016**, *365*, 511–519, doi:10.1007/s00441-016-2407-9.
25. Jenkins, W.S.; Vesey, A.T.; Vickers, A.; Neale, A.; Moles, C.; Connell, M.; Joshi, N.V.; Lucatelli, C.; Fletcher, A.M.; Spratt, J.C.; et al. In Vivo Alpha-V Beta-3 Integrin Expression in Human Aortic Atherosclerosis. *Heart* **2019**, *105*, 1868–1875, doi:10.1136/heartjnl-2019-315103.
26. Wilder, R.L. Integrin Alpha V Beta 3 as a Target for Treatment of Rheumatoid Arthritis and Related Rheumatic Diseases. *Annals of the Rheumatic Diseases* **2002**, *61*, ii96–ii99, doi:10.1136/ard.61.suppl_2.ii96.
27. Brenmoehl, J.; Miller, S.N.; Hofmann, C.; Vogl, D.; Falk, W.; Schölmerich, J.; Rogler, G. Transforming Growth Factor-B1 Induces Intestinal Myofibroblast Differentiation and Modulates Their Migration. *WJG* **2009**, *15*, 1431, doi:10.3748/wjg.15.1431.
28. Roberts, C.J.; Birkenmeier, T.M.; McQuillan, J.J.; Akiyama, S.K.; Yamada, S.S.; Chen, W.T.; Yamada, K.M.; McDonald, J.A. Transforming Growth Factor Beta Stimulates the Expression of Fibronectin and of Both Subunits of the Human Fibronectin Receptor by Cultured Human Lung Fibroblasts. *Journal of Biological Chemistry* **1988**, *263*, 4586–4592, doi:10.1016/S0021-9258(18)68822-2.
29. Wells, R.G.; Discher, D.E. Matrix Elasticity, Cytoskeletal Tension, and TGF- β : The Insoluble and Soluble Meet. *Sci. Signal.* **2008**, *1*, doi:10.1126/stke.110pe13.
30. Tiskratok, W.; Chuinsiri, N.; Limraksasin, P.; Kyawsoewin, M.; Jitprasertwong, P. Extracellular Matrix Stiffness: Mechanotransduction and Mechanobiological Response-Driven Strategies for Biomedical Applications Targeting Fibroblast Inflammation. *Polymers* **2025**, *17*, 822, doi:10.3390/polym17060822.
31. Sinhorim, L.; Duarte, L.; França, M.E.; Albuquerque, N.; Amorim, M.; do Nascimento, I.; Schleip, R.; Santos, G. Poster: Effects of Myofascial Reorganization on Viscoelastic Property in Women with Long COVID: A Myotonometry Study. *Journal of Bodywork and Movement Therapies* **2026**, *47*, 711, doi:10.1016/j.jbmt.2025.11.154.
32. Courbot, O.; Elosegui-Artola, A. The Role of Extracellular Matrix Viscoelasticity in Development and Disease. *npj Biol. Phys. Mech.* **2025**, *2*, 10, doi:10.1038/s44341-025-00014-6.
33. Mulsow, J.J.W.; Watson, R.W.G.; Fitzpatrick, J.M.; O'Connell, P.R. Transforming Growth Factor- β Promotes Pro-Fibrotic Behavior by Serosal Fibroblasts via PKC and ERK1/2 Mitogen Activated Protein Kinase Cell Signaling. *Annals of Surgery* **2005**, *242*, 880–889, doi:10.1097/01.sla.0000189606.58343.cd.
34. Cambria, E.; Blazeski, A.; Ko, E.C.; Thai, T.; Dantes, S.; Barbie, D.A.; Shelton, S.E.; Kamm, R.D. A Vascular Microphysiological Model of Lung Fibrosis Reveals That Myofibroblasts and IPF Patient-Derived Fibroblasts Impair Angiogenesis and Vasculogenesis. *Adv Funct Materials* **2026**, *36*, e15610, doi:10.1002/adfm.202515610.
35. Grant, C.A.; Twigg, P.C.; Tobin, D.J. Static and Dynamic Nanomechanical Properties of Human Skin Tissue Using Atomic Force Microscopy: Effect of Scarring in the Upper Dermis. *Acta Biomaterialia* **2012**, *8*, 4123–4129, doi:10.1016/j.actbio.2012.06.042.

36. Xia, J.; Wang, W.Y.; Jacobs, K.A.; Maniar, K.; Lin, D.; Jarman, E.H.; Matera, D.L.; Loesel, K.; Davidson, C.D.; Hiraki, H.L.; et al. Perivascular Matrix Densification Dysregulates Angiogenesis and Activates Pro-Inflammatory Endothelial Cells. *Advanced Science* **2026**, e10448, doi:10.1002/advs.202510448.

37. Singh, N.; Bharara Singh, A. S2 Subunit of SARS-nCoV-2 Interacts with Tumor Suppressor Protein P53 and BRCA: An in Silico Study. *Translational Oncology* **2020**, *13*, 100814, doi:10.1016/j.tranon.2020.100814.

38. Bao, Y.-N.; Yang, Q.; Shen, X.-L.; Yu, W.-K.; Zhou, L.; Zhu, Q.-R.; Shan, Q.-Y.; Wang, Z.-C.; Cao, G. Targeting Tumor Suppressor P53 for Organ Fibrosis Therapy. *Cell Death Dis* **2024**, *15*, 336, doi:10.1038/s41419-024-06702-w.

39. Wang, T.J.; Stecco, A. Fascial Thickness and Stiffness in Hypermobile EHLERS-DANLOS Syndrome. *American J of Med Genetics Pt C* **2021**, *187*, 446–452, doi:10.1002/ajmg.c.31948.

40. Wang, T.J.; Stecco, A.; Schleip, R.; Stecco, C.; Pirri, C. Change in Gliding Properties of the Iliotibial Tract in Hypermobile Ehlers–Danlos Syndrome. *J Ultrasound* **2023**, *26*, 809–813, doi:10.1007/s40477-023-00775-7.

41. Akhmetshina, A.; Palumbo, K.; Dees, C.; Bergmann, C.; Venalis, P.; Zerr, P.; Horn, A.; Kireva, T.; Beyer, C.; Zwerina, J.; et al. Activation of Canonical Wnt Signalling Is Required for TGF- β -Mediated Fibrosis. *Nat Commun* **2012**, *3*, 735, doi:10.1038/ncomms1734.

42. Ramanan, R.S.; Kesavan, K.V.; Ravikumar, V. Pulmonary Fibrosis in Post-COVID-19: Epithelial-Mesenchymal Transition as a Key Mechanism and Target for Therapy. *Inflammopharmacol* **2026**, *34*, 79–89, doi:10.1007/s10787-025-02074-5.

43. Ritelli, M.; Chiarelli, N.; Cinquina, V.; Bertini, V.; Piantoni, S.; Caproli, A.; Della Pina, S.E.L.; Franceschini, F.; Zarattini, G.; Gandy, W.; et al. Bridging the Diagnostic Gap for Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders: Evidence of a Common Extracellular Matrix Fragmentation Pattern in Patient Plasma as a Potential Biomarker. *American J of Med Genetics Pt A* **2025**, *197*, e63857, doi:10.1002/ajmg.a.63857.

44. Pratt, R.L. Hyaluronan and the Fascial Frontier. *IJMS* **2021**, *22*, 6845, doi:10.3390/ijms22136845.

45. Mifflin, R.C.; Pinchuk, I.V.; Saada, J.I.; Powell, D.W. Intestinal Myofibroblasts: Targets for Stem Cell Therapy. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **2011**, *300*, G684–G696, doi:10.1152/ajpgi.00474.2010.

46. Blundell, S.; Ray, K.K.; Buckland, M.; White, P.D. Chronic Fatigue Syndrome and Circulating Cytokines: A Systematic Review. *Brain, Behavior, and Immunity* **2015**, *50*, 186–195, doi:10.1016/j.bbi.2015.07.004.

47. Fede, C.; Petrelli, L.; Pirri, C.; Tiengo, C.; De Caro, R.; Stecco, C. Detection of Mast Cells in Human Superficial Fascia. *IJMS* **2023**, *24*, 11599, doi:10.3390/ijms241411599.

48. Draber, P. Mast Cell Chemotaxis—Chemoattractants and Signaling Pathways.

49. Özdemir, Ö.; Kasımoğlu, G.; Bak, A.; Sütüoğlu, H.; Savaşan, S. Mast Cell Activation Syndrome: An up-to-Date Review of Literature. *World J Clin Pediatr* **2024**, *13*, doi:10.5409/wjcp.v13.i2.92813.

50. Sumantri, S.; Rengganis, I. Immunological Dysfunction and Mast Cell Activation Syndrome in Long COVID. *Asia Pacific Allergy* **2023**, *13*, 50–53, doi:10.5415/apallergy.0000000000000022.

51. Pastwińska, J.; Żelechowska, P.; Walczak-Drzewiecka, A.; Brzezińska-Błaszczyk, E.; Dastyk, J. The Art of Mast Cell Adhesion. *Cells* **2020**, *9*, 2664, doi:10.3390/cells9122664.

52. Driscoll, T.P.; Bidone, T.C.; Ahn, S.J.; Yu, A.; Groisman, A.; Voth, G.A.; Schwartz, M.A. Integrin-Based Mechanosensing through Conformational Deformation. *Biophysical Journal* **2021**, *120*, 4349–4359, doi:10.1016/j.bpj.2021.09.010.

53. Kaltenbach, L.; Martzloff, P.; Bambach, S.K.; Aizarani, N.; Mihlan, M.; Gavrillov, A.; Glaser, K.M.; Stecher, M.; Thüner, R.; Thiriot, A.; et al. Slow Integrin-Dependent Migration Organizes Networks of Tissue-Resident Mast Cells. *Nat Immunol* **2023**, *24*, 915–924, doi:10.1038/s41590-023-01493-2.

54. Li, H.; Guo, Z.; Xiangdong, Q. Role of Mechanical Stimulus in Mast Cell Activation. *Digit Med* **2024**, *10*, doi:10.1097/DM-2023-00014.

55. Shimbori, C.; Upagupta, C.; Bellaye, P.-S.; Ayoub, E.A.; Sato, S.; Yanagihara, T.; Zhou, Q.; Ognjanovic, A.; Ask, K.; Gaudie, J.; et al. Mechanical Stress-Induced Mast Cell Degranulation Activates TGF- β 1 Signalling Pathway in Pulmonary Fibrosis. *Thorax* **2019**, *74*, 455–465, doi:10.1136/thoraxjnl-2018-211516.

56. Atiakshin, D.; Buchwalow, I.; Tiemann, M. Mast Cells and Collagen Fibrillogenesis. *Histochem Cell Biol* **2020**, *154*, 21–40, doi:10.1007/s00418-020-01875-9.

57. Wang, N.; Wang, J.; Zhang, Y.; Hu, S.; Zhang, T.; Wu, Y.; Sun, X.; Zhang, T.; Yang, S.; He, L. Substance P-induced Lung Inflammation in Mice Is Mast Cell Dependent. *Clin Experimental Allergy* **2022**, *52*, 46–58, doi:10.1111/cea.13902.
58. Aitella, E.; Romano, C.; Ginaldi, L.; Cozzolino, D. Mast Cells at the Crossroads of Hypersensitivity Reactions and Neurogenic Inflammation. *IJMS* **2025**, *26*, 927, doi:10.3390/ijms26030927.
59. Jemima, E.A.; Prema, A.; Thangam, E.B. Functional Characterization of Histamine H4 Receptor on Human Mast Cells. *Molecular Immunology* **2014**, *62*, 19–28, doi:10.1016/j.molimm.2014.05.007.
60. Obeagu, E.I. An Insight of Interleukin -6 and Fibrinogen: In Regulating the Immune System. *Journal of Biomedical Sciences* **2022**, *11*.
61. Kreß, L.; Hofmann, L.; Klein, T.; Klug, K.; Saffer, N.; Spitzel, M.; Bär, F.; Sommer, C.; Karl, F.; Üçeyler, N. Differential Impact of Keratinocytes and Fibroblasts on Nociceptor Degeneration and Sensitization in Small Fiber Neuropathy. *Pain* **2021**, *162*, 1262–1272, doi:10.1097/j.pain.0000000000002122.
62. CASTELL, J.V.; Andust, T. Interleukin-6 and the Acute Phase Response. **1990**, 265.
63. Maqsood, K.; Ahmad, S.; Saeed, A.; Roohi, N. Plasma Protein Biomarkers for Long COVID-19: Predictors of Symptom Severity and Mortality Risk. *Clinica Chimica Acta* **2025**, *575*, 120350, doi:10.1016/j.cca.2025.120350.
64. Ryu, J.K.; Yan, Z.; Montano, M.; Sozmen, E.G.; Dixit, K.; Suryawanshi, R.K.; Matsui, Y.; Helmy, E.; Kaushal, P.; Makanani, S.K.; et al. Fibrin Drives Thromboinflammation and Neuropathology in COVID-19. *Nature* **2024**, *633*, 905–913, doi:10.1038/s41586-024-07873-4.
65. Liao, C.; Lv, W.; Huang, J.; Diallo, M.; Tian, Z. Fibrinogen in Extracellular Matrix Remodeling: Functional Switching, Source Heterogeneity, and Biomaterial Translation. *Front. Cell Dev. Biol.* **2026**, *14*, 1874458, doi:10.3389/fcell.2026.1874458.
66. Korn, T.; Bettelli, E.; Oukka, M.; Kuchroo, V.K. IL-17 and Th17 Cells. *Annu. Rev. Immunol.* **2009**, *27*, 485–517, doi:10.1146/annurev.immunol.021908.132710.
67. Park, E.; Ciofani, M. Th17 Cell Pathogenicity in Autoimmune Disease. *Exp Mol Med* **2025**, *57*, 1913–1927, doi:10.1038/s12276-025-01535-9.
68. Almulla, A.F.; Thipakorn, Y.; Zhou, B.; Vojdani, A.; Maes, M. Immune Activation and Immune-Associated Neurotoxicity in Long-COVID: A Systematic Review and Meta-Analysis of 103 Studies Comprising 58 Cytokines/Chemokines/Growth Factors. *Brain, Behavior, and Immunity* **2024**, *122*, 75–94, doi:10.1016/j.bbi.2024.07.036.
69. Elizondo Solis, C.V.; Montemayor Zarazúa, A.P.; Ilizaliturri Guerra, O.; Silva Luna, K.; Arana Guajardo, A.C.; Garcia Pompermayer, M.R.; Purón González, E.; Lozano Plata, L.I.; Garza Elizondo, M.A. POS1438 MOLECULAR PATHWAYS ALTERED IN THE HYPERMOBILITY SPECTRUM DISORDER. *Annals of the Rheumatic Diseases* **2025**, *84*, 1448–1449, doi:10.1016/j.ard.2025.06.785.
70. Samarpita, S.; Srivastava, S.; Srikanth, M.; Miriam Jose, A.; Rithvik, A.; Rasool, M. IL-17A/IL-17RA Interaction Blockade Sensitizes Synovial Macrophages to Efferocytosis and PD-L1 Signaling via Rewiring STAT-3/ADAM17/MERTK Axis in Rheumatoid Arthritis Animal Model. *International Immunopharmacology* **2024**, *136*, 112343, doi:10.1016/j.intimp.2024.112343.
71. Ge, Y.; Huang, M.; Yao, Y. Efferocytosis and Its Role in Inflammatory Disorders. *Front. Cell Dev. Biol.* **2022**, *10*, 839248, doi:10.3389/fcell.2022.839248.
72. Di Girolamo, N.; Indoh, I.; Jackson, N.; Wakefield, D.; McNeil, H.P.; Yan, W.; Geczy, C.; Arm, J.P.; Tedla, N. Human Mast Cell-Derived Gelatinase B (Matrix Metalloproteinase-9) Is Regulated by Inflammatory Cytokines: Role in Cell Migration. *The Journal of Immunology* **2006**, *177*, 2638–2650, doi:10.4049/jimmunol.177.4.2638.
73. Wang, Y.; Jiao, L.; Qiang, C.; Chen, C.; Shen, Z.; Ding, F.; Lv, L.; Zhu, T.; Lu, Y.; Cui, X. The Role of Matrix Metalloproteinase 9 in Fibrosis Diseases and Its Molecular Mechanisms. *Biomedicine & Pharmacotherapy* **2024**, *171*, 116116, doi:10.1016/j.biopha.2023.116116.
74. Jia, S.Y.; Tang, X.-J.; Su, Y.; Liu, Y.-N.; Ming, Z.; Lin, J.-Y. The Role and Mechanisms of Matrix Metalloproteinase-9 in Peripheral Neuropathic Pain. *Front. Mol. Neurosci.* **2025**, *18*, 1647316, doi:10.3389/fnmol.2025.1647316.

75. Hajighasemi, F.; Darouni, L. Inhibition of VEGF and MMP-9 Production by Pregabalin in Human Immunocompetent Cells in Vitro. *European Respiratory Journal* **2020**, *56*, doi:10.1183/13993003.congress-2020.2040.
76. Dayer, C.; Stamenkovic, I. Recruitment of Matrix Metalloproteinase-9 (MMP-9) to the Fibroblast Cell Surface by Lysyl Hydroxylase 3 (LH3) Triggers Transforming Growth Factor- β (TGF- β) Activation and Fibroblast Differentiation. *Journal of Biological Chemistry* **2015**, *290*, 13763–13778, doi:10.1074/jbc.M114.622274.
77. Michaluk, P.; Mikasova, L.; Groc, L.; Frischknecht, R.; Choquet, D.; Kaczmarek, L. Matrix Metalloproteinase-9 Controls NMDA Receptor Surface Diffusion through Integrin B1 Signaling. *J. Neurosci.* **2009**, *29*, 6007–6012, doi:10.1523/JNEUROSCI.5346-08.2009.
78. Belin, S.; Maki, B.A.; Catlin, J.; Rein, B.A.; Popescu, G.K. Membrane Stretch Gates NMDA Receptors. *J. Neurosci.* **2022**, *42*, 5672–5680, doi:10.1523/JNEUROSCI.0350-22.2022.
79. Littlejohn, G.; Guymer, E. Modulation of NMDA Receptor Activity in Fibromyalgia. *Biomedicines* **2017**, *5*, 15, doi:10.3390/biomedicines5020015.
80. Lee, S.; Moon, H.; Kim, E. NMDAR Dysfunction in Autism Spectrum Disorders: Lessons Learned from 10 Years of Study. *Current Opinion in Neurobiology* **2025**, *92*, 103023, doi:10.1016/j.conb.2025.103023.
81. Dangmann, R. A Hypothesis to Explain the Potential Influence of Hormones on the Severity of Autism Spectrum Conditions in Women. *Medical Hypotheses* **2023**, *178*, 111136, doi:10.1016/j.mehy.2023.111136.
82. Deep, S.N.; Seelig, S.; Paul, S.; Poddar, R. Homocysteine-Induced Sustained GluN2A NMDA Receptor Stimulation Leads to Mitochondrial ROS Generation and Neurotoxicity. *Journal of Biological Chemistry* **2024**, *300*, 107253, doi:10.1016/j.jbc.2024.107253.
83. Petrova, B.; Syphurs, C.; Culhane, A.J.; Chen, J.; Chen, E.; Cotsapas, C.; Esserman, D.; Montgomery, R.R.; Kleinstein, S.H.; Smolen, K.K.; et al. MTHFR Allele and One-Carbon Metabolic Profile Predict Severity of COVID-19. *Proc. Natl. Acad. Sci. U.S.A.* **2025**, *122*, e2509118122, doi:10.1073/pnas.2509118122.
84. Courseault, J.; Umar, M.; Bordnick, P.; Simons, J.; Volic, M.; Stock, A.; Bix, G. Prevalence of MTHFR Polymorphisms in Patients With Hypermobile EHLERS-DANLOS Syndrome and Hypermobile Spectrum Disorders in a US Hypermobility Clinic. *ACR Open Rheumatology* **2024**, *6*, 399–402, doi:10.1002/acr2.11667.
85. Sener, E.F.; Oztup, D.B.; Ozkul, Y. MTHFR Gene C677T Polymorphism in Autism Spectrum Disorders. *Genetics Research International* **2014**, *2014*, 698574, doi:10.1155/2014/698574.
86. Cai, J.; Luo, Z.; Zhang, M.; Zhao, Z.; Ren, L.; Cheng, H. N-Methyl-D-Aspartate Receptors: Structure, Signaling and Roles in Atherosclerosis. *J Transl Med* **2026**, *24*, 1037, doi:10.1186/s12967-026-08399-1.
87. Huang, P.; Zhou, Y.; Li, X.-H.; Zhang, Y.-N.; Cheng, H.-P.; Fu, J.-F.; Liu, W.; Yue, S.; Luo, Z.-Q. N-Methyl-D-Aspartate Receptor Blockers Attenuate Bleomycin-Induced Pulmonary Fibrosis by Inhibiting Endogenous Mesenchymal Stem Cells Senescence. *Ann Transl Med* **2022**, *10*, 642–642, doi:10.21037/atm-22-2507.
88. Alim, M.A.; Grujic, M.; Ackerman, P.W.; Kristiansson, P.; Eliasson, P.; Peterson, M.; Pejler, G. Glutamate Triggers the Expression of Functional Ionotropic and Metabotropic Glutamate Receptors in Mast Cells. *Cell Mol Immunol* **2021**, *18*, 2383–2392, doi:10.1038/s41423-020-0421-z.
89. Xiao, B. Mechanisms of Mechanotransduction and Physiological Roles of PIEZO Channels. *Nat Rev Mol Cell Biol* **2024**, *25*, 886–903, doi:10.1038/s41580-024-00773-5.
90. Lei, M.; Wang, W.; Zhang, H.; Gong, J.; Cai, H.; Wang, Z.; Zhu, L.; Yang, X.; Wang, S.; Ma, C. Piezo1 Regulates Stiffness-Dependent DRG Axon Regeneration via Modifying Cytoskeletal Dynamics. *Advanced Science* **2024**, *11*, 2405705, doi:10.1002/advs.202405705.
91. Zhang, X.; Liu, J.; Deng, X.; Bo, L. Understanding COVID-19-Associated Endothelial Dysfunction: Role of PIEZO1 as a Potential Therapeutic Target. *Front. Immunol.* **2024**, *15*, 1281263, doi:10.3389/fimmu.2024.1281263.
92. Zeng, W.-Z.; Marshall, K.L.; Min, S.; Daou, I.; Chapleau, M.W.; Abboud, F.M.; Liberles, S.D.; Patapoutian, A. PIEZO1 Mediate Neuronal Sensing of Blood Pressure and the Baroreceptor Reflex. *Science* **2018**, *362*, 464–467, doi:10.1126/science.aau6324.

93. Yeh, S.-J.; Lung, C.-W.; Jan, Y.-K.; Lee, L.-L.; Wang, Y.-C.; Liao, B.-Y. The Relationship between Cardiovascular Baroreflex and Cerebral Autoregulation in Postural Orthostatic Tachycardia Disorder Using Advanced Cross-Correlation Function. *Sci Rep* **2024**, *14*, 25158, doi:10.1038/s41598-024-77065-7.
94. Ni, K.; Zhang, W.; Ni, Y.; Mao, Y.-T.; Wang, Y.; Gu, X.-P.; Ma, Z.-L. Dorsal Root Ganglia NR2B-mediated Epac1-Piezo2 Signaling Pathway Contributes to Mechanical Allodynia of Bone Cancer Pain. *Oncol Lett* **2021**, *21*, 338, doi:10.3892/ol.2021.12599.
95. Davis, H.E.; McCorkell, L.; Vogel, J.M.; Topol, E.J. Long COVID: Major Findings, Mechanisms and Recommendations. *Nat Rev Microbiol* **2023**, *21*, 133–146, doi:10.1038/s41579-022-00846-2.
96. Tong, R.L.; Kahn, U.N.; Grafe, L.A.; Hitti, F.L.; Fried, N.T.; Corbett, B.F. Stress Circuitry: Mechanisms behind Nervous and Immune System Communication That Influence Behavior. *Front. Psychiatry* **2023**, *14*, 1240783, doi:10.3389/fpsyt.2023.1240783.
97. Papadopoulou, P.; Theoharides, T.C. Neuroimmune Regulation of Microvascular Inflammation: The Heart–Brain Axis, Mast Cells, and the Protective Role of Flavonoids—A Comprehensive Review. *Biomedicines* **2026**, *14*, 1073, doi:10.3390/biomedicines14051073.
98. Severance, S.; Daylor, V.; Petrucci, T.; Gensemer, C.; Patel, S.; Norris, R.A. Hypermobility Ehlers-Danlos Syndrome and Spontaneous CSF Leaks: The Connective Tissue Conundrum. *Front. Neurol.* **2024**, *15*, 1452409, doi:10.3389/fneur.2024.1452409.
99. Shoelson, S.E. Inflammation and Insulin Resistance. *Journal of Clinical Investigation* **2006**, *116*, 1793–1801, doi:10.1172/JCI29069.
100. Plomgaard, P.; Bouzakri, K.; Krogh-Madsen, R.; Mittendorfer, B.; Zierath, J.R.; Pedersen, B.K. Tumor Necrosis Factor- Induces Skeletal Muscle Insulin Resistance in Healthy Human Subjects via Inhibition of Akt Substrate 160 Phosphorylation.
101. Shimobayashi, M.; Albert, V.; Woelnerhanssen, B.; Frei, I.C.; Weissenberger, D.; Meyer-Gerspach, A.C.; Clement, N.; Moes, S.; Colombi, M.; Meier, J.A.; et al. Insulin Resistance Causes Inflammation in Adipose Tissue. *Journal of Clinical Investigation* **2018**, *128*, 1538–1550, doi:10.1172/JCI96139.
102. Breier, N.C.; Paranjape, S.Y.; Scudder, S.; Mehr, S.E.; Diedrich, A.; Flynn, C.R.; Okamoto, L.E.; Hartmann, B.; Gasbjerg, L.S.; Shibao, C.A. Worsening Postural Tachycardia Syndrome Is Associated With Increased Glucose-Dependent Insulinotropic Polypeptide Secretion. *Hypertension* **2022**, *79*, doi:10.1161/HYPERTENSIONAHA.121.17852.
103. Goldstein, R.H.; Poliks, C.F.; Pilch, P.F.; Smith, B.D.; Fine, A. Stimulation of Collagen Formation by Insulin and Insulin-Like Growth Factor I in Cultures of Human Lung Fibroblasts*. *Endocrinology* **1989**, *124*, 964–970, doi:10.1210/endo-124-2-964.
104. Man, D.E.; Andor, M.; Buda, V.; Kundnani, N.R.; Duda-Seiman, D.M.; Craciun, L.M.; Neagu, M.N.; Carlogea, I.-S.; Dragan, S.-R. Insulin Resistance in Long COVID-19 Syndrome. *JPM* **2024**, *14*, 911, doi:10.3390/jpm14090911.
105. Potter, J.J.; Liu, X.; Koteish, A.; Mezey, E. 1,25-dihydroxyvitamin D3 and Its Nuclear Receptor Repress Human α_1 (I) Collagen Expression and Type I Collagen Formation. *Liver International* **2013**, *33*, 677–686, doi:10.1111/liv.12122.
106. Shany, S.; Sigal-Batikoff, I.; Lamprecht, S. Vitamin D and Myofibroblasts in Fibrosis and Cancer: At Cross-Purposes with TGF- β /SMAD Signaling. *AR* **2016**, *36*, 6225–6234, doi:10.21873/anticancerres.11216.
107. Mehrani, Y.; Morovati, S.; Tieu, S.; Karimi, N.; Javadi, H.; Vanderkamp, S.; Sarmadi, S.; Tajik, T.; Kakish, J.E.; Bridle, B.W.; et al. Vitamin D Influences the Activity of Mast Cells in Allergic Manifestations and Potentiates Their Effector Functions against Pathogens. *Cells* **2023**, *12*, 2271, doi:10.3390/cells12182271.
108. Hikmet, R.G.; Wejse, C.; Agergaard, J. Effect of Vitamin D in Long COVID Patients. *IJERPH* **2023**, *20*, 7058, doi:10.3390/ijerph20227058.
109. Matangkha, K.; Punyahotara, V.; Rintra, J.; Sittiprapaporn, P. Association Between Vitamin D Levels and Long COVID Signs and Symptoms. *Medical Sciences* **2025**, *13*, 199, doi:10.3390/medsci13030199.
110. Kodama, S.; Nakata, M.; Konishi, N.; Yoshino, M.; Fujisawa, A.; Naganuma, M.; Kobayashi, Y.; Hirai, Y.; Kitagawa, A.; Miyokawa, M.; et al. Vitamin D in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome After COVID-19 or Vaccination: A Randomized Controlled Trial. *Nutrients* **2026**, *18*, 521, doi:10.3390/nu18030521.

111. Chang, S.H.; Chung, Y.; Dong, C. Vitamin D Suppresses Th17 Cytokine Production by Inducing C/EBP Homologous Protein (CHOP) Expression. *Journal of Biological Chemistry* **2010**, *285*, 38751–38755, doi:10.1074/jbc.C110.185777.
112. Cai, Z.; Rui, S.; Huang, N.; Feng, F.; Luo, Y. The Role of Vitamin D in Sleep Regulation: Mechanisms, Clinical Advances, and Future Directions. *Front. Nutr.* **2025**, *12*, 1595813, doi:10.3389/fnut.2025.1595813.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.