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Mast Cells in Connective Tissue Regulation and Altered Regulation in Hypermobility Ehlers-Danlos Syndrome (hEDS): Why the Association of Mast Cell Activation Syndrome and hEDS?

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ABSTRACT

Mast cells (MC) arose early during the evolution of the immune system. While these cells are very involved in host defense against a variety of organisms, they are also found associated with many connective tissues of the musculoskeletal system. As MC contain granules with many potent biologically active mediators and can also synthesize others, their presence in connective tissues could pose a risk for compromise of connective tissue integrity. Despite such risk, the presence of MC in these tissues may imply that they also serve functions related to tissue homeostasis, repair and adaptation, and are capable of functioning in a variety of biomechanically active environments. Their dysregulation, such as in Mast Cell Activation Syndromes (MCAS) could contribute to conditions associated with loss of connective tissue integrity. Interestingly, MCAS has also been reported to be associated with subsets of patients with hypermobility Ehlers-Danlos syndromes (hEDS). This perspective article discusses the potential roles of MC in normal connective tissue states and then discusses aspects of the relationship between MC and hEDS. It is concluded that there is a need to better understand the role of MC in this context, and how the study of the involvement of MCAS and EDS presents a model to examine these relationships in detail.

1. INTRODUCTION

1.1. Purpose of the Article

The purpose of this article is to attempt to integrate a number of different lines of information regarding

the role of mast cells (MC) in connective tissues of the musculoskeletal (MSK) system with emerging findings associated with mast cell activation syndrome (MCAS). In addition, the apparent association of MCAS with conditions arising from alterations to the integrity of joint tissues (via mutations or as yet unknown mechanisms), such as hypermobility Ehlers-Danlos syndromes (hEDS), is discussed and gaps in understanding how these variations impact connective tissue regulation during responses to injury are discussed. Finally, a number of areas that need further investigation are identified that will fill gaps in our understanding of the role of MC in processes affecting connective tissue function.

This is a narrative perspective that was developed primarily via interrogation of PubMed from January 15, 2026, to its origins. Search terms included "mast cells and wound healing", "mast cells and tendons", "mast cells and intervertebral disc", "Mast cell activation syndrome", Mast cell activation disorders", "Mast cells and Ehlers-Danlos syndrome", "Mast cells and Marfan syndrome", "Mast cells and "Loey-Dietz syndrome", and variants of the indicated terms. Emphasis was placed on human studies and preclinical findings using as needed to support concepts.

1.2. Background

MC are very ancient cells, arising early during evolution [1]. In modern *Homo sapiens*, they arise in the bone marrow, enter the circulation and then migrate to tissues. MC are considered components of the innate immune system and are effectors of products of the specific immune system, immunoglobulin E (IgE) [2]. However, they can contribute to anaphylaxis via both IgE-dependent and IgE-independent pathways [3]. MC play important roles in host defense against a variety of microorganisms including bacteria, viruses, fungi and parasites [4, 5].

In the modern era, MC were first described in the 1800s [1] and were then mainly discussed in relation to allergies and asthma due to their role of binding IgE to specific receptors, leading to degranulation and release of mediators such as histamine, proteinases, and other factors [6]. Their role in anaphylaxis with very rapid response to triggers was/is a hallmark of MC reactivity. In contrast, asthma is a more chronic condition involving MC and inflammation [7].

However, MC also appear to serve a variety of other functions, particularly in the context of connective tissues of the musculoskeletal (MSK) system [8]. In normal ligaments of the knee, it has been shown that the sparse innervation can end associated with a mast cell [9], indicating that perhaps neuroregulatory functions are mediated via mast cells to amplify the influence of the nerves via mediators released from associated tissue mast cells following neuropeptide-induced degranulation. Similarly, MC have been reported in tissue associated with the enthesis of the Achilles tendon (AT) [10]. They are also found in the synovium of the knee [11, 12], the highly innervated joint capsule [13], as well as in close approximation to sensory nerve elements in skin [14]. A recent report has indicated that there are distinct functional subpopulations of MC [15], but whether the MC in different tissues, such as in tissues of the MSK system, are unique subpopulations of these cells remains to be determined. However, in mice mucosal MC differ from tissue MC in expression of cell-surface CD103 and granule proteases [16].

Thus, the sparse innervation of most joint tissues may exert normal regulatory functions via controlled "inflammation" at the level of MC degranulation and subsequent influence of MC cell-derived mediators on endogenous cells in the tissues. In such circumstances, tissue-associated MC may exert critical roles in tissue homeostasis, repair, as well as defense from adverse stimuli [17].

In a variety of conditions, mast cells are reported to be influenced by neuropeptides and transmitters [18, 19]. Thus, MC appear to be intimately involved with cells of neural origins and can be regulated by them.

In summary, MC are cells of the innate immune system that are reported to function in a variety of roles in MSK tissues as well as in host defense and allergic reactions. Their roles in tissues of the MSK system appear to be dependent, in part, on interactions with neural elements. Whether unique subsets of MC have specific roles in MSK tissues remains to be determined in detail.

2. ROLE OF MAST CELLS IN MSK CONDITIONS

2.1. Skin Wound Healing

Normal Skin Wound Healing:

A number of studies have indicated that MC may play a profibrotic role in normal wound healing but a consistent role across species has yet to be clearly defined [20-22]. Products of MC appear to facilitate a variety of fibroblast and vascular activities, as well as inflammatory activities early in the healing process. However, in mouse models where MC have been deleted, wound healing progresses fairly normally, thus questioning the need for MC in healing [20]. While mice are a "loose skin" species and skin wounds heal mainly by contraction, the need for MC in skin wound healing in domestic pigs, a "tight skin" species is also in question [23]. In the latter species, it was shown that treatment of excisional dorsal skin wounds on Yorkshire pigs, a strain of pig that heal normally, was not affected by immediate treatment of the animals with ketotifen, a mast cell stabilizer [23]. Therefore, MC may not be required for skin wound healing in either loose or tight skinned species unless there is some underlying compromise of the healing response.

Abnormal Human Skin Wound Healing and Mast Cells:

While a prominent role for MC in the normal healing of human skin has not been identified, MC have been implicated in abnormal healing of injuries to human skin. These include conditions such as keloid scars and hypertrophic scarring [24]. Keloids can be large growths of fibrous tissue that grow beyond the boundaries of the injury site [25, 26], with collagen deposition and myofibroblasts. There is a genetic component to the formation of keloids [27], with the risk for keloid formation higher in some races, such as Blacks and African Americans [28]. MC have been implicated in the dysregulation that occurs leading to keloid formation and progression [29-33], with many degranulated MC in keloid tissue [29]. In addition, a role for neural cells in keloids has also been reported [34]. Thus, MC, neural elements and myofibroblast interactions appear to be dysregulated in keloid formation and progression. It has also been reported that keloids are also a risk factor for development of arthrofibrosis following a total knee replacement [35] and therefore the genetic risk associated with keloid formation may not be location or site specific.

MC have also been implicated in the formation and progression of hypertrophic scarring, a common consequence of an injury such as a burn [36-39]. In contrast to keloids, hypertrophic scarring usually stays within the boundaries of the injury but are raised and often itch [40]. Similar to keloids, some races and ethnicities, such as those of the Black race, are at more risk for such scar development than others [40]. Also similar to keloids, nerve involvement in hypertrophic scars has been reported [41, 42].

Therefore, MC, nerves and myofibroblasts have been implicated in both keloid and hypertrophic scars. While implicated, some aspects of the involvement of MC and the cellular inter-relationships remain to be determined.

Preclinical Pig Models: Role of genetics in mast cell involvement

Domestic pigs are a tight skin species, similar to humans and a species with a physiology similar to humans. Porcine breeds are only ~15%-20% inbred as they exhibit defects with excessive inbreeding, again similar to humans. In contrast to the dorsal excisional skin wounds on Yorkshire pigs, such wounds on red Duroc pigs heal with an abnormal phenotype of hypercontracted and hyperpigmented scars [43]. Analysis of dorsal skin wounds on Yorkshire x red Duroc F1 animals revealed that the scars were still somewhat hypercontracted but not hyperpigmented [44]. Back cross Yorkshire x F1 animals exhibited neither hypercontraction nor hyperpigmentation [45, 46]. Therefore, there is a genetic component to the abnormal healing of dorsal wounds in red Duroc pigs.

That this abnormal healing involved mast cells comes mainly from the treatment of red Duroc pigs with the mast cell stabilizer ketotifen immediately after dorsal skin wound generation via the oral route. Such treatment led to the complete abrogation of the hypercontracted, hyperpigmented phenotype [23]. As oral mucosal wounds heal in a more normal manner compared to dorsal skin wounds in red Duroc pigs [47, 48], there appears to be some location effect of the abnormal phenotype of dorsal wound healing in this model. However, it has been noted that there are biomechanical differences between healing of medial collateral ligament healing between Yorkshire and red Duroc pigs [49], but whether these differences were

impacted by ketotifen treatment has not been investigated. Finally, the ability of fibroblasts from dorsal and ventral skin of red Duroc animals to contract collagen gels is reported to be intrinsically different [50], and therefore, there may be differences in the role of mast cells in the healing of dorsal and ventral skin wounds, but this needs further study. Such findings may also indicate that some of the abnormal dorsal healing phenotype of red Duroc pigs may reside in the fibroblasts and myofibroblasts, as well as nerves [51, 52], in addition to processes involving mast cells. As dorsal and ventral patterning arises from different cell populations, the above findings may provide avenues to generate additional details regarding the interactions between mast cells and the myofibroblasts.

In summary, evidence from these pig models indicates that mast cells play a central role in the development of an abnormal dorsal skin wound healing phenotype in red Duroc pigs, but evidence for their role in the normal healing of skin wound in Yorkshire animals could not be detected using drugs that interfere with mast cell functioning.

2.2. Tendon Healing and Tendinopathies

Tendons are connective tissues that function in mechanical active environments to convey muscle forces to bones to initiate movement and mobility. Some, such as the AT and patellar tendon (PT) function in a high load environment, while others function in lower load environments. Functioning in a high loading environment, the AT and PT are prone to develop overuse leading to chronic pain and disfunction labeled tendinopathy, tendinitis or tendinosis. The potential role of MC in tendon healing and related inflammatory processes has been discussed by Alim *et al.* [53], as well as Behzad *et al.* [54] and Dean *et al.* [55], but their role in tendon healing may still require more study [56].

Increased number of mast cells have been reported in human PT tissue affected by pain and presumed tendinopathy, and the numbers correlated with symptom duration [57], Mast cell numbers have also been reported to be elevated in the tendon sheaths of trigger fingers, a chronic condition involving tendons and tendon sheaths of the hand, as assessed by anti-mast cell tryptase staining [58]. MC have also been reported to be elevated in a rat tendon overuse model [59] and a rabbit flexor tendon healing model [60]. In the latter report, there were also elevations in myofibroblasts and neuropeptides during healing. This latter finding regarding neuropeptides is interesting and potentially highly relevant as neuropeptides can activate MC and induce degranulation and cytokine expression [61, 62]. Furthermore, neuropeptides and nerves are reported to play a role in tendinopathy [63] and in tendon healing [64-66]. Increased numbers of degranulated MC have been reported in a rat AT healing model and in close association with the NMDA-1 receptor, a glutamate receptor [67]. In addition, immobilizing an injured joint can lead to compromised healing and decreased expression of neuropeptide receptors on cells in a rat AT healing model [68].

Finally, inhibiting MC activation using extracellular vesicles from human iPSC ameliorated tendinopathy in a rat model [69], and treatment of CD-1 mice with sodium cromolyn, a MC stabilizer, following a PT injury compromised healing [70]. Thus, MC have been implicated in a variety of preclinical models and in humans regarding tendinopathy and healing of tendons. However, some of the MC involvement may also involve nerves and neuropeptides, with the latter impacting both MC and endogenous tenocytes. The timing and doses of neuropeptides may have an impact on whether outcomes are positive or negative [71, 72], and the cells involved are complicated and remain to be further detailed.

2.3. MC in Joint Contracture Development and Joint Trauma Outcomes

Trauma, including fractures, to joints mainly heals with outcomes restoring function. However, in 10% - 15% of cases, the healing process leads to development of a joint contracture with loss of function [73, 74]. In the case of joint contractures of the elbow following an injury, the loss of function can have severe consequences on quality of life and compromised daily living. Why joint contractures develop has been poorly understood, but more recent studies have implicated MC in their development.

Initially, it was determined that myofibroblasts were elevated in human elbow joint contractures [75-77], and then it was also determined that MC and neuropeptides were increased early and then subsequently during the chronic stages of the posttraumatic elbow contractures [78]. Interestingly, assessment of serum

levels of MC tryptase revealed that levels were elevated early after an elbow injury, with the highest levels observed for those with the most severe injuries, often requiring surgery and at risk for contractures [79]. Additional in vitro studies with human joint capsule fibroblasts, mast cells, neuropeptides and antagonists led to the hypothesis that a myofibroblast-mast cell-neuropeptide axis of fibrosis was operative in the development of joint contractures [80].

Testing such a hypothesis was accomplished via development and characterization of a rabbit model of joint contracture. A rabbit model consisting of a knee joint injury including the capsule followed by immobilization led to a joint contracture with a number of alterations to the joint capsule noted [81]. Many of the changes noted in the rabbit model correlated with similar changes in the analysis of human joint contracture samples [81]. Further support for the involvement of MC in contracture development in this model came from assessment of serum MC tryptase levels [82], where levels were elevated during contracture development and could serve as a surrogate marker for MC activation.

Subsequent studies using the MC stabilizer ketotifen in this rabbit model determined that early exposure to the drug led to a 50% reduction in joint contracture severity [83-85]. Exposure to the drug reduced myofibroblast hyperplasia and fibrosis, indicating that MC products were contributing to myofibroblast numbers and function. Decreases in nerve fibers in capsule tissue were also noted. Assessment of serum MC tryptase levels revealed that ketotifen treatment of the rabbits led to decreased serum levels of this proteinase [82].

The findings from both the human tissue analysis and the rabbit model led to the formation of the hypothesis that there was a "neuro-mast cell-myofibroblast axis" operative during joint contracture development involving the very innervated capsule [51, 52, 80]. While details regarding the validity of such an "axis" remain to be determined, it should be noted that exposure to ketotifen only reduced contracture severity by ~50%. Thus, the putative "axis" may not operate in a linear fashion (*i.e.*, nerves-neuropeptides—MC—myofibroblasts) but potentially in a more complicated cell-interaction manner [52] (represented in **Figure 1**). Thus, rather than using a single drug intervention (*i.e.*, ketotifen), to achieve a more effective outcome in preventing joint contractures may require a "cocktail" of drugs to impact the functioning of multiple cells in such an axis! This may include drugs to interfere with neuropeptides and their receptors, as well as those that influence myofibroblast activity.

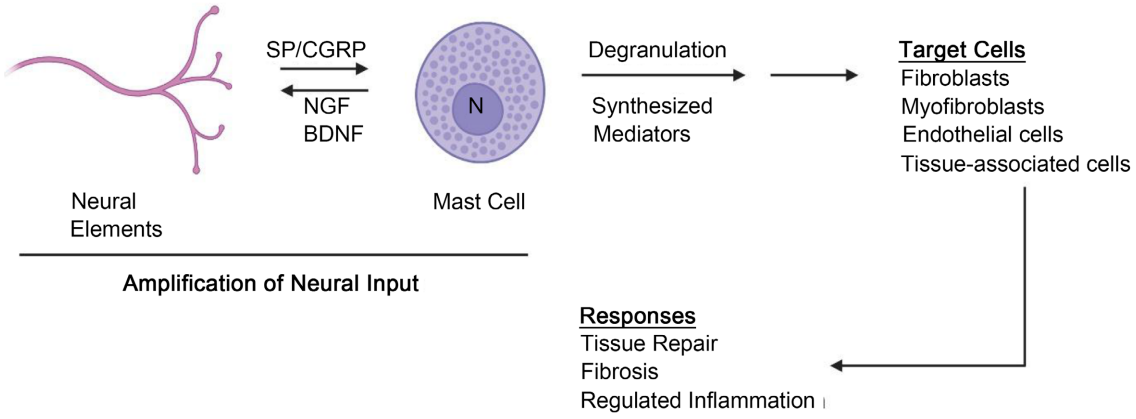

Figure 1. Connective tissue "neural-mast cell-fibroblast/endogenous cell axis". In this postulated axis of tissue regulation, neural elements can impact mast cells via neuropeptides such as SP and CGRP and vice-versa via NGF and BDGF. Subsequently activated mast cells can influence endogenous cells in the tissues such as fibroblasts to modulate their metabolic activity.

However, given the efficacy of ketotifen exposure in the pig and rabbit models, the safety profile of the drug, and the correlations with the human joint contracture tissue analysis, clinical trials have been initiated to assess the ability of ketotifen exposure to prevent or diminish development of a contracture following an elbow injury [73, 74]. The results of such trials should be released in the near future and after evaluation,

perhaps multi-drug composite interventions may be envisioned.

In summary, MC appear to participate in abnormal healing responses but are apparently not essential for processes leading to normal repair. Whether this is due to alterations in the MC themselves or to altered regulation of the MC, possibly by dysregulation of interactions with neural elements remains to be elucidated in detail. Thus, the role of MC in several biological processes is very context dependent, and one cannot generalize due to the complexity of biological regulation and the potential role of currently unknown variables. Thus, in some circumstances, mast cell inhibition reduces fibrosis but can also impair tendon healing in other models. In most studies, it cannot be determined whether the MC play a primary role early in the healing process or later as the drug interventions were started at the time of injury.

3. ROLE OF MC IN INTERVERTEBRAL DISC DEGENERATION AND SCIATICA

Intervertebral discs (IVD) can be viewed as complex organ systems comprised of multiple tissues organized in a specific fashion that contributes to function [86]. Two of the main components contributing to mechanical function are the annulus fibrosus (AF) and nucleus pulposus (NP). Both are designed to contribute to complementary aspects of IVD function, namely an internal NP surrounded by a complex collagen-rich AF matrix designed to resist compression and shear. The NP is hypocellular, aneural and avascular while the AF is hypocellular, hypovascular and hyponeural [86]. The NP contains detectable levels of MC, but the AF does not [86, 87].

With aging, changes to the IVD can be observed leading to a transformation from a collagen II-rich environment to an ECM more fibrocartilage-like [88, 89]. As the NP is both aneural and avascular, this means that the endogenous mast cells can potentially initially interact with the notochordal cells in the NP in a paracrine manner and also may participate in the events leading to the transformation of the NP (depicted in **Figure 2**).

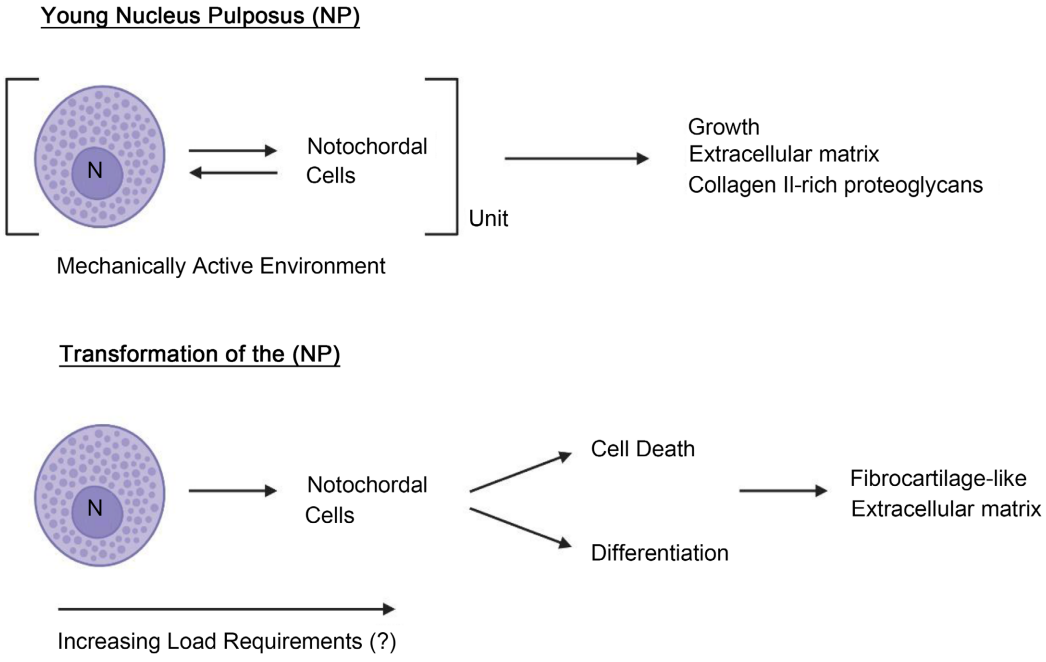

Figure 2. Potential interactions between mast cells and endogenous cells in the nucleus pulposus (NP) of the intervertebral disc. In the young NP, endogenous mast cells and the notochordal cells, the major endogenous cell type, form a hypothetical "unit" to regulate growth and maturation of the extracellular matrix. During the transformation of the NP to become more of a fibrocartilage tissue, the endogenous mast cells participate in the transformation via as yet unknown mechanisms to facilitate the transformation.

It is not clear when degeneration is initiated, but overt degeneration is likely a chronic condition and separate from aging alone discussed in [90]. Numerous reports and reviews in the literature have implicated MC in the development and progression of this degenerative process [87, 91-93]. In particular, MC may participate in the neovascularization and neoinnervation of the NP undergoing degeneration (depicted in Figure 3). These processes could be facilitated by the release of mediators such as VEGF [94] and NGF [95] and BDNF [92, 96] for neovascularization and neoinnervation, respectively.

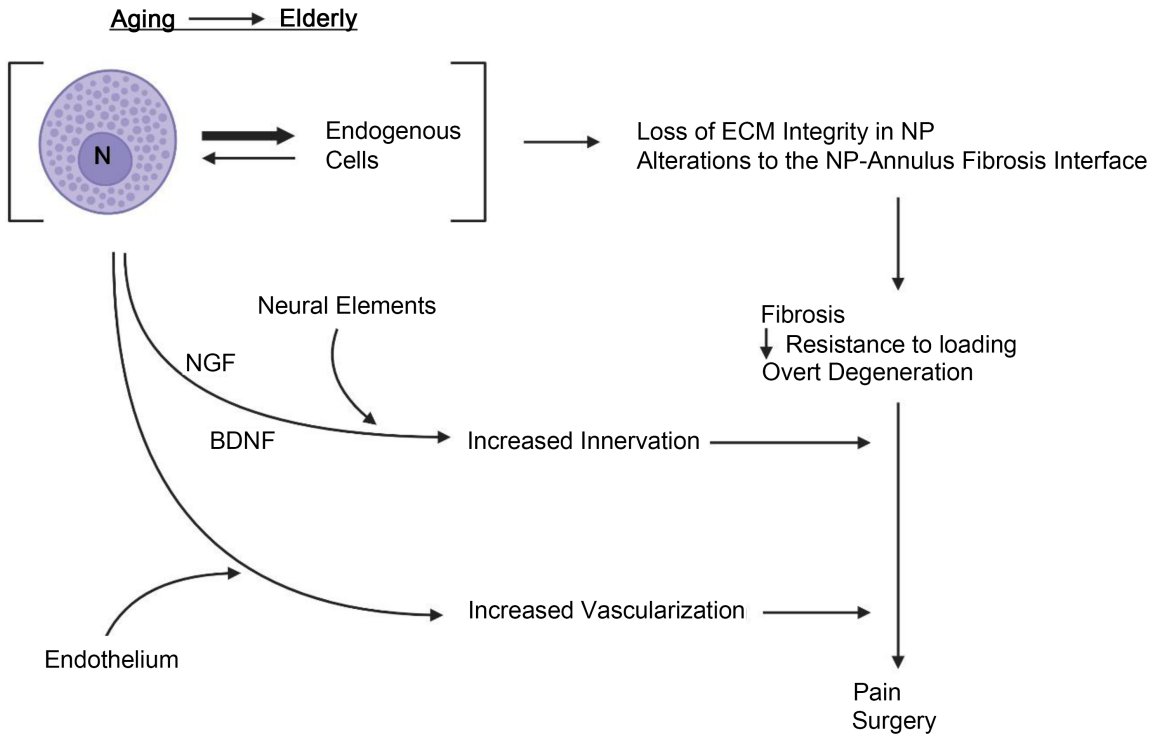

Figure 3. Potential role of mast cells in intervertebral disc degeneration. During normal aging, there appears to be a progressive loss of NP and AF integrity leading often to development of overt degeneration with concomitant symptoms such as pain. This degeneration is accompanied by neovascularization and innervation of the NP. Endogenous mast cells may participate in this process via release of mediators such as VEGF (neovascularization) and NGF + BDNF (innervation), as well as proinflammatory mediators affecting ECM synthesis by other endogenous cells.

In patient populations, MC can be detected in samples of tissue obtained at the time of surgery, so it is not possible to ascertain a role for MC in initiation of a degenerative process, only disease progression. Furthermore, information regarding the use of MC-targeting drugs or interventions in IVD degeneration could not be found in the available literature.

In contrast to IVD degeneration, which is a chronic condition evolving over years, sciatica is an acute IVD condition where a defect in tissue integrity leads to the sudden extrusion of part of the NP resulting in nerve impingement and severe pain [97]. Sciatica most often develops in those 30 - 50 years of age, so are a still fairly young population. Patients are usually treated with pain medication for 3 - 4 months as in ~85% - 90% of such cases, the extruded NP material is resorbed, and the nerve impingement resolves. Why 10% - 15% of the patients fail to resorb the extruded NP tissue is not known, but such patients require surgery to remove the extruded material and relieve the nerve impingement.

As MC appear to be regulated in part by mechanical loading [98, 99], the MC in the extruded NP could become released from any mechanical constraints of their natural environment leading to activation with

degranulation and release of proteinases, as well as altered responsiveness to proinflammatory mediators that lead to a further influx of inflammatory cells that contribute to destruction of the extruded materials and resolution of the pathology. Once removed from its natural environment NP has been shown to be pro-inflammatory [100], which is consistent with what may happen in a majority of sciatica patients. In contrast, in a small subset of patients (the 10% - 15% discussed above), the environment in the extruded NP material leads to MC degranulation but perhaps under the influence of adjacent neuropeptides from the nerve impingement such degranulation activates myofibroblasts to initiate a fibrotic response with the generation of a non-resorbable extruded tissue that leads to persistent pain and the need for surgery. Validation of this concept will require future research studies.

In summary, MC have been readily detected in degenerated disc tissues, but their presence in normal AF and NP remains to be determined in detail, with the latter likely due in part to methodologic challenges. In addition, as all human studies are cross sectional in nature, when MC are present it is not known if they played a role in early disease development, or are involved in later disease progression. Therefore, the role of MC in IVD disease initiation versus progression also remains to be elucidated. Similarly, the role of MC in the resolution of sciatica remains speculative. How MC participate in pro-fibrotic versus anti-fibrotic processes appears to be context related, due primarily to a current lack of understanding regarding all of the variables involved.

4. THE CONUNDRUM OF MAST CELL ACTIVATION DISORDERS/SYNDROMES AND THEIR ASSOCIATION WITH JOINT HYPERMOBILITY SPECTRUM DISORDERS

In most connective tissues of the MSK system, the numbers of resident MC are low and therefore must be regulated to retain their functions in such tissues. As all of these tissues are mechanically active, the resident MC are able to exist and function in such environments and respond to disruption of the mechanical aspects of the tissues [98, 99].

However, there are individuals in which the regulation of MCs is disrupted in a more systemic manner, leading to what are labeled Mast Cell Activation Disorders (MCAD) or Mast Cell Activation Syndromes (MCAS) [101-104]. MCAD are a heterogeneous group of clinical entities in which mast cell activation is central to the symptoms [104]. In contrast to MCAD, MCAS are a clinically defined set of conditions with an outlined set of criteria discussed in [104]. While these designations are evolving, in the present discussion the term MCAS will be used.

While MCASs are relatively rare conditions (~2% - 4%, discussed in [105-107]), it has been reported that up to ~25% of individuals with Joint Hypermobility Syndrome (JHS) also have MCAS [108, 109]. MCAS can impact a number of conditions beyond tissues of the MSK system and can be labeled as primary, secondary, or idiopathic discussed in [110]. Thus, questions related to the Why and How MCAS and JHS are related are a conundrum that needs to be addressed.

4.1. Mast Cell Activation Syndrome

MCAS conditions are somewhat rare but impactful diseases and may not be as rare as initially thought. Some reports indicate a prevalence of ~17% of the population, but others indicate a prevalence of only ~2% discussed in [105], 4% [107], or 4.4% MCAS [111]. The MC component may be clonal or non-clonal which may influence how the condition is treated [discussed in [103, 104, 107, 112]. MCAS is also often found in association with postural orthostatic tachycardia syndrome and hypermobility syndromes [113, 114], as well as skin conditions [115] and neurologic and psychiatric conditions [116]. Patients with MCAS can have elevated levels of mast cell mediators such as tryptase and metabolites of other mediators in serum and urine which can assist in the diagnosis [117].

Treatment of MCAS has addressed anaphylaxis as a major focus [103, 104, 107]. It is also important to determine the subtype of MCAS a patient has as some variants have a genetic basis, but the majority do not [104, 106, 107]. Thus, diagnostic parameters are critical to define. However, rapid measurement of serum mast cell tryptase can be used as a criterion for acute events associated with mast cell degranulation [118].

For many patients, the use of antihistamines can be a preventative approach, but they do not work for all patients. Other patients are treated with the humanized antibody omalizumab to target IgE/IgE expressing cells [102, 112, 119-123].

The molecular basis for the development of the subsets of MCAS is being defined, and that there are multiple subtypes that arise via different mechanisms is being investigated and definitions characterized and clarified [104]. Thus, MCAS is an umbrella term for the disorder and additional research is needed to provide more detail and understanding of how and why such syndromes develop and their consequences. In part this is due to MCAS arising in complex patients and issues around the diagnostic criteria employed discussed in [104-106].

4.2. Association of MCAS and hypermobility Ehlers-Danlos Syndromes (hEDS)

A significant number of individuals have joints with an excessive range of motion compared to the majority of humans, with many of them assigned as having JHS. These can include those with various forms of Ehlers-Danlos [124, 125], Marfan [126, 127], or Loey-Dietz [128] syndromes (reviewed in [129]). Nearly all of these syndromes are associated with genetic mutations of matrix molecules, except for hypermobile EDS (hEDS) which is a hypermobility syndrome for which no specific ECM molecule genetic abnormality has been described discussed in [129]. However, there is a report that a patient with hEDS had a mutation in the MIA3 gene which is a collagen transporter [130]. Thus, there is heterogeneity in the phenotypes associated with different genotypes, so background genes appear to influence both the organs affected and the extent of impact on tissues such as joints.

Mast cells have been reported to be involved in regulating the extracellular matrix of individuals with Marfan's Syndrome [131, 132], as well as hEDS and Hypermobile Spectrum Disorder (HSD) [133]. However, it is the strong association of MCAS with hEDS that is somewhat remarkable in that up to ~25% of hEDS patients also are reported to have MCAS discussed in [109, 113, 114]. However, only a small subset of patients with MCAS also have hEDS [134-137], and therefore MCAS can exist separately from hEDS.

4.3. The "Why and How" of the Association of MCAS and hEDS and JHS, and Consequences: What Lessons to Be Learned?

A limitation of a discussion regarding the "How and Why" of the association of MCAS and hEDS is that little is known about the "How and Why" of MCAS alone. Thus, one cannot conclude that the association is due to a unique environment generated by the hEDS via as yet undocumented mutations leading to disturbances in MC regulation. Why only 25% of hEDS patients are affected by the presence of MCAS may potentially mean that MCAS arises in only some forms of hEDS with specific currently unknown mutations, or secondarily due to alterations in a separate cell type, such as small neural fibers in some connective tissues [138]. Variation in background genes may also play a role in the elaboration of the phenotype, but this is a speculation at this point.

4.3.1. Could There Be Altered MC Function in hEDS Due to an Altered Organization of the ECM?

While specific gene alterations have not been reported for hEDS, the ECM has been reported to be altered from "normal" [128]. The finding of hEDS as well as altered skin characteristics in some patients [138], likely means that the altered ECM properties are not restricted to just tissues of the joints. However, some of the ECM alterations could be tissue-specific due to variation in background gene expression.

As MC bind to the local matrix and are likely regulated by such interactions via cell expression of integrins [139, 140] and possibly cell-surface lectins [141], discussed in [142] and the ECM. An altered content and organization of connective tissues in hEDS and JHS could lead to subsequent dysregulation of MC. As MC are present in mechanically active tissues such as those of the joints, skin and the heart, perhaps the compromised mechanical environment posed by hEDS also contributes to the MC being more readily activated to degranulate or secrete inflammatory mediators (depicted in **Figure 4**).

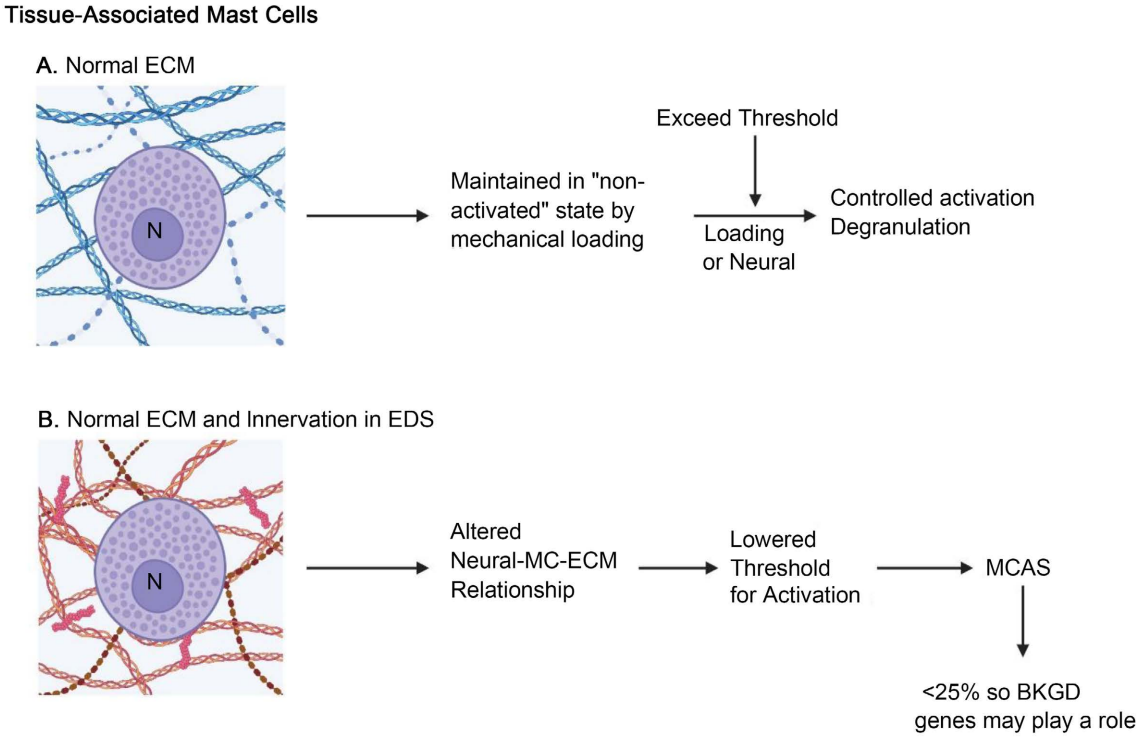

Figure 4. Possible mechanism for the association of MCAS and EDS. Panel A: In the normal ECM, mast cells are maintained in a "non-activated" state by interacting with the ECM via cell-surface integrins under loading of the tissue. Innervation of the tissue leads to normal regulation as per Figure 1. Panel B: In EDS with an altered ECM and a paucity of neural elements, there is an altered environment for stabilizing the mast cells via integrins and neural regulation. This leads to a decreased threshold for activation of the mast cells and onset of a form of MCAS. Whether this reflects a unique subpopulation of mast cells is unknown. Why the co-expression of MCAS and EDS is only ~25% is also unknown and may reflect the influence of background genes.

Thus, the form of MCAS arising in hEDS patients may be a unique subtype of MCAS. However, the fact that the incidence of ~25% of hEDS and JHS patients with MCAS would indicate that the association is more complicated and perhaps background genes and their expression may be limiting the elaboration of MCAS in these patients. Further studies regarding sex differences, serum levels of mast cell tryptase, joint contractures, and co-morbidities such as asthma and other complexities in hEDS patients with and without MCAS could lead to better understanding of the causes of MCAS and the basis for the association of MCAS and hEDS in only a subset of hEDS patients.

4.3.2. hEDS and MCAS, and Disrupted Neuroregulation

In several connective tissues, there is an intimate positional relationship between neural elements and mast cells [9, 14]. As discussed earlier, a nerve-mast cell-myofibroblast axis [8, 51, 52] has been proposed to influence abnormal skin wound healing, development of joint contractures, and other mast cell-involved processes. However, mast cells did not appear to be involved in the normal wound healing process as ketotifen treatment had no detectable impact on outcomes [23]. This dichotomy implies that perhaps this axis is kept under control under normal circumstances by neuroregulatory processes such that the potential for unintentional activation is minimized. This could be an active process, involving both an intact ECM and adequate neuro-derived maintenance of a threshold for activation of the tissue-associated mast cells. Therefore, if this regulatory system was functional, one could induce mast cell degranulation by an overactive

neuro component leading to neuroinflammation, and also a decreased threshold for mast cell activation if there was a deficiency of the neuro component in the tissue.

Relevant to this discussion are reports that individuals with some forms of EDS have peripheral neuropathy, with small nerve fibers in tissues such as skin [138, 143, 144]. Many with hEDS also have fibromyalgia [145, 146] and chronic fatigue syndrome [147-149]. Other reports indicate some individuals have autonomic disturbances [150] and issues regarding brain development. In total, there are several direct and indirect indications that the mutations in ECM molecules contribute to neuro-deficiencies or alterations to neuro systems that may be more central to biological regulation via a neuro-mast cell axis and also relevant regarding joint hypermobility and cardiovascular abnormalities. This speculation may explain the association of MCAS with EDS subtypes, but the basis for why it is only evident in 25% of the hEDS individuals requires more investigation.

While the above speculations regarding the MCAS-EDS association may explain, in part, the basis in that context, it does not explain the basis for MCAS in the absence of hEDS. Clearly more research is required to explore the basis for MCAS +/- hEDS, but also MCAS alone. This could be an exciting area for research that may have extensive implications beyond joint hypermobility.

Finally, it remains to be determined if the MCAS arising in the context of hEDS is due to a unique subset of MC, a subset associated with connective tissue impacted by the EDS. Therefore, further studies on the characteristics of the MC arising in hEDS individuals should be undertaken to perhaps confirm or refute this possibility.

In summary, a subset of individuals with hEDS have also been diagnosed with MCAS, but the association of these two conditions vary widely in different reports. As MCAS can occur independently of hEDS, it is not yet known whether the association of MCAS with hEDS is stochastic or arises due to the alterations contributing to development of hEDS. The mechanistic relationship for this association remains somewhat speculative until further details are elucidated. Details regarding the main uncertainties, including MCAS heterogeneity, the molecular basis for hEDS, the relationship between neuroregulation, the ECM in hEDS, and direct versus indirect causal relationships will be required to make solid conclusions in this area. Finally, details regarding the potential impact of MCAS on the characteristics of hEDS functional features needs more understanding.

5. CONCLUSIONS

Mast cells developed very early in evolution and most often associated with host defense and allergies. However, MC are found in many tissues of the MSK system where their role may have additional roles regarding tissue homeostasis, would repair and maintenance of tissue integrity while operating in mechanically active environments of different mechanical types and intensities, as well as different ECM composition and structure. In these tissues, they can also form paracrine relationships with different cell types (*i.e.*, subsets of fibroblasts, neural elements, notochordal cells, endothelial cells). Therefore, it is likely that tissue-associated MC are not passive occupants of the tissues but active participants in tissue regulation.

In this backdrop of MC and tissues of the MSK system is the emergence of MCAS in which MC appear to become readily activated and their control dysregulated. Such dysregulation may be either clonal or non-clonal/multiclonal. In the case of the non-clonal circumstance, it is not yet known if this represents a unique subpopulation of MC. The finding of an association of MCAS with hEDS, a condition known to lead to altered ECM composition, structure and function, may indicate that the regulation of subsets of tissue-associated MC in mechanically active environments requires an intact and functional ECM. Thus, operating in a compromised ECM may lower the threshold for activation directly or indirectly leading to enhanced activation. How such activation of MC may contribute to the compromise of the ECM in hEDS patients requires further investigation, as does further characterization of the MC involved to ascertain whether they represent a unique subset.

In conclusion, MC are potent cells of the immune system and are cells that may have roles that extend beyond those attributed to allergy and host defense to include connective tissue regulation. Their dysregulation,

such as in MCAS could pose a risk for loss of integrity of a number of connective tissues. Further understanding of the role of MC in connective tissues may alleviate such risk and provide new approaches to maintain and regenerate these tissues.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest regarding the preparation and publication of this article.

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