Tendon and Mast Cells

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Understanding the links between the tendon healing process, inflammatory mechanisms, and tendon homeostasis after tissue damage is crucial in developing novel therapeutics for human tendon disorders. The inflammatory mechanisms that are operative in response to tendon injury are not fully understood, but it has been suggested that inflammation occurring in response to nerve signaling, i.e., neurogenic inflammation, has a pathogenic role. In this review, we discuss the role of mast cells in the communication with peripheral nerves, and their emerging role in tendon healing and inflammation after injury.

Keywords: Tendon, Tenocytes, Collagen, Mast cells

1. Introduction

Tendon is a crucial component of the musculoskeletal system that connects muscle to bone and transmits force for the movement [1][2]. Tendon is a soft connective tissue and is predominately composed of water, which makes up 55–70% of the total tendon weight. The other major component of tendon is collagen, which represents about 60–85% of the dry weight of tendon [3]. In tendon architecture, fibrillar arrangement of triple-helical type I collagen molecules generates collagen fibers, which then combine to form fascicles and, ultimately, the tendon tissue. The type I collagen molecule contains two identical α1 chains and one α2 chain, which are encoded by col1a1 and col1a2, respectively [4]. The collagen fibrils are the fundamental force-transmitting element of tendon tissue, and are tightly arranged within the extracellular matrix. Type I collagen and associated extracellular matrix components are produced by tenocytes, which are fibroblast-like cells found between collagen fibers and in the surrounding of the endotenon [5]. Tendons also contain other cell types such as chondrocytes, vascular cells, synovial cells, tendon stem cells (TSCs) including mast cells. Tendon mast cells are in the normal state resident locally in the tendon tissue or in the loose connective tissue close to the paratenon, muscle–tendon junction, or bone–tendon junction [6]. However, during the tendon healing process, they may migrate to the injured site (tendon proper) following inflammation and nerve ingrowth [6][7]. In addition to tendon cells and collagen, other molecules like elastin and proteoglycans are also integral parts of the tendon [8]. There are two main markers of collagen metabolism: procollagen type III N-terminal propeptide (PIIINP) and procollagen type I N-terminal propeptide (PINP). Both have been used as early prediction markers for healing tendon and bone [9]. Procollagen type I and III are essential building blocks in all types of connective tissues, and PINP and PIIINP have been utilized as biomarkers to assess collagen metabolism in intact human Achilles tendons exposed to exercise and growth factor stimulation [9].

2. Data

Mast cells are highly granulated hematopoietic cells derived from the bone marrow. They circulate in the blood as immature progenitor cells, after which they home into tissues where they mature under the influence of local growth factors such as stem cell factor [10][11][12][13]. In their mature state, mast cells are characterized by a remarkably high content of electron-dense secretory granules. These contain a plethora of preformed mediators, including serglycin proteoglycans, proteases (e.g., chymase, tryptase, and carboxypeptidase A3), biogenic amines (histamine, serotonin, and dopamine), lysosomal hydrolases, growth factors, and certain cytokines (e.g., tumor necrosis factor-α (TNF-α)) [5][14][15]. When mast cells are activated, they typically respond by degranulation, whereby the preformed mediators are released to the extracellular space. Mast cell activation also leads to the de novo synthesis of a range of other mediators, including additional growth factors, cytokines, chemokines, as well as various lipid-derived mediators such as platelet-activating factor, prostaglandins, and leukotrienes (see Figure 2) [15]. Mast cells can be activated through a variety of mechanisms. Of these, crosslinking of IgE molecules bound to their high affinity receptors (FcεRI) on the mast cell surface represents the classical mode of mast cell activation. However, mast cells can be activated through several alternative pathways, including complement, engagement of toll-like receptors, and ligation of Mas-related G-protein coupled receptor member X2 (MRGPRX2)[16][17][18][19][20].

Mast cells have been suggested to have a number of beneficial functions, e.g., in the context of bacterial and parasite infection, as well as in wound healing and in the defense against various toxins [21][22][23][24][25]. Conversely, mast cells have also been implicated as detrimental players in several pathological settings. Most notably, mast cells are strongly implicated in allergic disorders but there is also evidence supporting the contribution of mast cells in various autoimmune diseases, fibrosis, cancer, skin inflammation, and metabolic disorders [5][26][27][28][29][30][31][32][33]. In addition, there is emerging evidence suggesting that mast cells potentially could be involved in conditions associated with neurogenic inflammation [17][34][35][36][37]. In support of a functional nerve:mast cell communication, mast cells are frequently found in close association with nerve endings [35][36][37]. However, the mechanisms by which mast cells could respond to nerve signaling have been mostly elusive.

The close location of mast cells and peripheral nerve endings raises the possibility that mast cells can be activated by different neurotransmitters that may be released from peripheral nerves in response to tendon injury. Such neurotransmitters include substance P, glutamate, CGRP, and neurokinin A (NKA) [38][39][40]. In line with a potential role for neurological mechanisms in mast cell activation, mast cells are known to express several receptors for neurotransmitters, e.g., neurokinin 1 receptor (NK1; receptor for substance P) and calcitonin receptor-like receptor (receptor for CGRP) [41][42][43]. Mast cells also express MRGPRX2 [18], and it has been shown that MRGPRX2 can be a more relevant receptor for substance P than is NK1 [44]. Mast cells also express corticotropin-releasing hormone receptor-1 and activity-modifying protein 1 (RAMP1) [45][46]. Further, recent findings have revealed that mouse mast cells express various glutamate receptors [47] (see also below). Altogether, this suggests that mast cells have the capacity to respond to a wide range of neurotransmitters that can be secreted by nerve endings in the context of tendon injury. Such neurotransmitters could potentially activate mast cells, and could also activate other cells (e.g., macrophages, fibroblasts) expressing the corresponding neurotransmitter receptors. This can lead to the release of cytokines and other proinflammatory mediators that could contribute to the pathology of tendon injury [48][49][50][51]. Indeed, mast cells are known to respond to substance P stimulation by secreting monocyte chemoattractant protein-1 (MCP-1), TNF-α, interleukin-8 (IL-8), IL-3, granulocyte–macrophage colony-stimulating factor, interferon-γ, and eotaxin [52][53]. Moreover, mast cell stimulation by CGRP and substance P causes the release of histamine from rat peritoneal mast cells [54] but does not activate human intestinal mast cells [55]. It has also been demonstrated that mast cells respond to glutamate by secreting proinflammatory cytokines and chemokines [47].

As discussed in this entry, there is emerging evidence to suggest that mast cells can contribute to neurogenic inflammation and the inflammatory reaction that accompanies tendon healing. It is plausible that the cytokines/chemokines released through this mechanism may contribute, either directly or indirectly, to the modulation of tendon healing and inflammation in such settings.

References

1. Patrick C. Nahirney; Pierre R. Dow; William K. Ovalle; Quantitative morphology of mast cells in skeletal muscle of normal and genetically dystrophic mice. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology* **1997**, *247*, 341-349, 10.1002/(sici)1097-0185(199703)247:3<341::aid-ar5>3.3.co;2-6.
2. Alim, M.A.; Grujic, M.; Ackermann, P.W.; Eliasson, P.; Kristiansson, P.; Peterson, M.; Pejler, G. Glutamate Triggers the Expression of Functional Ionotropic and Metabotropic Glutamate Receptors in Mast Cells. Cell Mol. Immunol. 2020.
3. Michael Kjær; M Kjaer; Role of Extracellular Matrix in Adaptation of Tendon and Skeletal Muscle to Mechanical Loading. *Physiological Reviews* **2004**, *84*, 649-698, 10.1152/physrev.00031.2003.
4. G. Nourissat; Francis Berenbaum; Delphine Duprez; Tendon injury: from biology to tendon repair. *Nature Reviews Rheumatology* **2015**, *11*, 223-233, 10.1038/nrrheum.2015.26.
5. Asadi, S.; Alysandratos, K.D.; Angelidou, A.; Miniati, A.; Sismanopoulos, N.; Vasiadi, M.; Zhang, B.; Kalogeromitros, D.; Theoharides, T.C. Substance P (SP) induces expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1) in human mast cells. J. Investig. Dermatol. 2012, 132, 324–329.
6. Deniz Ragipoglu; Anne Dudeck; Melanie Haffner-Luntzer; Martin Voss; Jochen Kroner; Anita Ignatius; Verena Fischer; The Role of Mast Cells in Bone Metabolism and Bone Disorders.. *Frontiers in Immunology* **2020**, *11*, 163, 10.3389/fimmu.2020.00163.
7. Michael J. Mienaltowski; David E. Birk; Structure, Physiology, and Biochemistry of Collagens. *Advances in Experimental Medicine and Biology* **2013**, *802*, 5-29, 10.1007/978-94-007-7893-1_2.
8. Michael J. Mienaltowski; David E. Birk; Structure, Physiology, and Biochemistry of Collagens. *Advances in Experimental Medicine and Biology* **2013**, *802*, 5-29, 10.1007/978-94-007-7893-1_2.

9. Asadi, S.; Alysandratos, K.D.; Angelidou, A.; Miniati, A.; Sismanopoulos, N.; Vasiadi, M.; Zhang, B.; Kalogeromitros, D.; Theoharides, T.C. Substance P (SP) induces expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1) in human mast cells. J. Investig. Dermatol. 2012, 132, 324–329.
10. Raddant, A.C.; Russo, A.F. Calcitonin gene-related peptide in migraine: Intersection of peripheral inflammation and central modulation. Expert Rev. Mol. Med. 2011, 13, e36.
11. Assas, B.M.; Pennock, J.I.; Miyan, J.A. Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. Front. Neurosci. 2014, 8, 23.
12. Li, W.W.; Guo, T.Z.; Liang, D.Y.; Sun, Y.; Kingery, W.S.; Clark, J.D. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. Anesthesiology 2012, 116, 882–895.
13. Green, D.P.; Limjunyawong, N.; Gour, N.; Pundir, P.; Dong, X. A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain. Neuron 2019, 101, 412–420.e3.
14. Eftekhari, S.; Warfvinge, K.; Blixt, F.W.; Edvinsson, L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J. Pain. 2013, 14, 1289–1303.
15. Murphy, P.G.; Hart, D.A. Plasminogen activators and plasminogen activator inhibitors in connective tissues and connective tissue cells: Influence of the neuropeptide substance P on expression. Biochim. Biophys. Acta 1993, 1182, 205–214.
16. G. Nourissat; Francis Berenbaum; Delphine Duprez; Tendon injury: from biology to tendon repair. *Nature Reviews Rheumatology* **2015**, *11*, 223-233, 10.1038/nrrheum.2015.26.
17. Hart, D.A.; Archambault, J.M.; Kydd, A.; Reno, C.; Frank, C.B.; Herzog, W. Gender and neurogenic variables in tendon biology and repetitive motion disorders. Clin. Orthop. Relat. Res. 1998, 44–56.
18. Le, D.D.; Schmit, D.; Heck, S.; Omlor, A.J.; Sester, M.; Herr, C.; Schick, B.; Daubeuf, F.; Fahndrich, S.; Bals, R.; et al. Increase of Mast Cell-Nerve Association and Neuropeptide Receptor Expression on Mast Cells in Perennial Allergic Rhinitis. Neuroimmunomodulation 2016, 23, 261–270.
19. Bring, D.K.; Reno, C.; Renstrom, P.; Salo, P.; Hart, D.A.; Ackermann, P.W. Joint immobilization reduces the expression of sensory neuropeptide receptors and impairs healing after tendon rupture in a rat model. J. Orthop. Res. 2009, 27, 274–280.
20. Okayama, Y.; Ono, Y.; Nakazawa, T.; Church, M.K.; Mori, M. Human skin mast cells produce TNF-alpha by substance P. Int. Arch. Allergy Immunol. 1998, 117, 48–51.
21. Kulka, M.; Sheen, C.H.; Tancowny, B.P.; Grammer, L.C.; Schleimer, R.P. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 2008, 123, 398–410.
22. Kulka, M.; Sheen, C.H.; Tancowny, B.P.; Grammer, L.C.; Schleimer, R.P. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 2008, 123, 398–410.
23. Kulka, M.; Sheen, C.H.; Tancowny, B.P.; Grammer, L.C.; Schleimer, R.P. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 2008, 123, 398–410.
24. Johnzon, C.F.; Ronnberg, E.; Pejler, G. The Role of Mast Cells in Bacterial Infection. Am. J. Pathol. 2016, 186, 4–14.
25. Abraham, S.N.; St John, A.L. Mast cell-orchestrated immunity to pathogens. Nat. Rev. Immunol. 2010, 10, 440–452.
26. Metz, M.; Piliponsky, A.M.; Chen, C.-C.; Lammel, V.; Åbrink, M.; Pejler, G.; Tsai, M.; Galli, S.J. Mast Cells Can Enhance Resistance to Snake and Honeybee Venoms. Science 2006, 313, 526–530.
27. Akahoshi, M.; Song, C.H.; Piliponsky, A.M.; Metz, M.; Guzzetta, A.; Abrink, M.; Schlenner, S.M.; Feyerabend, T.B.; Rodewald, H.R.; Pejler, G.; et al. Mast cell chymase reduces the toxicity of Gila monster venom, scorpion venom, and vasoactive intestinal polypeptide in mice. J. Clin. Investig. 2011, 121, 4180–4191.
28. Steinhoff, M.; Buddenkotte, J.; Lerner, E.A. Role of mast cells and basophils in pruritus. Immunol. Rev. 2018, 282, 248–264.
29. Marichal, T.; Tsai, M.; Galli, S.J. Mast cells: Potential positive and negative roles in tumor biology. Cancer Immunol. Res. 2013, 1, 269–279.
30. Church, M.K.; Kolkhir, P.; Metz, M.; Maurer, M. The role and relevance of mast cells in urticaria. Immunol. Rev. 2018, 282, 232–247.
31. Metz, M.; Grimbaldeston, M.A.; Nakae, S.; Piliponsky, A.M.; Tsai, M.; Galli, S.J. Mast cells in the promotion and limitation of chronic inflammation. Immunol. Rev. 2007, 217, 304–328.
32. Bradding, P.; Pejler, G. The controversial role of mast cells in fibrosis. Immunol. Rev. 2018, 282, 198–231.

33. Karasuyama, H.; Miyake, K.; Yoshikawa, S.; Yamanishi, Y. Multifaceted roles of basophils in health and disease. J. Allergy Clin. Immunol. 2018, 142, 370–380.

34. Anand, P.; Singh, B.; Jaggi, A.S.; Singh, N. Mast cells: An expanding pathophysiological role from allergy to other disorders. Naunyn-Schmiedebergs Arch. Pharmacol. 2012, 385, 657–670.

35. Shi, M.A.; Shi, G.P. Different roles of mast cells in obesity and diabetes: Lessons from experimental animals and humans. Front. Immunol. 2012, 3, 7.

36. Gupta, K.; Harvima, I.T. Mast cell-neural interactions contribute to pain and itch. Immunol. Rev. 2018, 282, 168–187.

37. Mittal, A.; Sagi, V.; Gupta, M.; Gupta, K. Mast Cell Neural Interactions in Health and Disease. Front. Cell Neurosci. 2019, 13, 110.

38. Abraham, S.N.; St John, A.L. Mast cell-orchestrated immunity to pathogens. Nat. Rev. Immunol. 2010, 10, 440–452.

39. Gruber, B.L.; Marchese, M.J.; Suzuki, K.; Schwartz, L.B.; Okada, Y.; Nagase, H.; Ramamurthy, N.S. Synovial procollagenase activation by human mast cell tryptase dependence upon matrix metalloproteinase 3 activation. J. Clin. Investig. 1989, 84, 1657–1662.

40. Magarinos, N.J.; Bryant, K.J.; Fosang, A.J.; Adachi, R.; Stevens, R.L.; McNeil, H.P. Mast cell-restricted, tetramer-forming tryptases induce aggrecanolysis in articular cartilage by activating matrix metalloproteinase-3 and -13 zymogens. J. Immunol. 2013, 191, 1404–1412.

41. Ackermann, P.W.; Finn, A.; Ahmed, M. Sensory neuropeptidergic pattern in tendon, ligament and joint capsule. A study in the rat. Neuroreport 1999, 10, 2055–2060.

42. Lian, O.; Dahl, J.; Ackermann, P.W.; Frihagen, F.; Engebretsen, L.; Bahr, R. Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. Am. J. Sports Med. 2006, 34, 1801–1808.

43. Raddant, A.C.; Russo, A.F. Calcitonin gene-related peptide in migraine: Intersection of peripheral inflammation and central modulation. Expert Rev. Mol. Med. 2011, 13, e36.

44. Assas, B.M.; Pennock, J.I.; Miyan, J.A. Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. Front. Neurosci. 2014, 8, 23.

45. Li, W.W.; Guo, T.Z.; Liang, D.Y.; Sun, Y.; Kingery, W.S.; Clark, J.D. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. Anesthesiology 2012, 116, 882–895.

46. Green, D.P.; Limjunyawong, N.; Gour, N.; Pundir, P.; Dong, X. A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain. Neuron 2019, 101, 412–420.e3.

47. Lian, O.; Dahl, J.; Ackermann, P.W.; Frihagen, F.; Engebretsen, L.; Bahr, R. Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. Am. J. Sports Med. 2006, 34, 1801–1808.

48. Asadi, S.; Alysandratos, K.D.; Angelidou, A.; Miniati, A.; Sismanopoulos, N.; Vasiadi, M.; Zhang, B.; Kalogeromitros, D.; Theoharides, T.C. Substance P (SP) induces expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1) in human mast cells. J. Investig. Dermatol. 2012, 132, 324–329.

49. Eftekhari, S.; Warfvinge, K.; Blixt, F.W.; Edvinsson, L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J. Pain. 2013, 14, 1289–1303.

50. Murphy, P.G.; Hart, D.A. Plasminogen activators and plasminogen activator inhibitors in connective tissues and connective tissue cells: Influence of the neuropeptide substance P on expression. Biochim. Biophys. Acta 1993, 1182, 205–214.

51. Hart, D.A.; Archambault, J.M.; Kydd, A.; Reno, C.; Frank, C.B.; Herzog, W. Gender and neurogenic variables in tendon biology and repetitive motion disorders. Clin. Orthop. Relat. Res. 1998, 44–56.

52. Le, D.D.; Schmit, D.; Heck, S.; Omlor, A.J.; Sester, M.; Herr, C.; Schick, B.; Daubeuf, F.; Fahndrich, S.; Bals, R.; et al. Increase of Mast Cell-Nerve Association and Neuropeptide Receptor Expression on Mast Cells in Perennial Allergic Rhinitis. Neuroimmunomodulation 2016, 23, 261–270.

53. Bring, D.K.; Reno, C.; Renstrom, P.; Salo, P.; Hart, D.A.; Ackermann, P.W. Joint immobilization reduces the expression of sensory neuropeptide receptors and impairs healing after tendon rupture in a rat model. J. Orthop. Res. 2009, 27, 274–280.

54. Okayama, Y.; Ono, Y.; Nakazawa, T.; Church, M.K.; Mori, M. Human skin mast cells produce TNF-alpha by substance P. Int. Arch. Allergy Immunol. 1998, 117, 48–51.

55. Kulka, M.; Sheen, C.H.; Tancowny, B.P.; Grammer, L.C.; Schleimer, R.P. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 2008, 123, 398–410.