6 Potential Role of Fascia in Chronic Musculoskeletal Pain

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Contents

Summary

Many empirically developed physical therapy techniques as well as alternative manual therapies (e.g., Rolfing, myofascial release) are aimed at treating fascia and other "unspecialized" connective tissues; however, compared with muscles, joints, and the nervous system, very little research has been devoted to the role of fascia in chronic musculoskeletal pain. One possible reason for this discrepancy is the lack of an integrative pathophysiological model linking connective tissue to known musculoskeletal pain mechanisms *(1)*. This chapter examines the potential role of fascia in musculoskeletal pain, especially regarding how connective tissue remodeling may interact with other factors such as fear of movement, muscle activity patterns and central nervous system plasticity.

Key Words: pain, musculoskeletal, connective tissue, fascia, remodeling, fibrosis, movement, plasticity, fibroblasts

1. DYNAMIC FIBROBLASTS AND PLASTIC CONNECTIVE TISSUE

A hallmark of connective tissue is its mutability, plasticity, or remodeling in response to varying levels of mechanical stress *(2)*. Connective tissue can become more or less stiff due to changes in its composition and architecture. The viscoelastic properties of connective tissue (e.g., stiffness, damping) are determined by its architecture, molecular

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composition (mainly collagen, elastin and glycosaminoglycans) and water, all of which are mutually interdependent *(3–5)*. Water content, for example, is dependent on both the concentration of negatively charged glycosaminoglycans (GAGs) that bind large amounts of water and on the organization, strength, and stiffness of the collagen fiber network, which resists tissue swelling *(3)*.

Fibroblasts secrete the main structural components of connective tissue (collagen, GAGs, and elastin) and therefore play a key role in determining the composition of the matrix. Fibroblasts also are able to perceive and respond to mechanical forces because they are linked to the extracellular matrix at specialized membrane complexes called focal adhesions or focal contacts *(6)*. These protein complexes essentially form a mechanical link between the cell's internal cytoskeleton and the extracellular matrix *(7)*. Mechanical stimuli applied to whole tissue, such as stretching, cause direct, local mechanical deformation of the cytoskeleton. When connective tissue is stretched, fibroblasts respond within minutes by expanding, flattening and actively reorganizing their cytoskeleton *(8)* (Figure 1). This active cellular response has been shown to involve specific intracellular signaling (Rho and Rac) as well as lamellipodia formation, actin redistribution and actomyosin contractility *(9,10)*. Mechanical deformation of cultured fibroblasts has been shown to directly influence the synthesis of key matrix components via cytoskeletal mechanotransduction mechanisms *(11)*. In other words, the amount of matrix protein secreted by fibroblasts is influenced by

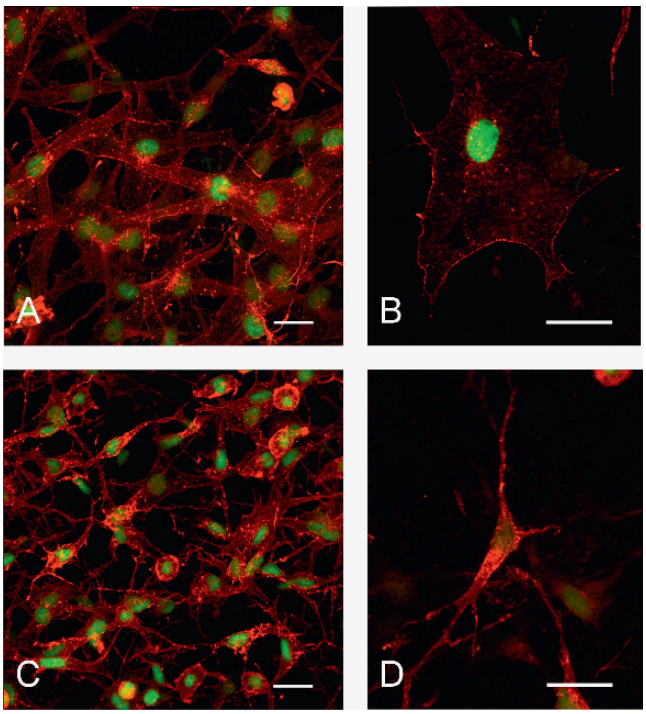

Fig. 1. Response of mouse subcutaneous tissue fibroblasts to tissue stretch ex vivo. **A,B**: Mouse subcutaneous tissue was incubated under stretch for 30 minutes immediately following excision, then fixed and stained with phalloidin, a specific stain for polymerized actin (red) and SYTOX nuclear stain (green). **C,D:** Control tissue incubated 30 minutes without stretch Fibroblast cell bodies became larger and flatter in the plane of the tissue in response to tissue stretch Scale bars, 40 μm.

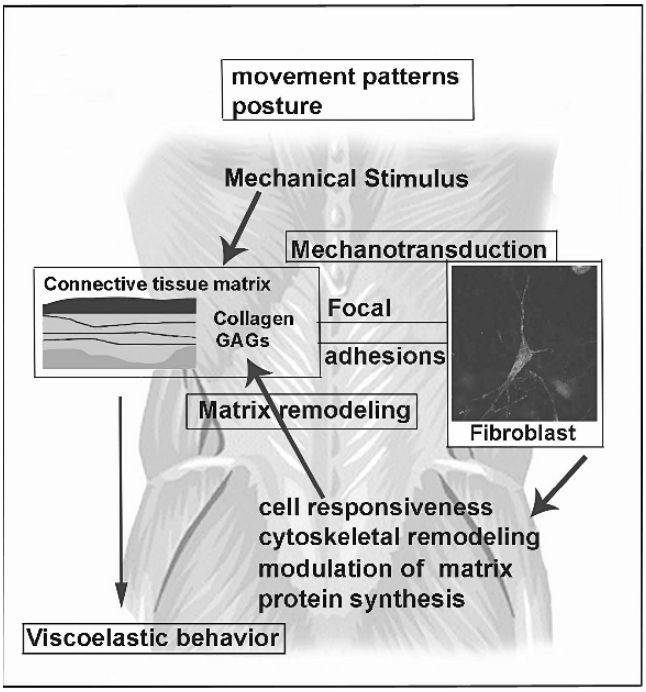

Fig. 2. Diagrammatic representation of relationships among tissue movement, cellular mechanotransduction, matrix remodeling, and tissue biomechanical properties.

the fibroblasts' mechanical environment. Changes in extracellular matrix composition due to mechanotransduction-mediated cellular effects, therefore, can have an important influence on the connective tissue's viscoelastic properties (Figure 2). Because changes in the tissue's viscoelastic properties (e.g., stiffness, damping) affect the degree of cellular deformation occurring when subsequent external forces are applied to the tissue *(7,12)*, fibroblasts actively influence the mechanical forces that act upon them over time. In vivo, an ongoing remodeling of connective tissue underlies physiological responses to changing levels of activity and movement patterns (e.g., immobilization, beginning a new exercise or occupation), as well as tissue repair following injury *(13)*.

Fibroblasts can also respond to chronic mechanical stimulation and injury by synthesizing increased amounts of alpha actin over several days and developing a more robust contractile apparatus, thus differentiating into smooth muscle-like cells known as myofibroblasts *(14)*. It also was recently shown that stimulation of connective tissue with specific pharmacological agonists could induce a measurable tissue contraction. *(15)* Fibroblasts, therefore, are dynamic cells that are likely to play a complex active role in determining connective tissue tension via cytoskeletal reorganization, active contraction/relaxation, and modification of matrix viscoelastic properties.

2. FIBROSIS: THE DARK SIDE OF CONNECTIVE TISSUE PLASTICITY

While connective tissue remodeling is essential for both normal and functional adaptation to changes in activity levels and response to injury, it can alternatively be harmful if it causes excessive collagen and matrix deposition. Decreased stress due to immobilization or hypomobility can cause connective tissue atrophy, architectural

disorganization, fibrosis, adhesions, and contractures *(16–20)*. Chronic degenerative changes can be accompanied by either increased tissue water (decreased collagen network integrity causing decreased resistance to swelling pressure), or decreased tissue water due to decreased GAG content *(21–23)*. Immobilization-induced atrophy tends to cause decreased collagen, GAG, and water content *(24,25)*, while fibrosis tends to result in collagen bundle accumulation and disorganization, increased interfibrillar contacts and restricted gliding of fibers relative to each other *(5,16,24,26–29)*. Collagen cross-links have been shown to increase in number and strength with increasing duration of immobilization *(30)*. Factors determining whether connective tissue remodeling will be appropriate or pathological include the amount of mechanical stress, the adequacy of tissue perfusion and oxygenation, and the presence of inflammation and cytokines such as TGFß-1 that promote fibrosis *(31,32)*. Regardless of its precipitating cause, connective tissue fibrosis is detrimental, as it leads to increased tissue stiffness and movement impairment.

3. CONNECTIVE TISSUE/MUSCLE INTERACTIONS

In muscle, plasticity of perimuscular and intramuscular connective tissue plays an important role in how muscle responds to mechanical stress. It has been shown, for example, that during the early phase of immobilization, loss of muscle length is primarily due to shortening of muscle-associated connective tissue, which is only later followed by actual shortening of muscle fibers *(33)*. The poorly understood phenomena of myofascial trigger points, taut muscle bands, and muscle spasm may also contribute to connective tissue remodeling and fibrosis. Although there is some controversy as to the definition and nature of these entities, and whether or not they are related to each other *(34–36)*, decreased tissue pH and increased levels of inflammatory cytokines were recently reported in painful myofascial trigger points *(37)*. Thus, the presence of painful muscle contraction or tender foci within muscle and/or perimuscular fascia may add to the factors promoting hypomobility and tissue fibrosis.

4. LINK BETWEEN PAIN, FEAR, AND MOVEMENT

Most episodes of acute musculoskeletal pain resolve with resumption of normal activities. In some cases, however, pain becomes recurrent or chronic. A number of studies *(38–40)* suggest that psychological factors such as emotional distress and pain-related behavior may play a key role in the development of recurrence and/or chronicity. A key component of pain-related behavior is fear of pain with consequent decrease in physical activity *(41)*. While rest may be initially important in the face of acute injury, it is increasingly recognized that timely resumption of physical activity is critical to successful rehabilitation *(42)*. However, after an episode of acute musculoskeletal pain, patients often remain sedentary because of fear that movement will cause pain. Such behavior is particularly detrimental, since decreased recreational activity leads to deconditioning, which further impacts emotional well-being *(43,44)*.

In addition, a growing body of evidence supports the notion that both pain and fear affect not only how much, but also the manner in which, patients with pain actually move. In chronic low back pain, for example, abnormal trunk muscle activity during postural perturbation, impaired control of trunk and hip movement during quiet standing, and abnormal postural compensation for respiration all have been documented

(45–47). Several models have been proposed to explain such abnormal movement patterns, including the "pain-spasm-pain" model (reflex sustained co-contraction of agonists and antagonist muscles) *(48)* and "pain adaptation" (slowing and decreased range of motion due to selective increased activation of antagonists) *(49)*. Recent experiments suggest that, in normal individuals, fear of pain by itself can cause altered muscle activation patterns *(50)*. Thus, patients with chronic musculoskeletal pain appear to have a constellation of motion-limiting muscle activation patterns that may be initiated or aggravated by emotional factors. In chronic musculoskeletal pain, decreased tissue movement is a potential key factor in the development of connective tissue fibrosis and the perpetuation of chronic pain.

5. RELATIONSHIP BETWEEN CONNECTIVE TISSUE PLASTICITY AND NEUROPLASTICITY

Connective tissue is richly innervated with mechano-sensory and nociceptive neurons *(51)*. Modulation of nociceptor activity has been shown to occur in response to changes in the innervated tissue. Tissue levels of protons, inflammatory mediators (prostaglandins, bradykinin), nerve growth factors (NGFs) and hormones (adrenaline) *(52–54)* all have been shown to influence sensory input to the nervous system. Conversely, nociceptor activation has been shown to modify the innervated tissue; release of Substance P from sensory C-fibers in the skin can enhance the production of histamine and cytokines from mast cells, monocytes and endothelial cells *(55,56)*. Increased TGFβ-1 production, stimulated by tissue injury and histamine release, is a powerful driver of fibroblast collagen synthesis and tissue fibrosis *(31,57,58)*. Thus, activation of nociceptors, and the subsequent cascade of local tissue response eventually leading to neurogenic inflammation and cytokine release (see Chapter 2), can by itself contribute to the development or worsening of fibrosis and inflammation, causing even more tissue stiffness and movement impairment.

6. CENTRAL NERVOUS SYSTEM SENSITIZATION

Ongoing pain is associated with *w*idespread neuroplastic changes at multiple levels within the nervous system *(59–61)*, including primary afferent neurons *(54)*, spinal cord dorsal horn *(62,63)*, brainstem, *(64)*, thalamus, limbic system and cortex. Recent neuroimaging data (see Chapter 4) have uncovered distinct "brain networks" involved in acute versus chronic pain, with chronic pain specifically involving regions related to cognition and emotions *(65)*. At the level of the somatosensory cortex, functional reorganization of somatosensory areas has been documented in chronic pain *(66)*. Indeed, current models increasingly view chronic pain as a multilevel response of the neuroaxis called the "pain neuromatrix" that includes both sensory and motor components *(67–69)*.

7. PATHOPHYSIOLOGICAL MODEL LINKING BEHAVIOR, CONNECTIVE TISSUE, AND NEUROPLASTICITY

In the hypothetical model shown in Figure 3, progression to chronic pain first involves changes in the amount and pattern of body movements, leading to connective tissue remodeling and locally increased tissue stiffness. Peripheral and central nervous system sensitization will then contribute to tissue inflammation with enhanced afferent,

nociceptive drive to the CNS followed by increased emotional distress, pain-related fear, and decreased movement. In patients with musculoskeletal pain, local connective tissue fibrosis may occur due to one or several of the following factors: (1) decreased activity, (2) changes in muscle activation patterns causing muscle co-contraction, muscle spasm, or myofascial trigger points, and (3) neurally mediated inflammation. Connective tissue remodeling may play an important role in the pathophysiology of musculoskeletal pain because (1) plasticity in response to changing mechanical loads is one of connective tissue's fundamental properties, and (2) pathological remodeling (fibrosis) due to changes in tissue movement is well documented in other types of connective tissues (e.g., ligaments, joint capsules).

In both the connective tissue and nervous system, plasticity responses are characterized by changes over time and the potential for reversibility. The hypothetical mechanism shown in Figure 3 is compatible with the complex natural history of musculoskeletal pain, including temporal variability (i.e., waxing and waning of symptoms and disability) and potential for "feed-forward" acute exacerbation of symptoms (i.e., acute flare-ups). An acute flare-up of pain may be triggered by any situation causing locally increased inflammatory cytokines, decreased tissue pH or oxygen content. In fibrosed connective tissue and muscle, blood and lymphatic flow may be chronically compromised by the disorganized tissue architecture and thus vulnerable to unusual muscle activity (e.g., beginning a new work activity or sport), or to conditions causing further decrease in perfusion such as prolonged sitting. Once local activation of nociceptors is initiated, peripheral and central nervous system sensitization mechanisms amplify both the tissue inflammation (via release of inflammatory neurotransmitters such as substance P) and the perceived pain. This leads to emotional distress, fear of movement, and, when persistent, deconditioning and its adverse long-term consequences; therefore, each exacerbation of pain potentially leads to greater movement restriction and fibrosis, setting the patient up for more painful episodes.

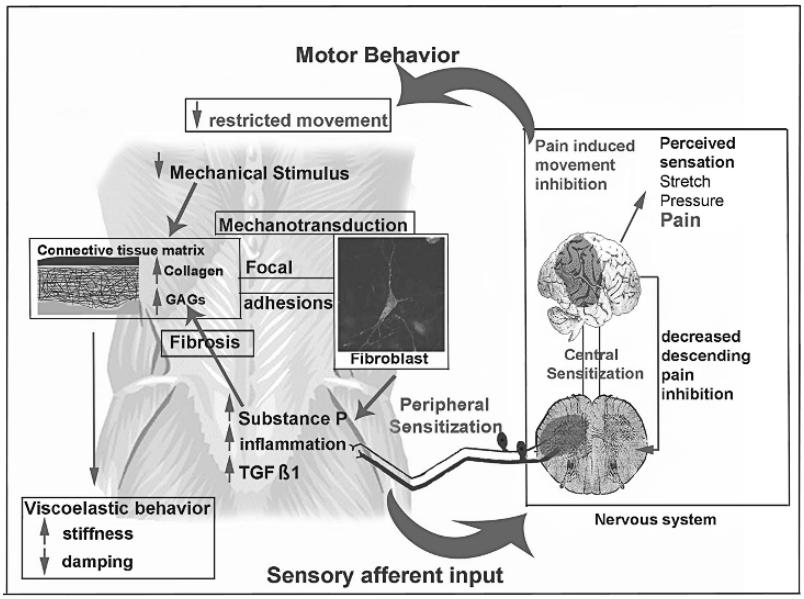

Fig. 3. Pathophysiological model for chronic musculoskeletal pain incorporating connective tissue remodeling, neuroplasticity, and emotional and motor behavior.

8. EFFECT OF TREATMENTS AND PLACEBOS

In addition to its role in the pathological consequences of immobility and injury, the dynamic and potentially reversible nature of connective tissue plasticity may be key to the beneficial effects of widely used physical therapy techniques, as well as several treatments considered within the realm of complementary and alternative medicine (CAM). Many of these therapies involve the external application of mechanical forces (e.g., massage, chiropractic manipulation, acupuncture), changes in specific movement patterns (e.g., movement therapies, tai chi, yoga) or more general changes in activity levels (e.g., increased recreational and therapeutic exercise) (Figure 4). Connective tissue remodeling also may be important in the therapeutic effect of pharmacological treatments commonly used for musculoskeletal pain via direct effects on tissues (anti-inflammatories), reduction of muscle spasm (muscle relaxants), and/or pain-induced fear of movement (analgesics, anxiolytics). The effect of placebos in musculoskeletal pain may also involve decreased fear of pain with consequent increased physical activity and the subsequent beneficial connective tissue remodeling effects. Improving our understanding of the physiological basis of these therapeutic techniques is key to developing more effective treatment strategies with minimal adverse effects. While manual or movement-based treatments have the advantage of not causing drug-induced side effects (e.g., gastritis, sedation), these treatments can potentially worsen pain if applied forces actually cause inflammation due to excessive tissue stretching or pressure.

A paradoxical aspect of connective tissue remodeling is that it potentially underlies both beneficial and harmful effects of mechanical forces, including those used therapeutically. Application of direct tissue stretch to ligaments and joint capsules needs to be gauged carefully to avoid causing excessive tissue inflammation *(13)*. Indeed, understanding how much force (or movement) is beneficial, and how much can be

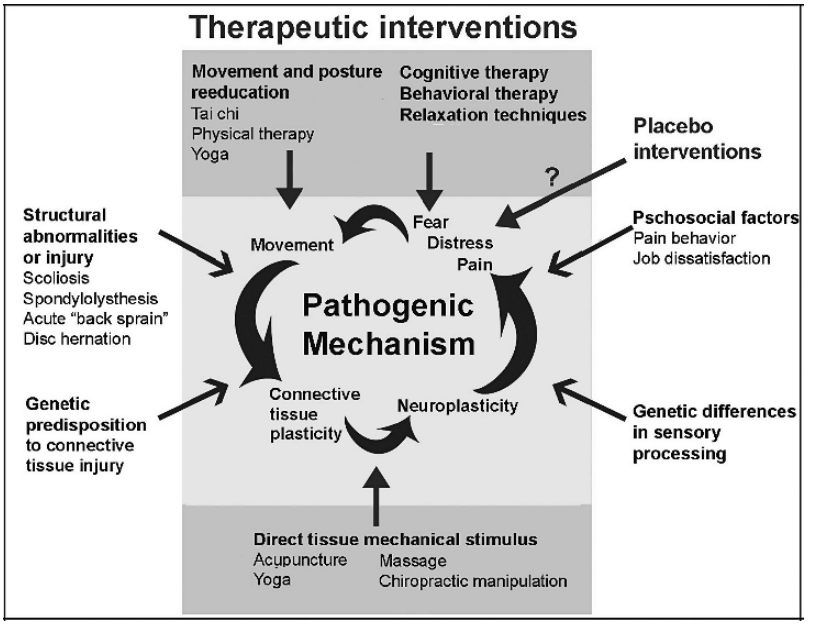

Fig. 4. Potential effects of therapeutic interventions on proposed musculoskeletal pain mechanism.

harmful is one of the greatest challenges of these clinical modalities and at this stage of understanding is often relegated into the realm of the art of medicine rather that to science. This scientific model suggests that behavior modification and movement reeducation may be most effective in the early stages of musculoskeletal pain before extensive tissue fibrosis has occurred and that combining these approaches with carefully applied direct tissue stretch may be necessary in cases of long-standing hypomobility with pronounced fibrosis and stiffness. Understanding the underlying pathophysiology will help optimize the selection of the best treatment or treatment combination. Some techniques such as yoga may act on multiple levels, causing direct tissue stretching as well as movement reeducation and relaxation.

In summary, plasticity of fascia and interstitial connective tissue may play an important role in both normal adaptive responses to changes in activity level, as well as maladaptive responses to pain and hypomobility. Treatments involving behavioral modification, movement reeducation, and direct mechanical stimulation of connective tissue all can potentially reverse connective tissue fibrosis, leading to increased mobility. The hypothetical model presented in this chapter is aimed at stimulating further research and encouraging integrative approaches to treatment.

REFERENCES

1. Langevin HM, Sherman KJ, Pathophysiological model for chronic low back pain integrating connective tissue and nervous system mechanisms. Med Hypotheses, 2007;68(1):74–80.
2. Tillman LJ, Cummings GS. 1992. Biologic Mechanisms of Connective Tissue Mutability, in Dynamics of Human Biologic Tissues Contemporary Perspectives in Rehabilitation. Volume 8. Currier DP, Nelson RM, Eds. F.A. Davis: Philadelphia, pp. 1–44.
3. Mow VC, Ratcliffe A. 1997. Structure and Function of Articular Cartilage and Meniscus, in Basic Orthopaedic Biomechanics. Mow VC, Hayes WC, Eds. Lippincott-Raven: Philadelphia, pp. 113–177.
4. Guilak F, Sah R, Setton LA. 1997. Physical Regulation of Cartilage Metabolism, in Basic Orthopaedic Biomechanics. Mow VC, Hayes WC, Eds. Lippincott-Raven: Philadelphia, pp. 179–207.
5. Woo S, Livesay GA, Runco TJ, Young EP. 1997. Structure and Function of Tendons and Ligaments, in Basic Orthopaedic Biomechanics. Mow VC, Hayes WC, Eds. Lippincott-Raven: Philadelphia, pp. 209–252.
6. Giancotti, FG, Ruoslahti E. Integrin signaling. Science 1999;285(5430):1028–1032.
7. Chicurel ME, Chen CS, Ingber DE. Cellular control lies in the balance of forces. Curr Opin Cell Biol 1998;10(2):23–29.
8. Langevin HM, et al., Dynamic fibroblast cytoskeletal response to subcutaneous tissue stretch ex vivo and in vivo. Am J Physiol Cell Physiol 2005;288(3):C747–C756.
9. Langevin HM, et al. Subcutaneous tissue fibroblast cytoskeletal remodeling induced by acupuncture: Evidence for a mechanotransduction-based mechanism. J Cell Physiol, 2006;207(3):767–774.
10. Langevin HM, et al. Fibroblast spreading induced by connective tissue stretch involves intracellular redistribution of alpha- and beta-actin. Histochem Cell Biol 2006;125(5):487–495.
11. Chiquet M. Regulation of extracellular matrix gene expression by mechanical stress. Matrix Biol 1999;18(5):417–426.
12. Brand RA. What do tissues and cells know of mechanics? Ann Med 1997;29(4):267–269.
13. Cummings GS, Tillman LJ. 1992. Remodeling of Dense Connective Tissue in Normal Adult Tissues, in Dynamics of Human Biologic Tissues Contemporary Perspectives in Rehabilitation. Volume 8. Currier DP, Nelson RM, Eds. F.A. Davis: Philadelphia, pp. 45–73.
14. Gabbiani G. The myofibroblast in wound healing and fibrocontractive diseases. J Pathol 2003;200(4):500–503.
15. Schleip R, Klingler W, Lehmann-Horn F. Active fascial contractility: Fascia may be able to contract in a smooth muscle-like manner and thereby influence musculoskeletal dynamics. Med Hypotheses 2005;65(2):273–277.
16. Savolainen J, Vaananen K, Vihko V, et al. Effect of immobilization on collagen synthesis in rat skeletal muscles. Am J Physiol 1987;252(5 Pt 2):R883–R888.

17. Uebelhart D, Bernard J, Hartmann DJ, et al. Modifications of bone and connective tissue after orthostatic bedrest. Osteoporos Int 2000;11(1):59–67.
18. Williams PE, Catanese T, Lucey EG, et al. The importance of stretch and contractile activity in the prevention of connective tissue accumulation in muscle. J Anat 1988;158:109–114.
19. Woo SLY, Mathews JV, Akeson WH, et al. Connective tissue response to immobility. Correlative study of biomechanical and biochemical measurements of normal and immobilized rabbit knees. Arthritis Rheum 1975;18(3): 257–264.
20. Akeson WH, Amiel D, Woo SL. Immobility effects on synovial joints the pathomechanics of joint contracture. Biorheology 1980;17(1–2):95–110.
21. Armstrong CG, Mow VC. Variations in the intrinsic mechanical properties of human articular cartilage with age, degeneration, and water content. J Bone Joint Surg Am, 1982;64(1):88–94.
22. Lyons G, Eisenstein SM, Sweet MB. Biochemical changes in intervertebral disc degeneration. Biochim Biophys Acta 1981;673(4):443–453.
23. Jenkins JPR, Hickey DS, Zhu XP, et al. MR imaging of the intervertebral disc: a quantitative study. Br J Radiol 1985;58(692):705–709.
24. Akeson WH, Amiel D, Mechanic GL, et al. Collagen cross-linking alterations in joint contractures: changes in the reducible cross-links in periarticular connective tissue collagen after nine weeks of immobilization. Connect Tissue Res 1977;5(1):15–19.
25. Akeson WH, Woo SLY, Amiel D, et al. The connective tissue response to immobility: biochemical changes in periarticular connective tissue of the immobilized rabbit knee. Clin Orthop Relat Res 1973;93:356–362.
26. Finsterbush, A, Friedman B. Early changes in immobilized rabbits knee joints: a light and electron microscopic study. Clin Orthop 1973;92:305–319.
27. Giannelli G, De Marzo A, Marinosci F, et al. Matrix metalloproteinase imbalance in muscle disuse atrophy. Histol Histopathol 2005;20(1):99–106.
28. Han XY, Wang W, Myllyla R, et al., mRNA levels for alpha-subunit of prolyl 4-hydroxylase and fibrillar collagens in immobilized rat skeletal muscle. J Appl Physiol 1999;87(1):90–96.
29. Kovacs EJ, DiPietro LA, Fibrogenic cytokines and connective tissue production. FASEB J 1994;8(11):854–861.
30. Grodin AJ, Cantu RI. 1993. Soft Tissue Mobilization, in Rational Manual Therapies. Basmajian JV, Nyberg R, Eds. Baltimore: Williams & Wilkins, pp. xii and 484.
31. Leask A, Abraham DJ, TGF-beta signaling and the fibrotic response. FASEB J 2004;18(7):816–827.
32. Hunt TK, Banda MJ, Silver IA. Cell interactions in post-traumatic fibrosis. Ciba Found Symp 1985;114:127–149.
33. Williams PE, Goldspink G. Connective tissue changes in immobilised muscle. J Anat 1984;138 (Pt 2):343–350.
34. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. Arch Phys Med Rehabil 1998;79(7):863–872.
35. Bohr T. Problems with myofascial pain syndrome and fibromyalgia syndrome. Neurology 1996;46(3):593–597.
36. Travell JG. 1990. Chronic myofascial pain syndromes. Mysteries of the History. In Advances in Pain Research and Therapy. Friction JR, Awad E, Eds. New York: Raven Press Ltd. pp. 129–137.
37. Shah JP, Phillips TM, Danoff JV, et al. An in-vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. J Appl Physiol 2005.
38. Hurwitz EL, Morgenstern H, Yu F. Cross-sectional and longitudinal associations of low-back pain and related disability with psychological distress among patients enrolled in the UCLA Low-Back Pain Study. J Clin Epidemiol 2003;56(5):463–471.
39. Dionne CE. Psychological distress confirmed as predictor of long-term back-related functional limitations in primary care settings. J Clin Epidemiol 2005;58(7):714–718.
40. Pincus T, Burton KA, Vogel S, et al. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine 2002;27(5):E109–E120.
41. Swinkels-Meewisse IEJ, Roelofs J, Oostenclorp RAB, et al. Acute low back pain: pain-related fear and pain catastrophizing influence physical performance and perceived disability. Pain 2006;120:36–43.
42. van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. Eur Spine J 2006;15(Suppl 1):S64–S81.
43. Hurwitz EL, Morgenstern H, Chiao C. Effects of recreational physical activity and back exercises on low back pain and psychological distress: findings from the UCLA Low Back Pain Study. Am J Public Health 2005;95(10):1817–1824.

44. Grotle M, Vollestad NK, Veierod MB, et al. Fear-avoidance beliefs and distress in relation to disability in acute and chronic low back pain. Pain 2004;112(3):343–352.
45. Reeves NP, Cholewicki J, Milner TE. Muscle reflex classification of low-back pain. J Electromyogr Kinesiol 2005;15(1):53–60.
46. Grimstone SK, Hodges PW. Impaired postural compensation for respiration in people with recurrent low back pain. Exp Brain Res 2003;151(2):218–224.
47. Mok, NW, Brauer SG, Hodges PW. Hip strategy for balance control in quiet standing is reduced in people with low back pain. Spine 2004;29(6):E107–E112.
48. Roland MO. A critical review of the evidence for a pain-spasm-pain cycle in spinal disorders. Clin Biomech 1986;1(2):102–109.
49. Lund JP, Donga R, Widmer CG, et al. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 1991;69(5): 683–694.
50. Moseley GL, Nicholas MK, Hodges PW. Does anticipation of back pain predispose to back trouble? Brain 2004;127(Pt 10):2339–2347.
51. Willis WD, Coggeshall RE. 1991. Sensory Mechanisms of the Spinal Cord, 2nd edition. Volume XIV. New York: Plenum Press, p 575.
52. Koltzenburg M. The changing sensitivity in the life of the nociceptor. Pain 1999;(Suppl 6):S93–S102.
53. Waldmann R, Champigny G, Bassilana F, et al. A proton-gated cation channel involved in acid-sensing. Nature 1997;386(6621):173–177.
54. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288(5472): 1765–1769.
55. Bessou P, Laporte Y. Etude des recepteurs musculaires innerves par les fibres afferents du groupe III (fibres myelinisees fines) chez le chat. Arch Ital Biol 1961;99:293–321.
56. Ansel JC, Kaynard AH, Armstrong CA, et al. Skin–nervous system interactions. J Invest Dermatol 1996;106(1):198–204.
57. Barnard JA, Lyons RM, Moses HL. The cell biology of transforming growth factor beta. Biochim Biophys Acta 1990;1032(1):79–87.
58. Sporn MB, Roberts AB. TGF-beta: problems and prospects. Cell Regul 1990;1(12):875–882.
59. Ji RR, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiol Dis 2001;8(1):1–10.
60. Boal RW, Gillette RG. Central neuronal plasticity, low back pain and spinal manipulative therapy. J Manipulative Physiol Ther 2004;27(5):314–326.
61. Coderre TJ, Katz J, Vaccarino AL, et al. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52(3):259–285.
62. Bolay H, Moskowitz MA. Mechanisms of pain modulation in chronic syndromes. Neurology 2002;59(5 Suppl 2):S2–S7.
63. Ikeda H, Heinke B, Ruscheweyh R, et al. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. Science 2003;299(5610):1237–1240.
64. Gebhart GF. Descending modulation of pain. Neurosci Biobehav Rev 2004;27(8):729–737.
65. Apkarian AV, Bushnell MC, Treede RD, et al. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9(4):463–484.
66. Flor H, Cortical reorganisation and chronic pain: implications for rehabilitation. J Rehabil Med 2003(41 Suppl):66–72.
67. Melzack R. From the gate to the neuromatrix. Pain 1999;(Suppl 6):S121–S126.
68. Moseley GL. A pain neuromatrix approach to patients with chronic pain. Man Ther 2003;8(3): 130–140.
69. Khalsa PS. Biomechanics of musculoskeletal pain: dynamics of the neuromatrix. J Electromyogr Kinesiol 2004;14(1):109–120.