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Biological Basis of Exercise-Based Treatments for Musculoskeletal Conditions

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Abstract

Exercise-based therapies are the cornerstone of rehabilitation programs. While the benefits of exercise on systemic and tissue function are generally accepted, mechanisms underlying these benefits are sometimes poorly understood. An improved understanding of the effects of mechanical loading on molecular and cellular processes has the potential to lead to more disease-specific and efficacious exercise-based therapies. The purpose of this paper is to review the current literature examining the role of mechanical signaling on muscle and cartilage biology.

Introduction

Exercise-based treatments play a critical role in the design of rehabilitation programs, and the systemic and local tissue benefits of exercise are generally accepted, although they are sometimes poorly understood. Likewise, clinical evaluation suggests that one-size-fits-all exercise regimens are largely ineffective, and evidence suggests that properly targeted exercise regimens may be met with improved outcomes. Greater specificity in designing exercise-based therapies requires elucidation of the mechanisms responsible for both beneficial and traumatic effects. An improved understanding of underlying molecular, cellular, and tissue responses to exercise is important for the development of targeted and specific rehabilitation protocols. Once identified, optimal loading patterns that have the potential to stimulate repair of tissues could be incorporated into exercise-based therapies and likely would lead to improved efficacy. Exercise-based strategies represent cost-effective means of treating musculoskeletal conditions, with the additional positive effects of improved weight management, cardiovascular health, and improved metabolic profiles, to name a few. The beneficial effects of loading on bone matrix homeostasis have long been recognized. However, more recent research also demonstrates important effects on other aspects of the musculoskeletal system, such as muscle and cartilage.

Muscle Effects of Exercise on Muscle

Widely recognized indications for muscle-loading protocols designed to enhance function may include the prevention of weakness, such as in the case of bouts of decreased mobility or immobility; strengthening programs to reverse the effect of age, disease, or injury; and treatments to improve balance and coordination. Less recognized, yet increasingly supported by emerging evidence, is the suggestion that exercise programs may similarly benefit muscle regenerative potential.

Review of Myofiber Anatomy/Satellite Cells

Muscle fascicles are comprised of several myofibers, defined as multinucleated, elongated muscle cells. A small proportion (approximately 4%) of these myonuclei, called satellite cells, have regenerative potential and are largely responsible for myofiber hypertrophy and repair [1]. Satellite cells, so named because of their location between the myofiber basal lamina and plasma membrane [2], reside in a normally quiescent state. However, in response to external stimuli, such as muscle loading or damage, satellite cells become activated and serve to repair or replace the damaged tissue. The activation of satellite cells in response to extrinsic cues is characterized by proliferative expansion (which is necessary to maintain a reservoir of satellite cells for future rounds of regeneration) and differentiation toward a myogenic lineage. The efficiency of this process is mediated by both cell-intrinsic and cell-extrinsic factors. Within the satellite cell niche, critical growth factors and support cells interact with satellite cells. Both exercise and muscle injury serve as important physiologic stimuli for the initiation of satellite cell activation and the onset of hypertrophy or repair processes.

Physiological Stimuli for Satellite Cell Incorporation into Myofibers

During the past decade an important number of studies revealed that exercise is capable of altering satellite cell behavior and number in human skeletal muscle [3, 4, 5, 6, 7, 8 and 9]. These studies challenged the view that satellite cells are only needed when the muscle fiber is injured in response to trauma or ongoing disease. Exercise protocols with different intensities have been shown to induce satellite cell activation and proliferation. Currently, several factors can be potential triggers for satellite cell activation during exercise, including exercise-induced disturbances in the mechanical environment of the satellite and alterations in local/systemic levels of many factors, such as decreased oxygen levels or changes in growth factors or cytokine concentrations [10]. Although the exercise-induced satellite cell pool expansion is well established, the exact implications of this cell expansion remain unknown. In muscles undergoing extreme hypertrophy in response to resistance training, the new cells incorporate the syncytium and thereby improve the nuclear machinery of the muscle fiber. However, when there is only modest or no fiber hypertrophy and when the exercise modality does not induce fiber damage, the implication of satellite cell activation and proliferation is less understood. Exercise can be seen as a physiological opportunity to renew and replenish this satellite cell pool in skeletal muscle, despite the lack of fiber hypertrophy [10].

Influence of Exercise/Mechanical Loading on Satellite Cell Regenerative Potential

Studies suggest that muscle regenerative potential is not necessarily dictated by just the intrinsic characteristics of muscle cells or muscle fiber receptors themselves [11,12 and 13]. Rather, systemic factors controlling critical molecular pathways appear to play a key role in determining the skeletal muscle regenerative capacity [11, 12 and 13]. Because physical activity promotes angiogenesis and the secretion of circulating growth factors critical for initiation of the myogenic cascade [14, 15 and 16], this begs the question, “Can muscle loading enhance skeletal muscle regenerative potential?” Indeed, when adult (12-month-old) wild-type mice were subjected to a chronic muscle loading protocol for 6 weeks in the presence of an angiogenesis inhibitor, a significant decrease in myofiber regeneration occurred, as compared to control counterparts subjected to the same loading protocol, but not exposed to the angiogenesis inhibitor [17]. These findings suggest that a loading-induced increase in skeletal muscle vascularity may play an important role in initiation of regenerative cascades following exercise. Therefore an improved understanding of the tissue and cellular mechanisms underlying exercise-based muscle benefits may help guide future studies for the development of targeted clinical interventions to stimulate angiogenesis for the maintenance of muscle mass and/or improvement of muscle healing.

Cartilage

Effects of Exercise on Cartilage

Degenerative joint disease is a very frequent if not inevitable part of aging. In the United States, the population affected by osteoarthritis comes in second only to the population affected by heart disease in terms of medical cost and disability [18]. Similarly, intervertebral disc degeneration and its sequelae are among the most common reasons for chronic back pain. Disc degeneration increases with age and is present in nearly all spines by age 50 years. Cartilage of the joints and intervertebral disc undergo degeneration with aging and suboptimal mechanical loading. Given that more than half of U.S. patients with joint degeneration do not meet recommended levels of activity [19 and 20], an improved understanding of beneficial types of exercise is much needed.

Review of Cartilage Biology

Cartilage is an avascular structure that is largely devoid of blood vessels, nerves, and lymphatics. Its dense extracellular matrix is composed mainly of collagens and proteoglycans. Within this extracellular matrix are sparsely dispersed chondrocytes that play an important role in the production of the matrix and its homeostasis. The unique composition of the matrix, particularly its glycosaminoglycan content, ensures its water-retaining capacity, cyclical fluctuations in the hydrostatic pressure, and fluid movement, which are essential to its specific mechanical demands [21].

Effects of Loading on Chondrocytes and Matrix

Chondrocytes have a limited potential for replication, which contributes to the limited intrinsic healing capacity of cartilage in response to injury, and their survival and function depends on an optimal chemical and mechanical environment. Chondrocytes respond to

various changes in their surrounding environment including growth factors, mechanical loading, changes in hydrostatic pressure, and even piezoelectric forces. The phenotype and behavior of chondrocytes is region specific, as is the response they exhibit to mechanical stress [22 and 23]. For example, human postmortem studies demonstrate that cartilage regions under higher load have higher aggrecan content and more robust collagen networks than do unloaded areas [24]. Similarly, in vivo models demonstrate decreased matrix synthesis and cartilaginous thinning in an immobilized limb [25], whereas the contralateral weight-bearing side exhibits an increase in synthesis and overall content of cartilage matrix [26 and 27]. These effects can be linked back to the molecular level, where immobility has resulted in decreased aggrecan gene expression and aggrecan production both in vivo and in vitro [28 and 29], while pressure resulted in up-regulation of aggrecan gene expression and content [30]. This increase in glycosaminoglycan content also was evident in a human in vivo study in which a prominent increase in glycosaminoglycan content following a moderate exercise routine was found in knee articular cartilage [31].

Interaction With Inflammation

In addition to its direct effects on matrix proteins, mechanical loading can affect matrix homeostasis by interacting with inflammatory and catabolic signaling pathways. Moderate activity levels can act as an anti-inflammatory signal by suppressing interleukin-1 β (IL-1 β) (an inflammatory cytokine) and other inflammatory mediators. On the other hand, high levels of activity can result in the opposite effect, with enhanced actions of IL-1 β [32, 33 and 34]. In addition to sensitizing nerve fibers, inflammatory mediators also can increase matrix breakdown. Matrix metalloproteases (MMPs) are responsible for significant catabolic activity in cartilage via cleaving of extracellular matrix proteins, such as aggrecan and collagens. Under normal conditions, the cartilage extracellular matrix continuously undergoes remodeling and a homeostatic balance exists between MMPs and their tissue inhibitors [35, 36 and 37]. However, high magnitudes of loading and inflammatory mediators have been shown to stimulate MMP expression. Similarly, moderate levels of loading have been shown to inhibit MMP production, thereby limiting matrix breakdown [38]. Within a moderate range, various in vitro and animal experiments that tested levels of IL-1 β , MMP-1, and cyclo-oxygenase-2 showed significant, rapid, and sustained reduction as a result of exercise and concomitant up-regulation of IL-10, an interleukin that plays an anti-inflammatory role, which suggests a beneficial effect [39, 40 and 41]. In fact, moderate levels of tensile loading have been shown to produce protection against an inflammatory stimulus in both articular chondrocytes and annulus fibrosus cells [42 and 43].

Effect of Different Types of Loading

Although the potential for beneficial effects of mechanical loading has been observed, a threshold effect has been demonstrated, with dependence on frequencies, magnitudes, and durations. The protective effects of moderate exercise and its positive impact on increasing cartilaginous synthesis and glycosaminoglycans content are well documented in various animal studies [44, 45 and 46], whereas going above acceptable loading measures increases matrix breakdown, as is evident in numerous in vitro studies [47 and 48] and in animal studies [49].

In general, continuous static compression is shown to down-regulate proteoglycan synthesis in a dose-dependent manner [50 and 51]. Similarly, impact loading in which a supraphysiological load is applied as a single bout or repetitive attacks is another harmful stimulus for cartilage tissue and is shown to stimulate degenerative changes both in vitro [52] and in vivo [53]. However, when the cartilage is subject to compression followed by release, synthesis of extracellular matrix and proteoglycans is induced, particularly when the earlier compression is supraphysiological and inhibitory [54 and 55].

On the other hand, when applying cyclic/intermittent compression or tensile stretch, variables such as loading amplitude, loading frequency, and regional variation within the tissue itself have been shown to affect the outcomes, and a model of either degeneration or anabolism can be created by modifying these variables [56, 57, 58 and 59].

Importantly, responses within cartilage are different between healthy and degenerative tissues; healthy tissues are much more responsive to mechanical signals and respond by increasing their gene expression of ECM components. This phenomenon is much less evident in degenerative tissue [60], which suggests that optimal mechanical loading parameters likely differ in normal and degenerative states. These differing parameters should be kept in mind when designing exercise-based protocols.

Conclusions

This improved understanding of the effects of mechanical loading induced by exercise has the potential to lead to more disease-specific and efficacious exercise-based therapies. By both targeting the specific physiological pathology and disease state and utilizing the most beneficial magnitudes, frequencies, and durations, novel exercise regimens that are informed by the available basic science have the potential to facilitate anti-inflammatory, anticatabolic, and even reparative effects. The various mechanical factors affecting musculoskeletal tissues demonstrate how an increased basic science understanding of the positive and negative effects of loading has the potential to lead to more efficient exercise regimens in the future.

References

1. Schmalbruch H, Hellhammer U. The number of satellite cells in normal human muscle. *Anat Rec.* 1976; 185:279–287. [PubMed: 937735]
2. Mauro A. Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol.* 1961; 9:493–495. [PubMed: 13768451]
3. Charifi N, Kadi F, Feasson L, Denis C. Effects of endurance training on satellite cell frequency in skeletal muscle of old men. *Muscle Nerve.* 2003; 28:87–92. [PubMed: 12811778]
4. Crameri RM, Langberg H, Magnusson P, et al. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. *J Physiol.* 2004; 558(Pt 1):333–340. [PubMed: 15121802]
5. Dreyer HC, Blanco CE, Sattler FR, Schroeder ET, Wiswell RA. Satellite cell numbers in young and older men 24 hours after eccentric exercise. *Muscle Nerve.* 2006; 33:242–253. [PubMed: 16315322]
6. Kadi F, Charifi N, Denis C, et al. The behaviour of satellite cells in response to exercise: What have we learned from human studies? *Pflugers Arch.* 2005; 451:319–327. [PubMed: 16091958]
7. Mackey AL, Esmarck B, Kadi F, et al. Enhanced satellite cell proliferation with resistance training in elderly men and women. *Scand J Med Sci Sports.* 2007; 17:34–42. [PubMed: 17305939]

8. Roth SM, Martel GF, Ivey FM, et al. Skeletal muscle satellite cell characteristics in young and older men and women after heavy resistance strength training. *J Gerontol A Biol Sci Med Sci*. 2001; 56:B240–B247. [PubMed: 11382785]
9. Verdijk LB, Gleeson BG, Jonkers RA, et al. Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men. *J Gerontol A Biol Sci Med Sci*. 2009; 64:332–339. [PubMed: 19196907]
10. Kadi F, Ponsot E. The biology of satellite cells and telomeres in human skeletal muscle: Effects of aging and physical activity. *Scand J Med Sci Sports*. 2010; 20:39–48. [PubMed: 19765243]
11. Carlson BM, Faulkner JA. Muscle transplantation between young and old rats: Age of host determines recovery. *Am J Physiol*. 1989; 256(6 Pt 1):C1262–C1266. [PubMed: 2735398]
12. Brack AS, Conboy MJ, Roy S, et al. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. *Science*. 2007; 317:807–810. [PubMed: 17690295]
13. Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature*. 2005; 433:760–764. [PubMed: 15716955]
14. Coggan AR, Spina RJ, King DS, et al. Skeletal muscle adaptations to endurance training in 60- to 70-yr-old men and women. *J Appl Physiol*. 1992; 72:1780–1786. [PubMed: 1601786]
15. Hepple RT, Mackinnon SL, Thomas SG, Goodman JM, Pyley MJ. Quantitating the capillary supply and the response to resistance training in older men. *Pflugers Arch*. 1997; 433:238–244. [PubMed: 9064638]
16. Andersen P, Henriksson J. Capillary supply of the quadriceps femoris muscle of man: Adaptive response to exercise. *J Physiol*. 1977; 270:677–690. [PubMed: 198532]
17. Brown, E.; Lexell, J.; Ferrari, R., et al. The role of vascularity in skeletal muscle regeneration in adult mice:. Presented at the International Society for Stem Cell Research 7th Annual Meeting; Barcelona; Spain. 2009 Jul.
18. Centers for Disease Control and Prevention. Arthritis prevalence and activity limitations—United States, 1990. *MMWR*. 1994; 43:433–438. [PubMed: 8202076]
19. Fontaine KR, Heo M, Bathon J. Are US adults with arthritis meeting public health recommendations for physical activity? *Arthritis Rheum*. 2004; 50:624–628. [PubMed: 14872507]
20. Hootman JM, Macera CA, Ham SA, Helmick CG, Sniezek JE. Physical activity levels among the general US adult population and in adults with and without arthritis.
21. Buckwalter JA, Mankin HJ. Articular cartilage: Tissue design and chondrocyte-matrix interactions. *Instr Course Lect*. 1998; 47:477–486. [PubMed: 9571449]
22. Lee DA, Noguchi T, Knight MM, O'Donnell L, Bentley G, Bader DL. Response of chondrocyte subpopulations cultured within unloaded and loaded agarose. *J Orthop Res*. 1998; 16:726–733. [PubMed: 9877398]
23. Aydelotte MB, Kuettner KE. Differences between subpopulations of cultured bovine articular chondrocytes: I. Morphology and cartilage matrix production. *Connect Tissue Res*. 1988; 18:205–222. [PubMed: 3219850]
24. Roberts S, Weightman B, Urban J, Chappell D. Mechanical and biochemical properties of human articular cartilage in osteoarthritic femoral heads and in autopsy specimens. *J Bone Joint Surg Br*. 1986; 68:278–288. [PubMed: 3958016]
25. Langenskiöld A, Michelsson JE, Videman T. Osteoarthritis of the knee in the rabbit produced by immobilization. *Acta Orthop Scand*. 1979; 50:1–14. [PubMed: 425824]
26. Jortikka MO, Inkinen RI, Tammi MI, et al. Immobilisation causes longlasting matrix changes both in the immobilised and contralateral joint cartilage. *Ann Rheum Dis*. 1997; 56:255–261. [PubMed: 9165998]
27. Helminen, HJ.; Kiviranta, I.; Sämänen, AM., et al. Effect of motion and load on articular cartilage in animal models. In: Kuettner, KE.; Schleyerbach, R.; Peyron, JG.; Hascall, VC., editors. *Articular Cartilage and Osteoarthritis*. New York, NY: Raveen Press; 1992. p. 501-510.
28. Otterness IG, Eskra JD, Bliven ML, Shay AK, Pelletier JP, Milici AJ. Exercise protects against articular cartilage degeneration in the hamster. *Arthritis Rheum*. 1998; 41:2068–2076. [PubMed: 9811063]

29. Djurasovic M, Aldridge JW, Grumbles R, Rosenwasser MP, Howell D, Ratcliffe A. Knee joint immobilization decreases aggrecan gene expression in the meniscus. *Am J Sports Med.* 1998; 26:460–466. [PubMed: 9617414]
30. Chen YJ, Zhang M, Wang JJ. Study on the effects of mechanical pressure to the ultrastructure and secretion ability of mandibular condylar chondrocytes. *Arch Oral Biol.* 2007; 52:173–181. [PubMed: 17056002]
31. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: A four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum.* 2005; 52:3507–3514. [PubMed: 16258919]
32. Agarwal S, Long P, Gassner R, Piesco NP, Buckley MJ. Cyclic tensile strain suppresses catabolic effects of interleukin-1beta in fibrochondrocytes from the temporomandibular joint. *Arthritis Rheum.* 2001; 44:608–617. [PubMed: 11263775]
33. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: A four month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum.* 2005; 52:3507–3514. [PubMed: 16258919]
34. Brisby H, Wei AQ, Molloy T, Chung SA, Murrell GA, Diwan AD. The effect of running exercise on intervertebral disc extracellular matrix production in a rat model. *Spine.* 2010; 35:1429–1436. [PubMed: 20592578]
35. Reboul P, Pelletier JP, Tardif G, Cloutier JM, Martel-Pelletier J. The new collagenase, collagenase-3, is expressed and synthesized by human chondrocytes but not by synovocytes: A role in osteoarthritis. *J Clin Invest.* 1996; 97:2011–2019. [PubMed: 8621789]
36. Lark MW, Bayne EK, Flanagan J, et al. Aggrecan degradation in human cartilage: Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. *J Clin Invest.* 1997; 100:93–106. [PubMed: 9202061]
37. Tortorella MD, Pratta M, Liu RQ, et al. Sites of aggrecan cleavage by recombinant human aggrecanase-1 (ADAMTS-4). *J Biol Chem.* 2000; 275:18566–18573. [PubMed: 10751421]
38. Sowa GA, Coelho JP, Bell KM, et al. Alterations in gene expression in response to compression of nucleus pulposus cells. *Spine J.* 2011; 11:36–43. [PubMed: 21056011]
39. Ferretti M, Gassner R, Wang Z, et al. Biomechanical signals suppress proinflammatory responses in cartilage: Early events in experimental antigen-induced arthritis. *J Immunol.* 2006; 177:8757–8766. [PubMed: 17142778]
40. Kiviranta I, Tammi M, Jurvelin J, Saamanen AM, Helminen HJ. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. *J Orthop Res.* 1988; 6:188–195. [PubMed: 3278079]
41. Helmark IC, Mikkelsen UR, Borglum J, et al. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: A randomized controlled trial. *Arthritis Res Ther.* 2010; 12:R126. [PubMed: 20594330]
42. Madhavan S, Anghelina M, Rath-Deschner B, et al. Biomechanical signals exert sustained attenuation of proinflammatory gene induction in articular chondrocytes. *Osteoarthritis Cartilage.* 2006; 14:1023–1032. [PubMed: 16731008]
43. Sowa G, Agarwal S. Cyclic tensile stress exerts a protective effect on intervertebral disc cells. *Am J Phys Med Rehabil.* 2008; 87:537–544. [PubMed: 18209665]
44. Kiviranta I, Tammi M, Jurvelin J, Saamanen AM, Helminen HJ. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. *J Orthop Res.* 1988; 6:188–195. [PubMed: 3278079]
45. Kostensky KS, Oláh ÉH. Functional adaptation of the articular cartilage. *Acta Biol Hung.* 1975; 26:157–164.
46. Vasan N. Effects of physical stress on the synthesis and degradation of cartilage matrix. *Connect Tissue Res.* 1983; 12:49–58. [PubMed: 6671382]
47. Korver THJ, van de Stadt RJ, Kiljan E, van Kampen GPJ, van der Korst JK. Effects of loading on the synthesis of proteoglycans in different layers of anatomically intact articular cartilage in vitro. *J Rheumatol.* 1992; 19:905–912. [PubMed: 1404127]

48. Wong M, Siegrist M, Cao X. Cyclic compression of articular cartilage explants is associated with progressive consolidation and altered expression pattern of extracellular matrix proteins. *Matrix Biol.* 1999; 18:391–399. [PubMed: 10517186]
49. Guilak F, Meyer BC, Ratcliffe A, Mow VC. The effects of matrix compression on proteoglycan metabolism in articular cartilage explants. *Osteoarthritis Cartilage.* 1994; 2:91–101. [PubMed: 11548233]
50. Dekel S, Weissinan SL. Joint changes after overuse and peak overloading of rabbit knees in vivo. *Acta Orthop Scand.* 1978; 4Y:519–528. [PubMed: 216227]
51. Jones IL, Klämfeldt A, Sandström T. The effect of continuous mechanical pressure upon the turnover of articular cartilage proteoglycans in vitro. *Clin Orthop.* 1982; 165:283–289. [PubMed: 7075072]
52. Radin EL, Parker HG, Pugh JW, Steinberg RS, Paul IL, Rose RM. Response of joints to impact loading: III: Relationship between trabecular microfractures and cartilage degeneration. *J Biomech.* 1973; 6:51–57. [PubMed: 4693868]
53. Newberry WN, Mackenzie CD, Haut RC. Blunt impact causes changes in bone and cartilage in a regularly exercised animal model. *J Orthop Res.* 1998; 16:348–354. [PubMed: 9671930]
54. Burton-Wurster N, Vernier-Singer M, Farquhar T, Lust G. Effect of compressive loading and unloading on synthesis of total protein, proteoglycan, and fibronectin by canine cartilage explants. *J Orthop Res.* 1993; 11:717–729. [PubMed: 8410472]
55. Gray ML, Pizzanelli AM, Lee RC, Grodzinsky AJ, Swann DA. Kinetics of the chondrocyte biosynthetic response to compressive load and release. *Biochim Biophys Acta.* 1989; 991:415–425. [PubMed: 2730919]
56. Kim YJ, Sah RL, Grodzinsky AJ, Plaas AH, Sandy JD. Mechanical regulation of cartilage biosynthetic behavior: Physical stimuli. *Arch Biochem Biophys.* 1994; 311:1–12. [PubMed: 8185305]
57. Larsson T, Aspden RM, Heinegard D. Effects of mechanical load on cartilage matrix biosynthesis in vitro. *Matrix.* 1991; 11:388–394. [PubMed: 1787831]
58. Uchida A, Yamashita K, Hashimoto K, Shimomura Y. The effect of mechanical stress on cultured growth cartilage cells. *Connect Tissue Res.* 1988; 17:305–311. [PubMed: 2850135]
59. Sowa GA, Coelho JP, Vo NV, Bedison R, Chiao A, Davies C. Determination of annulus fibrosus cell response to tensile strain as a function of duration, magnitude and frequency. *J Orthop Res.* In press.
60. Le Maitre CL, Frain J, Fotheringham AP, et al. Human cells derived from degenerate intervertebral discs respond differently to those derived from non-degenerate intervertebral discs following application of dynamic hydrostatic pressure. *Biorheology.* 2008; 45:563–575. [PubMed: 19065005]