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Mechanical Signalling in Osteoarticular Tissues

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Within a physiological range exposure to mechanical loads is required to maintain bone, cartilage and associated connective tissues in a healthy state. Conversely withdrawal of these mechanical stimuli or overloading can lead to connective tissue breakdown and degenerative diseases. Over the last few decades there has been a large increase in our knowledge of how mechanical forces are recognised by connective tissue cells and how these forces regulate cell function and tissue homeostasis. Mechanical forces applied to connective tissues are recognised by cell mechanoreceptors which then activate signal cascades resulting in altered gene expression, protein production and tissue remodelling. The nature of these mechanoreceptors, the signalling pathways and secreted paracrine/autocrine molecules that further regulate the process are discussed.

Key words: cartilage, mechanoreceptors, osteoarthritis

INTRODUCTION

Connective tissues including bone[1,2], cartilage[3], tendon[4] and skeletal muscle require exposure to mechanical forces to remain in a healthy state. The impact of mechanical forces on bone and cartilage is seen early in life where it is essential for normal embryonic development and morphogenesis of the skeleton and joints. The response of adult tissues was epitomised by Wolff's observations on bone. He observed that in a healthy person or animal bone will adapt to the loads it is placed under. An increase in load leads to bone remodeling with the bone becoming stronger to resist that sort of loading. When loading decreases, the bone will atrophy as there is no stimulus for continued remodeling that is required to maintain bone mass. The response to mechanical stresses in most connective tissues can be considered as having a bell shaped distribution with too little loading resulting in atrophy and excess mechanical stimulation leading to tissue damage. The ability to alter structure in response to mechanical loading is termed tissue mechanical adaptation.

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Within a physiological range, mechanical loading of connective tissues that occurs as a result of normal, everyday activity, is sufficient to keep connective tissues healthy. Physical exercise where increased loads are applied increases connective tissue performance. Such changes are clearly seen in athletes where skeletal muscle bulk and strength increases but other connective tissues are similarly affected. Tennis players who start training before puberty have increased bone mass in dominant arms[5]. Exercise increases proteoglycan synthesis and articular cartilage thickness[6]. With exercise the mechanical strength and collagen content of tendons rises[7]. The requirement for mechanical loading to maintain connective tissue is evident in paraplegics, patients on prolonged bed rest and in astronauts. The bones in paralysed and underused limbs are architecturally and mechanically inferior, immobilized tendons lose mechanical strength[8]. Overloading and under loading of articular cartilage result in loss of cartilage matrix and development of osteoarthritis[9].

MOST CONNECTIVE TISSUE CELLS ARE MECHANOSENSITIVE

Adaptation in response to mechanical loading requires that cells within connective tissue receive information from the environment. Cells exposed to mechanical loads modify the environment, essentially the connective tissue composition, so that it is appropriate for the new range of mechanical stresses to which it is now exposed. This pro-

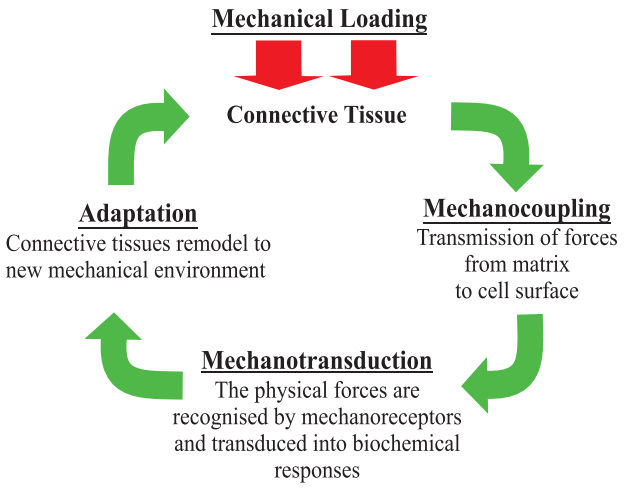

Fig. 1 Response of connective tissues to mechanical loading.

cess has a number of phases[10]. Forces at the macroscopic level are translated through the extracellular matrix (Fig. 1) to the mechanosensitive cell - mechanocoupling. The mechanical forces at the cell membrane of the mechanosensitive cell are then transduced into biochemical signals within the cell - mechanotransduction. Effector cells, most commonly but not exclusively the mechanosensitive cells, initiate tissue modelling/remodelling. Most connective tissue cells appear to be mechanosensitive. In cartilage chondrocytes sense mechanical stimuli and as effector cells produce both matrix macromolecules and proteases required for tissue turnover and homeostasis. Similarly the tenocyte appears to have a major role in mechanical tissue adaptation in tendons[11]. In bone tissue remodelling involves complicated interactions between progenitor cells, endothelial cells, osteoclasts and bone forming cells. Osteocytes appear to be the most important mechanosensitive cell in bone stimulating bone remodelling through paracrine effects on osteoprogenitor cells and osteoclasts[1,2].

MECHANOCOUPLING

Bone, cartilage, tendon and ligaments are exposed to a range of mechanical forces *in vivo*. The loads encountered by cartilage and tendon are exposed much higher than that of bone[12]. Forces of three to seven times body weight are generated in the hip and knee on with normal to rapid walking. Forces are applied rapidly with up to 20 MPa being produced in the hip within milliseconds on standing or climbing stairs. The achilles tendon may encounter forces of four to twelve times body weight during walking and running[13]. Normal activity appears to result in strains of only 10 microstrain at the surface of bone although this can rise 300 folds during vigorous exercise.

Of course connective tissue cells are not directly exposed to these mechanical forces. The surrounding extracellular matrix is protective and acts to absorb, transmit and dissipate these forces and the forces perceived by the cells are expected to be much smaller. Indeed the nature of the mechanical signal that is finally sensed by the cell is not entirely clear and may be the summation of a number of different changes in the physicochemical environment. In cartilage dynamic compression induces hydrostatic pressure gradients, fluid flow, streaming potentials, alterations in matrix water content, fixed charge density, mobile ion concentrations, and changes in pH and osmotic pressure[14] as well as chondrocyte deformation. Loading of bone generates up to 5000 microstrain at the osteocyte cell surface and pressure gradients that stimulate interstitial fluid flow through the osteocytic lacunar network[15,16]. Tensile loads at the tissue level are converted into tensile, shear and compressive strains perceived by tendon cells[17].

MECHANOTRANSDUCTION

The physiochemical changes, including changes in cell shape, cell membrane deformation and fluid flow that occur within connective tissue during mechanical loading are recognised by cell mechanoreceptors. Mechanoreceptor activation stimulates a variety of intracellular cell signalling cascades that regulate gene expression, changes in protein expression and tissue remodelling. Integrins, mechanosensitive ion channels, and connexins have each been identified as candidate mechanoreceptors[18-21].

Integrins

Integrins are heterodimeric transmembrane glycoproteins comprising **α** and **β** subunits. Each **α** and **β** subunit has an extracellular domain, a single transmembrane region, and a cytoplasmic tail. The extracellular domain provides the ligand-binding site for matrix molecules. The cytoplasmic tail is coupled to both the cytoskeletal network and signalling molecules such as focal adhesion kinase (FAK) allowing transduction of mechanical signals transmitted through the matrix into biochemical responses within the cell[22]. Integrins mediate cellular responses to stretch, elevated hydrostatic pressure, fluid shear stress, and osmotic forces[23]. The mechanisms of

integrin dependent mechanotransduction are being clarified. Stretch may increase tension and activate integrins that are bound to the extracellular matrix. Subsequent activation of a subset of unoccupied integrins inducing their binding to matrix ligands proteins and stimulation of intracellular signalling can amplify the signal. Other mechanical forces probably act similarly, increasing activation of integrins to stimulate cell adhesiveness and signalling. The cytoskeleton also responds mechanically to forces channelled through integrins by rearranging its interlinked actin microfilaments, microtubules and intermediate filaments[24].

A variety of integrins, many of which may function as mechanoreceptors, are expressed by chondrocytes and bone cells. Roles for $\alpha 5\beta 1$, $\alpha V\beta 5$ and $\alpha V\beta 3$ have been demonstrated *in vitro* but $\alpha 5\beta 1$ integrin, the classical fibronectin receptor, appears to be the major integrin mechanoreceptor in connective tissues. The anabolic response of human articular chondrocytes to mechanical stimulation is $\alpha 5\beta 1$ dependent and involves phosphorylation of focal adhesion proteins including FAK and paxillin[25]. Integrins may be part of larger mechanoreceptor complexes including accessory molecules such as CD47 that may control integrin activation[26]. Roles for $\beta 1$ integrins as osteocyte mechanoreceptors have been demonstrated in a conditional knock out model where absence of the $\beta 1$ integrin limits the response of bone to disuse[27].

Stretch-activated Ion channels

Stretch-activated or stretch-sensitive ion channels (SACs) open as a consequence of mechanical deformation of the cell membrane[20]. SACs are directly activated by mechanical forces applied along the plane of the cell membrane that induce membrane tension and distortion of the lipid bilayer. These result in conformational changes which alter opening or closing rates of the channels permitting ion flux[24]. Application of mechanical forces perpendicular to the cell membrane, as seen with hydrostatic pressure, appears to be less effective in activating SACs[20]. Activation of calcium permeable SACs leads to local increase in intracellular calcium levels and stimulation of downstream calcium-dependent intracellular signal cascades. SACs sensitive to gadolinium are necessary for load and fluid flow related cellular responses in both chondrocytes and bone cells.

Connexins

Connexins are widely expressed in connective tissue where networks of cells are seen such as in bone, tenndon and meniscus. They probably act to allow propagation of a mechanical stimulus through a tissue. They are a superfamily of twenty-one transmembrane proteins that form gap junctions and hemichannels[21]. Gap junctions allow continuity between cells permitting diffusion of ions, metabolites and small signaling molecules such as cyclic nucleotides and inositol derivatives. Cx43 is the most abundant connexin present in skeletal tissue. Conditional deletion of reduces mineral apposition rate to mechanical loading and Cx43 hemichannels are important for fluid shear induced PGE_2 and ATP release in osteocytic cells[28]. Connexins and gap junctions are present at the tip of osteocyte dendritic processes and between these processes and osteoblasts indicating their potential importance in permitting cell–cell communication among the osteocytic network although propagation may be only directed from osteocytes to osteoblasts[29]. Cx32 and Cx43 are important in tenocyte mechanotransduction[30]. Cx32 junctions form a communication network arranged along the line of principal loading and stimulate collagen production in response to strain. In contrast the Cx43 network links tenocytes in all directions and is inhibitory for collagen production. In cartilage the importance of connexins for responses to mechanical loads is less clear but may have roles as part of the primary cilia.

Primary Cilia

Primary cilia are solitary, immotile cilium present in most cells including chondrocytes and bone cells. They are microtubule-based organelles, growing from the centrosome to extend from the cell surface and contain large concentrations of cell membrane receptors, including integrins. They function both as chemosensors and mechanosensors[31,32]. Bending of the cilium upon matrix deformation or with fluid flow is thought to cause cilium bending, pulling on associated matrix receptors and activation of the mechanoreceptors[33]. In addition to integrins, Cx43 hemichannels are also present on primary cilia and by regulating ATP release cilia and activation of purine receptors cilia-associated connexins may also be involved in mechanotransduction.

INTRACELLULAR SIGNAL CASCADES ACTIVATED BY MECHANICAL SIGNALS

Stimulation of connective tissue cell mechanoreceptors is followed by generation of the secondary messenger molecules and activation of a cascade of downstream signalling events that regulate gene expression and cell function. Many intracellular signalling pathways are known to be activated by mechanical forces applied to

tissues and cells including heterotrimeric guanine nucleotide binding proteins (G-proteins), protein kinases and transcription factors. These pathways that regulate tissue modelling/remodelling may be activated directly as a consequence of mechanoreceptor signalling or indirectly following production of autocrine/paracrine acting molecules.

The phosphoinositide3 kinase –Akt/Protein kinase B (PKB) pathway

PKB/Akt is a protein family of serine/threonine kinases that have multiple roles including inhibition of apoptosis by phosphorylation and inactivation of pro-apoptotic factors. Integrin-dependent activation of phosphoinositide3 kinase (PI3 kinase) by mechanical forces regulates PKB activity and can inhibit cell death. Inactivation of the PI3-K/PKB pathway may be important in deleterious effects of mechanical overloading of cartilage and bone loss in response to withdrawal of loading[34].

Mitogen-activated protein kinases

Mitogen-activated protein (MAP) kinases regulate multiple cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. ERK1/2, JNK and p38, of critical importance in regulation of matrix protein and protease gene expression have each been shown to be activated in chondrocytes, bone cells and fibroblasts[2,35,36] following mechanical stimulation. Different mechanical stimuli may activate different MAPKs and through this mechanism differential cellular responses may occur. MAPK responses may also be cell type dependent. Mechanical stimulation induced ERK1/2 activation in bone cells requires calcium-dependent ATP release whilst in cartilage activation, under certain circumstances, is dependent on FGF-2 rather than through integrin mechanoreceptors[37].

The NF-kappa B pathway

In bone cells NF-κB, a protein complex that acts as a transcription factor, is directly stimulated by mechanical stimulation is dependent on intracellular calcium release[38]. In chondrocytes biomechanical signals within the physiological range block NF-κB activity and proinflammatory chondrocyte responses[39]. Mechanical stimuli that induce catabolic rather than anabolic responses in chondrocytes induces rapid nuclear translocation of NF-κB subunits p65 and p50 in a similar manner to IL1β.[40]

GROWTH FACTORS AND AUTOCRINE / PARACRINE SIGNALING EVENTS IN MECHANOTRANSDUCTION

As part of the cellular response to mechanical stimulation mechanosensitive connective tissue cells release a range of soluble mediators. These may be present in the cell and available for immediate release, or secretion may depend de novo synthesis by enzymatic activity or transcriptional activation and protein production. These mediators, including prostaglandins, nitric oxide, cytokines, growth factors, and neuropeptides are involved in downstream tissue modelling and remodelling responses initiated by the mechanosensitive cell or other effector cells. Production of soluble mediators by connective tissue cells in response to mechanical stimulation however may also be intrinsic to mechanotransduction pathways. Autocrine and paracrine activity allows increased regulation of the cellular response to mechanical stimuli by permitting cross talk between different components of a mechanotransduction cascade. As the cellular responses to mechanical stimuli and soluble mediators activate similar signal cascades inducing either anabolic or catabolic responses, it would be expected that they may be antagonistic, additive or synergistic. Anabolic cytokines and growth factors enhance production of matrix under mechanical loading conditions whilst anabolic mechanical stimuli antagonise the effects of catabolic cytokines such as IL1β[41].

Prostaglandins, Nitric Oxide and Adenosine triphosphate (ATP)

Prostaglandins, predominantly PGE_2, NO and ATP are synthesised and released when bone cells and chondrocytes are mechanically stimulated. Both PGE_2 and NO are required for the anabolic response of bone to mechanical loading *in vivo*. Prostaglandin production is integrin dependent requiring an intact cytoskeleton and activation of SACs, PKC, and PLA_2. PGE_2 may influence responses to mechanical loading by regulating osteocyte gap junction expression[42], RANKL expression and osteoclastogenesis. In cartilage PGE_2 induced by mechanical loads is catabolic. Mechanical loading of chondrocytes by physiological stimuli inhibits production of PGE_2 and NO whereas damaging high impact loading induces PGE_2 release[43]. Following mechanical stimulation bone cells and chondrocytes release ATP which can bind and activate purinergic receptors on these and adjacent cells. Both metabotropic P2Y receptors and ionotropic P2X receptors, have been shown to be involved in mechanical load activated signal cascades in chondrocytes and bone cells and may have physiological roles. Osteopaenia, as a

result of $P2X_7$ deficiency is potentially a result of reduced responsiveness to mechanical loading of the skeleton[44].

Cytokines and Growth Factors

Interleukin 4 (IL4) and interleukin 1β (IL1β) autocrine/paracrine activity is seen in the integrin-dependent mechanotransduction cascade of chondrocytes (IL4 and IL1β) and bone cells (IL1β) to mechanical stimulation[45]. These molecules are secreted within 20 minutes of the onset of mechanical stimulation, suggesting release from preformed stores. IL4 release relies on secretion of the neuropeptide substance P which binds to its NK1 receptor. Both IL4 and substance P are necessary but not sufficient for the increased expression of aggrecan mRNA and decrease in MMP3 mRNA induced by the mechanical stimulus suggesting cross talk with other mechanosensitive signaling pathways. IL1β is involved in the early mechanotransduction pathway of both osteoarthritic chondrocytes and human trabecular bone derived cells[46,47]. Mechanical loading may also induce release or activation of sequestered growth factors in extracellular matrix which will then act on near-by resident connective tissue cells. Basic fibroblast growth factor (FGF2) is a possible mediator of mechanical signalling in cartilage through such a mechanism[37]. Dynamic compression of porcine cartilage induces release of FGF2 with activation of ERK MAP kinase, synthesis and secretion of tissue inhibitor of metalloproteinases 1 (TIMP-1). In contrast FGF2 production by bovine cartilage is inhibited by 1 hour of compressive stress of 20 MPa[48]. This mechanical induced suppression of FGF2 is blocked IL4 indicating further roles for this pleiotropic cytokine in the regulation of chondrocyte responses to mechanical stimulation.

SUMMARY

Connective tissues face a wide range of mechanical stresses during daily activity. Many of these will act to maintain connective tissues, including bone cartilage and tendons in a healthy state. Moderate exercise can improve the strength and function of connective tissues but withdrawal of mechanical stimuli, acute mechanical injury and chronic overloading leads to tissue damage and diseases such as osteoarthritis and osteoporosis. Acute mechanical trauma will directly disrupt the collagenous network of connective tissues by physical means but will also stimulate a variety of cellular changes including activation of catabolic and pro-apoptotic pathways.

Increased knowledge of mechanoreceptors and mechanotransduction pathways are informing on how mechanical stresses regulate connective tissue homeostasis. New insights as to how adverse mechanical environments have detrimental effects on connective tissue should allow development of novel therapeutic interventions such as mechanomimetics to preserve or reconstitute connective tissue in ageing and disease.

REFERENCES

1. Turner CH. Bone strength: current concepts. Ann N Y Acad Sci 2006;1068:429-446.
2. Rubin J, Rubin C, Jacobs CR. Molecular pathways mediating mechanical signaling in bone. Gene 2006;367:1-16.
3. Grodzinsky AJ, Levenston ME, Jin M, Frank EH. Cartilage tissue remodeling in response to mechanical forces. Annu Rev Biomed Eng 2000;2:691-713.
4. Wang JH. Mechanobiology of tendon. J Biomech 2006;39:1563-1582.
5. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, Oja P, Vuori I. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. Ann Intern Med 1995;123:27-31.
6. Kiviranta I, Jurvelin J, Tammi J, Saamanen AM, Helminen HJ. Weight bearing controls glycosaminoglycan concentration and articular cartilage thickness in the knee joints of young beagle dogs. Arthritis Rheum 1987;30:801-809.
7. Woo SLY, Ritter MA, Amiel D, Sanders TM, Gomez MA, Kuei SC, Garfin SR, Akeson WH. The biomechanical and biochemical properties of swine tendons—long term effects of exercise on the digital extensors. Connect Tissue Res 1980;7:177-183.
8. Yamamoto N, Ohno K, Hayashi K, Kuriyama H, Yasuda K, Kaneda K. Effects of stress shielding on the mechanical properties of rabbit patellar tendon. J Biomed Eng 1993;115:23-28.
9. Tammi M, Säämänen AM, Jauhiainen A, Malminen O, Kiviranta I, Helminen H. Proteoglycan alterations in rabbit knee articular cartilage following physical exercise and immobilization. Connect Tissue Res 1983;11:45-55.
10. Duncan RL, Turner CH. Mechanotransduction and the functional response of bone to mechanical strain. Calcif Tissue Int 1995;57:344-358.
11. Screen HRC, Shelton JC, Lee DA,Bader DL. Cyclic tensile strain upregulates collagen synthesis in isolated tendon fascicles. Biochem Biophys Res Commun

2005;336:424-429.
12. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 1984;66:397-402.
13. Giddings VL, Beaupré GS, Whalen RT, Carter DR. Calcaneal loading during walking and running. Med Sci Sports Exerc 2000;32:627-634.
14. Urban JP. The chondrocyte: a cell under pressure. Br J Rheumatol 1994;33:901-908.
15. Han Y, Cowin SC, Schaffler MB, Weinbaum S. Mechanotransduction and strain amplification in osteocyte cell processes. Proc Natl Acad Sci USA 2004:101:16689-16694.
16. Burger EH, Klein-Nulend J. Mechanotransduction in bone - role of the lacuno-canalicular network. FASEB J 1999;13:S101-S112.
17. Screen HRC, Lee DA, Bader DL, Shelton JC. Development of a technique to determine strains in tendons using the cell nuclei. Biorheology 2003;40:361-368.
18. Ingber D. Integrins as mechanochemical transducers. Curr Opin Cell Biol 1991;3:841-848.
19. Millward-Sadler SJ, Salter DM. Integrin-dependent signal cascades in chondrocyte mechanotransduction. Ann Biomed Eng 2004;32:435-446.
20. Martinac B. Mechanosensitive ion channels:molecules of mechanotransduction. J Cell Sci 2004;17:2449-2460.
21. Müller U. Cadherins and mechanotransduction by hair cells. Curr Opin Cell Biol 2008;20:557-566.
22. Giancotti FG, Ruoslahti E. Integrin signaling. Science 1999;285:1028-1032.
23. Katsumi A, Orr AW, Tzima E, Schwartz MA. Integrins in mechanotransduction. J Biol Chem 2004;279:12001-12004.
24. Ingber DE. Cellular mechanotransduction: putting all the pieces together again. FASEB J 2006;20:811-827.
25. Lee HS, Millward-Sadler SJ, Wright MO, Nuki G, Salter DM. Integrin and mechanosensitive ion channel-dependent tyrosine phosphorylation of focal adhesion proteins and beta-catenin in human articular chondrocytes after mechanical stimulation. J Bone Miner Res 2000;15:1501-1509.
26. Orazizadeh M, Lee HS, Groenendijk B, Sadler SJ, Wright MO, Lindberg FP, Salter DM. CD47 associates with alpha 5 integrin and regulates responses of human articular chondrocytes to mechanical stimulation in an in vitro model. Arthritis Res Ther 2008;10:R4.
27. Phillips JA, Almeida EA, Hill EL, Aguirre JI, Rivera MF, Nachbandi I, Wronski TJ, van der Meulen MC, Globus RK. Role for beta1 integrins in cortical osteocytes during acute musculoskeletal disuse. Matrix Biol 2008;27:609-618.
28. Roberto Civitelli. Cell-cell communication in the osteoblast/osteocyte lineage Arch. Biochem. Biophys 2008;473:188-192.
29. Yellowley CE, Li Z, Zhou Z, Yellowley CE, Li Z, Zhou Z, Jacobs CR, Donahue HJ. Functional gap junctions between osteocytic and osteoblastic cells. J Bone Miner Res 2000;15:209-217.
30. Waggett AD, Benjamin M, Ralphs JR. Connexin 32 and 43 gap junctions differentially modulate tenocyte response to cyclic mechanical load. Eur J Cell Biol 2006;85:1145-1154.
31. Whitfield JF. The solitary (primary) cilium--a mechanosensory toggle switch in bone and cartilage cells. Cell Signal 2008;20:1019-1024.
32. Poole CA, Jensen CG, Snyder JA, Gray CG, Hermanutz VL, Wheatley DN. Confocal analysis of primary cilia structure and colocalization with the Golgi apparatus in chondrocytes and aortic smooth muscle cells. Cell Biol Int 1997;21:483-494.
33. Malone AM, Anderson CT, Tummala P, Kwon RY, Johnston TR, Stearns T, Jacobs CR. Primary cilia mediate mechanosensing in bone cells by a calcium-independent mechanism. Proc Natl Acad Sci USA 2007;104:13325-13330.
34. Dufour C, Holy X, Marie PJ. Transforming growth factor-beta prevents osteoblast apoptosis induced by skeletal unloading via PI3K/Akt, Bcl-2, and phospho-Bad signaling. Am J Physiol Endocrinol Metab 2008;294:E794-801.
35. Fitzgerald JB, Jin M, Chai DH, Siparsky P, Fanning P, Grodzinsky AJ. Shear- and compression-induced chondrocyte transcription requires MAPK activation in cartilage explants. J Biol Chem 2008;283:6735-6743.
36. Jeon YM, Kook SH, Son YO, Kim EM, Park SS, Kim JG, Lee JC. Role of MAPK in mechanical force-induced up-regulation of type I collagen and osteopontin in human gingival fibroblasts. Mol Cell Biochem 2009;320:45-52.
37. Vincent T, Saklatvala J. Basic fibroblast growth factor: an extracellular mechanotransducer in articular cartilage? Biochem Soc Trans 2006;34:456-457.
38. Chen NX, Geist DJ, Genetos DC, Pavalko FM, Duncan RL. Fluid shear-induced NFkappaB translocation in osteoblasts is mediated by intracellular calcium release. Bone 2003;33:399-410.
39. Anghelina M, Sjostrom D, Perera P, Nam J, Knobloch

T, Agarwal S. Regulation of biomechanical signals by NF-kappaB transcription factors in chondrocytes. Biorheology 2008;45:245-256.
40. Agarwal S, Deschner J, Long P, Verma A, Hofman C, Evans CH, Piesco N. Role of NF-kappaB transcription factors in antiinflammatory and proinflammatory actions of mechanical signals. Arthritis Rheum 2004;50:3541-3548.
41. Chowdhury TT, Bader DL, Lee DA. Dynamic compression counteracts IL-1 beta-induced release of nitric oxide and PGE2 by superficial zone chondrocytes cultured in agarose constructs. Osteoarthritis Cartilage 2003;11:688-696.
42. Cherian PP, Siller-Jackson AJ, Gu S, Wang X, Bonewald LF, Sprague E, Jiang JX. Mechanical strain opens connexin 43 hemichannels in osteocytes: a novel mechanism for the release of prostaglandin. Mol Biol Cell 2005;16:3100-3106.
43. Jeffrey JE, Aspden RM. Cyclooxygenase inhibition lowers prostaglandin E2 release from articular cartilage and reduces apoptosis but not proteoglycan degradation following an impact load in vitro. Arthritis Res Ther 2007;9:R129.
44. Ke HZ, Qi H, Weidema AF, Zhang Q, Panupinthu N, Crawford DT, Grasser WA, Paralkar VM, Li M, Audoly LP, Gabel CA, Jee WS, Dixon SJ, Sims SM, Thompson DD. Deletion of the P2X7 nucleotide receptor reveals its regulatory roles in bone formation and resorption. Mol Endocrinol 2003;17:1356-67.
45. Salter DM, Millward-Sadler SJ, Nuki G, Wright MO. Integrin-interleukin-4 mechanotransduction pathways in human chondrocytes. Clin Orthop Relat Res 2001;391:S49-60.
46. Salter DM, Lee HS. Mechanotransduction in normal and ostoearthritic human chondrocytes. J Med Sci 2003;23:183-190.
47. Salter DM, Wallace WH, Robb JE, Caldwell H, Wright MO. Human bone cell hyperpolarization response to cyclical mechanical strain is mediated by an interleukin-1beta autocrine/paracrine loop. J Bone Miner Res 2000;15:1746-1755.
48. Fujiwara Y, Uesugi M, Saito T. Down-regulation of basic fibroblast growth factor production from cartilage by excessive mechanical stress. J Orthop Sci 2005;10:608-613.