Nontraditional Modification to Articular Cartilage

Vasili Karas, M.S.[1] Neil Ghodadra, M.D.[2] Ellen Kroin, B.S.[1] Brian J. Cole, M.D., M.B.A.[1]

[1] Division of Sports Medicine, Department of Orthopedics, Rush University Medical Center, Chicago, Illinois
[2] Division of Sports Medicine, Department of Orthopedics, Southern California Orthopedic Institute, Van Nuys, California

Address for correspondence and reprint requests Brian J. Cole, M.D., M.B.A., Professor, Division of Sports Medicine, Department of Orthopedics, Rush University Medical Center, 1611 West Harrison Street, Suite 300, Chicago, IL 60612 (e-mail: bcole@rushortho.com).

J Knee Surg 2012;00:1–6.

Abstract

Biomechanical imbalance, trauma, and age-related degeneration often lead to chondral lesions which may lead to overt osteoarthritis over time. Such cartilage pathology is frequently accompanied by persistent pain and loss of normal joint function. As a result, patients who suffer from biologically active articular cartilage lesions are often unable to function in both high level activities and exhibit compromised activities of daily living. The limited potential for self-regeneration of hyaline cartilage has led to the emergence of new technologies to solve this difficult clinical problem. Treatment of arthritis and chondral lesions includes alleviation of pain and return of function through pharmacologic intervention and/or attempts at cartilage reparative, restorative and reconstructive options.

Keywords

- cartilage repair
- osteoarthritis
- platelet rich plasma
- growth factor
- mesenchymal stem cells

Biomechanical imbalance, trauma, and age-related degeneration often lead to chondral lesions which may lead to overt osteoarthritis over time. Such cartilage pathology is frequently accompanied by persistent pain and loss of normal joint function. As a result, patients who suffer from biologically active articular cartilage lesions are often unable to function in both high level activities and exhibit compromised activities of daily living. The limited potential for self-regeneration of hyaline cartilage has led to the emergence of new technologies to solve this difficult clinical problem. In the event that the chondral lesion remains superficial to the subchondral bone, repair relies on the proliferation of surrounding cells and cells within the synovium as lesions are not exposed to the cellular and protein components of circulating blood. Lesions that include the subchondral bone and expose the marrow cavity rely on components therein for regeneration and repair. Cartilage synthesized without exogenous intervention usually resembles type 1 fibrous cartilage with inferior biomechanical properties when compared with native, hyaline cartilage replete with type 2 collagen.[1]

Treatment of arthritis and chondral lesions includes alleviation of pain and return of function through pharmacologic intervention and/or attempts at cartilage reparative, restorative and reconstructive options.[2] Systemic pharmacologic treatments for degenerative arthritis aim to reduce inflammation and decrease associated pain. Topical treatments include nonsteroidal antiinflammatories such as diclofenac gels that isolate the pathologic joint localizing treatment and decreasing the possibility of systemic side effects. Traditional injectables such as cortisone injections and viscosupplementation have been found to decrease pain for short and medium time periods. Corticosteroids have been shown to provide a 30 to 50% decrease in pain which is most evident in the first 4 weeks after treatment.[3] Viscosupplementation with various formulations and molecular weights of hyaluronic acid has been shown to impart similar, but longer lasting results.[4]

It is our purpose to discuss the nontraditional and innovative nonsurgical treatments for articular cartilage pathology. Weight loss, physical therapy, oral antiinflammatories, and corticosteroids are, at present, the standard of care for conservative treatment modalities for arthritis. The use of biologic injectables such as growth factors, platelet rich plasma (PRP), autologous conditioned plasma (ACS[Q1]), and stem cell therapy are currently under investigation and will be the present focus. Although the clinical evidence supporting the use of these modalities is sparse, their potential is clear as is the need for their continued development. Q1

received
November 8, 2011
accepted after revision
December 28, 2011

DOI http://dx.doi.org/10.1055/s-0032-1308822.
ISSN 1538-8506.

Growth Factors and Cytokines

Osteoarthritis is largely a cytokine-driven disease process. The synovial membrane, cartilage, and subchondral bone are all potential factors in cartilage degeneration as each is capable of producing large amounts of cytokines. A thorough understanding of the clinically relevant interactions between cytokines, mediators, growth factors, and mechanisms of action in this local environment is needed to ameliorate cartilage degeneration caused by the catabolic milieu present in osteoarthritis. Accompanying the increased interest in nontraditional treatment methods for articular cartilage disease is an increased interest in the use of cytokines as the basis for biological treatments such as PRP and ACS.

Growth factors are commonly defined as biologically active polypeptides that contribute to the regulation of growth and homeostasis of tissues throughout life.[5,6] The use of growth factors such as transforming growth factor (TGF), fibroblast growth factor (FGF), and bone morphogenic (BMP) to influence cell differentiation and anabolism is a possible solution in the context of osteoarthritis.[7–9] Recent basic science studies have shown an increasingly important role for growth factors in cartilage regeneration and have become the basis for the potential clinical benefits for modification of articular cartilage.[9,10]

TGF-β1 has been shown, in vitro, to stimulate the synthesis of extracellular matrix within cartilage, induce synovial proliferation, and increase mesenchymal stem cell (MSC) proliferation.[11–14] Positive effects of TGF-β1 have also been documented in cartilage defects within rabbit models.[15–19] Despite the positive effects of TGF-β1, safety concerns, specifically the presence of osteophytes and synovial fibrosis in murine and lapine studies, have limited extensive human testing.[14,20] Albeit on a smaller scale, compared with TGF-β1, TGF-β3 has been shown to stimulate extracellular matrix formation in animal models[21–23] without these adverse effects.

BMP-2 is a close structural relative to both TGF-β1 and TGF-β3 and has been studied extensively in fracture care and spine surgery. The clinical success of BMP-2 in orthopedics has spurred basic science research investigating its potential effect on cartilage regeneration. In multiple studies, it has been shown in vitro to partially reverse dedifferentiated chondrocytes found in osteoarthritic models.[24] In addition, BMP-2 stimulates the synthesis and turnover of extracellular matrix, and specifically, that of proteoglycans and type II collagen. Augmentation of a microfracture model with BMP-2 has also been reported in a rabbit model. Although surgical intervention is beyond the present scope, it is valuable to note that BMP-2 may guide differentiating cells to produce more hyaline-like cartilage.[25–27] Although the effects of BMP-2 on chondrocyte metabolism seem promising, synovial thickening, fibrosis, and, in some cases, osteophytes have been shown to develop after multiple injections.[28] In addition, a recent animal study suggests temporal limitations to the use of BMP-2.[29] Although the efficacy of BMP-2 seems promising, further studies are needed to develop the most efficacious dosing, timing, and route of administration.

BMP-7/OP-1 is the most investigated member of the TGF-β superfamily for its potential to regenerate articular cartilage. Not only does BMP-7 increase ECM synthesis, it decreases the activity of catabolic cytokines such as IL-1, IL-6, IL-8, MMP-1, and MMP-7.[30] BMP-7 expression has been shown to decrease with age. Although decreased BMP-7 expression is a factor in cartilage breakdown, BMP-7 continues to have autocrine effects for both anabolism and catabolism.[31–34] Finally, although basic science studies suggest a beneficial effect from the administration of BMP-7, recent basic science and clinical literature has not shown a trend between endogenous levels of BMP-7 and higher symptomatic pain relief in patients with osteoarthritis.[35] The efficacy of BMP-7 seems to be clear, however the need to develop the proper dosing, timing, and route of administration remains uncertain.

Insulin-like growth factor-I has been investigated within the context of cartilage metabolism in both native and pathologic states.[30,36–39] IGF-1 has been shown to increase the anabolic response and decrease catabolism.[40] In contrast to evidence found in BMP-7, IGF-1 shows a decreased responsiveness in aging and osteoarthritic cartilage.[41,42] Although IGF-1 may not be a viable option alone, it may offer a synergistic effect in conjunction with other growth factors.[36] Further studies are necessary to determine the optimal combination of growth factors.

Recent evidence suggests that platelet-derived growth factor (PDGF) has a possible place in cartilage repair based on its role in wound healing and stimulation of ECM proliferation in bone growth.[43–46] Multiple animal studies have shown that PDGF has an excellent safety profile when used in isolation. PDGF has had an increasingly prominent role in research and media as i*n vivo* use of PDGF remains largely within the context of PRP. PRP has been used successfully in various clinical situations and has drawn national attention as it has shown promising results for tendon healing.

Blood-Derived Products

Although growth factors show promise, they must be carefully synthesized and stored and are thus very expensive to produce. As evidenced above, they may also have a synergistic effect and would thus require varied concentrations of multiple growth factors; a practice that is not sanctioned by the American Food and Drug Administration. Thus, there has been a recent resurgence in interest in the use of the body's own combination of growth factors and cytokines using autologous blood as a medium from which to extract growth factor and cytokine-containing components such as platelets.

Autologous Conditioned Plasma

Autologous conditioned serum (ACS) was developed in the mid-1990s and marketed under the name Orthokine (Arthrex, Inc., Naples, FL). It has been reported to not only be beneficial in the treatment of osteoarthritis, but also be beneficial in rheumatoid arthritis, spinal disorders, and muscle injuries in humans.[47–51] To prepare an ACS injection, human whole blood from the patient is incubated with medical-grade glass beads or spheres, exposed to chromium sulfate, and placed into a centrifuge to separate into the plasma with platelets.[48] ACS is believed to be effective through its increased concentrations of cytokines and growth factors. Multiple studies have shown that the expression of IL-4, IL-10, IL-1Ra (receptor antagonist), fibroblastic growth factor-1, hepatocyte growth factor, and TGF-β1 are increased in human ACS. While there is an increase in these antiinflammatory agents, there is no increase in proinflammatory cytokines-like IL-1β or TNF-α.[47]

In particular, IL-1Ra expression has been shown to increase as much as 140-fold in ACS. IL-1Ra is a competitive receptor antagonist of IL-1, a proinflammatory cytokine that triggers the destruction of hyaline cartilage and its matrix.[48] Thus IL-1Ra may play a role in the clinical improvement of osteoarthritis patients injected with ACS. IL-1 has also been identified as being the major mediator of cartilage loss in osteoarthritis. Currently, it is not clear if all biologically active IL-1 receptors need to be blocked to have a significant impact on treating conditions such as osteoarthritis, however, it is known that other antiinflammatory cytokines that are expressed in ACS also affect IL-1 receptor signaling.[48] In gene therapy studies, it was found that IL-1Ra decreases synovial effusion, gross articular cartilage erosion, and synovial membrane vascularity as compared with placebo-treated joints.[47]

To induce the de novo production of IL-1Ra, aspirated venous blood is incubated with borosilicate glass spheres in a syringe. The antiinflammatory cytokines, which are produced by peripheral blood leukocytes, accumulate and are recovered within the serum. The cytokine concentrations do vary between individual samples and their synergistic action contributes to the effects.[48] After centrifugation, ACS can be injected into the osteoarthritic area in a series of six intraarticular injections twice a week for 3 weeks.[47,52]

Platelet Rich Plasma

The contemporary definition of PRP is a sample of plasma with a 2-fold or more increase in platelet concentration or greater than 1.1×10^6 platelets/μL.[53] Presently, several different manufacturers have developed systems for PRP preparation for augmentation or as primary orthopaedic treatments.[54] It is important to understand that preparations differ across manufacturers in final platelet count, presence of leukocytes and number of centrifugations for preparation.

The concept of PRP as a possible treatment for osteoarthritis derives from the platelet's role in wound healing[55] as platelets contain many of the cytokines and growth factors delineated above. In addition, platelets contain approximately another 1500 proteins, some of which modulate the inflammatory response inherent in degenerative joint disease as well as the attraction of fibroblasts and stem cells to the site of injury.[56,57]

The use of PRP and its reported clinical success in treating various tendon pathologies throughout the body has led to increased interest in its potential role in cartilage repair. The use of PRP as treatment for articular cartilage repair is new, and thus there is sparse data on the clinical outcomes of its use. In the laboratory, injected PRP has been shown to increase production of chondrocytes and MSCs leading to increased proliferation and synthesis of extracellular matrix, collagen II, and proteoglycans.[58,59] In animal models, damaged cartilage treated with PRP also demonstrated higher degree of degeneration when compared with control. In a recent trial of hyaluronic acid versus PRP for the treatment of osteoarthritis, Kon et al[60] compares the two treatment modalities over a 6-month time period to evaluate patient-reported outcomes. The study concludes that 3 weekly injections of autologous PRP, when compared with a series of three HA injections, show more and longer efficacy in mitigating the symptoms of osteoarthritis. They also conclude that younger, more active patients with presumably a lesser degree of cartilage degeneration, improve to a higher degree with PRP injections as compared with HA. These results are the most promising to date. However a randomized control trial, with more objective outcomes is needed to shed more definitive light on PRP as a treatment for cartilage degeneration.[60] A recent 24-month follow-up to has recently been published that suggest a tapering decrease in pain and the increase in function found in the short term by the time patients reach 24 months.[61]

Stem Cell Therapy

Stem cell therapy serves as another possible method of treatment of articular cartilage defects. Not only do MSCs, have the ability to self-renew, but they possess the potential to differentiate into other specialized cells when placed in appropriate culture conditions.[62] For the purpose of treating cartilage defects, MSCs need to be differentiated toward chondrongenic lineage of cells and more specifically toward the formation of hyaline Type 2 cartilage. Aside from MSC differentiation properties, they also have a trophic activity and secrete bioactive factors that have a protective immunoregulatory effect on the local tissue environment. Their antiinflammatory and differentiation properties make MSCs good contenders for a possible tissue repair modality in osteoarthritis.[63]

Both synovial membrane-derived, bone marrow-derived MSC (BMSC), and adipose-derived stem cells (ASC) from adult tissues have the potential to form a hyaline-like cartilage matrix, with the latter being a more abundant and minimally morbid source (hildner). For example, recent studies suggest that the infrapatellar fat pad of adult knees is a good source of cells that can be induced to differentiate into chondrocytes that synthesize cartilage matrix molecules.[63] BMSC and ASC require a different growth factor treatment to differentiate into the sought after material. Aggrecan upregulation in ASC is seen when treated with bone morphogenetic protein 6 (BMP-6), while in BMSC, TGF-β3 is needed instead. In addition, several studies have concluded that BMSC are more easily differentiated toward the chondrogenic lineage than ASC.[62,63]

Park et al showed that MSCs from both bone marrow and periosteum formed hyaline cartilaginous tissue when transplanted into cartilage defects in rats. This study also demonstrated that MSCs derived from bone marrow was superior to adipose-derived MSCs in forming hyaline cartilage in vivo.[64] Bone marrow, synovium, adipose tissue, and muscle of adult rabbits have also been studied to compare their in vivo chondrogenic potential. Results have shown that the potential of synovial and bone marrow MSCs to repair cartilage defects is higher than those from skeletal muscle and adipose tissue, and they produced more cartilage matrix than the other cells in the cartilage defects. More specifically, the MSCs taken from the synovial tissue had the greatest proliferation potential.[65]

Wakitani et al performed a clinical study using bone marrow-derived MSCs re-suspended in a collagen type I gel and transplanted with autologous periosteal flap. This cell-containing scaffold was placed into osteoarthritic cartilage defects in the patients' medial femoral condyles. This was compared with patients who were transplanted with a cell-free scaffold in a similar defect.[66] Results showed that the cell-treated groups clinical scores were not significantly different 64 months after transplantation compared with the control group. In this situation, longer observation might be required and/or MSC transplantation may not be as effective in an osteoarthritic knee environment.[66] However, both the arthroscopic and histological scores were better in the group treated with the MSC transplant.[66] In addition, three future case reports from the same group did report that the clinical symptoms in the patients with the MSC-transplant had improved.[65]

In another clinical study, human bone marrow MSCs were used to treat a 20×30 mm full thickness cartilage medial femoral condyle defect in a 31-year-old male athlete. Bone marrow was aspirated from the patient 4 weeks before surgery and the cells were expanded in culture and then covered with an autologous periosteal flap once transferred to the defect. In a 7-month postsurgical evaluation, the defect was covered with a hyaline-like type of cartilage tissue. This smooth tissue also stained positively with Safranin-O. Clinically, the patient's symptoms involved significantly and was able to return to full physical activity level with no pain or complications.[65,67]

Conclusions

Since articular cartilage defects have limited intrinsic regenerative properties, there is an interest in providing nontraditional modifications to injured articular cartilage in patients. To explore methods to repair articular cartilage, transplantation of various progenitor cells other than chondrocytes is under investigation with renewed vigor to provide additional solutions to articular cartilage repair. Recent basic science and clinical research has initiated a paradigm shift in our understanding of the role of cytokines, growth factors, and stem cells in potential cartilage repair. Although results have been promising in animal studies, extensive human clinical studies are necessary to ascertain the benefit of the use of growth factors or blood-derived products to repair articular cartilage defects.

References

1 Nehrer S, Breinan HA, Ramappa A, et al. Matrix collagen type and pore size influence behaviour of seeded canine chondrocytes. Biomaterials 1997;18(11):769–776

2 McNickle AG, Provencher MT, Cole BJ. Overview of existing cartilage repair technology. Sports Med Arthrosc 2008;16(4):196–201

3 Bellamy N, Campbell J, Gee T, Robinson V, Bourne R, Wells G. Efficacy of intra-articular corticosteroid treatment in knee osteoarthritis. Cochrane Review 2010;64:494–494[Q2] Q2

4 Gigante A, Callegari L. The role of intra-articular hyaluronan (Sinovial) in the treatment of osteoarthritis. Rheumatol Int 2011;31(4):427–444

5 Quintana L, zur Nieden NI, Semino CE. Morphogenetic and regulatory mechanisms during developmental chondrogenesis: new paradigms for cartilage tissue engineering. Tissue Eng Part B Rev 2009;15(1):29–41

6 Gaissmaier C, Koh JL, Weise K. Growth and differentiation factors for cartilage healing and repair. Injury 2008;39(Suppl 1):S88–S96

7 Hill DJ, Logan A. Peptide growth factors and their interactions during chondrogenesis. Prog Growth Factor Res 1992;4(1):45–68

8 Hoffmann A, Gross G. BMP signaling pathways in cartilage and bone formation. Crit Rev Eukaryot Gene Expr 2001;11(1–3):23–45

9 Plaas A, Velasco J, Gorski DJ, et al. The relationship between fibrogenic TGFβ1 signaling in the joint and cartilage degradation in post-injury osteoarthritis. Osteoarthritis Cartilage 2011;19(9):1081–1090

10 Puetzer JL, Petitte JN, Loboa EG. Comparative review of growth factors for induction of three-dimensional in vitro chondrogenesis in human mesenchymal stem cells isolated from bone marrow and adipose tissue. Tissue Eng Part B Rev 2010;16(4):435–444

11 Dickhut A, Dexheimer V, Martin K, Lauinger R, Heisel C, Richter W. Chondrogenesis of human mesenchymal stem cells by local transforming growth factor-beta delivery in a biphasic resorbable carrier. Tissue Eng Part A 2010;16(2):453–464

12 Fan H, Hu Y, Li X, et al. Ectopic cartilage formation induced by mesenchymal stem cells on porous gelatin-chondroitin-hyaluronate scaffold containing microspheres loaded with TGF-beta1. Int J Artif Organs 2006;29(6):602–611

13 Re'em T, Kaminer-Israeli Y, Ruvinov E, Cohen S. Chondrogenesis of hMSC in affinity-bound TGF-beta scaffolds. Biomaterials 2012;33(3):751–761

14 Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF-beta and osteoarthritis. Osteoarthritis Cartilage 2007;15(6):597–604

15 Wang W, Li B, Yang J, et al. The restoration of full-thickness cartilage defects with BMSCs and TGF-beta 1 loaded PLGA/fibrin gel constructs. Biomaterials 2010;31(34):8964–8973

16 Olivos-Meza A, Fitzsimmons JS, Casper ME, et al. Pretreatment of periosteum with TGF-beta1 in situ enhances the quality of osteochondral tissue regenerated from transplanted periosteal grafts in adult rabbits. Osteoarthritis Cartilage 2010;18(9):1183–1191

17 Guo X, Park H, Young S, et al. Repair of osteochondral defects with biodegradable hydrogel composites encapsulating marrow mesenchymal stem cells in a rabbit model. Acta Biomater 2010;6(1):39–47

18 Fan H, Liu H, Zhu R, et al. Comparison of chondral defects repair with in vitro and in vivo differentiated mesenchymal stem cells. Cell Transplant 2007;16(8):823–832

19 Guo X, Zheng Q, Yang S, et al. Repair of full-thickness articular cartilage defects by cultured mesenchymal stem cells transfected with the transforming growth factor beta1 gene. Biomed Mater 2006;1(4):206–215

20 Bakker AC, van de Loo FA, van Beuningen HM, et al. Overexpression of active TGF-beta-1 in the murine knee joint: evidence for synovial-layer-dependent chondro-osteophyte formation. Osteoarthritis Cartilage 2001;9(2):128–136

21 Tang QO, Shakib K, Heliotis M, et al. TGF-beta3: A potential biological therapy for enhancing chondrogenesis. Expert Opin Biol Ther 2009;9(6):689–701

22 Fan H, Tao H, Wu Y, Hu Y, Yan Y, Luo Z. TGF-β3 immobilized PLGA-gelatin/chondroitin sulfate/hyaluronic acid hybrid scaffold for cartilage regeneration. J Biomed Mater Res A 2010;95(4):982–992

23 Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet 2010;376(9739):440–448

24 Gouttenoire J, Valcourt U, Ronzière MC, Aubert-Foucher E, Mallein-Gerin F, Herbage D. Modulation of collagen synthesis in normal and osteoarthritic cartilage. Biorheology 2004;41(3–4):535–542

25 Claus S, Aubert-Foucher E, Demoor M, et al. Chronic exposure of bone morphogenetic protein-2 favors chondrogenic expression in human articular chondrocytes amplified in monolayer cultures. J Cell Biochem 2010;111(6):1642–1651

26 Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet 2010;376(9739):440–448

27 Toh WS, Liu H, Heng BC, Rufaihah AJ, Ye CP, Cao T. Combined effects of TGFbeta1 and BMP2 in serum-free chondrogenic differentiation of mesenchymal stem cells induced hyaline-like cartilage formation. Growth Factors 2005;23(4):313–321

28 Postlethwaite AE, Raghow R, Stricklin G, Ballou L, Sampath TK. Osteogenic protein-1, a bone morphogenic protein member of the TGF-β superfamily, shares chemotactic but not fibrogenic properties with TGF-β. J Cell Physiol 1994;161(3):562–570

29 Krawczak DA, Westendorf JJ, Carlson CS, Lewis JL. Influence of bone morphogenetic protein-2 on the extracellular matrix, material properties, and gene expression of long-term articular chondrocyte cultures: loss of chondrocyte stability. Tissue Eng Part A 2009;15(6):1247–1255

30 Elshaier AM, Hakimiyan AA, Rappoport L, Rueger DC, Chubinskaya S. Effect of interleukin-1beta on osteogenic protein 1-induced signaling in adult human articular chondrocytes. Arthritis Rheum 2009;60(1):143–154

31 Chubinskaya S, Hurtig M, Rueger DC. OP-1/BMP-7 in cartilage repair. Int Orthop 2007;31(6):773–781

32 Gavenis K, Schneider U, Wallich R, Mueller-Rath R, Schmidt-Rohlfing B, Andereya S. Effects of low concentrated BMP-7 administered by co-cultivation or plasmid transfection on human osteoarthritic chondrocytes. Int J Artif Organs 2010;33(6):339–347

33 Hunter DJ, Pike MC, Jonas BL, Kissin E, Krop J, McAlindon T. Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. BMC Musculoskelet Disord 2010;11:232

34 Hunter DJ, Pike MC, Jonas BL, Kissin E, Krop J, McAlindon T. Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. BMC Musculoskelet Disord 2010;11:232

35 Schmal H, Niemeyer P, Zwingmann J, Stoffel F, Südkamp NP, Mehlhorn AT. Association between expression of the bone morphogenetic proteins 2 and 7 in the repair of circumscribed cartilage lesions with clinical outcome. BMC Musculoskelet Disord 2010;11:170

36 Chubinskaya S, Hakimiyan A, Pacione C, et al. Synergistic effect of IGF-1 and OP-1 on matrix formation by normal and OA chondrocytes cultured in alginate beads. Osteoarthritis Cartilage 2007;15(4):421–430

37 Busschers E, Holt JP, Richardson DW. Effects of glucocorticoids and interleukin-1 beta on expression and activity of aggrecanases in equine chondrocytes. Am J Vet Res 2010;71(2):176–185

38 Allen KD, Adams SB Jr, Mata BA, et al. Gait and behavior in an IL1β-mediated model of rat knee arthritis and effects of an IL1 antagonist. J Orthop Res 2011;29(5):694–703

39 Ley C, Svala E, Nilton A, et al. Effects of high mobility group box protein-1, interleukin-1β, and interleukin-6 on cartilage matrix metabolism in three-dimensional equine chondrocyte cultures. Connect Tissue Res 2011;52(4):290–300

40 Davies LC, Blain EJ, Gilbert SJ, Caterson B, Duance VC. The potential of IGF-1 and TGFbeta1 for promoting “adult” articular cartilage repair: an in vitro study. Tissue Eng Part A 2008;14(7):1251–1261

41 Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011;7(1):33–42

42 Fortier LA, Miller BJ. Signaling through the small G-protein Cdc42 is involved in insulin-like growth factor-I resistance in aging articular chondrocytes. J Orthop Res 2006;24(8):1765–1772

43 Eli N, Oragui E, Khan W. Advances in meniscal tissue engineering. Ortop Traumatol Rehabil 2011;13(4):319–326

44 Brandl A, Angele P, Roll C, Prantl L, Kujat R, Kinner B. Influence of the growth factors PDGF-BB, TGF-beta1 and bFGF on the replicative aging of human articular chondrocytes during in vitro expansion. J Orthop Res 2010;28(3):354–360

45 Gomez-Camarillo MA, Almonte-Becerril M, Vasquez Tort M, Tapia-Ramirez J, Kouri Flores JB. Chondrocyte proliferation in a new culture system. Cell Prolif 2009;42(2):207–218

46 Mishima Y, Lotz M. Chemotaxis of human articular chondrocytes and mesenchymal stem cells. J Orthop Res 2008;26(10):1407–1412

47 Frisbie DD, Kawcak CE, Werpy NM, Park RD, McIlwraith CW. Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. Am J Vet Res 2007;68(3):290–296

48 Wehling P, Moser C, Frisbie D, et al. Autologous conditioned serum in the treatment of orthopedic diseases: the orthokine therapy. BioDrugs 2007;21(5):323–332

49 Milano G, Deriu L, Sanna Passino E, et al. The effect of autologous conditioned plasma on the treatment of focal chondral defects of the knee. An experimental study. Int J Immunopathol Pharmacol 2011;24(1, Suppl 2):117–124

50 Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair. Clin Orthop Relat Res 2011;469(10):2706–2715

51 Georg R, Maria C, Gisela A, Bianca C. Autologous conditioned plasma as therapy of tendon and ligament lesions in seven horses. J Vet Sci 2010;11(2):173–175

52 Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage 2009;17(2):152–160

53 Miller Y, Bachowski G, Benjamin R, Eklund D, Hibbard A, Lightfoot T. Practice Guidelines for Blood Transfusion: A Compilation from Recent Peer-Reviewed Literature. Washington, DC:American Red Cross;2007

54 Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg 2009;17(10):602–608

55 Nurden AT, Nurden P, Sanchez M, Andia I, Anitua E. Platelets and wound healing. Front Biosci 2008;13:3532–3548

56 Qureshi AH, Chaoji V, Maiguel D, et al. Proteomic and phospho-proteomic profile of human platelets in basal, resting state: insights into integrin signaling. PLoS ONE 2009;4(10):e7627

57 Senzel L, Gnatenko DV, Bahou WF. The platelet proteome. Curr Opin Hematol 2009;16(5):329–333

58 Mishra A, Tummala P, King A, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. Tissue Eng Part C Methods 2009;15(3):431–435

59 Akeda K, An HS, Okuma M, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthritis Cartilage 2006;14(12):1272–1280

60 Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 2011;27(11):1490–1501

61 Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2011;19(4):528–535
62 Hildner F, Albrecht C, Gabriel C, Redl H, van Griensven M. State of the art and future perspectives of articular cartilage regeneration: a focus on adipose-derived stem cells and platelet-derived products. J Tissue Eng Regen Med 2011;5(4):e36–e51
63 Toghraie FS, Chenari N, Gholipour MA, et al. Treatment of osteoarthritis with infrapatellar fat pad derived mesenchymal stem cells in Rabbit. Knee 2011;18(2):71–75
64 Park J, Gelse K, Frank S, von der Mark K, Aigner T, Schneider H. Transgene-activated mesenchymal cells for articular cartilage repair: a comparison of primary bone marrow-, perichondrium/periosteum- and fat-derived cells. J Gene Med 2006;8(1):112–125
65 Koga H, Muneta T, Nagase T, et al. Comparison of mesenchymal tissues-derived stem cells for in vivo chondrogenesis: suitable conditions for cell therapy of cartilage defects in rabbit. Cell Tissue Res 2008;333(2):207–215
66 Wakitani S, Goto T, Young RG, Mansour JM, Goldberg VM, Caplan AI. Repair of large full-thickness articular cartilage defects with allograft articular chondrocytes embedded in a collagen gel. Tissue Eng 1998;4(4):429–444
67 Kuroda R, Ishida K, Matsumoto T, et al. Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells. Osteoarthritis Cartilage 2007;15(2):226–231