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SYMPOSIUM: CLINICALLY RELEVANT STRATEGIES FOR TREATING CARTILAGE AND MENISCAL PATHOLOGY

The Role of Growth Factors in Cartilage Repair

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Abstract

Background Full-thickness chondral defects and early osteoarthritis continue to present major challenges for the patient and the orthopaedic surgeon as a result of the limited healing potential of articular cartilage. The use of bioactive growth factors is under consideration as a potential therapy to enhance healing of chondral injuries and modify the arthritic disease process.

Questions/purposes We reviewed the role of growth factors in articular cartilage repair and identified specific growth factors and combinations of growth factors that have the capacity to improve cartilage regeneration. Additionally, we discuss the potential use of platelet-rich plasma, autologous-conditioned serum, and bone marrow concentrate preparations as methods of combined growth factor delivery.

Methods A PubMed search was performed using key words cartilage or chondrocyte alone and in combination with growth factor. The search was open for original manuscripts and review papers and open for all dates. From these searches we selected manuscripts investigating the effects of growth factors on extracellular matrix synthesis and excluded those investigating molecular mechanisms of action.

Results By modulating the local microenvironment, the anabolic and anticatabolic effects of a variety of growth factors have demonstrated potential in both in vitro and animal studies of cartilage injury and repair. Members of the transforming growth factor-β superfamily, fibroblast growth factor family, insulin-like growth factor-I, and platelet-derived growth factor have all been investigated as possible treatment augments in the management of chondral injuries and early arthritis.

Conclusions The application of growth factors in the treatment of local cartilage defects as well as osteoarthritis appears promising; however, further research is needed at both the basic science and clinical levels before routine application.

Introduction

Growth factors are a group of biologically active polypeptides produced by the body that can stimulate cellular division, growth, and differentiation. In articular cartilage, numerous growth factors work in concert to regulate development and homeostasis of articular cartilage throughout life [39]. Therefore, growth factors offer promising treatments for enhanced regeneration of cartilage in focal articular cartilage defects or in situations of more widespread cartilage loss such as those that occur in osteoarthritis (OA). When considering an injured or osteoarthritic joint, the effects of any treatment such as growth factors on the cartilage, synovial lining, ligaments, tendons, meniscus, any exposed subchondral bone as well as on mesenchymal stem cells (MSCs) that gain access to the articular environment should be collectively considered.

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Numerous anabolic growth factors stimulate chondrocyte synthesis of proteoglycans, aggrecan and type II collagen, induce synoviocyte and MSC proliferation, drive chondrogenic differentiation of MSCs, and decrease the catabolic effects of cytokines such as interleukin-1 (IL-1) and the matrix metalloproteinases (MMP) (Table 1). In addition to being proanabolic and anticatabolic to restore cartilage in naturally occurring disease, an ideal growth factor for general cartilage tissue engineering or regeneration in OA would be effective regardless of the patient's age or the presence of OA and would have no detrimental effects on either the cartilage or the synovial lining.

In addition to growth factors, the need for cells and a scaffold in a composite repair procedure is a widely accepted tenet. The relative magnitude, but not typically the direction, of the effect that a growth factor will have on cell proliferation or matrix synthesis could be altered by the type of cell or scaffold in the composite. In this review we focus on the growth factors that have promise in articular cartilage repair and not on the types of cells or biomaterials used for scaffolds as previously reviewed [19, 37, 52].

Historically, most growth factors have been evaluated on an independent basis, rather than in combination, to assess their effects on cartilage homeostasis in vitro or in vivo. Given the array and interactions of growth factors that are necessary for proper cartilage development and homeostasis, it is unlikely that any single growth factor will lead to complete cartilage repair or affect the arthritic milieu, but rather a combination approach will be required.

The purposes of our review were to first summarize the role of growth factors in articular cartilage repair and identify specific growth factors and combinations of growth factors that have the capacity to improve cartilage regeneration and second to explore the potential use of

Table 1. Summary of the effect of growth factors on chondrocytes/cartilage, synovium, and mesenchymal stem cells in vitro and in vivo

Growth factor	Chondrocytes/cartilage	Synovium	Mesenchymal stem cell	References
TGF-β1	Stimulates synthesis of ECM Decreases catabolic activity of IL-1 and MMPs	Causes synovial proliferation and fibrosis Induces chemotaxis of inflammatory leukocytes to synovium Induction of osteophyte formation	Increases proliferation and ECM production Downregulates collagen type 1 gene expression	7, 8, 27, 47, 89, 92
BMP-2	Stimulates synthesis of ECM Partial reversal of dedifferentiated phenotype in OA Increased ECM turnover (increased aggrecan degradation)	Presumed role in maturation of osteophytes Multiple injections lead to synovial fibrosis Stimulates synovial thickening in experimental OA	Increases proliferation and ECM production Downregulates collagen type 1 gene expression	10, 27, 38, 47, 92
BMP-7	Stimulates ECM synthesis Decreases cartilage degradation through decreasing activity/ expression of numerous ILs and MMPs	Decreases expression of MMPs and aggrecanase Does not appear to cause osteophyte formation or synovial fibrosis	Inhibits cell proliferation Inconsistent ability to induce chondrogenesis alone Potentiates chondrogenic differentiation with TGF-βs resulting in increased ECM synthesis and decreasing collagen type 1 compared with TGF-β alone	5, 40, 65, 81, 82
IGF-I	Stimulates ECM synthesis Decreases matrix catabolism except in aged and OA cartilage	Protective effect on synovium resulting in decreased thickening and decreased evidence of chronic inflammation	Stimulates cell proliferation Increases expression of ECM Additive effect when combined with TGF-β	29, 52, 67, 96
FGF-2	Decreases aggrecanase activity Antagonizes PG synthesis Upregulates MMPs	Induces synovial proliferation Inflammatory and induces osteophyte formation when used alone	Increases PG synthesis Increases cell proliferation	24, 41, 64, 87
FGF-18	Increases chondrocyte proliferation and stimulates ECM in vitro and in injured joints but not in normal joints	Induces synovial thickening Enlargement of chondrophytes in experimental OA		24, 25, 66
PDGF	No adverse effect in normal joints	No adverse effect in normal joints	Induces proliferation	43, 57

TGF-β1 = transforming growth factor-β1; BMP = bone morphogenetic protein; IGF-I = insulin growth factor I; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; ECM = extracellular matrix; IL = interleukin; MMP = matrix metalloproteinase; OA = osteoarthritis; PG = proteoglycan.

platelet-rich plasma, autologous-conditioned serum, and bone marrow concentrate preparations as methods of combined growth factor delivery in light of recent laboratory and clinical studies.

Search Strategies and Criteria

A PubMed search was performed using key words cartilage or chondrocyte alone and in combination with growth factor. The search was open for original manuscripts and review papers and open for all dates. From these searches we included papers that investigated the effects of growth factors on extracellular matrix synthesis and excluded those investigating molecular mechanisms of action.

Transforming Growth Factor-β Superfamily

Growth factors from the transforming growth factor-β (TGF-β) superfamily are structurally related and only active as homo- or heterodimers linked together with a single disulfide bond [96]. In cartilage repair, the three most thoroughly investigated members of the TGF-β superfamily include TGF-β1, bone morphogenetic protein-2 (BMP-2), and BMP-7 (also known as osteogenic protein-1 [OP-1]). More recently, in vitro studies of cartilage-derived morphogenetic protein (CDMP)-1 (also known as GDF-5; growth differentiation factor-5) and CDMP-2 have been performed and all show some capacity to stimulate cartilage matrix synthesis, but not all have been investigated in vivo and therefore will not be further reviewed as current potential treatments to enhance cartilage repair. In an elegant side-by-side comparison of the anabolic and anticatabolic activities of BMP-2, -4, -6, and -7 and CDMP-1 and -2, proteoglycan synthesis was stimulated to a greater extent by BMP-2, -4, and -7 with BMP-7 treatment resulting in maximal proteoglycan synthesis [18]. Furthermore, only BMP-7 showed consistent anticatabolic activity as indicated by restoration of proteoglycan synthesis after IL-1 treatment.

Transforming Growth Factor-β1 and -β3

TGF-β1 stimulates chondrocyte synthetic activity and decreases the catabolic activity of IL-1 [10]. In vitro, TGF-β1 stimulates chondrogenesis of synovial lining and bone marrow-derived MSCs [30, 50]. There have also been promising studies in rabbits in which TGF-β1 enhanced repair of cartilage defects [21]. However, in mouse and rabbit animal studies, numerous deleterious side effects of TGF-β1 supplementation have been reported, including stimulation of synovial proliferation and fibrosis, attraction of inflammatory leukocytes to the synovial lining, and induction of osteophyte formation [7, 10]. Given these serious safety concerns that are not components of other growth factor-based strategies, TGF-β1 therapy is not presently a viable option for use in the articular environment.

TGF-β3 also stimulated extracellular matrix (ECM) synthesis and has been evaluated in vitro in rabbit models of acute cartilage injury [29, 50, 51]. These studies were short term (8 weeks) and primarily looked at cartilage repair and not the synovial membrane and should be interpreted with caution given the potential for deleterious side effects of TGF-β1 in cartilage repair.

Bone Morphogenetic Protein-2

In vitro data indicate BMP-2 stimulates matrix synthesis and interestingly is capable of reversing chondrocyte dedifferentiation to some extent as indicated by an increase in synthesis of cartilage-specific collagen type IIB in dedifferentiated/OA chondrocytes [41]. The effect of BMP-2 on MSCs is similar to that of TGF-β1 with increased ECM production and decreased expression of collagen type 1 [30]. When injected into murine knees, chondrophytes induced by BMP-2 were found in the location where the growth plates meet the joint space [91]. In the rabbit trochlear groove, BMP-2-impregnated collagen sponges implanted into full-thickness cartilage defects enhance cartilage repair compared with empty defects or defects filled with collagen sponge alone. The enhanced repair remained evident 1 year after implantation [3]. In a mouse model of IL-1-induced cartilage degeneration, BMP-2 enhanced cartilage matrix turnover as evidenced by increased aggrecan degradation and increased collagen type II and aggrecan expression [11]. An increase in matrix turnover might indicate a reparative response after cartilage injury or OA, but it is unclear how an increase in a catabolic mechanism such as aggrecan degradation would be of benefit in a cartilage repair procedure.

Bone Morphogenetic Protein-7/Osteogenic Protein-1

BMP-7/OP-1 has been investigated for its capacity to regenerate articular cartilage and currently appears to be the gold standard growth factor for cartilage repair [16]. Like other anabolic growth factors, BMP-7 stimulates cartilage matrix synthesis and decreases catabolic activity of numerous catabolic cytokines, including IL-1, IL-6, IL-8, MMP-1, and MMP-13 [27]. However, unlike other chondrogenic growth factors, these effects of BMP-7 are

not affected by age or OA [16]. BMP-7 is synthesized by chondrocytes and its gene and protein expression decrease with aging and cartilage degeneration, but degenerate cartilage is still able to respond to the anabolic cues of BMP-7 [17, 63]. How aged cartilage responds to the effects of BMP-7 is presently undefined. BMP-7 inhibits MSC proliferation but stimulates ECM synthesis in both synovial and bone marrow-derived MSCs [68, 84]. Chondrogenic differentiation of MSCs is enhanced when BMP-7 is in combination with TGF-β3.

BMP-7 acts synergistically with other anabolic growth factors such as insulin-like growth factor-I (IGF-I) [54]. In animal studies, BMP-7 appears effective in regeneration of osteochondral or focal chondral defects [16]. Administration of BMP-7 is also promising for the treatment of OA [43], but there are fewer animal model studies than there are for the treatment of focal cartilage lesions. In a rabbit ACL injury model, BMP-7 reduced cartilage degeneration [5] and decreased expression of MMPs in the cartilage and synovial membrane compared with untreated limbs [6]. Although BMP-7 is highly effective at stimulating bone repair, it does not appear to lead to osteophyte formation when administered into a joint nor does it stimulate uncontrolled fibroblast proliferation leading to joint fibrosis. In vitro studies indicate that the physiological range for BMP-7 anabolic activity is 50 to 200 ng/mL. Although the exact timing, frequency, or concentration of dosing for in vivo applications is not known, existing studies indicate that effective target concentrations can be reached in the synovial environment through direct injection or inclusion of BMP-7 in a composite scaffold. Collectively, the data suggest that BMP-7 therapy would lead to substantial clinical improvement in cartilage repair procedures; however, the addition of IGF-I might result in even greater healing potential.

Insulin-like Growth Factor-I

The role of IGF-I in articular cartilage metabolism has been extensively investigated in both health and disease [20, 61, 64, 73, 93]. When added exogenously to monolayer or explant cultures of normal articular cartilage from a variety of species, IGF-I induces a plethora of anabolic effects and decreases catabolic responses [78, 80, 90]. Chondrogenic differentiation of MSCs is induced by IGF-I but is enhanced when IGF-I and TGF-β1 are used in combination [56, 95].

The premise that IGF-I is required to maintain articular cartilage integrity is supported by an in vivo study in rats in which chronic IGF-I deficiency led to the development of articular cartilage lesions [24]. In animal models, IGF-I has led to enhanced repair of extensive cartilage defects and protection of the synovial membrane from chronic inflammation [32, 40]. However, there is a decreased capacity of chondrocytes to respond to IGF-I with age [4, 12, 31, 53, 55, 59] and in OA [23, 53, 55, 80]. Evidence suggests an uncoupling of IGF-I responsiveness in OA with IGF-I having the ability to robustly simulate matrix synthesis with the inability to decrease matrix catabolism [70].

Despite the diminished ability of IGF-I to decrease catabolism in aged and OA cartilage, studies suggest that a combination of IGF-I and BMP-7 results in greater repair potential than either growth factor alone [15, 54]. These studies demonstrated that in general, BMP-7 was more potent than IGF-I in stimulating matrix synthesis in aged and OA cells, but the greatest increase in matrix synthesis was observed after combination treatment with BMP-7 and IGF-I.

Fibroblast Growth Factor Family

Two members of the fibroblast growth factor (FGF) family have been investigated for their role in cartilage homeostasis, FGF-2 and FGF-18 [25]. In cartilage, FGF-2 (also known as basic FGF [bFGF]) is found in relative abundance in the pericellular matrix of cartilage [14]. On loading, FGF-2 becomes bound to cell surface receptors and activates anabolic pathways leading to decreased aggrecanase activity but no apparent change in proteoglycan content. In FGF-2 knockout mice, accelerated OA was noted in both unoperated mice and in those undergoing transection of the anterior horn of the medial meniscus. In the surgical OA group, subcutaneous administration of FGF-2 (1 μg every other day) suppressed the OA to a level not different from control mice. However, there is evidence suggesting that FGF-2 antagonizes proteoglycan synthesis mediated by IGF-I and/or OP-1, can upregulate MMPs, and results in synovial proliferation through protection from apoptosis [25]. Furthermore, animal models suggest intra-articular administration of FGF-2 results in inflammation and osteophyte formation [67] and does not aid in healing of cartilage defects [86]. A more recent rabbit study demonstrated improved healing of osteochondral lesions using a highly porous scaffold soaked in low-dose FGF-2 (10 μg/mL) compared with higher doses of FGF-2 (100 μg/mL) or scaffold without FGF-2, suggesting an inverse dose response [57]. FGF-2 treatment of bone marrow-derived MSC monolayer cultures results in enhanced proteoglycan synthesis and cell proliferation [88]. However, given the numerous potentially deleterious effects on the articular environment, the use of FGF-2 in cartilage repair is questionable.

Although there is less literature regarding the role of FGF-18 and cartilage homeostasis, it appears more

promising than FGF-2 and elicits several anabolic effects on chondrocytes [25, 26]. In a rat model of rapid and severe OA, intra-articular administration of FGF-18 resulted in reduced cartilage degeneration scores with increased cartilage thickness of the tibial plateau, but also increased synovial thickness and chondrophyte formation [69]. The role of FGF-18 in repair of focal cartilage lesions is yet to be defined.

Platelet-derived Growth Factor

Platelet-derived growth factor (PDGF) exists as a homodimer (PDGF-AA or PDGF-BB) or a heterodimer (PDGF-AB). Evidence to support the use of PDGF in cartilage repair is extrapolated from the role of PDGF in wound healing or stimulation of matrix synthesis in growth plate chondrocytes [81]. In vivo, when injected into the knee of skeletally immature rats, no adverse effects were noted in the cartilage or synovial membrane [45]. Presently, the most commonly used form of PDGF is within the milieu of platelet-rich plasma (PRP) as discussed subsequently.

Growth Factors in Combination

In addition to those growth factors mentioned, there are several others that have been evaluated for their role in chondrogenesis and it could be concluded that these factors will therefore be important during cartilage regeneration or repair. These growth factors include vascular endothelial growth factor (VEGF), BMP-12, BMP-13, FGF-4, FGF-8, Wnt3a, and Wnt7a, but there are presently too little in vitro or in vivo data to fully discuss here for current applications in cartilage repair [36, 40, 75, 85]. Clearly numerous growth factors are needed to properly sequence chondrogenesis and it is likely that more than a single growth factor will be needed to achieve hyaline cartilage tissue in a reparative procedure. It is becoming increasingly clear that growth factors can work synergistically to enhance cartilage matrix synthesis as in the case of BMP-7 and IGF-I [54], and IGF-I, FGF-2, and TGF-β differentially regulate their own and each other's gene expression and protein production in vitro [85]. Based on the concept that a combination of bioactive growth factors is likely necessary for cartilage repair, and the increasing application of autogenous biologics for tissue engineering, recent attention has been given to the use of PRP, autologous-conditioned serum (ACS), and bone marrow concentrate (BMC) in cartilage repair techniques. Another advantage of PRP and BMC is that on clotting, they form three-dimensional scaffolds to fill the cartilage defect and act as a guide for neochondrogenesis in situ.

Platelet-rich Plasma

PRP is defined by the American Red Cross as a sample of plasma with a twofold or more increase in platelet concentration above baseline levels or greater than 1.1×10^6 platelets/μL [65]. Presently, a number of different manufacturers have introduced systems for PRP preparation allowing for both intraoperative and outpatient use of PRP for a variety of orthopaedic pathologies [42]. There are classification schemes that categorize platelet concentrates based on relative concentrations of platelets, leucocytes, and fibrin, and although it is important to recognize and understand that there are obvious differences between types of platelet concentrates that are being used, the general term/abbreviation PRP is used herein [22, 42].

The concept that application of PRP would improve cartilage repair is based on the physiological role of platelets in wound healing [71]. In response to tissue injury, clots rich in platelets and fibrin form a scaffold for subsequent healing. There are over 1500 proteins within platelets and among them are growth factors stored in platelet α granules that are known to play important roles in the normal healing response, including PDGF, VEGF, TGF-β, FGF, and EGF [76, 83, 87]. Through modulation of the inflammatory response, promotion of local angiogenesis, attraction of fibroblasts and local stem cells to the site of injury, and an induction of autocrine growth factor production by uninjured adjacent cells, platelets and their products are instrumental in normal tissue repair and regeneration.

The application of PRP in cartilage repair is relatively new and therefore there are limited publications investigating its use. Chondrocytes and MSCs exposed to PRP both have increased cell proliferation and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared with controls [1, 66]. Synoviocytes from patients with OA cultured in PRP demonstrated increased hyaluronic acid production and secretion, suggesting that PRP could potentially serve as an endogenous source of chondroprotection and joint lubrication after intra-articular application [2]. In a rabbit model, osteochondral defects were treated with either autogenous PRP in a poly-lactic-glycolic acid (PLGA) carrier, PLGA alone, or left untreated [89]. The PRP group demonstrated a higher extent of cartilage regeneration as well as an increased production of the glycosaminoglycans in the ECM.

In a cohort of 30 patients comparing injections of PRP with hyaluronic acid (HA) in the management of OA, the success rate for the pain subscale reached 33.4% for the PRP group compared with 10% for the HA group ($p = 0.004$) [79]. Additionally, the percent reductions in the physical function subscale and overall WOMAC [9] at 5 weeks were also associated solely with treatment

modality in favor of PRP with $p = 0.043$ and $p = 0.010$, respectively.

Kon et al. treated 115 knees of patients with four intra-articular PRP injections given every 21 days and followed the patients for 12 months [49]. Patients evaluated in this study included 58 with degenerative chondral lesions (Kellgren-Lawrence 0 [48]), 33 with early OA (Kellgren-Lawrence I–III), and 24 with advanced OA (Kellgren-Lawrence IV). A substantial improvement in International Knee Documentation Committee (IKDC) [47] and EuroQol (EQ-VAS) scores [28] was noted at the end of therapy and at both the 6- and 12-month time points. The IKDC subjective scores as well as the EQ-VAS score also demonstrated major improvements at the end of therapy. The authors concluded that treatment with PRP is safe and effective at improving pain, function, and quality of life in patients with degenerative articular pathology.

Autologous-conditioned Serum

Autologous-conditioned serum is generated by incubation of venous blood with glass beads, which results in increased concentration of growth factors such as PDGF and TGF and in some reports increased concentration of IL-1 receptor antagonist protein, which blocks the catabolic cytokine IL-1 [35]. In vivo studies in horses and humans support the use of ACS in the treatment of OA [8, 35]. However, a recent report assessing the in vitro effects of ACS on OA explant tissues did not support the use of ACS in the treatment of OA [77]. The authors found ACS contained increased levels of anti-inflammatory as well as proinflammatory cytokines, in particular TNF-alpha, but application of ACS to OA cartilage explant tissues did not have a net direct effect on cartilage metabolism. Improved appropriately powered clinical studies and increased length of followup should resolve the contradiction between current in vivo and in vitro data.

Bone Marrow Concentrate

BMC, like PRP, is generated through density gradient centrifugation of bone marrow aspirate. The advantage of BMC over PRP is that it contains MSCs, which have demonstrated benefits in the regeneration of cartilage and other tissues of the musculoskeletal system [13, 33, 92, 94]. MSCs represent only 0.001% to 0.01% of mononuclear cells of bone marrow aspirate [58, 72] and the concept of concentrating bone marrow aspirate to generate BMC is to increase the numbers of both platelets (and therefore growth factors) in addition to MSCs. Like PRP, BMC is a fully autogenous biologic that can be generated patient-side and forms a scaffold when clotted. Also, like PRP, BMC contains platelets and therefore is a rich source of growth factors, including PDGF and TGF-β [60, 82]. These growth factors are not only contained within the α granules of platelets, but they are also secreted by MSCs [62, 74] and can induce chondrogenesis of MSCs [13, 44, 46].

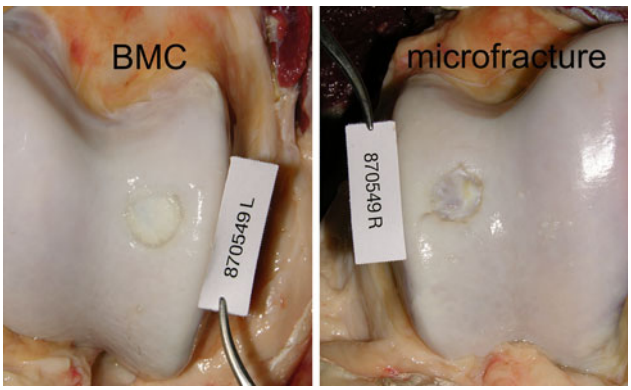

Fig. 1 Bone marrow concentrate (BMC) enhances articular cartilage regeneration. In an equine model of 15 mm diameter, full-thickness cartilage defects on the lateral trochlear ridge of the femur, BMC resulted in improved cartilage tissue formation at 8 months compared with microfracture treated defects.

In an equine model of extensive (15-mm diameter) full-thickness cartilage defects, BMC resulted in improved cartilage repair compared with microfracture using both short-term arthroscopic inspection as well as in longer-term macroscopic, histologic, and quantitative MRI analyses (Fig. 1) [34]. Differences between BMC and microfracture observed arthroscopically at 12 weeks persisted at 8-month evaluation. In particular, repair tissue in BMC-treated defects was much better integrated into surrounding normal cartilage; the tissue was thicker and had a smoother surface. The results of this study indicate that BMC results in substantial improvements in both biochemical and structural components of neocartilage repair matrix. Clinically, BMC and PRP are simple to generate and easy to administer by needle injection to fill articular or osteochondral defects for tissue repair (Fig. 2). Clinical studies are needed to determine the ability of BMC grafting to relieve clinical symptoms and to determine the long-term durability of the repair tissue formed. Gobbi and Bathan have described a similar BMC procedure using a BMC paste in human cartilage defects, but full outcome analysis has not yet been performed on a large case series [38].

Discussion

The appropriate treatment for cartilage injury remains a clinical challenge despite advances in surgical procedures and techniques. Bioactive growth factors are currently

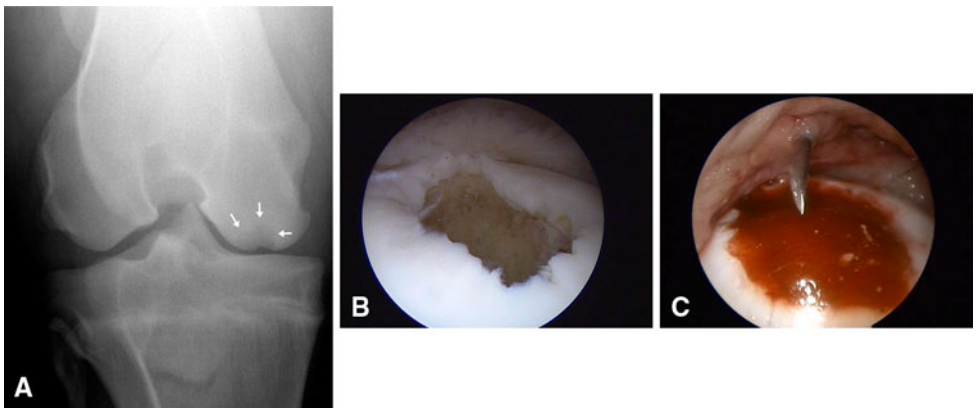

Fig. 2A–C Clinical application of bone marrow concentrate (BMC) to treat a (**A**) large medial femoral condylar osteochondral cyst (arrows). Arthroscopic image (**B**) of the cyst after débridement and (**C**) transarthroscopic BMC administration under gas arthroscopy using an 18-gauge spinal needle.

being considered as therapeutic possibilities to enhance healing of chondral injuries and modify early degenerative arthritis. The purposes of our review were therefore to first review the role of growth factors in articular cartilage repair and identify specific growth factors and combinations of growth factors that potentially improve cartilage regeneration and second to explore the potential use of PRP, ACS, and BMC preparations as methods of combined growth factor delivery in light of recent laboratory and clinical studies.

We acknowledge limitations of our review. First, we conducted a PubMed search using the broad search terms of cartilage or chondrocyte alone or in combination with growth factor. We did not use any other databases (eg, EMBASE, Google Scholar). This would necessarily limit the articles we identified. Second, we had no stringent criteria for selecting manuscripts among those identified. This might lead to potential bias in the articles selected. We emphasized inclusion of manuscripts related to preclinical or clinical applications of growth factors in articular cartilage with the aim to provide general recommendations to the clinician.

One potential method for improving clinical outcomes is to alter the local biologic environment where cartilage is damaged. Individual growth factors in animal models have demonstrated the ability to enhance cartilage production as well as decrease catabolic activity. To date, BMP-7 remains the gold standard growth factor with the ability to both decrease catabolic cytokines and stimulate cartilage matrix synthesis. IGF has also been studied in animal models but has demonstrated limited ability to affect chondrocytes in OA. The FGF and TGF-β families have demonstrated questionable ability to repair cartilage with additional deleterious effects on the articular environment. Currently, the most commonly used forms of combination growth factor therapy are PRP, ACS, and BMC.

There are currently limited publications on any single or combination of growth factors (PRP, ACS, or BMC) in the preclinical or clinical setting. Although the use of growth factors in treating both local cartilage defects as well as OA appears promising, clearly further research will be needed to help guide clinicians in this regard. The biggest obstacles are entrenched in intellectual property limiting the combination of recombinant growth factors, the arduous and resource-intense regulatory pathway, and the lack of any near-term solution for the reimbursement environment. Study design will inevitably require a truly randomized prospective trial in which patients and evaluators are blinded as to the treatment options in addition to a formal characterization of the therapeutic being used. Although these issues are not insurmountable, the most likely agents to succeed in this regard are likely to include the polygrowth factor environment provided by the PRP products.

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