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REVIEW ARTICLE

M. Pecina · M. Jelic · S. Martinovic · M. Haspl
S. Vukicevic

Articular cartilage repair: the role of bone morphogenetic proteins

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Introduction

Joint surface repair is still a major challenge in modern medicine because the factors initiating cartilage formation, maturation, and repair are poorly understood. Specific biological challenges include the variable quality and quantity of the cartilage produced, decreasing responsiveness with age, bonding to the adjacent cartilage, and restoration of the subchondral bone [36]. Injury to cartilage initiates a specific reparative response. In lesions of the articular cartilage with no collagen damage a loss of non-collagenous matrix occurs, leading eventually to complete repair of the damaged matrix [6]. In more severe cases, where there is a damage of the fibrillar network and cell death, the articular cartilage does not heal [33, 44].

Over the past several decades in clinical orthopaedic work, techniques to treat chondral defects included abrasion, drilling, micro-fracturing of the underlying bone, tissue autografts, allografts, and cell transplantation [1, 3, 15, 16, 21, 26, 27, 28, 34, 40, 41, 51]. In recent years more has been learned about various growth factors that stimulate chondrocyte differentiation and cartilage matrix production, but to date no procedure has been fully successful in achieving properly structured regenerative articular cartilage.

M. Pecina (✉) · M. Haspl
Department of Orthopaedic Surgery, School of Medicine,
University of Zagreb, Salata 7, 10000 Zagreb, Croatia
e-mail: marko.pecina@zg.hinet.hr
Tel.: +385-1-4818833, Fax: +385-1-4818810

M. Jelic
Departments of Orthopaedic Surgery and Anatomy,
School of Medicine, University of Zagreb,
10000 Zagreb, Croatia

S. Martinovic · S. Vukicevic
Department of Anatomy, School of Medicine,
University of Zagreb, 10000 Zagreb, Croatia

The role of bone morphogenetic proteins in articular chondrocyte metabolism

So far there is little evidence of any cell division in healthy adult articular cartilage. However, chondrocytes cultured in medium proliferate in response to serum growth factors. The time needed for the doubling of chondrocytes depends on the articular cartilage layer from which the cells were cultured and their density. Chondrocyte proliferation is more rapid in low-density than high-density cultures. Chondrocytes cultured from the deeper zones of tissue doubled more rapidly than those cultured from middle and superficial cartilage zones [50]. Subpopulations of human articular chondrocytes maintained in medium containing human adult serum, which has lower concentrations of growth factors than does foetal serum, show little change in the number of cells during the culture period. No difference in proliferation is reported between cells from the superficial and deep zones [2].

In vitro studies have, during the last few years, identified bone morphogenetic proteins (BMPs) as modulators of articular cartilage chondrocyte metabolism, and it is known that structural macromolecules of extracellular matrix bind BMPs. Chondrocytes in tissue culture progressively lose their phenotype in monolayer cultures. Dedifferentiation of chondrocytes is minimised in explant cultures of articular cartilage in which chondrocytes are encased in their own extracellular matrix [42].

In short-term cartilage explant cultures BMP-4 stimulates dose-dependently the proteoglycan synthesis [30] and a decrease in catabolism. BMP-4 also increases the levels of expression of type II collagen and proteoglycan aggrecan in short-term cultures. This enhancement of cartilage phenotype by BMP-4 is largely independent of the culture conditions. It has also been shown that BMP-4, besides promoting the chondrocyte phenotype, has a weak mitogenic effect in monolayer and micromass cultures [31]. BMP-4 also induces bone in ectopic subcutaneous endochondral bone formation assays in rats, which includes transient cartilage formation. How-

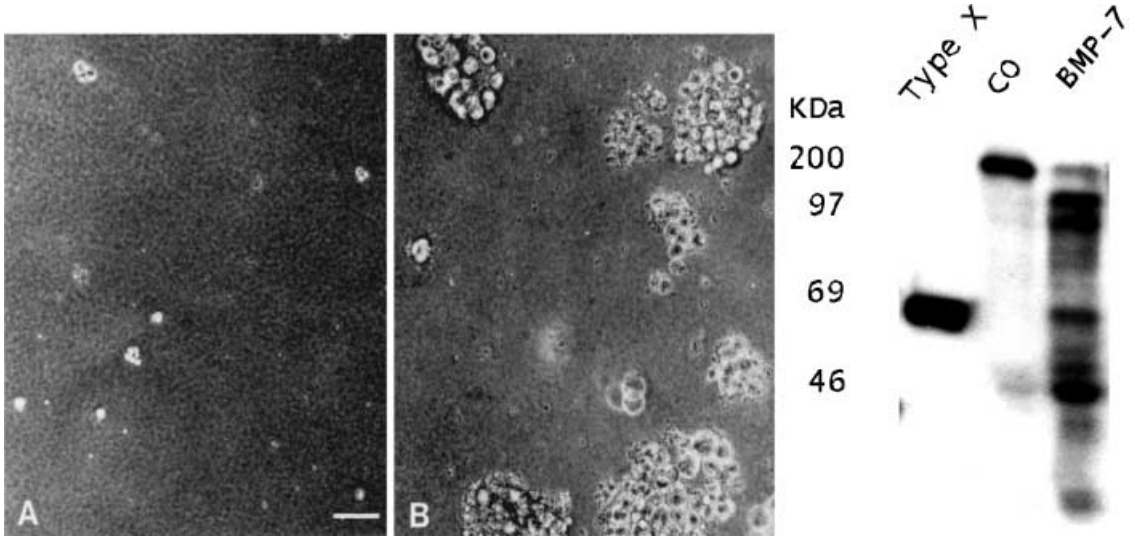

Fig. 1 BMP-7 induces clonal proliferation and maturation of day 15 chick sternal chondrocyte agarose cultures in serum-free medium. Cells were grown in agarose for 3 weeks in chemically defined medium at a density of 1×10^5 cells/well. Photomicrographs of living cultures treated with **a** control, bar 25μm. **b** BMP-7 (50 ng/ml); *right panel* collagen biosynthesis gel; type X collagen (positive control); lane CO, control cells; lane BMP-7, cells treated with 50 ng/ml of BMP-7

ever, the mitogenic effect seen in vitro has a limited significance in tissue repair due to the dense collagen network of articular cartilage that "imprisons" chondrocytes.

In studies on long-term monolayer articular chondrocyte cell cultures up to 28 days, BMP-2 is found to stimulate proteoglycan synthesis [45] while not affecting cell proliferation, the expression of type X collagen, or osteocalcin synthesis. It also enhances the expression of type II collagen and increases the expression of aggrecan [45].

When bovine articular chondrocytes are grown for up to 5 weeks in the presence of 0.5% or 10% serum in combination with BMP-7, they do not hypertrophy, as determined by cell size, the absence of type X collagen expression and synthesis, and alkaline phosphatase activity. The presence of BMP-7 results in increased matrix synthesis. This data suggest that primary mammalian articular chondrocytes are not able to hypertrophy in conditions previously shown to allow hypertrophy of both chick sternal and articular chondrocytes (Fig. 1). BMP-7 in this study was crucial for the maintenance of articular chondrocyte phenotypes by preserving collagen II synthesis [9].

When extending these studies to chick sternal chondrocyte growth and maturation in high density monolayer suspension and agarose cultures for up to 5 weeks, BMP-7 dose dependently promoted chondrocyte maturation associated with enhanced alkaline phosphatase activity, and increased mRNA levels and protein synthesis of type X collagen in both the presence and absence of serum [8]. The pivotal role of BMPs in the development and regeneration process of the skeleton suggests it also plays a role in the repair of articular cartilage defects.

In osteochondral defect studies investigators drill holes through the calcified zone into the subchondral bone. Chondral defects, however, do not damage the calcified cartilage zone and thus do not enter the subchondral bone. The junction between hyaline articular cartilage and the zone of calcified cartilage is called the "tidemark" and represents the mineralization front [22]. Studying the healing phenomena of articular cartilage lesions led to the conclusion that it is essential to expand the existing cell population in order to increase the total pool of healthy cells contributing to the matrix repair. This might be obtained through increased cell proliferation, chemotaxis of cells, or both, from neighbouring tissues such as the underlying bone, the synovium, or both [49]. Growth and differentiation factors can be used in this regard [18], with BMPs being good candidates [43, 53]; others include the recently discovered cartilage-derived morphogenetic proteins (CDMPs), novel TGF-β superfamily members whose cartilage-specific localisation pattern suggests a potential role in chondrocyte differentiation [7, 52].

Full-thickness cartilage defects (osteochondral defects) and cartilage regeneration

Regeneration of full-thickness cartilage defects, which involves cartilage, subchondral bone, and bone marrow, has been studied by drilling holes in the articular cartilage of animal knee joints [49]. These defects undergo repair and a new layer of bone and cartilage is formed, but the macromolecular organisation and the biochemical characteristics of the matrix are imperfect. The persistent high levels of type I collagen and the substitution of the cartilage-specific proteoglycans by other types, such as dermatan sulphate-containing proteoglycans, illustrate such imperfect healing [14, 44]. This produces a repair tissue with fibrillations and extensive degenerative changes that occur after about 3 months, and finally a

complete loss of tissue integrity [5, 35]. Most investigations on articular cartilage healing in vivo have been performed on animal models using osteochondral or full-thickness cartilage defects. Different BMPs have been used. It has been demonstrated that recombinant human BMP-2 (rhBMP-2) with a collagen carrier significantly improves new tissue formation in osteochondral defects in NZW rabbits 6 months and 1 year following surgery [13, 47, 48]. BMP-2-treated defects had a significantly better histological appearance than untreated defects (those left empty or filled with a collagen sponge). The histological features, which showed improvement, were integration at the margin, cellular morphology, architecture within the defect, and reformation of the tidemark. The total scores were also better for the defects treated with rhBMP-2 than for the untreated defects [47, 48]. However, although integration of new and old cartilage in treated animals was better when compared to controls, it is still considered the weakest point in that study.

In another model in which BMP-3 (osteogenin) was combined with porous hydroxyapatite (HA) in dog cartilage, full-thickness defects significantly enhanced transformation of ingrowing fibrous tissue into hyaline cartilage [37]. However, the integration at the margin of newly formed and old tissue was again incomplete.

Another BMP, BMP-7, can improve regeneration of full-thickness cartilage defects in rabbits 3 months following implantation. Histological examination of 20 osteochondral rabbit knee defects revealed significantly different healing of defects treated with BMP-7 compared to those left empty or treated with a collagen gel only. Defects not treated with BMP-7 were filled with several types of tissue 8 weeks following the procedure. However, osteochondral defects treated with BMP-7 were completely bridged with abundant tissue resembling immature cartilage. New tissue consists of small rounded cells organised in columns and embedded in compact extracellular matrix. Rebridgement was complete in superficial layers, which protruded above the surface of intact chondrocytes. In some defects deeper areas had still not fused with surrounding cartilage [17]. These results suggest the potential role of BMP-7 as an articular cartilage repair inducer, but 8 weeks is too early to draw conclusions relating to tissue integration and the architecture of newly formed cartilage.

Osteochondral defect healing with BMP-7 was also evaluated in another study with NZW rabbits in which defects were made in the femoral patellar grove. Grossly, after 12 weeks, it was shown that BMP-7-treated defects showed repair that was continuous with the adjacent intact cartilage and was translucent. Maturing cartilage was present. It looked similar to, and had the same thickness as, the intact surrounding articular cartilage. In comparison, the repair tissue in control sites, which were treated either with no implant or with matrix only, was filled primarily with fibrous tissue or what appeared to be fibrocartilage. The newly formed tissue was not continuous with the surrounding cartilage and was opaque and non-homogenous. Histologically, moderate degeneration of the cartilage was noted at the interfaces of the defect; large clusters of chondrocytes were seen at the interface, and there were fissures separating the intact cartilage from the repair tissue [11, 12]. The integration of newly formed cartilage with old, intact cartilage was reported as satisfactory by these authors. However, the observation time period of 12 weeks post-operatively was insufficient to evaluate the quality of integration and the duration of the newly formed cartilage [12].

In another study osteochondral defects in goat knee joints were studied 4 months after treatment with rhBMP-7 implanted on a collagen carrier. Treated animals showed partial or complete healing after 4 months, and only one of three untreated animals showed some cartilage formation [29].

Studies on articular cartilage healing using periosteum transplants in rabbits show that the periosteum, when transplanted into osteochondral defects, induces new cartilage-like tissue formation that contains 90% collagen II and is replaced by bone in the subchondral regions [39]. It is suggested that periosteum has an articular cartilage healing potential because of factors including orientation of the cambium layer, and post-operative factors such as the application of continuous passive motion and the maturity of the experimental animals [38, 46]. Although the underlying molecular mechanism leading to periosteal articular cartilage healing in osteochondral defects is not understood, it has been shown by different investigators that periosteum contains chondrocyte precursor cells that form cartilage during limb development, and express various BMPs during fracture healing [19, 38].

The majority of studies on articular cartilage regeneration have used osteochondral defects as a model of tissue repair. However, these models show incomplete old and new tissue integration, which is unrelated to the method of treatment or the size of the defect in adult animals. These data suggest that the newly formed tissue in osteochondral defects lacks the support of the underlying bone, which leads to disintegration of the intact and new tissue. It also seems that a growth factor is mostly targeting bone cells from the subchondral bone, which eventually produces bone matrix and not cells that produce cartilage matrix and form new cartilage. This observation suggests reconsideration of the value of the particular model.

Chondral defects and cartilage regeneration

Regeneration of articular cartilage chondral defects was studied in sheep by damaging a complete chondral layer (using a specially designed instrument) without damaging the subchondral bone, and using the continuous application of BMP-7 delivered via an extra-articularly positioned mini-osmotic pump [24, 25]. Two 10 mm chondral defects were created in each knee – one on the medial condyle and the other on the trochlea of the femur. These defects were then randomly treated by either BMP-7 or by acetate buffer via an extra-articularly posi-

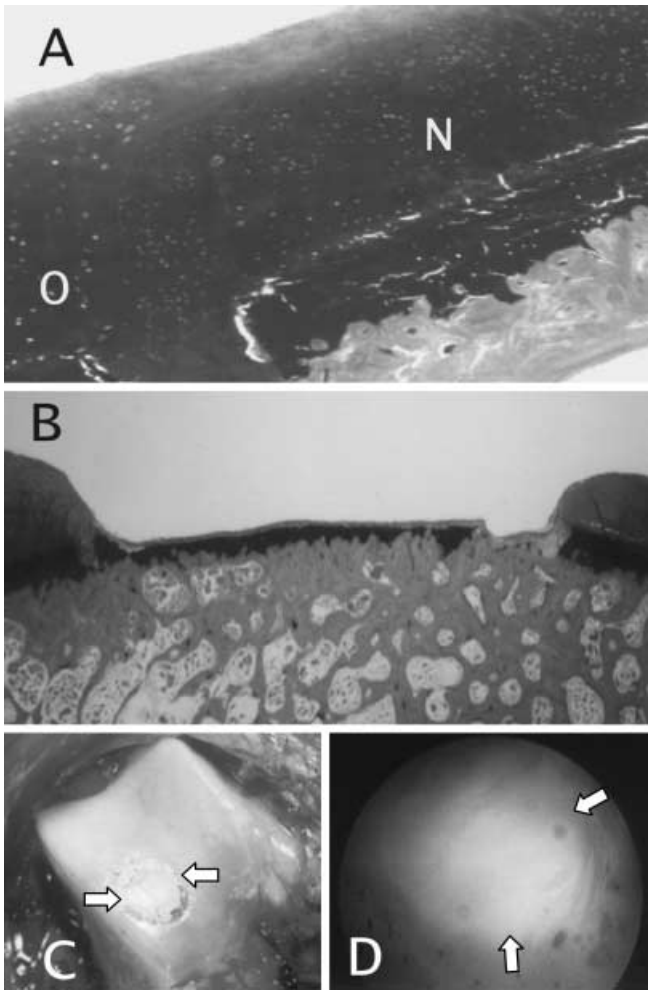

Fig. 2 **a** Regenerated joint cartilage filled the defect area of a joint treated with bone morphogenetic protein-7 (BMP-7, OP-1) at 3 months following surgery, ×5, toluidine blue staining. The bonding between old (marked *O* in Fig. 2a) and newly formed cartilage (marked *N* in Fig. 2a) in a BMP-7-treated defect shows no gaps at the junction site. **b** No cartilage formation in a defect treated with a buffer vehicle, ×5, toluidine blue staining. **c** Macroscopic image of a trochlear chondral defect with no signs of cartilage regeneration. **d** Arthroscopic imaging of a trochlear defect treated with BMP-7 at 15 weeks following surgery appears to be filled with a newly formed tissue

tioned mini-osmotic pump connected to the joint by polyethylene tubing.

Commercially available mini-osmotic pumps (Alza Pharmaceuticals, Palo Alto CA, USA) were pre-tested in vitro and proved to be a reliable method of slowly releasing the protein that was biologically active in a cell-based assay that measures alkaline phosphatase activity in an osteosarcoma cell line (ROS) in vitro [24].

In this study, for the first time, results were determined by arthroscopy at the end points of 3 and 6 months following surgery[20]. At 3 months defects treated with both low- and high-dose BMP-7 were filled with newly formed cartilage, pre-cartilaginous tissue, and connective tissue at the top of the defect (Fig. 2a, d). In control knees there were no signs of cell ingrowth into the defect (Fig. 2b, c). Defects treated with BMP-7 were filled with new cartilage, which was well fused to the old cartilage (Fig. 2a). None of the control defects showed healing at 6 months following surgery. In BMP-7-treated knees newly formed cartilage was still well fused to the pre-existing cartilage, and stained positive for type II collagen [24, 25].

The continuous presence of BMP-7 during the 2–4 weeks following surgery seemed to have attracted surrounding mesenchymal-like cells from the synovium into the defect area, and then transformed into chondrocytes. BMP may therefore be delivered to a joint space without a carrier in concentrations that are beneath the threshold for initiating ossification in the surrounding soft tissues.

In studies using an osteochondral defect model in rabbits and the rhBMP-2 [13, 47, 48] or BMP-7 [17], the repair tissue does not fuse with the pre-existing adjacent cartilage either in treated or untreated defects. The reason for the different ability of newly synthesised cartilage to fuse in osteochondral versus chondral defects could be that, in chondral defects, the underlying bone supports the reparative process and the ingrowing cells come from the synovium [23] and not from the bone marrow. Additional evidence supporting this concept came from the study of Sellers et al. [47, 48], which demonstrated that BMP-2 accelerated the rate of repair of subchondral bone with a subsequent improvement in the morphological features of cartilage in rabbits with osteochondral defects. Although it seems that the tissue integration in adult animals is unrelated to the method of treatment or the size of the defect, the majority of studies have used osteochondral defects, which lack support of the underlying bone resulting in biomechanical instability of the regenerative tissue. It is of interest that articular cartilage defects undergo spontaneous repair in a foetal lamb joint repair model, suggesting a different interaction between foetal chondrocytes and extracellular matrices [36].

A cytokine-based therapy for damaged cartilage would be clinically more useful and efficient than cell-based therapies, which involve removal of autologous cells derived from bone marrow [54] or from cartilage [4], followed by expansion in culture, and then by a second operation for implantation into the defect. A single operation in which a cytokine is used to elicit repair of cartilage would substantially expedite the treatment process as well as reduce costs. It has been recently reported that the expression of BMP-7 mRNA in human cartilage samples did not decrease with ageing and could be increased two-fold in OA cartilage, suggesting a role for BMPs in OA [10]. Apart from BMPs, good candidates in this regard would also be the recently discovered CDMPs with their cartilage-specific localisation pattern, which suggests a potential role in chondrocyte differentiation [7, 32]. The ability of BMP-7 to accelerate and improve cartilage repair in chondral defects emphasises its importance as a candidate for cartilage repair in human osteoarthritis.

Conclusion

BMPs have an important role in articular cartilage chondrocyte differentiation and production and maintenance of the matrix. Several animal experiments on the healing of articular cartilage defects have been performed using BMPs as a repair-signalling molecule. These studies have shown that BMPs act as differentiation factors, which depend on environmental conditions. Data suggest that cartilage repair with BMPs acting on the environment of articular cartilage may become an alternative to current clinical techniques. So far it has been shown that BMPs are good candidates for articular cartilage repair in animal osteochondral and chondral models.

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