Rheumatology : Current Research

Adachi et al. Rheumatology 2012, S3
DOI: 10.4172/2161-1149.S3-001

Research Article Open Access

Synovium in the Transitional Zone between the Articular Cartilage and the Synovial Membrane Contains Stem Cells and has Greater Chondrogenic Differentiation Potential than Synovium in Other Locations

Nobuo Adachi*, Ayato Miyamoto, Masataka Deie, Atsuo Nakamae, Tomoyuki Nakasa and Mitsuo Ochi

Department of Orthopaedic Surgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Abstract

Purpose: There were two aims of the present study. (i) to determine differences in chondrogenic potential between synovial cells located in the transitional zone between the articular cartilage and the synovial membrane and those cells in other locations and (ii) to determine the location of mesenchymal stem cells in the synovium.

Methods: Synovium was obtained from two different locations in 8-week-old male Sprague-Dawley rats. In Group A, the synovium was harvested from the transitional zone between the articular cartilage and the synovial membrane in the femoral condyle. In Group B, the synovium was harvested from an area 5 mm medial to the transitional zone of the femoral condyle. Synovial cells in both groups were isolated and cultured in monolayer culture system and the proliferation of cells in the first passage was compared between Groups A and B. In addition, passage 3 cells were pellet-cultured to induce chondrogenesis for the evaluation of the chondrogenic potential of the synovial cells.

The expression of anti-ATP-binding cassette G-subfamily member 2 (ABCG2), a mesenchymal stem cell marker, was assessed using a real-time polymerase chain reaction in both groups. In a related procedure, both knees of 8-week-old male mice were harvested and cut axially. The synovium in the transitional zone between the cartilage and synovial membrane was examined immunohistochemically by staining with an ABCG2 monoclonal antibody.

Results: The synovial cells in Group A demonstrated greater proliferation potential than those in Group B. Synovial cells derived from Groups A showed greater chondrogenic differentiation potential than those in B with respect to pellet size or the intensity of staining with toluidine blue. ABCG-2 expression was significantly higher in Group A than in Group B and ABCG2-stained cells were more prevalent in the synovium of the transitional zone than in the synovium located in other locations.

Conclusion: The synovium in the transitional zone between the articular cartilage and the synovial membrane contains mesenchymal stem cells and has a greater chondrogenic differentiation potential than synovium located in other sites.

Keywords: Synovium; Transitional zone; Chondrogenesis; Mesenchymal stem cell; Cartilage repair

Introduction and our Previous Research

Recently, synovial-derived mesenchymal cells have been the focus of much attention in the orthopaedic field, because several studies have demonstrated that these cells have multipotent stem cells which can differentiate several lineages under appropriate differentiating conditions [1-6]. Therefore, there is a possibility that synovium which contains synovial mesenchymal stem cells can contribute to cartilage repair *in vivo*. As a matter of fact, when we perform arthroscopy of the knee or total knee arthroplasty for patients with osteoarthritis (OA) or rheumatoid arthritis, we sometimes observe invasion of synovium in the transitional zone between the articular cartilage and synovial membrane into the cartilage defect as if the synovium is repairing the cartilage defect.

In 1996, Hunziker EB and Rosenberg LC [7] reported the recruitment of mesenchymal cells from the synovial membrane into the partial-thickness cartilage defect. They histologically found a continuous layer of mesenchymal cells extending from the synovial membrane across the superficial tangential zone of normal articular cartilage into the defect, indicating that the cells that were recruited for the repair process were synovial in origin. Rothwell [8] reported on synovium transplantation onto the articular cartilage defect of the sheep knee joint. At one year after transplantation, the grafted area had been largely replaced by fibrocartilage of variable differentiation. At two years after transplantation, much fibrocartilage appeared to have undergone either redifferentiation into disorganized fibrochondroid tissue or had developed secondary degenerative change. Allard et al. [9] studied the structure of the synovium-cartilage junction. In the synovium-cartilage junction, a wedge-shaped tongue of tissue was found to cover the cartilage surface. In the superficial zone, fibroblastic-shaped cells are seen in continuity with the adjacent synovial lining cells. They described that the periosteal tissue adjacent to the synovium-cartilage junction has the potential to repair cartilage defects. Thus, recently the role of the synovium in the transitional zone between the articular cartilage and the synovial membrane in cartilage repair has been documented [1,10-13]. Those reports indicate that the synovium in the transitional zone between the articular cartilage and the synovial membrane may have the potential to repair cartilage defects.

We previously reported the role of the synovium in the transitional

***Corresponding author:** Nobuo Adachi, Department of Orthopaedic Surgery, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan, Phone: +81-82-257-5231; Fax: +81-82-257-5234; E-mail: nadachi@hiroshima-u.ac.jp

Received December 06, 2011; **Accepted** January 26, 2012; **Published** February 10, 2012

Citation: Adachi N, Miyamoto A, Deie M, Nakamae A, Nakasa T, et al. (2012) Synovium in the Transitional Zone between the Articular Cartilage and the Synovial Membrane Contains Stem Cells and has Greater Chondrogenic Differentiation Potential than Synovium in Other Locations. Rheumatology S3:001. doi:10.4172/2161-1149.S3-001

zone between the cartilage and synovium membrane in cartilage defects *in vivo* [14]. Here, we describe a brief summary of the study.

Using 8-week-old Sprague Dawley (SD) rats and green fluorescent protein (GFP) transgenic rats, a full-thickness cartilage defect was created at the medial condyle of the femur and the synovium 5 × 5 mm extending up to the cartilage defect was resected in the left knee (cartilage defect without synovium group) but not resected in the right knee (cartilage defect with intact synovium group). In the cartilage defect of the synovium transplantation group, after the creation of a full-thickness cartilage defect and resection of the synovium, the synovium of the GFP rats was transplanted into the unilateral knee. We evaluated the repaired tissue in cartilage defects histologically and immunohistochemically and the expression of aggrecan and type II collagen in the repaired tissue was also investigated using reverse transcriptase-polymerase chain reactions (RT-PCR). Those evaluations were done at 2, 4, 6 and 8 weeks after surgery. At 6 and 8 weeks after surgery, we found that the defect was filled with cartilage-like tissue in the cartilage defect with intact synovium group and in the cartilage defect with synovium transplantation group, but not in the cartilage defect without synovium group. GFP positive cells were observed in the repaired tissue and expression of aggrecan and type II collagen was found in the cartilage defect with synovium transplantation group. Our conclusion was that the synovium in the transitional zone between the articular cartilage and the grafted synovial membrane invades the cartilage defects where the cells could be detected as GFP-positive cells. They considered that those cells might take part in the repair and induce chondrogenesis.

The next step should be to determine the different types of chondrogenic potential of synovial cells depending on their location or the localization of mesenchymal stem cells in the synovium. Thus, the aims of the present study were (1) to determine the differences in chondrogenic potential between synovial cells in the transitional zone and those cells in another location and (2) to clarify the location of mesenchymal stem cells in the synovium.

Materials and Methods

The experimental protocol of the present study was approved by the Ethics Committee of Hiroshima University. The study was performed on 8-week-old male Sprague-Dawley rats and 8-week-old male wild-type mice.

Rat studies

Six Sprague-Dawley rats were anesthetized using sodium pentobarbital (50 mg/kg, i.p.) and their knee joints were opened via the paramedian approach. In Group A, synovium was harvested from the transitional zone between the articular cartilage and the synovial membrane at the femoral condyle; in Group B, the synovium was harvested from an area 5 mm medial to the transitional zone of the femoral condyle. Bilateral samples were taken from each rat in Groups A and B, yielding 12 samples per group.

Proliferative potential in monolayer culture: All synovial tissues were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% heat-inactivated fetal bovine serum (FBS, Sigma-Aldrich, St. Louis, OM) and penicillin-streptomycin-fungizone (Bio-Whittakar, ML) on 6-cm dishes for 4 days at 37°C under 5% humidified CO_2. When the synovial cells were attached to the dishes, the synovium was removed. Adherent synovial cells identified on the culture dishes were then cultured in monolayers in the same medium described above in 10-cm dishes. The medium was changed every 3rd day to remove nonadherent cells until the cells reached confluence. At confluence, synovial cells were plated at an initial density of 50 cells/cm^2 (passage 1). Thereafter, cells were replated at a density of 50 cells/cm^2 every 14 days until their expansion potential was lost. At the end of each passage, the number of cells on each plate was counted and used for intergroup comparisons of the proliferation potential of synovial cells.

Chondrogenic potential in pellet culture: In addition to the culture conditions described above, 2.5 × 10^5 cells from passage 3 of each sample were placed in a 15-mL polypropylene tube (Becton Dickinson, Franklin Lakes, NJ) and centrifuged for 5 min at 1500 r.p.m. The supernatant was eluted, the pellets were resuspended in 1 mL DMEM and samples were centrifuged again for 5 min at 1500 r.p.m. This procedure was repeated a second time and the resulting cell pellets were cultured at 37°C under 5% humidified CO_2 in chondrogenic basal media consisting of DMEM supplemented with 50 μg/mL ascorbate-2-phosphate (Sigma-Aldrich, St. Louis, MO), 40 μg/mL proline (Nacalai Tesque, Kyoto, Japan), 50 μg/mL ITS-A supplement (Invitrogen, Carlsbad, CA), 1.25 mg/mL bovine serum albumin (Sigma-Aldrich, St. Louis, MO), 10 ng/mL transforming growth factor (TGF)-β3 (Sigma-Aldrich, St. Louis, MO), 100 nM dexamethasone (Sigma-Aldrich, St. Louis, MO) and 500 ng/mL bone morphogenetic protein 2 (Yamanoushi Pharmaceutical, Tokyo, Japan)) using a modified version of Johnstone's technique [15,16]. After 3 weeks in culture, the size and the weight of the cell pellets were measured and then the pellets were embedded in paraffin, cut into 5-μm sections and stained with Toluidine blue, to evaluate the degree of chondrogenesis.

Real-time polymerase chain reaction: The expression of anti-ATP-binding cassette G-subfamily member 2 (ABCG2) as a mesenchymal stem cell marker was assessed using real-time polymerase chain reaction (PCR) of the synovium from both groups. Published reports have identified the *ABCG2* gene in stem cells in a variety of tissues and have suggested that it may be a useful marker for stem cells [17,18].

RNA was obtained from each synovial cell sample using the Qiagen RNA isolation kit (Qiagen, Tokyo, Japan) according to the manufacturer's instructions. For cDNA synthesis, mRNA (1.0 μg) was reverse transcribed (QuantiTect® Reverse Transcription; Qiagen, Tokyo, Japan). Real-time PCR analysis using gene-specific primer pairs was performed using the Qiagen QuantiTect® SYBR Green PCR Kit (Qiagen, Tokyo, Japan) according to the manufacturer's instructions. SYBR Real-Time PCR was performed using a MiniOpticon Real-Time PCR Detection System (Biorad Laboratories, Hercules, CA, USA) with the following thermal profiles: 95°C for 10 min, followed by 40 cycles of 15 s at 94°C, 30 s at 60°C and 30 s at 72°C. All experiments were performed in duplicate. Primer sequences for rat ABCG2 were as follows:

sense 5′-CTCTCCCCCCAGCATTTCA-3′;

and antisense, 5′-CTGGGAACTGCTGCCATGG-3′.

Mouse studies

Rat ABCG2 monoclonal antibodies (mAbs) was not available at the time of the experiment. The present study, with ABCG2 as the cell marker, required the use of mice rather than rats for immunohistochemical evaluation of mesenchymal stem cells.

Six 8-week-old male wild-type mice were used. The mice were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and their knee joints were opened via the paramedian approach. The soft tissue around the knee was removed and the femoral condyles were dissected and cut axially. For immunohistochemical studies, the synovium in the

transitional zone between the cartilage and synovial membrane was stained with ABCG2 mAb, as described below.

Tissue samples were embedded in OCT compound for frozen sectioning. Samples were cross-sectioned into 6 μm slices, mounted on silane-coated glass slides, air-dried before being fixed with 4.0% paraformaldehyde at 4˚C for 5 min and then stained as follows. Sections were washed three times with cold phosphate-buffered saline (PBS) for 3 min each time, permeated with 0.1% Triton X-100 in PBS for 30 min at room temperature and blocked with 0.1% Triton X-100 in 10% goat serum for 1 h at room temperature. Sections were then incubated overnight at 4˚C with a mouse mAb against ABCG2 (1:100; Chemicon International, Billerica, MA). The following day, sections were washed with PBS, incubated with anti-mouse IgG antibody for 30 min at room temperature and then incubated at room temperature with a biotinylated goat anti-mouse immunoglobulin and streptavidin-peroxidase conjugate for 30 min. The streptavidin-peroxidase was then visualized using diaminobenzidine. Slides were dehydrated before being mounted with mounting medium.

Statistical Analysis

Data are expressed as the mean±SD.

In the study of proliferative potential, the accumulated cell number of Groups A and B was analyzed using the Mann–Whitney test. $P < 0.05$ was considered significant.

In the study of Real-Time PCR, the ratio of ABCG2 expression between Groups A and B was analyzed using the Mann–Whitney test. $P < 0.05$ was considered significant.

Results

Cell culture

Proliferative potential of synovial cells: Synovial cells in Groups A and B retained the ability to proliferate up to passage 9. In passage 7, the accumulated cell number of Group A and B was $11.10\times10^6\pm0.663$ and $9.42\times10^6\pm0.409$, respectively. In passage 8, the accumulated cell number of Group A and B was $12.44\times10^6\pm0.477$ and $10.14\times10^6\pm0.195$, respectively. In passage 9, the accumulated cell number of Group A and B was $14.08\times10^6\pm0.239$ and $11.44\times10^6\pm0.182$, respectively. Significant differences were found between Groups A and B in passage 7, 8 and 9 ($P < 0.05$).

The synovium in Group A demonstrated a higher proliferation rate compared with that in Group B (Figure 1).

Histological findings for pellet cultures: During *in vitro* chondrogenesis, the pellets increased in size and weight due to the production of extracellular matrix, indicating that the measurement of the size and the weight of the pellets is an easy and useful method to evaluate the chondrocyte differentiation potential of a group of cells.

Cartilage-like tissue stained with Toluidine blue was found in both groups (Figure 2).

Synovial cells derived from Groups A showed greater chondrogenic differentiation potential than those in B with respect to pellet size or the intensity of staining with Toluidine blue.

Real-time PCR studies

Real-time PCR measurements showed that the expression of *ABCG2* mRNA was 1.25 ± 0.11-folds higher in Group A than in Group B ($P < 0.05$) (Figure 3).

Immunohistochemical evaluation of ABCG2 staining

ABCG2-stained cells were more prevalent in the synovium of the transitional zone than in the synovium located elsewhere (Figure 4).

Discussion

As we stated in the introduction, in a previous study, we observed that synovium located in the transitional zone between the articular cartilage and the synovial membrane invaded cartilage defects and exhibited chondrogenic potential *in vivo* [14]. Other studies have shown that synovial cells can differentiate into chondrocytes *in vitro* [1-3,10]. One study harvested synovium from the knees of New Zealand white rabbits, which was then isolated and cultured in agarose suspension with TGF-β, before being identified as type II collagen-

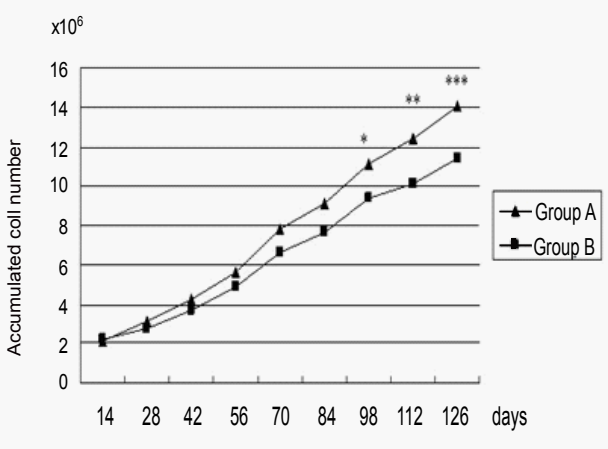

Figure 1: Proliferation potential of cultured synovial cells in Group A (in which the synovium was harvested from the transitional zone between the articular cartilage and the synovial membrane at the femoral condyle) and Group B (in which the synovium was harvested from an area 5 mm medial to the transitional zone of the femoral condyle). The synovium from Group A exhibited a higher proliferation rate than did the synovium from Group B. (*, **, ***: P<0.05).

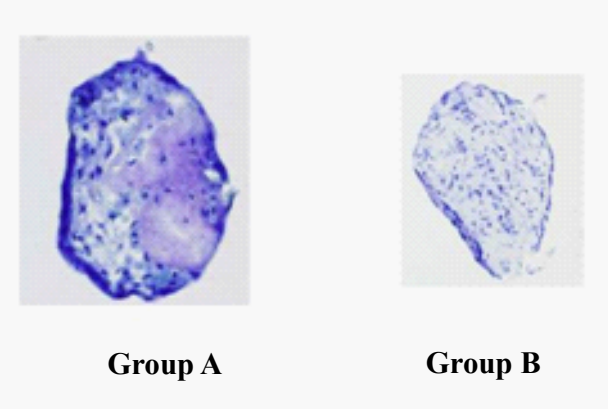

Figure 2: Examination of chondrogenesis in pellet cell cultures in Group A (in which the synovium was harvested from the transitional zone between the articular cartilage and the synovial membrane at the femoral condyle) and Group B (in which the synovium was harvested from an area 5 mm medial to the transitional zone of the femoral condyle). Cartilage-like tissue (stained with Toluidine blue) was found in both groups. Synovial cells derived from Group A showed greater chondrogenic differentiation potential than those in B with respect to pellet size and the intensity of staining with Toluidine blue.

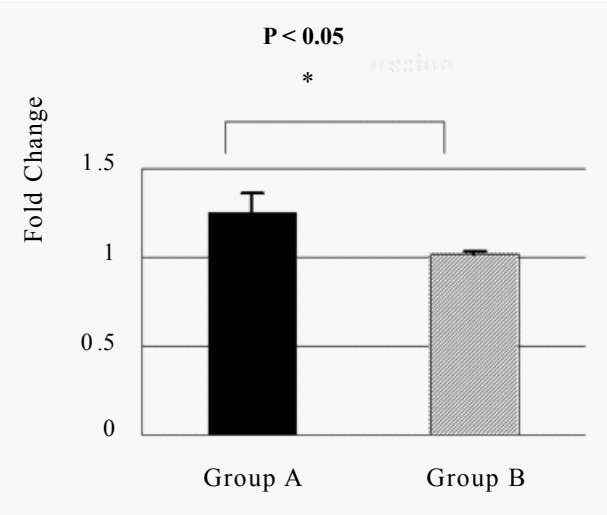

Figure 3: Real-time polymerase chain reaction measurement of *ABCG2* expression in Group A (in which the synovium was harvested from the transitional zone between the articular cartilage and the synovial membrane at the femoral condyle) and Group B (in which the synovium was harvested from an area 5 mm medial to the transitional zone of the femoral condyle). *ABCG2* mRNA expression was 1.25 ± 0.11-fold higher in Group A than in Group B (**P<0.05*).

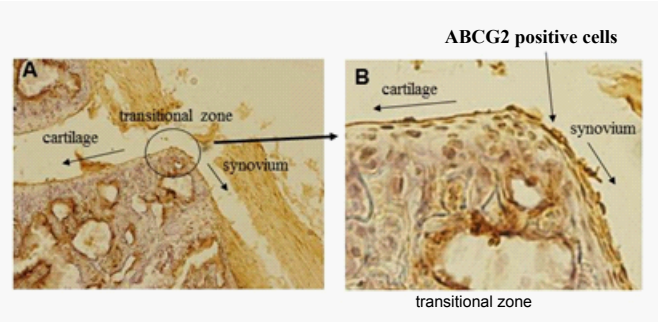

Figure 4: Immunohistochemical evaluation of staining using an ABCG2 monoclonal antibody. **A:** ABCG2-stained cells were more prevalent in the synovium of the transitional zone than in the synovium located elsewhere. (x200) **B**: Magnification image of ABCG2-stained cells in the transitional zone. (x400).

positive cells, which are indicative of chondrogenesis [4]. In another study, de Bari et al. [1] isolated human multipotent mesenchymal stem cells from the synovium and demonstrated that these cells were capable of chondrogenesis, osteogenesis, myogenesis, and adipogenesis under certain culture conditions, indicating that the synovium is capable of multipotent differentiation. In yet another study, Sakaguchi et al. [5] reported that synovium-derived mesenchymal stem cells had greater potential for both proliferation and chondrogenesis *in vitro* than mesenchymal stem cells derived from the bone marrow, periosteum, adipose tissues, or muscles.

Following on from these studies, the next challenge is to identify the location of mesenchymal stem cells with the greatest potential for proliferation and chondrogenesis. Recent studies have documented a role for the synovium located in the transitional zone between the articular cartilage and the synovial membrane in repairing cartilage defects [9,11-14,19-21]. We orthopaedic knee surgeons sometimes observe a synovium invasion from the transitional zone between the articular cartilage and the synovial membrane in to the adjacent cartilage defect of the femoral condyle in osteoarthritic or rheumatoid arthritic knees, as if the synovium moves to repair the defect.

In our present rat study, we demonstrated that synovium from the transitional zone had greater proliferative potential than synovium located in other locations, as well as higher *ABCG2* expression (as demonstrated by real-time PCR). These results indicate that the synovium in the transitional zone between the articular cartilage and the synovial membrane may have greater proliferative potential because of a resident population of mesenchymal stem cells. We also demonstrated greater chondrogenic differentiation potential in the synovial cells derived from the transitional zone, as shown by the larger pellet size and dense toluidine blue staining. Thus, the assessment of synovial chondrogenic potential requires further investigation using other indices, such as quantitative evaluation of glycosaminoglycan.

In the present mouse study, we identified the mesenchymal stem cells in the synovium in the transitional zone between the articular cartilage and the synovial membrane using immunohistochemical staining for ABCG2. Many mesenchymal stem cells were found in the synovium from the transitional zone between the articular cartilage and the synovial membrane. A recent study in humans identified a perivascular niche of postnatal mesenchymal stem cells in the bone marrow [22]. In addition, Rüger et al. [23] reported finding a population of cells that expressed CD34 on their surface but lacked the endothelial cell marker CD31 in synovial tissue from patients with rheumatoid arthritis and OA. By identifying endothelial precursor cells in the synovial tissue from these patients, Rüger et al. [23] provide evidence of vasculogenesis induced by precursor cells that arise in situ or from circulating progenitors. Taken together, these findings, along with those of the present study, suggest that the perivascular niche of postnatal mesenchymal stem cells in the synovium reported by Shi et al. [22] is located in the transitional zone between the articular cartilage and the synovial membrane.

We recognize several limitations in this study. First, PCR evaluation was not controlled without any house-keeping genes. The second limitation is that we did not use rat's ABCG2 antibodies for immunohistochemical staining, because it was not commercially available at the time of the experiment. We should perform further study using rat's ABCG2 antibodies to obtain more convincing data. The immunohistochemical staining of ABCG2 in this study was also lacking control groups.

In conclusion, the synovium in the transitional zone between the articular cartilage and the synovial membrane seems to have a greater potential for repairing cartilage defects than synovium in other areas. It is likely that this increased potential arises from the fact that the synovium in this region contains a resident population of mesenchymal stem cells.

References

1. De Bari C, Dell'Accio F, Tylzanowski P, Luyten FP (2001) Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 44: 1928-1942.
2. Fickert S, Fiedler J, Brenner RE (2003) Identification, quantification and isolation of mesenchymal progenitor cells from osteoarthritic synovium by fluorescence automated cell sorting. Osteoarthritis Cartilage 11: 790-800.
3. Iwata H, Ono S, Sato K, Sato T, Kawamura M (1993) Bo n e morphogenetic protein-induced muscle- and synovium-derived cartilage differentiation in vitro. Clin Orthop Relat Res: 295-300.
4. Nishimura K, Solchaga LA, Caplan AI, Yoo JU, Goldberg VM, et al. (1999) Chondroprogenitor cells of synovial tissue. Arthritis Rheum 42: 2631-2637.

5. Sakaguchi Y, Sekiya I, Yagishita K, Muneta T (2005) Comparison of human stem cells derived from various mesenchymal tissues: superiority of synovium as a cell source. Arthritis Rheum 52: 2521-2529.

6. Yoshimura H, Muneta T, Nimura A, Yokoyama A, Koga H, et al. (2007) Comparison of rat mesenchymal stem cells derived from bone marrow, synovium, periosteum, adipose tissue, and muscle. Cell Tissue Res 327: 449-462.

7. Hunziker EB, Rosenberg LC (1996) Repair of partial-thickness defects in articular cartilage: cell recruitment from the synovial membrane. J Bone Joint Surg Am 78: 721-733.

8. Rothwell AG (1990) Synovium transplantation onto the cartilage denuded patellar groove of the sheep knee joint. Orthopedics 13: 433-442.

9. Allard SA, Bayliss MT, Maini RN (1990) The synovium-cartilage junction of the normal human knee. Implications for joint destruction and repair. Arthritis Rheum 33: 1170-1179.

10. Panasyuk A, Colantuoni G, Khatib AM, Lomri A, Mitrovic DR (2003) Human synovium produces substances that inhibit DNA and stimulate proteoglycan and collagen synthesis by cultured human articular chondrocytes and synovial fibroblasts. Scand J Rheumatol 32: 240-246.

11. Shiozawa S, Shiozawa K, Fujita T (1983) Morphologic observations in the early phase of the cartilage-pannus junction. Light and electron microscopic studies of active cellular pannus. Arthritis Rheum 26: 472-478.

12. Thompson AM, Stockwell RA (1983) An ultrastructural study of the marginal transitional zone in the rabbit knee joint. J Anat 136: 701-713.

13. Vidinov N, Djerov A (2002) Ultrastructural changes in the transitional zone between articular cartilage and synovial membrane during the development of experimental osteoarthrosis. Int Orthop 26: 137-140.

14. Miyamoto A, Deie M, Yamasaki T, Nakamae A, Shinomiya R, et al. (2007) The role of the synovium in repairing cartilage defects. Knee Surg Sports Traumatol Arthrosc 15: 1083-1093.

15. Sekiya I, Larson BL, Vuoristo JT, Reger RL, Prockop DJ (2005) Comparison of effect of BMP-2, -4, and -6 on in vitro cartilage formation of human adult stem cells from bone marrow stroma. Cell Tissue Res 320: 269-276.

16. Johnstone B, Hering TM, Caplan AI, Goldberg VM, Yoo JU (1998) In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. Exp Cell Res 238: 265-272.

17. Bunting KD (2002) ABC transporters as phenotypic markers and functional regulators of stem cells. Stem Cells 20: 11-20.

18. Zhou S, Schuetz JD, Bunting KD, Colapietro AM, Sampath J, et al. (2001) The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nat Med 7: 1028-1034.

19. Allard SA, Muirden KD, Maini RN (1991) Correlation of histopathological features of pannus with patterns of damage in different joints in rheumatoid arthritis. Ann Rheum Dis 50: 278-283.

20. Chu CQ, Field M, Abney E, Zheng RQ, Allard S, et al. (1991) Transforming growth factor-beta 1 in rheumatoid synovial membrane and cartilage/pannus junction. Clin Exp Immunol 86: 380-386.

21. Palmer DG, Selvendran Y, Allen C, Revell PA, Hogg N (1985) Features of synovial membrane identified with monoclonal antibodies. Clin Exp Immunol 59: 529-538.

22. Shi S, Gronthos S (2003) Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. J Bone Miner Res 18: 696-704.

23. Rüger B, Giurea A, Wanivenhaus AH, Zehetgruber H, Hollemann D, et al. (2004) Endothelial precursor cells in the synovial tissue of patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 50: 2157-2166.

This article was originally published in a special issue, **Chondrogenic Progenitor Cell Responses to Cartilage Injury** handled by Editor(s). Dr. Abeles Micha, University of Connecticut Health Center, USA