Reduced Chondrogenic and Adipogenic Activity of Mesenchymal Stem Cells From Patients With Advanced Osteoarthritis

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Objective. Mesenchymal stem cells (MSCs) are resident in the bone marrow throughout normal adult life and have the capacity to differentiate along a number of connective tissue pathways, among them bone, cartilage, and fat. To determine whether functionally normal MSC populations may be isolated from patients with advanced osteoarthritis (OA), we have compared cells from patients undergoing joint replacement with cells from normal donors. Cell populations were compared in terms of yield, proliferation, and capacity to differentiate.

Methods. MSCs were prepared from bone marrow aspirates obtained from the iliac crest or from the tibia/femur during joint surgery. In vitro chondrogenic activity was measured as glycosaminoglycan and type II collagen deposition in pellet cultures. Adipogenic activity was measured as the accumulation of Nile Red O–positive lipid vacuoles, and osteogenic activity was measured as calcium deposition and by von Kossa staining.

Results. Patient-derived MSCs formed colonies in primary culture that were characteristically spindle-shaped with normal morphology. The primary cell yield in 36 of 38 cell cultures from OA donors fell within the range found in cultures from normal donors. However, the proliferative capacity of patient-derived MSCs was significantly reduced. There was a significant reduction in in vitro chondrogenic and adipogenic activity in cultures of patient-derived cells compared with that in normal cultures. There was no significant difference in in vitro osteogenic activity. There was no decline in chondrogenic potential with age in cells obtained from individuals with no evidence of OA.

Conclusion. These results raise the possibility that the increase in bone density and loss of cartilage that are characteristic of OA may result from changes in the differentiation profile of the progenitor cells that contribute to the homeostatic maintenance of these tissues.

Mesenchymal stem cells (MSCs) isolated from human bone marrow have the capacity to differentiate along a number of connective tissue lineages, including bone, cartilage, and adipose tissue (1–3). These cells may play a role in cartilage and bone homeostasis and contribute to the regeneration of tissues following injury, for instance, in the case of bone fracture. Osteoarthritis (OA) is associated with degenerative changes in both bone and cartilage (4–7) and it is interesting to speculate that MSCs could function to resist these changes. The degradative process in OA is characterized by a breakdown of the components of the extracellular matrix surrounding articular chondrocytes and a change in the activity of the chondrocytes themselves (7). Although many studies have looked at the changes in chondrocyte function that accompany the development of OA, there is, to date, little information available on chondroprogenitor cell populations in OA and the role that they may play in the pathogenesis of the disease.

MSC cultures from marrow are expanded from adherent cell populations comprising colony-forming units–fibroblastic (8). Earlier studies of MSC cultures from OA patients showed that the colony-forming efficiency and alkaline phosphatase activity were not altered by the disease (9,10). However, proliferative capacity
(10) and osteogenic potential (11,12) were significantly reduced with age. An age-related decline in osteogenic potential has also been demonstrated in mouse and rat marrow stem cells (13–17).

The association between increased bone mineral density and advanced OA has been widely described (18–22). In one study, bone volume of the femoral neck was increased 72% in OA patients compared with that in controls, while in osteoporotic patients, there was a 20% decrease (23). OA has also been associated with an increased rate of bone turnover (19,22) and proliferation of defective bone with increased trabecular thickness (24), decreased numbers of trabeculae (25,26), and a porous and more textured subchondral bone plate (27).

Many of the changes that occur in OA and osteoporosis suggest an inverse relationship between the two diseases (28,29). Osteoporosis is characterized by increased formation of marrow adipose tissue and decreased bone volume (30), and MSCs from osteoporotic patients have significantly reduced osteogenic capacity (31). However, there is currently no information on the adipogenic potential of stem cells in either the osteoporotic or the OA environment.

We evaluated the multilineage character of MSCs from patients undergoing joint replacement surgery for OA. The potential of the cells to undergo differentiation along chondrogenic (1,32), osteogenic (33), and adipogenic (2) pathways was investigated. Bone marrow samples from the tibia or femur (T/F), and aspirates from the iliac crest (IC), were harvested from patients undergoing either hip replacement or knee replacement. MSCs were prepared from these samples and compared with cells isolated from the IC aspirates obtained from a control group of older donors with no symptoms of OA.

**PATIENTS AND METHODS**

**Protocol design and patient population.** The Ethics Committee of St. Vincent’s Hospital and Medical Center (New York, NY) approved all procedures. Patients scheduled to receive a total hip or total knee replacement as a result of OA were enrolled in the protocol and were fully informed of all procedures prior to signing a consent form. Bone marrow aspirate was obtained from the IC and from either the proximal end of the femur after hip arthroplasty or the distal femur or proximal tibia (T/F) after knee arthroplasty. A total of 25 patients (58% female, 42% male) were enrolled in the study (mean ± SD age 71 ± 7 years, range 59–82 years). All patients underwent either total hip replacement (30%) or total knee replacement (70%). The mean (±SD) body mass index was 30.4 ± 7.4 kg/m². Several patients were obese and had difficulty with ambulation. In addition, several patients had hypertension. MSCs were successfully cultured from 20 of 22 T/F aspirates and 16 of 20 IC aspirates and cryopreserved at the end of primary culture. In the case of 2 additional patients, the marrow aspirates from both sites were combined at the site of collection and these were treated as single specimens.

MSCs were cultured from 10 normal donors without any symptoms of OA (mean ± SD age 43.5 ± 11.3 years, range 23–61 years). A subset of this population, consisting of 7 donors ages 43 years or older, was used as the control group for all differentiation assays (mean ± SD age 49.1 ± 5.9 years, ranging 43–61 years). MSCs from both the OA patients and the normal donors were thawed concurrently and expanded in culture to the end of passage 1 or passage 2 to obtain sufficient cells to perform the 3 differentiation assays simultaneously.

**Isolation and expansion of human MSCs from normal donors.** Bone marrow aspirates (~75 ml) were obtained from the IC of normal donors after their provision of informed consent. MSCs were isolated and expanded in culture as described previously, with minor modifications (1,2,33). The aspirates were washed once with Dulbecco’s phosphate buffered saline (DPBS; Gibco, Grand Island, NY). The cell-containing fraction was gently layered onto a Percoll cushion (1.073 gm/ml; Gibco) at a density of 1–3 × 10⁶ nucleated cells/ml, and centrifuged at 1,100g for 30 minutes at 20°C. The nucleated cell fraction with a density of 1.073 gm/ml at the interface was collected, washed once with DPBS, and resuspended in MSC culture medium (10% fetal bovine serum [FBS] in Dulbecco’s modified Eagle’s medium containing 1.0 gm/liter glucose [DMEM-LG] with antibiotic/antimycotic supplements; Gibco). Cells were plated at 1.6 × 10⁵ cells/cm² in T-185 flasks (Nunc, Naperville, IL). Cultures were maintained at 37°C in a humidified atmosphere and 5% CO₂. At the end of primary culture, adherent colonies were detached by treatment with 0.05% trypsin and 0.53 ml M EDTA (Gibco) and the cells were cryopreserved in 10% DMSO/90% FBS until used.

**Isolation and expansion of MSCs from OA patients.** In the case of OA patients, in whom the aspirate volume was low (2–10 ml), MSCs were isolated using a Percoll density gradient, as described above, only when the total nucleated cell count in the marrow was ≥1 × 10⁶ cells/ml after the preliminary wash. When fewer nucleated cells were recovered, the marrow was washed an additional 2 times with DMEM-LG, resuspended in culture medium, and plated directly in flasks (plating density 1.87 × 10³–5.1 × 10³ cells/cm²). These cells were then cultured and cryopreserved as described above.

**Chondrogenic differentiation.** MSCs were washed with incomplete chondrogenic media (ICM), consisting of DMEM containing 4.5 gm/liter glucose (DMEM-HG) supplemented with 1 mM sodium pyruvate (Sigma, St. Louis, MO), 0.1 mM ascorbic acid–2-phosphate (Wako, Richmond, VA), 1 × 10⁻⁷ M dexamethasone (Sigma), 1% ITS+ (Collaborative Biomedical Products, Bedford, MA), and antibiotics. Cells were cultured in pellet format as described previously (1,32). Briefly, 200,000 cells were placed in a 15-ml conical polypropylene tube, washed with ICM, and resuspended in 0.5-ml complete chondrogenic media (CCM) (ICM containing 10 ng/ml recombinant human transforming growth factor β3; Oncogene Science, Cambridge, MA). Cells were centrifuged at 500g for 5 minutes at 20°C. The pellets were maintained in culture with 1 pellet/tube and 0.5 ml CCM/tube. Medium was changed every 2–3 days. Chondrogenic pellets were harvested at 7, 14, and 21
days for glycosaminoglycan (GAG) quantitation (n = 3) and histologic evaluation (n = 1).

**Histologic and immunocytochemical analysis.** Pellets were harvested and fixed in 10% buffered formalin for 2 hours at room temperature. The fixed pellet was dehydrated by treatment with a series of graded alcohols, cleared by treatment with xylene and xylene substitute, and infiltrated with paraffin. Paraffin sections (8 μm) were deparaffinized using xylene and rehydrated in alcohol. Sulfated GAG was visualized by staining with 0.5% Toluidine blue for 5 minutes at 60°C. Type II collagen was detected using monoclonal antibody C4F6 (34). Endogenous peroxidase activity was blocked by a 15-minute incubation in 0.3% H2O2 in methanol. Sections were then pretreated with 40 μM/ml chondroitinase ABC (Seikagaku, Rockville, MD) in 0.1M Tris–acetate, pH 7.6, containing 1% (weight/volume) bovine serum albumin (BSA) for 30 minutes at 37°C for optimal antigen retrieval. Residual enzyme was removed with two 5-minute washes with Tris buffered saline (TBS) and 10% volume/volume normal goat serum was placed on the section for 1 hour at room temperature to block nonspecific background staining. Primary antibody was diluted to 10 μg/ml with TBS containing 1% BSA immediately prior to use and placed on the sections for 2 hours at room temperature. After washing with TBS to remove residual primary antibody, reactivity was detected using biotinylated goat anti-rabbit secondary antibody and streptavidin–peroxidase. Peroxidase activity was visualized using diamino benzidine (Kirkegaard & Perry, Gaithersburg, MD) as substrate. The sections were counterstained with hematoxylin.

**GAG and DNA measurement.** Chondrogenic pellets were washed with DPBS and digested with 200 μl papain solution (1 μg/ml in 50 mM sodium phosphate, pH 6.5, containing 2 mM N-acetyl cysteine and 2 mM EDTA) for 16 hours at 65°C. GAG was measured by reaction with 1,9-dimethylmethylene blue (35) using shark chondroitin sulfate as standard. DNA quantitation was carried out using the PicoGreen double-stranded DNA quantitation kit from Molecular Probes (Eugene, OR) with phage lambda DNA as standard.

**Osteogenic differentiation.** Osteogenesis was assessed by quantifying the amount of calcium deposited by MSCs cultured in monolayer with osteogenic supplements for 18 days. Control cultures were incubated with MSC culture medium and osteogenesis was induced by adding 0.1 μM dexamethasone, 10 mM β-glycerophosphate, and 50 μM ascorbic acid–2-phosphate to this medium. Calcium was measured using the Sigma Diagnostics Calcium kit. Alkaline phosphatase activity was detected qualitatively using naphthol AS-MX phosphate as a substrate and calcium deposition was determined using von Kossa staining (3,32).

**Adipogenic differentiation.** MSCs were plated at 200,000 cells/well in a 6-well plate and grown to confluence in MSC medium. Adipogenic differentiation was induced by subjecting confluent monolayers to 3 rounds of adipogenic treatments. Each consisted of 48–72 hours in adipogenic induction medium (DMEM-HG, 10% FBS, 1 μM dexamethasone, 0.5 mM methyl-isobutylxanthine, and 10 μg/ml insulin), followed by 48–72 hours in maintenance medium (DMEM-HG, 10% FBS, and 10 μg/ml insulin). Cells were assayed after an additional week in maintenance medium. Control wells (n = 2) were cultured in this medium to the end of the experiment. All wells were incubated for 20 minutes with Nile Red to measure neutral lipid accumulation and 4′,6-diamidino-2-phenylindole (1 μg/ml) to measure DNA in the presence of 0.02% saponin. For histologic analysis, lipid vacuoles were detected by Oil Red O staining.

**Fluorescence-activated cell sorter analysis.** Analysis of cell preparations by flow cytometry was carried out at the end of primary culture as described previously (2) using the antibodies SH-2, SH-3, and SH-4, which recognize surface antigens on human MSCs. The absence of CD45-positive cells was also used to determine purity of the MSC cultures.

**RESULTS**

**Growth of MSCs from OA donors.** Marrow aspirates were obtained from 25 patients undergoing joint replacement as a result of OA, and MSCs were successfully cultured from 23 of these patients. Samples obtained from 1 patient were discarded because they contained bone fragments. A T/F aspirate obtained from an additional patient had a total nucleated cell count of 1.5 × 10⁶ (3.3 × 10⁵ nucleated cells/ml aspirate) and no colonies were formed during primary culture; no IC sample was obtained from this patient.

MSCs were successfully expanded from 20 of 22 T/F aspirates and 16 of 20 IC aspirates. The cells isolated from these marrow aspirates formed colonies in primary culture that were characteristically spindle-shaped with a fibroblastic morphology (Figure 1A, left panel). Analysis of cell preparations at the end of primary culture for expression of the MSC surface antigens SH-2 (CD105) and SH-3 by flow cytometry (Figure 1B) indicated that the cells represented a homogeneous population. Furthermore, the cells were CD45-negative and SH-4-positive (Figure 1C), consistent with other observations regarding human MSCs (2).

The cells formed a monolayer after subculture (Figure 1A, right panel). In 2 additional cases, the aspirates from both sites were combined at the collection site and cultured as single specimens. For these 38 samples, the mean (±SD) cell yield fell within the range found in a historic database of previously cultured MSCs from healthy donors (mean ± SD 2.7 × 10⁴ ± 1.9 × 10⁴ cells/cm²; range 0.75 × 10³–5.8 × 10⁴ cells/cm²). In 36 of these cultures, the cell yield fell within the range found in a historic database of previously cultured MSCs from healthy donors (mean ± SD 2.7 × 10⁴ ± 1.9 × 10⁴ cells/cm²; range 1.2 × 10³–1.1 × 10⁴ cells/cm²; n = 219) (Murphy JM: unpublished observations).

The total nucleated cell yield for 28 marrow aspirates obtained from OA patients was >1 × 10⁶ cells/ml and the MSC-containing fraction was isolated by Percoll centrifugation prior to culture. There was no difference between sites of marrow harvest with respect to nucleated cell count post-Percoll (P = 0.92) or yield at the end of primary culture (P = 0.68). Two Percoll-
fractionated cultures that failed to form colonies had a significantly lower plating density compared with the successful cultures \( (P = 0.03 \text{ using Mann-Whitney rank sum test}) \) (Figure 2A). The total nucleated cell yield for 16 marrow aspirates from OA donors was \( <1 \times 10^8 \text{ cells/ml} \) and these cultures were established by direct plating. Four of these failed to form attached colonies. The median plating density of these failed cultures \( (9.9 \times 10^4 \text{ cells/cm}^2) \) (Figure 2B) was not significantly lower than that of the successful cultures.

A total of 25 OA samples \( (n = 13 \text{ T/F and } n = 12 \text{ IC}) \) and 7 normal samples from older donors were cultured to the end of passage 1. The proliferation rate of the cells was compared using the increase in cell number per 24 hours of culture (Figure 2C). All cultures included in this analysis were \(<100\% \text{ confluent at the time of trypsinization and counting. The median proliferation rate of MSCs isolated from normal older donors was significantly higher than that of MSCs isolated from either the IC marrow } (P = 0.016) \text{ or from the T/F site } (P = 0.006) \text{ of OA donors. However, there was no significant difference in terms of site of marrow harvest } (P = 0.724).

**Multipotentiality of human OA MSCs.** The capacity of cells from OA donors to differentiate along 3 defined lineage pathways was determined using 12 cultures. The proportion of cultures positive for osteogenesis, adipogenesis, and chondrogenesis was 100%, 83%, and 75%, respectively.

**Chondrogenic differentiation of culture-expanded human OA MSCs.** Normal donors \( (n = 10, \text{ age range } 23–61 \text{ years}) \) were tested for chondrogenesis to determine if there was an age-associated change in

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**Figure 1.** Morphology of patient-derived mesenchymal stem cells. Cells formed single colonies in primary culture (A; left panel) and a monolayer after subculture (A; right panel). Analysis of cell preparations at the end of primary culture by flow cytometry, using the antibodies SH2, SH3, SH4, and CD45, indicated that cell preparations were uniformly SH2- and SH3-positive (B) and SH4-positive and CD45-negative (C).
the capacity of the cells to differentiate along this pathway. These donors, free of any symptoms of disease, showed no correlation between chondrogenic capacity and age, at least as far as cellular synthesis of GAG was concerned ($r = 0.228$, $r^2 = 0.0522$, $P = 0.53$) (Figure 3A).

In the case of the patient-derived cells, the amount of GAG deposited by the preparations that were positive for chondrogenesis ($n = 9$) was compared with that deposited by MSCs from normal older donors ($>43$ years, $n = 7$) (Figure 3B). This showed that the chondrogenic activity of MSCs from OA patients was significantly reduced compared with the population of older normal donors. This was the case for cells obtained from bone marrow aspirates at the T/F ($P = 0.032$) and the IC ($P = 0.046$). When samples from OA donors were compared in terms of site of harvest, there was no significant difference in chondrogenic capacity (Figure 3B).

Type II collagen expression was assessed by immunocytochemical staining of sections of pellets. Cells
from an OA donor (Figure 3C) and older normal donors (results not shown) deposited type II collagen after 14 days.

**Osteogenic differentiation of culture-expanded human OA MSCs.** Normal donors (n = 7, age range 43–61 years) were tested to determine if there was an age-associated change in the capacity of the cells to differentiate along the osteogenic pathway (Figure 4A). There was no correlation between the deposition of calcium by MSCs from these donors and age (r = 0.205, r² = 0.0421, P value for slope compared with 0 = 0.66). When both normal and OA donors were included in this analysis (n = 15, age range 43–82 years), the values for r (0.336) and r² (0.113) were higher, but the P value of 0.22 again indicated no interdependence of osteogenic activity with age.

Osteogenic differentiation was assessed by measurement of calcium deposition (Figure 4B) and by histologic detection of alkaline phosphatase activity and calcium (Figure 4C) in cultures maintained for 18 days under osteogenic conditions. All MSC preparations evaluated in this study were capable of elaborating a calcium-rich matrix when compared with control cells incubated in media without osteogenic supplements. Statistical comparison of the osteogenic capacity of MSCs from normal older donors and of patient-derived
MSCs from both the T/F and IC sites showed that there was no significant difference between these groups (Figure 4B).

Histologic assessment of cultures of MSCs obtained from OA donors in the presence and absence of osteogenic supplements was carried out (Figure 4C). These cells were capable of formation of a mineralized layer with marked von Kossa-positive staining when cultured in the presence of osteogenic supplements. There was no difference in terms of histologic appearance between cells obtained from the IC or from the T/F. There was no evidence of mineralization in control cultures.

**Adipogenic differentiation of culture-expanded human OA MSCs.** Normal donors (n = 7, age range 43–61 years) were tested to determine if there was an age-associated change in the capacity of MSCs to differentiate to a lipid-depositing cell (Figure 5A). There was...
no correlation between lipid deposition by MSCs from these donors and age ($r = 0.206$, $r^2 = 0.0424$, $P$ value for slope compared with 0 = 0.66).

The capacity of MSCs from OA donors and from normal older donors to undergo adipogenic differentiation was determined. All MSC preparations from normal donors ($n = 7$) and 83% of preparations from OA donors ($n = 12$) were capable of adipogenic differentiation as determined by accumulation of Oil Red O-positive lipid vacuoles (Figure 5C). The degree of accumulation of lipid-filled vacuoles varied between patients, and the ability of MSCs from OA patients to undergo adipogenic differentiation was significantly less than that of normal MSCs as determined using quantitation of Nile Red fluorescence (Figure 5B). Lipid deposition by MSCs from the T/F aspirates was significantly reduced (54% of that in normal donors; $P = 0.0002$). The same was true of MSCs cultured from IC aspirates (37% of that in normal donors; $P < 0.0001$). There was no significant difference in the site of harvest in adipogenic activity (Figure 5B).

**DISCUSSION**

This study was conducted to evaluate populations of MSCs resident in the bone marrow of patients with advanced OA. Cells were prepared from marrow aspirates obtained at the time of joint replacement surgery. In some cases, the volume of aspirate obtained was small (<1 ml), but colony-forming adherent cells were recov-
ered in 87% of cultures initiated. In those Percoll-fractionated cultures where MSCs failed to attach and form colonies, the initial plating density was low (Figure 2A). These represented a very small proportion of all the cultures prepared. In other cultures that were prepared by direct plating, there was no correlation between plating density and colony formation (Figure 2B), but again, the failed preparations were a small proportion of the total. These observations indicate that there is no decline in colony-forming efficiency of stem cells from bone marrow obtained from OA patients, which is consistent with the earlier observations made by Oreffo and coworkers (9). The MSCs from OA donors were morphologically indistinguishable from the cultures of normal MSCs, and cell yield at the end of primary cultures from 95% of successful cultures was comparable with that obtained for a large number of normal, healthy donors.

The proliferative capacity of the patient-derived cells was clearly lower than that in normal controls (Figure 2C), which would account for the decreased colony size observed in primary cultures of MSCs from elderly donors (9). The results presented here suggest that the loss of proliferative capacity of cells from OA patients is not age- or site-dependent, but is associated with disease. It is important to stress, however, that because of a scarcity of marrow samples from normal elderly donors, the groups were not strictly age-matched, and so the impact of age cannot be completely ruled out. In the context of cell therapy applications in OA, these findings might then suggest that the preparation of an effective dose of autologous cells would be more difficult because of the reduced proliferative capacity, but would not be ruled out. This conclusion may impact clinical applications that involve the use of autologous cells for tissue engineering or for gene delivery. It must also be borne in mind that the altered capacity of these cells may result from changes in cytokines and growth factors associated with OA.

MSCs from OA patients did not differ significantly from the normal population with respect to osteogenic differentiation in vitro (Figure 4). The extent to which MSCs from normal donors undergo osteogenic differentiation was not age-dependent. However, several studies (11–17) have demonstrated that there is an age-related decrease in osteogenic potential of MSCs. Furthermore, the osteogenic potential of cells derived from individuals with osteoporosis is greatly compromised (31). In the present study, the osteogenic potential of MSCs from patients with severe OA, with an average age of 71 years, was equivalent to or greater than that shown by MSCs from normal controls (average age 49 years). Significant bony changes, including osteophyte formation, subchondral bone sclerosis, and ultimately focal necrosis of subchondral bone are associated with the pathology of OA (4,5) and some studies have suggested that the primary defect in OA may be bone-associated, with secondary changes in the articular cartilage (23–25). In many ways, the disease is associated with proliferation of defective bone (24–27) and increased bone mineral density and volume (18–23). Such changes in the bone structure in the OA joint suggest that osteoprogenitor cell populations may play a significant role.

The dramatic degeneration of articular cartilage in joints affected with OA raises many questions about the underlying mechanisms of cartilage homeostasis. In this study, we speculated that chondroprogenitor cells in the bone marrow might contribute to the maintenance of normal cartilage. We found that the ability of MSCs from patient bone marrow to undergo chondrogenic differentiation was significantly reduced compared with that in controls (Figure 3). This change was disease-associated and not age-associated and suggests that this may indeed be a contributory factor in OA. Evaluation of cell preparations from a larger pool of OA and normal older donors will obviously add clarity to this point. Studies that take into account any sex-related differences and effects of different clinical histories will also be important. There is an additional opportunity in the elucidation of control pathways in chondrogenesis and how they may be differently modulated in OA. This opens up possibilities for the identification of specific gene targets that may be useful in developing future therapies for OA.

Although the decline in the differentiation capacity of chondroprogenitor cells in OA patients may play a role in the degradation of articular cartilage, there are certainly other factors involved. The synthesis of aggregan by chondrocytes decreases with age, as does the rate at which it is incorporated into aggregates (36,37). Changes in chondrocyte function such as these may be a primary factor in OA, and the changes in progenitor cell function described here may be of secondary importance.

The decreased adipogenic activity of MSCs from OA patients again reflects abnormal stem cell activity associated with the development of disease (Figure 5). There was a slight increase in lipid deposition by MSCs from normal donors with age, but this age-related increase was not significant with the limited numbers used in this study. In general, there is an increase in bone marrow adipose tissue with age (30) and in osteoporosis
(38), and the role, if any, of adipogenic precursors in OA will be the subject of further evaluation.

MSCs from OA donors appear to differ from those in the normal population in several respects; they have less proliferative capacity, and they are less active in chondrogenic and adipogenic differentiation. Such changes in cell function may play a role in the development of OA, which raises questions about the role of resident progenitor cells in other degenerative diseases, such as osteoporosis, rheumatoid arthritis, and osteonecrosis.

REFERENCES


