Inflammatory status and cartilage regenerative potential of synovial fibroblasts from patients with osteoarthritis and chondrocytosis

S. Fiorito, L. Magrini¹, J. Adrey², D. Mailhé² and D. Brouty-Boyé³

Objectives. To evaluate the inflammatory status and the cartilage regenerative potential of pathological synovial fibroblasts from patients with osteoarthritis (OA) compared with non-inflamed synovium (NS)-derived cells from patients with chondrocytosis.

Methods. The inflammatory cell phenotype was investigated based on the constitutive and inducible surface expression and secretion of various effector molecules using flow cytometry or ELISA assays. The capacity of cells to produce cartilage-like extracellular matrix was assessed using acid Alcian blue staining and type II collagen immunostaining after treatment with transforming growth factor β1 (TGF-β1).

Results. OA and NS fibroblasts consistently expressed CD29, CD44, CD49e, CD54, CD90 and CD106. Expression of high-affinity receptors for IL-4, IL-15, CXCL8 and CXCL12 was also detected but only intracellularly. All types of fibroblasts spontaneously released abundant amounts of CXCL12, CCL2, IL-6 and tissue inhibitor of metalloproteinase 1, while the production of IL-11, TGF-β1, matrix metalloproteinase 1 (MMP-1) and MMP-9 was detected at moderate levels. Several other secreted factors remained undetectable. No statistically significant differences were noted between the two groups of fibroblasts. Treatment with the proinflammatory cytokine tumour necrosis factor α (TNF-α) up-regulated the same set of surface and secreted molecules, including CD54, CD106, membrane IL-15, CCL2 and CCL5. Under TGF-β1 treatment and adipogenic culture conditions, both OA and NS fibroblasts displayed chondrogenic and adipocytic activities that were reduced in OA compared with NS cells.

Conclusions. OA synovial fibroblasts did not display a distinct activated inflammatory phenotype compared with NS cells. However, they did differ in their reduced ability to produce cartilage-like matrix. This difference may be an additional important factor contributing to OA pathogenesis.

Key words: Synovial fibroblast, Inflammatory phenotype, Chondrogenic activity, Osteoarthritis, Chondrocytosis.

Osteoarthritis (OA) is classically defined as a progressive degenerative rather than an inflammatory disease, and is characterized by deterioration of cartilage, focal cartilage loss and osteocyte formation. The existence and relevance of inflammatory changes in OA synovial membrane have been demonstrated by many authors. OA and rheumatoid arthritis (RA) synovium have been shown to display a similar spectrum of inflammatory alterations, with a lesser degree of inflammation in OA. Analysis of the different cell populations in inflammatory infiltrates in RA and OA synovium showed that the distribution pattern was similar in the two types of diseases, the main histological differences being the intensity of mononuclear cell infiltrates and the degree of fibrosis [1]. The expression of both interleukin-1 (IL-1) and tumour necrosis factor (TNF) in OA synovial membranes seems to be similar to that seen in RA, the differences being quantitative rather than qualitative [2, 3]. More recently, it was found that activated synovial and peripheral blood lymphocytes had similar Th1 profiles, and the intracytoplasmic expression of interferon-γ (IFN-γ) and IL-2 was comparable in OA and RA patients; however, RA lymphocytes were less able to produce these cytokines [4].

Most studies focused on the role of chondrocytes as the main cellular population involved in cartilage matrix degradation and defective repair in OA. Thus, it was reported that the expression of p55 TNF-α and type I IL-1 receptors was increased, and the production of the metalloproteinases MMP-1 and MMP-3 [5, 6] enhanced in association with the decrease in their physiological inhibitor, tissue inhibitor of metalloproteinase 1 (TIMP-1) [7]. Furthermore, significantly elevated nitrite levels have been detected in sera of OA patients when compared with normal controls. Moreover, increased expression of inducible nitric oxide synthetase, cyclooxygenase 2 and phospholipase A2 by human OA chondrocytes has also been reported when stimulated by IL-1 and TNF-α. In addition, abnormalities of mechanotransduction leading to aberrant chondrocyte activity, i.e. the absence of a chondroprotective response, have been recently demonstrated in OA chondrocytes compared with normal chondrocytes [8]. This strengthens the hypothesis that chondrocytes are the most important cellular source of inflammatory mediators in OA [9–11].

In the last few years, however, there has been growing evidence that the synovial fibroblast could be an effector cell of tissue destruction in inflammatory synovitis and play a key role in...
modulating the local cellular and cytokine microenvironment and conditioning the inflammatory infiltrate [12, 13]. Recently, qualitatively comparable chromosomal aberrations, affecting mainly chromosomes 1 and 7, were observed in synovial fibroblasts of patients with OA and RA. Since relevant genes coding for cytokines/growth factors, transcription factors, signal-transduction molecules and matrix formation-related molecules are located on chromosome 7, this could imply functional consequences or just reflect a common response to inflammatory stimuli in rheumatic diseases [14].

It is well established that tissue damage results from an imbalance between injuring factors and the repair process, this latter being generally impaired in the late stages of disease. Adult bone marrow-derived mesenchymal progenitor cells (MPCs), which are able to differentiate along various mesenchymal cell lineages (including chondrocytes, osteocytes and adipocytes) upon appropriate stimuli, have recently been shown to display reduced chondrogenic activity in patients with advanced OA [15]. MPCs have also been isolated from articular synovium and it has been proposed that they participate in local cartilage regeneration during arthritic diseases [16, 17]. These results raise the possibility that the chondrogenic activity of mesenchymal fibroblastic progeny might also be affected in OA synovium.

The aim of this study was to evaluate the inflammatory status and chondrogenic activity of cultured OA synovial fibroblasts compared with cells from non-inflamed synovium (NS) but associated with chondropathy, in order to better define the contribution of fibroblasts to the pathogenesis of OA.

Materials and methods

**Patient characteristics**

Inflamed synovial tissue (based on histological criteria) was obtained from two male and four female patients (age range 59–79 yr) with end-stage osteoarthritis (OA) and undergoing total hip prosthetic replacement surgery. The diagnosis was based on clinical and radiological criteria. Tissue that was identified as NS on histological criteria was obtained from three male and two female patients (age range 18–61 yr) suffering from knee chondropathy (post-traumatic or post-dysplastic) and undergoing diagnostic knee arthroscopy. All tissue biopsies were obtained after the patients had given their informed consent.

**Cell culture**

Primary cultures were established from minced tissues in 10% FCS-RPMI 1640 medium (Life Technologies, Cergy-Pontoise, France). Upon confluence, cells were trypsinized and further subcultured at a 1:2 split ratio. All cultures were shown to be negative for CD31 and CD11b and homogeneously (>90%) positive for ASO2 (CD90), excluding recognized on human fibroblasts [18], before being used in experiments between passages 3 and 5. In some experiments, confluent cultures were treated for 3 days with human recombinant (r) TNF-α (R&D Systems, Abingdon, UK) at an optimal standard dose of 50 ng/ml.

**Immunofluorescence staining**

Cells were stained with the various antibodies listed in Table 1, according to conventional direct and indirect techniques [19]. A rabbit purified polyclonal antibody anti-human IL-15 from PeproTech (Tebu, Le Perray-en-Yvelines, France) was used. In some cases, cells were permeabized by treatment with ORTHOPermeaFix (Ortho Diagnostic Systems, Roissy, France) before antibody incubation to monitor intracellular antigen expression. Unspecific staining was determined using identical non-reactive isotype antibodies. Cells were analysed on a FACScan™ (BD Biosciences, Franklin, NJ, USA) using the Cell Quest (BD Biosciences) and WinMDI software programs (Scripps Research Institute, La Jolla, CA, USA).

**Enzyme-linked immunosorbent assay (ELISA)**

Aliquots of supernatants were collected from confluent cultures (1.2 x 10^6 cells/cm^2) between passages 3 and 5, filtered, and stored at −20°C until analysis. Standard ELISAs for various cytokines and chemokines (CXCL12/SDF-1, CCL2/MCP-1, CCL-3/MIP1-α and CCL-5/RANTES) were performed with commercial kits from R&D Systems according to the manufacturer’s instructions. The Mann Whitney U test was used for statistical analysis. Differences between study groups were considered significant at P values <0.05.

**In vitro assay of chondrogenic activity**

A micromass culture assay was used as described by De Bari et al. [16]. Briefly, 20-μl droplets of cell suspension (2 x 10^5 cells/ml) were seeded into 24-well plates. After 3h of adherence without medium, fresh culture medium (1 ml) was added. One day after plating and every other day, the culture medium was changed and human recombinant transforming growth factor β-1 (TGF-β1; R&D Systems), prepared according to the manufacturer’s instructions, was added at a final concentration of 10 ng/ml. Identical amounts of diluents were added to parallel cultures as controls. After 5 days, the cultures were rinsed, fixed with methanol for 30 min at −20°C, and examined for cartilage matrix deposition by staining with acid Alcian blue (0.5% Alcian blue GX; Sigma, Saint Quentin Fallavier, France; pH 0.2). For collagen type-II immuno-

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**Table 1. List of antibodies used in the study**

<table>
<thead>
<tr>
<th>Clone (label)</th>
<th>Antigen</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>NS1-Ag4-1</td>
<td>STRO-1</td>
<td>Iowa Hybridoma Bank (Iowa City, USA)</td>
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<tr>
<td>SFC112T4D 11(T4) (PE)</td>
<td>CD4</td>
<td>BD Biosciences</td>
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<tr>
<td>25.3 (FITC)</td>
<td>CD11a/LFA-1</td>
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<tr>
<td>Bear1</td>
<td>CD11c/Mac-1</td>
<td>Beckman Coulter</td>
</tr>
<tr>
<td>B1.49.9</td>
<td>CD25/IL-2Rα</td>
<td>Beckman Coulter</td>
</tr>
<tr>
<td>4B4 (FITC)</td>
<td>CD29/β1</td>
<td>BD Biosciences</td>
</tr>
<tr>
<td>JC/70A</td>
<td>CD31/PECAM-1</td>
<td>DAKO (Trappes, France)</td>
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<td>MAB89</td>
<td>CD40</td>
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<tr>
<td>J173</td>
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<td>BD Biosciences</td>
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<td>CD48/ VLA-α4</td>
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<tr>
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<td>CXCR4/ SDF-1R</td>
<td>BD Pharmingen</td>
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**References**

[12] and [13].

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[18] and [19].
staining, 100 μl of cell suspension was seeded into 12-well plates. The micromasses were grown in 2 ml of culture medium and treated daily with TGF-β1 for 3 weeks. The cultures were then fixed with 10% formalin, embedded in paraffin, and processed for immunostaining using mouse anti-human type II collagen mAb (Chemicon International, Euromedex, Souffelweyersheim, France) as described [16].

In vitro assay of adipogenic activity

Confluent cultures were grown in adipogenic induction medium consisting of 10% FCS growth medium supplemented with 1 μM dexamethasone and 100 μg/ml 3-isobutyl-1-methylxanthine (Sigma) [20]. After 3–4 weeks, cells were fixed with 10% formalin and stained with oil red O solution (Sigma).

Ethical approval was not required for our study.

Results

Surface phenotype of synovial fibroblasts

OA and NS synovial fibroblasts were analysed for the constitutive expression of various surface molecules known to be implicated in the inflammatory cellular response. As summarized in Table 2, homogeneous (>90% positive cells) expression of the adhesion-related molecules CD29 (β1), CD49e (VLA-5), CD44, CD54 (ICAM-1), CD106 (VCAM-1) and CD90 (Thy-1) was detected whatever the culture type, while CD11a (LFA-1) and CD40 were less consistently expressed. All cultures were found to be negative for CD4 and CD49d. Furthermore, the constitutive expression of high-affinity receptors (R) for cytokines IL-2, IL-4 and IL-15 as well as CD132/Rαc for IL-2 and CXCR3 and CXCR4 for chemokines CXCL8 (IL-8) and CXCL12, respectively, were barely detected on the cell surface whereas highly expressed intracellularly (data not shown). Likewise, no constitutive surface expression of membrane ligands (L), including TNF-related activation-induced cytokine (TRANCE), c-kitL and Flt-3L, was observed, but all were detected intracellularly (data not shown).

Chemokine and cytokine profile of synovial fibroblasts

As illustrated in Fig. 1, OA and NS synovial fibroblasts constitutively produced large amounts of the chemokines CXCL12 (median production 1130 pg/ml for OA and 960 pg/ml for NS) and CCL2 (4500 and 8500 pg/ml, respectively). In contrast, chemokines CCL3 (median production 13.5 pg/ml for OA and 14.0 pg/ml for NS) and CCL5 (9.0 and 15.3 pg/ml, respectively) were generally detected at the limit of cytokine detection and accuracy by ELISA. Moreover, IL-6 (median production 3100 pg/ml for OA and 1800 pg/ml for NS), IL-11 (370 and 70 pg/ml, respectively), TGF-β1 (186 and 199 pg/ml) and stem cell factor (SCF) (13 and 39 pg/ml) were detected in both OA and NS cells. Other proinflammatory molecules, including IL-2, IL-15, granulocyte-colony stimulating factor (G-CSF), granulocyte monocyte-colony stimulating factor (GM-CSF), CD40L and Flt-3L, consistently remained undetectable whatever the synovial culture type. Additionally, elevated levels of the metalloproteinase TIMP-1 (median production 34 000 for OA and 24 000 pg/ml for NS) were also produced in the two types of synovial fibroblasts, while MMP-1 (1100 and 250 pg/ml, respectively) and MMP-9 (270 and 260 pg/ml) were detected in lower amounts. It should be noted that, although the values of the median production of some of the
secreted molecules appeared different between OA and NS cells, the differences were not statistically significant.

Surface adhesion molecule expression and chemokine production in synovial fibroblasts after long-term TNF-α treatment

To evaluate and compare the response of OA and NS fibroblasts to chronic inflammatory conditions, each type of cell was exposed to the optimal standard dose of 50 ng/ml of TNF-α, a potent mediator of inflammatory functions, for 3 days. Flow cytometry analysis revealed increased expression of CD54 and CD106 in the two types of synovial fibroblasts, as judged by changes in mean fluorescence intensity (39 ± 3 vs 7.6 ± 0.3 for CD54 expression in treated and control OA cells, respectively; 73 ± 12 vs 9.4 ± 0.6 for CD54 expression in treated and control NS cells, respectively; 36 ± 7 vs 19 ± 2 for CD106 expression in treated and control OA cells, respectively; and 23 ± 5 vs 18 ± 2 for CD106 expression in treated and control NS cells, respectively) as well as the induced expression of a membrane form of IL-15 (Fig. 2). No change was detected in the expression of other surface molecules, including CD11a, CD29 and CD132 (data not shown).

Fig. 2. Stimulation of surface molecule expression in OA and NS synovial fibroblasts by TNF-α. Cells were incubated in the absence (thin histograms) or presence (thick histograms) of TNF-α (50 ng/ml) for 3 days and stained with the indicated labelled antibodies for flow cytometry analysis. Vertical bars indicate the mean fluorescence intensity in cells treated with isotype-matched control antibodies. Representative data from the various OA and NS cultures are shown.

Fig. 3. Stimulation of chemokine production in OA and NS synovial fibroblasts by TNF-α. Bars show the mean and s.d. *P < 0.05 vs untreated cells. See Fig. 2 for experimental conditions.
When chemokine production was evaluated in cell culture supernatants by ELISA, increased amounts of CCL-2 and CCL-5 were detected in both OA and NS fibroblasts under TNF-\(\alpha\) treatment, while CXCL12 and CCL3 levels remained unchanged (Fig. 3).

**In vitro chondrogenic and adipogenic activity of synovial fibroblasts**

In addition to conventional adhesion-related surface molecules, OA and NS synovial fibroblasts also homogeneously expressed several other specific markers of bone marrow-derived MPCs, such as SH2 (CD105), SH3, SH4 (CD73) and CD166 (ALCAM), while STRO-1, a more immature mesenchymal stem cell antigen, was weakly expressed (Fig. 4) [21, 22]. To determine whether synovial fibroblasts were also able to give rise to the diverse bone marrow mesenchymal lineages, cells were grown as micromasses and treated with 10 ng/ml of TGF-\(\beta1\) for 5 days to induce chondrogenic differentiation. All NS cell-derived micromasses tested were stained with acid Alcian blue, which revealed the hyaline-like cartilage nature of the extracellular matrix produced within the micromasses (Fig. 5). Some of them showed some cell condensation, but no differences in cell numbers were noted between treated

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**Fig. 4.** Expression of mesenchymal stem cell markers in OA and NS synovial fibroblasts. Cells were stained with indicated antibodies (black histograms) or with isotype-matched control antibodies (grey histograms) and analysed by flow cytometry.
and untreated micromasses (data not shown), indicating that Alcian blue reactivity and cell condensation resulted more from elevated matrix production than from increased cell number upon TGF-β1 treatment. In addition to Alcian blue-positive matrix, expression of type II collagen was also detected, as assessed by immunostaining after a 3-week TGF-β1 treatment (Fig. 6). Untreated control cultures were all negative (data not shown).

When cultured in adipogenic induction medium, OA and NS cell-derived cultures also demonstrated adipogenic activity, as evidenced by the accumulation of lipid-filled vacuoles and somewhat reduced oil red O staining in OA cells (Fig. 7). No significant differences in the number of adipogenic cells (approximately 15–35%), however, were monitored in OA compared with NS cells.

Discussion

Numerous reports have documented the broad repertoire of surface and secreted molecules that fibroblasts express and produce, supporting the view that these cells can interact with the different cell types they are associated with within a tissue or organ. However, differences in phenotypic and functional characteristics of fibroblasts have been shown to depend on the anatomical site and pathological status of their tissue of origin [19, 23, 24]. For articular synovia, most studies on inflammatory cell status have compared fibroblasts isolated from OA and RA patients without necessarily including non-inflamed synovial tissue-derived cells. For a better understanding of the contribution fibroblasts in OA, it was important to discriminate between intrinsic and diseased cell features before ascribing diseased tissue-specificity.

By comparing cells isolated from OA and NS tissue, our results clearly show that OA fibroblasts did not display a distinct activated inflammatory phenotype once cultured ex vivo. Thus, the two synovial cell types equally expressed the same set of cell surface adhesion-related molecules, i.e. integrins β1, CD54, CD106 and CD44, which are known to regulate the recruitment and retention of inflammatory cells. Likewise, they both equally produced the same panel of effector molecules, prominently the two chemokines CXCL12 and CCL2 and the three proinflammatory cytokines IL-6, IL-11 and TGF-β1. It should be noted that most of the above adhesion and effector molecules have been found to be spontaneously expressed and produced to variable extents in fibroblasts from various normal and pathological tissue sources once non-specifically activated by in vitro culture conditions [23, 24]. Interestingly, some of them, including IL-6 and CCL2, appeared to be produced at similarly elevated levels in fibroblasts from chronically inflamed RA synovium [25], suggesting that they

Fig. 5. In vitro chondrogenic activity of OA and NS synovial fibroblasts. Cells were plated in micromass cultures and treated with TGF-β1 for 5 days, after which micromasses were fixed and stained with acid Alcian blue.

Fig. 6. Immunohistological analysis of OA and NS synovial fibroblast-derived micromasses treated with TGF-β1 for 3 weeks. Deparaffined sections were incubated with human anti-type II collagen and counterstained with toluidine blue. Bar = 50 μm.

Fig. 7. In vitro adipogenic activity of OA and NS synovial fibroblasts maintained under adipogenic conditions for 3 weeks and stained with oil red O. Bar = 50 μm.
are probably part of the normal rather than the diseased tissue-specific response to inflammation.

It has been proposed that, in chronic inflammation, fibroblasts might fail to switch off effector molecule production, thereby contributing to sustained recruitment and inappropriate lymphocyte retention [13]. Consistent with the view that OA, unlike RA, is not a chronic inflammatory disease but a transient, acutely resolving inflammatory condition, essentially the same effector molecules were found to be up-regulated in OA and NS synovial fibroblasts in response to prolonged stimulation with TNF-α, a culture condition that mimics chronic inflammatory conditions in vivo. Thus, among the various effector molecules tested in the two types of fibroblast, TNF-α selectively stimulated CD54, CD106 and membrane IL-15 expression and the production of the two chemokines CCL3 and CCL5. Therefore, a similarity exists in the constitutive and inducible expression/release pattern of several mediators of inflammation between OA and NS fibroblasts, suggesting more normal acutely rather than chronically activated fibroblasts in the synovial tissue from OA patients. Like most activated tissue-derived fibroblasts, OA cells can effectively participate in the acute inflammatory process through the various effector molecules they produce. For example, TGF-β1, which has been shown to sustain CXCR4 on T cells, can allow, in association with CXCL12, perivascular T cell retention within the synovium [26]. Likewise, membrane IL-15, the biologically active form of the cytokine that has recently been reported to be exposed on human fibroblasts either constitutively or after TNF-α stimulation, can stimulate, by contact, the survival, proliferation and differentiation of target cells for IL-15, such as T lymphocytes and natural killer cells [27, 28].

The selective TNF-α-induced increase in CCL5 production in both OA and NS synovial fibroblasts may be of particular interest in the context of local cartilage regeneration during the inflammatory process. Indeed, CCL5 has recently been reported to contribute to chondrocyte activation and collagen degradation [29]. Synovial fibroblasts may thus contribute to matrix degradation by their activated production of cytokines affecting chondrocyte functions. It should be noted that OA and NS synovial fibroblasts themselves did not differ in their constitutive production of metalloproteinases MMP-1, MMP-9 and inhibitor TIMP-1. However, stimulation of MMP release by TNF-α has recently been reported in OA synovial fibroblasts without affecting TIMP-1 secretion, suggesting an imbalanced cartilage regenerative process in this disease [30].

Another relevant finding with regard to the contribution of fibroblasts to local cartilage regeneration in OA pathogenesis is the reduced chondrogenic activity that OA synovial fibroblasts displayed compared with NS cells. It is noteworthy that these latter cells derived from a non-inflamed tissue in close contact with deteriorated cartilage. Even though not truly normal, they nevertheless demonstrated higher chondrogenic activity than OA synovial fibroblasts. Furthermore, although the NS cells were derived from younger donors, compared with OA patients, donor age should not be an important influencing factor since it has been shown not to affect the differentiation potential of human synovial MPCs, notably chondrogenesis [16].

With respect to mesenchymal potential, both OA and NS synovial fibroblasts expressed most of the markers characteristic of multipotent bone marrow-derived MPCs. Although used as standards for other tissue-derived MPCs [17], many of these have been found to be commonly expressed in most types of fibroblast, demonstrating the close relationship between tissue fibroblasts and bone marrow MPCs. In contrast, the chondro-adipogenic activity reported here appeared typical of synovial fibroblasts. Indeed, fibroblasts isolated from other anatomical sites distant from bone marrow, i.e. spleen and liver, did not display such a capacity even though they all retained mesenchymal MPC marker expression (unpublished results). Because synovial fibroblasts from OA patients, like OA bone marrow-derived mesenchymal stem cells, displayed reduced chondrogenic differentiating potential [15], it is tempting to speculate that innate dysfunctions with respect to chondrogenesis may confer increased susceptibility to this rheumatic disease. Preserving the chondrogenic activity of synovial fibroblasts may thus be a potential target for preventing deterioration and focal cartilage loss in OA.

### References


