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Chondrocyte-derived cells and matrix at the rheumatoid cartilage-pannus junction identified with monoclonal antibodies

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Summary. In the cartilage-pannus junction of 14 patients with rheumatoid arthritis (RA) and seven patients with osteoarthritis (OA), monoclonal antibodies to keratan sulphate (KS) and chondroitin sulphate (CS) stained a transitional fibroblastic zone (TFZ) within the pannus in nine RA patients and one OA patient. In three patients this was clearly localised to the cytoplasm of cells in this zone, but in all remaining cases KS and CS could be demonstrated in the surrounding matrix. This area was distinguished from adjacent pannus which contained many blood vessels and cells positive for MHC Class II antigen. Specific markers for glycosaminoglycans have been employed to demonstrate that chondrocyte-derived cells and matrix contribute to the changes seen at the cartilage-pannus junction in RA-affected joints.

Key words: Rheumatoid arthritis – Articular cartilage – Histocytochemistry – Glycosaminoglycans – Pannus tissue

Introduction

Pannus is a blanket of tissue covering the cartilage surface and filling the erosions and defects observed in rheumatoid joints [1–3]. Hypotheses as to the origins of pannus based on morphological and histochemical studies [4–12] have resulted in considerable difference of opinion and debate in the current literature [13–14]. Although the conventional view is that pannus consists of tissue derived from the adjacent synovium which has grown over the cartilage surface, some investigators have emphasised the contribution made by the underlying cartilage [9–10, 13–14].

In this study, we have demonstrated for the first time the contribution that cartilage makes to the formation of rheumatoid pannus, by using specific markers to detect the cartilage components keratan sulphate and chondroitin sulphate.

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Materials and methods

Preparation of specimens. Samples of synovial-cartilage junction and cartilage covered by pannus (cartilage-pannus junction) were obtained from operative specimens of 14 patients with rheumatoid arthritis (definite or classical, according to the criteria of the American Rheumatism Association) [15], who were undergoing joint-replacement surgery. In addition, samples of synovial-cartilage junction were similarly obtained from seven patients with osteoarthritis.

The tissue was fixed in ethanol and embedded in paraffin wax. Sequential sections 5 μm thick were then cut perpendicularly to the articular surface. Each section was stained with haematoxylin and eosin (H+E) to assess morphology and with Safranin O to assess the presence of proteoglycan. Only sections in which a definite junction could be recognised were included in the study. These were obtained from 35 blocks of tissue.

Enzyme histochemistry. One section from each block was stained for chloracetate esterase (CAE). The incubation medium comprised 10 mg Naphthol AS-D Chloracetate (Sigma Chemical Co., Poole, UK) in 1 ml dimethyl formamide, which was added to 30 mls; 0.1 *M* phosphate buffer (pH 6.8) and 0.8 ml hexazotised pararosanalin. Sections were incubated in fresh medium for 30 min at room temperature and counterstained with Mayers haematoxylin [16].

This enzyme stain results in bright-red staining of the cytoplasm of polymorphonuclear leucocytes and mast cells.

Immunohistochemistry. Sections were examined using an indirect immunoperoxidase technique with several primary antibodies (as detailed in Table 1).

The monoclonal antibody (MAb) MZ 15, recognises keratan sulphate in articular cartilage and cornea only [17]. Sections prepared using this MAb were examined with and without pretreatment with chondroitinase ABC (Sigma) at 37 °C for 45 min.

The monoclonal antibodies to chondroitin sulphate used (9A2, 3B3 and 1B5) recognise unsaturated determinants on chondroitin sulphate 4 and 6, and non-sulphated chondroitin sulphate, respectively. These epitopes are generated by digestion with chondroitinase ABC and remain attached to proteoglycan, one on each chondroitin sulphate residue. In immunolocalisation studies in rat, staining with 1B5 was restricted to cartilage, whereas 9A2 stained some perivascular connective tissues and 3B3 stained basement membranes; synovial membrane was not investigated [18].

The secondary antibodies used were either rabbit anti-mouse or goat anti-rabbit conjugated with peroxidase (Sigma) used at a dilution of 1 in 100 with phosphate-buffered saline. Normal calf serum was used to block non-specific binding; endogenous

Table 1. Primary antibodies

Reagent	Class	Dilution	Specificity	Source and reference
Monoclonal antibodies				
MZ 15	Mouse IgG_1	1 in 1000	Keratan sulphate	Dr. F. M. Watt, Kennedy Institute, London [17]
1-B5 9A2 3B3	Mouse IgG_1 IgG_1 IgM	1 in 50	Chondroitin sulphate	Prof. B. Caterson, University of West Virginia, Morgantown, VA [18]
Tal-1B5	Mouse IgG_1	1 in 1000	MHC class II antigens DR+DQ	Dr. J. G. Bodmer, ICRF, London [19]
Thy-1 (F15-42-1)	Mouse IgG_1	1 in 100	Endothelial cells Immature T cells ?Fibroblasts	Dr. J. W. Fabre, East Grinstead, Sussex, UK [20]
Polyclonal antibodies				
α_1-ACT[a]	Rabbit IgG	1 in 100	Macrophages Mast cells	Dakopatts, Copenhagen [21]
S100	Rabbit IgG	1 in 100	Chondrocytes + others (see reference)	Dakopatts, Copenhagen [22]

[a] α_1-antichymotrypsin

peroxidases were blocked with 0.1% hydrogen peroxide in methanol. Negative controls, omitting primary antibody, were run with each experiment. For the MAbs to chondroitin sulphate residues, omission of chondroitinase ABC digestion served as an additional negative control.

Results

Morphology from routine stains

On examination with routine stains (H+E and Safranin O) different types of pannus could be recognised in our sections. The most notable distinguishing feature was the nature of the junction between pannus and articular cartilage (C-P junction), which allowed the characterisation of two main types. In the first type, the junction was clearly discernable as a distinct margin (Fig. 1a). In the second type, the junction was indistinct and consisted of a transitional fibroblastic zone (TFZ) of spindle-shaped cells within a collagenous matrix (Fig. 1b). In all the sections in which a TFZ was observed, the overlying pannus tissue was rich in blood vessels. Where a distinct margin without a TFZ was observed, the overlying pannus was usually less vascular and of variable cellularity. Pannus consisting

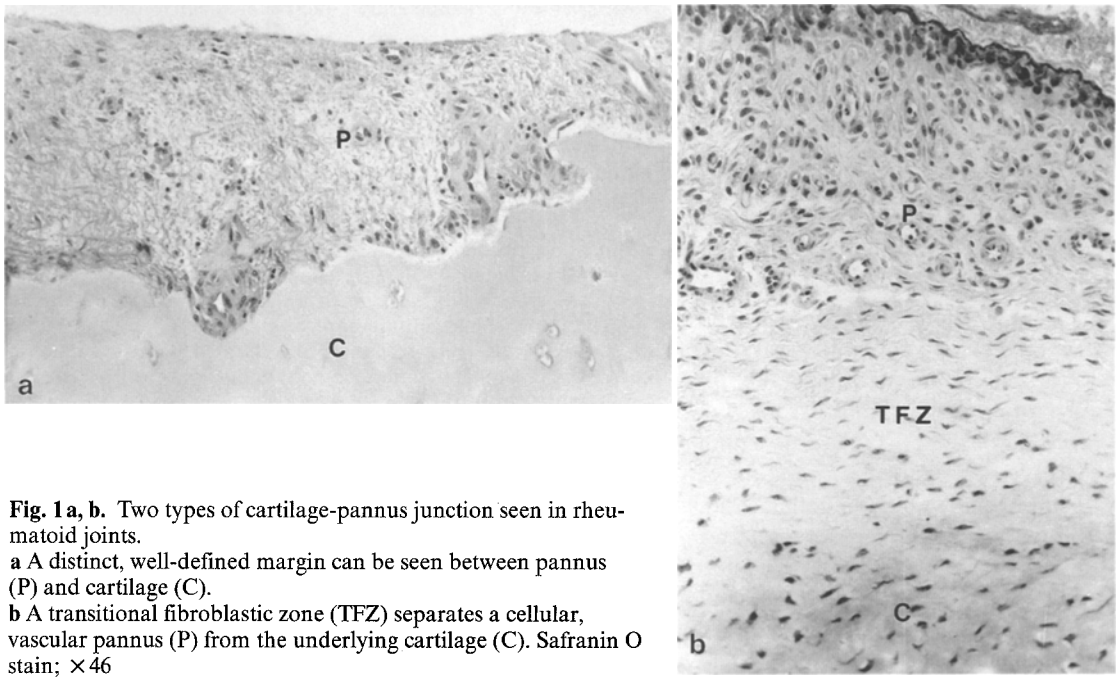

Fig. 1a, b. Two types of cartilage-pannus junction seen in rheumatoid joints.
a A distinct, well-defined margin can be seen between pannus (P) and cartilage (C).
b A transitional fibroblastic zone (TFZ) separates a cellular, vascular pannus (P) from the underlying cartilage (C). Safranin O stain; ×46

entirely of acellular fibrous tissue was not seen in the sections, but has been described [4].

In six RA patients more than one block of tissue was examined. In two of these patients, both types of pannus were seen in sections cut from different blocks of the same joint. However in the other four patients, from whom two to five blocks of tissue were examined, the type of pannus was constant within the joint.

The size of the TFZ varied between sections (range 3–20 cells in depth), and in some sections the TFZ occupied up to 50% of the total depth of the pannus. This zone did not stain with Safranin O and therefore did not appear to contain proteoglycan as judged by conventional metachromatic staining.

Staining with Keratan sulphate and chondroitin sulphate

The spindle-shaped cells and matrix within the TFZ stained positively with the monoclonal antibody to keratan sulphate (KS), despite being Safranin-O negative. Staining of the TFZ matrix was seen in all ten patients (nine RA; one OA) whose pannus contained a transitional zone, and this was greatly enhanced by pretreatment with chondroitinase. The matrix staining within this area, although occasionally somewhat patchy, was so strong in some sections that it was difficult to ascertain whether there was also cytoplasmic staining (Fig. 2). However, in sections that had not been pre-treated with chondroitinase ABC, definite cytoplasmic staining of the cells within the TFZ was seen in three of the ten patients (Fig. 3). There was no positive staining for KS in the more superficial pannus or the adjacent synovial membrane. In particular, fibroblastic cells and fibrous tissue within synovial membrane was not stained by this antibody. In some sections, KS-positive cells intermingled closely with vascular endothelium and macrophages (Fig. 4).

Monoclonal antibodies to chondroitin sulphate (CS) produced positive staining of the TFZ matrix in all the above ten patients, in the same distribution as was found with KS antibodies (Fig. 5). However, no definite cytoplasmic staining of the TFZ cells was seen. The CS mAbs were used together in a 'cocktail' to maximise staining. There was no staining, however, of either the superficial vascular pannus or the adjacent synovial membrane. Nevertheless, some residual KS and CS was demonstrated in the underlying cartilage in all of the sections, even those that were completely Safranin-O negative. These markers are therefore more sensitive indicators of the presence of glycosaminoglycans in tissue sections than conventional metachromatic staining.

Staining with other markers

In the rheumatoid pannus 30%–40% of the cells stained for MHC Class II antigen (Fig. 6a). In sequential sections these cells were also stained positively by α_1-antichymotrypsin (α_1-ACT) (Fig. 6b). In 12 of the 14 RA patients no cells positive for chloracetate esterase (CAE) were found at the C-P junction, suggesting that the α_1-ACT positive cells were macrophages rather than mast cells. Only in one section were mononuclear CAE-positive cells (mast cells) seen at the junction.

The cells positive for both α_1-ACT and Class II antigen were largely confined to areas of cellular pannus and were not found within the cartilage or TFZ. They were, however, seen in close proximity to both cartilage and the TFZ. The occasional Class II positive cell seen within these underlying structures may have originated from protruding invaginations of cellular pannus.

Sections from the OA patient with a cellular pannus and a TFZ had fewer Class II positive cells, but otherwise resembled the RA pannus. Another OA patient had a few cells positive for α_1-ACT and DR on the surface of the pannus, but these were negative for all the other markers used. Pannus was not present in the other five OA patients. CAE-positive cells were not seen in any of the OA joints in this study.

Antibodies to Thy-1 and S100 protein were used in an attempt to characterise the origin of the TFZ cells further. The monoclonal antibody to human Thy-1 used in this study has been found to react with cultured fibroblasts and with fibroblasts in connective tissues [20]. However it did not stain any of the spindle-shaped cells within the TFZ, nor did it stain any of the mononuclear cells within the cellular pannus. It did, however, as has also been found in another study [23], bind to the endothelial cells of blood vessels in the synovial membrane.

S100 protein is thought to be involved in calcium-modulated cellular processes, and has been identified in normal human chondrocytes [22]. None of the cells in the pannus stained positively with this antibody, and morphologically identifiable chondrocytes were positively stained in only three sections.

Polymorphonuclear leucocytes were not identified at the C-P junction in any of the specimens. However, in one RA patient with a flare in disease activity at the time of surgery, many polymorphs were present in the superficial pannus and adjacent synovial membrane. These cells, recognised by their characteristic multilobed nuclei and CAE positivity, were situated within vessels or embedded in surface fibrin. Only the occasional polymorph was seen within the tissue substance, and none were seen immediately adjacent to the articular cartilage. Polymorphs were only occasionally found within the superficial pannus or synovial membrane in other sections.

Clinical correlations

There were no clinical differences between the patients with rheumatoid arthritis who had a well-defined C-P junction and those who had a TFZ (Table 2a). In particular, there was no difference in disease duration prior to joint replacement. There was no correlation with treatment received, particularly with respect to second-line drugs and steroids (data not shown).

Pannus was identified in two out of seven of the osteoarthritic joints (Table 2b). In the one patient in whom

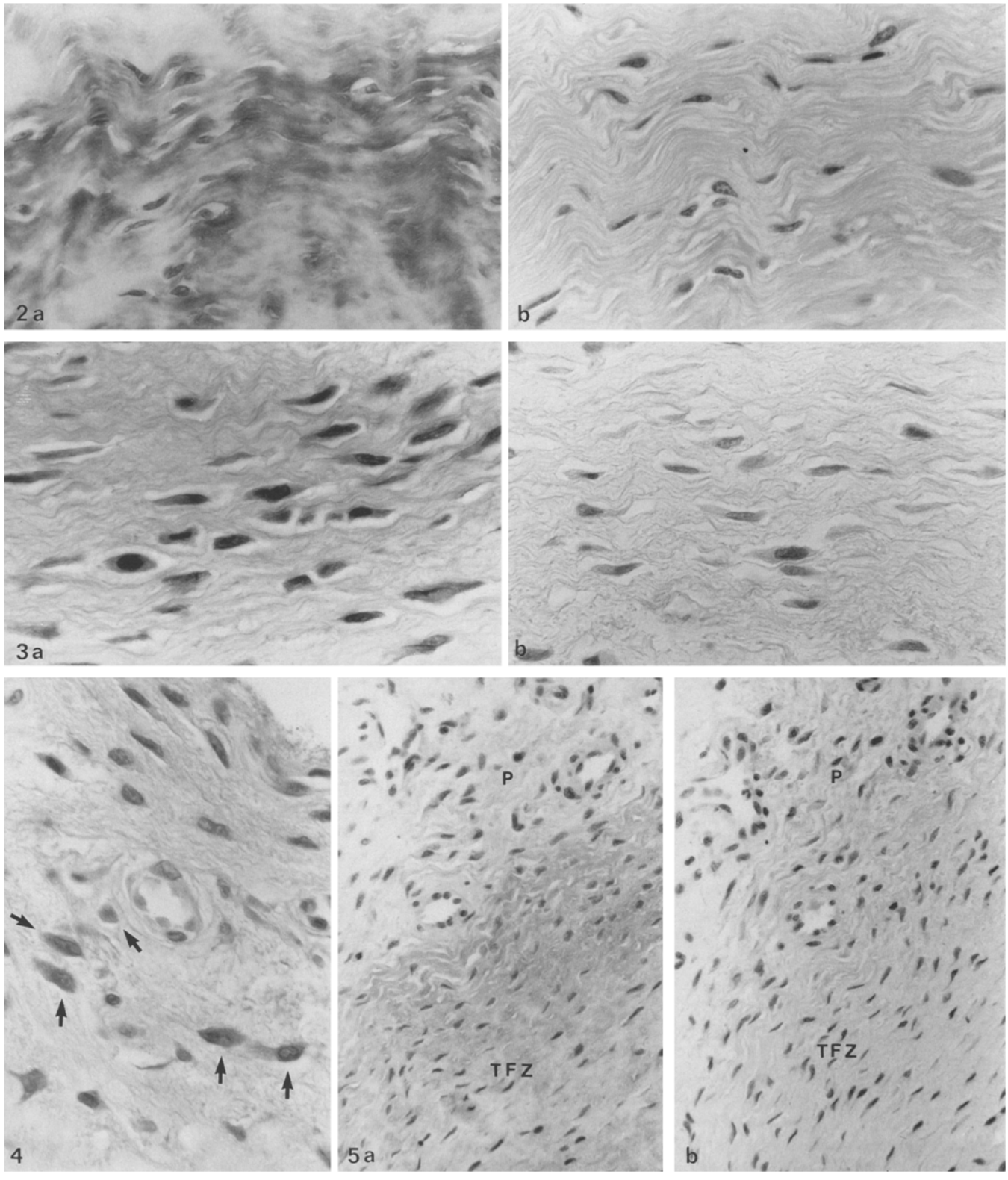

Fig. 2. **a** Staining of the transitional fibroblastic zone with MZ 15 (antibody against keratan sulphate) in a section pretreated with chondroitinase ABC. There is staining of the collagenous matrix and of the cytoplasm of some of the spindle-shaped cells. **b** The control section shows no staining. Immunoperoxidase; haematoxylin counterstained; ×182

Fig. 3. **a** Cytoplasmic staining of the spindle-shaped cells in the transitional fibroblastic zone with MZ 15. The matrix has also been stained, but less intensely than the chondroitinase-pretreated section (Fig. 2a). **b** There is no staining on the control section. Immunoperoxidase; haematoxylin counterstained; ×182

Fig. 4. Cells positive for keratan sulphate (arrows) are seen in close proximity to vascular endothelium and macrophages in the more superficial pannus. Immunoperoxidase; haematoxylin counterstained; ×152

Fig. 5. **a** With the monoclonal antibodies to chondroitin sulphate, staining is confined to the matrix of the transitional fibroblastic zone (TFZ). There is no staining of the cells or matrix within the vascular pannus (P). **b** The control section (non-immune serum) is negative. Immunoperoxidase; haematoxylin counterstained; ×85

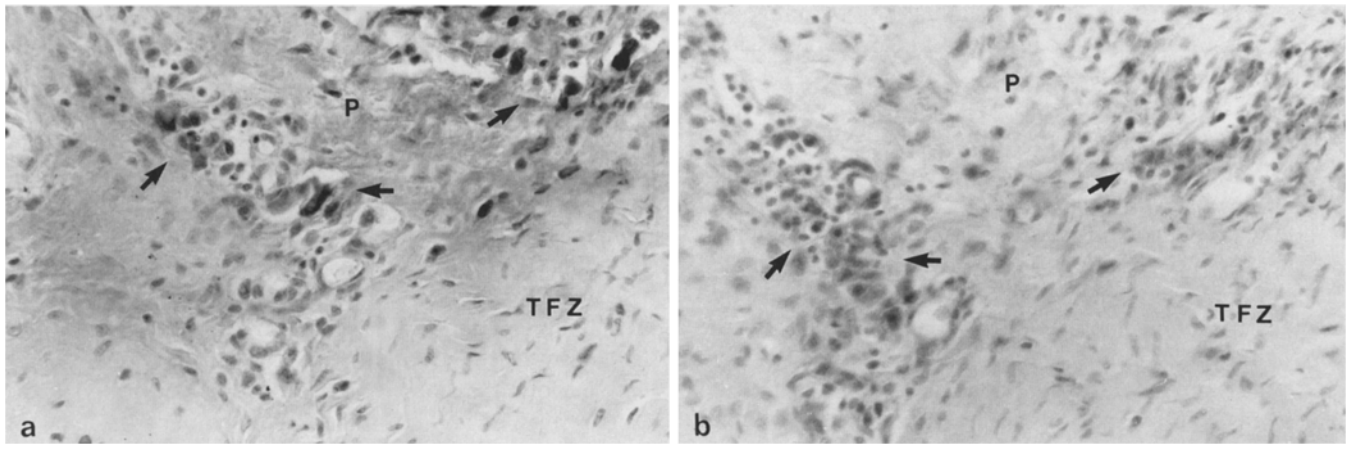

Fig. 6. Sequential sections showing the junction between vascular pannus (P) and the transitional fibroblastic zone (TFZ), **a** stained with antibody to α_1-antichymotrypsin. **b** Stained with Tal-1B5 (Class II antigen). Cells positive for both markers (arrows) can be found within the vascular pannus but not within the TFZ. Positive cells appear to be particularly prominent near blood vessels and adjacent to the TFZ. Immunoperoxidase; haematoxylin counterstained; ×73

Table 2 a, b. Details of patients in relation to type of cartilage-pannus junction (CPJ). CPJ = cartilage-pannus junction; TFZ = transitional fibroblastic zone; H = hip; K = knee; W = wrist; E = elbow; MT = metatarsal; F = female; M = male

a

RA patients	Distinct CPJ (no TFZ)	Indistinct CPJ (TFZ)
No. of patients[a]	7	9
Blocks of tissue	11	13
Joint sampled	2H; 3K; 2MT	4H; 3K; 1W; 1E
Age range (mean)	38–70 years (58.4)	23–82 years (53.7)
Sex	5F:2M	8F:1M
Disease duration (mean)	3–23 years (16.7)	5–30 years (17.7)

b

OA patients	Distinct CPJ	Indistinct CPJ	No pannus
No. of patients	1	1	5
Blocks of tissue	4	2	5
Joint sampled	1H	1H	5H
Age range (mean)	78 years	64 years	59–80 years (69.4)
Sex	F	F	3F:2M
Disease duration (mean)	2 years	10 years	3–8 years (4.8)

[a] Two patients had one example of each type of pannus in the joint sampled (actual no. of RA patients in study = 14)

vascular pannus with a TFZ was observed, the initial clinical presentation was that of an inflammatory synovitis. In the other OA patient with pannus, a distinct margin separated the cartilage from a narrow layer of Class II positive cells. There were no obvious clinical differences between this patient and those without pannus.

Discussion

The conventional view that pannus overlying cartilage is entirely formed from adjacent synovial membrane has been challenged by some authors, who claim that pannus is formed from dedifferentiation of the articular cartilage [9–10, 13], or at least that cartilage may partly contribute to the formation of pannus [14, 24–25]. These varying views are largely based on morphological data, since conventional histochemical stains do not provide direct evidence. Other factors could include selection of samples from patients at different stages of the disease process, and the exclusion of tissue thought to represent inactive pannus [11]. A major limitation of most studies, including our own, is that specimens obtained from joint replacements are from patients with relatively late-stage disease, and the cellular events in such tissues may not be representative of early changes.

Attempts have been made to determine the sequence of events in the formation of pannus. Shiozawa et al. [5] have emphasized the importance of the fibroblast in the early stage of pannus formation prior to the appearance of

macrophage-like cells. The appearance of blood vessels within pannus is thought by some (4–5) to represent a later stage in the disease process.

The origin of the area of pannus which we have referred to as the transitional fibroblastic zone (TFZ) has been a subject of speculation. Some authors have suggested that it might originate from articular cartilage [14, 25]. An alternative interpretation has been proposed by Fassbender [8], who views this zone as having originated from immature mesenchymoid cell formations which destroy cartilage and mature into fibroblasts, leading to the production of a fibrous scar on the hyaline cartilage.

In this study, the use of monoclonal antibodies directed against specific components of articular cartilage showed that the TFZ, seen between vascular pannus and cartilage, contains cells and matrix which possess both KS and CS. Since the marker for KS used in this study is specific for cartilage [17], these results show that this layer of pannus is derived from the articular cartilage rather than the adjacent synovial membrane. The localisation of CS in the same area is further evidence in support of this concept. The KS and CS staining of the TFZ clearly delineates it from the overlying vascular pannus. The absence of KS and CS in cells or matrix of the superficial vascular pannus and of the adjacent synovial membrane, which also contains fibroblasts and collagen, distinguishes them from the "fibroblastic" cells and matrix in the TFZ.

The absence of staining for CS epitopes with MAbs 9A2 and 3B3 seen in perivascular connective tissues and basement membranes implies that the sensitivity of our staining technique was only sufficient to detect the numerous epitopes for CS present in cartilage-derived tissues. In addition, fixation may have resulted in some loss of CS, particularly from soft tissues. Detailed information about the variability of staining with these MAbs in different species, and about CS distribution in synovial membrane, is not available. These results suggest that it is unlikely that the TFZ cells are derived from "true" fibroblasts, or that immature cells originating from the superficial pannus have become capable of synthesizing KS and CS.

Fibroblast-specific markers would further assist characterization, and the monoclonal antibody to human Thy-1 has been used as a potential marker [20]. However, in this study no staining of this type of cell was seen. The lack of S 100 protein in the TFZ was not considered to argue against its origin from chondrocytes, since the protein may not be expressed in altered chondrocytes. The absence of this protein from cells within pannus has similarly been found by another group [26].

The close correlation between TFZ and overlying vascular tissue raises the possibility of interactions between vascular endothelium and chondrocytes; for example, involving interleukin-1 production by endothelial cells [27] and its "catabolin-like" activity on chondrocytes [28]. Such a mechanism could lead to depletion of proteoglycan in the matrix and transformation of chondrocytes to a fibroblastic form.

The proximity of a prominent number of macrophages in both types of pannus, however, emphasizes the important role of these cells in the destructive process. In this study, Class II antigen expression appeared to be restricted to macrophages and was not shown by chondrocytes or cells in the TFZ. Klareskog et al. [29] were also unable to clearly demonstrate Class II expression in chondrocytes, as in tissue sections it is impossible to be certain that the occasional DR-positive cell seen within the cartilage does not originate from invasive pannus. However, Burmester et al. [30] have found Class II positivity in a proportion of chondrocytes eluted from rheumatoid cartilage.

The formation of the TFZ from the underlying cartilage results in an indistinct C-P junction. This type of junction may only appear at a stage in cartilage destruction where the collagen framework of the cartilage matrix is no longer able to maintain the typical morphological structure of chondrocytes. Barrie [9] has described this metaplastic change in articular cartilage as eventually resulting in fibrocartilage formation. The appearance of cells in the TFZ is also similar to that described as "chondrocyte transformation" in cultured cartilage tissue by Fell and Jubb [31]. In addition, it is well known that isolated chondrocytes in culture assume a fibroblastic shape [32].

Junctions in which cellular pannus is seen distinctly from cartilage without a TFZ may represent an earlier stage in the disease process or possibly a different mechanism of cartilage destruction. The observation that these changes can also occur in a patient with OA suggests that this process may not be specific to RA, but might occur in other inflammatory arthropathies.

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