

Synovial cells express thymidine phosphorylase in inflammatory and neoplastic synovial tissue

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Synovial cells (SCs) in pathological conditions of synovial tissue were analyzed by means of paraffin-immunohistochemistry in points of immunological phenotypes, which are usually expressed in monocytes/macrophages and dendritic cells. Paraffin sections of 4 cases of non-inflammatory and non-neoplastic synovial tissue, each 1 case of non-specific chronic synovitis and of granulomatous synovitis, 5 cases of rheumatoid arthritis (RA), and 1 case of benign giant cell tumor (GCT) were used. SCs in non-inflammatory and non-neoplastic synovial tissue revealed weak or strong immunoreactivity with CD68 and LN-3 (Ia-like antigen) but did not with thymidine phosphorylase (TP). SCs in RA expressed strong immunoreactivity with TP. GCT tumor cells showed strong immunoreactivity with CD68, LN-3 and TP. T- and B-cell lymphoproliferative lesions were noted in RA, whereas T-cell-dominated one was seen in the other conditions. Germinal centers (GCs) in RA associated some CD3-positive T-cells. Consequently, it was recognized that SCs are of monocytes/macrophage lineage. In pathological conditions SCs expressed TP especially in RA. The expression of TP in SCs in RA suggested non-neoplastic genetic alteration in the expression of TP in the pathological conditions. The unusual expression of TP may induce unusual lymphoproliferative lesion in RA. But the expression of TP in GCT might be as a tumor growth inhibitory factor.

Key words: Synovial cells, thymidine phosphorylase, rheumatoid arthritis, giant cell tumor, immunohistochemistry

Introduction

Synovial epithelioid cells are categorized as the rounded cells (A-type) and the highly branched cells (B-type) by electron-microscopic findings (Barland et al.: 1962) and are thought to be derived from monocytes/macrophages because of their expression of Ia-like antigen (Winchester and Burmester: 1981, Burmester et al.: 1983). And the epithelioid synovial cells play a role as T-cell-cooperative dendritic cells in an inflammatory lesion (Lindsley et al.: 1993, Bombara et al.: 1993). Synovial giant cell tumor is reported to be of synovial cells (Wilkinson et al.: 1993). Furthermore, the synovial cells in rheumatoid arthritis are reported to have mutation in p53 gene (Firestein et al: 1997, Aupperle et al.: 1998).

On the other hand, thymidine phosphorylase (TP) has

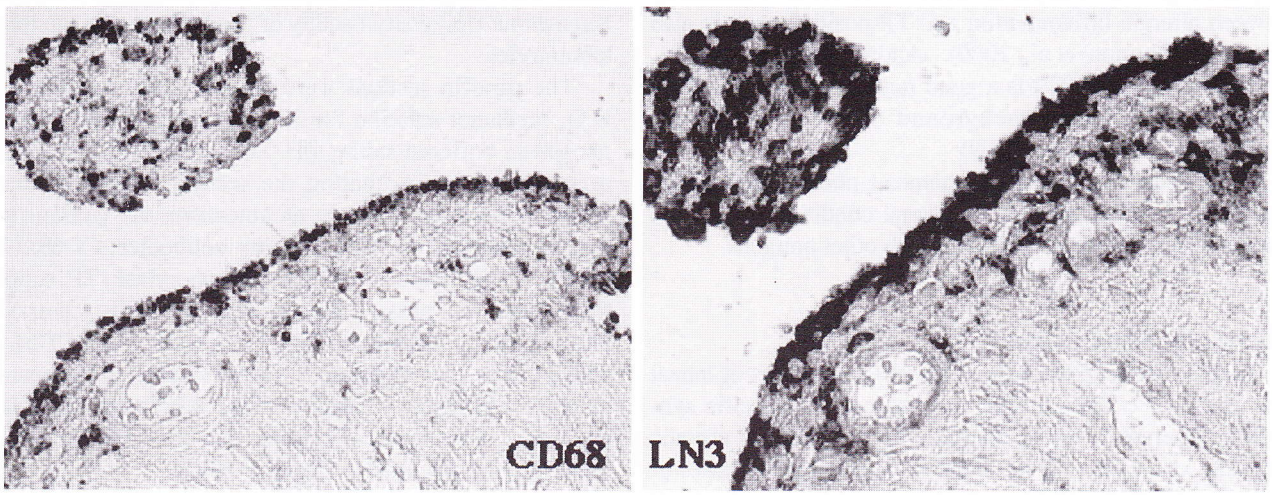

Figure 1. Expression of CD68 and LN3 in non-inflammatory and non--neoplastic synovial tissue (bursal cyst)
The epithelioid synovial cells expressed strong LN3 immunoreactivity and moderate to weak CD68 one.

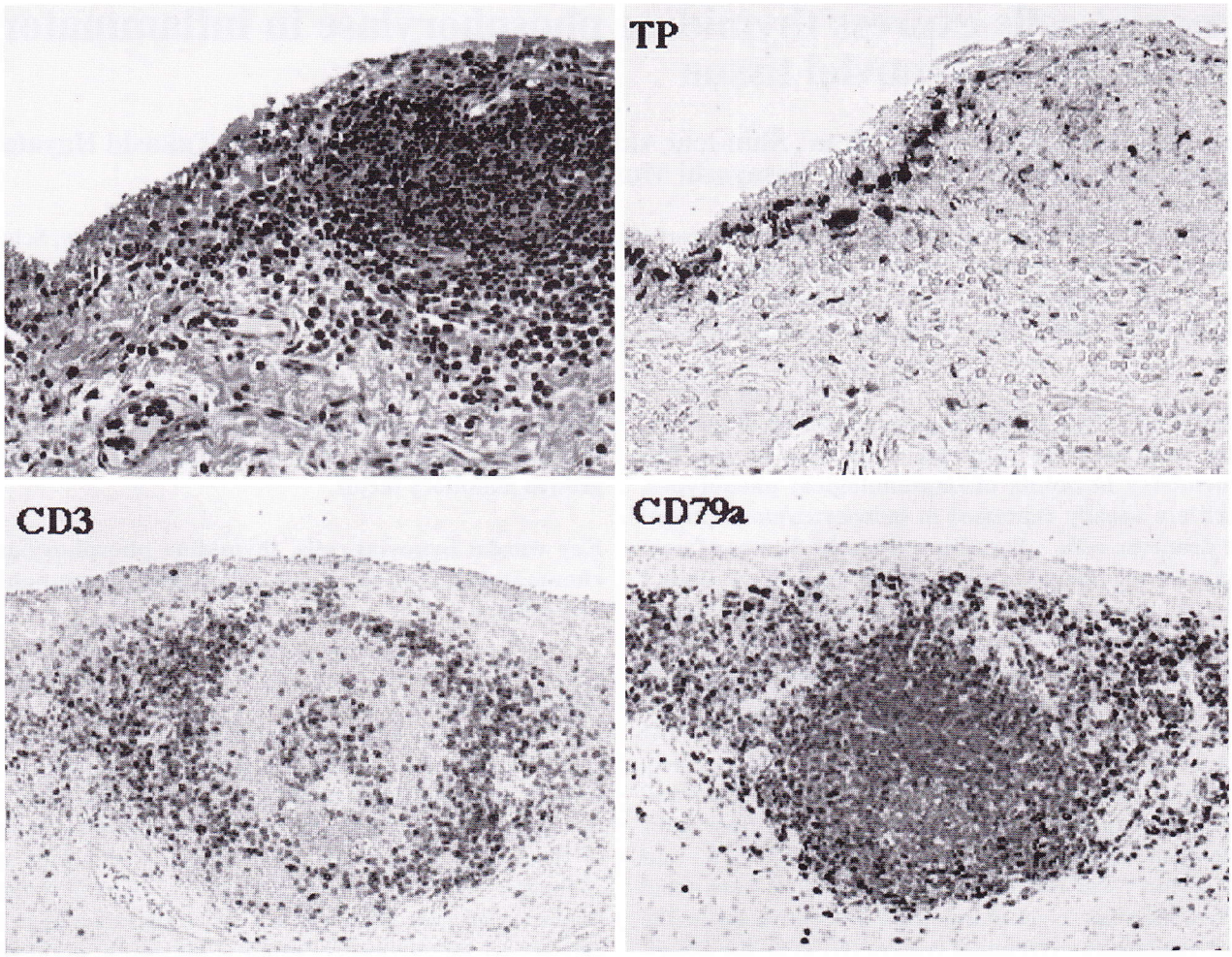

Figure 2. Synovial tissue in rheumatoid arthritis (RA)
Left upper: H.E. stain. Epithelioid synovial surface cells and lymphocytic follicles.
Right upper: Immunostain of thymidine phosphorylase (TP). Some of the surface cells revealed strongly positive stain of TP in their cytoplasm. A few stromal cells were also positive for TP.
Left lower: Immunostain of CD3. The CD3-positive T-cells were located in the perifollicular areas and in the germinal center.
Right lower: Immunostain of CD79a. The CD79a-positive B-cells formed lymph follicles and were seen in the perifollicular areas.

been studied from points of its effects on angiogenesis and neoplastic growth (Akiyama: 2000). A close relationship between allergic inflammation and TP-positive cells is also reported (Nishimoto et al.: 2000). And we found that thymidine phosphorylase (TP) is a good marker of differentiating dendritic cells in the background of T-cell malignant lymphomas (Hasui et al.: 1999).

In this study immunohistochemical phenotypic expression of TP in synovial cells in several conditions of human synovial tissue has been analyzed with other antigens.

Materials and Methods

Paraffin sections of synovial tissue in two cases of bursal cyst, one case of pseudogout, one case of non-specific synovial proliferative lesion, one case of non-specific chronic synovitis, one case of granulomatous synovitis, five cases of rheumatoid arthritis (RA), and one case of benign giant cell tumor (GCT) were used for this study. These synovial lesions were diagnosed in Second Department of Pathology, Kagoshima University Faculty of Medicine and in the related laboratories.

The paraffin sections were dewaxed, incubated in 0.3% H_2O_2 methanol solution for 30 min and hydrated in 0.05M phosphate buffered saline, pH 7.6. After antigen-retrieval pretreatment by incubating the sections in 0.01M citrate buffer, pH 6.0 for 5 min in an autoclave, the sections were reacted with the following primary antibodies; CD68, LN-3 (Ia-like antigen), anti-thymidine phosphorylase (TP, supplied from Prof. Akiyama S, Kagoshima University), anti-S100 protein, anti-muramidase, CD3, CD4, CD8, CD5, CD56 and CD79a. The reacted antibodies were visualized by means of avidin-biotin complex method (Elite ABC) and DAB-H_2O_2 reaction. After nuclear counterstain by Hematoxylin, the sections were mounted in plastic medium.

Table 1. Synovial cell expression of immunological phenotypes which are usually seen in monocytes/macrophages and dendritic cells

	CD68	TP	LN3	Mur
Non-inflammatory and non-neoplastic lesions (4 cases)				
Surface cells	+/- to 3+	- to +/-	1+ to 3+	- to +/-
Stromal cells	+/- to 1+	- to +/-	+/- to 3+	- to +/-
Non-specific inflammation (1 case)				
Surface cells	1+	-	1+	+/-
Stromal cells	1+	1+	2+	- to +/-
Granulomatous inflammation (1 case)				
Surface cells	-	2+	-	-
Granuloma cells	1+	2+	2+	+/-
Rheumatoid arthritis (RA) (5 cases)				
Surface cells	- to 3+	- to 3+	+/- to 2+	- to 1+
Stromal cells	- to 1+	+/- to 2+	- to 2+	- to +/-
Benign giant cell tumor (1 case)				
Surface cells	3+	3+	3+	-
Stromal cells	2+	1+	1+	-
Atypical (large) stromal cells	3+	3+	3+	-
Multinuclear giant cells	-	-	-	-

3+: strongly expressed, 2+:moderately expressed, 1+:weakly expressed, +/-: barely expressed and -: not expressed

Results

In non-inflammatory and non-neoplastic synovial tissue, synovial surface cells were positive for CD68 and LN3 (Ia-like antigen), as shown in Fig. 1 and in Table 1, although they revealed various histological appearances, such as epithelioid, proliferative and flat figures. Synovial stromal cells were obviously positive for LN3 (Ia-like antigen) and weakly positive for CD68 (Table 1). Synovial cells were negative for TP, muramidase and S100 protein.

In the inflammatory synovial tissue, synovial surface cells expressed less CD68 and more TP than those in the non-inflammatory and non-neoplastic ones in spite of the same immunoreactivity with LN-2. In granulomatous inflammation, synovial surface epithelioid cells expressed TP immunostaining but did not CD68 and LN3 (Table 1). Synovial surface epithelioid cells in RA revealed the same tendency in the immunoreactivity with these antigens (Fig. 2, Table 1). Synovial stromal cells expressed stronger TP immunoreaction than the synovial surface cells in some cases. In RA, the expression of TP was inversely proportional to that of CD68 in the both surface and stromal cells.

Inflammatory cells revealed a dominance of T-cells in the non-inflammatory and inflammatory synovial tissues other than those in RA. In RA, inflammatory cells comprised T-cells and B-cells and revealed lymph follicle formation, of which germinal centers associated some T-cells (Fig. 2).

GCT tumor comprised several multinuclear giant cells, some atypical stromal cells and many stromal cells. The atypical stromal cells expressed strong CD68, LN-3 and TP immunoreactivity, as the synovial surface cells did (Table 1). The stromal cells revelaed somewhat granular immunoreaction with CD68 and weaker stain of LN-3 and TP than the atypical stromal cells and the surface cells. But most of multinuclear giant cells were negative for these three antigens (Table 1).

Discussion

Synovial surface and stromal cells expressed both of CD68 and LN-3 (Ia-like antigen) immunoreactivity. As reported (Winchester & Burmester: 1981, Burmester et al.: 1983), synovial surface and stromal cells were thought to be derived from monocytes/macrophages.

In the inflammatory synovial tissue, the stromal synovial cells expressed TP. TP was reported to be induced in fibroblast-like synovial cells in vitro under cytokines (Waguri et al.: 1997, Muro et al.: 1999) and was reported also to be expressed in dendritic cells forming background meshwork of peripheral T-cell lymphomas (Hasui et al.: 1999), suggesting correlation between TP-positive dendritic cells and T-cells. Therefore, some synovial stromal cells may act as monocytes/macrophages-derived T-cell-associated dendritic cells, as suggested previously (Winchester & Burmester: 1981, Lindsley et al.:1993, Bombara et al. 1993, Waguri et al.: 1997).

On the other hand, the synovial cells in RA were reported to have genetic alterations in p53 gene (Firestein et al.: 1997, Aupperle et al.: 1998), although it was reported that p53 mutation was not primary event in RA pathogenesis (Sugiyama et al: 1996, Tak et al.: 1999, Lee et al.: 2000). But Fibroblast-like synoviocytes have mutation in p53 gene (Tak et al.: 1999), of which the target is human metalloproteinase (MMP)-1 (Sun et al.: 1999, 2000). And it is suggested by Pozza et al. (2000) that the mutation in p53 gene is immportant pathogenetic factor in RA and that nerve cell growth factor may initiate its pathogenesis. At least, stromal synovial cells have genetic alternation in their gene. The multinuclear cells revealed no or weak immunoreactivity with CD68, LN-3 and TP, whereas the atypical stromal cells indicated strong reaction with these antibodies. The true neoplastic cells of GCT are the atypical stromal cells. Therefore, It is possibly suggested that under the non-neoplastic

genetic alteration synovial cells express strong TP immunostaining and induce an unusual inflammation in RA (Asai et al.: 1993, Waguri et al.:1997). It is suggested at the same time that neoplastic alteration in synovial cells included expression of TP, although it is reported that TP is a tumor growth inhibitory factor (Asai et al.: 1992).

Consequently, the expression of TP in synovial cells was observed in a pathological condition of synovial tissue. Especially in RA and benign neoplastic synovial tissue, further studies are necessary to see whether TP is expressed in synovial cells primary under the non-neoplastic genetic alteration or secondary under some kinds of lymphokines/cytokines of inflammatory cells, although the results of this study prefer the former to the latter. And further studies are also needed to see that TP is induced as a growth inhibitory factor in benign GCT.

Acknowledgment

Authors thanked Dr. Sadao Tanaka (Department of Pathology, Kagoshima-shi Medical Association's Hospital), Dr. Hiroshi Shirahama (Department of Pathology, Imakiire General Hospital) and Dr. Kazunobu Sueyoshi (Department of Pathology, Kagoshima Municipal Hospital) for their help to get surgical materials for this study.

The authors thanked Miss. Yoshiko Arimura and Miss. Yukari Nishimura for their help in the immunohistochemistry, and Dr. Mitsuharu Nomoto and Dr. Shinichi Kitajima (the Second Department of Pathology, Kagoshima University) for their help in preparing this article.

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