The Thickening of Basement Membrane in Synovial Capillaries in Rheumatoid Arthritis

T. Matsubara, M. Velvart, B. F. Odermatt, M. A. Spycher, J. R. Rüttner, and K. Fehr

1 Department of Pathology, University Hospital, CH-8091 Zürich, Switzerland
2 Department of Rheumatology, University Hospital, CH-8091 Zürich, Switzerland

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Summary. Synovial tissues from seven rheumatoid arthritis (RA) patients were used for the ultrastructural investigation of capillary cellular components and basement membranes (BM). Attention has been specially paid to the mechanism of BM thickening of the capillaries in the inflammatory sites.

The capillary BM were multilamellated in the inflammatory sites. The multilamellation was characteristic not only in the BM surrounding the endothelial cells and pericytes but also in the BM between these two types of cells. Cell debris was frequently encountered between the multilamellated BM. The hyperplasia and various stages of degeneration of the endothelial cells were observed in these regions. Some endothelial cells were activated and occasionally located in capillaries containing degenerated endothelial cells. The high incidence of these findings indicates the following hypotheses.

The accelerated rate of death and replenishment of capillary cellular components may play a role in BM thickening in the inflammatory sites of RA synovium. These cells may not only produce one layer of BM in their life-time but may also be activated to produce excessive amounts of BM components to make several layers.

Key words: Basement membranes – Basement membrane thickening – Synovial capillaries – Rheumatoid arthritis – Endothelial cells

Introduction

Basement membranes (BM) separate parenchymal, endothelial, and epithelial cells from underlying connective tissue and provide elastic support to these cells. BM are composed of several components [1-4] and are considered to form a barrier to the passage of macromolecules.

Thickening of BM has been investigated in association with age [5,6], diabetes mellitus (see [18] for review), and other pathological conditions [7-14]. The mechanism of BM thickening has been studied in detail by Vracko and Benditt [15-20] by investigating skeletal muscle capillaries of patients with diabetes mellitus and the experimental model of multiple layers of BM. The results indicate that the thickening of BM is caused by accelerated rate of death and replenishment of capillary cellular components which usually make a single layer only once in their lifetime. However, whether this hypothesis applies to every instance of capillary BM thickening or not remains unknown.

In rheumatoid arthritis (RA), capillaries characterized by an irregular, discontinuous, and frequently multilamellated BM have been investigated as well as pathological changes of capillary cellular components [9, 11-13]. The altered BM barrier is taken as a phenomenon which is reflected by the cellular synovial exudate, although the mechanism of this change has not been sufficiently explained.

We studied the thickening of BM of the capillaries in the inflammatory sites of RA synovium in relation to the pathological changes of capillary endothelial cells and pericytes. Then we hypothesized with regard to the mechanism of capillary BM thickening in RA synovium. We have paid particular attention to the different mechanisms of BM thickening in the inflammatory sites of RA synovium in comparison with that described in diabetes mellitus and other experimental conditions.

Materials and Methods

Samples. Synovial tissues were obtained from 7 patients (3 males and 4 females) diagnosed as having classic RA. Their ages ranged from 32 to 61 years. Diabetes mellitus was not a factor in these 7 cases, as determined by physical examination and laboratory testing. Duration of the disease ranged from 8 to 17 years. Three patients were seropositive, 4 seronegative. Two patients were systematically non-reactive, with a blood sedimentation rate of less than 10 mm/h. However, in all patients focal inflammatory signs were positive. Three patients underwent synovectomy of the elbow joint with radial head resection, 1 patient synovectomy of the wrist joint, 2 patients corrective osteotomy of the metatarsophalangeal joint, and 1 patient total knee replacement. Synovial tissue was obtained through surgery in all cases, and macroscopically the tissue suggestive of active inflammation (reddish and edematous) was separated from underlying collagenous tissue and studied for the entire investigation by transmission electron
microscopy (TEM). At the same time some parts of the separated tissue were checked by light microscopy.

TEM Procedures. The tissue specimens were sectioned by a razor blade, then fixed with 2.5% glutaraldehyde phosphate buffer saline (PBS) for 3 h at 4°C. After rinsing in PBS, the sections were fixed with 1% osmium tetroxide PBS for 2 h at 4°C. The sections were rinsed in PBS, dehydrated in a series of alcohol, placed in a 50% propylene oxide and Epon 812 mixture overnight, and then embedded in Epon 812. Semi-thin sections were cut on an LKB 8800 ultrotome III with a glass knife, stained with toluidine blue, and then examined. Ultra-thin sections were cut with a diamond knife, and stained with uranyl acetate and lead citrate. Stained ultra-thin sections were examined in an EM 201 Philips electron microscope.

Results

General Light Microscopic Observations
Mild synovial protrusion into the joint space as slender villous projections was observed in all cases. Varying lining cell proliferation was seen in all cases. Under the lining cells numerous lymphocytes, inflammatory cells, and occasionally plasma cells had infiltrated the interstitial connective tissue. Lymphocyte infiltration was mainly perivascular and two out of seven cases exhibited typical lymphoid follicles. Vascular changes were prominent in all cases. Vascular congestion and erythrocyte extravasation were frequently seen and some vascular lumen were occasionally plugged completely by inflammatory cells, organized thrombi, and fibrin-like materials. In two cases, vasculitis manifested by the infiltration of vessel walls with polymorphonuclear leucocytes and monocytes was frequently observed. In proliferated capillaries, various stages of endothelial hyperplasia and the obliteration of the lumen by endothelial cells were often observed in all cases.

Electron Microscopic Observations of Synovial Capillaries
Capillaries with thickened BM separating them from interstitial connective tissue were often encountered in inflammatory sites (Fig. 1). These thickened areas were frequently lamellated by electron dense layers, resembling a cross-section of a tree trunk. At higher magnification, these electron dense layers were discontinuous and often fused in several parts (Fig. 2). Usually, the layers closest to endothelial cells and pericytes were more continuous than those located near interstitial connective tissue. The latter were often irregular and sometimes disrupted to such an extent that they looked amorphous rather than lamellated. Thickened areas of BM were often asymmetrical and it was quite noticeable that BM located between the endothelial cells and pericytes were thickened (Fig. 3). Between each layer of BM, debris from degenerated cells was often seen (Fig. 4). These degenerated cells had lost their normal cytoplasmic density and were devoid of cell organelles, which were sometimes ruptured into the cytoplasm. Capillary endothelial cells were frequently degenerated and sometimes lost their configurations, making a gap between the adjacent endothelial cells. However, in most cases...