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Fibroblastic reticular cells and fibroblast-like cells determined by monoclonal antibodies B-F45 and B-D46 in humans

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ABSTRACT

Objective: Identification of stromal microenvironmental components of lymphoid organs is relatively harder at light microscopic level as few markers, which are mostly not very specific, are available to be used for such a purpose. We screened a large panel to determine monoclonal antibodies (mAbs) those reactive with fibroblasts/fibroblast-like cells aiming to obtain further evidence for the organization and function of this cell group.

Methods: Tissue samples of forty patients undergoing surgery in Otorhinolaryngology, Obstetrics and Gynecology, Orthopedics and Traumatology, Cardiovascular Surgery and General Surgery Departments, Hacettepe University Medical Faculty Hospital, Ankara, Turkey, due to different pathologies obtained as partial specimens of surgery which were

apart from pathological examination were immunostained by indirect immunoperoxidase method in Histology and Embryology department in 2003.

Results: Among the screened monoclonal antibodies, monoclonal antibodies B-F45 and B-D46 reacted with the members of the family, therefore examined in detail in available human organs. Among the unique staining patterns of these mAbs, reactivity on fibroblastic reticular cells, perineural sheet cells pericryptal/perivillous fibroblasts were striking.

Conclusion: Both mAbs will provide useful tools for further studies on stromal network of peripheral lymphoid organs and peripheral nerves.

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A group of cells share same characteristic features of fibroblasts but carrying out various different functions depending on the different locations with unusual features, therefore it is rather hard to distinguish these cell types using a clear-cut set of criteria from fibroblasts. Results of numerous structural and experimental studies lead to a gradually increasing number of related cells including, fibroblasts of various locations (tendons, dermis, cornea for example), fat storing (Ito) cells of liver, pericryptal and villous fibroblasts of intestine, interstitial cells of pulmonary alveolar septa, a

group of secretory cells (inner medullary interstitial cells of kidney, leydig cells of testis and theca interna cells of ovaries), perineural sheet cells, fibroblast-like cells in myenteric plexuses, myofibroblasts in tumors and granulation tissues, and dendritic cells in certain compartments of lymphoid organs as reviewed by Komura.¹ Basic functions carried out by this family of cells are: 1. Production of extracellular matrix components (for example predominantly by fibroblasts and many other cell types), 2. Mechanical support (for example interstitial cells in many organs including

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lymphoid organs), 3. Intercellular communication forming special microenvironments (for example lymphoid dendritic cells), 4. Forming barriers providing a non-immune defense mechanism (for example perineural cells), 5. Gentle contraction, (for example myofibroblasts) 6. Endocrine secretion (for example medullary interstitial cells, leydig cells) 7. Storage of vitamin A (Ito cells of liver). As expected and well documented, all of above mentioned cell types exhibit structural features and antigenic profile related to their specific locations and functions.² In common, basic features of fibroblasts include: spindle shape with processes; smooth contoured elliptical or elongated nucleus, well developed granular endoplasmic reticulum and golgi apparatus, vimentin filaments, and lack of basal lamina and intercellular junctions. However some of fibroblast-like cells, myofibroblasts and certain other cell types of the family have basal lamina or -like substances and intercellular junctions of all types besides sharing common features of fibroblasts. A clear cut definition of a myofibroblast is also rather difficult as reported by Eyden.³ Grouping of such a wide variety of cells under the term of fibroblast (-like) family is based on shared structural properties and experimental studies demonstrating the fibroblastic origin of most of the members. Still it is rather difficult to validate such a grouping or classification possibly reflecting variable forms of cells arising from a single cell type under special circumstances and seemingly it will be a matter of discussion until lineage specific markers are well documented. Attempts of developing mAbs specific for fibroblasts, or applying histochemical or enzyme histochemical techniques, or both, to determine fibroblasts or related members of this family provided valuable data however none of these is entirely fibroblast specific.⁴⁻⁸ We screened a large panel of antibodies aiming to determine a specific marker for fibroblastic reticular (reticulum) cells (FRCs) or fibroblast-like cells. Among these monoclonal antibodies 2 were distinctly reactive with some members of this cell population. Both antibodies were originally raised against endothelial cells and were reactive with most vascular endothelia. Detailed examinations for the reactivity of these mAbs on various human tissues were carried out and findings are presented.

Methods. Tissue samples of 40 patients whose ages ranged between 2 months 70 years undergoing surgery in Otorhinolaryngology, Obstetrics and Gynecology, Orthopedics and Traumatology, Cardiovascular Surgery, General Surgery Departments, Hacettepe University Medical Faculty Hospital, Ankara, Turkey, due to different pathologies were obtained as partial specimens of

Table 1 - Tissue samples and clinical diagnosis of the patients from which the samples were obtained.

Organ	Clinical diagnosis (n of cases)
Palatine tonsil	Ig deficiency (1) chronic infection (2)
Nasopharyngeal tonsil	Ig deficiency (1) chronic infection (2)
Thymus	TGA, VSD, PVI (1), TOF (1), TGA (1)
Lymph node	Ig deficiency (1) colon cancer (1) gastric cancer (1)
Spleen	Post-traumatic splenectomy (2)
Placenta	Term pregnancy (3)
Small intestine	Intraabdominal mass (1) crohn's disease (1) biliary atresia (1) hemangioma (1) vesico urethral reflux (1)
Large intestine	Hirschprung's disease (8), anal atresia (1), biliary atresia (1), hemangioma (1), rectal inflammation (1), appendectomy (2) colostomy closure (2), colon cancer (1), duplication (1)
Ig - immunoglobulin, TGA - transposition of great arteries, VSD - ventricular septal defect, PVI - pulmoner valve insufficiency, TOF - tetralogy of fallot	

surgery which were apart from pathological examination (**Table 1**). All tissue specimens were immediately frozen in liquid nitrogen, and stored at -30°C until sectioned. Cryostat sections (6-8µm thick) were taken on gelatin-coated slides and kept in humidity-free containers at room temperature until the staining was performed during the following week.

Antibodies and staining procedure. The mAb B-F45 and B-D46 were produced and generated at Diaclone following the immunization of Balb/c mice with the endothelial cell line EAHY926 (kind gift by Edgell et al.⁹ Spleen cells were fused to the X6.3/AG.8653 myeloma according to the conventional protocols. The immunoglobulin (Ig) G-secreting clones were screened for specific production of anti endothelial antibody. Hybridoma cloning was performed by limited dilution. B-F45 and B-D46 are IgG2b and IgG1 isotype mAbs, IgG was isolated from ascitic fluids by ion exchange chromatography.

The immunostaining procedure (indirect immunoperoxidase) used in the study has been described in detail elsewhere.¹⁰ Sections were fixed in acetone for 10 minutes and air-dried for at least 30 minutes. Sections were then incubated for 60 minutes with mAbs. After washing in 0,01 M phosphate buffered saline (PBS) pH 7.4, the slides were covered with a 1:200 dilution of anti-mouse IgG peroxidase (Sigma Cat no: A9044) in PBS containing 0.2% bovine serum albumin (Sigma Cat no: A-7034) and 1% normal human serum. After

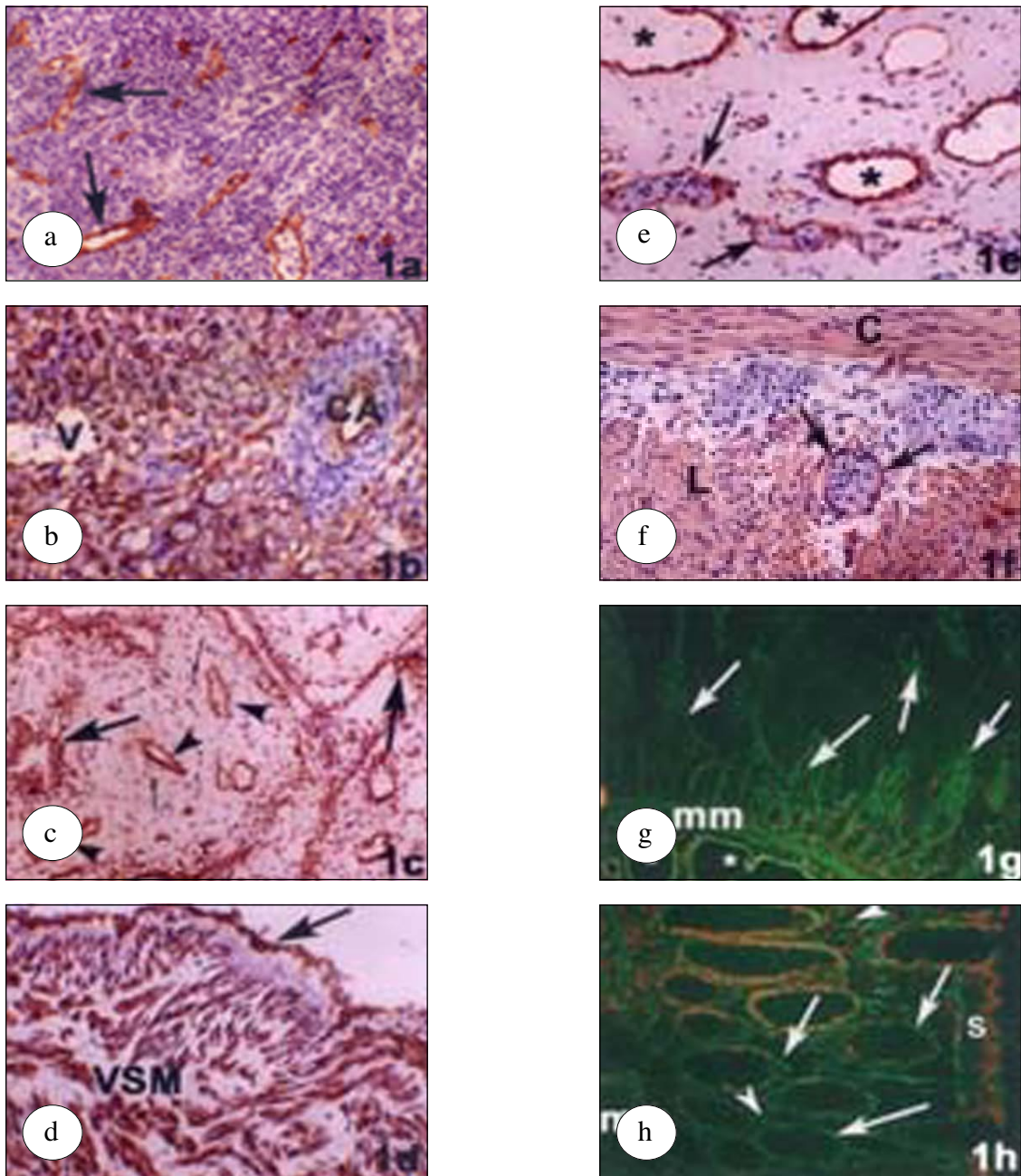


Figure 1 - Micrographs showing (a-f) Were stained with B-F45 mAb using an indirect immunoperoxidase method, all hematoxylin counter stained. (a) A section through paracortex of lymph node. Endothelium of all types of blood vessels including high endothelial venules (arrows) are reactive. Original magnification x 20. (b) Section through PALS and adjacent red pulp of spleen. Central artery (CA) endothelium and vascular smooth muscle, trabecular vein endothelium (V) and sinusoidal endothelium are reactive. Original magnification x 10. (c) Section through synovium. Vascular endothelium and smooth muscle (*), synoviocytes (arrows) and some fibroblast (thin arrow) are reactive. Original magnification x 10. (d) Section through umbilical vein. Endothelium (arrow) and vascular smooth muscle (VSM) are reactive. Original magnification x 20. (e) Section through submucosa of small intestine. Vascular endothelium and smooth muscle (*), perineural cells of submucosal plexus (arrows) are reactive. Original magnification x 40. (f) Section through muscularis externa of colon. Inner circular (C) and outer longitudinal (L) visceral smooth muscle is reactive while myenteric plexus is not. Perineural sheet cells of a nerve fiber extending through muscle layer are also reactive (arrow). Original magnification x 40. (g & h) Are stained with B-F45 mAb using an FITC-labeled indirect immunofluorescence method, propidium iodide/antifade counter stained. (g) Section through small intestine. Vasculature (*), muscularis mucosa (mm), villous core and perivillous fibroblasts (arrows) are reactive. Original magnification x 20. (h) Section through colon mucosa with Lieberkühn crypts and surface epithelium (s). Pericryptal fibroblasts (arrows), capillaries (arrowheads) and mm are reactive. Original magnification x 40.

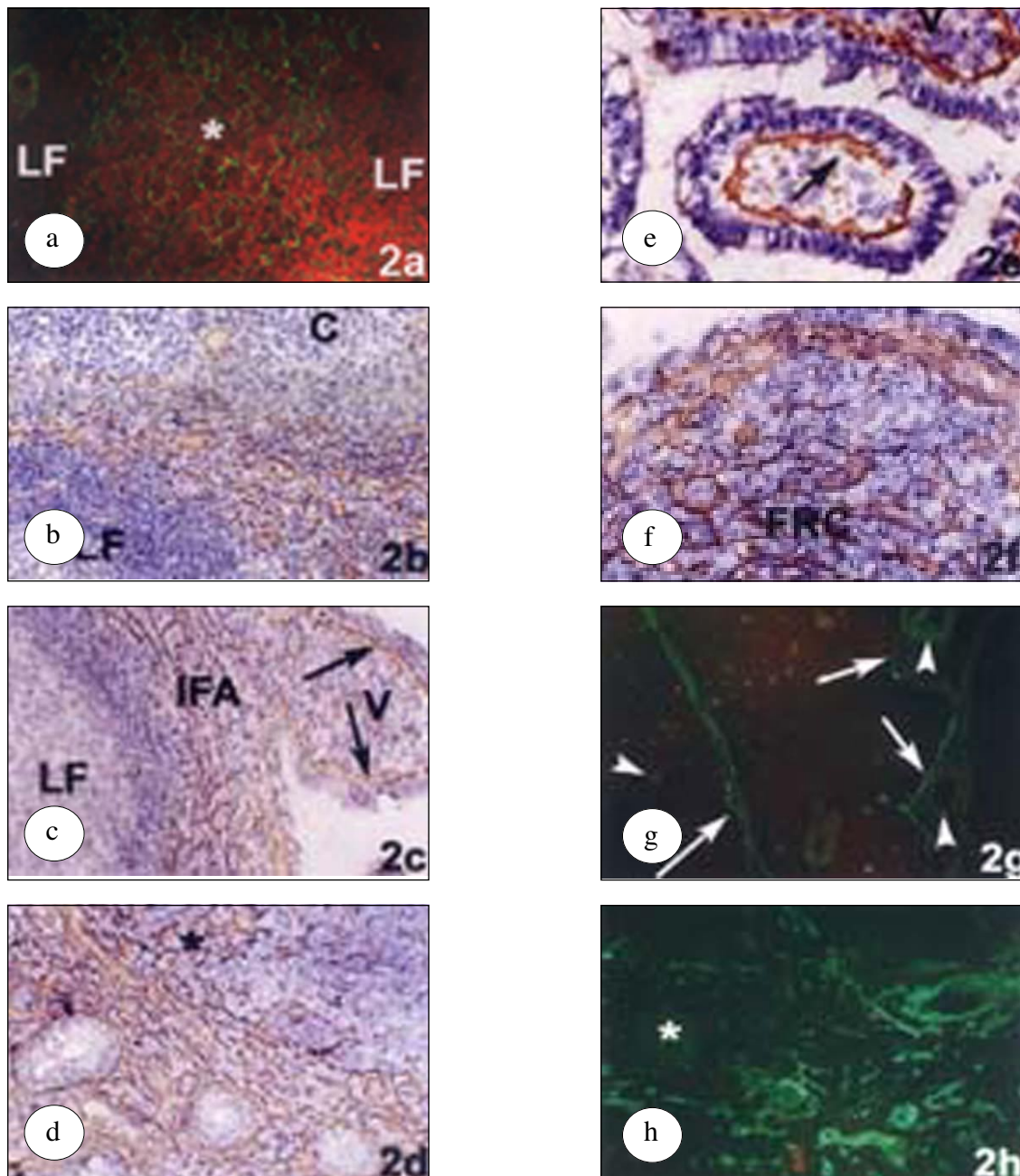


Figure 2 - Micrographs showing (a-h) Are stained with B-D46 mAb using an FITC-labeled indirect immunofluorescence method, propidium iodide/antifade counter stained. (b-f) Are stained with B-D46 mAb using an indirect immunoperoxidase method, all hematoxylin counter stained. a) In the interfollicular area located between 2 follicles (LF) of a tonsil section strong immunoreactivity of fibroblastic reticular cell network (*) is seen. Original magnification x 20. (b) In tonsilla pallatina, both the vascular endothelium and fibroblastic reticular network in interfollicular area are reactive. Crypt (C), lymphoid follicle (LF). Original magnification x 20. (c) Section through intestinal mucosa consisting of a villus (V) and a lymphoid follicle (LF). Perivillous fibroblasts (arrow), some fibroblasts in the villus core, subepithelial fibroblast layer, vasculature and fibroblastic reticular cell network in the interfollicular area (IFA) are reactive. Original magnification x 20. (d) Section through intestinal mucosa with a lymphoid follicle and several Lieberkühn crypts. Pericryptal fibroblasts (arrows) and fibroblastic reticular cell network (*) are reactive. Original magnification x 20. (e) Higher power micrograph of intestinal villi sections. Perivillous fibroblasts are strongly B-D46 (+). Original magnification x 40. (f) Section through follicle associated epithelium in small intestine. Subepithelial fibroblasts and fibroblastic reticular cell (FRC) network are both reactive being stronger on FRC network. Original magnification x 40. (g) Section through the cortices of adjacent thymic lobules. Reactivity on type-1 thymic epithelial cells (arrows) and vasculature (arrowhead) are seen. Original magnification x 20. (h) Section through thymic medulla with Hassall's corpuscle (*). Medullary epithelial cells/macrophages? with dendritic processes and vasculature are reactive. Original magnification x 20.

washing in PBS the slides were stained for peroxidase activity with 3,3'-diaminobenzidine-tetrahydrochloride (Sigma Cat no: D-5637) (0.5mg/ml Tris-HCl buffer, pH 7.6, containing 0.01% H₂O₂.) Counterstaining with hematoxylin was carried out. The control staining was performed by omitting the first (primary antibody) step and using an irrelevant mAb. For indirect immunofluorescence staining the same steps were applied up to the secondary antibody step. Sections were then incubated with FITC labeled anti-mouse IgG (DAKO code no: F-0479) for 30 minutes, washed in PBS 3 x 10 minutes and covered by one drop of propidium iodide/antifade (Oncor cat. no: S1370-6) solution. Both peroxidase and FITC labeled sections were then examined and photographed by using Leica DMR - reflection contrast microscope-RCM (Wetzlar-Germany) with a DC200 digital camera (Leica, Wetzlar-Germany).

Results. Monoclonal antibodies B-F45 and B-D46 were found to be reactive with vascular endothelium of all types of blood vessels being relatively stronger for BF-45. However both mAbs had additional reactivity on vascular and visceral smooth muscle in various tissue samples. Another unique additional reactivity was observed on fibroblasts and members of fibroblast-like cell family for both mAbs. Data on various organs is summarized below. B-F45: Endothelial lining of arteries, veins and capillaries were strongly reactive for B-F45 in all organ samples examined. Vascular smooth muscle in larger caliber vasculature was also strongly reactive. Additional reactive cells or tissue components, of both, were listed below for each organ: Palatine/nasopharyngeal tonsils, lymph nodes: High endothelial venules (**Figure 1a**), spleen: Sinusoidal endothelium (**Figure 1b**), synovium: Synoviocytes and some fibroblasts (**Figure 1c**), umbilical cord: Umbilical artery & vein and fibroblasts in Wharton's jelly (**Figure 1d**), small intestine: Visceral smooth muscle (muscularis mucosa and muscularis externa), perineural cells in submucosal and myenteric plexus, core and perivillous fibroblasts (**Figures 1e & 1g**), colon: Visceral smooth muscle (muscularis mucosa), perineural sheet cells, pericryptal fibroblasts (**Figures 1f & 1h**). In thymus and placenta, only vascular elements were reactive. B-D46: Palatine tonsil, nasopharyngeal tonsil: High endothelial venules, fibroblastic reticular cells in T-zones, crypt and surface epithelium basally (**Figures 2a & 2b**), lymph node: High endothelial venules, fibroblastic reticular cells in T-zones, thymus: Type-1 thymic epithelial cells (**Figures 2g & 2h**), umbilical cord: Umbilical artery and vein and fibroblasts in Wharton's jelly, vascular smooth muscle, placenta: Villous (embryonic) mesenchyme, amniotic

epithelium basal compartment, chorionic fibroblasts, small intestine: Visceral smooth muscle (muscularis mucosa and muscularis externa), perivillous/pericryptal fibroblasts, fibroblastic reticular cells in interfollicular area of mucosa associated lymphoid tissue (**Figures 2c, 2e & 2f**), colon: Visceral smooth muscle (muscularis mucosa), pericryptal fibroblasts. Perivillous/cryptal fibroblasts and FRCs (if an adjacent mucosa associated lymphoid tissue was present) appeared to be collectively forming a confluent network of cellular processes in intestine samples (**Figure 2d**). In spleen and synovium only vascular elements were reactive.

Discussion. Resident stromal components of the lymphoid organs are of special importance as they mediate the organization of numerous interactions between immune system cells (for example antigen presenting cells, macrophages, lymphocytes) and also provide a target home for extensive traffic of cells and soluble mediators like cytokines, chemokines for the establishment of appropriate immune reactions. Though the microscopic anatomy of lymphoid organs is extensively studied still little is known regarding the cellular elements of stroma in detail.¹¹ There are several reasons for this: 1. Stromal cell specific markers are rather restricted, 2. Dynamic nature of the cells displaying different structural properties depending on the functional state (exhibiting in between forms) does not allow clear cut distinction of different cells types using ultrastructural criteria alone, 3. Conflicting terminology describing same or similar cell types by various authors, 4. Lineage or origin specific markers for most of the cell types are not still available for the proper discrimination of a certain cell, 5. Recent findings even make it harder to establish reliable criteria for the determination of classical cell types like mesenchymal cells bearing cytokeratin filaments of epithelial cells,¹² fibroblasts with myofilaments etc. Data arising from the studies in lymphoid tissue is even more conflicting regarding the antigenic profile of cells populating the T-cell areas of lymphoid organs. Dendritic cells forming the stromal network of T-zones are termed as fibroblastic reticulum cells (FRCs) providing a special microenvironment for the extensive traffic of lymphocytes into these organs during antigenic challenge.¹³⁻¹⁶ Dendritic cells of bone marrow origin are also located within the same compartments representing the interdigitating cells (IDCs) of T-zones. In a relatively recent review, Steinman et al¹⁷ stated that T-cell areas are exclusively composed of a network of migrating dendritic cells (IDCs) and they did not use the term fibroblastic reticulum cell. However, Gretz et al¹⁸ described

compartments (corridors, conduits formed along the meshwork of fibroblastic reticulum cells continuing with sinus lining cells, which are closely associated both related structurally and possibly functionally to each other) carrying out important functions in T cell traffic and priming in lymph node. It is still not clear whether the cellular network of T-cell areas are composed of a unique/single cell type or not. Antigenic profile of these cells is also variable (for example expression of MHC-Class II antigens and certain other cell surface antigens present on both dendritic cells or other leukocyte types), or both. Therefore this special network seemed to be composed of resident cells (FRCs) and migrating antigen presenting cells (IDCs, arising from Langerhans cells of epidermis, migrating to lymph nodes via lymphatics as veiled cells) and macrophages. Our observations using B-D46 mAb revealed an extensive network of cellular processes in T-cell zones of peripheral lymphoid organs. Although some integrin chains expressed by FRCs reveal this network to some extent we did not observe a similar pattern of staining in the examination of more than thousand mAbs against cell surface antigens. Follicular dendritic cells (FDCs) forming the special microenvironment of lymphoid follicles were commonly believed to be arising from local mesenchymal cells.^{8,19,20} However FDCs were non-reactive for B-D46 antigen in the present study. These data together suggests that yet undefined B-D46 antigen is expressed later in development during further differentiation of T-cell zone reticular cells and possibly induced by the recirculating cell population invading this compartment. In mucosa associated lymphoid tissue co-expression of the antigen B-D46 on both FRCs and perivillous/pericryptal fibroblasts was also interesting. Both cells are members of fibroblast-like cell family and they form a confluent network of cellular processes collectively providing a special microenvironment in MALT. In tonsils a relatively weaker expression was present in the basal compartment of crypt and surface epithelium which was also confluent with underlying FRC network. Expression of B-D46 on type-1 thymic epithelial cells (TECs) and some medullary cells with dendritic processes is previously reported.²¹ We observed the same staining pattern in the present study and type-1 TECs which represent a unique cell group at the interface of thymic tissue with surrounding connective tissue reactive with limited number of mAbs. It should not be missed that antigenic profile is dynamic in most cases extensively switching upon stimulatory conditions present in the microenvironment. Monoclonal antibody B-D46 was substantially expressed by stromal components of certain compartments of lymphoid organs that are under high antigenic exposure thus the antigen recognized by this mAb is

a strong candidate of a relatively specific function related antigen in these locations. B-F45 mAb being strongly expressed by endothelial cells of all types of vasculature was the second fibroblast-like cell reactive molecule also expressed by fibroblast-like cell family members broadly. Mesenchymal cells in umbilical cord; villus core, perivillous and pericryptal fibroblasts in intestine; synoviocytes; some tissue fibroblasts and perineural sheet cells were all reactive for BF-45. Specific reactivity of B-F45 on perineural sheet cells will be helpful for studies directed to examination of peripheral nervous system. Another interesting finding was, expression of more restricted B-D46 on embryonic mesenchymal cells of placental villi but not on more broadly expressed BF-45. B-D46 is also expressed on basal compartment of amniotic epithelium and chorionic mesenchymal cells. Myofibroblastic differentiation of lymphoid stroma, amnio-chorionic fibroblasts and fibroblasts in inguinal hernia sacs is previously reported.²²⁻²⁴ Expression of B-D46 on these cell groups supports their fibroblast-like (myofibroblastic) nature.

In general, most endothelial markers, including B-F45 and B-D46, are also reactive with other tissue components like vascular smooth muscle with the exception of few antigens including CD31, which has an exclusively endothelial cell restricted tissue distribution. However, we believe that identification of the antigens recognized by these mAbs will be very beneficial as these data will help greatly to understand the function of this cell groups in special compartments of the organs examined. Fibroblast (-like) or FRC specific markers are important for also pathologists to determine tumors of this cell group origin.²⁵⁻²⁷ Especially B-D46 is a good candidate to be helpful to determine tumors of FRC origin in lymphoid organs. Antigens recognized by both mAbs are under investigation.

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