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Vascular and Nonvascular Expression of INCAM-110

A Target for Mononuclear Leukocyte Adhesion in Normal and Inflamed Human Tissues

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Inducible cell adhesion molecule 110 (INCAM-110), is a 110-kd adhesion receptor for lymphocytes and monocytes identified on cytokine-activated endothelium. Using immunoperoxidase techniques, little or no INCAM-110 was detected on endothelium in normal human tissues. In contrast, INCAM-110 was expressed in postcapillary venules in a variety of active inflammatory processes. In acute appendicitis, INCAM-110 was found coincident with strong expression of endothelial leukocyte adhesion molecule 1 (ELAM-1), a cytokine-inducible molecule that functions in neutrophil adhesion. However, in certain chronic inflammatory processes (eg, sarcoidosis), INCAM-110 was observed without simultaneous ELAM-1 expression. Anti-INCAM-110 antibody E1/6 also marked several extravascular cell types, including lymphoid dendritic cells, some tissue macrophages, synovial lining cells, and reactive mesothelial cells. These data suggest a role for endothelial INCAM-110 in the pathophysiology of both acute and chronic inflammatory reactions. Furthermore INCAM-110 may function as an adhesion molecule for mononuclear leukocytes in a variety of extravascular sites. *(Am J Pathol 1991, 138:385–393)*

At sites of inflammation, vascular endothelial cells undergo functional and morphologic changes collectively referred to as endothelial activation.[1–3] Inflammatory/immune cytokines, including interleukin-1 (IL-1)[4] and tumor necrosis factor/cachectin (TNF),[5,6] induce functional changes in human endothelial cells (HEC) *in vitro*, including increased adhesiveness for leukocytes.[7–11] Studies using *in vivo* models have demonstrated that cytokines produce changes corresponding to endothelial activation when introduced into tissues,[12–17] suggesting that endothelial activation *in vivo* may be, at least in part, a response to cytokines produced at foci of incipient inflammation.

Inducible cell adhesion molecule 110 (INCAM-110), identified by monoclonal antibody E1/6, is a 110-kd glycoprotein expressed on cytokine-activated HEC.[18,19] In culture, endothelial cells respond to IL-1 or TNF by increasing surface expression of INCAM-110 (10- to 15-fold), which is sustained for at least 48 hours. Initially INCAM-110 was defined by its capacity to mediate adhesion of human and murine melanoma cells.[18,19] More recently, it was recognized that INCAM-110 supports the adhesion of peripheral blood lymphocytes (PBL) and monocytes, but not polymorphonuclear leukocytes (PMN), to activated endothelium by a mechanism independent of the leukocyte cell surface molecule LFA-1 (CD11a/CD18).[20]

Two other cytokine-inducible endothelial adhesion molecules have been identified. Endothelial leukocyte adhesion molecule 1 (ELAM-1) is a transiently expressed (peak 4 hours, decline by 24 to 48 hours) 115-kd glycoprotein that mediates PMN adhesion to activated endothelial cells.[21,22] Endothelial leukocyte adhesion molecule 1 is not expressed *in vivo* by vascular endothelium of normal tissues, but has been detected in venules associated with certain inflammatory conditions, including appendicitis and acute granulomatous lymphadenitis.[2,23] Intercellular adhesion molecule 1 (ICAM-1),[24,25] a member of the immunoglobulin gene superfamily,[26,27] is a 90-kd glycoprotein expressed on a variety of cell types, including vascular endothelium.[25,28] It has been implicated

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in the adhesion of PMN,[29–32] lymphocytes,[33] and monocytes[32] through its interaction with leukocyte LFA-1.[34,35] Like INCAM-110, ICAM-1 demonstrates sustained expression on cytokine-activated endothelium.[28]

We now report the distribution of INCAM-110 in normal human tissues and its expression in certain inflammatory conditions, and comparison with that of ELAM-1. Our data indicate that INCAM-110 is expressed by activated endothelium, and by several nonvascular cell types, including populations of dendritic cells and tissue macrophages. This pattern of cellular expression strongly suggests a role for INCAM-110 in lymphocyte function in multiple settings.

Materials and Methods

Monoclonal Antibodies

Antibody E1/6 (IgG1), which was used to identify INCAM-110, was raised against TNF-activated HEC,[19] and was maintained in RPMI-1640 supplemented with 10% horse serum, 1 mmol/l (millimolar) sodium pyruvate, and 0.1 mmol/l nonessential amino acids (Gibco Laboratories, Grand Island, NY). Antibody E1/7 (IgG2a), also raised against TNF-activated HEC, recognizes ICAM-1 as determined by immunoprecipitation and gel electrophoresis, and by binding to COS cells transfected with a cDNA-encoding ICAM-1.[20] Antibody H4/18 (IgG2a) recognizes ELAM-1.[21] Hybridoma culture supernatants containing antibodies E1/6, E1/7, or H4/18 were used for these studies. Monoclonal antibodies recognizing factor VIII–related antigen, keratin proteins (AE1 + AE3), monocytes/macrophages (EBM 11), and follicular dendritic cells (DRC-1) were obtained from Dako Corporation (Santa Barbara, CA). The irrelevant antibody K16/16 (IgG1, cell culture supernatant) was used routinely as negative control in parallel sections. Proportions of vessels staining were estimated visually.

Tissues and Immunohistochemistry

Normal and diseased human tissues were selected from fresh surgical specimens or from a bank of frozen tissue in the Department of Pathology, Brigham and Women's Hospital (Boston, Massachusetts). Certain normal tissues, including heart, normal aorta, brain, kidney, and lung specimens, were obtained from autopsies performed at the Brigham and Women's Hospital and Children's Hospital (Boston, MA).

Cryostat sections (4 to 6 μ) were fixed in freshly prepared 2% paraformaldehyde/0.0075M phosphate-buffered saline (PBS; pH 7.3) at 4°C for 10 to 15 minutes. The sections were then washed in PBS/0.2% gelatin, and primary antibodies applied at optimal concentrations (typically 1:10 dilutions for cell culture supernatants) for 18 hours at 4°C. Sections were then washed and incubated for 30 to 60 minutes with biotinylated horse anti-mouse immunoglobulins (1:80, Vector, Burlingame, CA). After a third wash, sections were exposed to avidin:biotin-peroxidase:diluent (1:1:80, Vector 'Elite') for 30 minutes. Diaminobenzidine (1 mg/ml in 0.1 mol/l [molar] TRIS/saline buffer with 0.02% hydrogen peroxide) or aminoethylcarbazol (AEC, 0.02% in 5% dimethyl formamide, 0.2% sodium acetate buffer, pH 5, with 0.02% hydrogen peroxide) were employed as chromogens. Alternatively, sections were exposed to primary antibodies, rinsed briefly with 0.1 mol/l TRIS buffer/0.9% NaCl, washed in 0.1 mol/l TRIS buffer with 1% porcine serum, and exposed to peroxidase-conjugated rabbit anti-mouse immunoglobulin (1:80 dilution in 0.1 mol/l TRIS buffer, pH 7.3; Dako) for 30 to 60 minutes (25°C). Sections were then rinsed and washed, and exposed to peroxidase-conjugated swine anti-rabbit immunoglobulin (1:80 dilution; Dako) for 30 to 60 minutes. Comparable staining reactions were obtained using the two methods. The latter method proved useful in avoiding nonspecific staining due to endogenous biotin in certain tissues.

Results

INCAM-110 Expression in Normal Human Tissues

Organized Lymphoid Tissue

In uninflamed peripheral lymph node, vascular endothelial cells, including those of the high endothelial venules, exhibited little or no expression of INCAM-110 (Figure 1A). Similarly INCAM-110 was not expressed by vascular structures of mucosa-associated lymphoid tissue in small intestine (Figure 1B) or appendix. In contrast, anti–ICAM-1 antibody E1/7 bound to these high endothelial venules.

Anti–INCAM-110 antibody E1/6 reacted strongly with cells of dendritic morphology in follicular centers and interfollicular zones of peripheral lymph node and tonsil (Figure 1A, C, D).[20] A similar pattern of staining in lymphoid follicles was observed in parallel sections exposed to antibody DRC-1, which marks follicular dendritic cells. Little or no INCAM-110 was detected on mantle or interfollicular zone lymphocytes, or on peripheral blood lymphocytes.[20] Expression by a portion of follicular lymphocytes or other follicular cells (eg, macrophages), however, has not been excluded. Inducible cell adhesion molecule 110 was also expressed by cells of dendritic

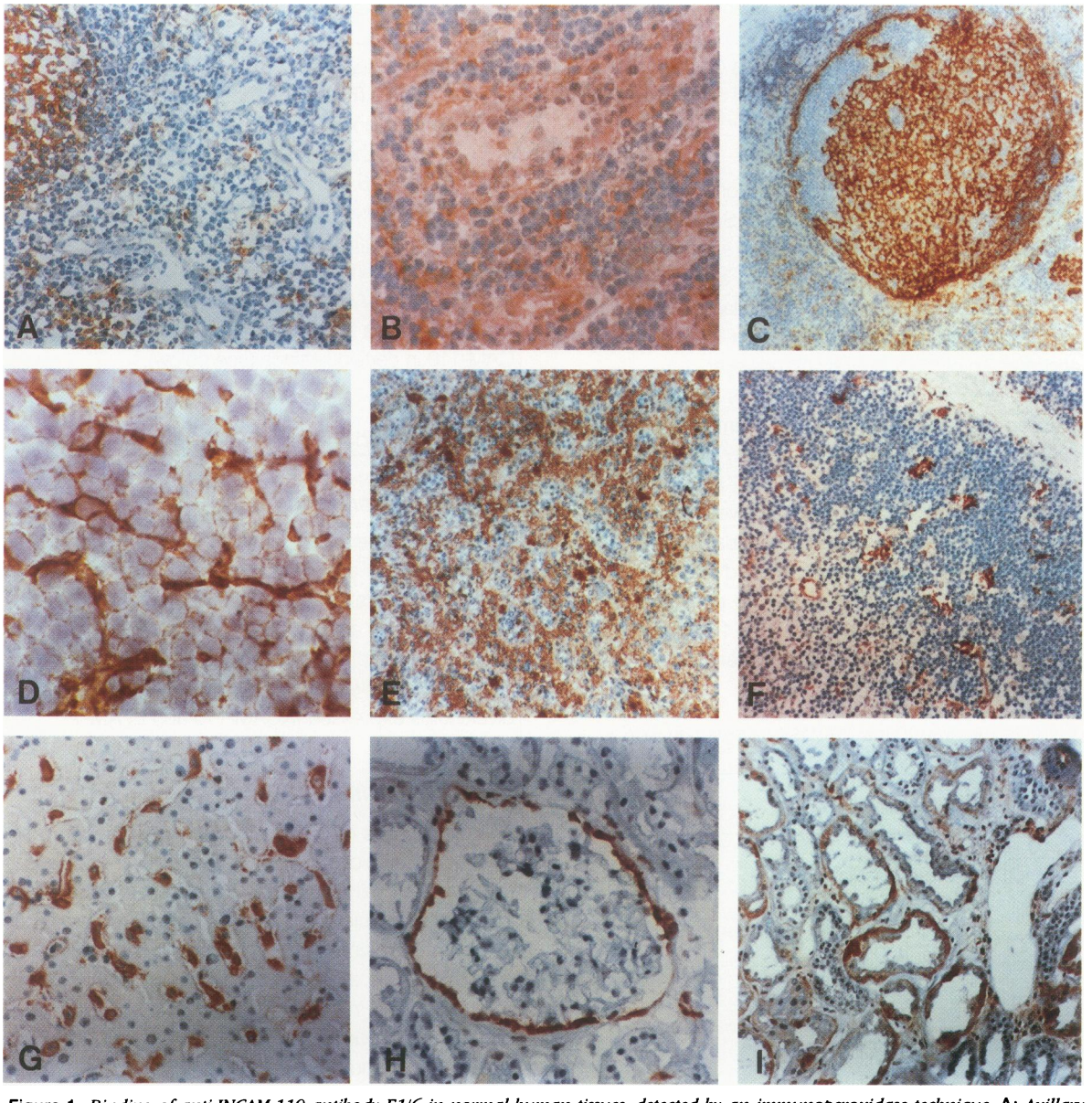

Figure 1. *Binding of anti-INCAM-110 antibody E1/6 in normal human tissues, detected by an immunoperoxidase technique.* **A:** *Axillary lymph node: follicular centers were positive, while high endothelial venules were nonreactive.* **B:** *Small intestinal mucosal lymphoid tissue: high endothelial venules were nonreactive.* **C:** *Tonsil: follicular dendritic cells reacted intensely with antibody E1/6, with occasional polarization of follicles, as illustrated. Mantle zone and interfollicular lymphocytes appeared nonreactive.* **D:** *Tonsil: cells morphologically compatible with interdigitating reticulum cells bound antibody E1/6.* **E:** *Splenic red pulp: splenic cords bound antibody E1/6 moderately, in a diffuse pattern. A similar pattern of reactivity was noted in parallel sections stained with anti-monocyte/macrophage antibody EBM 11.* **F:** *Fetal thymus: scattered large cells, consistent with macrophages, expressed INCAM-110. Thymocytes and the majority of epithelial cells appeared nonreactive.* **G:** *Liver: Kupffer cells were moderately reactive. Hepatocytes and hepatic endothelial cells did not bind antibody E1/6.* **H:** *Kidney: parietal epithelial cells exhibited strong staining, with nonreactivity of glomerular tufts.* **I:** *Kidney: tubular epithelial cells reacted focally; venules were negative.*

morphology in mucosal lymphoid tissue of small intestine and appendix.

Antibody E1/6 bound extensively to splenic cords in red pulp (Figure 1E), probably reflecting expression of INCAM-110 by reticular macrophages (as assessed by comparison with reactivity of antibody EBM 11). Scattered mononuclear cells in white pulp, most with dendritic morphology, expressed INCAM-110. Endothelial cells of splenic arterioles were occasionally reactive. In fetal thymus, antibody E1/6 marked a population of thymic cortical cells containing abundant cytoplasm (Figure 1F). A similar distribution of staining was observed with anti-monocyte/macrophage antibody EBM 11 in parallel sections. Keratin proteins and Ia antigens, expressed by thymic epithelial cells and nurse cells, were present in distributions different from that of INCAM-110. Taken together, these studies suggest that INCAM-110 is expressed by thymic macrophages, but not by most thymic

epithelial cells. Antibody E1/6 also bound weakly to scattered mononuclear cells in thymic medulla, and to endothelial cells in some medullary venules (Figure 1F).

Nonlymphoid Tissues

Vascular endothelium in most normal tissues expressed little or no INCAM-110. Sometimes anti-INCAM-110 antibody E1/6 reacted sporadically with small vessel endothelium in venules, and rarely, arterioles. Endothelium of normal aorta and large caliber artery was unreactive. Reactivity was noted focally in arterial endothelium of the vasa vasora, however.

Extralymphoid tissue macrophages also variably expressed INCAM-110 (Table 1). For example, a proportion of hepatic Kupffer cells bound antibody E1/6 (Figure 1G) in the majority of cases. Hepatocytes, as well as endothelia of sinusoids and central veins, were unreactive.

In some tissues, select epithelial cells also expressed INCAM-110 or an antigenically related structure. In the renal cortex, antibody E1/6 bound to parietal epithelial cells of the glomerular capsule (Figure 1H) in all samples studied. Staining of glomerular capillaries was not detected; trace reactivity in mesangium was rarely observed. Renal tubular epithelium, including collecting ducts, also focally bound antibody E1/6 (typically about 10% of tubules) (Figure 1I). Inducible cell adhesion molecule 110 was not detected in numerous other epithelial cells, including those of skin and gastrointestinal tract.

Antibody E1/6 was not observed to bind to fibroblasts, neural cells (cerebrum, cerebellum, peripheral nerve), nor to skeletal, cardiac, or smooth muscle cells. Trophoblastic cells and most vessels in the normal placenta did not express INCAM-110. Other nonimmune cells, including synoviocytes and mesothelial cells, may express INCAM-110 in certain settings (see below).

Table 1. *Binding of Anti-INCAM-110 Antibody E1/6 in Noninflamed Human Tissues*

Organ (n)	E1/6 Reactive	E1/6 Nonreactive
Lymphoid Tissues		
Lymph node (4)	Follicular dendritic cells	Endothelial cells
	Interdigitating reticulum cells	
Spleen (2)	Dendritic cells	Lymphocytes
	Macrophages	Endothelial cells
Thymus (4)	Macrophages	Cortical thymocytes
	Endothelial cells (−/+)	Epithelial cells
Peyer's patch (2)	Follicular dendritic cells	Endothelial cells
Nonlymphoid Tissues		
Skin (4)	—	Epidermis
	—	Fibroblasts
	—	Endothelial cells
Lung (9)	Endothelial cells (−/+)	Pneumatocytes
		Bronchial epithelium
Liver (4)	Kupffer cells	Hepatocytes
		Endothelial cells
Kidney (4)	Parietal epithelium (++)	Glomerular tuft
	Tubular epithelium (−/+)	Endothelial cells
Brain (2)	—	Neurons
	—	Glial cells
	—	Endothelial cells

INCAM-110 Expression in Inflammation

Acute Inflammation

In acute appendicitis, strong INCAM-110 expression was detected in endothelium of dilated serosal venules (Figure 2A). Parallel sections stained with anti–ELAM-1 antibody H4/18 also showed intense reactivity (Figure 2B), as shown previously by Cotran and coworkers.[23] Similarly venular endothelium in a case of acute colonic diverticulitis expressed INCAM-110 and ELAM-1.

Lymphadenitis

In four cases of granulomatous lymphadenitis diagnosed as sarcoidosis, venular endothelium expressed INCAM-110 focally (range, 10% to more than 50% of high endothelial venules) (Figure 2C), whereas little or no ELAM-1 expression was detected in the same vessels in parallel sections, as previously demonstrated.[2,23] Epithelioid histiocytes in sarcoidal lymphadenitis were occasionally trace reactive for INCAM-110, but the majority were negative. Inducible cell adhesion molecule 110 was focally expressed by venular endothelium in three cases morphologically consistent with toxoplasmic lymphadenitis (range, 5% to 30% of vessels) (Figure 2D). Consistent with previous studies (see reference 2, and unpublished data from A Dawson, JS Pober, and RS Cotran), little or no endothelial ELAM-1 expression was noted (Figure 2E). Concurrent INCAM-110 and ELAM-1[23] expression was detected in two examples of lymphadenitis diagnosed as cat scratch disease. Inducible cell adhesion molecule 110 staining was stronger and more widespread than ELAM-1 in these cases. Focal endothelial expression of INCAM-110 was also detected in two cases of dermatopathic lymphadenitis.

Dermatoses

Endothelial expression of INCAM-110 was detected in vessels (almost exclusively venules) in single cases of

erythema multiforme (Figure 2F), bullous lupus erythematosus, pityriasis lichenoides chronica, miliaria rubra, eczematous dermatitis, and subcutaneous pilonidal sinus. In addition, strong INCAM-110 expression was detected in venules of cutaneous delayed hypersensitivity reaction (streptokinase/ streptodornase at 23 hours, and tuberculin at 72 hours) associated with mononuclear inflammatory cell infiltrate, and in a cutaneous insect bite reaction (Figure 2G).[20] ELAM-1 staining was also present in these specimens, consistent with previous observations[2,23] (Figure 2H). As was the case with normal skin, little or no INCAM-110 was detected in urticarial reactions (two cases) or in a case of chronic dermatitis with sparse inflammatory infiltrate.

In inflamed dermis, antibody E1/6 bound to a population of mononuclear cells, most with the morphologic appearance of macrophages. While most small lymphocytes appeared negative, INCAM-110 expression by lymphoid cells could not be excluded. Antibody E1/6 also bound to a population of extravascular dendritic cells (Figure 2I) not detected in normal skin. Some vascular pericytes in inflamed skin bound antibody E1/6, sometimes with negative endothelium in the same vessel. Consistent with previous reports,[36,37] expression of ICAM-1 in vascular structures and in epidermal keratinocytes appeared to be upregulated in inflammation. Inducible cell adhesion molecule 110 was not detected in keratinocytes.

Synovitis

INCAM-110 was only rarely expressed by vascular endothelial cells in two samples of synovium obtained from patients with degenerative joint disease. In four cases of chronic rheumatoid synovitis (Figure 2J, K), INCAM-110 was detected in venules associated with chronic inflammatory cell infiltration. Antibody E1/6 also bound extensively to hyperplastic synovial lining cells. Endothelium in these samples exhibited expression of ELAM-1 that appeared to vary with disease activity. Typically, immunohistochemical reactivity for INCAM-110 was stronger and more extensive than for ELAM-1. In reactive synovium, extravascular cells consisting predominantly of macrophages also expressed INCAM-110.

Other Conditions

In five of nine samples of lung tissue (obtained from surgical specimens and autopsies), vascular endothelium in a portion of the microvessels (typically 10% to 30%) reacted weakly to moderately with anti–INCAM-110 antibody.[19] Although ELAM-1 was not detected in these cases, it is likely that this variable expression of INCAM-110 in lung vasculature represents low-level endothelial activation associated with intercurrent disease rather than tissue-specific constitutive expression. In a single case, lung tissue from a patient with leukemia and terminal sepsis strongly expressed INCAM-110 (Figure 2L), and showed widespread expression of ELAM-1. In some cases, scattered pulmonary macrophages appeared to express INCAM-110.

Binding of antibody E1/6 to mesothelial cells was not detected in normal tissue samples. In the lung specimen containing activated endothelium (as determined by strong expression of both ELAM-1 and INCAM-110), mesothelial cells reacted intensely with antibody E1/6 (Figure 2L), suggesting that mesothelial cell expression of INCAM-110 (or a related molecule) may also be inducible.

Discussion

Increasing evidence suggests that leukocyte entry into areas of inflammation is regulated, at least in part, by endothelial expression of leukocyte-selective adhesion molecules. Endothelial leukocyte adhesion molecule 1 is a member of the newly described family of vascular *selectins*,[38] (also designated LECCAMs[39]), which includes the lymphocyte homing receptor Mel-14 and granule membrane protein 140 (GMP-140). Endothelial leukocyte adhesion molecule 1 appears to function primarily in the adhesion of PMN,[21,22] but may also contribute to the adhesion of subpopulations of mononuclear leukocytes. Endothelial leukocyte adhesion molecule 1 is transiently expressed by cytokine-activated endothelium *in vitro*, declining toward basal levels by 24 to 48 hours, suggesting its role in acute inflammatory processes. Intercellular adhesion molecule 1[24,25] interacts directly with the leukocyte surface molecule LFA-1,[34,35] found on PMN, monocytes, and lymphocytes. Because increased expression of ICAM-1 in activated endothelium *in vitro* is more sustained than ELAM-1,[28] it has been suggested than ICAM-1 may play a role in mediating or sustaining chronic inflammatory processes.

Previous studies using the baboon model demonstrated endothelial expression of ELAM-1 in skin by 2 hours after local injection of TNF, with a decrease in expression by 24 hours.[17] The expression of ELAM-1 correlated with PMN influx. Increased endothelial ICAM-1 expression was detected somewhat later than ELAM-1 (by 6 to 9 hours after cytokine administration), corresponding to the onset of mononuclear cell infiltration, and remained elevated through 48 hours.[17] However, two lines of evidence suggest that ICAM-1 is not the sole mediator of lymphocyte recruitment. First anti–ICAM-1 antibodies block only a small portion of the adhesion of lymphocytes to activated endothelium *in vitro*.[33] Second patients with the syndrome referred to as leukocyte adhesion deficiency (LAD), characterized by a lack of leu-

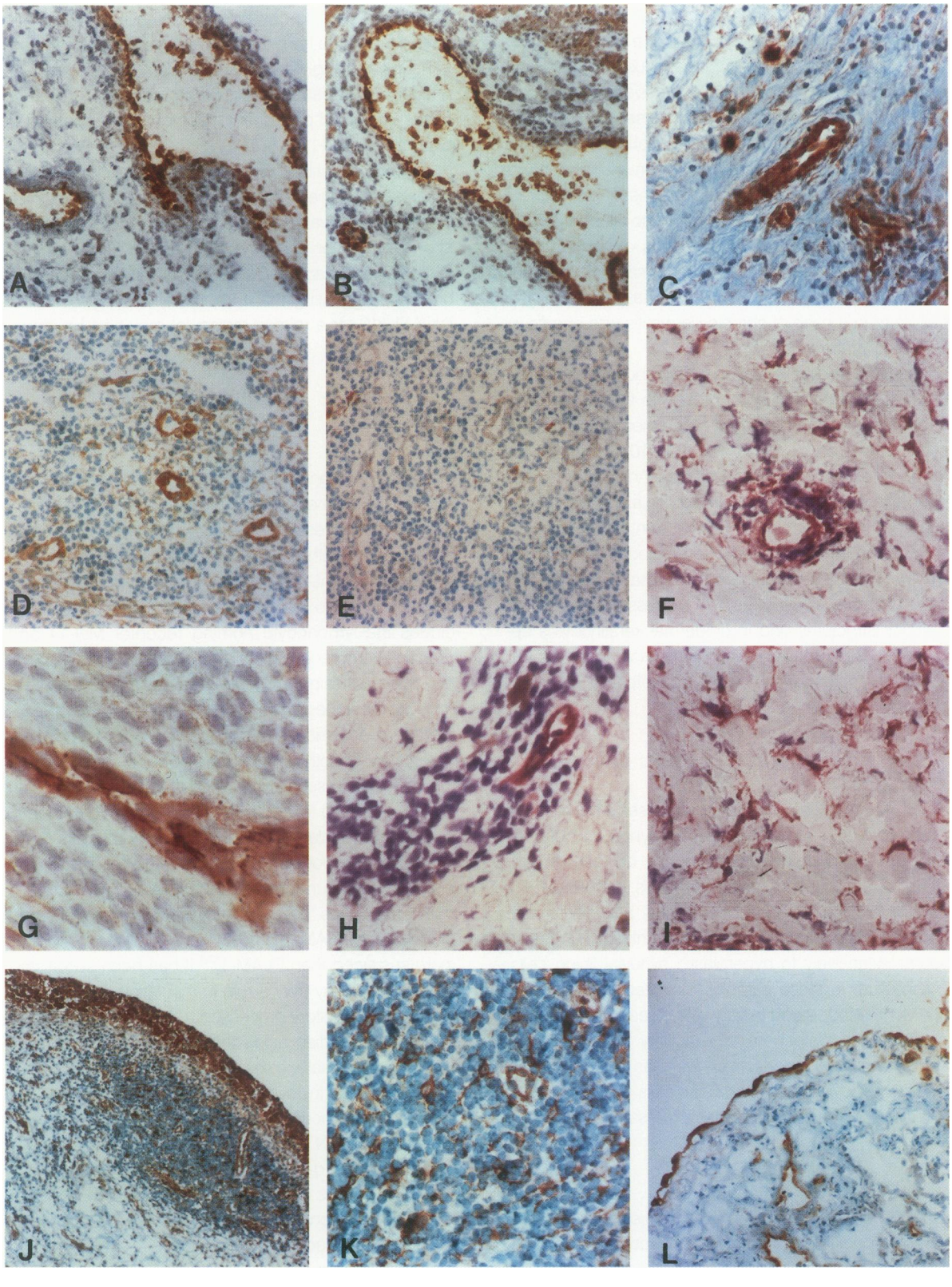
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Figure 2. *INCAM-110 and ELAM-1 expression in inflamed tissues. Sections were reacted either with anti-INCAM-110 antibody E1/6, or with anti-ELAM-1 antibody H4/18.* **A, B:** *Acute appendicitis: venular endothelium concurrently expressed INCAM-110 and ELAM-1, respectively.* **C:** *Lymph node, sarcoidosis: venular endothelium in areas of fibrosis and granuloma formation expressed INCAM-110. Vessels in parallel sections expressed little or no ELAM-1.* **D, E:** *Lymph node, toxoplasmosis: scattered venules bound anti-INCAM-110 antibody E1/6 (D) but not anti-ELAM-1 antibody H4/18 (E).* **F:** *Skin, erythema multiforme: endothelial cells in scattered venules associated with mononuclear cell infiltration expressed INCAM-110, as did a population of spindle cells in the dermis.* **G:** *Skin, insect bite reaction: intense reactivity of endothelial cells with antibody E1/6 in venules associated with mononuclear cell infiltrate.* **H:** *Skin, erythema multiforme: venular endothelial cells were also reactive with anti-ELAM-1 antibody H4/18.* **I:** *Skin, erythema multiforme: dermal spindle cells expressing INCAM-110. Similar cell populations expressing INCAM-110 were noted in delayed hypersensitivity responses and in other chronic inflammatory skin conditions.* **J, K:** *Synovium, rheumatoid arthritis: hyperplastic synovial lining cells reacted with anti-INCAM-110 antibody E1/6, while lymphoid and stromal cells were negative. Scattered dendritic-type cells, as well as high endothelial venules also were reactive.* **L:** *Lung, sepsis: venular endothelial cells and reactive mesothelial cells strongly expressed INCAM-110. Mesothelial cells in samples of uninflamed lung tissue were nonreactive.*

kocyte cell surface CD11/CD18 molecules,[40] successfully mount delayed hypersensitivity reactions (primarily lymphocytes and monocytes), despite an inability to generate normal PMN responses to inflammatory stimuli. These observations led to the recognition of INCAM-110 as an adhesion receptor for mononuclear leukocytes.[20]

Endothelial INCAM-110, originally identified as an adhesion target for melanoma cells,[18,19] appears to function in the adhesion of lymphocytes and monocytes (but not PMN) to activated endothelial cells *in vitro* by a mechanism independent of LFA-1.[20] Recently Osborn et al[41] isolated a cDNA from cytokine-activated endothelium by RNA subtraction cloning that encodes a new member of the immunoglobulin gene superfamily, designated vascular cell adhesion molecule 1 (VCAM-1). Leukocyte cell surface VLA-4, the $\alpha 4\beta 1$ integrin, has been shown to interact with VCAM-1 in mediating lymphocyte adhesion.[42] Anti–INCAM-110 antibody E1/6 was recently found to recognize COS cells transfected with a cDNA clone encoding a portion of VCAM-1 (Aruffo A, Bevilacqua MP: Unpublished observation), suggesting that these species represent the same, or closely related, molecules.

These studies demonstrate that ELAM-1[23] and INCAM-110 are both strongly expressed in cases of appendicitis, potentially promoting influx of both PMN and mononuclear leukocytes. Inducible cell adhesion molecule 110 and ELAM-1 were also coexpressed by activated endothelium in florid dermal delayed hypersensitivity[2,23] and active rheumatoid arthritis. In contrast, INCAM-110 was expressed by postcapillary venules in more indolent chronic inflammatory reactions (eg, sarcoidosis) with little or no concurrent ELAM-1 expression,[2,23] indicating that INCAM-110 expression may be more sustained than ELAM-1 in certain instances, or that it may be expressed independently. Taken together, current data suggest that INCAM-110 and ELAM-1 may function in the recruitment of lymphocytes and PMN, respectively, while ICAM-1 may support the recruitment of both leukocyte types.

The expression of INCAM-110 in lymphoid tissue is unlike that described for the vascular addressins, which are constitutively expressed in certain high endothelial venules and function in lymphocyte recirculation to peripheral[43] and mucosal[44] lymphoid tissue. LPAM, a murine lymphocyte homing receptor for mucosal lymphoid tissues, is an integrin in which the α chain is homologous to human $\alpha 4$.[45] Although the high endothelial ligand for LPAM in mucosal tissue has not been determined, our human tissue expression data suggest that it is distinct from INCAM-110/VCAM-1. However INCAM-110 may account, at least in part, for a mechanism of lymphoid cell adhesion to inflammatory endothelium in rheumatoid synovium.[46]

In extravascular sites, an epitope reactive with antibody E1/6 was found in lymphoid dendritic cells of tonsil, peripheral lymph node, and spleen. Certain tissue macrophages also bound antibody E1/6. It has not been determined whether these extravascular epitopes reflect the presence of functional molecules identical to endothelial INCAM-110. Dendritic cells[47] and macrophages[48] present antigen to lymphoid effector cells in immune reactions. Studies in the murine system have demonstrated the existence of an antigen-independent mechanism for T-cell adhesion to isolated dendritic cells.[49] It is possible that INCAM-110, or a related molecule, on dendritic cells and macrophages supports lymphocyte adhesion, and may thus play a role in antigen presentation or lymphocyte activation. Recently, it has been demonstrated that antibody E1/6 blocks adhesion of activated B lymphoblasts to germinal centers, suggesting that the follicle expresses a functional INCAM-110 molecule.[50] Although lymphocytes in blood and in most tissues appear to express little or no INCAM-110, expression by lymphoid cells has not been excluded.

The present studies demonstrate that INCAM-110, an adhesion receptor for mononuclear leukocytes, is expressed by vascular endothelium in a variety of inflammatory reactions. Taken together, *in vitro* functional data[19,20] and distribution in human tissues suggest that INCAM-110 plays a role in recruitment of lymphocytes and monocytes into foci of inflammation. Furthermore INCAM-110 (or a related molecule) may promote lymphocyte interactions with certain extravascular cell types (eg, dendritic cells), possibly influencing immune function. Of

particular interest is the potential role of INCAM-110 in mediating lymphocyte influx during transplant rejection. Ongoing studies of INCAM-110 expression in cardiac transplant rejection,[51] and in graft-*versus*-host reactions, may help to elucidate the role of INCAM-110 in immune-mediated tissue injury.

Acknowledgments

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