Interleukin-1β Induces Tissue- and Cell Type–Specific Expression of Adhesion Molecules In Vivo

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Abstract—We examined the tissue distribution of adhesion molecule gene expression in mice treated intravenously with interleukin (IL)-1β. E-selectin mRNA expression was selectively induced in the heart by IL-1β, but only slight or no induction was observed in other organs. On the other hand, intercellular adhesion molecule-1 mRNA expression was inducible in all organs examined, although it showed the strongest induction in the lung and the weakest responses in the brain and skin. Vascular cell adhesion molecule-1 mRNA was also inducible in all organs with the exception of the skin, but it was induced most markedly in the lung and the heart. The accessibility of IL-1β to the heart was less than that to other organs except the brain. Similar tissue-specific induction of these mRNAs was also seen when tumor necrosis factor (TNF)-α or lipopolysaccharide was substituted for IL-1β. Analysis of E-selectin mRNA expression in the heart by in situ hybridization indicated that expression was most prominent in microvascular endothelial cells and some other stromal cells, but this transcript was not seen in the lung. Although intercellular adhesion molecule-1 mRNA expression was restricted to the endothelium lining the capillaries and small arteries in the heart, its distribution in the lung covered not only the endothelium but also the cells composing the alveolar septa. In contrast, vascular cell adhesion molecule-1 mRNA expression was most prominent in endothelial cells of larger vessels in both the heart and the lung. Our results demonstrate that expression of adhesion molecules is tissue- and cell type–specific and that endothelial cells differentially express adhesion molecules depending on the size of the blood vessels. (Arterioscler Thromb Vasc Biol. 1998;18:1292-1303.)

Key Words: gene expression ■ endothelium ■ adhesion molecules ■ interleukin-1β ■ tumor necrosis factor-α

Because chemotaxis and accumulation of leukocytes have been demonstrated to be critical events not only in inflammation but also in injury after ischemia and reperfusion and the development of atherosclerosis, the prevention of these events has been suggested to be beneficial. Indeed, it has recently been reported that antibodies against adhesion molecules (reviewed in Reference 5) and chemokines prevent acute inflammation, ischemia-reperfusion injury, rejection of transplanted organs, and autoimmune disease. Although it has been demonstrated that there are a number of chemokines and adhesion molecules that have similar functions, it remains to be elucidated whether these molecules show redundant abilities only or whether each of them possesses a specific role. The specific roles of these molecules may result not only from their specific functions but also from their differential expression. Chemokine gene expression in vivo has been well investigated by Hamilton and colleagues and has been induced in organ- and cell type–specific fashion by systemic treatments with proinflammatory stimuli.

However, expression of endothelial adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 has been studied mostly in vitro with human umbilical vascular endothelial cells, which have been shown to differ from microvascular endothelial cells in their capacity to induce these molecules in vitro. Whether tissue-specific regulation of the expression of endothelial adhesion molecules exists is not fully understood. Although Becker-Andre et al has reported that gene expression of E-selectin and ICAM-1 is differentially induced in the heart and the lung when murine E-selectin is cloned, the reason for this differential expression has not been clarified. Because it has been shown that adhesion molecules are inducible in cells besides vascular endothelial cells, we have systematically investigated the tissue-specific expression of three major adhesion molecules (E-selectin, ICAM-1, and VCAM-1) and determined the cell types responsible for such tissue-specific expression.

Our results demonstrate that adhesion molecule gene expression is organ- and cell type–specific and that it is inducible not only in endothelial cells but also in other cell types in specific organs. Furthermore, the expression of each adhesion molecule in endothelial cells differs, depending on the type and size of the blood vessels involved. These findings suggest that each adhesion molecule plays a specific role in inflammation in specific organs, angiitis, or atherosclerosis, in which specific blood vessels are affected.
Preparation of RNA and Northern Blot Hybridization

Total RNA was extracted from ~0.7 to 1 g of each organ removed after intravenous treatment by homogenization with a Polytron sonicator/homogenizer for 2 minutes in guanidine isothiocyanate–CsCl according to previously published methods.20

Equal amounts of RNA (20 μg) were denatured and subjected to electrophoresis in a 1% agarose-formaldehyde gel. The RNA was then blotted by capillary transfer onto nylon membranes (Boehringer Mannheim Yamanouchi). The blots were prehybridized for 6 hours at 42°C in 50% formamide, 1% SDS, 5× SSC, 1× Denhardt’s solution (0.02% Ficol, 0.02% BSA, and 0.02% polyvinylpyrrolidone), 0.25 mg/mL denatured herring testis DNA, and 50 mmol/L sodium phosphate buffer pH 6.5. Hybridization was carried out at 42°C for 12 to 18 hours with 7×10^6 cpm of denatured probe. The filters were washed for 30 minutes at room temperature in 0.1% SDS–2× SSC for 15 to 30 minutes at 55°C in the same solution. The blots were then exposed to XAR-5 x-ray film (Eastman Kodak) with Dupont Cronex Lightening Plus intensifying screens at ~70°C. In some experiments, the blots were reused by stripping and rehybridizing with different probes. Expression of α-tubulin was used as an internal control in all experiments. In addition, the RNA load per lane was assessed by ethidium bromide staining of the original agarose gel after capillary transfer.

In Situ Hybridization

In situ hybridization was performed using the method described by Stoler.21 Antisense and sense radiolabeled ^35S-RNA probes for E-selectin, ICAM-1, and VCAM-1 were prepared by in vitro transcription from T3 and T7 RNA polymerase promoters, respectively, in the pBluescript plasmid system. In brief 62.5 μCi of ^35S-CTP was added to reaction mixtures in a total volume of 20 μL consisting of 40 mmol/L Tris HCl, pH 7.5; 6 mmol/L MgCl2; 2 mmol/L spermidine; 10 mmol/L NaCl; 10 mmol/L DTT; 1 U/μL RNase inhibitor; 0.5 mmol/L each of ATP, UTP, and GTP; 10 μmol/L unlabeled CTP; linearized template equivalent to 1 μg of whole plasmid; and 40 U of either T3 or T7 RNA polymerase. The reaction was allowed to proceed for 3 to 4 hours at 37°C. The DNA template was removed by addition of 1.5 U of RNase-free DNase for 30 minutes at 37°C. Proteins and free ribonucleotides were removed by phenol–chloroform–isoamyl alcohol extraction followed by ethanol precipitation. All probes were made to ~350 bases long by controlled alkaline hydrolysis.

Whole bodies of mice were fixed by cardiac perfusion with 4% buffered paraformaldehyde after the animals had been anesthetized with ether. Hearts and lungs were removed, excised, and immersed overnight in the same fixative. Tissues were then embedded in paraffin, sectioned, and stained with hematoxylin-eosin (Vector Laboratories)–treated slides. After deparaffinization in xylene and hydration through a graded ethanol series, sections were digested with proteinase K (1 μg/mL) for 30 minutes at 37°C, washed in distilled water, and acetylated in freshly prepared acetic anhydride solution, pH 8.0, for 10 minutes. After one wash in 2× SSC, sections were dehydrated through a graded ethanol series. The hybridization mixture (600 mmol/L NaCl; 10 mmol/L Tris HCl, pH 8; 1 mmol/L EDTA; 50% formamide; 1× Denhardt’s solution; 10% dextran sulfate; 100 μmol/L DTT; 0.2% SDS; and 0.5 mg/mL yeast tRNA) containing 0.135 μg/mL of radiolabeled RNA probe was applied to each section and covered with a silanized coverslip. Hybridization was carried out for 16 hours at 45°C in light mineral oil. Excess probe was removed by washing in chloroform followed by washing for 1 hour in 4× SSC containing 1 mmol/L DTT. After dehydration, the slides were stringently washed at 60°C for 15 minutes in a buffer containing 300 mmol/L NaCl; 10 mmol/L Tris HCl, pH 8; 1 mmol/L EDTA; 50% formamide; and 100 μmol/L DTT. After a brief wash in 2× SSC, the slides were digested for 30 minutes at 37°C with 25 μg/mL RNase A in buffer containing 500 mmol/L NaCl; 10 mmol/L Tris HCl, pH 8.0; and 1 mmol/L EDTA. After a 30-minute wash at 37°C in the same buffer without the enzyme, sections were rinsed again in 4 L of 2× SSC and washed at high stringency in 0.1× SSC.
at 60°C, followed by dehydration through a graded ethanol series containing 300 mmol/L ammonium acetate and air drying before autoradiography. Autoradiography was performed by dipping the slides into NTB-2 autoradiography emulsion (Eastman Kodak) liquefied at 45°C and diluted 1:1 (vol/vol) in 600 mmol/L ammonium acetate. After they were dried, the slides were stored in light-proof boxes containing desiccant and exposed at 4°C for 6 to 10 days. The exposed slides were developed in Kodak D19 developer for 2.5 minutes, rinsed in 2% acetic acid for 30 seconds, and fixed in Rapid Fixer (Chugai Photo Chemical Co Ltd) for 5 minutes. After they were washed in tap water, the slides were counterstained with hematoxylin with or without eosin. Sections from untreated and IL-1β-treated mice were always processed in parallel with the same batches of probes and reagents.

**Immunohistochemical Analysis**

To obtain monoclonal antibodies against mouse E-selectin, cell membranes from a Chinese hamster ovary cell line (CHO K1) transfected stably with pEoNeo expression vector (a kind gift from Dr A. Yoshimura) containing the mouse E-selectin cDNA were used for immunization of rats. Wistar rats (4 weeks old) purchased from Charles River Japan, Inc (Yokohama, Japan) were immunized once by foot pad subcutaneous injection with the Chinese hamster ovary cell membranes (prepared from 8×10⁶ cells) emulsified with an equal volume of Freund’s complete adjuvant (Chemicon Inc) and were repeatedly immunized (once a week for 1 month) with the membranes only. A hybridoma clone producing an IgM antibody that blocked adhesion of HL-60 promyelocytes to the Chinese hamster ovary cells expressing mouse E-selectin was the source of a monoclonal antibody named 67SG. Anti-mouse ICAM-1 monoclonal antibody (KAT-1) was purchased from Seikagaku Corp.

Five hours after administration of IL-1β (50 ng per mouse), the mice were killed; the hearts and the lungs were infiltrated with warm OCT compound and snap-frozen in LN₂. Sections of the frozen hearts were cut to be 4-μm thick by use of a cryostat and were mounted on glass slides. Sections were fixed in acetone for 5 minutes, air dried, and stained individually with anti–E-selectin (67SG) or anti–ICAM-1 (KAT-1) monoclonal antibody (5 mg/mL) for 45 minutes at room temperature. Staining for the presence of the indicator antibody was achieved with the Vectastain biotin/avidin peroxidase system (Vector Labs Inc). Sections were incubated with diaminobenzidine at 100 mg/mL for 5 minutes, counterstained with hematoxylin, and then permanently mounted with coverslips.

**Distribution of Radioiodinated IL-1β**

The mice were injected with radioiodinated, recombinant IL-1β via the tail vein with 5×10⁶ cpm (10 ng) of IL-1β and were killed 1 hour later. The radioactivity per milligram of wet tissue weight in the liver, kidney, heart, lung, brain, and skin was determined by excising the different tissues and measuring radioactivity by gamma scintillation spectrometry.

**Results**

**Tissue-Specific Gene Expression of Adhesion Molecules in IL-1β-Treated Mice**

C57BL/6 female mice were injected intravenously with IL-1β (50 ng per mouse) or vehicle (PBS). The animals were killed 2 hours later and samples of liver, kidney, heart, lung, brain, and skin were prepared. Total RNA isolated from each tissue was analyzed by Northern blot hybridization for specific mRNA content. Surprisingly, E-selectin mRNA expression was induced specifically in the heart. On the other hand, ICAM-1 mRNA expression was induced in almost all organs examined, although its strongest induction was seen in the heart and lung. Similar to ICAM-1 mRNA, VCAM-1 mRNA was also induced in various organs with the exception of the skin. Additionally, it is interesting to note that in the brain VCAM-1 mRNA showed stronger induction than did the two other adhesion molecules. α-Tubulin mRNA was expressed at almost equivalent levels in the different tissues examined, although slightly higher levels of expression were seen in the lung and brain. Thus, adhesion molecule gene expression differs, depending on the organs examined.

IL-1β–induced gene expression of adhesion molecules occurred rapidly (within 1 hour), transiently (nearly undetectable by 4 hours) in both heart and lung, and with the same time course (Figure 2). This pattern of expression was also seen in the kidney and liver (data not shown). As shown in Figure 1, E-selectin mRNA expression was induced selectively in the heart, whereas ICAM-1 and VCAM-1 mRNAs were induced more abundantly in the lung and equivalently in both organs (also see Figure 2).

Because the differential expression of adhesion molecules in the tissues was influenced by differential access of the injected stimulus to the tissue, the tissue distribution of IL-1β was determined 1 hour after intravenous injection of radioiodinated IL-1β by exciting the different tissues and measuring their radioactivity on a per weight basis (the Table). In contrast to increased gene expression of adhesion molecules in the heart, the accessibility of IL-1β to the heart was rather low, ie, approximately half the value of that in the liver, lung, or skin. Although IL-1β accumulated abundantly in the kidney, this accumulation might have become inactivated after its passage through metabolic processes, or it may have been stored in the kidney before excretion into the urine. On
the other hand, IL-1β injected intravenously showed little access to the brain, probably owing to the blood-brain barrier.

To further examine the concentration dependence of IL-1β-driven mRNA expression in the heart and lung, a dose-response profile for intravenous IL-1β was obtained (Figure 3). Treating animals with a series of increasing doses of IL-1β illustrated that the induction of E-selectin mRNA was dose dependent, with minimal response seen at 0.5 ng per mouse in the heart, although a slight induction of E-selectin mRNA in the lung was observed at 50 ng per mouse. Whereas ICAM-1 mRNA expression was augmented by IL-1β at 0.5 ng per mouse in both organs, the sensitivity of VCAM-1 mRNA expression in response to IL-1β was a little higher in the heart than in the lung.

With respect to the observation that the accessibility of IL-1β to the heart was about half of that to the lung, the response of E-selectin mRNA induction in the heart was estimated to be ~200-fold more sensitive than that in the lung. In the case of VCAM-1 mRNA induction, the heart was considered to be 20-fold more sensitive than the lung.

**Greater Heart-Specific Induction of E-Selectin mRNA Expression After Treatment With IL-1β Than With TNF-α**

To assess the stimulus specificities of adhesion molecule gene expression, we compared the effects of systemic treatment with IL-1β, TNF-α, or LPS in both the heart and lung. Mice were injected intravenously with IL-1β (10 ng per mouse), TNF-α (100 ng per mouse), or LPS (500 ng per mouse). Two hours later, total RNA was prepared from the heart and lung and then examined for mRNA content (Figure 4). Although treatment with TNF-α or LPS induced ICAM-1 and VCAM-1 gene expression in a similar manner to IL-1β treatment in both organs, induction of E-selectin mRNA expression by TNF-α or LPS was less marked than that by IL-1β. Thus, E-selectin expression in the heart differed, depending on the type of stimulus applied.
In Situ Hybridization Analysis of mRNA Expression of Adhesion Molecules

To determine the cell types responsible for gene expression of adhesion molecules, sections from the heart and lung were examined by in situ hybridization. Sections from the hearts and lungs of control and IL-1β- or TNF-α-treated animals were hybridized with 35S-radiolabeled sense or antisense cRNA probes for the adhesion molecules. Sense-strand probes hybridized poorly with sections from both untreated and treated mice (data not shown). Analysis of heart sections from IL-1β-treated animals by hybridization with the anti-sense E-selectin mRNA probe revealed markedly elevated signals (Figure 5C and 5D), whereas sections from untreated animals showed weak signals (Figure 5A and 5B), similar to those seen with sense-strand probes. Signals of E-selectin mRNA were detected not only in a diffuse, scattered pattern but also in a sporadically aggregated pattern. Close examination demonstrated that the grains with the latter pattern were localized over stromal cells with elongate nuclei and not over the cardiac muscle cells (Figure 5E and 5F), suggesting that IL-1β treatment induced E-selectin mRNA expression not only in endothelial cells lining the capillary beds but also in other stromal cells. When TNF-α was substituted for IL-1β, localization of E-selectin mRNA expression was similar (data not shown). Analysis of lung sections from IL-1β-treated mice revealed no increased signal for E-selectin mRNA (data not shown). Diffuse signals of ICAM-1 mRNA in the hearts of IL-1β-treated mice were detected in a scattered pattern, probably due to the endothelial cells lining capillary vessels and not cardiac muscle cells (Figure 6). Interestingly, endothelial cells lining the small arteries in the heart revealed induction of ICAM-1 mRNA expression, although they did not show detectable E-selectin mRNA. On the other hand, diffuse signals of ICAM-1 mRNA were also detected in the lungs of IL-1β-treated mice, including endothelial cells lining the blood vessels but not bronchial epithelial cells (Figure 7C and 7D); close examination revealed that the cells composing the alveolar septa (other than endothelial cells) also expressed ICAM-1 mRNA (Figure 7E and 7F). In contrast to E-selectin and ICAM-1 expression, VCAM-1 mRNA expression was observed mainly in endothelial cells lining the larger blood vessels in both the heart and lung in response to IL-1β treatment (Figure 8). Endocardial cells in both ventricles were also positive for VCAM-1 mRNA expression (data not shown).

To further demonstrate that the increases in message levels of adhesion molecules in response to proinflammatory stimuli were associated with increased expression of proteins, immunohistochemical studies for E-selectin and ICAM-1 were performed (Figure 9). No staining was detected in tissue sections from IL-1β-treated mice without specific antibodies against the adhesion molecules (Figure 9A). Analysis of heart sections from IL-1β-treated mice with anti–E-selectin antibody revealed that immunostaining was detected in a linear pattern parallel to the cardiac muscle cells (probably due to endothelial cells lining the capillary vessels) as well as sporadically over the cells with elongate nuclei (Figure 9C and 9D), whereas heart sections from untreated mice showed few immunostained spots for E-selectin (Figure 9B). Analysis of lung sections from the IL-1β-treated mice revealed low detection of E-selectin (data not shown). Immunostaining for ICAM-1 in the hearts of IL-1β–treated mice was detected in a linear pattern parallel to the cardiac muscle cells and also over the endothelial cells lining the small blood vessels (Figure 9E). Immunostaining for ICAM-1 was also detected in the lungs of IL-1β–treated mice over all cells except bronchial epithelial cells (data not shown). These immunohistochemical studies demonstrate that the expression pattern of each adhesion molecule is identical with that of each message level.

Discussion

The results presented here demonstrate that expression of endothelial adhesion molecules by systemic treatment with proinflammatory stimuli is induced in a tissue-specific fashion. In particular, the induction of E-selectin mRNA expression was heart specific (Figure 1), consistent with the previous study by Becker-Andre et al. This heart-specific induction was not due to high accessibility of the injected stimulus, or due to different time course of gene expression (the Table and Figure 2) and did not depend on the kind of stimulus applied (Figure 4). Although E-selectin expression is believed to be restricted to endothelial cells,22,23 a recent study of renal diseases, such as glomerulonephritis, showed that
E-selectin was expressed in the parietal epithelium of glomeruli and in the tubular epithelium. Therefore, there are two possible explanations for the heart-specific induction of E-selectin: vascular endothelial cells in the heart may be different from those in any other organ with regard to E-selectin expression, or specific cells other than vascular endothelial cells in the heart may produce E-selectin in response to IL-1β. To determine the cell types in the heart responsible for E-selectin mRNA expression in response to IL-1β treatment, sections from the hearts were examined by

Figure 5. In situ hybridization analysis of E-selectin mRNA expression in hearts from IL-1β-treated mice. C57BL/6 mice were untreated (A and B) or treated with IL-1β (50 ng per mouse) in 0.1 mL of PBS (C–F) and killed 1 hour later, followed by cardiac perfusion with 4% buffered paraformaldehyde. Tissue sections from the heart were hybridized with either sense (data not shown) or antisense cRNA probe for E-selectin radiolabeled with 35S-CTP. After autoradiography, slides were lightly stained with hematoxylin and examined by bright-field (A, C, and E) or dark-field (B, D, and F) illumination. Magnification: ×62.5 (A–D), ×250 (E and F). White particles represent silver grains marking positive signals for E-selectin mRNA under dark-field illumination. Arrows indicate stromal cells with elongate nuclei on which silver grains were aggregated. Ar indicates small artery. Similar results were obtained in three experiments.
Expression of E-selectin mRNA was detected not only in a diffuse pattern (which is suggested to show expression in microvascular endothelial cells) but also sporadically in other stromal cells. In contrast, E-selectin mRNA expression was scarcely or not detected in the IL-1β-treated lung tissue, in which the relative contents of blood vessels and mononuclear phagocytes are more abundant than in the heart (data not shown). On the other hand, although ICAM-1 mRNA expression was restricted to endothelial cells in the heart treated with IL-1β (Figure 6), it was also induced in cells composing the alveolar septa besides endothelial cells in the lung (Figure 7).
context, it has been reported that stromal as well as vascular endothelial cells in the spleen or in vitro can express ICAM-1 mRNA in response to stimuli.15,16 These results indicate that both the microvasculature and stromal cells are functionally distinct with regard to the expression of adhesion molecules as well as chemokines,10,11 depending on the anatomic sites (organs), and that both microvascular endothelial and stromal cells in the heart and stromal cells in the lung have a high

Figure 7. In situ hybridization analysis of ICAM-1 mRNA expression in lungs from IL-1β-treated mice. C57BL/6 mice were untreated (A and B) and treated with IL-1β (C–F). One hour later, animals were killed, followed by cardiac perfusion with 4% paraformaldehyde. Tissue sections from lungs were hybridized with either sense (data not shown) or antisense cRNA probe for ICAM-1 radiolabeled with 35S-CTP. After autoradiography, the slides were lightly stained with hematoxylin and eosin and examined under light-field (A, C, and E) or dark-field (B, D, and F) illumination. Magnification: ×62.5 (A–D), ×250 (E and F). Br indicates bronchus; BV, blood vessel; and Al, alveolus. Similar results were obtained in three experiments.
Figure 8. In situ hybridization analysis of VCAM-1 mRNA expression in hearts and lungs of IL-1β-treated mice. C57BL/6 mice were untreated (A and B) or treated with IL-1β (C–F) and killed 1 hour later, followed by cardiac perfusion with 4% paraformaldehyde. Tissue sections from hearts (A–D) and lungs (E and F) were hybridized with either sense (data not shown) or antisense cRNA probe for ICAM-1 radiolabeled with 35S-CTP. After autoradiography, the slides were lightly stained with hematoxylin and examined under light-field (A, C, and E) or dark-field (B, D, and F) illumination. Magnification ×62.5. Ar indicates artery; BV, pulmonary blood vessel; and Br, bronchus. Similar results were obtained in three experiments.
capacity to specifically induce E-selectin and ICAM-1, respectively.

Although positive signals for E-selectin mRNA expression in the IL-1β–treated hearts were observed in endothelial cells lining the microvascular vessels and not in those lining small arteries and veins (Figures 5 and 9), ICAM-1 mRNA expression was detected in endothelial cells lining both types of vessels (Figures 6, 7, and 9). Furthermore, VCAM-1 mRNA expression was observed mainly in endothelial cells lining the larger vessels (Figure 8). Thus, we have demonstrated that endothelial cells are different, depending on the size of blood vessels and with regard to expression of adhesion molecules.

The tissue-specific expression of chemokines and adhesion molecules may result from the different microenvironments...
in each tissue. Furthermore, stromal and endothelial cells may be differentiated in a tissue-specific fashion, since it has recently been reported that endothelial cells in different vascular beds may vary in their capacity to induce adhesion molecules in vitro.\textsuperscript{12,13} Whether the augmented induction of E-selectin mRNA expression in the heart resulted from the tissue-specific microenvironments or differentiation of endothelial and stromal cells was not determined in this study, and further investigations are necessary.

The heart-specific induction of E-selectin mRNA expression by IL-1\( \beta \) treatment was more marked than that by TNF-\( \alpha \) treatment, although both treatments induced ICAM-1 and VCAM-1 mRNAs equivalently in the heart and the lung (Figure 4). This finding suggests that intracellular signals evoked by IL-1\( \beta \) and TNF-\( \alpha \) are different, at least in part, for induction of E-selectin mRNA, although in vitro studies have reported that both IL-1\( \beta \) and TNF-\( \alpha \) induce E-selectin equivalently in human vascular endothelial cells.\textsuperscript{22,23} Because treatment with IL-1\( \beta \) or TNF-\( \alpha \) induces nuclear factor-\( \kappa B \) activation, which plays a significant role in the expression of many adhesion molecules,\textsuperscript{24-26} other intracellular signal(s) required for the full expression of E-selectin mRNA are considered to be induced by IL-1\( \beta \) but not by TNF-\( \alpha \). This possibility is currently under investigation in our laboratory.

Tissue-specific expression of chemokines and adhesion molecules is important for the design of treatment regimens with fewer side effects. It has been demonstrated that IL-1 and TNF-\( \alpha \) are synthesized and released in response to hypoxia and that they induce the expression of adhesion molecules in the heart.\textsuperscript{27,28} Inhibition of leukocyte adhesion to endothelial cells with the use of antibodies against endothelial adhesion molecules such as ICAM-1 and E-selectin has been shown to have a protective effect against the myocardial injury that normally occurs after ischemia/reperfusion.\textsuperscript{5,29} Because E-selectin expression was shown to be induced in a heart-specific manner in this study, heart-specific protection of the myocardium after coronary angioplasty for ischemic heart disease as well as treatment for myocarditis may be possible by inhibiting E-selectin. On the other hand, the soluble form of E-selectin has been demonstrated to induce angiogenesis,\textsuperscript{30} suggesting that it may be useful for formation of collateral circulation in stable ischemic heart disease.

Although both VCAM-1 and ICAM-1 have been demonstrated to be induced in endothelial cells in atherosclerotic lesions,\textsuperscript{31,32} VCAM-1 is expressed much more selectively in lesions than in ICAM-1 (Figure 8). Therefore, manipulation of VCAM-1 has the potential as a treatment for atherosclerosis as well as for angiitis affecting large vessels, with fewer side effects than those due to ICAM-1. Furthermore, it has recently been reported that VCAM-1 is a very important endothelial adhesion molecule in brain inflammation.\textsuperscript{33,34} Consistent with our results in which VCAM-1 expression was induced in the brain more abundantly than the other adhesion molecules tested, despite the limited access to the brain of the intravenously injected stimulus (Figure 1 and the Table). Thus, the expression patterns of adhesion molecules clarified in this in vivo study may facilitate development of better treatment regimens for various diseases, with fewer side effects.

References


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