Detection of Soluble Adhesion Molecules in Pleural Effusions*

Jörg C. Hoffmann, MD; Hartmut Krüger; Jörg Lührs, MD; and Hinrich Hamm, MD

Purpose: Multiple immune functions such as activation of T cells and monocytes or cytolysis of tumor cells are mediated via the adhesion receptor/ligand pairs CD2/LFA-3 and LFA-1/ICAM-1. Because soluble forms of LFA-3 (sLFA-3) and ICAM-1 (sICAM-1) can interfere with these functions, we asked whether increased levels of sLFA-3 and/or sICAM-1 can be found in malignant or inflammatory effusions compared with transudates.

Methods: sLFA-3 and sICAM-1 levels were measured by enzyme-linked immunoassays in pleural effusions from 70 patients (6 transudates, 10 inflammatory, 47 malignant, and 7 other effusions). Twenty pleural fluid samples were tested in parallel for the complete sLFA-3 molecule or sLFA-3-domain 1 only.

Results: Increased levels of sICAM-1 were found in all types of exudates compared with transudates. Highest levels of sICAM-1 were measured in malignant exudates, particularly in effusions caused by mesotheliomas, non-small lung cancers, and gynecologic malignancies. This was also true for sLFA-3. However, sLFA-3 levels were not increased in inflammatory effusions. sLFA-3 levels correlated significantly with protein, cholesterol, lactate dehydrogenase, and sICAM-1 levels. Comparison of sLFA-3-domain 1 and the complete sLFA-3 molecule revealed identical sLFA-3 levels, suggesting the absence of nonfunctional split products.

Conclusions: Elevated levels of the complete sLFA-3 molecule were found in malignant pleural effusions, while sICAM-1 level was elevated in both inflammatory and malignant effusions. Secretion of sICAM-1 and sLFA-3 by tumor cells might block T-cell-mediated immune functions such as tumor cytotoxicity. Alternatively, secretion of soluble adhesion molecules might reflect the generalized inflammation within the pleural space.

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Key words: CD2; ICAM-1; LFA-1; LFA-3; malignancy; pleural effusion; soluble adhesion molecules

Abbreviations: BSA=bovine serum albumin; ELISA=enzyme-linked immunosorbent assay; FCS=fetal calf serum; ICAM-1=intercellular adhesion molecule 1; LDH=lactate dehydrogenase; LFA-1=lymphocyte function-associated antigen 1; LFA-3=lymphocyte function-associated antigen 3; mAb=monoclonal antibody; NK=natural killer (cell); PBS=phosphate-buffered saline solution

Adhesion molecules are involved in immune surveillance of tumor cells by cytotoxic T lymphocytes and natural killer (NK) cells. Apart from the antigen-specific T-cell receptor/major histocompatibility complex interaction, two adhesion pathways have been shown to be important for T cell and NK cell cytotoxicity, the CD2/LFA-3 and LFA-1/ICAM-1 interaction. While CD2 expression is limited to T cells and NK cells, ICAM-1 and LFA-3 are expressed on most human cell types. Both CD2 and LFA-3 have two extracellular domains. While sterical binding is mediated by each domain 1, domain 2 connects domain 1 to the membrane. ICAM-1 and LFA-3 membrane expression is readily upregulated after cytokine stimulation of normal cells and tumor cells. In addition to their involvement in cytotoxic reactions, these two receptor/ligand pairs mediate important immune functions such as monocytic activation, B-cell differentiation, and T-cell activation.

Although initially described as membrane-anchored molecules, ICAM-1 and LFA-3 also exist as soluble molecules (sICAM-1 and sLFA-3). Elevated levels of sICAM-1 were found in sera of most patients with malignant and inflammatory illnesses. In vitro studies have shown that both molecules (sICAM-1 and sLFA-3) can be released upon stimulation with various cytokines. They bind to their counter-receptors,
Table 1—Characteristics of Patients With Pleural Effusions

<table>
<thead>
<tr>
<th>Group</th>
<th>Cause</th>
<th>No.</th>
<th>Age,* yr</th>
<th>Protein,† g/L</th>
<th>Cholesterol,† mmol/L</th>
<th>LDH,† U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transudate</td>
<td></td>
<td>6</td>
<td>64 (32-87)</td>
<td>16.7 (3.8)</td>
<td>0.77 (0.16)</td>
<td>73 (14.1)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Pleuropneumonia</td>
<td>4</td>
<td>60.5 (45-86)</td>
<td>35.9 (3.4)</td>
<td>2.4 (0.2)</td>
<td>509 (219)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td>1</td>
<td>77</td>
<td>40</td>
<td>1.6</td>
<td>181</td>
</tr>
<tr>
<td>Autoimmune</td>
<td></td>
<td>1</td>
<td>59</td>
<td>51</td>
<td>3.6</td>
<td>241</td>
</tr>
<tr>
<td>Non-specific</td>
<td></td>
<td>4</td>
<td>37.8 (24-55)</td>
<td>49.3 (2.1)</td>
<td>3.48 (0.61)</td>
<td>340 (99)</td>
</tr>
<tr>
<td>Malignant</td>
<td>Primary lung tumor</td>
<td>6</td>
<td>66.7 (63-73)</td>
<td>39.2 (2.5)</td>
<td>2.15 (0.2)</td>
<td>858 (319)</td>
</tr>
<tr>
<td></td>
<td>Small cell carcinoma</td>
<td>3</td>
<td>62.3 (54-76)</td>
<td>38 (10)</td>
<td>1.35 (0.35)</td>
<td>86 (34)</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>1</td>
<td>86</td>
<td>25</td>
<td>0.8</td>
<td>311</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>1</td>
<td>80</td>
<td>38</td>
<td>0.1</td>
<td>335</td>
</tr>
<tr>
<td></td>
<td>Alveolar carcinoma</td>
<td>1</td>
<td>66.8 (43-84)</td>
<td>39 (3.1)</td>
<td>2.55 (0.36)</td>
<td>661 (252)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Breast carcinoma</td>
<td>11</td>
<td>58.6 (41-78)</td>
<td>35.9 (2.5)</td>
<td>1.96 (0.18)</td>
<td>250 (43)</td>
</tr>
<tr>
<td></td>
<td>Ovarian carcinoma</td>
<td>7</td>
<td>60.7 (41-70)</td>
<td>40.8 (3.5)</td>
<td>2.3 (0.31)</td>
<td>346 (82)</td>
</tr>
<tr>
<td></td>
<td>Uterine carcinoma</td>
<td>3</td>
<td>55.3 (43-66)</td>
<td>28.3 (3.5)</td>
<td>1.33 (0.29)</td>
<td>181 (136)</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma of unknown</td>
<td>3</td>
<td>75.3 (75-76)</td>
<td>40.3 (4.7)</td>
<td>2.63 (0.41)</td>
<td>184 (68)</td>
</tr>
<tr>
<td></td>
<td>Gastric carcinoma</td>
<td>1</td>
<td>60</td>
<td>41</td>
<td>2.8</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>Colon carcinoma</td>
<td>1</td>
<td>76</td>
<td>41</td>
<td>1.6</td>
<td>332</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma</td>
<td>1</td>
<td>65</td>
<td>55</td>
<td>2.1</td>
<td>131</td>
</tr>
<tr>
<td>Other</td>
<td>Pseudochylothorax</td>
<td>1</td>
<td>27</td>
<td>51</td>
<td>4.3</td>
<td>5,030</td>
</tr>
<tr>
<td></td>
<td>Unclear/multiple causes</td>
<td>6</td>
<td>62.7 (26-93)</td>
<td>37.7 (3.2)</td>
<td>1.88 (0.24)</td>
<td>428 (218)</td>
</tr>
</tbody>
</table>

*Mean (range).
†Mean (±SEM).
*unknown origin.

ie, LFA-1 and CD2, blocking the LFA-1/ICAM-1 and the CD2/LFA-3 interaction. Blocking such interactions results in inhibition of immune functions mediated via these molecules, eg, cytotoxic reactions.5,6,8,29-31 We therefore asked whether sICAM-1 and sLFA-3 levels are elevated in malignant and/or inflammatory pleural effusions and whether these molecules correlate with diagnostic markers that are generally used to differentiate transudates from exudates, eg, protein, cholesterol, and lactate dehydrogenase (LDH) levels.

MATERIALS AND METHODS

Patients

We investigated a series of 76 consecutive patients (31 male and 45 female patients) with pleural effusions who were admitted to Hannover Medical School (Hannover, Germany). Thoracentesis was performed using ultrasound guidance. The samples were centrifuged at 500 g for 10 min and the supernatants were stored at −28°C for further analysis. Separated specimens were forwarded for bacteriologic, cytologic, and biochemical studies. Cholesterol was measured by the cholesterol-oxidase-PAP method at 25°C, protein by the biuret method, and LDH by enzyme reaction using a kit at 25°C (all by Boehringer Mannheim; Mannheim, Germany). Protein, cholesterol, and LDH levels were measured in all patients except two, who had multiple previous analyses.

Individual case classification was carried out by two experienced investigators (J.C.H. and H.H.) according to a standardized protocol. The diagnosis was based on all available clinical and biochemistry information (patient files, chest radiographs, bacteriologic and cytologic, protein, cholesterol, and LDH), and, if available, CT, thoracoscopy, and histology. Six patients had to be excluded from the study because of nonspecific binding in both assays (see below). The characteristics of the remaining 70 patients are shown in Table 1.

sLFA-3 Assay (for Domain 1)

sLFA-3 was measured by a sandwich-type enzyme-linked immunosorbent assay (ELISA) using the anti-LFA-3 monoclonal antibody (mAb) TS2/9 (IgG1, American Tissue Culture Collection [ATCC; Rockville, Md]) as coating antibody and the anti-LFA-3 mAb AICD58.1 (IgG2a, kindly provided by Dr. S.C. Meuer; Heidelberg, Germany) directed at different epitopes of LFA-3 domain 1.3 The assay was performed essentially as previously described.15 Briefly, a 96-well flat-bottom microtiter plate was coated with 100 μL of mAb TS2/9 (5 μg/mL) overnight in the cold room. After 2 washes with phosphate-buffered saline solution (PBS)/0.1% polysorbate (Tween 20; Sigma, Munich, Germany), the plates were blocked with PBS/5% bovine serum albumin (BSA) for 1 h followed by washing twice and antigen incubation using nonlabeled serum or dilutions of recombinant LFA-3. After 2 and 5 times washing, plates were incubated with 5 μg/mL of mAb AICD58.1 or an irrelevant isotype-matched mAb directed at HLA class I (W6/32, IgG2a, ATCC) for 1 h. Finally, after washing 3 times the wells were incubated for 1 h with goat anti-mouse IgG2a coupled to alkaline phosphatase (Dunn; Asbach, Germany), washed 3 times, and developed at room temperature using p-nitrophenyl-phosphate (Sigma; Munich, Germany). The reaction was stopped after 15 min by the addition of 3 M NaOH, and the absorbance was determined at 405 nm using an ELISA reader (Titertek). Nonspecific binding was defined as an absorbance of more than twice the background absorbance using the control mAb. These samples were excluded from the study (nine samples). Intra-assay variation was between 3% and 6.4%, interassay variation was between 2.8% and 7.6%.
sLFA-3 Assay (Domain 1 and 2)

The complete LFA-3 molecule was measured by a sandwich-type enzyme-linked immunosassay as above using the anti-LFA-3 mAb AICD58.16 as coating antibody and AICD58.6 as second antibody. All other steps were identical to the sLFA-3-domain 1 ELISA.

siCAM-1 Assay

siCAM-1-1 was measured by a sandwich-type ELISA employing the anti-siCAM-1 mAb GP98.14 (IgG2a) as coating mAb and GP98.11 (IgG1, both kindly provided by Dr. J.P. Johnson; Munich, Germany) as secondary mAb. Hybridoma cell lines were grown in Rosewell Park Memorial Institute (RPMI; Gibco, Eggenstein, Germany) medium plus 10% fetal calf serum (FCS) (cc-pro; Karlsruhe, Germany), 1% penicillin/streptomycin, 2% glutamin (both Gibco, Eggenstein, Germany), and 100 IU/mL recombinant human IL-6 (kindly provided by M. Färber; Sandzü, Germany). The complete assay was performed in a cold room unless otherwise noted. A 96-well flat-bottom microtiter plate was coated with 100 µL of 1:2,000 dilution of unlabeled goat antimouse IgG2a (Dunn; Germany) overnight. After 2 washes with PBS/0.1% polysorbat the plates were blocked with PBS/1% BSA for 1 h followed by washing twice and incubation with 2.5 pg/mL of mAb GP98.14 for 1 h. Thereafter, 50 µL of antigen (serial dilutions of a standard serum of 240 ng/mL, previously determined by a commercially available ELISA from T-cell science, Bad Nanheim, Germany) or a 1:10 dilution of pleural effusion samples was added in duplicate. After 2 h and 5 times washing, plates were incubated with 2.5 pg/mL of mAb GP98.11 or TS2/9 as control mAb for 1 h. Finally, after washing 3 times, the wells were incubated for 1 h with goat antimouse IgG1 coupled to alkaline phosphatase at a dilution of 1:2,000 (Dunn; Germany), washed 3 times, and developed at room temperature using p-nitrophenyl-phosphate (Sigma). The reaction was stopped after 45 min by the addition of 3 M NaOH and the absorbance was determined at 405 nm using an ELISA reader (Tittertek; Wiesbaden, Germany). Nine samples were excluded because of nonspecific binding. Intra-assay variation was between 3.3% and 4.4%, and interassay variation was between 2.4% and 3.5%.

Statistical Analysis

All measurements are shown as mean±SEM unless otherwise noted. To compare different patient groups, the Wilcoxon rank sum test for independent samples, ie., Mann Whitney U test, was applied. Spearman’s rank correlation coefficient was used to compare different clinical and laboratory measurements with sLFA-3- or siCAM-1-levels.

RESULTS

siCAM-1-Levels in Pleural Effusions

Significantly elevated siCAM-1 levels were found in all types of exudative pleural effusions (inflammatory: 335.1±35.1 ng/mL, n=10; malignant: 401.9±40.2 ng/mL, n=46; others: 379.4±87 ng/mL, n=5) as compared with transudative effusions (90.2±20 ng/mL, n=6) (Fig 1, top). Since malignant effusions showed highest levels and constituted the largest group of samples, subgroup analysis was performed dividing samples into effusions due to primary lung tumors (small cell and non-small cell lung cancer), primary tumors of the pleura (mesotheliomas), and effusions due to metastasis consisting of nongynecologic tumors, breast cancer, and gynecologic tumors (ovarian and uterine carci-

mas). Interestingly, pleural effusions due to mesotheliomas had significantly higher siCAM-1 levels (647.2±106.9 ng/mL, n=9) as compared with small cell lung cancers (248.2±26.5 ng/mL, n=6) or breast cancers (233.4±17.3 ng/mL, n=11) (p=0.005 and <0.0001, respectively). In addition, effusions caused by gynecologic tumors had significantly increased siCAM-1 levels (365.4±48.7 ng/mL, n=9) when compared with breast cancer samples (p=0.01) (Fig 1, bottom).

sLFA-3-Levels in Pleural Effusions

Inflammatory pleural effusion had similar sLFA-3 levels (9.0±1.1 ng/mL, n=8) as transudative effusions (6.1±1.4 ng/mL, n=6). In contrast, malignant and other exudative effusions had significantly increased sLFA-3 levels (malignant: 13.4±0.8 ng/mL, n=47; others: 15.3±2.8 ng/mL, n=5) when compared with transudates (p=0.002 and 0.01, respectively) (Fig 2, top). Subgroup analysis of malignant effusions again revealed highest levels for effusions due to gynecologic tumors (14.9±1.4 ng/mL, n=10). These levels were significantly increased as compared with malignant

Fig 1. Concentrations of soluble ICAM-1 (siCAM-1) in different types of pleural effusions. Top: siCAM-1 levels of transudates (T, n=6), inflammatory effusions (IF, n=10), malignant effusions (M, n=46), and other effusions (O, n=5). Bottom: subgroup analysis of malignant effusions. Shown are siCAM-1 levels of small cell lung cancers (SCC, n=6), non-small cell lung cancers (NSCC, n=5), mesothelioma (Meso, n=9), breast cancer (Breast, n=11), gynecologic malignancies (GynM, n=10), and other metastatic malignancies (OMM, n=5). Indicated are means (circles) ±2 SEM (thin bars).

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effusions caused by small cell lung cancer (8.8±0.5 ng/mL, n=6) (p=0.005). The elevation of sLFA-3 levels of mesotheliomas and non-small lung cancers (13.4±1.7 ng/mL, n=9, and 18.4±4.6 ng/mL, n=5) did not reach statistical significance compared with small cell lung cancer (p = 0.07 and p = 0.05, respectively) (Fig 2, bottom).

**Molecular Structure of sLFA-3 in Pleural Effusions**

Previous studies have shown that sLFA-3 is only functionally active in its complete form consisting of domain 1 and 2. Because the sLFA-3-ELISA in this study is directed against domain 1 of LFA-3, it detects both the complete molecule and LFA-3 split products containing domain 1 only. Therefore, 20 pleural effusion samples were additionally measured with an ELISA against the complete molecule (domain 1 and 2). A significant correlation was found between sLFA-3 levels measured for the complete molecule and domain 1 only (r = 0.83, p < 0.0001) and there was no difference between sLFA-3 measured by both ELISAs, suggesting that nonfunctional split products are not present in pleural effusions (Fig 3).

**Correlation of sLFA-3 and sICAM-1 With Diagnostic Parameters of Pleural Effusions**

A small but significant correlation was found between sICAM-1 and sLFA-3 levels in 62 pleural effusions investigated (r = 0.43, p = 0.001). In addition, sLFA-3 correlated significantly with protein (r = 0.48, p < 0.0001), cholesterol (r = 0.36, p = 0.004), and LDH levels (r = 0.28, p = 0.03). In contrast, no correlation was found between sICAM-1 and these parameters or with soluble adhesion molecules and age (Table 2).

**Discussion**

We found increased concentrations of the soluble adhesion molecules sICAM-1 and sLFA-3 in exudative pleural effusions, particularly malignant effusions caused by non-small cell lung cancers, mesotheliomas, and gynecologic tumors. While sICAM-1 level was increased in all exudates, including inflammatory pleural effusions, sLFA-3 levels in inflammatory effusions were only slightly increased compared with transudates.

Lung lymphocytes previously have been shown to be involved in tumor defense and lung inflammation. 32-38 Lymphocytes express adhesion molecules on their surface to interact locally with epithelial, endothelial, and stromal cells, as well as macrophages. 32-36 Together with cytokines, these molecules normally allow intercellular communication, which is required for host defense against pathogens or tumor cells. 34,35 In addition, they are thought to be involved in different types of lung inflammation because T-cell activation, B-cell differentiation, as well as monocyte and neu-

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**Figure 2.** Concentrations of soluble LFA-3 (sLFA-3) in different types of pleural effusions. Top: sLFA-3 levels of transudates (T, n=6), inflammatory effusions (IF, n=9), malignant effusions (M, n=47), and other effusions (O, n=4). Bottom: subgroup analysis of malignant effusions. Shown are sLFA-3 levels of small cell lung cancers (SCC, n=6), non-small cell lung cancers (NSCC, n=5), mesotheliomas (Meso, n=9), breast cancers (Breast, n=11), gynecologic malignancies (GynM, n=10), and other metastatic malignancies (OMM, n=6). Indicated are means (circles) ±2 SEM (thin bars).

**Figure 3.** Molecular structure of sLFA-3 in pleural effusions. Shown are concentrations for sLFA-3 domain 1 (sLFA-3-D1) only as compared with the complete sLFA-3 molecule (sLFA-3-D1+D2).
trophil activation are mediated via adhesion molecules. The receptor/ligand pairs, CD2/LFA-3 and LFA-1/ICAM-1, are needed for host defense against tumor cells and for local inflammatory reactions. After cell activation, the membrane expression of CD2, LFA-3, and ICAM-1 have been shown to be increased. In addition, the ligand binding affinity of both CD2 and LFA-1 is enhanced by cell activation.

Cell stimulation, eg, by cytokines, not only upregulates the membrane expression of ICAM-1 and LFA-3 but can also lead to release of soluble forms of these molecules. Possible functions of these soluble adhesion molecules are (1) interference with effective adhesion by competition with cell-bound ligands, and (2) triggering a response in the ligand binding cells. Alternatively, soluble adhesion molecules may merely be epiphenomena resulting from cell death (eg, cytolysis) or in association with membrane expression. In certain compartments such as the pleural space, they could either reflect capillary leakage or result from local production.

Previous in vitro studies suggest that release of soluble LFA-3 and ICAM-1 is not related to cell death. In our patient population, no correlation was found between sICAM-1 and LDH, a laboratory marker associated with cytolysis. The correlation of sLFA-3 with LDH was poor ($r=0.25$). Therefore, cytolysis does not appear to be responsible for increased sLFA-3 and sICAM-1 levels. Protein and cholesterol levels reflect capillary leakage in pleural effusions. A slight but significant correlation was found between sLFA-3 and cholesterol as well as sLFA-3 and protein levels. Neither protein nor cholesterol levels correlated with sICAM-1. Thus, sLFA-3 but not sICAM release seems to be due in part to capillary leakage. However, the correlation of sICAM-1 with sLFA-3 levels suggests a similar release mode for both molecules. To this end, sICAM-1 seems to be released within the pleural space and sLFA-3 seems to be released by both capillary leakage and local production.

In the past, release of sLFA-3 and sICAM-1 has been shown to be somewhat independent of its membrane expression because some tumor cell lines show strong membrane expression but no release of sLFA-3. However, almost all tumor cell lines that secrete sICAM-1 and sLFA-3 in the first place enhance their membrane expression and their sICAM-1/sLFA-3 release on stimulation. To this end, production of soluble adhesion molecules often indirectly reflects membrane expression. One might, therefore, envisage a situation in which inflammatory processes within the pleura due to either malignancy or lung inflammation may lead to cytokine secretion, increased expression of membrane-bound ICAM-1 and LFA-3, as well as increased release of soluble ICAM-1 and LFA-3. Just looking at inflammation, this might be a regulatory mechanism to limit adhesion processes by interference with cell-cell interactions. As a side effect of the nonspecific inflammatory response, increased levels of soluble adhesion molecules might interfere with effective cytotoxic reactions impairing the host ability to control tumor cells.

Among malignant effusions, soluble adhesion molecules, alternatively, may be released by tumor cells themselves, particularly after local cytokine stimulation. Again, by competition with membrane-bound LFA-3 and/or ICAM-1, these soluble molecules may interfere with cell-cell adhesion, which is required for effective tumor defense by cytotoxic T lymphocytes or NK cells. This might be a mechanism of tumor cells to escape tumor cell surveillance by cytotoxic lymphocytes. Indeed, we and others have shown in vitro that soluble forms of LFA-3 and/or ICAM-1 can interfere with cytotoxic reactions. To be functionally active, sLFA-3 must comprise the complete molecule consisting of domains 1 and 2. Therefore, split products such as LFA-3 domain 1 bind only weakly, whereas the complete LFA-3 molecule (domains 1 and 2) binds strongly to CD2. sLFA-3 in pleural effusions exists in a potentially active form comprising the complete extracellular part of LFA-3 consisting of both domains. This is particularly relevant because increased sLFA-3 concentrations were measured by an ELISA against domain 1 of LFA-3, which also detects its nonfunctional split products. Furthermore, adequate concentrations have to be reached before sLFA-3 and/or sICAM-1 can block cellular interactions. These minimum concentrations have been reported to be 100 to 200 ng/mL for sLFA-3 and about 1,000 ng/mL for sICAM-1. Such sICAM-1 levels can be reached by only some malignant pleural effusions, while sLFA-3 concentrations in this range are unlikely. However, if only some cells, eg, tumor cells, produce the majority of these molecules, adequate local concentrations could be reached. The concentrations for triggering of the ligand binding cells are thought to be much higher than for blocking cellular interactions. Even locally such concentrations are highly unlikely to be reached in vivo.

| Table 2—Correlation of sLFA-3 and sICAM-1 With Markers of Pleural Effusions |
|---------------------------------|------|-----|------|------|
| Parameter                       | r | p Value | n | r | p Value | n |
| Protein                        | 0.48 | <0.0001 | 63 | 0.21 | 0.09 | 65 |
| Cholesterol                    | 0.36 | 0.004 | 63 | 0.05 | NS | 65 |
| LDH                            | 0.25 | 0.03 | 63 | 0.1 | NS | 65 |
| Age                            | -0.05 | NS | 65 | 0.14 | NS | 67 |

$r$=correlation coefficient.

$^1$NS=not significant.
In conclusion, increased levels of a potentially active form of sLFA-3 were found in malignant pleural effusions, while sICAM-1 was found to be elevated in both inflammatory and malignant effusions. Therefore, sICAM-1 and sLFA-3 may be an epiphenomenon of the generalized inflammation in both malignant and inflammatory pleural effusions. By interference with cell-cell interactions, they may either limit the extent of inflammation or, alternatively, inhibit effective cytosis of tumor cells by cytotoxic T lymphocytes and NK cells.

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