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DANCE ROUND

WE DANCE ROUND *IN A RING AND SUPPOSE,*
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

CELL ADHESION MOLECULES IN PLEURAL EFFUSIONS WITH DIFFERENT ETIOLOGY

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• The pleura, including the mesothelial and underlying mesenchymal cells and extracellular matrix, is often involved in pathological processes of not completely defined mechanisms. Pleural cells are specialized in performing barrier and secretory functions and require careful study to gather a meaningful clinical information.

A variety of agents can affect the pleura causing inflammation, effusions, and fibrosis. The mesothelial cells are a major source of chemokines (1), such as monocyte chemotactic peptide-1 (MCP-1) and interleukin-8 (IL-8), which are mediators for cell migration through the pleural region (2).

Inflammation and tumor metastasis in pleura remain a significant clinical problem. The role of cell adhesion molecules (CAM) in these processes is currently being explored.

THE BALANCE BETWEEN MEMBRANE-BOUND AND SOLUBLE INTERCELLULAR ADHESION MOLECULE-1 AS A REGULATORY MECHANISM FOR TUMOR METASTASIS IN PLEURA

• Intercellular adhesion molecule-1 (ICAM-1, CD54)belongs to the immunoglobulin supergene family and binds the leukocyte function-associated antigenrl (LFA-1, CDlla/CD18). Tumor necrosis factor-a (TNF-cc), interferon (INF) -a, INF-P, andlNF-y upregulate ICAM-1 on different cell types, including endothelial and inflammatory cells. The soluble form of ICAM-1 (sICAM-1) contains the larger part of the extracellular portion of the membrane-bound ICAM-1 (3).

As a part of an ongoing study, we performed an immunocytochemical investigation on ICAM-1 expression on mesothelial cells in malignancy-associated pleural effusions. We found out that the cytological detection of malignant cells in pleural fluid correlates with a low percentage of ICAM-1-immunopositive mesothelial cells (4). As a source of chemokines (2) and by expressing ICAM-1 as a ligand of LFA-1 (5), mesothelial cells participate in the migration into and accumulation of inflammatory cells in the pleural cavity. It seems likely that sICAM-1 released in the serum retains a capacity to bind LFA-1. The effect may be attenuation of inflammation by inhibiting extravasation of leukocytes to inflamed tissues (6).

Tumor cells are also known to express ICAM-1 (7, 8). Cultured human tumor cells treated with cytokines showed an increased expression of ICAM-1 and shedding into the culture medium (9). It was demonstrated a double increase of ICAM-1 expression on tumor cells in pleural effusions after immunotherapy (8). In malignancy, the activation of T cells and monocytes or cytolysis of tumor cells are mediated *via* the receptor/ligand pairs CD2/LFA-3 andLFA-l/ICAM-1. Soluble forms ofLFA-3(sLFA-3) and sICAM-1 can interfere in these interactions.

Elevated levels of sLFA-3 and sICAM-1 in malignant effusions were established (10). Secretion of sICAM-1 and sLFA-3 by tumor cells may block T cell-mediated tumor cytotoxicity. This may be a mechanism for tumor cells to escape the immune surveillance (11, 12). ThelowICAM-1-immunoreactivityonmesothelial cells in the presence of pleural metastasis could be explained with the high level of sICAM-1 released by the tumor cells in the serum and pleural fluid which may interfere in the interaction between mesothelial and inflammatory cells, thus damaging the mesothelial barrier.

MACROPHAGES IN THE PLEURAL CAVITY - WHERE THEY COME FROM AND HOW THEY PARTICIPATE IN THE TUMOR DEFENCE

• The macrophages are antigen presenting cells playing a crucial role in nearly all types of immune responses. Blood monocytes interact with vascular endothelial cells expressing L-selectin, a4(5l integrin and P2 integrin responsible for the extravasation of monocytes into tissues and serosal cavities, where they are called macrophages (13). However, macrophages are not equivalent to mature resident body cavity cells. Only a small fraction of mononuclear phagocytes in effusions are of blood origin. It was suggested that macrophages renew themselves from a local pleural stem cell population and disputed whether these stem sells are mesothelial cells (14). It is known that LFA-1 and CD 1 Ib/CD 18 are expressed on monocyte-macrophages but not on mesothelial cells. In our study, we observed LFA-1- and GDI lb/CD18-immunopositive cells with morphological signs intermediate of macrophages and mesothelial cells, in nearly all exudative or transudative pleural effusions. Thus we give another evidence for the hypothesis about a mesothelial origin of a certain clone of the pleural cavity macrophages (14).

Yet another interesting point is that tumor cells of various histological types in pleural effusions have been shown to express high ICAM-1-immunoreactivity (7, 8). Our results show that a high percentage of LFA-1 and CD 1 Ib/CD 18 macrophage immunopositivity correlates with the presence of malignant cells in pleural effusions. This suggests that tumor cell invasion induce a continuous state of p2 integrin upregulation in macrophages. We assume that *via* ICAM-1/P2 integrin interaction macrophages can recognize tumor cells and mediate lysis by a direct cell-to-cell, juxtacrine way. These findings arise the question whether the percentage of LFA-1 and CD lib/CD 18-immu no positive macrophages in malignant pleural effusions correlate with patient survival.

DOES A COMPREHENSIVE ASSESSMENT OF CELL ADHESION MOLECULE EXPRESSION ON CELLS IN PLEURAL FLUID IMPROVE THE ETIOLOGICAL DIAGNOSIS

• The results of many studies, including ours, concerning CAM expression in pleural effusions, maybe summarized and interpreted in the light of a definite etiology. This requires a complex evaluation of data from CAM expression on mesothelial and inflammatory cells in different pleural diseases. Accordingly, in our previous work we performed a multifactor analysis of a large number of cytomorphological variables (15). Recently, we investigated the expression of several CAM, such as LFA-1, CDllb/CD18, ICAM-1, platelet-endothelial cell adhesion molecule-l(PECAM-l,CD31), and E-cadherin, on pleural fluid cells (Table 1). We measured the percentage of immunopositivity of a certain adhesion molecule in a certain cell population. These variables are analyzed *via* discriminating analysis. If the etiological groups of pleural effusions have CAM specificity it would be possible to work out different informants for the different etiological types. To our preliminary data of tuberculous, parapneumonic and malignant pleural effusions, we have worked out three informants including the following variables: LFA-1-immunopositive lymphocytes and LFA-1-, CD1 lb/CD18- and PECAM-1-immunopositive macrophages. Further studies should be directed to such a comprehensive analysis. This may provide a correct view about the adhesive specificity of pleural disorders and a key for their diagnosis, monitoring and prognosis.

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Table 1. *Panel of cell adhesion molecules (CAM) expressed on cells in the pleural fluid*

CAM	Cells in pleural fluid
ICAM-1 (CD54)	Mesothelial cells, lymphocytes, tumor cells
LFA-1 (CD11a/CD18)	Monocyte-macrophages, lymphocytes
CD11b/CD18	Monocyte-macrophages, lymphocytes
PECAM-1 (CD31)	Monocyte-macrophages, lymphocytes
E-cadherin	Mesothelial cells, tumor cells

REFERENCES

1. Teran LM, Davies DE. The chemokines: their potential role in allergic inflammation. *Clin Exp Allergy* 1996; 26: 1005-1019

2. Antony VJW, Hott SL, Kunkel SW, Godbey MD, Burdick, Stieter RM. Pleural mesothelial cell expression of C-C (Monocyte Chemotactic Peptide) and C-X-C (Interleukin-8) chemokines. *AmJRespirCellMolBiol* 1995; 12:581-588

3. Reinhardt KM, Zilling D, Brinckmann W, Krammer B, Blann AD, Steiner M. Investigation of soluble adhesion molecules in cancer: beneficial approach or expensive toy? The case of soluble intercellular adhesion molecule-1 (sICAM-1). *BiomedRev* 1994; 3: 73-75

4. Kalev D, Micheva I, Dikranian K. Low immunoreactivity of mesothelial cells to ICAM-1 in patients with lung cancer and malignant pleural effusions compared to paramalignant. *Sartse-Byal Drob* 1996; 2: 41-44 (in Bulgarian)

5. Mutti L, Piacenza A, Valenti V, Castagueto B, Betta PG. Expression of intercellular adhesion molecule-1 (1C AM-1) by reactive mesothelial cells in pleural effusions. *Pathologica* 1993; 85: 725-728

6. Shiota J, James G, Wilson, Marukawa N, Tetsuya O, Masaro K. Soluble intercellular adhesion molecule-1 (sICAM-1) antigen in sera of bronchial asthmatics. *Chest* 1996; 109: 94-99

7. Schardt C, Heymanns J, Schardt C, Rotsch M, Havemann K. Differential expression of the intercellular adhesion molecule-1 (ICAM-1) in lung cancer cell lines of various histological types. *Eur J Cancer* 1993; 29A: 2250-2255

8. Kitsuki H, Uchiyama A, Yochida T, Torisu M. OK-432-induced enhancement of ICAM-1 expression on tumour cells positively correlates to therapeutic effects for malignant effusion. *Clin Immunol Immunopathol* 1994; 71: 89-95

9. Tsujisake M, Imai K, Hirata H *et al.* Detection of circulating intercellular adhesion molecule-1 antigen in malignant diseases. *Clin Exp Immunol* 1991; 85: 3-8

10. Hoffmann JC, Dengler TJ, Knoll PA *et al.* A soluble form of the adhesion receptor CD58 (LFA-3) is present in human body fluids. *Eur J Immunol* 1993; 23: 3003-3010

11. Hoffmann JC, Kruger H, Luhrs J, Mann H. Detection of soluble adhesion molecules in pleural effusions. *Chest* 1996; 110: 107-113

12. Meuer SC, Schraven B, Samstag J. Molecular mechanisms mediating lymphocyte recirculation, inflammation and metastasis formation. *Am RevRespir Dis* 1993; 148 (Suppl): S65-S69

13. Luscinskas FW, Kansas GS, Han Ding, Pizcueta P, Schleiffenbaum BE, Tedder TE *et al.* Monocyte rolling, arrest and spreading on IL-4-activated vascular endothelium under flow is mediated *via* sequential action of L-selectin, (il-integrins, and (i2-integrms. *JCellBiol* 1994; 125: 1417-1427

14. Spriggs Al, Boddington MM. Cells of serous fluids. Macrophages. In: Spriggs Al, Boddington MM, editors. *Atlas of serous fluid cytopathology.* Dordrecht, Kluwer Academic Publishers, 1989; 24-27

15. Kalev D. Diagnostic and prognostic value of cytological reactive changes in benign and malignant pleural effusions. PhD Thesis, Medical University of Varna, 1994 (in Bulgarian)

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