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 antigen 1 (LFA-1, CDllla/CD18). Tumor necrosis factor-a (TNF-ce), interferon (INF) -a, INF-P, and INF-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 cytolytic of tumor cells are mediated via the receptor/ligand pairs CD2/LFA-3 and LFA-1/ICAM-1. Soluble forms of LFA-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). The low ICAM-1 immunoreactivity on mesothelial 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, α4β1 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 cells are mesothelial cells (14). It is known that LFA-1 and CD11b/CD18 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 lb/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 1 lb/CD 18-immunopositive 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, CD11b/CD18, ICAM-1, platelet-endothelial cell adhesion molecule-l (PECAM-1/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-, CD11b/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

<table>
<thead>
<tr>
<th>CAM</th>
<th>Cells in pleural fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1 (CD54)</td>
<td>Mesothelial cells, lymphocytes, tumor cells</td>
</tr>
<tr>
<td>LFA-1 (CD11a/CD18)</td>
<td>Monocyte-macrophages, lymphocytes</td>
</tr>
<tr>
<td>CD11b/CD18</td>
<td>Monocyte-macrophages, lymphocytes</td>
</tr>
<tr>
<td>PECAM-1 (CD31)</td>
<td>Monocyte-macrophages, lymphocytes</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>Mesothelial cells, tumor cells</td>
</tr>
</tbody>
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