

DANCE ROUND

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

ROBERT FROST

INVESTIGATION OF SOLUBLE ADHESION MOLECULES IN CANCER: BENEFICIAL APPROACH OR EXPENSIVE TOY? THE CASE OF INTERCELLULAR ADHESION MOLECULE-1 (sICAM-1)

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Adhesion molecules are key topobiological components in almost any kind of cell-cell and cell-matrix interaction in both human physiology and pathology. Heterogeneous processes as platelet adhesion to subendothelial matrix components or leukocyte extravasation at sites of tissue damage are at least in part mediated by adhesion molecules and their corresponding receptors (counterreceptors). Using a multitude of modern analytical and preparative approaches ranging from "simple" immunohistochemistry to cloning and gene transfer, *in vitro* studies provided detailed data on a variety of adhesion molecules and their receptors (reviewed in 1). However, compared to the speedy accumulation of basic knowledge the evaluation of the diagnostic usefulness of adhesion molecules is still in its infancy.

Adhesion molecules can be divided into several families including integrins, cadherins, selectins, immunoglobulin superfamily and others. Every family consists of a growing number of individual molecules which share some common characteristics.

What criteria have to be made adhesion molecules

reliable diagnostic parameters? First, soluble forms should exist to ensure measurement in blood or other body fluids. If such forms exist analytical procedures for their estimation have to be developed and carefully evaluated for the intended use. If this can be achieved, numerous additional questions will arise including reference values, specificity, sensitivity and predicative power for a given disease or its complication etc. Finally, the cost-benefit ratio will be considered due to worldwide limited financial resources for health-care institutions

It is not surprising that disorders associated with the highest morbidity and mortality, including cardiovascular diseases, diabetes and cancer, were the candidates for diagnostic improvement using investigation of various adhesion molecules (reviewed in 2). Furthermore, in these diseases adhesion molecules may play a pathogenic role, e.g. monocyte adherence to vascular endothelium in early atherogenesis or attachment of tumor cells to form metastasis.

As it is unrealistic to review available data on every adhesion molecule, we will restrict our efforts to the

proposed diagnostic usefulness of soluble intercellular adhesion molecule-1 (sICAM-1). ICAM-1 (CD54) belongs to the immunoglobulin superfamily of adhesins and binds to the leukocyte integrin ($\alpha_5\beta_1$) (CD11a/CD18). A circulating, soluble form of ICAM-1 (sICAM-1) has been demonstrated using Western Blotting (3) and an enzyme immunoassay was established (4). Currently, at least three enzyme immunoassays for the determination of sICAM-1 are commercially available. However, due to inherent features of enzyme immunoassay technology (antibody specificity, calibration materials etc) these assays measure different concentration of sICAM-1 in healthy subjects as well as in various diseases. Therefore, results obtained by using different assays are only partly comparable. Authorities responsible for laboratory standardization are requested to coordinate efforts to standardize these assays.

Elevated serum levels of sICAM-1 have been reported in a variety of diseases including inflammatory, immune and infectious disorders, atherosclerosis, diabetes and others(2).

A number of studies have described increased sICAM-1 in cancer of different origin (2,5,6) including melanoma (7), gastrointestinal (8-10), urological (6) and hematological (6,11) malignancies. Each of these studies is essentially preliminary and longitudinal data is not available. Furthermore, convincing evidence for a good correlation to tumor staging and grading has not yet been communicated. An intriguing question concerns the cellular source of raised sICAM-1 in cancer patients. It has been proposed that sICAM-1 is shed from the tumor cell surface but there is limited evidence to support this idea (8). Alternatively, elevated sICAM-1 could be derived from endothelial cells and immune cells thus reflecting general cell activation within the host's defence system. Similar mechanisms are believed to contribute to increased sICAM-1 in type 1 diabetes mellitus due to its autoimmune pathogenesis (12).

Data from cell culture studies suggest that various cytokines (IL-1 α , IL-6, TNF α , interferon etc) may be involved in the regulation of adhesion molecules expression (8,10). Therefore, it can not be excluded

that sICAM-1 reflects cytokine-mediated upregulation and/or release of this particular adhesion molecule from the cell surface. As IL-6 is of central importance in the onset of an acute phase reaction we attempted to correlate sICAM-1 with the presence of an ongoing acute phase response in colorectal cancer patients. Although no correlation could be demonstrated, patients with present acute phase response revealed significantly higher sICAM-1 than the acute phase-negative subgroup (Reinhardt et al 1994, submitted). Additional studies into the specificity of sICAM-1 for a given tumor and its progression are urgently needed.

Expression of cell-bound ICAM-1 and shedding from the cell surface are apparently processes with different underlying regulation with consequences for tumor immunology and immunotherapy. Non-MHC-restricted cytotoxicity of tumor-infiltrating lymphocytes directed against tumor cells is at least in part mediated by tumor cell-bound ICAM-1. Shedding of surface ICAM-1 from melanoma cells inhibits the cytotoxic lymphocyte response probably due to the inability of tumor antigen recognition by sICAM-1-occupied lymphocyte ligands (13). This mechanism is considered important for the tumor cells escape from host's immune response resulting in rapid tumor progression and spread. Interestingly, recent data indicate that cytokine-mediated upregulation of tumor cell-bound ICAM-1 is not always accompanied by increased shedding (14). This discrepancy might be a central point for the effectiveness of immunotherapy in cancer. Augmentation of tumor cell-bound ICAM-1 without concomitantly enhanced shedding probably increases the lymphocyte-mediated cytotoxicity against the tumor. Conversely, if both processes are upregulated, the net effect could be expected to be unchanged thus making immunostimulatory therapy an ineffective approach in these patients. It may be that data on systemic sICAM-1 and basal and cytokine-stimulated expression and shedding of ICAM-1 from individual tumor cells will be included in the approach to individualise tumor immunotherapy.

Although current results on ICAM-1 might cause controversy and sometimes confusion, the data and ideas outlined so far may contribute to the conver-

sion of investigation of ICAM-1 in clinical oncology from an expensive toy to a reliable parameter for the benefit of our tumor patients.

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