Expression of Intercellular Adhesion Molecule-1 (ICAM-1) in Benign Naevi and Malignant Melanomas

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Intercellular adhesion molecule-1 (ICAM-1) is a membrane-bound glycoprotein that is a ligand for lymphocyte function-associated antigen-1 (LFA-1) and is important for a number of cell adhesions in immune reactions. The molecule is expressed by several cell types (e.g. macrophages, endothelial cells, keratinocytes, melanoma cells and cell lines) and there are some indications that expression of this molecule in melanocytic lesions is confined to malignant tumours and is more pronounced in metastatic and advanced tumours than in earlier lesions. In an attempt to elucidate this issue, we have studied biopsy samples from benign naevi (n=7) and malignant melanomas (n=33) regarding reactivity with monoclonal anti-ICAM-1 (CD54). The results indicate that the great majority of malignant melanomas are ICAM-1-positive. The most abundant staining is seen in metastatic melanomas. In primary melanomas, staining is more variable and generally weaker. However, no correlation was found between the degree of ICAM-1 labelling and the degree of tumour invasion. Furthermore, ICAM-1 expression was not confined to malignant lesions, but was also seen in benign naevi. These data contrast with earlier reports and indicate that ICAM-1 expression is unlikely to be of major prognostic or diagnostic value in melanocytic tumours. ***Key word: ICAM-1.***

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Intercellular adhesion molecule-1 (ICAM-1) is a 90 to 114 kD membrane-bound glycoprotein that is encoded by genes of the super immunoglobulin (Ig) family and consists of five extracellular domains, a transmembrane portion, and a cytoplasmic tail (1, 2, 3). The molecule is a ligand for LFA-1 (1, 4), and there is now ample evidence that adhesion between LFA-1-positive leukocytes and ICAM-1-positive antigen-presenting cells is crucial for many immune reactions (5, 6).

Whereas LFA-1 is confined to haemopoietic cells (7), ICAM-1 is more widely distributed and has been identified not only on antigen-presenting macrophages, but also on activated lymphoid cells, thymic epithelium, endothelial cells, and keratinocytes in diseased skin (8, 9, 10).

More recently, ICAM-1 has also been detected on melanoma cells and cell lines (11–14), and there are some indications that expression of this molecule occurs mainly in metastatic melanomas and advanced primary tumours (13, 14). These findings have suggested that ICAM-1 may play a role in the metastatic or invasive potential of these neoplasms. In an attempt to elucidate this issue, we have studied biopsy samples from benign naevi and malignant melanomas immunohistologically for reactivity with monoclonal anti-ICAM-1 (CD54).

MATERIAL AND METHODS

Biopsy samples

Biopsy samples were obtained fresh, frozen in a mixture of 2-methylbutane and dry ice and stored at −80°C until staining. The diagnoses are listed in Table I and were made in accordance with standard histological criteria, as described in detail elsewhere (15).

Processing of biopsy samples

Cryostat sections were air-dried overnight at room temperature, fixed in acetone for 10 min and either stained immediately or wrapped in aluminium foil and stored at −80°C until staining. In the latter instance, sections were allowed to warm to room temperature prior to unwrapping.

Immunohistological staining procedures

Cryostat sections were incubated with monoclonal anti-ICAM-1 (R6-5-D6 (9)) and stained using either the alkaline phosphatase:anti-alkaline phosphatase (APAAP) technique (16) or a three-stage immunoperoxidase method.

Table I. Results of the staining of benign naevi and malignant melanomas.

Diagnosis*	No. of cases	ICAM−1+	ICAM−1−
Benign naevi	7	7	0
SSM, level III	8	7	1
SSM, levels IV + V	8	7	1
LM, level III	1	1	0
NM, levels IV + V	4	2	2
Melanoma metastases	12	11	1

*SSM, superficial spreading melanoma; LM, lentigo malignant melanoma; NM, nodular melanoma.

RESULTS

Results from the staining of benign naevi and malignant melanomas are summarized in Table I.

In 7 benign naevi (6 intradermal naevi and 1 halo naevi) the tumour cells were ICAM-1-positive in all cases (see Fig. 1). Six cases were strongly reactive, while the remaining naevus showed a weaker reactivity.

In primary malignant melanomas, 17 of 21 cases were ICAM-1-positive. The pattern and intensity of the staining reaction was variable. Nine casesshowed a weak focal staining of the tumour cells at the periphery of the lesion; 4 cases showed an intermediate degree of staining with either scattered foci of positive cells or a more generalized, but weaker labelling of most of the cells; and 4 cases showed a strong staining of most of the tumour cells. No correlation was found between the pattern or intensity of the staining and the level of invasion (see Table I).

In melanoma metastases, 11 of 12 cases were strongly positive. The remaining case was ICAM-1-negative.

Keratinocytes above the benign naevi were ICAM-1-negative in all cases, while a small number of keratinocytes were ICAM-1-positive in 4 of the 21 cases of malignant melanoma. In all sections studied, ICAM-1-positive endothelial cells could also be found.

DISCUSSION

Several observations have suggested that host immune reactions play a critical role for the behaviour of malignant melanomas. It is well known that malignant melanomas may regress spontaneously, that many melanomas are surrounded by a heavy inflammatory infiltrate, that the inflammatory cells often express activation associated markers (17) and that melanoma cells may express molecules (e.g. HLA-DR) which are implicated in interactions be-

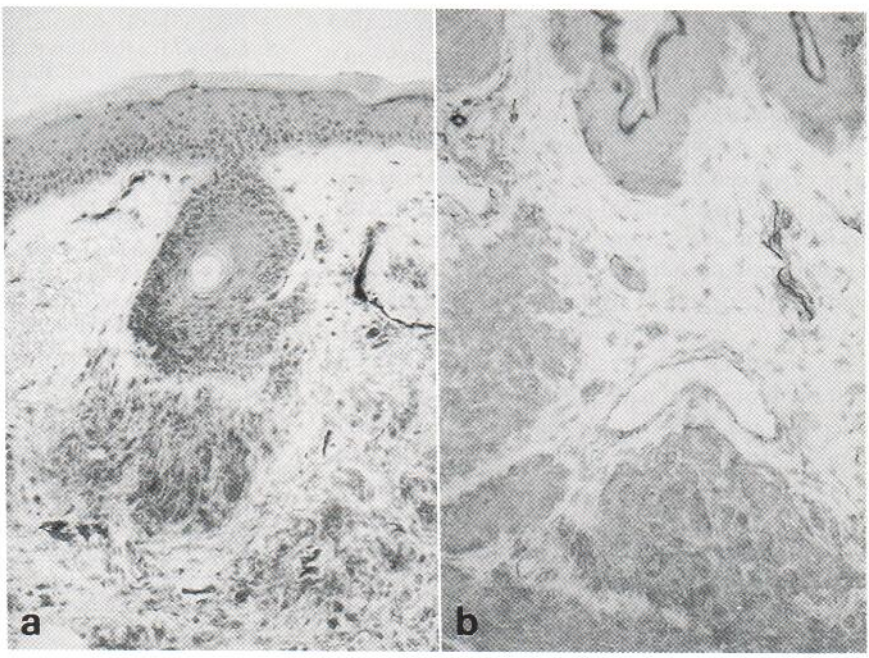

Fig. 1 Benign naevi stained for ICAM-1 with monoclonal antibody R6-5-D6 with the use of a three-stage immunoperoxidase method (A and B, 200 and 300, respectively). There is a labelling of both endothelial cells and the benign naevus cells.

tween leukocytes and target cells (18). However, attempts to correlate these features with prognosis and/or level of tumour invasion have not been successful.

Intercellular adhesion molecule-1 (ICAM-1) is a 90 to 114 kD membrane-bound cell adhesion molecule that is involved in immune reactions and acts as a ligand for lymphocyte function-associated antigen-1 (LFA-1) (1, 4). The expression of ICAM-1 is regulated by cytokines, and recent studies have shown that melanoma cells and cell lines may be ICAM-1-positive (11–14). Furthermore a correlation between level of invasion and ICAM-1 expression has been found (13, 14). These findings have attracted considerable interest because of the possible use of ICAM-1 as a diagnostic and prognostic marker in melanoma.

In this study, biopsy samples from benign naevi and malignant melanomas have been examined regarding reactivity with monoclonal anti-ICAM-1 (CD54). The results indicate that the great majority of metastatic and primary melanomas are positive for ICAM-1. The most abundant staining was seen in metastatic lesions in which virtually all of the tumour cells were strongly ICAM-1-positive. In primary melanomas, staining was more variable and generally weaker. No correlation was found between the expression of ICAM-1 and the level of invasion. Furthermore, ICAM-1 was not confined to malignant lesions, but was also seen in all benign naevi.

These findings are in contrast to other recent studies which have suggested that ICAM-1 expression is rare in benign naevi and is directly correlated to level of invasion in malignant lesions (see above). There are no obvious explanations for the discrepancy between these studies and the present report. It has been suggested that the expression of ICAM-1 by the melanoma cells might result from secretion of cytokines by the surrounding lymphocytic infiltrate and that the degree of activation of these cells might be more pronounced in deep than in superficial lesions (resulting in a greater secretion of cytokines and therefore a stronger ICAM-1 expression in the deep lesions). However, in this report, no correlation was found between the expression of ICAM-1 and the degree of lymphocytic infiltrate or the level of invasion. Furthermore we found ICAM-1 expression in benign naevi. These tumours are relatively inactive with few or no surrounding lymphocytes and hence should not be expected to be exposed to significant amounts of cytokines.

In conclusion, whatever the mechanism(s) of ICAM-1 expression in melanomas might be, our results indicate that expression of this molecule is unlikely to be of major significance in terms of prognosis and/or diagnosis of these neoplasms.

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