Differential Expression of Melanoma Associated Antigens in Acral Lentigious Melanoma and in Nodular Melanoma Lesions

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ABSTRACT

The reactivity in an avidin-biotin complex immunoperoxidase reaction with a large panel of anti-human melanoma associated antigen (MAA) and anti-HLA monoclonal antibodies of 24 primary and 11 metastatic acral lentigious melanoma (ALM) lesions was compared to that of 12 primary and 12 metastatic nodular melanoma (NM) lesions. The expression of the membrane bound vitronectin receptor, M, 110,000 MAA, M, 97,000 MAA, and intercellular adhesion molecule-1 was significantly lower in both primary and metastatic ALM lesions than in their NM counterparts. Furthermore, primary ALM lesions displayed a significantly lower expression than primary NM lesions while metastatic ALM lesions displayed a significantly lower expression than metastatic NM lesions. These antigenic differences do not reflect an antigenic paucity of ALM cells, since ALM lesions express a higher level of tyrosinase than NM lesions and a level of HLA Class I antigens similar to that of NM lesions.

In view of the use of HMW-MAA, M, 97,000 MAA, and GD, in immunoscintigraphy and/or in immunotherapy, it is noteworthy that the three antigens are expressed in a similar high percentage of ALM metastases and of primary and metastatic NM lesions, while the HMW-MAA is expressed in a markedly lower percentage of primary ALM lesions than M, 97,000 MAA and GD. However, the degree of heterogeneity of HMW-MAA within a positive primary ALM lesion, as measured by the percentage of stained melanoma cells, is lower than that of M, 97,000 MAA and GD.

The expression of the antigens investigated in ALM and NM lesions was not correlated with the presence of lymphocyte infiltrates, melanin content of melanoma cells, and epithelioid and spindle type of melanoma cells in the lesions. On the other hand, the survival of patients with ALM was inversely correlated with the expression of intercellular adhesion molecule 1 or HMW-MAA in their primary lesions. A potential role of HMW-MAA in the course of the disease is suggested by its significantly higher expression in metastatic than in primary ALM lesions. Since the expression of HMW-MAA in primary ALM lesions is not associated with known prognostic parameters, the present study suggests that expression of HMW-MAA may be an additional prognostic parameter in ALM, if the present results are confirmed in a large patient population.

INTRODUCTION

ALM differs from NM in a number of properties. They include incidence in different ethnic groups, site of anatomic localization, clinical course, and histopathological characteristics (for review, see Refs. 1–3). Furthermore, whether ALM and NM cells display the same or different antigenic profile remains to be determined.

The hybridoma methodology has been successfully applied to develop MoAb to a number of MAA with distinct structural and functional properties (for review, see Refs. 4 and 5). Investigations performed mainly in NM have shown that some MAA meet the criteria to be used for immunoscintigraphy and immunotherapy (for review, see Ref. 6), while others appear to be correlated with progression of malignancy and may be used as prognostic markers (7–9). In the present investigation we have compared the reactivity of ALM and NM primary and metastatic lesions with a large panel of anti MAA and anti-HLA MoAb, since this information may contribute to our understanding of the genesis of these two types of melanoma and of the functional role of MAA and HLA antigens in the biology of melanoma cells and may aid in the selection of MAA to be utilized in immunodiagnostic and immunotherapeutic approaches to the various types of melanoma.

MATERIALS AND METHODS

Melanoma Tissues. Melanoma lesions were obtained from patients who underwent surgery in the Department of Dermatology, Kumamoto University Medical School, Kumamoto, Japan. Twenty-four primary ALM lesions in vertical growth phase were obtained from 16 male and 8 female patients with an average age of 67 years (range, 38–91 years); 5 had Stage I melanoma, 6 had Stage II, 12 had Stage III, and 1 had Stage IV. Eleven metastatic ALM lesions were obtained from 7 male and 4 female patients with an average age of 66 years (range, 52–91 years); 9 had Stage III melanoma and 2 had Stage IV. Twelve primary NM lesions in vertical growth phase were obtained from 7 male and 5 female patients with an average age of 60 years (range, 25–85 years); 2 had Stage II melanoma and 10 had Stage III. Twelve metastatic NM lesions were obtained from 8 male and 4 female patients with an average age of 66 years (range, 52–80 years); 2 had Stage III melanoma and 10 had Stage IV. The diagnosis of ALM and NM was based on the anatomic site of lesions and on clinical and histopathological characteristics. Tissues were processed within 15 min following surgical removal. Each tumor tissue was divided into two parts. One-half was fixed in 10% buffered formaldehyde and processed for routine histology. The other half of the specimen was snap frozen in liquid nitrogen and stored at −80°C until use. Four-μm-thick cryostat sections were dried and fixed in absolute acetone for 1 min. Under these fixed conditions cryostat sections could be stored for at least 3 months at −20°C without loss of reactivity with anti-MAA and anti-HLA MoAb.

MoAb and Conventional Antisera. The anti-membrane bound MAA MoAb included the MoAb 225.28, TP41.2, and TP61.5 to distinct determinants of HMW-MAA (10), anti-VEA-R MoAb TP36.1, anti-M, 115,000 MAA MoAb 345.134 (11), anti-M, 110,000 MAA MoAb M111 (12, 13), anti-M, 100,000 MAA MoAb 376.96 (14), anti-M, 97,000 MAA MoAb 96.5 (15), anti-ICAM-1 MoAb CL203.4 (16, 17), MoAb B1.1 to a determinant expressed by CEA molecules and melanoma cells (CEA-MAA) (18), anti-NGF-R MoAb 1, 82–11 (19), anti-HLA 4 S. Ferrone, unpublished results.
Indirect Immunoperoxidase. This assay was performed utilizing the Vectastain ABC kit according to the manufacturer's instructions. The staining intensity was graded: —, when no staining was detected; ±, when the staining was faint, or barely detectable; +, when the lymphocyte infiltrate was unifocal; ++, when the lymphocyte infiltrate was multifocal, and ++++, when the lymphocyte infiltrate was extensive. The melanin content was scored as —, when no melanin was detected; ±, when the content was low, and +, when the content was high.

Statistical Analysis. Differences in the expression of each antigen in terms of presence or absence in the various types of lesions were analyzed by using the exact probability matrix test. Differences in the expression of each antigen in the various types of lesions were analyzed with the Aspin-Welch t test. The coexpression of antigens in the various types of lesions was tested using the correlation coefficient test. The relationship of the expression of each antigen with the thickness of primary lesions, lymphocyte infiltrate, and melanin content of melanoma cells was tested with the stratification analysis H test. Survival curves were calculated by using the method of Kaplan and Meier (30). Differences between survival curves were analyzed with a log rank test (31).

RESULTS

The results of immunohistochemical staining of 24 primary and 11 metastatic ALM lesions and of 12 primary and 12 metastatic NM lesions with anti-MAA and anti-HLA MoAb are summarized in Table 1. Representative staining patterns are shown in Figs. 1–4. The following points are noteworthy.

Primary ALM lesions expressed a significantly lower level of G0, ganglioside MoAb R24 (20), anti-9-O-acytely-G0, ganglioside MoAb ME311 (21), anti-G0, ganglioside MoAb ME361 (22), and anti-G0, ganglioside MoAb 3F8 (23). The anti-cytodplasmic MAA MoAb were included the anti-M, 94.000-75.000-70.000-25.000 MAA MoAb 82.11R24ME311ME3613F8465.12PAL-M2PAL-M,TMH-1H2-140-1NAMB-1CL413SPV-L3B7/21SpecificityHMW-MAAVN-RM,G,DI ganglioside MoAb R24 (20), anti-9-O-acetyl-GD1 ganglioside MoAb ME311 (21), anti-GD1 ganglioside MoAb ME361 (22), and anti-GD1 ganglioside MoAb 3F8 (23). The anti-cytodplasmic MAA MoAb included the MoAb H2-140-1 to a monomorphic class I antigen, HLA-DR, HLA-DQ, HLA-DP, and could be easily distinguished from brown positive results. Negative controls were performed by replacing primary antibody with supernatant from the murine myeloma cell line P3-X63-Ag8.653. A lesion was classified as negative, when no staining of melanoma cells was detected. The percentage of stained melanoma cells in each section and the staining intensity were estimated independently by two investigators. Variations in the percentage of stained cells enumerated by the two investigators were 10% or less. The average percentage was calculated and used as a result; each value has been rounded off to the nearest multiple of 10. The staining intensity was graded: —, when no staining was detected; ±, when the staining was faint, or barely detectable; +, when the staining was homogenous; ++, when the staining was strong and homogenous. Cells graded as ± were included in the positive cells in the calculation of the percentage of stained cells.

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Histopathological Analysis of Lesions. The presence of epithelioid and spindle type melanoma cells, the degree of lymphocyte infiltrate, and the melanin content in melanoma cells were evaluated by using the hematoxylin-eosin staining. The percentage of melanoma cells with epithelioid and spindle characteristics was determined by counting the number of nests of cells with spindle characteristics in one whole section of each lesion. The degree of lymphocyte infiltrate was scored as −, when no lymphocyte was detected; ±, when the lymphocyte infiltrate was scarce; +, when the lymphocyte infiltrate was unifocal; ++, when the lymphocyte infiltrate was multifocal, and ++++, when the lymphocyte infiltrate was extensive. The melanin content was scored as −, when melanin was not detected; ±, when the content was low, and +, when the content was high.

Color of melanin pigment was changed to green by Giemsa solution and could be easily distinguished from brown positive results. Negative controls were performed by replacing primary antibody with supernatant from the murine myeloma cell line P3-X63-Ag8.653. A lesion was classified as negative, when no staining of melanoma cells was detected. The percentage of stained melanoma cells in each section and the staining intensity were estimated independently by two investigators. Variations in the percentage of stained cells enumerated by the two investigators were 10% or less. The average percentage was calculated and used as a result; each value has been rounded off to the nearest multiple of 10. The staining intensity was graded: −, when no staining was detected; ±, when the staining was faint, or barely detectable; +, when the staining was homogenous; ++, when the staining was strong and homogenous. Cells graded as ± were included in the positive cells in the calculation of the percentage of stained cells.

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RESULTS

The results of immunohistochemical staining of 24 primary and 11 metastatic ALM lesions and of 12 primary and 12 metastatic NM lesions with anti-MAA and anti-HLA MoAb are summarized in Table 1. Representative staining patterns are shown in Figs. 1–4. The following points are noteworthy.

Primary ALM lesions expressed a significantly lower level of membrane bound HMW-MAA, VN-R, M, 110,000 MAA, and M, 100,000 MAA than primary NM lesions. The P values were <0.0001 and <0.0001 for the percentage of lesions stained and of melanoma cells stained in the lesions by anti-HMW-MAA MoAb 225.28, 0.014 and <0.0001 for those stained by anti-
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Fig. 1. Immunoperoxidase staining with anti HMW-MAA MoAb 225.28 of 4-μm cryostat sections of an ALM primary lesion (A), an ALM metastatic lesion (B), and a NM primary lesion (C). × 100. MoAb 225.28 does not stain melanoma cells (M) in junction and dermis of ALM primary lesion but stains melanoma cells in dermis of ALM metastatic lesion and of NM primary lesion. epi, epidermis; M, melanoma cells; arrows, melanophages.

Fig. 2. Immunoperoxidase staining with anti T4-tyrosinase MoAb TMH-1 of 4-μm cryostat sections of an ALM primary lesion (A) and a NM primary lesion (B). × 100. MoAb TMH-1 stains melanoma cells (M) in ALM lesion but does not stain melanoma cells (M) in NM lesion. epi, epidermis; M, melanoma cells; arrows, stained melanocytes.

Fig. 3. Immunoperoxidase staining with anti-G0 ganglioside MoAb R24 (A) and with anti 9-O-acetyl-G0 ganglioside MoAb ME311 (B) of 4-μm consecutive cryostat sections of an ALM primary lesion. × 100. MoAb R24 stains the large majority of melanoma cells, while MoAb ME311 stains a low percentage.

VN-R MoAb TP36.1, 0.0111 and 0.0146 for those stained by anti-M, 110,000 MAA MoAb M111, and 0.0334 and 0.0059 for those stained by anti-M, 100,000 MAA MoAb 376.96. A significantly lower percentage of primary ALM lesions than of NM primary lesions was stained by anti-M, 97,000 MAA MoAb 96.5 (P = 0.0163), anti-9-O-acetyl-G0, MoAb ME311 (P = 0.0116), anti-HLA-DQ MoAb SPV-L3 (P = 0.0253), and anti-HLA-DP MoAb B7/21 (P = 0.0307), while a significantly higher percentage of primary ALM lesions than of NM primary lesions was stained by anti-T4-tyrosinase MoAb TMH-1 (P = 0.0336). However, the difference in the percentage of melanoma cells stained by this latter group of MoAb in primary ALM and NM lesions was not significantly different. A significantly lower percentage of melanoma cells was stained in primary ALM lesions by anti-M, 115,000 MAA MoAb 345.134 (P = 0.0005), by anti-ICAM-1 MoAb CL203.4 (P = 0.0063), by anti-cytoplasmic MAA MoAb 465.12 (P = 0.0012), and by anti-TF-R MoAb PAL-M1 (P = 0.0138) than in primary NM lesions.
However, the difference in the percentage of ALM and NM lesions stained by the latter four MoAb did not reach the level of statistical significance.

The percentage of melanoma cells stained by anti-ICAM-I MoAb CL203.4 in ALM metastatic lesions was significantly ($P = 0.0008$) lower than that in NM metastatic lesions, although the percentage of lesions was not significantly different. Furthermore, a significantly lower percentage of metastatic ALM lesions than of metastatic NM lesions was stained by anti-$M_{110,000}$ MAA MoAb M111 ($P = 0.0373$) and anti-CEA-MAA MoAb B1.1 ($P = 0.0272$). No significant difference was found in the percentage of melanoma cells stained by the latter two MoAb in ALM and NM metastases.

ALM primary lesions expressed a significantly lower level of HMW-MAA than ALM metastases, in terms of both percentage of lesions ($P = 0.0019$) and percentage of melanoma cells ($P = 0.0029$) stained by MoAb 225.28. This finding is corroborated by the markedly higher percentage of melanoma cells stained by MoAb 225.28 in metastases than in autologous primary lesions in two of the six patients investigated (Table 2). To exclude the possibility that the differences observed reflected the differential expression of the determinant recognized by anti-HMW-MAA MoAb 225.28 and not of HMW-MAA molecules, ALM lesions were stained also with MoAb TP41.2 and TP61.5 which recognize distinct and spatially distant determinants from that defined by MoAb 225.28. A very good concordance was obtained in the staining pattern obtained with the three anti-HMW-MAA MoAb. Furthermore, incubation of ALM primary lesions with a pool of the three anti-HMW-MAA MoAb enhanced the intensity of staining but did not change the percentage of stained melanoma cells (Table 3). Representative staining patterns are shown in Fig. 4.

Primary NM lesions differed from metastatic NM lesions only in the expression of 9-O-acetyl-$G_D$. The percentage of primary lesions stained by MoAb ME311 was significantly higher ($P = 0.0361$) than that of metastatic lesions. However, the percentage of melanoma cells stained in the two types of lesions was not significantly different.

In view of the use of HMW-MAA, $M_{97,000}$ MAA and $G_D$ as markers for immunoscintigraphy and/or as targets for immunotherapy (32-36), their expression in the various types of lesions is noteworthy. The three types of MAA are expressed in a high percentage of primary and metastatic NM lesions and of metastatic ALM lesions; $G_D$ is expressed in a higher percentage of primary ALM lesions than $M_{97,000}$ MAA and HMW-MAA. The percentage of melanoma cells stained by anti-HMW-MAA MoAb in primary and metastatic NM lesions and in metastatic ALM lesions is higher than that stained by anti-$M_{97,000}$ MAA and anti-$G_D$ MoAb, but lower in primary ALM lesions. The pattern of expression of HMW-MAA in primary ALM lesions is different from that of $M_{97,000}$ MAA and $G_D$ since at least 80% of melanoma cells were stained by

**Fig. 4.** Immunoperoxidase staining with anti HMW-MAA MoAb 225.28 (A and C) and with the pool of MoAb 225.28, TP41.2, and TP61.5 to distinct determinants of HMW-MAA (B and D) of 4-μm consecutive cryostat sections of ALM primary lesions. Incubation with the pool of anti-HMW-MAA MoAb 225.28, TP41.2, and TP61.5 enhances the intensity of staining. A and $B$, $\times$ 100; C and $D$, $\times$ 200.
anti-HMW-MAA MoAb 225.28 in 4 of the 5 lesions which express this antigen. On the other hand, the percentage of melanoma cells stained by anti-M, 97,000 MAA MoAb 96.5 or by anti-GD₃ MoAb R24 was at least 80% in only 9 of the 15 lesions which express the M, 97,000 MAA and in only 10 of the 20 which express GD₃.

The concordance in the expression of the various types of antigens analyzed varied in ALM and NM lesions: in primary ALM lesions a statistically significant (P < 0.0001) correlation was found between HMW-MAA and ICAM-1 expression, GD₂ + GD₃ and 9-O-acetyl-GD₂ expression, HLA-DR, -DP, and -DP antigen expression and TF-R and MoAb PAL-M; defined M, 100,000 MAA expression. In ALM metastases, a statistically significant (P < 0.0001) correlation was found between ICAM-1 and HLA-DR, -DQ, and -DP antigen expression, GD₂ and NGF-R expression, HLA-DR and -DQ antigen expression and HLA-DR and -DP antigen expression. In primary NM lesions a statistically significant (P < 0.0001) correlation was found between CEA-MAA and GD₃ expression, HLA-DR and -DQ expression and HLA-DR and -DP antigen expression. In NM metastases only the correlation between HLA-DQ and -DP antigen expression was statistically significant (P < 0.0001).

The thickness of primary ALM lesions was significantly (P = 0.0282) correlated only with the expression of ICAM-1. This analysis could not be performed for primary NM lesions, since almost all the lesions analyzed were at least 4 mm thick.

In ALM and NM lesions no correlation was found between the expression of any of the antigens analyzed and the presence of lymphocyte infiltrates, melanin content of melanoma cells, and the epithelioid and spindle type of melanoma cells. A mean of 35% spindle cells (ranges between 10 and 50%) was found in 8 primary ALM lesions; spindle cells were not detected in primary NM lesions; 50% spindle cells were found in 1 metastatic ALM lesion and a mean of 27% spindle cells (ranges between 10 and 50%) was found in 3 metastatic NM lesions.

The expression of HMW-MAA and ICAM-1 in primary ALM lesions was inversely correlated with the survival of the patients (Fig. 5) with P values of 0.01 and 0.04, respectively. An inverse relationship was also found between VN-R expression in primary ALM lesions and patients’ survival but did not reach the level of statistical significance.

DISCUSSION

The present study has compared for the first time the antigenic profile of ALM and NM primary and metastatic lesions utilizing a large panel of anti-MAA and anti-HLA MoAb. To minimize the sources of variability among patients the lesions analyzed in the present investigation were obtained all from patients under treatment at the Department of Dermatology, Kumamoto University Medical School, Kumamoto, Japan. The expression of the antigens has been evaluated by enumerating the percentage of melanoma cells stained by MoAb in frozen sections of melanoma lesions. This method is less quantitative than analysis of melanoma cells stained following isolation from melanoma lesions. However, it avoids artifacts caused by the loss of melanoma cell subpopulations during the isolation procedure and by the contamination of melanoma cells with other types of cells. The results have been analyzed with statistical tests to provide a quantitative evaluation of the differences in the expression of the antigens by the various types of melanoma lesions. Primary and metastatic ALM lesions express a significantly lower level of several MAA than their NM counterparts. The latter include HMW-MAA, M, 97,000 MAA, 9-O-acetyl-GD₃ and GD₂-GD₃, which have a low expression also in uveal melanoma lesions (36). The antigenic differences between ALM and NM lesions do not reflect an antigenic paucity of ALM cells, since the latter display a higher reactivity with anti-Tyrosinase MoAb than NM cells and a similar reactivity with anti-HLA Class I MoAb. Since most, if not all, MoAb used in the present investigation were derived from mice immunized with melanoma cells originated from NM lesions, it will be of interest to generate MoAb from mice immunized with ALM cells to determine whether the latter express different types of MAA and to compare their expression with that by NM cells.

Data about the antigenic profile of primary and metastatic ALM and NM lesions deserve some comments. In both types of melanoma, the expression of ICAM-1 is not significantly lower in primary than in metastatic lesions. This finding is at variance with results that we (8) have previously reported. This discrepancy is only apparent and reflects the inclusion in the present study of a high percentage of primary lesions thicker than 1.5 mm since in the present investigation as well as in the previous one (8) the expression of ICAM-1 in primary lesions has been found to be directly correlated with their thickness. In agreement with the results of our previous study (8), the expression of ICAM-1 in primary ALM lesions was inversely correlated with the survival of the patients. This analysis could not be performed for patients with NM, since 8 of the 12 primary lesions tested were at least 5 mm thick. In agreement with Thurin et al. (21), we have found that 9-O-acetyl-GD₃ is expressed in a higher percentage of primary than of metastatic NM lesions. Furthermore, HMW-MAA has been shown for the first time to display a significantly lower expression in primary than in metastatic ALM lesions. This differential expression is likely to be a qualitative and not a quantitative phenomenon, since incubation of melanoma lesions with a pool of MoAb recognizing distinct determinants of HMW-MAA
increased the intensity of staining but did not affect the reactivity pattern. This finding is different from that obtained with uveal melanoma lesions; a pool of three anti-HMW-MAA MoAb stained uveal melanoma lesions which were not stained by individual MoAb (37). Whether the preferential expression of HMW-MAA in ALM metastases is a fortuitous phenomenon or reflects a functional role of these antigens in the metastatic process of ALM cells is not known. The latter possibility is supported by two lines of evidence which suggest a role of HMW-MAA in melanoma cell attachment to other cells and to cell substrates in tissues. HMW-MAA is expressed on microspikes at the cell surface of melanoma cells, a domain at the cell periphery that is involved in cell-cell interactions and contact of cell footpads to substrates (38). Furthermore, binding of anti-HMW-MAA MoAb to melanoma cells markedly reduces colony formation in soft agar, presumably through interference with cell-cell interactions (39). The role of HMW-MAA in the metastatic process of melanoma cells may also account for the statistically significant correlation we have found between its expression in primary ALM lesions and the unfavorable clinical course of the disease. If the latter correlation is not a casual event, an alternative possibility is that HMW-MAA expression is a marker of the degree of malignancy of melanoma cells. Whatever the mechanism it is noteworthy that the expression of HMW-MAA in primary ALM lesions shows no correlation with other known prognostic parameters such as tumor thickness and lymphocytic infiltrate (40). If additional studies in large numbers of patients corroborate the present finding, then expression of HMW-MAA in primary ALM lesions may become an additional prognostic parameter.

HMW-MAA, M, 97,000 MAA, and/or G10, are being used as markers for immunoscintigraphy and/or as targets for active and passive immunotherapy (32–36). Since the major application of these approaches are metastatic diseases, the distribution of these MAA in ALM and NM metastases has practical implications to optimize immunoscintigraphy and immunotherapy of melanoma. Although the three MAAs are expressed in a similar percentage of metastatic lesions, the degree of heterogeneity, as indicated by the percentage of melanoma cells stained within each lesion, is higher for M, 97,000 MAA and G10, than for HMW-MAA. These results are in agreement with those recently reported by Berd et al. (41) who have analyzed with a cytofluorograph melanoma cells isolated from lesions and stained with MoAb. Therefore, approaches which utilize the HMW-MAA as a marker or as a target are likely to be less susceptible to false negative results than those which utilize the other two types of MAA.

The expression of HLA Class I and Class II antigens we have found in both ALM and NM lesions in the present investigation is higher than that we and others have found in various types of melanoma, including NM (for review, see Refs. 42 and 43). Since some of the MoAb used in the present investigation were also used in other studies, their specificity cannot account for the described differences. The latter may reflect the sensitivity of the immunohistochemical technique used and/or the different characteristics of the patients with melanoma investigated.

The lower expression of HLA Class II antigens in ALM primary lesions than in NM lesions is noteworthy, since it can contribute to our understanding of the mechanism(s) regulating the expression of these antigens by melanoma cells. The extent of lymphocyte infiltrate in the ALM primary lesions analyzed is not markedly different from that in the NM lesions. In view of the suggested role of IFN-γ secreted by infiltrating lymphocytes in the induction of HLA Class II antigens on melanoma cells (44), the lower expression of HLA Class II antigens by ALM cells than by NM cells may reflect either a differential susceptibility to HLA Class II antigen induction and/or differences in the secretion of cytokines by the infiltrating lymphocytes. Alternatively, if expression of HLA Class II antigens by melanoma cells reflects their stage of differentiation (12), the present results suggest that melanoma cells in ALM primary lesions are more differentiated than those in NM primary lesions. The latter possibility is supported by the higher expression of tyrosinase in ALM cells than in NM cells.

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