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# Vitiligo- and melanoma-associated hypopigmentation: a similar appearance but a different mechanism

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**Abstract.** The significance of the association between the appearance of hypopigmentation in patients with melanoma and the prognosis is still not clear. It was postulated that, in melanoma, an immune response is responsible for the destruction of the malignant as well as the normal pigmented cells, and that the eventual development of vitiligo-like patches in melanoma patients improves their prognosis. We studied the level of anti-melanoma antibodies in the sera of patients with melanoma with hypopigmentation and compared it to the titer in patients with melanoma only, to the titer of patients with vitiligo, and to that of healthy subjects. Only IgG-type antibodies were found in the sera of patients with vitiligo, with melanoma, or with melanoma with hypopigmentation. No significant differences in the titer of anti-melanoma antibodies could be found between the patients with melanoma when subgrouped according to the initial stage and the status of the disease at the time when the test was carried out. Statistically significantly ($P < 0.001$) higher titers of antibodies were detected in the sera of patients with vitiligo in comparison to the lower titers in the other groups. Our results point to a similar immunobiological status, which probably does not give any advantage to patients with melanoma with hypopigmentation compared to patients without it. The appearance of hypopigmentary plaques in melanoma patients should be regarded, in our opinion, as a concomitant immunological phenomenon of the disease.

**Key words:** Malignant melanoma – Vitiligo – Hypopigmentation – Anti-melanoma antibodies – Marker – Melanoma-associated antigens

## Introduction

Vitiligo is a dermatological disorder characterized by patches of hypopigmentation on the skin [25, 30] and by the presence of autoantibodies against melanocytes [16]. The average level of antibodies to melanocytic surface antigens in the sera of th patients increases with the extent and activitiy of the disease [26]. Anti-melanocyte antibodies have been reported in only 50% of the patients with minimal vitiligo, but in 93% of patients with more extensive disease [29].

In a recent study we found that autoantibodies derived from patients with vitiligo bound to melanoma cells and, in the presence of complement, exerted a cytotoxic effect on these cells. The ability of the autoantibodies to lyse melanoma cells was exemplified also in a study with melanoma-bearing mice in vivo [11].

Melanoma is an immunogenic tumor, and patients with this tumor may develop antibodies to antigens of melanoma cells [6]. These antibodies may react either with the melanoma cells or with normal melanocytes [5], and thus induce melanoma-associated hypopigmentation (MAH or a "vitiligo-like" effect) in these patients.

The association between malignant melanoma and hypopigmentation is not clear. It has been postulated that an immune response might be responsible for the destruction of melanoma cells and the normal pigmented cells [14]. It has also been suggested that the presence of vitiligo-like patches in melanoma patients may indicate a beter prognosis [8, 9, 19, 22, 31].

The aim of this work was to examine the level of anti-melanoma antibodies in the sera of patients with melanoma with hypopigmentation and to compare it to the titer in patients with melanoma, patients with vitiligo and healthy subjects.

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| Characteristic | No. patients |
|---|---|
| Number | 78 |
| Male | 41 |
| Female | 37 |
| Age (years | 15–87 (mean 52.8) |
| Site of primary tumor | |
| Lower limgs | 26 |
| Trunk | 22 |
| Head and neck | 13 |
| Upper limbs | 8 |
| Eye | 4 |
| Thumb | 2 |
| Vagina | 1 |
| Nasal sinuses | 1 |
| Unknown | 1 |
| Stage (TNM UICC 1989) | |
| TxN0 | 3 |
| T1N0 | 11 |
| T3N0 | 14 |
| T4N0 | 11 |
| TxN0M1 | 2 |
| TxN1 | 6 |
| T2N0 | 9 |
| T3N1 | 3 |
| T4N1 | 4 |
| Disease status at the time of test | |
| No evidence of disease | 45 |
| On adjuvant IFN | 3 |
| No treatment | 42 |
| Local recurrence | 3 |
| Before treatment | 3 |
| Metastases | 30 |
| On chemotherapy | 5 |
| Steroids | 1 |
| IFN α | 2 |
| S/P immuno/chemotherapy | 21 |
| Terminal | 1 |

IFN, interferon

## Materials and methods

### *Patients*

A group of 78 patients with histologically proven melanoma, visiting the oncology ward or the out-patient clinic in The Tel-Aviv Medical Center from November 1992 through April 1993 were included in the study. The patients' characteristics are listed in Table 1. The most frequent site of the primary lesion (26% of cases) was the lower limb, followed the trunk (22%) and the head and neck region (13%). Most of the melanomas (54/78; 69%) were detected in stage I, 54% of the patients had no evidence of disease at the time the enzyme-linked immunosorbent assay (ELISA) was carried out, while 38% had overt metastatic disease. The clinical data of 8 patients with co-existing malignant melanoma and hypopigmentation are presented in Table 2. The control groups included 50 age-adjusted healthy volunteers and 10 patients with localized vitiligo.

### *Methods*

*Sers.* Sera were collected from the patients and healthy volunteers, divided into aliquots of 0.5 ml, and stored at –20° C until assayed.

*Cells.* B-16-F10 mouse melanoma cells were obtained from the Americn Tissue Culture Collection, and the M-14 human melanoma cell line was kindly donated by S. Ferrone, New-York Medical College, Valhala, N. Y. The cells were maintained in culture in RPMI-1640 medium supplemented with 10% fetal calf serum.

*Enzyme-linked immunosorbent assay detection of anti-melanoma antibodies.* Anti-melanocyte autoantibodies in patients with vitiligo are identifiable by immunofluorescence, immunoprecipitation, hemabsorption and Wester-blot analysis [13, 26, 29]. However, the most convenient and reproducible method to detect anti-melanocyte or anti-melanoma antibodies is, in our opinion, the ELISA. This assay, originally developed by Bystryn et al. [15] to assess the anti-melanoma antibodies, was modified in our laboratory. According to our version, based on our accumulated experience, 96-microwell tissue-culture plates with concave bottom (Nunc Ltd., Denmark) were coated with 2% bovine serum in phosphate-buffred saline (PBS). The sera from the volunteers or patients with melanoma to be tested for the presence of anti-melanoma antibodies were added to the wells in duplicate, in twofold dilutions, from 1:2 through 1:16. Two wells in each plate served as blanks and contained medium instead of serum. Samples containing $(1-2)\times10^4$ B-16 or M-14 melanoma cells were added to each well in a volume of 50 µl and incubated overnight at 4° C. The plates were then centrifuged (Sorval RT 6000 B) for 5 min at 1500 rpm at 4° C, and rinsed three times with 1% bovine serum followed once by PBS. Anti-(human IgG)- or anti-(human-IgM)-conjugated alkaline phosphatase (Sigma Ltd., USA), diluted to 1:2000 in 1% bovine serum, in a final volume of 100 µl was added to each well, and incubated for 1 h at 37° C. The plates were then centrifuged (Sorval RT 6000 B) for 5 min at 1500 rpm at 4° C, and rinsed three times in 1% bovine serum, followed once by PBS. A 10-mg sample of *p*-nitrophenyl disodium phosphate (Sigma Ltd., USA) was added with 0.05 M $NaHCO_3$ and 20 µl 1 M $MgCl_2$ to each plate. The plates were incubated at 37° C for 25 min. The absorbance was read by a Dynatech (UK) spectrophotometer at 405 nm.

*Statistics.* Statistical work-up included descriptive statistics, distribution analysis and one-way analysis of variation (ANOVA). A $P$ value below 0.05 was considered as statistically significant.

## Results

Localized hypopigmentation in association with malignant melanoma in our series appeared in 8 out of 78 patients (10.3%) during the course of the disease. Only anti-(human IgG) antibodies were found in the sera of all groups of subjects. In patients with melanoma, with either localized or spread disease, and in the control group, a very low binding of anti-melanoma antibodies to the melanoma cells was detected. Similar binding results were obtained with human M-14 melanoma cells, serving as targets in the ELISA assay. Statistically, there was no significant difference in absorbance values between the control and the whole patient group with melanoma. We could not detect differences in the titer of anti-melanoma antibodies between the patients with melanoma when subgrouped according to the initial stage and the status of the disease at the time when the test was carried out (T1–4 N0M0 or T1–4 N1M0 with no evidence of disease, or with local or systemic recurrences). Statistically significantly high titers of antibodies were detected in the sera of patients with vitiligo ($P < 0.001$) in comparison to the low titers in patients with melanoma, melanoma and hypopigmentation and the control group (Table 3; Fig. 1). The latter three groups showed similar titers.

**Table 2.** Clinical data of patients with malignant melanoma and hypopigmentation

| No. | Age (years) | Sex | Site of the primary | Extent of melanoma | Previous treatments | Site fo vitiligo |
|---|---|---|---|---|---|---|
| 1 | 47 | F | Right shoulder (Breslow 2.8 mm) | Metastatic | Excision of brain metastasis, radiotherapy to brain, chemotherapy, immunotherapy: IFN, IL-2 | Knees |
| 2 | 35 | M | Left leg (Breslow ?) | Lymph node involvement | Lymph node dissection, chemotherapy | No data |
| 3 | 32 | F | Left thigh | Lymph node involvement | Lymph node dissection, chemotherapy | Hands, palms |
| 4 | 47 | M | Unknown | Metastatic | Radiotherapy to spine, immunotherapy: IFN, IL-2 | No data |
| 5 | 67 | M | Left sole (Breslow 1.48 mm) | Lymph node involvement | Lymph node dissection, chemotherapy | Face, neck, trunk, arms |
| 6 | 46 | F | Left sole (CLark L3–L4) | Lymph node involvement | Lymph node dissection, BCG + melphalan | Palm (dorsum) |
| 7 | 80 | M | Right thumb (subungual) | Metastatic (subungual) | Immunotherapy: IFN | Upper trunk |
| 8 | 45 | M | Right shoulder (Brslow 0.75 mm) | Primary excised (regression) | Follow-up | No data |

IL-2, interleukin-2

**Table 3.** Serum levels of anti-melanoma antibodies measured by enzyme-linked immunosorbent assay in patients with melanoma, vitiligo, melanoma and associated hypopigmentation and in healthy controls (mean absorbance ± SD), see graphic presentation in Fig. 1

| | Absorbance for a serum dilution of: | | | | |
|---|---|---|---|---|---|
| Group | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 |
| Controls | 0.610±0.166 | 0.562±0.187 | 0.505±0.189 | 0.475±0.193 | 0.372±0.170 |
| Vitiligo | 1.420±0.221 | 1.023±0.189 | 0.784±0.263 | 0.612±0.248 | 0.527±0.215 |
| Melanoma | | | | | |
| T1–4N0M0 | 0.638±0.405 | 0.466±0.325 | 0.303±0.210 | 0.241±0.216 | 0.110±0.190 |
| T1–4N1M0 | 0.716±0.455 | 0.424±0.356 | 0.368±0.355 | 0.317±0.340 | 0.275±0.324 |
| Metastatic | 0.723±0.360 | 0.496±0.265 | 0.311±0.175 | 0.245±0.170 | 0.120±0.179 |
| Loc. rec. | 0.726±0.286 | 0.415±0.136 | 0.181±0.025 | 0.116±0.030 | 0.100±0.021 |
| Mel.+MAH | 0.427±0.191 | 0.272±0.090 | 0.157±0.050 | 0.081±0.017 | 0.064±0.017 |

Loc. rec., local recurrence; Mel. + MAH, melanoma and melanoma-associated hypopigmentation

In our series, although small, there was no striking difference between the course of the disease in melanoma patients with or without MAH. For example, the aggressiveness of a subungual melanoma with MAH (patient 7) was no different from that expected for such disease without MAH. This patient expired 19 months following the amputation. Since some of the patients were still on follow-up, the survival of those with MAH could not be compared, to those without it.

## Discussion

The significance of the development of melanoma-associated hypopigmentation ("vitiligo" or "vitiligo-like") in melanoma patients is a controversial issue. It has been suggested that patients with melanoma have the ability to destroy malignant pigmened cells, as well as normal melanocytes, and to form hypopigmentation, hence the prognosis of patients with melanoma and hypopigmentation may be better [22]. Lerner has shown that melanoma progressed slower and even regressed in animals with melanoma that developed vitiligo [21]. Vitiligo arose spontaneously in chimpanzees immunized with melanoma cells [18], and horses in which melanoma regressed spontaneously developed vitiligo [21]. Bystryn has even suggested that vitiligo may be regarded as "an experiment of nature that accomplishes the goal of melanoma immunotherapy" [5]. Therefore some authors have concluded that the presence of vitiligo in melanoma patients improves their prognosis [8, 9, 19, 31]. It has been reported by Koh et al. [19] that the 5-year survival of 8 patients with melanoma and vitiligo was 60%, compared to 30% for melanoma patients without hypopigmentation having a similar spread of the disease. Similarly, Nordlund et al. [31] observed that 65% of 51 patients with melanoma and vitiligo survived for 5 years, while only 50% of melanoma patients without hypopigmentation, having similar stages of the disease, had a

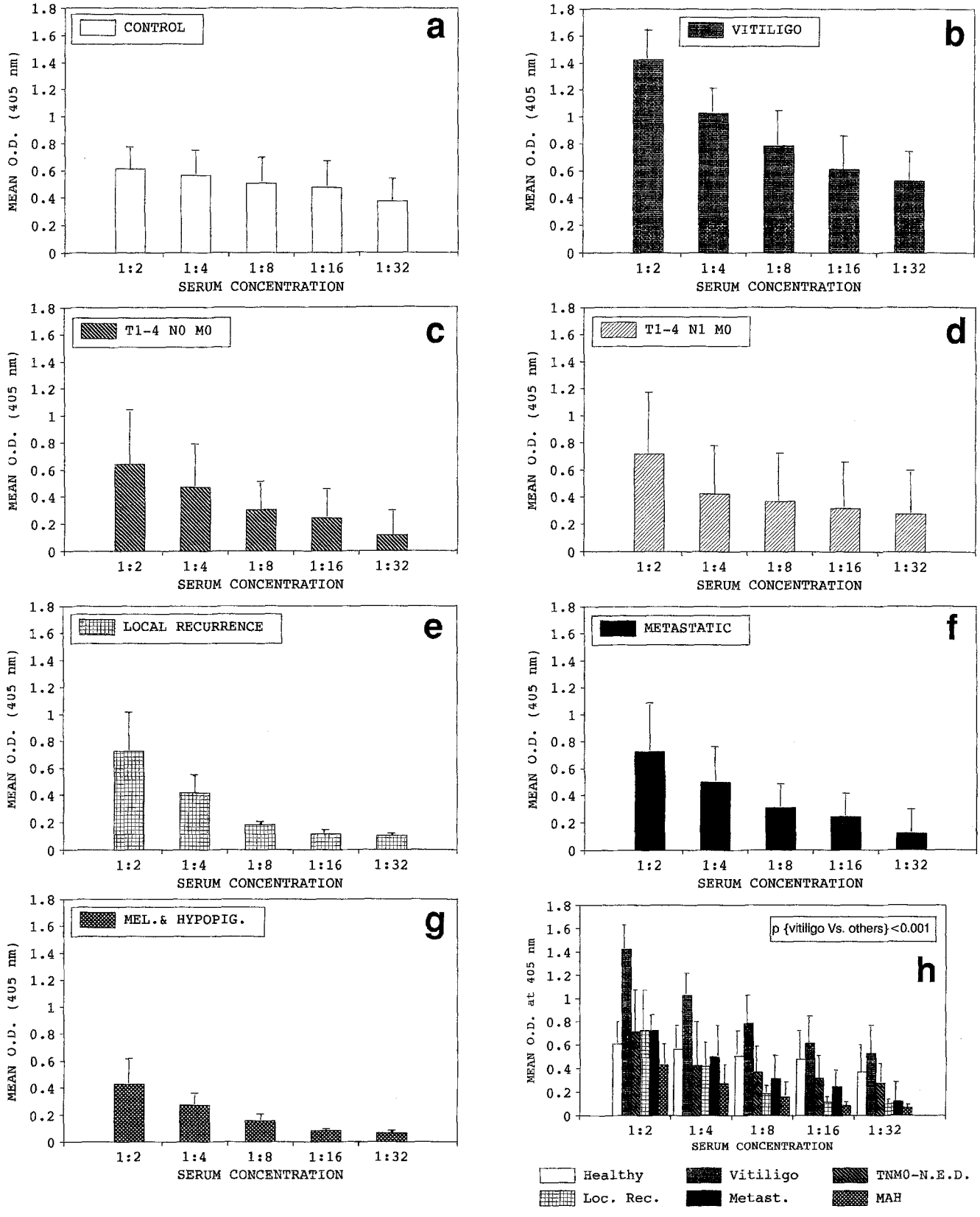


**Fig. 1a–h.** Serum levels of anti-melanoma antibodies determined by enzyme-linked immunosorbent assay [mean absorbance (*O. D.*) ± SD] in: **a** healthy controls; **b** vitiligo; **c** T1–4N0M0 melanoma with no evidence of disease (NED); **d** T1–4N1M0 melanoma and NED; **e** local recurrence; **e** local recurrence; **f** metastatic disease; **g** melanoma and hypopigmentation; **h** comparison between the groups: all the patients with either T1–4N0M0 melanoma or T1–4N1M0 and NED were grouped together to constitute the TNM0-NED patients. Patients with vitiligo had a significantly ($p < 0.001$) higher titer of anti-melanoma antibodies than the other groups. No significant differences in the titer of anti-melanoma antibodies could be found between the patients with melanoma when subgrouped according to the initial stage and the status of the disease at the time when the test was carried out

5-year survival. In the series reported by Bystryn et al. [8] an *actual* average 5-year survival of $91 \pm 7.1\%$ was found for a group of 46 melanoma patients with vitiligo compared with 74.8% *expected* 5-year survival for this group, based on individual risk factors. There was no difference in the survival between patients with a halo-hypopigmentation around the primary lesion compared with those with distant hypopigmentation. When vitiligo appeared late in the course of the disease the prognosis is was hopeless [6]. In contrast to the above, other authors have claimed that there had been no advantage to the patients in having combined malignant melanoma and hypopigmentation [20, 33].

The results obtained in the present study, i. e., similar antibody titers in both groups of patients, point to a similar immunobiological status which may not give any advantage to patients with melanoma and hypopigmentation over patients without MAH. This assumption supports the notion that patients with melanoma and hypopigmentation do not have a better prognosis.

The appearance of hypopigmentary plaques in melanoma patients should be regarded, in our opinion, as a concomitant immunological phenomenon of the disease. Since melanoma is an immunogenic tumor, which is often treated successfully with immunotherapy, the immune response towards this tumor includes development of anti-melanoma antibodies, as well as a cellular response. Our failure to detect free anti-melanoma antibodies in the sera of patients with melanoma may be explained either by the reaction of these antibodies with shed melanoma-associated antigens or by their absorption on antigens on melanoma cells. However, freshly removed tumor cells from patients with disseminated disease showed no bound antibodies to the membrane surface [24]. Other authors have suggested that free anti-melanoma antibodies are present only at very early stages of the disease, and disappear during the follow-up, concurrently with the disease progression [23, 27]. Our data showed, however, that even at very early stages such as T1N0M0 or T2N0M0 no anti-melanoma antibodies could be detected. It might be possible that such antibodies were present only when the disease was still in a subclinical stage. Moreover, these antibodies are capable of binding to normal melanocytes, and forming immune complexes [14, 23, 24] and blocking antibodies [24] resulting in hypopigmentary plaques. Reduced antigenicity or antigenic modification in melanoma cells [32], or the inability of the patient to produce an immune response towards the melanoma [32] could also result in an undetectable anti-melanoma antibody titer. It should be noted that patients with unmeasurable antibodies could still respond to immunization with autologous melanoma antigens by producing anti-melanoma antibodies [24, 28].

Vitiligo in the general population should be distinguished from the appearance of hypopigmentary areas in patients with malignant melanoma. Vitiligo is considered an autoimmune disorder, in which anti-melanocyte autoantibodies develop and destroy the normal melanocytes. Vitiligo is often associated with several autoimmune disorders such as hyperthyroidism, hypothyroidism, pernicious anemia, alopecia areata, hypoparathyroidism and diabetes mellitus [16]. Patients with vitiligo may have organ-specific autoantibodies: anti-adrenal cytoplasm), anti-(thyroid cytoplasm), anti-thyroglobulin, anti-(parietal cell), anti-(thyroid microsome), and anti-(pancreatic islet cell) antibodies [3, 4]. Our assumption that melanoma-associated-hypopigmentation is different from autoimmune vitiligo, is further supported by another study recently performed in our laboratory (unpublished data): employing ELISA, the presence of common autoantibodies in the sera of melanoma patients with or without hypopigmentation compared to normal control groups was evaluated. No detectable free antibodies against double- or single-stranded DNA, histones, cardiolipin, mitochondria, smooth muscle, ribonucleoproteins, actin, poly(I) or poly(G) were found in any of these patients, as also reported by us in other cancer patients [36]. Such autoantibodies were found in autoimmune vitiligo [3, 4, 16].

Vitiligo associated with an anti-melanoma immune response could be mediated by T cells, as well as by anti-melanoma antibodies. The role of T lymphocytes in the immune response towards melanoma cells and antigens is complicated. Melanoma antigens trigger $CD8^+$ cytotoxic lymphocytes while being presented by the HLA system. T cells recognize antigens only after they have been processed and degraded into peptides and complexed with cell-surface glycoproteins encoded by the major histocompatibility complex. The surface molecules of melanoma cells, as well as cytotoxic lymphocytes, include class I and class II HLA antigens [31].

Melanoma antigens are specifically recognized by by human tumor-infiltrating lymphocytes (TIL) [2]. Specific interaction of the T-cell receptor with MHC class I antigen and the relevant tumor antigen on the target cell surface is required for tumor lysis [17].

Early melanoma evokes an antigen-derived T cell response, which becomes attenuated with the progression of the disease. Melanoma cells of early disease act as competent antigen-presenting cells, presenting tumor-associated antigens to $CD4^+$ lymphocytes. This function is lost with tumor progression, probably because of dysfunction of HLA class II molecules. As the disease progresses, structural abnormalities occur in the HLA-DR $\beta 1$ gene products, which abrogate their capacity to present tumor-associated antigens directly to T cells [1].

In autoimmune vitiligo, as well as in other autoimmune disorders, the number of $CD4^+$ lymphocytes and the ratio $CD4^+/CD8^+$ were both increased [12, 34]. An increase in the number of helper T cells combined with a decrease in the number of suppressor cells led to over-production of autoantibodies [10]. Similar observations were made in the first-degree relatives of vitiligo patients [35].

The role of T lymphocytes in the induction of MAH has not been defined yet. It is possible that common antigens to melanocytes and melanoma cells are responsible for the mistargeting events and for the destruction of the "innocent bystander" normal melanocytes [2].

In conclusion, the titer of anti-melanoma antibodies in patients with melanoma with or without hypopigmentation or in healthy subjects was low, compared to that in patients with autoimmune vitiligo. Melanoma-associated hypopigmentation resembles autoimmune vitiligo in appearance, but results most probably from another immunological mechanism.

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